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HMGB1 in Health and Disease

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Abstract

Complex genetic and physiological variations as well as environmental factors that drive emergence of chromosomal instability, development of unscheduled cell death, skewed differentiation, and altered metabolism are central to the pathogenesis of human diseases and disorders. Understanding the molecular bases for these processes is important for the development of new diagnostic biomarkers, and for identifying new therapeutic targets. In 1973, a group of non-histone nuclear proteins with high electrophoretic mobility was discovered and termed High-Mobility Group (HMG) proteins. The HMG proteins include three superfamilies termed HMGB, HMGN, and HMGA. High-mobility group box 1 (HMGB1), the most abundant and well-studied

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HMG protein, senses and coordinates the cellular stress response and plays a critical role not only inside of the cell as a DNA chaperone, chromosome guardian, autophagy sustainer, and protector from apoptotic cell death, but also outside the cell as the prototypic damage associated molecular pattern molecule (DAMP). This DAMP, in conjunction with other factors, thus has cytokine, chemokine, and growth factor activity, orchestrating the inflammatory and immune response. All of these characteristics make HMGB1 a critical molecular target in multiple human diseases including infectious diseases, ischemia, immune disorders, neurodegenerative diseases, metabolic disorders, and cancer. Indeed, a number of emergent strategies have been used to inhibit HMGB1 expression, release, and activity *in vitro* and *in vivo*. These include antibodies, peptide inhbitiors, RNAi, anti-coagulants, endogenous hormones, various chemical compounds, HMGB1-receptor and signaling pathway inhibition, artificial DNAs, physical strategies including vagus nerve stimulation and other surgical approaches. Future work further investigating the details of HMGB1 localizationtion, structure, post-translational modification, and identifccation of additional partners will undoubtedly uncover additional secrets regarding HMGB1's multiple functions.

1 Introduction and Historical Background

In 1879, Walther Flemming, a trailblazing German cytologist, identified chromosomes using aniline dyes (Paweletz, 2001). We now know that chromosomes contain all genes that transfer well-defined characteristics from parents to offsprings. Chromosomes are actually packages of condensed chromatin, which is a nucleoprotein complex, residua of our archaeal past. The precise interaction between DNA and chromosomal protein regulates the structure, dynamics, and function of chromosomes, which in turn facilitates genomic stability and gene regulation (Andrews and Luger, 2011; Elgin and Weintraub, 1975; Stein et al., 1974). Histones, including H1, H2A, H2B, H3, and H4, are the predominant class of positively-charged chromosomal proteins (Campos and Reinberg, 2009). Histones tightly bind to negatively-charged DNA to condense it into a more compact structure, termed a nucleosome. A nucleosome is the basic repeating unit of chromatin with repetitive histone octamer units, which are typically wrapped with 147 base pairs of DNA. The second class of chromosomal proteins is composed of several relatively low-abundance, tissue-specific, high salt-urea insoluble proteins (Earnshaw and Mackay, 1994; Wakabayashi et al., 1974). These proteins include the nuclear matrix proteins, the chromosome scaffold protein, and the enzymes responsible for regulation of major DNA-associated events (e.g., replication, transcription, repair, and recombination). The third class of chromosomal proteins, and second most abundant, is the high mobility group (HMG) proteins including HMGB, HMGN, and HMGA. Compared with histones, HMG proteins have been highly conserved throughout evolution and loosely bind to chromatin without targeting individual DNA sequences but rather DNA structure (Bianchi and Beltrame, 1998; Einck and Bustin, 1985). Besides performing nuclear functions, several HMG proteins, including HMGB1 (Scaffidi et al., 2002; Wang et al., 1999), HMGB2 (Pusterla et al., 2009), and HMGN1 (Yang et al., 2012a) exert significant extracellular activity and function as damage-associated molecular pattern molecules (DAMPs). Recent genetic, biochemical, and cell biological analyses have greatly improved our understanding of the structure and function of HMG proteins in DNA-related processes, development, differentiation, aging, and cancer (Bianchi and Agresti,

2005; Bustin et al., 1990; Hock et al., 2007). In this review, we will briefly introduce the HMG protein members and focus on the physiological and pathological role of HMGB1 in health and disease. We believe that understanding of the HMG family is a link to our evolutionary past and a deeper understanding the bridge to our future.

1.1 Discovery of the HMG Protein

Ernest Johns from the Chester Beatty Research Institute, London is the pioneer of HMG research. In 1973, Ernest Johns and colleagues Graham Goodwin and Clive Sanders first isolated two groups of proteins from calf thymus chromatin by 0.35M NaCl extraction (Goodwin and Johns, 1973; Goodwin et al., 1973). One group of proteins was easily soluble in 10% trichloroacetic acid and migrated rapidly in polyacrylamide gel electrophoresis systems with no signs of aggregation. Based on its mobility, they called them “high-mobility group” proteins, namely HMG proteins (Goodwin et al., 1973). Partial fractionation of these HMG proteins by gel filtration revealed that they contained at least two proteins, namely protein 1 (HMG-1) and protein 2 (HMG-2). These two proteins are composed of over 55% acidic/basic amino acids with about 10^5 molecules of HMG-1 and -2 per cell nucleus (Goodwin and Johns, 1973; Goodwin et al., 1973). In contrast, the other group of proteins contained much fewer basic amino acids and migrated more slowly in polyacrylamide gel electrophoresis systems. They therefore called them “low-mobility group” proteins (Goodwin et al., 1973). Johns and his colleagues further demonstrated that HMG proteins can be extracted by 5% perchloric acid and have 40–50 % α-helix structures which are sensitive to pH around neutrality and the urea concentration (Baker et al., 1976; Cary et al., 1976). In addition to HMG1 and 2, Ernest Johns and colleagues separated other HMG proteins with perchloric acid extracts and divided HMG in two groups: the higher (e.g., HMG-1 and HMG-2) and lower (e.g., HMG-14, HMG-17, and HMG-Y) molecular weight proteins (Brown et al., 1980; Cockerill et al., 1983; Goodwin et al., 1980). Currently, a number of HMG proteins have been discovered in several species with the following properties (Bustin et al., 1990): (1) extractable from chromatin using 0.35 M NaCl; (2) soluble in 5% perchloric acid or tricloroacetic acid; (3) < 30 kDa in molecular weight with a high content of charged amino acids; (4) rapidly mobile in polyacrylamide gels; (5) sensitive to extensive post-translational modifications such as phosphorylation, acetylation, and poly-ADP-ribosylation; and (6) tissue- and development-dependent expression. In general, HMGs serve as architectural transcription factors that regulate not only special gene transcription but also global genomic stability by interacting with nucleotides, histones, transcription factors, and other chromosomal or nuclear proteins (Bianchi and Agresti, 2005; Grosschedl et al., 1994; Zlatanova et al., 1999).

1.2 Nomenclature Changes

In 2001, Michael Bustin from the National Cancer Institute, USA organized the HMG Chromosomal Protein Nomenclature Committee and recategorized these proteins into three superfamilies, renaming them as HMGB (formerly known as HMG-1/2), HMGA (formerly known as HMG-14/17), and HMGN (formerly known as HMG-I/Y) (Figure 1) (Bustin, 2001). Members of a gene family are sequentially numbered (e.g., HMGB1, HMGB2, HMGA1, HMGA2, HMGN1, and HMGN2). Small letters indicate the splice variants of genes (e.g., HMGA1a, HMGA1b and HMGA1c). Each HMG superfamily contains a

characteristic sequence motif with distinct cellular functions. HMG-box is the functional motif of the HMGB family; nucleosomal binding domain is the functional motif of the HMGN family; AT-hook is a DNA-binding motif with a preference for A/T rich regions and is the functional motif of the HMGA family. HMG proteins have the unique ability to recognize individual DNA structures from chromatin through functional motifs in a sequence-independent way. As architectural elements of chromosomes, HMG proteins bind or bend DNA structures, which contribute to sustaining DNA-dependent activity. Of note, the functional motifs of HMG proteins have also been discovered in other proteins, especially nuclear proteins, which are termed HMG-motif proteins such as the HMG-box family. There are two significant differences between canonical HMG proteins and HMG-motif proteins. HMG proteins are ubiquitous, abundant in almost all cells, and bind to DNA in a sequence-independent way, whereas HMG-motif proteins less abundant, are only present in specific cell types, and bind to DNA in a sequence-dependent manner (Bustin, 1999; Segall et al., 1994). The new nomenclature established rules to name genes and proteins belonging to the HMG family, which has contributed to our communication in research. For more detailed information about HMG nomenclature, a list of the HMG proteins in individual species can be found at the following link: http://www.informatics.jax.org/mgihome/nomen/hmg_family.shtml#G

1.3 HMG Families

1.3.1 HMGAs—The HMGA family has two basic members (HMGA1 and HMGA2) and was firstisolated in HeLa cells by Søren Laland and colleagues in 1983 (Lund et al., 1983). HMGA1a (human, 107 amino acids, 11.6 kDa; previously, HMG-I; HMGI; HMG I; HMG-I/Y; a-protein), HMGA1b (human, 96 amino acids, 10.6 kDa; previously, HMG-Y; HMGY; HMG Y) and HMGA1c (human, 179 amino acids, 19.6 kDa; previously, HMG-I/R) are proteins produced from alternative splicing of HMGA1 genes (Friedmann et al., 1993; Johnson et al., 1989; Nagpal et al., 1999). HMGA1a and HMGA1b share a core sequence except for an internal deletion of 11 residues in HMGA1b. Chromosomal localization studies show that the HMGA1 gene is located at human chromosomal band 6p21 (Friedmann et al., 1993) and mouse chromosome 17 (Johnson et al., 1992), whereas HMGA2 (previously HMGI-C) is located at human chromosomal band 12q14–15 (Chau et al., 1995) and mouse chromosome 10 (Ashar et al., 1995). Each HMGA protein contains three small similar but independent functional AT-hook motifs and an acidic C terminal tail (Reeves, 2000, 2001). AT-hook motif is an auxiliary protein motif that cooperates with other DNA binding activities to regulate chromatin structure and transcription. The core AT-hook stretch sequence is positively-charged Pro-Arg-Gly-Arg-Pro (with RGRP being invariant), flanked on either side by other positively-charged lysine/arginine residues, first described in the HMGAs (Tkachuk et al., 1992). The multiple or single AT-hook motif is also found in many other non-HMGA proteins such as transcription factors and chromatin-remodeling components (Aravind and Landsman, 1998; Singh et al., 2006). As an architectural transcription factor, HMGA-mediated gene expression is completed mainly through AT-hook motif. Binding DNA by HMGA AT-hook can lead to DNA structural or conformational changes such as bending, straightening, unwinding, or inducing loop formation (Maher and Nathans, 1996). In addition to their DNA-binding characteristics, HMGAs have the ability to change the structure of bound protein substrates, including

transcription factors, possibly by interacting through their acidic C terminal tail-mediated protein-protein (Yie et al., 1997). HMGAs not only have many partners, but also compete with the histone H1 for chromatin binding sites. A number of transcription factors can physically interact with HMGA proteins. HMGAs are not only key factors within enhanceosomes, which are multiple protein complexes including transcription factors and cofactors located upstream or downstream of the gene promoter (Reeves and Beckerbauer, 2001), but also mediate long-range enhancer-promoter interactions during gene transcription (e.g., β-globin and IL-2Rα) (Reeves, 2003). Thus, HMGAs regulate the expression of a large number of genes by DNA/protein binding and long/short-range mechanisms. In addition, post-translational modifications including phosphorylation, methylation, acetylation, sumoylation, and poly-ADP-ribosylation are essential to regulate HMGA substrate binding and their biological activities (Bianchi and Agresti, 2005; Reeves and Beckerbauer, 2001; Zhang and Wang, 2010). In particular, the HMGAs are the most heavily phosphorylated proteins in the nucleus (Lund et al., 1985), and HMGA phosphorylation by cyclin-dependent kinase 1 (CDK1/Cdc2) significantly decreases DNA binding affinity in the G2/M phase of the cell cycle (Nissen et al., 1991). In addition, casein kinase 2 (CK2) (Palvimo and Linnala-Kankkunen, 1989), protein kinase C (PKC) (Xiao et al., 2000), homeodomain-interacting protein kinase-2 (HIPK2) (Kim et al., 1999), and NIMA-related kinase 2 (Nek2) (Di Agostino et al., 2004) can phosphorylate HMGA1 proteins during cell death, the DNA damage response, and meiosis. The interaction between these upstream signal events remains unknown.

Both HMGA1 and HMGA2 are undetectable or very sparse in normal, fully-differentiated cells and adult tissues, but predominantly expressed during embryonic development in stem cells, undifferentiated cells, and neoplastic tissues (Cleynen and Van de Ven, 2008; Copley et al., 2013). In addition, HMGA1 is inducibly expressed following various environmental stimuli including the presence of growth factors, cytokines, endotoxin, retinoic acid, virus, or hypoxia (Liu et al., 2001). These expression properties indicate important roles of HMGAs in development, differentiation, cancer, and immunity. Indeed, HMGA1 and HMGA2 have different roles in development. HMGA1$^{-/-}$ mice have a cardiac hypertrophy phenotype (due to increased class II calcium/calmodulin-dependent protein kinase [CaMKII] expression), hematological malignancies, and type 2 diabetes (due to decreased insulin receptor expression) (Fedele et al., 2006; Foti et al., 2005), whereas HMGA2−/− mice have the dramatic phenotype called “pygmy,” which is characterized by treduced fat tissue, craniofacial defects, and slow growth due to a longer cell cycle of embryonic fibroblasts (Xiang et al., 1990; Zhou et al., 1995). In addition, both HMGA2$^{-/-}$ and HMGA1$^{-/-}$ male mice are infertile due to impaired spermatogenesis (Chieffi et al., 2002; Liu et al., 2003). HMGA1 is also important for lymphohematopoietic differentiation, because the loss of HMGA1 in embryonic stem cells causes impairment of T and myeloid cell development and leads to an increase in B-cells (Battista et al., 2003) by up regulation of recombination activating gene 2 (RAG2) expression (Battista et al., 2005).

Increasing evidence indicates that aberrantly-expressed HMGAs contribute to cancer initiation, promotion, and progression (Fedele and Fusco, 2010; Fusco and Fedele, 2007). HMGA overexpression and rearrangements are a hallmark of both malignant and benign neoplasia. Elevated HMGA1 expression correlates with metastatic potential in malignant

epithelial tumors such as those of the lung, breast, prostate, colon, gastric, and pancreas, as well as renal and thyroid cancer. In contrast, elevated HMGA2 expression is observed in breast cancer, sarcomas, pancreatic cancer, head and neck/oral squamous cell carcinomas, melanoma, hepatoblastoma, and ovarian and non-small cell lung cancer. Rearrangements in HMGA2 genes are found in both benign (e.g., lipomas, uterine leiomyomas, and pulmonary chondroid hamartomas) and malignant (e.g., inflammatory myofibroblastic tumors and liposarcomas) mesenchymal tumors. HMGA1 is an independent prognostic factor in patients with pancreatic cancer. Patients with HMGA1-negative tumors have a better prognosis with longer median survival (Liau et al., 2008). Several transcription factors (e.g., Sp1, Sp3, AP-1, and E2F1), microRNAs (e.g., let-7, miR-196a-2, and microRNA-296) and signals (e.g., Wnt/β-catenin signaling) contribute aberrantly to HMGA expression in tumors (De Martino et al., 2009; Ferguson et al., 2003; Motoyama et al., 2008; Wend et al., 2013; Zhang et al., 2014b). In addition, oncogenic genes such as K-RAS, N-RAS, and c-Myc can induce HMGA1 overexpression during cell transformation (Li et al., 2013i). *In vitro* suppression of HMGA expression by RNAi decreases tumor cell proliferation and restores chemotherapy sensitivity (Liau et al., 2007; Watanabe et al., 2009), whereas overexpression of HMGAs by gene transfection promotes neoplastic transformation and increases chemotherapy resistance (Di Cello et al., 2008; Fedele et al., 1998). Moreover, transgenic mice overexpressing HMGA1 or HMGA2 produce a neoplastic phenotype (Arlotta et al., 2000; Baldassarre et al., 2001; Fedele et al., 2002; Fedele et al., 2005; Zaidi et al., 2006), whereas HMGB1$^{-/-}$ mice are resistant to chemically-induced skin carcinogenesis (Visone et al., 2008). Multiple molecular mechanisms contribute to the oncogenic activities of HMGAs. These mechanisms include uncontrolled cell cycling (Tessari et al., 2003), enhancement of transcription factor DNA-binding activity (Vallone et al., 1997), inhibition of apoptosis activity (Esposito et al., 2012), impairment of the DNA damage response (Pentimalli et al., 2008), promotion of inflammatory mediator production (Hillion et al., 2008; Perrella et al., 1999), regulation of cancer stem cells (Yanagisawa and Resar, 2013), downregulation of potential tumor-suppressor genes (Martinez Hoyos et al., 2009), upregulation of epithelial-mesenchymal transition (Morishita et al., 2013; Thuault et al., 2006), functioning as a competing endogenous RNA for microRNA (e.g., let-7 and MicroRNA-137) (Kumar et al., 2014; Liang et al., 2013a), and enhancement of autophagy-mediated aerobic glycolysis (Ha et al., 2012a). However, HMGAs also exerts anti-proliferative properties in some cells (Fedele et al., 2006), calling for further study of HMGA1 as potential therapeutic agent in cancer treatment.

1.3.2 HMGNs—The HMGN family has been found only in vertebrates and has five members: HMGN1 (human, 100 amino acids, 10.6 kDa), HMGN2 (human, 90 amino acids, 9.3 kDa), HMGN3 (human, 99 amino acids, 10.6 kDa), HMGN4 (human, 90 amino acids, 9.5 kDa), and HMGN5 (human, 282 amino acids, 31.5 kDa) (Furusawa and Cherukuri, 2010; Hock et al., 2007; Kugler et al., 2012). HMGN2 is the most conserved member of HMGNs. Chromosomal localization studies show that the HMGN1 gene is located at human chromosomal band 21p22 and mouse chromosome 16; the HMGN2 gene is located at human chromosomal band 1p36 and mouse chromosome 4; the HMGN3 gene is located at human chromosomal band 6p14 and mouse chromosome 9; the HMGN4 gene is located at human chromosomal band 6p21; and HMGA5 is located at human chromosomal band

Xp13. HMGNs usually contain a bipartite nuclear localization signal (NLS), a highly-conserved nucleosome-binding domain (NBD), and a negatively charged regulatory domain (RD) within the C terminus. The major function of HMGNs is to bind nucleosomes and to regulate chromatin structure and function. The invariant sequence RRSARLSA in NBD is the core sequence of HMGNs that recognizes specifically generic structural features of the 147-bp nucleosome (Ueda et al., 2008). HMGNs have specific effects on gene transcription both locally and globally and sometimes acting in a cell-specific manner (Cuddapah et al., 2011; Kugler et al., 2012; Rochman et al., 2011). In addition, HMGNs are highly mobile and compete with the linker histone H1 for nucleosome access, which can cause chromosome relaxation and enhance gene transcription (Catez et al., 2002; Ding et al., 1997). Moreover, HMGNs facilitate epigenetic change by modulating the levels of posttranslational histone modifications (e.g., phosphorylation of H3, acetylation of H3K14, acetylation/methylation of H3K9, and phosphorylation of H2AS1) (Barkess et al., 2012; Lim et al., 2004; Lim et al., 2005). Although it binds to chromatin with very similar affinities, the expression and function of HMGNs in cellular differentiation and development are quite different.

HMGN1 (previously HMG-14; HMG14; HMG 14) and HMGN2 (previously HMG-17; HMG17; HMG 17) are ubiquitously expressed in embryonic tissues (Crippa et al., 1991; Lehtonen and Lehtonen, 2001), highly expressed in stem cells and undifferentiated cells, and downregulated in fully differentiated cells following organogenesis (Crippa et al., 1991; Furusawa et al., 2006; Lehtonen and Lehtonen, 2001; Pash et al., 1990). HMGN1$^{-/-}$ mice are subfertile and have slight defects in corneal epithelium maturation due to an absence of p63 expression (Birger et al., 2006). In particular, HMGN1$^{-/-}$ mice have identifiable phenotypes following stress. For example, loss of HMGN1 in mice renders them hypersensitive to both UV and ionizing radiation promoting increased tumorigenicity due to loss of the active G2-M checkpoint and impaired DNA repair (Birger et al., 2005; Birger et al., 2003). In addition, HMGN1$^{-/-}$ MEFs are hypersensitive to stressful stimuli and have an altered transcription profile and response (Birger et al., 2003; Lim et al., 2004; Lim et al., 2005; Rubinstein et al., 2005). Transient depletion of HMGN1 and HMGN2 proteins following injection of antisense oligonucleotides in one-cell or two-cell mouse embryos delayed cell cleavage during pre-implantation development (Mohamed et al., 2001). In contrast, overexpression of HMGN1 is observed in a mouse model of Down's syndrome, suggesting a possible role for HMGN1 in post-natal development and mental retardation (Potier et al., 2006). In *Xenopus*, overexpression or disruption of HMGN1 or HMGN2 expression leads to significant developmental defects in post-blastula embryos (Korner et al., 2003). Thus, HMGN1 and 2 protein levels are tightly linked to cell differentiation and tumorigenesis. HMGN1 can also be released to the extracellular space and function as a DAMP (Yang et al., 2012a). Extracellular HMGN1 promotes antigen-specific immune responses by ligating TLR-4. Intracellular HMGN1 is required for OVA- and LPS-induced innate and adaptive immune responses (Yang et al., 2012a). The mechanism enabling HMGN1 release is unknown.

HMGN3 (previously, Trip7) with two splice variants (HMGN3a and HMGN3b) are expressed in a tissue-, variant-, and developmental stage-specific manner (Kugler et al., 2013; West et al., 2001). Although the tissue distributions and functions of HMGN3a and

HMGN3b are similar, the structures of various splice variants are significantly different. HMGN3a contains classical HMGN domains (NLS, NBD, and RD), whereas HMGN3b only has NLS and NBD domains and lacks an RD domain. HMGN3 is highly expressed in the eye, brain, and pancreatic endocrine cells (β and α cells), suggesting a potential role for HMGN2 in eye development, brain activity, and glucose homeostasis (Ito and Bustin, 2002; Kurahashi et al., 2010; Ueda et al., 2009; West et al., 2001). Indeed, HMGN3$^{-/-}$ mice develop normally but have a mild diabetic phenotype due to partial downregulation of GLUT2 (a major transporter of glucose) as well as a glucagon-insulin production imbalance (Kurahashi et al., 2010; Ueda et al., 2009). In addition, HMGN3 is indirectly regulated by thyroid hormone and interacts with it in *Xenopus laevis* (Amano et al., 2002).

HMGN4 was discovered via a GenBank database search by Michael Bustin and colleagues in 2004 (Birger et al., 2001). However, at present, the biological function of HMGN4 is unknown, although its sequence is known to be closely related to that of HMGN2 (Birger et al., 2001). HMGN5 (previously BP1, NBD-45) was also discovered via a GenBank database search by Michael Bustin and colleagues in 2000 (Shirakawa et al., 2000). Compared to other HMGNs, HMGN5 has a unique molecular structure and size (Shirakawa et al., 2000). HMGN5 contains classical HMGN domains (NLS, NBD and RD), but the C-terminal domain is unusually long and contains a unique acidic amino acid repeat (Rochman et al., 2009). Although the structures are highly similar, the HMGN5 protein sequence has only a 59% amino acid conservation between human and mouse. The expression of HMGN5 protein varies significantly between cells and tissues during embryonic development (Shirakawa et al., 2000). In addition, HMGN5 expression is upregulated with the development of several cancers, including squamous cell carcinoma, breast and bladder cancer, renal cell carcinoma, and gliomas (Gerlitz, 2010; Ji et al., 2012b; Li et al., 2006a; Qu et al., 2011; Tang et al., 2008b; Wahafu et al., 2011). Knockout of HMGN5 by RNAi inhibits cell proliferation and increases apoptosis in cancer cells (Chen et al., 2012b; Ji et al., 2012b; Zhang et al., 2012c).

In summary, HMGNs bind directly to nucleosomes, modulate epigenetic modifications, and influence chromatin structure, which in turn have multiple roles in the regulation of cell differentiation, organ development, and tumorigenesis.

1.3.3 HMGBs—The high-mobility group box (HMGB) protein family is the most abundant protein family among HMGs (Goodwin and Johns, 1978). The HMGBs are highly conserved and have four members (HMGB1, HMGB2, HMGB3, and HMGB4). Interestingly, knockout of mouse HMGB1, HMGB2, and HMGB3 genes clearly results in identifiable phenotypes, although the encoded proteins share ~80% amino acid sequence identity. Each HMGB (HMGB1–4) contains two DNA binding domains (termed HMG boxes A and B). HMGB1–3 has an acidic C-terminal tail, whereas HMGB4 lacks this tail (Thomas and Travers, 2001). Each HMGB box binds to DNA without any significant sequence specificity and can induce DNA conformational and structural changes (Agresti and Bianchi, 2003; Ueda and Yoshida, 2010). The acidic C-tails of HMGBs can bind other nuclear proteins, even HMG boxes, to regulate their affinity for a variety of distorted DNA structures. Besides HMGBs, several proteins have been identified with the HMG box

(termed the HMG-box family). The differences between the HMGBs and HMG-box family are described below.

1.3.3.1 The HMG-box Family: The HMG box is a novel type of protein motif that mediates DNA-binding (Landsman and Bustin, 1993). Each protein within the HMG-box family has at least one HMG-box (Figure 2). The mammalian HMG-box family can be divided into two main groups based on abundance, function, and DNA specificity (Griess et al., 1993; Laudet et al., 1993; van Houte et al., 1995). The first protein group contains multiple HMG-box domains with little or no sequence-specific DNA binding and an acidic C-tail. These proteins include HMGBs (HMGB1–4) with two HMG-boxes, mitochondrial transcription factor (TFAM) with two HMG-boxes, upstream binding factor (UBF) with six HMG-boxes, and SP100-HMG nuclear autoantigen with two HMG-boxes (Stros et al., 2007b). TFAM, a transcription factor for mitochondrial DNA, plays a critical role in maintaining the amount of mitochondrial DNA in a promoter-specific manner (Kanki et al., 2004) or a cAMP-dependent phosphorylation manner (Lu et al., 2013a). In addition, TFAM can be released into the extracellular space during infection and injury, and function as a DAMP to regulate immune and inflammatory responses (Chaung et al., 2012). The nuclear transcription factor UBF, including UBF1 and UBF2, is important for activation of ribosomal RNA transcription by associating with RNA polymerases (O'Mahony and Rothblum, 1991; Schnapp et al., 1994). In contrast, the tumor suppressor Rb can inhibit UBF expression, suggesting a potential role for UBF in tumorigenesis (Cavanaugh et al., 1995). SP100-HMG, a splicing variant of SP100, functions as a transcriptional activator or repressor (Seeler et al., 1998). The interrelationship between HMGBs and the various HMG-box families is unclear.

The second group in the HMG-box family consists of highly diverse, much less abundant proteins and contains a single HMG-box domain with DNA binding sequence-specificity. These proteins include lymphoid enhancer-binding factor 1 (LEF1), T-cell factor 1 (TCF1), TCF3, thymocyte selection-associated HMG box protein (TOX), sex determining region Y (SRY), sex determining region Y-box (SOX), brahma-related gene -associated factor (BAF57), polybromo-1 (PB1), Wolf-Hirschhorn syndrome candidate 1 protein (WHSC1), HMG-box transcription factor 1 (HBP1), HMG box transcription factor (BBX), capicua transcriptional repressor (CIC), and structure-specific recognition protein 1 (SSRP1). The major functions of these proteins are described below.

LEF1, a key transcription factor of Wnt signaling, is expressed specifically in pre-B and T-cells and regulates cell differentiation (Giese et al., 1991; Metzeler et al., 2012; Milatovich et al., 1991). $LEF1^{-/-}$ mice die shortly after birth but have no apparent lymphoid defects (van Genderen et al., 1994). TCF1 is expressed specifically in cells of the T-cell lineage (Oosterwegel et al., 1993) and loss of TCF1 leads to deficient T-cell development (Verbeek et al., 1995). In contrast, TCF3 is expressed specifically in gastric epithelium, hair follicles, and keratinocytes of the skin (Korinek et al., 1998). TCF1 is an effector, whereas TCF3 is a repressor of Wnt signaling during embryonic development and gene expression (Yi et al., 2011). TOX is highly expressed in the thymus and has a critical role in immunity via three subfamily proteins: TOX2, TOX3, and TOX4 (Aliahmad et al., 2012; Wilkinson et al., 2002). Loss of TOX in mice leads to deficient development of T cells (Aliahmad and Kaye,

2008), natural killer cells, (Aliahmad et al., 2010) and lymphoid tissue inducer cells (Aliahmad et al., 2010). Mammalian SRY on the short arm of the Y chromosome encodes a nuclear factor-like protein harboring a DNA-binding domain known as the HMG box (Ferrari et al., 1992; Sinclair et al., 1990). SRY and its related SOX are sex-determining factors (Harley and Goodfellow, 1994; Werner et al., 1995). They have similar structures, but differing tissue-specific expression patterns. The SOX proteins comprise nearly half of all human HMG-box proteins. SRY and SOX are also important for organ development and cell type specification (Wegner, 1999). In humans, deletion or mutation of Sox proteins can cause developmental defects and congenital diseases. BAF57 and PB1 are chromatin-remodeling factors involved in gene regulation and cell cycle control by alteration of DNA-nucleosome topology (Domingos et al., 2002; Link et al., 2005). Mutation or aberrant expression of BAF57 has been observed in many tumor patients (Balasubramaniam et al., 2013; Hah et al., 2010; Kiskinis et al., 2006; Link et al., 2008). WHSC1 is expressed ubiquitously during early development and is involved in chromosomal translocations and histone-lysine N-methyltransferase activity (Hartlerode et al., 2012; Nimura et al., 2009; Pei et al., 2013; Sarai et al., 2013; Yang et al., 2012f). HBP1, as a tumor suppressor protein (Escamilla-Powers et al., 2010; Li et al., 2011b; Zhang et al., 2006), negatively regulates G and S1 phase progression and Wnt signaling (Berasi et al., 2004; Escamilla-Powers et al., 2010; Pan et al., 2013; Sampson et al., 2001; Tevosian et al., 1997; Xiu et al., 2003). BBX functions as a transcription factor and is necessary for cell cycle progression from the G1 to S phase (Stros et al., 2007b). CIC is a transcriptional repressor and plays a role in development of the central nervous system and lung alveolarization (Kim et al., 2013a; Lee et al., 2011b). SSRP1 is a component of the “facilitates chromatin transcription, FACT” complex, a general chromatin factor that acts to reorganize nucleosomes (Kasai et al., 2005). SSRP1 play multiple roles in mRNA elongation, DNA replication, and DNA damage response (Dyer et al., 1998; Keller et al., 2001; Orphanides et al., 1999; Spencer et al., 1999; Yarnell et al., 2001; Zeng et al., 2002).

Collectively, the HMG-box family has a unique role in DNA-dependent processes (transcription, replication, and repair) and their common mechanism of chromatin remodeling in biology and disease.

1.3.3.2 Mammalian HMGBs

1.3.3.2.1 HMGB1: HMGB1 (previously HMG1; HMG-1; HMG 1; amphoterin; p30) expression is the most highly expressed of all the HMG family members. There are about 10^6 molecules of HMGB1 per cell, which is only an order of magnitude less than the core histones (Romani et al., 1979). HMGB1 has been extremely conserved during evolution and originated before the divergence of the protostomes and deuterostomes approximately 525 million years ago (Sharman et al., 1997). In contrast, HMGB1 pseudogenes, dysfunctional relatives of HMGB1 genes, arose relatively late in evolution, approximately one million years ago (Stros and Dixon, 1993). The homolog of mammalian HMGB1 has been identified in yeast (termed Nhp6A/B), drosophila (termed HMG-D and DSP1), chironomidae, echinoderms, bacteria, plants, fish, and *C. elegans* (Table 1) (Bustin, 2001; Giavara et al., 2005; Wu et al., 2003). The mRNA of HMGB1 is polyadenylated (Bustin et al., 1981), and the protein sequence of HMGB1 displays a 100% homology between mouse and rat and a

99% homology between rodent and human (Ferrari et al., 1994; Gariboldi et al., 1995; Wen et al., 1989). The C terminus contains two amino acids that differ between mice and humans. In all cells, HMGB1 can shuttle between the nucleus and cytoplasm, and normal HMGB1 accumulates in nuclei to bind chromatin (Isackson et al., 1980). HMGB1 is the most mobile protein in the nucleus, crossing this organelle into the cytosol within 1–2 seconds (Phair et al., 2004; Sapojnikova et al., 2005; Scaffidi et al., 2002). Given its mobility, HMGB1 has been found in the cytosol (e.g., mitochondria (Stumbo et al., 2008) and lysosome (Gardella et al., 2002)), in the cellular membrane, and extracellular space when its nuclear localization signal (NLS) is modified (Kuehl et al., 1985). The subcellular location of HMGB1 changes depending on cell type, tissue, and stress signals. HMGB1 is widely-expressed in various tissues and high HMGB1 levels are found particularly in the spleen and thymus (Prasad and Thakur, 1990a). The expression of HMGB1 in myeloid cells is higher than in lymphoid cells (Cabart et al., 1995) and correlates with the differentiation stage of these cells (Seyedin et al., 1981). Expression of HMGB1 is upregulated in cancer, but downregulated during aging (Muller et al., 2004; Prasad and Thakur, 1990a), suggesting a critical role in development and cancer. HMGB1 is an early maker of oligodendrocytes in the developing rat spinal cord (Daston and Ratner, 1994). HMGB1 is essential for life because $HMGB1^{-/-}$ mice die shortly after birth due to the downregulation of glucocorticoid receptor and the inability to use glycogen stored in the liver (Calogero et al., 1999). In contrast, glucose administration prolongs survival of $HMGB1^{-/-}$ mice, but these mice die before reaching sexual maturity (Calogero et al., 1999). Double knockout of HMGB1 and HMGB2 in mice or zebrafish embryos results in a significant deficiency in Wnt signaling and posterior digit development (Itou et al., 2011). Both endogenous and exogenous HMGB1 are required for pre-implantation embryo development in the mouse (Cui et al., 2008). Injection of HMGB1 siRNA into the zygote increases apoptosis (Cui et al., 2008). Overexpression of HMGB1 in cardiac tissue by transgenic methods significantly increases survival and protects mice against myocardial infarction by enhancing angiogenesis and cardiac function (Kitahara et al., 2008). We and others recently demonstrated that conditional knockout of HMGB1 in the pancreas (Kang et al., 2013b), liver (Huang et al., 2013a), or macrophages (Yanai et al., 2013) renders mice more sensitive to pancreatitis, liver ischemia/reperfusion injury, and sepsis, respectively. Of note, using various HMGB1 conditional knockout strategies may cause substantially different functional phenotypes in the liver and heart (Huebener et al., 2014). The threshold for the HMGB1 requirement to function in various biological processes may differ and may also depend on the cell type.

The HMGB1 protein is fully functional in cells of mammalian origin. Nuclear HMGB1 is engaged in many DNA activity-associated events (e.g., DNA replication, repair, recombination, transcription, and genomic stability). In addition to its nuclear function, HMGB1 plays a significant extracellular role in inflammation, immunity, cell growth, cell proliferation, and cell death. HMGB1 is massively released into the extracellular space by dead or dying cells. Extracellular HMGB1 functions as a DAMP to alert the innate immune system by recruiting inflammatory, smooth muscle cells, mesangioblasts, and stem cells. In addition, extracellular HMGB1 functions as an immune adjuvant to trigger a robust response to activation or suppression of T cells, dendritic cells, and endothelial cells. Activated immune cells (e.g., macrophages, monocytes, and dendritic cells) and endothelial cells also

secrete HMGB1, which in turn forms a positive feedback loop that causes the release of additional cytokines and chemokines following engagement of multiple receptors. Thus, HMGB1 sustains a long-term inflammatory state under stress. Interestingly, extracellular HMGB1 has antibacterial, cell growth, and mitotic activity. These extracellular HMGB1 activities are not only mediated by receptors, but also by its Redox state and structure (Tang et al., 2012). Besides its nuclear and extracellular roles, cytoplasmic HMGB1 binds many proteins involved in autophagy (Tang et al., 2010c), cancer progression, and possibly the unconventional secretory pathway (Lee et al., 2010a). HMGB1 not only binds to DNA, but also interacts with many apparently unrelated proteins by recognizing short amino acid sequence motifs (Dintilhac and Bernues, 2002). For example, the motifs PXXPXP and WXXW (where X can be any amino acid) can interact with box A and box B of HMGB1, respectively (Dintilhac and Bernues, 2002). Thus, HMGB1 may be involved in many cell processes by promoting protein protein interactions (Table 2). These important structures and functions of mammalian HMGB1 both inside and outside the cell in health and disease will be discussed below.

1.3.3.2.2 HMGB2: HMGB2 (previously HMG2; HMG-2; HMG 2) is very similar to HMGB1 (>80% identity) at the amino acid level. It is widely expressed in early embryos, especially in stem cells (Abraham et al., 2013a), and its expression is restricted mainly to the lymphoid organs and testis in adult mice (Ronfani et al., 2001). The mechanism of transcriptional regulation of HMGB2 expression is unclear. HMGB2$^{-/-}$ mice have increased susceptibility to apoptosis and have defects in spermatogenesis (Ronfani et al., 2001), chondrocyte development (Taniguchi et al., 2011; Taniguchi et al., 2009b), neurogenesis (Abraham et al., 2013b) and Wnt signaling (Taniguchi et al., 2009a). Thus, HMGB2 plays a critical role in the regulation of fertility, osteoarthritis, neuronal degeneration, and aging (Ly et al., 2000). Like HMGB1, HMGB2 participates in chromosomal processing and assembly by binding DNA with no sequence-specificity or specific proteins or post-translational modifications. HMGB2 can be phosphorylated by casein kinase 2 (CK2) (Stemmer et al., 2003; Stemmer et al., 2002) and acetylated by CREB-binding protein (CBP) (Pasheva et al., 2004). *In vitro*, HMGB2 can bind to multiple partner proteins, which in turn promotes or represses transcription and recombination activities of these partner proteins. These proteins include steroid hormone receptors (Boonyaratanakornkit et al., 1998), SSRP1 (Lichota and Grasser, 2001), p53 (Stros et al., 2002), p73 (Stros et al., 2002), chromatin transcription-enabling activity (CTEA) (Guermah et al., 2006), neurons expressing huntingtin (Htt) (Qi et al., 2007), endoplasmic reticulum-associated complex (SET) (Fan et al., 2002), Rag1 recombinase (Aidinis et al., 1999; Swanson, 2002a), EBV nuclear antigen 1 (EBNA-1) (Jourdan et al., 2012), ATP-binding cassette transporter 1 (ABCF1) (Lee et al., 2013c), pluripotency factor Oct4 (Campbell and Rudnicki, 2013), and LEF1 (Taniguchi et al., 2009a). In addition, increased HMGB2 levels h, like HHMGB1, facilitates efficient nonviral gene delivery (Sloots and Wels, 2005), which may be useful for gene therapy (Balani et al., 2009). Overexpression of HMGB2 increases topoisomerase II alpha expression (Stros et al., 2009) and correlates with the progression of several tumors such as skin, liver, and bladder cancer (Kwon et al., 2010a; Sharma et al., 2008; Wang et al., 2013j). Like HMGB1, HMGB2 is secreted by myeloid cells and has mitogenic and chemoattractant functions by binding to RAGE (Pusterla et al., 2009). However, the pro-inflammatory activity of

extracellular HMGB2 is significantly lower than that of HMGB1 (Ueno et al., 2004). Extracellular HMGB2 is increased in experimental and clinical acute lung injury (Ueno et al., 2004), suggesting a possible role for HMGB2 in tissue injury. In addition, extracellular HMGB2 has antimicrobial activity in intestinal tissue, but the mechanism remains unknown (Kuchler et al., 2013). The presence of serum anti-HMGB2 antibodies may contribute to inflammatory bowel disease (Takaishi et al., 2012), suggesting a possible role for extracellular HMGB2 in the regulation of autoimmunity.

1.3.3.2.3 HMGB3: HMGB3 (previously HMG2a; HMG-2a; HMG 2a [HMG-4]) is an X-linked member of the HMGBs and was originally discovered in 1998 by Marco Bianchi and colleagues as an expressed sequence tag (EST) preferentially expressed in embryonic tissues (Vaccari et al., 1998). HMGB3 protein is highly expressed in the embryo and hardly detectable in adult tissues (Vaccari et al., 1998). HMGB3 expression is regulated by several miRNAs, including miR-206, miR-205, miR-10A, and miR-21 (Elgamal et al., 2013; Maciotta et al., 2012; Zhu et al., 2013c). $HMGB3^{-/-}$ mice are viable and HMGB3 is required for eye and brain development (Terada et al., 2006). Importantly, HMGB3 is expressed in most lymphoid and myeloid progenitors and HMGB3 levels are associated with myeloid and B-cell differentiation as well as hematopoietic stem cell self-renewal and proliferation (Nemeth et al., 2005; Nemeth et al., 2003; Nemeth et al., 2006; Somervaille et al., 2009; Tsuzuki and Seto, 2013). HMGB3 has a special role in leukemogenesis (Lilljebjorn et al., 2007). The formation of HMGB3-NPU98 fusion protein is a new oncogene identified in leukemia and significantly promotes malignant transformation in recipient mice (Petit et al., 2010). HMGB3 overexpression is associated with progression and poor prognosis of solid tumors such as breast, gastric, and non-small cell lung cancers (Elgamal et al., 2013; Gong et al., 2013; Song et al., 2013). However, the effect of HMGB3 in tumor therapy and the extracellular role of HMGB3 remain unknown.

1.3.3.2.4 HMGB4: HMGB4 was discovered as a new member of mammalian HMGBs in 2009 by Irwin Davidson and colleagues (Catena et al., 2009). HMGB4 is mainly expressed in germ cells of the testis and weakly in the brain, but not in other tissues. HMGB4 protein has a molecular mass of 21 kDa and lacks the acidic tail (Catena et al., 2009). Compared with HMGB1, HMGB4 is usually a transcriptional repressor and is encoded by an intronless gene (Catena et al., 2009). Similar to other HMGBs, HMGB4 has a potential role in tumor development. For example, overexpression of HMGB4 by gene transfection inhibits breast cancer cell proliferation through an LXCXE- or LXCXD-dependent mechanism, whereas it increases radiosensitivity through an LXCXE- or LXCXD-independent mechanism (Wang et al., 2012c). HMGB4 has high affinity to cisplatin-modified DNA, suggesting a potential role in the regulation of anticancer activity of cisplatin (Park and Lippard, 2012). Nothing is known about the phenotype of HMGB4-deficient mice. The biological function of HMGB4 remains largely unknown.

1.3.3.3 Plant HMGBs: Plant HMGs, first isolated from wheat germ, have a different structure than animal HMGs (Launholt et al., 2006; Spiker, 1984; Spiker et al., 1978). In the past few years, HMGAs and HMGBs, but not HMGNs, have been isolated and biochemically characterized from various plants (Grasser, 1995). HMGB proteins are

expressed ubiquitously in the plant and usually in the nucleus (Grasser et al., 2007; Pedersen and Grasser, 2010). Compared with other eukaryotes, plant HMGBs have multiple members in the same species. For example, *Arabidopsis thaliana* has six HMGBs (HMGB1–HMGB6) with some common characteristic structural properties despite of the variable molecular size (Grasser et al., 2004). Each member contains a single, central HMG-box DNA-binding domain, a basic N-terminal domain, and an acidic C-terminal domain. This plant HMG-box domain has 75 amino acid residues and three α-helices to form an L-shaped fold with an 80° angle between the arms, which has a higher similarity to the B box domain of mammals. Plant HMGBs also are architectural chromosomal proteins and have a potential role in plant development and stress response by regulating transcription factor activity (Grasser et al., 2007; Pedersen and Grasser, 2010). Recent studies revealed that *Arabidopsis* HMGB2/3 and B4 proteins are predominantly nuclear but also exist in the cytoplasm, suggesting an as yet-unknown cytoplasmic function of these chromosomal HMG proteins (Merkle and Grasser, 2011).

The expressions of HMGB2, HMGB3, and HMGB4 are upregulated in response to cold stress, whereas the expression of HMGB2 and HMGB3 is downregulated in response to drought or salt stress (Kwak et al., 2007). Overexpressing HMGB2 and HMGB5, but not HMGB4, in *Arabidopsis* retarded germination and subsequent growth in response to salt and drought stress (Kwak et al., 2007). These findings suggest that different HMGBs are involved in response to several environmental stressors. Both the absence and overexpression of HMGB1 in *Arabidopsis* leads to shorter roots and affects their sensitivity to genotoxic agents (Lildballe et al., 2008). Further studies systematically analyzing plants lacking or overexpressing HMGB variants in varying environments will be essential to understand the role of these architectural chromosomal proteins in plant stress responses.

2. HMGB1 Structure

2.1 Primary Structure

The primary structure of HMGB1 includes the linear sequence of its amino acid structural units. Human HMGB1 has 215 amino acid residues and forms two DNA binding domains (HMG A box [9–79aa], HMG B box [95–163aa]) and a C-terminal acidic tail (186–215aa) (Figure 3A) (Bianchi et al., 1992). The DNA binding domains are necessary for efficient DNA bending and flexure without sequence specificity. DNA binding domains contain nuclear-emigration signals (NES), which are mediated by nuclear exportin chromosome-region maintenance 1 (CRM1). In contrast, the steady state of HMGB1 is located in the nucleus due to two nuclear-localization signals: NLS1 (28–44aa) and NLS2 (179–185aa) (Bonaldi et al., 2003). The change of NES and NLS induce abnormal HMGB1 location. HMGB1 can bind a number of proteins and these interactions are important for HMGB1's activity and function. Residues 150–183 are responsible for binding to RAGE for cell migration (Huttunen et al., 2002), whereas residues 89–108 and residues 7–74 are responsible for binding to TLR4 and p53 transactivating domains for inflammation and gene transcription, respectively. The extracellular B box has been reported to recapitulate pro-inflammatory activity, whereas the A box acts as an HMGB1 antagonist (Li et al., 2003). The anti-inflammatory activity of HMGB1 A box is enhanced when fused with the C-

terminal acidic tail (Gong et al., 2010b). Residues 201–205 in the C-terminal acidic tail region are responsible for the antibacterial activity of HMGB1 (Gong et al., 2009). The C terminus is full of acidic amino acid residues (30 aspartate and glutamic acid) and this region was previously thought to protect the A-box and B-box during emigration from the nucleus. In addition, the C terminus i regulates DNA binding/bending by intramolecular interaction with the N-terminals of DNA-binding domains (especially cysteine residues) (Stros, 1998; Wang et al., 2007b) as well as intermolecular interaction with histones H1 and H3 (especially lysine residues) (Cato et al., 2008; Sheflin et al., 1993; Ueda et al., 2004) (Kawase et al., 2008). Removal of the C-terminal tail renders HMGB1 with low-affinity binding to DNA and protein in cell free systems (Stros et al., 1994c). In the cell, overexpression of HMGB1 lacking the C-terminal tail inhibits various reporter gene expression (Aizawa et al., 1994). HMGB1 mutations have been rarely identified in cancers from the stomach, endometrium, and bone according to the COSMIC cancer database (http://cancer.sanger.ac.uk/cosmic/gene/analysis?ln=HMGB1#muts). The function of HMGB1 mutations in cancer, if any, has not yet been determined (Xiang et al., 1997).

2.2 Secondary Structure

Secondary structure refers to highly regular local sub-structures motifs in proteins, including the alpha helix and the beta sheets, which was firstly described in 1951 by Linus Pauling and colleagues (Pauling et al., 1951). The two HMG boxes of HMGB1 are structurally similar to a characteristic DNA-binding domain consisting of 3 alpha helices (helix I, helix II, and helix III) and two loops (loop I and loop II), which then arranges in an “L” shape with an angle of 80° between the two arms (Figure 3B) (Hardman et al., 1995; Ohndorf et al., 1999; Stott et al., 2006; Thomas and Travers, 2001; Weir et al., 1993). Compared with the B box, the A box has a high alpha helix content and is more positively-charged and straight than that found in helices I/II (Abdul-Razzak et al., 1989; Webb and Thomas, 1999). The short arm contains helix I and helix II, whereas the long arm contains helix III and an N-terminal unstructured segment in parallel with the helix. The “L” shape structure from HMGB1 box B domain is defined by a number of conserved, predominantly aromatic residues (Phe14, Phe17, Trp45, Lys53, and Tyr56) that are located in the junction between the two helical arms (Weir et al., 1993). The rings of Phel7, Trp45, and TyrS6 pack at right angles to each other, while Phel4 lies between helix I and helix II. The conserved basic residues (Lys26, Lys 39, and Arg 22) are mainly distributed around the concave surface in between the two arms, indicating that they may be involved in DNA binding. The minor groove of the DNA molecule binds to the concave side of the boxes with no sequence specificity. The current model of HMGB1-mediated DNA binding/bending suggest that HMGB1 is involved in chromatin remodeling in a “hit and run” transient fashion (Gerlitz et al., 2009).

2.3 Tertiary Structure

The tertiary structure of a protein is the final specific geometric shape that a protein assumes. The alpha helixes and beta sheets are folded into a compact tertiary structure by several molecular interactions including ionic bonds, hydrogen bonds, hydrophobic interaction, and disulfide bonds. The interaction between HMGB1 domains and the C terminus maintains the tertiary structure (Carballo et al., 1984; Cary et al., 1984). In addition, three cysteines are encoded at positions 23, 45, and 106 of HMGB1. The two

vicinal Cys23–Cys45 residues can rapidly form an intramolecular disulfide bond via the process of oxidative folding (Figure 3C). Disulfide bonds are extremely rare in cytosolic proteins since cytosol is generally a reducing environment. A serine for cysteine substitution of C106 leads to HMGB1 translocation from the nucleus to the cytosol (Hoppe et al., 2006). In addition, reduced HMGB1 and oxidized HMGB1 interact with different receptors and have altered DNA binding activities. Thus, changes in the cellular redox environment can regulate the structure, location, and function of HMGB1 (Hoppe et al., 2006; Tang et al., 2011e).

2.4 Quaternary structure

The quaternary structure of a protein describes the interactions between different peptide chains that make up the protein. Complexes of two or more polypeptides (i.e. multiple subunits) are called multimers. Different methods used to extract HMGB1 may change HMGB1 structure. Indeed, native HMGB1 exists in homodimer and oligomer forms, whereas acid-extracted HMGB1 does not (Marekov et al., 1984). In addition, exogenous HMGB1 can bind to other proteins or chemicals in dimer, trimer, tetramer, and oligomer forms (Li et al., 2011e; Riuzzi et al., 2007). Thus, different purification steps and extraction methods may modify and impair the function of HMGB1.

3. HMGB1 Function

3.1 Nuclear HMGB1

Nuclear HMGB1 acts as a DNA chaperone with DNA binding and bending activities and regulates a number of key DNA events (Figure 4).

3.1.1 Nucleosome Stability and Sliding—Chromatin is a dynamic structure and the basic unit nucleosomes' stability plays important roles in a number of DNA-related processes. HMGB1 is involved in nucleosome assembly and chromatin replication (Bonne-Andrea et al., 1984a, b; Mathew et al., 1979). It is clear that HMGB1 and linker histones (H1 and H5) are the major proteins that bind to linker DNA between successive nucleosomes in the chromatin fiber (Carballo et al., 1983; Nightingale et al., 1996; Smerdon and Isenberg, 1976; Thomas and Stott, 2012; Yamada et al., 2004; Yu and Spring, 1977). These proteins share many features of DNA-binding behavior, although they are structurally unrelated (Zlatanova and van Holde, 1998b). An early study indicated that HMGB1 protects linker DNA on the side opposite to that protected by linker histones (An et al., 1998). We now know that they have opposing effects on nucleosome assembly and stability (Paull et al., 1993). H1 stabilizes the nucleosome engendering less mobility, whereas HMGB1 relaxes the nucleosome and makes chromatin more accessible at the distorted site (Cato et al., 2008; Travers, 2003). The interaction between HMGB1 and linker histones (H1 and H5) occurs through their acidic and basic tails, respectively (Cato et al., 2008). This interaction between HMGB1 and H1 facilitates DNA-protein complex formation (Totsingan and Bell, 2013), DNA ligation reactions (Yamanaka et al., 2002) and enables stress-induced gene silencing (e.g., pro-inflammatory cytokine TNF-α) (El Gazzar et al., 2009). The interaction between HMGB1 and H1 is regulated by pH, local ionic concentration, and redox state (Kohlstaedt and Cole, 1994b; Kohlstaedt et al., 1987). HMGB1 suppresses nucleosome assembly at

physiological ionic strength (Waga et al., 1989). Besides its cooperation with histones, HMGB1 can replace linker histones H1 and H5 in nucleosomes *in vitro* (Ner and Travers, 1994; Varga-Weisz et al., 1994) or in development (Ura et al., 1996) or directly compete with various DNA substrates (Zlatanova and van Holde, 1998b). Increased transient interaction between HMGB1 and nucleosomal linker DNA can activate ATP-utilizing chromatin assembly and remodeling factor/ chromatin accessibility complex (ACF/CHRAC) pathway, which in turn promotes nucleosome sliding (Bonaldi et al., 2002). The C terminus of HMGB1 is required for activation of the ACF/CHRAC pathway (Bonaldi et al., 2002). In addition, acetylated HMGB1 assists nucleosome mobilization induced by switch/sucrose nonfermentable (SWI/SNF), but does not affect its ATPase activity in *in vitro* assay (Ugrinova et al., 2009a). HMGB1 does not directly form a complex with either ACF/ CHRAC or SWI/SNF, although some HMG-box proteins are direct components of chromatin remodeling complexes such as BAF57 in human SWI/SNF and SSRP1 in FACT. The interaction between HMGB1 and these HMG-box proteins in chromosome remolding is not yet clear. It is also important to determine if HMGB1 regulates specific histone modifications, which are also involved in nucleosome stability (Andrews and Luger, 2011). In addition to the the linker histones (H1 and H5), HMGB1 can interact with the core histones. HMGB1 binds H2A and H2B by it's A and B boxes (Bernues et al., 1986; Bernues et al., 1983), whereas it binds H3 and H4 by its A box and acidic tail (Bernues et al., 1986; Bernues et al., 1983; Stros, 1987; Ueda et al., 2004). In general, the interaction between HMGB1 and nucleosomes is highly reversible during the dynamic process of chromatin remodeling (Falciola et al., 1997).

3.1.2 Nucleosome Number and Genome Chromatinization—The number of nucleosomes decrease and DNA damage increases during aging (Feser et al., 2010; O'Sullivan et al., 2010), suggesting that global alterations within nucleosomes reflect a programmed chromatin-level response to aging. Age-dependent reprogramming and epigenetic integrity may also serve as a target for cancer initiation. Early studies demonstrated that the expression of HMGB1 decreases, whereas the acetylation of HMGB1 increases with advancing age (Prasad and Thakur, 1988, 1990a; Thakur and Prasad, 1991). Age-dependent HMGB1 changes are associated with DNA double-strand break accumulation in the mouse brain (Enokido et al., 2008). Thus, HMGB1 levels and modifications may reflect the functional state of chromatin. Surprisingly, HMGB1 not only regulates nucleosome organization, but also biogenesis. Mammalian and yeast cells lacking HMGB1 contain 20–30% less histones and nucleosomes and more RNA transcripts (Celona et al., 2011), many of them promoting expression of inflammatory genes including chemokines. Exogenous HMGB1 promotes the assembly of chromatin *in vitro* by virtue of its DNA chaperone activity (Celona et al., 2011). These findings indicate that HMGB1 contributes to genome chromatinization by sustaining the number, and possibly location, of nucleosomes. Although total gene expression is increased in HMGB1$^{-/-}$ cells, some specific genes are significantly down regulated when HMGB1 is lost (Celona et al., 2011; Krynetskaia et al., 2008). In contrast, overexpression of HMGB1 in cells leads to gene transcription along with relaxation of chromatin structure (Ogawa et al., 1995). This finding raises some questions such as: how do HMGB1 levels balance global and local gene expression? What checkpoint is responsible for surveillance at the nucleosomal level?

Interestingly both histones H3 and H4 exist in archaea, and although they are true 'prokaryotes', there may be some value in more closely examining them for ancient HMG motifs (Ammar et al., 2012).

3.1.3 Nuclear Catastrophe and Nucleosome Release—The nucleosome acts as a DAMP when it is released from the nuclei into the extracellular space during DNA damage (e.g. DNA strand scission), creation of neutrophil extracellular traps and cell death (Hamana and Kawada, 1989). Circulating nucleosomes, including histones and genomic DNA, are significantly elevated in patients with cancer, stroke, trauma, sepsis, and autoimmune diseases (Holdenrieder et al., 2008; Holdenrieder and Stieber, 2009). We recently demonstrated that deficiency of endogenous pancreatic HMGB1 led to exaggeration of L-arginine-induced pancreatitis, associated with nuclear catastrophe and nucleosome release. This in turn, recruited and activated inflammatory cells with subsequent HMGB1 release locally and into the circulation (Kang et al., 2013b). Serum levels of tissue enzymes (e.g., amylase, lactate dehydrogenase, and pancreatic myeloperoxidase) and pro-inflammatory cytokines were significantly higher in conditional pancreas-specific HMGB1 knockout mice when compared with their wild-type control littermates. Moreover, neutralizing extracellular histone and HMGB1 conferred protection against acute pancreatitis in these pancreas-specific HMGB1 knockout mice. Thus, intracellular HMGB1 may serve in a previously underappreciated negative regulator of inflammation, shedding light on the role of the innate immune response in infection and tissue damage. In addition, conditional knockout of HMGB1 in the liver also increases nucleosome release and accelerates liver reperfusion ischemic injury (Huang et al., 2013a). Thus, stress that induces HMGB1 translocation from the nucleus may enhance inflammation by allowing nucleosome release from terminally damaged cells. The nonspecific DNA-binding and -bending protein HMGB1 not only regulates nucleosome stability and biogenesis, but also nucleosome release, which provides a novel link between chromosomal instability and inflammation in disease. Intracellular HMGB1 and H1-mediated chromatin remodeling in leukocytes inhibits pro-inflammatory cytokine (TNF-α and IL-1β) transcription during endotoxin tolerance (El Gazzar et al., 2009). More recently, conditional knockout of HMGB1 in macrophages decreased autophagy, which in turn increased pro-inflammatory cytokine production in sepsis in an animal infection model (Yanai et al., 2013). These findings clearly suggest that HMGB1 is an intracellular, anti-inflammatory nuclear chromatin modulator.

3.1.4 DNA Binding—Besides acting as an architectural protein in chromosomes, HMGB1 acts as a DNA chaperone in the nucleus. HMGB1 binds to DNA with structure-specificity, but not sequence-specificity (Yu et al., 1977). Recognition and alteration of DNA structure plays a significant role in regulating DNA-related processes. The flanking sequences of HMG-boxes A and B as well as the acidic C terminal have the ability to regulate their DNA binding activities (Sheflin et al., 1993; Stros, 1998, 2001; Stros et al., 1994c; Teo et al., 1995b; Wisniewski and Schulze, 1994). Compared with the single HMGB-box, DNA binding is enhanced when the two domains are covalently connected (A+B) *in vitro* (Reddy et al., 2005; Stros, 1998, 2001; Yoshioka et al., 1999). Binding of HMGB1 to DNA is also regulated by post-translational modifications (e.g., phosphorylation, acetylation, and oxidization) (Assenberg et al., 2008), pH, ions (e.g., calcium and Mg^{2+}) (Makiguchi et al.,

1984; Stros et al., 1990) and the presence of another cationic factor, spermine (Van den Broeck et al., 1994). pH affects interactions between DNA and high-mobility group protein HMG1 (Kohlstaedt and Cole, 1994a). In many cases, HMG boxes bind to the minor groove of linear B-type DNA transiently and distort the double helix sharply to a larger bending angle of to 90° or greater (Zimmerman and Maher, 2008). These HMGB1-mediated architectural changes at the distorted site contribute to multiprotein complex assemblies that control DNA-related events. In addition, HMGB1 binds with relatively high affinity to distorted and damaged DNA. These DNA structures include H-DNA (Jain et al., 2005), hemicatenated DNA loops (hcDNA), (Jaouen et al., 2005), psoralen-DNA interstrand cross-link (ICL) (Reddy et al., 2005), hemicatenated DNA loops (Stros et al., 2004), duplex DNA[poly (dAdT). (dTdA) and poly (dGdC). (dCdG).] (Muller et al., 2001), four-way DNA junctions (Gaillard and Strauss, 1994; Grasser et al., 1998; Hill and Reeves, 1997; Stros and Muselikova, 2000; Teo et al., 1995a), supercoiled DNA and DNA modified with anticancer drug cisplatin (Stros, 2001), semicatenated DNA loops (Gaillard and Strauss, 2000), supercoiled plasmid DNA (Grasser et al., 1998), supercoiling of nicked-circular DNA (Sheflin et al., 1993), UV-damaged DNA (Pasheva et al., 1998), tandem repeats of dTG (Gibb et al., 1997), tandem repeats of (GCC)n (GGC)m DNA (Zhao et al., 1996), kinked DNA (Falciola et al., 1994), and supercoiled plasmids (Bustin and Soares, 1985). Of these structures, four-way DNA (Holliday) junctions and cisplatin-modified DNA are among the best-documented.

Four-way DNA junction is a mobile junction between four strands of DNA that is generated as an intermediate in genetic recombination and connected by mutual exchange of strands (Lilley and Clegg, 1993). Four-way DNA junction simulates the structure of the linker DNA strands near the entrance and exit points of nucleosomes. Except for genetic recombination, the four-way DNA junction is also involved in replication-related events. Proteins, including specific enzymes and HMG box proteins that bind and resolve four-way DNA junctions, can be regarded as a paradigm for the recognition of DNA structure (Zlatanova and van Holde, 1998a). The first reported HMGB1 binding to four-way DNA junction was published in 1989 by Marco E. Bianchi and colleagues (Bianchi et al., 1989). Reduced HMGB1, but not oxidized HMGB1, can effectively compete with H1 for binding to such four-way DNA junctions (Polanska et al., 2014; Varga-Weisz et al., 1994).

Cisplatin, or cis-diamminedichloroplatinum (II), is an effective anticancer drug in the treatment of several solid tumors including ovarian, genitourinary, lung, head, and neck cancers. Cisplatin and its second generation analogues carboplatin and oxaliplatin induce cell death by binding to DNA preferentially at the N7 position of guanine bases, inhibiting replication and transcription. The first report of HMGB1 binding to cisplatin-DNA by Stephen J. Lippard and colleagues was published in 1992 (Bruhn et al., 1992; Pil and Lippard, 1992). HMGB1 binds to platinated lesions on DNA with specificity for 1,2-d (GpG) and d (ApG) intrastrand cross-links (Pil and Lippard, 1992), which account for about 90% of the cisplatin-DNA adducts formed *in vivo* (Eastman, 1987; Fichtinger-Schepman et al., 1985). In addition, HMGB1 also binds to interstrand cross-linked versus undamaged DNA, but not 1,3-intrastrand cross-links (Kasparkova et al., 2003). Compared with box B, HMGB1 box A has a higher binding affinity for platinated DNA, although box B can

enhance box A's affinity (Jung and Lippard, 2003). This process is also regulated by the redox state of HMGB1 as well as the C-terminal domain (Park and Lippard, 2011; Yusein-Myashkova et al., 2013). For example, the reduced box A has a 10-fold greater platinated DNA binding affinity than the oxidized box A (Park and Lippard, 2011; Wang et al., 2013f). Although HMGB1 inhibits cisplatin-DNA damage repair (Huang et al., 1994; Ugrinova et al., 2009b), the final influence of HMGB1 expression in cisplatin sensitivity depends on cell types. For example, hormone-induced HMGB1 up-regulation in breast and ovarian cancer cells contributes to the anticancer activity of cisplatin (He et al., 2000). In contrast, knockout of HMGB1 in MEFs does not change cisplatin-mediated cell death (Wei et al., 2003). These findings suggest the importance of cell type in determining the ability of this and probably other cisplatin-DNA-binding proteins to influence the efficacy of the drug (Wei et al., 2003). The ability of H1 to bind cisplatin-DNA in an *in vitro* competition assay is much stronger than that of HMGB1 (Yaneva et al., 1997), suggesting that the dynamic change of H1 levels in the nucleus (Zlatanova and Van Holde, 1992) may regulate the HMGB1-mediated cisplatin-DNA damage response. In addition, HMGB1 levels regulate cisplatin sensitivity in different cells by directly affecting DNA replication (Hoffmann et al., 1997) as well as replication protein A's DNA binding activity (Patrick and Turchi, 1998).

3.1.5 DNA Bending—After binding DNA, HMGB1 can bend and change DNA conformation by unwinding (Javaherian et al., 1978; Javaherian et al., 1979; Yoshida et al., 1984), looping (Paull et al., 1993; Paull and Johnson, 1995; Stros et al., 1994c), or compacting DNA (Javaherian et al., 1978). This HMGB1 DNA bending activity contributes to several DNA processes, especially enhancing DNA dynamic flexure. The DNA bending activity of HMGB1 was initially reported in 1993 by the research groups of Stephen J. Lippard and Reid C. Johnson (Paull et al., 1993; Pil et al., 1993). Stephen J. Lippard and colleagues demonstrated HMGB1's DNA bending activity by ligase-mediated ring closure assays, and this activity is maintained by HMG boxes (Pil et al., 1993). Reid C. Johnson and colleagues found that HMGB proteins from HeLa or bovine nuclear extract have extraordinary DNA-bending activity, as demonstrated by their ability to promote circularization of very short DNA fragments. This DNA bending activity of HMGB1 promotes the assembly of the Hin invertasome, a topologically complex structure in Hin-mediated site-specific DNA inversion (Paull et al., 1993). Similar DNA bending activity has been confirmed in other HMGB1-related homologs, including yeast Nhp6A/B and drosophila HMG-D. The structural basis for the DNA bending activity of HMG box has been identified in a number of *in vitro* assays (Thomas and Travers, 2001). A basic DNA binding/bending model involves intercalation of bulky hydrophobic amino acid residues of the HMG-boxes between successive base-pairs within the DNA minor groove, accompanied by partial unwinding, widening of the minor groove, and bending towards the major grove (Stros, 2010). This process is tightly controlled by a number of factors, including intercalating residues of the HMG-box, N- and C-terminal flanking sequences of the HMG-box, post-translational modifications of HMGB1 (e.g., phosphorylation, acetylation, and oxidization) as well as structural features of bent DNA (Furuita et al., 2011; Stros, 1998, 2010; Thomas and Travers, 2001; Ugrinova et al., 2007). The HMGB1-mediated DNA recognition mechanism has been confirmed by NMR studies (Furuita et al., 2009). B box is known to be far more effective at bending linear DNA, whereas the A box binds

preferentially to pre-bent DNA. This DNA binding and bending activity of HMGB1 can change the DNA helical structure by unwinding the double helix or inducing supercoiling of the DNA (Javaherian et al., 1978; Javaherian et al., 1979). The acidic tail is specifically involved in HMGB1-mediated Mg^{2+}-, Ca^{2+}-dependent unwinding of DNA double-helix (Yoshida, 1983, 1987). In addition, HMGB1 (either individual or arranged in tandems or multi-domain proteins) can enhance apparent DNA flexibility by looping, which is involved in the regulation of transcriptional initiation (Paull et al., 1993; Paull and Johnson, 1995; Stros et al., 1994c). The cysteine-sulfhydryl group of the HMG-box is specifically involved in HMGB1-mediated DNA looping, which is also regulated by the calcium level of the acidic C tail (Stros et al., 1994b). Microsatellites are repeating sequences of 2–6 base pairs of DNA. An *in vitro* study demonstrated that HMGB1 has varying DNA bending activities for individual microsatellites. Given that microsatellite instability is increased in human genetic diseases and cancer, HMGB1 may be involved in microsatellite instability-associated disease by regulation of DNA mismatch repair (Takayanagi et al., 1997).

3.1.6 V(D)J Recombination—V(D)J recombination, also known as somatic recombination, is the antigen receptor gene rearrangement process that generates diversity among T cell receptors (Sadofsky, 2001). Recombination is initiated by the lymphoid-specific recombination activating gene (RAG)-1 and RAG2 proteins, which recognize specific recognition sequences (termed recombination signal sequences or RSSs). Each RSS consists of a conserved heptamer and nonamer separated by a nonconserved spacer. RAG, which has nuclease activity, leads to double-strand breaks at RSSs. Following DNA cleavage by RAG, the nicked strand is converted to a hairpin and then the broken ends are joined by several proteins involved in DNA damage responses (Gellert, 2002). HMGB1 plays an essential role in V(D)J recombination by formation of RAG-RSS-HMG complexes to enhance RAG1/RAG2 activity (Agrawal and Schatz, 1997; Dai et al., 2005; Grundy et al., 2009; Little et al., 2013; Swanson, 2002a, b). The knowledge of their interconnection is essential for our understanding of immune cell development.

3.1.7 Gene Transcription—Transcription factors are proteins that bind to specific DNA sequences at promoters, thereby generally controlling gene transcription. HMGB1 is able to change transcription rates and gene expression via several different mechanisms (Singh and Dixon, 1990). These include: 1) sustaining nucleosome dynamics and number at a global level, 2) promoting interaction with the TBP (TATA binding protein)/TATA-box complex (Das and Scovell, 2001; Sutrias-Grau et al., 1999), the conserved lymphokine elements-0 (CLE0) (Marrugo et al., 1996) and long terminal repeat (LTR) (Naghavi et al., 2003) affecting recruitment of other general transcription factors, 3) enhancing interaction with RNA polymerase (transcription by RNA polymerase II), 4) promoting enhanceosome assembly (Ellwood et al., 2000; Mitsouras et al., 2002), 5) removing transcriptional blocks (Waga et al., 1988), or 6) acting as an activator, enhancer, repressor, or silencer locally by interfering with several sequence-specific transcription factors to their cognate DNA (Table 2). These transcription factors include steroid nuclear receptors (e.g., androgen, glucocorticoid, progesterone, and mineralocorticoid receptors) (Onate et al., 1994; Verrijdt et al., 2002), Hox, Sox (Zhang et al., 2013k), Oct (Harrison and Whitehouse, 2008), p53 (Banerjee and Kundu, 2003; Imamura et al., 2001; McKinney and Prives, 2002; Rowell et

al., 2012; Zhang et al., 2003), p73 (Stros et al., 2002), the retinoblastoma protein (RB), nuclear factor-κB (NF-κB)/Rel (Agresti et al., 2003; Brickman et al., 1999), estrogen receptor (Chau et al., 1998; Romine et al., 1998), sterol regulatory element-binding proteins (SREBPs) (Najima et al., 2005), Up-stream stimulatory factor 1 (USF1) (Marmillot and Scovell, 1998), NF-Y (Stros et al., 2009), HNF1α (Yu et al., 2008), ETs (Shiota et al., 2008), PU.1 (Mouri et al., 2008), replication and transcription activator (RTA) (Song et al., 2004), and Dof2 (Krohn et al., 2002). Among them, the interaction between p53 and HMGB1 is the best documented.

p53 regulates a number of gene expressions and is the most frequently altered gene in human cancer. HMGB1 stimulated p53 DNA binding to linear DNA *in vitro* and increased p53 activity *in vivo* in a transfection assay (Jayaraman et al., 1998). That binding to pre-bent (e.g. minicircle) DNA is not facilitated by HMGB1 (McKinney and Prives, 2002) suggesting that HMGB1 promotes binding to linear DNA through its DNA-bending activity. Although the individual HMG boxes (A and B) and C-terminus can facilitate binding to p53 (McKinney and Prives, 2002), the A box has a strong p53 binding activity by using cross-linking chemical and biophysical measurements (Rowell et al., 2012). HMGB1 regulates p53 not only on the transcription activity, but also on its subcellular localization and phosphorylation (Krynetskaia et al., 2009). These findings suggest that HMGB1 regulates p53 at multiple levels.

HMGB1 is a critical member of the transcriptional regulatory network which regulates hematopoietic stem cell (HSC) multipotency and self-renewal. Many (18) genes confer a clear repopulation advantage to HSCs (Deneault et al., 2009). Among them, HMGB1, FOS, TCFEC, and SFPI1 regulate HCS activity via a non-cell-autonomous phenomenon (Deneault et al., 2009). In addition, HMGB1's association with other transcription factors (OCT4/POU5F1, NANOG, and DPPA5) regulates embryonic stem cell differentiation (Adjaye et al., 2005). These findings suggest that HMGB1 regulates gene expression not only autonomously, but as part of a coordinated network.

3.1.8 DNA Replication—DNA contains two strands wrapped around each other in a helix, and its replication is the process of generating new DNA bands from one old single-stranded DNA. This single-stranded DNA serves as template for RNA priming and DNA synthesis. DNA polymerase is a critical enzyme in the process of DNA replication. In addition, helix-destabilizing protein is responsible for maintaining the single-stranded DNA structure by interaction with DNA polymerase during replication fork advances. Early studies indicated that HMGB1 isolated from rat liver acts as a DNA helix-destabilizing protein to stimulate activity of DNA polymerases α and β *in vitro* (Bonne et al., 1979; Bonne et al., 1982; Duguet et al., 1977). Thus, HMGB1 antibody inhibits the HMGB1-mediated polymerizing activity of DNA polymerase *in vitro* (Alexandrova et al., 1984). Interestingly, only isolated HMGB1 from regenerating liver, but not normal liver, has this activity. The role of HMGB1 in DNA replication is modulated by post-translational modification. The phosphorylated form of HMGB1 significantly decreases the HMGB1-mediated polymerizing activity of DNA polymerase, although it did not influence HMGB1 binding to single stranded DNA (Bonne et al., 1979; Duguet et al., 1977). In contrast, the acetylated form of HMGB1 proteins can bind and stimulate DNA polymerase activity *in*

vitro (Alexandrova and Beltchev, 1988). A more recent study indicated that native, recombinant, and tailless HMGB1 proteins act significantly different in the regulation of DNA replication in an *in vitro* replication assay of closed circular DNA. In this study, the authors found that native HMGB1 isolated from tumor cells and phosphorylated recombinant HMGB1 by PKC inhibited DNA replication (Topalova et al., 2008). This inhibition effect can be further reversed by HMGB1 acetylation and removal of the acidic tail (Topalova et al., 2008). Taken together, these results show that HMGB1 participates in DNA replication from mammalian cells (Bonne-Andrea et al., 1986) and viruses (Cotmore and Tattersall, 1998) by positive or negative regulation of DNA polymerase activity. The role of HMGB1 in DNA replication remains unknown.

3.1.9 DNA Repair—DNA damage caused by various sources results in changes in molecular structure, such as a break in a DNA strand, a missing base from the DNA backbone, or a chemically changed base such as 8-OHdG. Recognition of DNA damage is a dynamic process, namely DNA damage response, including activation of cell cycle checkpoint, commencement of transcriptional programs, initiation of DNA repair, or induction of apoptosis if DNA repair fails. The DNA repair rate depends on many factors, including HMGB1 levels. HMGB1 has a dual role in DNA repair and cell death. In many cases, loss of HMGB1 or increased HMGB1 translocation from the nucleus to the cytoplasm could increase DNA damage, decrease DNA repair efficiency, and increase cell death in response to chemotherapy, irradiation, and oxidative stress. HMGB1 directly binds to a variety of bulky DNA lesions, allowing it to participate in DNA repair pathways.

3.1.9.1 DNA Mismatch Repair: DNA mismatch repair is an evolutionarily conserved genome maintenance pathway that corrects mismatches generated during DNA synthesis and homologous recombination. In 2004, HMGB1 was reported to be involved in DNA mismatch repair initiation and excision (Yuan et al., 2004). Recombinant human HMGB1 partially fractionated from HeLa cell extracts promotes mismatch excision through its interaction with MutSα, a critical component of DNA mismatch repair machinery (Yuan et al., 2004). In addition, recombinant human HMGB1 can replace replication protein A, a protein that binds single-stranded DNA, in a reconstituted human DNA mismatch repair system (Zhang et al., 2005). However, a recent study indicated that HMGB1 is not essential for 5-directed mismatch repair compared with the extracts derived from HMGB1+/+ and HMGB1$^{-/-}$ MEFs (Genschel and Modrich, 2009). One possible reason for this different finding is that mammalian cell extracts may possess a second activity, which provides a mismatch repair function that is redundant with respect to HMGB1 (Genschel and Modrich, 2009).

3.1.9.2 Base Excision Repair: Base excision repair is an evolutionarily-conserved pathway that corrects base lesions generated from oxidative, alkylation, deamination, and depurinatiation/depyrimidination damage (Robertson et al., 2009). There are two sub pathways, the short-patch and long-patch, involved in base excision repair. The short-patch pathway leads to insertion of a single nucleotide, whereas the long-patch pathway is involved in insertion of at least two nucleotides. These two sub pathways are initiated by DNA glycosylase that recognizes a damaged base or a base in a specific DNA sequence, and

then removes the base by hydrolysis of the N-glycosylic bond. In 2007, HMGB1 was identified as a regulator of the base excision repair pathway by its DNA binding and protein interaction activity (Prasad et al., 2007). The major findings from this study include: HMGB1 accumulates in the sites of cellular oxidized DNA base damage and then binds to dRP lyase substrates, an intermediate in the base excision repair pathway; HMGB1 can physiologically interact with multiple key enzymes (e.g., APE, FEN-1, and pol β) to enhance their activity during base excision repair; HMGB1$^{-/-}$ MEFs exhibit more resistance to the methylating agent methyl methanesulfonate, suggesting that that the absence of HMGB1 does not significantly impact methyl methanesulfonate-induced damage repair. These findings suggest that HMGB1 inhibits the short-patch pathway and stimulates the long-patch pathway at different stages (Goula et al., 2009; Liu et al., 2010c).

3.1.9.3 Nucleotide Excision Repair: Nucleotide excision repair is an important general pathway that corrects many different types of DNA damage, including the UV component of sunlight, bulky chemical adducts, DNA intrastrand crosslinks, and some forms of oxidative damage. Given the affinity of HMGB1 for a number of nucleotide excision repair substrates (e.g. DNA damaged by cisplatin, UV, BPDE, etc.) (Malina et al., 2002), a number of studies have confirmed the critical role of HMGB1 in the regulation of the nucleotide excision repair pathway (Lange and Vasquez, 2009). HMGB1, molecularly “repair shielding” via DNA binding activity (Pil and Lippard, 1992; Takahara et al., 1995), inhibits nucleotide excision repair following cisplatin lesion (Huang et al., 1994; Lanuszewska and Widlak, 2000; Malina et al., 2002; Mitkova et al., 2005; Patrick et al., 1997; Ugrinova et al., 2009b; Yusein-Myashkova et al., 2013). The HMGB1-mediated inhibitory effect on the repair of cisplatin-damaged DNA is accomplished through the acidic domain (Mitkova et al., 2005). However, HMGB1’s protein interaction activity may enhance nucleotide excision repair in some cases. Indeed, recent studies indicate that HMGB1 can bind DNA damage recognition complex proteins such as XPC-RAD23B, XPA, and RPA to enhance interactions between nucleotide excision repair proteins on triplex-directed psoralen interstrand crosslinks (Lange et al., 2009; Lange and Vasquez, 2009; Reddy et al., 2005). Based on this finding, HMGB1$^{-/-}$ MEFs exhibit significantly decreased DNA repair ability, which in turn promotes cell death as well as gene mutation in response to UV irradiation and psoralen/UVA treatment (Lange et al., 2008). In contrast, some HMGB1$^{-/-}$ MEFs were more resistant to the nucleoside analogs 5-fluorouracil, araC, mercaptopurine, and thiopurine than the isogenic wild-type cell lines (Krynetskaia et al., 2008). Collectively, these findings from these studies suggest that HMGB1 has a dual role in the regulation of nucleotide excision repair depending on stimuli type and chromatin content.

3.1.9.4 Double Strand Break Repair: Double strand break repair is an important pathway during the cell cycle that corrects the DNA double-strand break generated by ionizing radiation, radio-mimetic chemicals, and other type of DNA lesion (Jackson, 2002). Two sub pathways, the nonhomologous end joining (NHEJ) and homologous recombination (HR) pathways, are responsible for double strand break repair (Rothkamm et al., 2003). NHEJ is initiated by the recognition and binding of the Ku70/Ku80 heterodimer proteins, which recruits and holds the catalytic subunit of DNA protein kinase (DNA-PK$_{CS}$) to the ends of double-strand breaks (DSBs) to promote a repairing process. HR is mediated by using

extensive homology to restore the sequence at the break site (Jackson, 2002). *In vitro*, recombinant mammalian HMGB1 can activate DNA-PKcs in the absence of Ku protein (Yumoto et al., 1998) and function as DNA-binding regulatory components for DNA-PKcs to enhance ligation reaction of DNA double strand breaks during V(D)J recombination (Nagaki et al., 1998; Yumoto et al., 1998). Given the role of HMGB1 in activating DNA-PKcs *in vitro*, it will be important to investigate whether HMGB1-mediated V(D)J recombination is completed partly by NHEJ (Downs, 2007).

3.1.10 Telomere and Telomerase—A telomere is a region of repetitive nucleotide sequences (TTAGGG) at the end of a chromosome. Telomeres not only protect chromosome ends against erosion and degradation, but also prevent activation of DNA damage checkpoints. Telomere length is maintained as a result of a dynamic equilibrium between lengthening and shortening. Telomere shortening is caused by incomplete DNA replication and nucleolytic degradation. In contrast, telomere lengthening primarily results from increased telomerase activity. Telomerase contains two main core components: a catalytic protein subunit (telomerase reverse transcriptase, TERT), and an RNA subunit (telomerase RNA, TR). In addition, shelterin, a six-subunit protein complex (TRF1, TRF2, TIN2, Rap1, TPP1, and POT1), protects human telomeres. An early study indicated that loss of HMGB1 in yeast and mammalian cells promotes chromosomal instability and telomere aberrant events (Giavara et al., 2005). A recent study demonstrated that $HMGB1^{-/-}$ MEFs exhibited mild telomere shortening, but significantly decreased telomerase activity and DNA damage. Possible reasons for this process include interaction between HMGB1 and TERT/TR and HMGB1-mediated transcription upregulation of TR (but not TERT). Interestingly, HMGB2 plays an opposing role in the regulation of telomerase activity, and $HMGB2^{-/-}$ MEFs exhibit increased telomerase activity. However, change HMGB1 level in *Arabidopsis thaliana* does not affect telomerase activity and chromatin architecture (Schrumpfova et al., 2011). The complex roles of HMGB1 in coordinating the DNA damage response and telomere dynamic and genomic stability remain to be further elucidated. It is important to determine whether HMGB1 directly binds or bends telomere's repetitive nucleotide sequences.

3.1.11 Gene Transfer—Transposition of DNA is the process of a DNA sequence that can change its position within the genome, which will create or reverse mutations and alter genome size. Based on this theory, several DNA transposition systems, including Sleeping Beauty transposon system, have been developed to insert a gene or DNA sequence into chromosomes of vertebrate animals for gene therapy or offer a new model to study gene function and DNA recombination. The Sleeping Beauty transposon system contains a Sleeping Beauty (SB) transposase and a transposon designed in 1997 by Zsuzsanna Izsvák and colleagues (Ivics et al., 1997). This system-mediated transposition is a dynamic process including: (1) SB transposase binding to its cognate inverted repeat/direct repeat elements, (2) SB synaptic complex formation, (3) excision separating the transposon from the donor DNA, and (4) integration of the transposon into chromosomal DNA (Ivics et al., 1997; Ivics et al., 2004). HMGB1 acts as a cellular cofactor of SB transposase, and physically interacts with SB to enhance SB binding to the inner direct repeat element via its binding activity, which in turn stimulates synaptic complex formation and DNA recombination (Zayed et al.,

2003). Thus, overexpression of HMGB1 by gene transfection has the ability to enhance SB-mediated transposition efficiency, which provides a novel DNA transposition system for gene transfer (Zayed et al., 2004). Besides the SB system, HMGB1 has the ability to enhance other DNA transposition systems such as herpes simplex virus/Sleeping Beauty (HSV/SB) amplicon vector platform (de Silva et al., 2010; Peterson et al., 2007). These findings make HMGB1 an excellent candidate for improving gene transfer in gene therapy.

3.1.12 Gene Delivery—Transfection is the process by which nucleic acids (DNA or RNA) are introduced into mammalian cells. It is a widely-used molecular and cellular technology to change gene expression by using various lipids, chemical, or physical methods. HMGB1 significantly enhances transfection efficiency in several systems by its nuclear localization signals and DNA binding ability (Bottger et al., 1988; Namiki et al., 1998; Shen et al., 2009b; Shen et al., 2010; Siu et al., 2012). The TAT-high mobility group box-1 A box peptide (TAT-HMGB1A) and its variants have the ability to deliver DNA into cells without cytotoxicity (Han et al., 2009; Yi et al., 2012). Thus, HMGB1 may be useful as a non-toxic gene delivery carrier in gene therapy (Kim et al., 2008b; Yi et al., 2012).

3.2 Cytosolic HMGB1

Early studies suggest that expression of HMGB1 is high in hepatic tissues and the brain, suggesting that HMGB1 functions in both the nucleus and cytoplasm (Bustin and Neihart, 1979; Mosevitsky et al., 1989). Subsequent studies investigated the levels and distribution of HMGB1 between the nucleus and cytoplasm in different cells and tissues. Localization of HMGB1 in the cytoplasm has been confirmed in living fibroblasts (Einck et al., 1984), thymocytes (Guillet et al., 1990) and several different tissues (e.g., liver, kidney, heart, and lung) (Kuehl et al., 1984). The normal ratio of nuclear to cytoplasmic HMGB1 is about 30:1 (Kuehl et al., 1984). Currently, we know that HMGB1 normally is located in the nucleus and translocates from the nucleus to the cytosol, including mitochondria and lysosome, following various stressors (e.g., cytokine, chemokine, heat, hypoxia, H_2O_2, and oncogene). Although the function of cytosolic HMGB1 still remains poorly studied, we demonstrated that the main function of HMGB1 in cytoplasm is to function as a positive regulator of autophagy, which we first reported in 2010 (Tang et al., 2010c). Autophagic stimuli promote the translocation of HMGB1 to the cytosol and cytosolic HMGB1 binds to Beclin-1 to induce autophagy to degrade damaged organelles and unused proteins (Tang et al., 2010c). We introduce details about the interaction between HMGB1 and autophagy in the “Autophagy” section.

Another potential function for cytosolic HMGB1 is involvement in the unconventional secretory pathway, found based on mass spectrometry-mediated binding partner analysis in 2010 (Lee et al., 2010a). In this study, the authors identified numerous HMGB1-binding partners in nuclear and cytosol fraction. Interestingly, cytoplasmic HMGB1 is overexpressed and colocalized with lysosomal protein in colon, liver, and gastric cancer cells. Among the cytoplasmic HMGB1-binding proteins, nine of the identified proteins are related to protein translocation and secretion. Of these, annexin A2, myosin IC isoform a, myosin-9, and Ras-related protein Rab10 are directly involved in the process of unconventional protein secretion, which has been confirmed by an immunopreciptation experiment (Lee et al.,

2010a). These identified HMGB1-binding molecules provide new clues about the cytoplasmic functions of HMGB1 in cancer cells.

3.3 Membrane HMGB1

HMGB1 has been reported to be present on cell surface membranes involved in neurite outgrowth (Merenmies et al., 1991), platelet activation (Fuentes et al., 2014; Maugeri et al., 2012b), cell differentiation (Passalacqua et al., 1997), erythroid maturation (Hanspal and Hanspal, 1994), adhesion (Parkkinen and Rauvala, 1991) and innate immunity (Ciucci et al., 2011) through a different mechanism. In 1991, Heikki Rauvala and colleagues showed that HMGB1 is distributed to the filopodia of the advancing plasma membrane in process-growing neuroblastoma cells and is also deposited into the substrate-attached material, suggesting a role of HMGB1 in neurite outgrowth (Merenmies et al., 1991). Later, a study indicated that HMGB1 is distributed to spread laminin in N18 (mouse neuroblastoma) and HT1080 (human fibrosarcoma) cells and promote the generation of surface-bound plasmin, which mediates cell adhesion and invasion (Parkkinen et al., 1993; Parkkinen and Rauvala, 1991). During murine erythroleukemia (MEL) cell differentiation, HMGB1 is released and accumulates in cell membranes without extensive modification of the native molecular structure (Passalacqua et al., 1997). An unclassical secretory signal peptide, N-terminal 18 amino acids of HASPB, could efficiently deliver HMGB1 on the cell surface (Zhu et al., 2011a). HMGB1 is present in erythroblast-macrophage contact, which is involved in macrophage-mediated erythroid proliferation and maturation in a homophilic manner (Hanspal and Hanspal, 1994). Activated platelets induce the formation of neutrophil extracellular traps (NETs), an important innate immune mechanism to fight pathogenic bacteria. NETs are primarily composed of chromatin components bound to granular and selected cytoplasmic proteins (Brinkmann and Zychlinsky, 2012). During platelet activation, HMGB1 translocates to the membrane and is then released (Maugeri et al., 2012b), which mediates NET formation and function (Mitroulis et al., 2011; Tadie et al., 2013). HMGB1 is widely expressed on the cell-surfaces of human cord blood cells, especially myeloid dendritic cell precursors, which are involved in HMGB1 release and the immune response during inflammation (Ciucci et al., 2011).

3.4 Extracellular HMGB1

HMGB1 can be actively secreted by immune cells or passively released by dead, dying, or injured cells. Extracellular HMGB1 has multiple activities and is involved in several processes such as inflammation, immunity, migration, invasion, proliferation, differentiation, antimicrobial defense, and tissue regeneration (Figure 5). Native HMGB1 proteins from eukaryotic sources have the same (though less pronounced) biological activity *in vitro* compared to recombinant HMGB1 proteins from prokaryotic sources (Zimmermann et al., 2004).

3.4.1 Cell Differentiation—Cell differentiation is a process in which a less generic cell develops into a more specialized cell type. Many diseases are closely associated with problems from cell differentiation. Thus, it is important to investigate the structure and function of cell differentiation factors in development and disease. It is clear that the level of intracellular HMGB1 correlates with cell differentiation into several cells types such as T

cells (Russanova and Ando, 1985), cancer cells (Seyedin et al., 1981), and stem cells (Adjaye et al., 2005; Deneault et al., 2009). Extracellular HMGB1 is also involved in cell differentiation. The first report about extracellular HMGB1 function from Edon Melloni, Bianca Sparatore, and colleagues was published in 1995 (Melloni et al., 1995a, b). They found that HMGB1 promotes MEL cell differentiation if present in cell culture medium. Indeed, the same group originally identified HMGB1 as differentiation-enhancing factor (DEF), which is intracellularly expressed in undifferentiated growing MEL cells (Sparatore et al., 1990). During chemical (e.g., hexamethylenebisacetamide)-induced cell differentiation, HMGB1 is released into the extracellular space in a calcium-dependent manner (Melloni et al., 1995a; Sparatore et al., 1996b; Sparatore et al., 1993a). Once released, HMGB1 binds to receptors on the membrane of MEL and then promotes erythroid differentiation by active protein kinase C, a critical protein in MEL cell differentiation (Melloni et al., 1995a; Passalacqua et al., 1997; Patrone et al., 1996; Sparatore et al., 1996b; Sparatore et al., 1993b). These receptors involved in HMGB1-mediated MEL cell differentiation include the ionotropic glutamate N-methyl-D-aspartate receptor (NMDAR) and unknown 65 kD protein, but not RAGE (Pedrazzi et al., 2012; Sparatore et al., 2002). Structurally, the N-terminal region of HMGB1 is responsible for promoting MEL cell differentiation (Sparatore et al., 1996a). A peptide from extracellular HMGB1 maintains the differentiation stimulatory activity of the whole protein by limited proteolysis (Sparatore et al., 2001). Besides MEL cells, extracellular HMGB1 promotes the differentiation of chronic lymphocytic leukemia (Jia et al., 2014a), stem cells (Pistoia and Raffaghello, 2011), dendritic cells, and T cells.

3.4.2 Inflammatory Response—In 1999, Haichao Wang and colleagues made breakthrough progress in uncovering the extracellular role of HMGB1 in inflammation and infection. They demonstrated that HMGB1 functions as a late mediator with cytokine activity in sepsis, a systemic inflammatory response syndrome resulting from microbial infection. Currently, a number of studies have demonstrated that HMGB1 can selectively bind multiple receptors (e.g., RAGE and TLRs) to active macrophages (He et al., 2012b), monocytes (Andersson et al., 2000), neutrophils (Park et al., 2003; Silva et al., 2007), eosinophils, astrocytes (Pedrazzi et al., 2007), fibroblasts (Guo et al., 2011; Hou et al., 2011b; Hreggvidsdottir et al., 2009), keratinocytes (Dejean et al., 2012), dendritic cells (Yang et al., 2007), natural killer cells, T and endothelial cells (e.g., vascular endothelial cells (Fiuza et al., 2003; Treutiger et al., 2003), airway epithelial cells (Kim et al., 2012a; Wolfson et al., 2011; Wu et al., 2013c), and intestinal epithelial cells (Huang et al., 2012c; Sappington et al., 2002)) to produce cytokines (e.g., TNF (Agnello et al., 2002; Andersson et al., 2000; Kim et al., 2010b; Park et al., 2003; Wu et al., 2013c), IL-1α (Andersson et al., 2000), IL-1β (Andersson et al., 2000; Park et al., 2003), IL-1RA (Andersson et al., 2000), IL-6 (Agnello et al., 2002; Andersson et al., 2000; Hou et al., 2011b; Kim et al., 2010b), IL-8 (Andersson et al., 2000; Dejean et al., 2012; Park et al., 2003; Treutiger et al., 2003; Wu et al., 2013c), IL-10 (Wu et al., 2013c), macrophage inflammatory protein (MIP)-1α (Andersson et al., 2000; Wu et al., 2013c), MIP-1β (Andersson et al., 2000; Wu et al., 2013c), IL-12 (Matsuoka et al., 2010), RANKL (Kim et al., 2010b), IL-11 (Kim et al., 2010b), IL-17 (Kim et al., 2010b)), chemokine (e.g., CCL5 (Pedrazzi et al., 2007), CXCL1 (Pedrazzi et al., 2007), CXCL2 (Pedrazzi et al., 2007), CCL2 (Pedrazzi et al., 2007), CCL20

(Pedrazzi et al., 2007) and CCL3 (Pedrazzi et al., 2007)), adhesion molecules (ICAM-1, VCAM-1 and E-selectin), growth factor (G-CSF (Treutiger et al., 2003)), antigen (CD40 (Matsuoka et al., 2010)) and other inflammatory associated proteins (e.g., tissue factor (TF) (Lv et al., 2009), inducible nitric oxide synthase (iNOS) (Ren et al., 2006; Sappington et al., 2002), mucin 8 (Kim et al., 2012a), inhibitor-signal transducer and activator of transcription-1 (SOCS-1) (Li et al., 2011c)). Molecular mechanisms underlying the potential pro-inflammatory activity of HMGB1 include active several signaling pathways (e.g., P38 (He et al., 2012b; Kim et al., 2010b; Park et al., 2003; Wolfson et al., 2011), ERK (Park et al., 2003), JNK (Kim et al., 2012a; Wu et al., 2013c), PI3K/Akt (Hou et al., 2011b; Kim et al., 2012a), JAK (Li et al., 2011c), Src (Hou et al., 2011b; Huang et al., 2012c), ELK-1 (Treutiger et al., 2003), SIRT1 (Kim et al., 2010b), HSP27 (Wolfson et al., 2011)) and transcriptional factors (NF-κB (Dejean et al., 2012; He et al., 2012b; Hou et al., 2011b; Kim et al., 2010b; Park et al., 2003; Silva et al., 2007; Treutiger et al., 2003; Wu et al., 2013c), STAT1 (Guo et al., 2011; Li et al., 2011c), and EGR1 (Lv et al., 2009)). In addition, high-purity HMGB1 has weak pro-inflammatory activity by itself (Rouhiainen et al., 2007), but can bind with DAMP or PAMP (e.g., IL-1β (Hreggvidsdottir et al., 2009), LPS (Hreggvidsdottir et al., 2009), CpG-ODN (Hreggvidsdottir et al., 2009), Pam3CSK4 (Hreggvidsdottir et al., 2009), lipids (Rouhiainen et al., 2007), DNA or nucleosome) to amplify their pro-inflammatory activity in a synergistic manner (Table 3) (Pisetsky, 2011; Pisetsky et al., 2011). Thus, HMGB1 is an important mediator of acute lung injury (Abraham et al., 2000), brain injury (Agnello et al., 2002), islet loss (Matsuoka et al., 2010), cytoskeletal rearrangement (Wolfson et al., 2011), intestinal barrier disruption (Sappington et al., 2002), vascular barrier disruption (Wolfson et al., 2011), precancerous lesions (Dejean et al., 2012), fibrinolysis (Roussel et al., 2011), and thrombosis (Ito et al., 2007c). Inhibition of HMGB1 release and/or activity significantly decreases the inflammatory response, tissue injury, and death in animals. The importance of HMGB1 as a pro-inflammatory cytokine has been shown in many inflammation- and immunity-associated diseases.

3.4.3 Cell Migration—Cell migration, a central process in the development and maintenance of multicellular organisms, occurs in many physiological and pathological processes (Ilina and Friedl, 2009). Interactions of chemokines and their receptors mediate cell migration. A number of studies have indicated that HMGB1 acts as a potential host cell-derived, chemotactic factor to promote migration of several cell types (Degryse and de Virgilio, 2003). These cells include neurites (Fages et al., 2000), smooth muscle cells (Degryse et al., 2001), myoblast cells (Fages et al., 2000), tumor cells (Fages et al., 2000; Huttunen et al., 2002; Palumbo and Bianchi, 2004; Palumbo et al., 2004), hepatic stellate cells (Wang et al., 2013b), stem cells (Palumbo et al., 2009; Palumbo et al., 2007; Palumbo et al., 2004), endothelial cells (Furlani et al., 2012), keratinocytes (Ranzato et al., 2009), monocytes (Pedrazzi et al., 2007; Rouhiainen et al., 2004), dendritic cells (Dumitriu et al., 2007; Yang et al., 2007), and neutrophils (Orlova et al., 2007; Palumbo et al., 2009; van Zoelen et al., 2009). The potential mechanisms include HMGB1-mediated signaling transduction (e.g., ERK (Degryse et al., 2001; Ranzato et al., 2009), Cdc42 (Fages et al., 2000), Rac (Fages et al., 2000), JNK (Wang et al., 2013b), PI3K/AKT (Wang et al., 2013b) and Src (Palumbo et al., 2009)), transcriptional factor activation (NF-κB), and chemokine production. These findings suggest that extracellular HMGB1-mediated migration maybe

contribute to the recruitment of innate immune cells (Degryse et al., 2001) and stem cells (Palumbo and Bianchi, 2004; Palumbo et al., 2004) to sites of infection and injury, wound healing and tissue regeneration (Degryse et al., 2001; Palumbo and Bianchi, 2004; Palumbo et al., 2004), atherosclerosis and restenosis after vascular damage (Degryse et al., 2001), microvascular rolling and adhesion (Furlani et al., 2012), and tumor invasion and metastasis (Huttunen et al., 2002) (Fages et al., 2000; Palumbo and Bianchi, 2004; Palumbo et al., 2004). In general, RAGE is required for HMGB1-mediated cell migration. Interestingly, HMGB1 not only stimulates, but also inhibits migration in some cells. For example, exogenous HMGB1 selectively inhibits VEGF-induced cell migration in pulmonary artery endothelial cells (HPAECs), but not human umbilical vein endothelial cells (HUVECs) (Bauer et al., 2013). Moreover, the IRF3-dependent TLR4 pathway is required for HMGB1-mediated migration inhibition in HPAECs (Bauer et al., 2013).

3.4.4 Tissue Regeneration—Tissue regeneration is a process of regeneration of a wide variety of complex structures, allowing host tissue to regrow after injury or damage. Several dynamic events contribute to tissue regeneration, including wound healing, cell death, dedifferentiation, and stem cell proliferation/recruitment. In addition, the polarity and position of structures in regrown tissues must integrate with preexisting body structures (King and Newmark, 2012). HMGB1 promotes scratch wound closure of keratinocytes via reorganization of the actin cytoskeleton and disruption of the key junctional protein (Ranzato et al., 2009).

Accumulating evidence indicates that HMGB1 can stimulate myocardial regeneration, which may facilitate cardiac repair (Abarbanell et al., 2011; Germani et al., 2007; Limana et al., 2013; Limana et al., 2005), cardiomyocyte hypertrophy (Su et al., 2012), or cardiac fibrosis (Wang et al., 2014e). In a mouse model of myocardial infarction, HMGB1 administration promoted proliferation and differentiation of cardiac stem cells into cardiomyocytes (Limana et al., 2005), suggesting that HMGB1 is a potent inducer of myocardial regeneration following myocardial infarction. HMGB1 regulates electrical remodeling (Liu et al., 2010b), inotropic effect (Hagiwara et al., 2008f), and Notch signaling (Limana et al., 2013), which maybe contribute to heart repair. In addition, HMGB1 leads to cardiac hypertrophy and cardiac fibrosis through activation of calcineurin (a calcium-dependent serine-threonine phosphatase) or upregulation of collagens I/III and TGF-β1, respectively (Su et al., 2012; Wang et al., 2014e). These finding suggests that HMGB1 is a therapy target of cardiac disorder. Except for myocardial regeneration, HMGB1 promotes myogenesis in skeletal muscle by activation of mitogen-activated protein kinase (MAPK), upregulation of myogenin and myosin heavy chain expression, and induction of muscle creatine kinase (De Mori et al., 2007; Sorci et al., 2004). HMGB1 also promotes epithelial regeneration through recruitment of epithelial progenitors to injured tissue (Tamai et al., 2011). HMGB1 induces human lung endothelial cell cytoskeletal rearrangement and barrier disruption (Wolfson et al., 2011). In addition, HMGB1 promotes periodontal remodeling and repair (Wolf et al., 2012; Wolf et al., 2013a; Wolf et al., 2013b; Wolf et al., 2013c).

3.4.5 Angiogenesis—Angiogenesis, or the formation of new blood vessels from pre-existing capillaries, is involved in various physiologic and pathologic processes such as

inflammation, wound repair, and tumor growth. In an endothelial-sprouting assay, exogenous HMGB1 induces endothelial cell migration and sprouting in a dose-dependent manner, suggesting that HMGB1 may be involved in angiogenesis (Schlueter et al., 2005). In 2006, Marco Presta and colleagues first confirmed that HMGB1 is an angiogenic molecule (Mitola et al., 2006). They demonstrated that extracellular HMGB1 induces a proangiogenic phenotype in endothelial cells and triggers a potent angiogenic response *in vivo* in the chicken embryo chorioallantoic membrane (Mitola et al., 2006). They also found that extracellular HMGB1 exerts potent angiogenic activity by activating the MAPK ERK1/2 pathway (Mitola et al., 2006). Activation of HMGB1 and its receptor RAGE results in the activation of NF-κB, which upregulates leukocyte adhesion molecules and the production of pro-inflammatory cytokines and angiogenic factors, thereby promoting inflammation and angiogenesis (van Beijnum et al., 2008). In addition, TLR4 is selectively required for HMGB1-mediated neovascularization (Lin et al., 2011). HMGB1 in complex with heparin also induces angiogenesis (Wake et al., 2009b). HMGB1 stimulates integrin-dependent homing of endothelial progenitor cells in ischemic regions and improves neovascularization (Chavakis et al., 2007). Importantly, HMGB1 has been shown to be upregulated in the serum or tissue specimens of patients with angiogenesis-associated diseases, especially cancer (Yang et al., 2014d). Rapid tumor growth is accompanied by reduced microvessel density, resulting in chronic hypoxia that often leads to necrotic areas within the tumor. These hypoxic and necrotic regions exhibit increased expression of angiogenic growth factors, including vascular endothelial growth factor (VEGF), and attracts macrophages, which also produce a number of potent angiogenetic cytokines and growth factors. Treatment with HMGB1 increases the secretion of VEGF, but not VEGF-C, in human oral squamous cell carcinoma cells. The effect of HMGB1 is abrogated by HMGB1-neutralizing antibody (van Beijnum et al., 2006) and suppression of RAGE expression (Sasahira et al., 2007).

3.4.6 Bacterial Killing—In 2002, Cecilia K. Zetterström and colleagues first found that HMGB1 is produced by human adenoid tissue and exerts potent antibiotic activity. The kinetics of bacterial killing by HMGB1 was found to be rapid within a time frame of seconds or minutes (Zetterstrom et al., 2002). Later, the same group discovered that HMGB1 is highly expressed by Sertoli cells in human as well as rat testes. The purification of HMGB1 from human and rat testes by reversed-phase high-performance liquid chromatography also exerts significant antibiotic activity against several types of bacteria (Zetterstrom et al., 2006). These findings suggest that HMGB1 may facilitate the first line of defense against invading bacteria. NET is an important mechanism of bacterial killing. Interestingly, HMGB1 promotes NET formation through interactions with TLR4 (Tadie et al., 2013), suggesting that HMGB1 may promote NET-mediated bacterial killing. However, exogenous HMGB1 also has the ability to diminish neutrophil-mediated bacterial killing after HMGB1 binds to RAGE (Tadie et al., 2012a). These findings suggest that HMGB1-mediated bacterial killing occurs in a receptor-dependent way.

3.4.7 Proliferation—HMGB1 activates cell proliferation signals in several cells, including smooth muscle cells (Porto et al., 2006), T cells (Sundberg et al., 2009), mesoangioblasts (Palumbo et al., 2004), cardiac stem cells (Limana et al., 2005), and various cancer cells.

HMGB1 is not only released by smooth muscle cells, but also promotes the proliferation and migration of smooth muscle cells, which facilities atherosclerotic plaque formation (Porto et al., 2006). *In vitro*, HMGB1 induces the migration and proliferation of both adult and embryonic mesoangioblasts and disrupts the barrier function of endothelial monolayers (Palumbo et al., 2004), although some reports suggest that HMGB1 is a proliferation inhibitor of human mesenchymal stem cells (Meng et al., 2008). HMGB1 promotes proliferation of cardiac stem cells and myocardiocytes, which facilitates tissue regeneration (Limana et al., 2005) and cardiomyocyte hypertrophy (Su et al., 2012; Wang et al., 2014e). HMGB1 regulates the proliferation of lymphocytes in a time- and dose-dependent manner (Wang et al., 2008b). However, HMGB1 only acts as a proliferation signal for T cells in the presence of suboptimal doses of anti-CD3 antibody and RAGE (Sundberg et al., 2009). In cancer cells, reduced HMGB1 promotes proliferation, whereas oxidized HMGB1 induces apoptosis. Thus, the redox state of HMGB1 regulates tumor cell survival and death.

3.4.8 Cell Death—Several reports have indicated that an excessive accumulation of extracellular HMGB1 is cytotoxic and leads to cell death (e.g. apoptosis and necrosis) and tissue injury (Kikuchi et al., 2009a). In addition, HMGB1 can induce a special form of cell death in glioblastoma cells, which lack the typical features of apoptosis, autophagy, or classic necrosis (Gdynia et al., 2010). Exogenous HMGB1 can enter host mitochondria by an endocytosis-independent mechanism and result in the formation of vacuolated giant mitochondria and a rapid depletion of mitochondrial DNA (Gdynia et al., 2010). Exogenous HMGB1 can rhHMGB1 localizes to the mitochondria and induces the formation of giant mitochondria, which is independent of TLR2, TLR4, or RAGE signaling (Gdynia et al., 2010). However, reactive oxygen species-mediated JNK activation is required for this process (Gdynia et al., 2010). Future studies will have to examine the molecular basis of HMGB1 uptake and subsequent giant mitochondria formation.

3.4.9 Cellular Senescence—Cellular senescence is a state of permanent cell-cycle arrest when proliferating cells respond to stress, including oncogenetic stress (Campisi and d'Adda di Fagagna, 2007). In addition to cell death, senescence is considered an important mechanism for mammalian cells to suppress tumorigenesis. During senescence, HMGB1 translocates from the nucleus to the cytoplasm and is then released to the extracellular space (Davalos et al., 2013). Once released, oxidized HMGB1 binds to TLR4 and induces IL-6 production and release, which promotes age-associated inflammation. Interaction between HMGB1 and p53 determine the onset of senescence. p53, but not ATM, is required for HMGB1 translocation as well as altered HMGB1 expression (downregulation and upregulation)-induced senescence (Davalos et al., 2013).

3.4.10 microRNA Biogenesis—microRNAs (miRNAs) are approximately 22-nucleotide small RNAs that act as negative or positive gene transcriptional regulators involved in human health and disease. Several reports have indicated a potential role of HMGB1 in the regulation of microRNA expression involved in inflammation, cardiac remodeling, and cancer. The microRNA expression profile is significant in human peripheral blood mononuclear cells (PBMCs) following DAMP and PAMP stimulation. In particular, miR-34c expression in human PBMCs depends on the presence of HMGB1 within cells

serving as a source of lysates or conditioned media from stressed cells (Unlu et al., 2012). HMGB1 increases the expression of miR-206, which contributes to downregulation of tissue inhibitor of metalloproteinase 3 (TIMP3), a physiological regulator of cardiac regeneration (Limana et al., 2011). In addition, the binding of HMGB1 to RAGE increases the expression of miR-221 and miR-222 in papillary thyroid cancer cells, which facilitates tumor growth and migration (Mardente et al., 2012). These findings suggest that HMGB1 facilitates microRNA biogenesis, although the molecular mechanism remains unknown.

3.4.11 Efferocytosis—Efferocytosis is an uptake process of apoptotic cells by macrophages and other phagocytic cell populations. Efferocytosis dysfunction may lead to excessive accumulation of late apoptotic and/or secondary necrotic cells and subsequent inflammatory response. Compared with milk fat globule-EGF factor 8 (MFG-E8) (Miksa et al., 2009; Wang et al., 2013k), HMGB1 is a negative regulator of efferocytosis by its C-terminal acidic tail (Banerjee et al., 2010) and poly(ADP-ribosyl)ation (Davis et al., 2012b). Extracellular HMGB1 inhibits efferocytosis by binding phosphatidylserine or $\alpha_v\beta_3$ integrin in apoptotic neutrophils or phagocytic macrophages, respectively (Friggeri et al., 2010; Liu et al., 2008a). Compared with unmodified HMGB1, PARylated HMGB1 has a higher affinity for phosphatidylserine and RAGE (Davis et al., 2012b). Thus, extracellular HMGB1-mediated efferocytosis inhibition may enhance inflammatory responses during apoptosis. Interestingly, intracellular HMGB1 is also a negative regulator of efferocytosis by binding to Src (Banerjee et al., 2011), whereas RAGE enhances efferocytosis in macrophages by binding to PtdSer (Friggeri et al., 2011; He et al., 2011) and to free DNA. It is thus important to determine why HMGB1 and RAGE both interact with PtdSer, but show opposite outcomes to efferocytosis.

3.4.12 Neurotransmitters—Neurotransmitters are endogenous chemicals (e.g., acetylcholine, norepinephrine, dopamine, gamma aminobutyric acid, glutamate, serotonin, and endorphin) that transmit signals from one neuron to the next across synapses. The vagus nerve can modulate systemic inflammation and HMGB1 release through the alpha7 nicotinic acetylcholine receptor (alpha7nAchR), suggesting a potential role of neurotransmitters in the regulation of HMGB1 release. In contrast, extracellular HMGB1 also has the ability to stimulate the release of glutamate and its analogues from gliosomes by binding to RAGE and glial glutamate-aspartate transporter (GLAST), suggesting a critical role of HMGB1 in the regulation of glutamate homeostasis in the brain (Bonanno et al., 2007).

3.4.13 Immune Response—The immune system is divided into two parts, the innate and adaptive systems, which protect the body against pathogens, destroying cancer cells and foreign substances. The innate immune system, including several cell types (e.g., macrophages, neutrophils, mast cells, basophils, eosinophils, dendritic cells, natural killer cells, and $\gamma\delta$ T cells) is the first line of defense immediately available to fight against invading microorganisms. The adaptive immune response depends on B and T lymphocytes, which are specific for particular antigens and typically takes four to seven days to respond. It is clear that HMGB1 plays a critical role in the regulation of innate and adaptive immune responses by direct effects or cell-cell interaction (Bianchi and Manfredi, 2007; Dumitriu et

al., 2005b; Manfredi et al., 2009). HMGB1 acts as an adjuvant for several vaccines (Grover et al., 2013; Li et al., 2013b; Li et al., 2011g; Wang et al., 2013h).

3.4.13.1 Macrophages: Macrophages differentiate from circulating PBMCs, common progenitor cells for many cell types such as dendritic cells and mast cells. Macrophages are important effector cells of the immune system that contribute to host defense, wound healing, and immune regulation. Many pro-inflammatory stimuli can induce macrophage secretion of HMGB1 into the extracellular space. Extracellular HMGB1 can further prolong the inflammatory response by stimulating macrophages to produce cytokines/chemokine by TLR2, TLR4, or RAGE (He et al., 2012b). In addition, HMGB1 has the ability to inhibit macrophage-mediated efferocytosis, which prevents macrophages from clearing dead cells and DAMP release (Friggeri et al., 2010; Liu et al., 2008a). Interestingly, pretreatment with HMGB1 leads to endotoxin and lipoteichoic acid tolerance in bone marrow-derived macrophages and the acute monocytic leukemia cell line THP-1 by downregulation NF-KB activity (Aneja et al., 2008; Robert et al., 2010). However, RAGE is required for HMGB1-mediated endotoxin tolerance, whereas TLR2 and TLR4 are required for HMGB1-mediated lipoteichoic acid tolerance (Aneja et al., 2008; Robert et al., 2010). More recently, endogenous HMGB1 has been found to be required in endotoxin tolerance in macrophages (Li et al., 2013d), and conditional knockout of HMGB1 in macrophages was found to cause animal death in response to endotoxemia and bacterial infection (Yanai et al., 2013). Thus, HMGB1 can activate or inhibit macrophage function in the innate immune response, which maybe depend on receptors, location, and reaction phase.

3.4.13.2 Neutrophils: Neutrophils, eosinophils, and basophils are known as granulocytes due to the presence of multi-lobed nuclei and granular cytoplasm. Neutrophils, also called polymorphonuclear cells (PMNs), are the most abundant leukocyte and kill microorganisms by phagocytosis, a process which typically leads to cytoplasmic vacuolar degeneration by production of reactive oxygen species. HMGB1 is an effective stimulus of neutrophil activation to produce cytokines (Park et al., 2003; Silva et al., 2007). Like in macrophages, HMGB1 also inhibits phagocytosis of apoptosis by neutrophils (Liu et al., 2008a). In contrast, HMGB1 mediates NET formation in neutrophils and facilitates type I IFN production in a TLR9-dependent way in systemic lupus erythematosus (Garcia-Romo et al., 2011).

3.4.13.3 Mast Cells: Mast cells are derived from haematopoietic stem cells and reside particularly in connective tissue and in the mucous membranes. When activated, mast cells can release granule-associated mediators such as histamine and heparin, which induce immediate allergic inflammation with recruitment of basophils, neutrophils and macrophages (Metcalfe et al., 1997). There is no information about the direct effect of exogenous HMGB1 on mast cell activity. Mast cell- deficient mice are protected from trauma partly through decreased circulating HMGB1 levels, suggesting a possible role of mast cells in the regulation of HMGB1 release (Cai et al., 2011). Similarly, mast cells were able to regulate cell death-mediated HMGB1 release in an animal sepsis model (Ramos et al., 2010). However, the mast cell effector histamine cannot induce HMGB1 release in rheumatoid arthritis (Adlesic et al., 2007). In contrast, histamine directly inhibits HMGB1

activity (Takahashi et al., 2013a) and mast cell protease chymase directly degrades HMGB1 (Roy et al., 2014). These findings suggest that mast cells have different roles in the regulation of HMGB1 release, activity, and levels during the inflammatory response.

3.4.13.4 Basophils: Basophils are an extremely rare type of granulocyte containing cytoplasmic granules that stain with basophilic dyes. When activated, basophils can release histamine, which is important in the development of allergic reactions such as asthma and allergic rhinitis. In addition, basophils play roles in the defense against parasites. Although sputum or serum HMGB1 is increased in patients with asthma (Watanabe et al., 2011) and allergic rhinitis (Salpietro et al., 2013), respectively, the direct interaction between HMGB1 and basophils is currently unknown.

3.4.13.5 Eosinophils: Eosinophil, a type of granulocyte, contains cytoplasmic granules that are easily stained by eosin or other acid dyes. When activated, eosinophils can release eosinophil granule proteins such as major basic protein (MBP), eosinophil peroxidase (EPO), eosinophil-derived neurotoxin (EDN), and eosinophilic cationic protein (ECP), which are implicated in the pathogenesis of numerous inflammatory processes such as parasites infection, asthma, allergy, and tumor (Lotfi et al., 2007). Exogenous HMGB1 has the ability to induce eosinophil migration, adhesion, survival, and degranulation (Lotfi et al., 2009). RAGE may be required for HMGB1-mediated eosinophil activation (Curran and Bertics, 2011; Lotfi et al., 2009). Upregulation of HMGB1 contributes to the pathogenesis of eosinophilic chronic rhinosinusitis with nasal polyps (Chen et al., 2014b).

3.4.13.6 Dendritic Cells: Dendritic cells (DCs) are the most powerful antigen-presenting cells (APCs) which play critical roles not only in the defense of microbial pathogens in the innate immune system but also in the regulation of the adaptive immune response. Major DC functions include antigen presentation and subsequent activation of T cells, immune tolerance, and immune memory. DC-based immunotherapy is an important way to treat human diseases, especially cancer and autoimmune disease. Increasing evidence from *in vitro* and *in vivo* studies suggests that HMGB1 is a critical regulator of DC maturation and function. Activated DCs (Tsung et al., 2007b) and other inflammatory cells, as well as dying cells, can release HMGB1 into the extracellular milieu (Dong Xda et al., 2007; Semino et al., 2005; Zou et al., 2013). This released HMGB1 further promotes DC as well as human plasmacytoid DC (Dumitriu et al., 2005a) maturation and migration (Campana et al., 2009) (Dumitriu et al., 2007) via several receptors such as RAGE (Manfredi et al., 2008; Tian et al., 2007), TLR2 (Curtin et al., 2009), TLR4 (Fang et al., 2013a), and TLR9 (Dumitriu et al., 2005c; Messmer et al., 2004; Tian et al., 2007). In addition, binding of HMGB1 to other DAMPs (nucleosome) (Urbonaviciute et al., 2008) or PAMPs (CpG-DNA) (Ivanov et al., 2007) can promote DC maturation. Released HMGB1 mediates natural killer cell-DC crosstalk (Balsamo et al., 2009; Melki et al., 2010; Saidi et al., 2008; Semino et al., 2005). HMGB1 suppresses the human plasmacytoid DC response to TLR9 agonists (Popovic et al., 2006). The interaction between HMGB1 and TLR4 is required for the DC-mediated antitumor immune response in conventional anticancer therapies such as chemotherapy and irradiation (Aguilera et al., 2011; Apetoh et al., 2007; Apetoh et al., 2008; Fucikova et al., 2011). In some cases, HMGB1 directly inhibits DC function in anti-cancer immunity

(Kusume et al., 2009). In contrast, TIM3 decreases this effect (Chiba et al., 2012b; Tang and Lotze, 2012).

3.4.13.7 NK Cells: Natural killer (NK) cells, a type of lymphocyte, play a major role in the early phase of host-rejection to both tumors and virally-infected cells. When activated by interferon or macrophage/monocyte-derived cytokines, NKs release cytotoxic molecules such as granzymes and perforin, which lead to the destruction and killing of binding non-self cells and viruses. In addition to cytotoxic molecules, NKs secrete several cytokines, including IFN-γ, TNF-α, IL-12 and HMGB1. IL-18 contributes to HMGB1 release from NK-stimulated immature DCs. Once released, HMGB1 promotes DC maturation and limits NK's cytotoxicity during NK-immature DC crosstalk (Semino et al., 2005; Semino et al., 2007). HMGB1-mediated NK-DC crosstalk is important in the regulation of HIV infection and viral replication partly by inhibition of apoptosis (Gougeon and Bras, 2011; Gougeon et al., 2012; Melki et al., 2010; Saidi et al., 2008). In addition to secretion, NK cells can passively release HMGB1 after acute toxic liver damage, which is CXCR3-dependent (Zaldivar et al., 2012). In addition, HMGB1 binding to TLR4 increases expression of natural killer group 2D (NKG2D) ligands by renal tubular epithelial cells (Chen et al., 2011a). HMGB1 combined with other cytokines (IL-2, IL-1, or IL-12) contributes to IFN-γ release from macrophage-stimulated NK cells (DeMarco et al., 2005). These findings suggest that HMGB1 regulates NK cell function at multiple levels such as cytotoxicity, cytokine release, and ligand expression.

3.4.13.8 T Cells: T cells, a type of lymphocyte, play a central role in cell-mediated adaptive immune responses. A specific combination of cytokine signals leads to the differentiation of naïve T cells into different effectors (Th1, Th2 and Th17) and regulatory T cell subsets. T cells can release HMGB1 in response to several stimuli or cell-cell contact in co-cultures (Jiang et al., 2013; Kawahara et al., 2007). In addition, HMGB1 released from DCs regulates polarization of CD4+ T cells (Messmer et al., 2004) and mediates cell-cell interactions (Kohka Takahashi et al., 2013). HMGB1 at low doses has no effect on the proliferation activity of CD4+ T cells, but promotes Th1 cytokine production. In contrast, HMGB1 at high doses suppresses the proliferative response and induces Th2 polarization of CD4+ T lymphocytes. HMGB1 also induces differentiation of splenic DCs to IL-10-producing $CD11c^{low}CD45RB^{high}$ DCs, which in turn suppresses T lymphocyte function with shifting of Th1 to Th2 *in vitro* (Liu et al., 2011d). HMGB1 mediates proliferation of T cells, including CD4+ and CD8+, in response to suboptimal anti-CD3 antibody stimulation. (Sundberg et al., 2009). In addition to effector T cells, HMGB1 regulates the proliferation, function, and balance of regulator T cells (e.g., Treg and Th17). For example, HMGB1 inhibits CTLA4 and Foxp3 expression, as well as IL-10 release in Treg cells in a RAGE-dependent way (Dumitriu et al., 2005c; Zhang et al., 2011f). HMGB1 is a chemoattractant for Treg and promotes its survival and suppressive function (Wild et al., 2012a), indicating a pro-tumor role of HMGB1 in the tumor microenvironment (Wild et al., 2012b; Zhang et al., 2011f). Indeed, HMGB1 suppresses CD8 T cell-dependent antitumor immunity via enhancing Treg-mediated immune suppression by production of IL-10 (Liu et al., 2011f). However, in some cases, HMGB1 treatment induces downregulation expressions of Treg cell phenotypes (Huang et al., 2012b). These findings suggest a dual role of HMGB1 in the

regulation of Treg. In contrast, HMGB1 promotes Th17 cell proliferation, differentiation, and activation in the setting of several autoimmune and inflammatory diseases, such as rheumatoid arthritis (He et al., 2012d; Shi et al., 2012b), myocarditis (Su et al., 2011), acute allograft injection (Duan et al., 2011), chronic hepatitis B (Li et al., 2014a).

γδ T cells represent a small subset of T cells that possess a distinct T-cell receptor (TCR) on their surface, which is important in innate immune responses, especially in the mucosal immunity of gut, respiratory tract and urogenital system. The HMGB1-TLR4-IL-23 pathway in macrophages induces the generation of IL-17-producing γδ T cells, which mediate neutrophil infiltration and damage-induced liver inflammation (Wang et al., 2013l).

3.4.13.9 B Cells: B cells, a type of lymphocyte, play a major role in making antibodies against antigen, performing the role of antigen-presenting cells in activation of immune memory. Moreover, B cells also secrete cytokines, especially IL-10, to inhibit the inflammatory response. This special subset is termed regulatory B cells (Mauri and Bosma, 2012). Several studies indicate that HMGB1 has a role in the regulation of B cell activation. Single HMGB1 or HMGB1-DNA immune complex promotes the proliferation and activation of auto reactive B cells, which requires several receptors including RAGE, TLR9, or B cell receptor (Avalos et al., 2010; McDonnell et al., 2011; Tian et al., 2007). In addition, the serum level of HMGB1 significantly correlates with autoantibody production (e.g., anti-dsDNA antibody) in patients with autoimmune diseases such as systemic lupus erythematosus (Wen et al., 2013), suggesting a potential role of HMGB1 in B cell-mediated antibody production. The function of HMGB1 in regulatory B cells remains unknown.

3.4.13.10 MDSC Cells: Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of myeloid origin cells including myeloid progenitors and immature macrophages, immature granulocytes, and immature DCs at different stages of differentiation (Gabrilovich and Nagaraj, 2009). MDSCs are known to have remarkable ability to suppress both the cytotoxic activities of NK and NKT cells and the adaptive immune response mediated by CD4+ and CD8+ T cells during cancer and inflammation (Gabrilovich and Nagaraj, 2009). HMGB1 promotes recruitment and migration of MDSCs in the tumor microenvironment, which contributes to colon cancer metastasis after curative surgery (Li et al., 2013f). In addition, IL-17 and IL-23 production from the activated HMGB1-RAGE pathway increases accumulation of MDSCs in melanoma tumor tissues, which contributes to tumor growth. In addition, loss of RAGE in mice markedly delays oncogentetic K-RAS-derived neoplasia formation (Kang et al., 2012b) and limits MDSC accumulation (Vernon et al., 2013). These findings suggest that the HMGB1-RAGE pathway promotes tumor growth and metastasis partly by increasing MDSC accumulation and limiting the antitumor immune response.

4 HMGB1 Release

4.1 Active Release

In response to exogenous microbial products (such as endotoxin (Wang et al., 1999), CpG-DNA (Ivanov et al., 2007) (Jiang et al., 2005) lysophosphatidylcholine (LPC) (Gardella et al., 2002), or mycobacterial infection (Grover et al., 2008)) or endogenous host stimuli (e.g.,

TNF-α (Wang et al., 1999), IFN-α (Jiang and Pisetsky, 2006), IFN-β (Lu et al., 2014), IFN-γ (Rendon-Mitchell et al., 2003), hydrogen peroxide (Tang et al., 2007e), nitric oxide (Tamura et al., 2011), peroxynitrite (Loukili et al., 2011), hyperlipidemia (Haraba et al., 2011a), hyperglycemia (Kim et al., 2011a), kynurenic acid (Tiszlavicz et al., 2011), neuropeptide Y (Zhou et al., 2013a), ATP (Eun et al., 2014)) or other stimuli (ethanol (Whitman et al., 2013), photodynamic therapy (Korbelik et al., 2011), natural DNA or synthetic oligonucleotides (Jiang and Pisetsky, 2008b), and ultraviolet B (Chakraborty et al., 2013)), immune cells (e.g., macrophages, monocytes, neutrophils, DCs, NKs), fibroblasts, or epithelial cells actively release HMGB1 into the extracellular space. HMGB1 cannot be actively secreted via the classical endoplasmic reticulum-Golgi secretory pathway due to lack of a leader signal sequence. Instead, several mechanisms have been reported to be involved in HMGB1 translocation from the nucleus to the cytoplasm and subsequent release (Figure 6).

4.1.1 Post Transcriptional Modifications—In 2003, Alessandra Agresti, Marco E. Bianchi, and colleagues first demonstrated that HMGB1 is acetylated at two NLS by PCAF, CBP, and p300 which results in HMGB1 cytoplamsic translocation and secretion by activated monocytic cells (Bonaldi et al., 2003). Similarly, both deacetylase inhibitors (TSA) and mimics acetylated lysine by mutation of six lysine to glutamine, causing the relocalization of HMGB1 from the nucleus to the cytoplasm (Bonaldi et al., 2003). Recent studies suggest that JAK/STAT1 mediates HMGB1 acetylation (Lu et al., 2014). Sirtuin 6 (SIRT6) belongs to the sirtuin family of NAD (+)-dependent deacetylases and has been implicated in the regulation of oxygen/glucose deprivation -induced HMGB1 release (Lee et al., 2013d). In addition to acetylation, phosphorylation and ADP-ribosylation may be other requisite steps for HMGB1 nucleocytoplasmic translocation. In particular, classical protein kinase C mediates HMGB1 phosphorylation (Oh et al., 2009). These findings suggest that the interaction between different post transcriptional modifications finally determines HMGB1 location. However, we still do not know whether these post transcriptional modifications are competitively, cooperatively, or independently regulated.

4.1.2 CRM1-mediated Nuclear Export—CRM1, a member of the importin β superfamily of nuclear transport receptors, recognizes and exports proteins containing a leucine-rich NES (Hutten and Kehlenbach, 2007). In addition to protein nuclear export, CRM1 also mediates RNA transport. In addition, CRM1 is also involved in centrosome duplication and spindle assembly during mitosis. Several inflammatory stimuli can enhance the interaction between CRM1 and HMGB1, and CRM1 inhibitor significantly inhibits HMGB1 translocation from the nucleus to the cytoplasm. Thus, CRM1 is the nuclear transport of HMGB1. In response to oxidative stress, cytoplasmic Hsp72 translocates to the nucleus, where it interacts with nuclear proteins including HMGB1, and prevents oxidative stress-induced HMGB1 cytoplasmic translocation and release (Tang et al., 2007b). Moreover, overexpression of Hsp72 inhibits CRM1 translocation and interaction between HMGB1 and CRM1 in macrophages following LPS or TNF-α treatment (Tang et al., 2007c).The expression of CRM1 is unregulated in several cancers and is a potential anti-cancer drug target. It is unclear whether the change of CRM1 expression in normal and cancer cells will cause HMGB1 translocation and release in cancer.

4.1.3 ROS Signaling Pathway—Reactive oxygen species (ROS) are free radicals that contain the oxygen atom, which are generated during various metabolic and biochemical reactions. ROS include superoxide anion ($O_2^{\bullet -}$), hydroxyl radical ($^{\bullet}OH$), hydrogen peroxide (H_2O_2), and singlet oxygen ($^1O_2$). ROS have multifarious effects in signal transduction, but in excess can result in oxidative damage, cell death, and various diseases. It is clear that ROS are the major signals responsible for both HMGB1 active and passive release in immune and non-immune cells. H_2O_2 actives the MAPK and NF-κB pathways, which in turn promotes HMGB1 release in macrophages and monocytes (Tang et al., 2007e). Antioxidants such as NAC (Tsung et al., 2007a), quercetin (Tang et al., 2009), edaravone (Kato et al., 2009), pyrrolidine dithiocarbamate (Zhang et al., 2010), and resveratrol (Delucchi et al., 2012) significantly inhibit HMGB1 release in several animal infection and injury models.

Heme oxygenase-1 (HO-1) is a cytoprotective enzyme that plays a critical role in defending the body against oxidant-induced injury during inflammatory processes. HO catalyzes the first and rate-limiting step in the oxidative degradation of heme to CO, biliverdin, and ferrous iron. Biliverdin and CO have anti-inflammatory properties. Increasing evidence suggests that loss of HO-1 increases HMGB1 release, whereas upregulation of HO-1 inhibits HMGB1 release in response to inflammatory stimulus (Chen et al., 2013b; Clerigues et al., 2012; Garcia-Arnandis et al., 2010a; Gong et al., 2008; Jang et al., 2012; Park et al., 2013; Sakai et al., 2012; Tsoyi et al., 2009; Wang et al., 2013g; Yun et al., 2010).

The nuclear factor erythroid 2-related factor (Nrf2) is a master transcription factor that regulates redox balance and stress response by controlling the basal and induced expression of an array of antioxidant response element-dependent genes. Loss of NRF2 decreased HO-1 expression and increased HMGB1 release in CLP-induced sepsis and ischemic/reperfusion injury (Ha et al., 2011b; Ha et al., 2012b; Hwa et al., 2012; Kim et al., 2013b; Park et al., 2013; Tsoyi et al., 2011a; Wang et al., 2014c).

4.1.4 Calcium Signaling Pathway—Calcium ions, one type of important intracellular messenger, regulate multiple cellular processes by exerting allosteric regulatory effects on many enzymes and proteins. Numerous proteins, channels, and pumps regulate calcium ion production and move between the cytosol and intracellular stores. Calcium-mediated signaling is involved in HMGB1 nucleocytoplasmic shuttling and release during infection (Zhang et al., 2008c) and sterile inflammation (Tsung et al., 2007a). This process is tightly regulated by calcium/calmodulin-dependent protein kinase (CaMK) I and IV, which promote serine phosphorylation of HMGB1 (Zhang et al., 2011d; Zhang et al., 2008c). In addition, calcium regulates PKC activity and the IFN-β signaling pathway, which is also involved in HMGB1 release (Ma et al., 2012b; Oh et al., 2009). Thus, inhibition of calcium signaling by inhibitors (e.g., STO609 and CV159) or knockdown/knockout of CaMK I and IV decrease HMGB1 release and protect animals against ischemia/reperfusion injury or sepsis (Hataji et al., 2010; Tsung et al., 2007a; Zhang et al., 2008c).

4.1.5 NO Signaling Pathway—Nitric oxide (NO) is an important cellular signaling molecule produced by NO synthase from L-Arginine, O_2, and NADPH. It is a powerful vasodilator with a short half-life of a few seconds in the blood and plays a role in many

physiological and pathological processes. In macrophages, an inducible NO synthase (iNOS or NOS2) is produced after activation by endotoxins or cytokines and generates copious amounts of NO presumably to help kill or inhibit the growth of invading microorganisms or neoplastic tissue. However, excessive iNOS will cause inflammation partly by promoting HMGB1 release (Tsoyi et al., 2010). In addition, HMGB1 also induces iNOS expression, facilitating the development of inflammatory injury (Ren et al., 2006).

4.1.6 TNF-α Dependent Mechanism—IFN-γ and LPS stimulate macrophages to release TNF and HMGB1 in a time-dependent manner. Interestingly, the release of HMGB1 by IFN-γ and LPS depends on TNF production. TNF inhibition by using $TNF^{-/-}$ macrophages or TNF-neutralizing antibodies partly inhibits IFN-γ- and LPS-induced HMGB1 release in macrophages, suggesting that a TNF-dependent mechanism is involved in HMGB1 release (Chen et al., 2004; Rendon-Mitchell et al., 2003). In addition, CD14 and JAK/STAT1 act as upstream signal to regulate TNF production and HMGB1 release in response to LPS and IFN-γ, respectively (Rendon-Mitchell et al., 2003). Thus, there is crosstalk between different signals to regulate HMGB1 release from activated macrophages.

4.1.7 Notch Dependent Mechanism—Notch signaling is a highly conserved pathway involved in diverse developmental and physiological processes. Dysregulation of Notch signaling is associated with several human disorders, especially cancer. In mammals, there are four Notch receptors (Notch-1 to -4) and five Notch ligands (Delta-like-1, -3, and -4 and Jagged-1 and -2). The expression of Jagged-1 is increased in LPS-induced macrophages, which is JNK-dependent. A potent Notch inhibitor, DAPT, inhibits LPS-induced HMGB1 release in macrophages. In addition, recombinant soluble Jagged-1, Delta-like-1, or -4 amplified LPS induced inflammatory responses. These findings suggest that LPS-induced Notch signaling activation regulates HMGB1 release (Tsao et al., 2011).

4.1.8 NF-κB-Dependent Mechanism—Activation of NF-κB plays a central role in inflammation and immunity through its ability to induce production and release of multiple pro-inflammatory cytokines and chemokines (Oeckinghaus et al., 2011). There are two major NF-κB pathways, namely the canonical and the noncanonical pathways, in mammals. In the canonical pathway, NF-κB/p65 is retained in the cytoplasm until it is activated in response to several stimuli such as cytokines, LPS, growth factors, and antigen receptors. After activation by phosphorylates, IκB proteins, and its subsequent proteasomal degradation, NF-κB/p65 translocates to the nucleus to induce targeted gene expression either alone or in combination with other transcription factor families. Inhibition of the canonical NF-κB pathway decreases HMGB1 release in activated immune cells (Wang et al., 2013a; Watanabe et al., 2013; Yang et al., 2014a; Zhang et al., 2010). However, the essential role of NF-κB in the regulation of HMGB1 release remains a subject of future investigation.

4.1.9 MAPK-Dependent Mechanism—MAPKs, a family of highly-conserved serine/threonine protein kinases, are involved in the regulation of a number of cellular processes, including inflammation, immunity, differentiation, and cell survival and death. There are three major classes of MAPKs in mammals: ERK, JNK, and p38, which divergently

contribute to HMGB1 release in different inflammatory and injury models (Zhou et al., 2013a).

4.1.10 STAT-Dependent Mechanism—STATs (signal transducers and activators of transcription) are transcription factors that contain STAT1–6. STAT1 and STAT2 have a central role in the interferon system. Binding of a growth factor or cytokine to its cell surface receptor results in the activation of the Janus kinases (JAK1 and JAK2), which in turn, induce STAT phosphorylation, dimerization, nuclear translocation, and STAT-mediated gene transcription. Increasing evidence suggests that JAK-mediated STAT1 and STAT3 activation is required for HMGB1 expression, modification, and/or release under several stressors such as LPS, IFN, and mechanical stress (Hao et al., 2013; Hui et al., 2009; Kim et al., 2009; Liu et al., 2007a; Wolfson et al., 2013). Thus, inhibition of the JAK/STAT pathway prevents HMGB1 release and protects against sepsis and ischemic reperfusion injury (Hui et al., 2009; Pena et al., 2010). Exogenous HMGB1 has the ability to induce activation of the STAT1 and STAT3 pathways (Conti et al., 2013; Guo et al., 2011; Li et al., 2011c). These findings suggest that a loop exists between HMGB1 and STAT1/3 signaling in inflammation.

4.1.11 Inflammasome-Dependent Mechanism—Inflammasome, a multiprotein oligomer, is activated by DAMPs and PAMPs that link the sensing of microbial products and metabolic stress to the proteolytic activation of proinflammatory cytokines such as IL-1β and IL-18 (Schroder and Tschopp, 2010). Inflammasomes have recently been shown to play an important role in mediating HMGB1 release from activated immune cells (Barlan et al., 2011; Craven et al., 2009; Lamkanfi et al., 2010; Lippai et al., 2013; Willingham et al., 2009; Willingham et al., 2007) or cancer cells (Miller et al., 2014). Thus, inflammasome-deficient mice or inflammasome inhibitor can inhibit HMGB1 release and protects mice against sepsis or I/R injury (Kamo et al., 2013; Xiang et al., 2011; Zhu et al., 2011b). LPS can induce ATP release and P2Y2 receptor upregulation, which in turn triggers the activation of inflammasome and enhanced HMGB1 release (Eun et al., 2014). Importantly, this process is mediated by double-stranded RNA (dsRNA)-dependent protein kinase (PKR), which promotes inflammasome assembly by directly interacting with inflammasome components (e.g., NOD-like receptor (NLR) family pyrin domain-containing 3 (NLRP3), NLRP1, NLR family CARD domain containing protein 4 (NLRC4), and absent in melanoma 2 (AIM2)) (Lu et al., 2012a; Schroder and Tschopp, 2010). Thus, loss of PKR or using PKR inhibitor in immune cells (macrophages and DCs) significantly inhibits inflammasome activation and release of IL-1β, IL-18, and HMGB1 (Li et al., 2013e; Lu et al., 2012b). Of note, some inflammasome components such as NLRP3 regulate HMGB1 release through inflammasome-independent pathways (Willingham et al., 2009). It is unclear whether other inflammatory signaling pathways are involved in inflammasome-mediated HMGB1 release (Lamkanfi and Dixit, 2011).

4.1.12 p53-Dependent Mechanism—HMGB1 and p53 form a complex that regulates DNA repair and the balance between tumor cell death and survival (Livesey et al., 2012c). Loss of HMGB1 increases p53 cytoplasmic translocation, whereas loss of p53 increases HMGB1 cytoplasmic translocation in colon cancer cells, suggesting that the HMGB1/p53

complex affects the cytoplasmic localization of the reciprocal binding partner (Livesey et al., 2012c). However, cytoplasmic translocation in hepatocytes and circulating levels of HMGB1 are greater in wild type rats than in p53+/− rats following carcinogen administration, suggesting that p53 promotes inflammation-associated hepatocarcinogenesis by inducing HMGB1 release (Yan et al., 2013a).

4.1.13 PPAR-Dependent Mechanism—Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor family and function as transcription factors regulating gene expression. There are three PPARs (PPARα, PPARβ/δ, and PPARγ), which play essential roles in the regulation of cellular differentiation, development, metabolism, inflammation, and tumorigenesis. Recent studies indicate that PPAR is a negative regulator of HMGB1 release in activated macrophages after treatment with LPS or Poly (I:C). The administration of PPARγ ligand rosiglitazone protects against sepsis and decreases HMGB1 release *in vivo* and *in vitro* (Hwang et al., 2012).

4.1.14 Cell-Mediated HMGB1 Release—Several reports indicate that HMGB1 release is mediated by cell-cell interaction. HMGB1 release during NK-DC crosstalk has been well-studied. Interestingly, interplay between dying cells and immune cells also induces HMGB1 release. For example, exposure of apoptotic cells to macrophages stimulates the release of HMGB1 in macrophages, which provides an explanation for the mechanism for apoptosis-mediated sepsis lethality (Qin et al., 2006). In addition, impaired clearance of apoptotic cells also leads to HMGB1 release, which in turn induces TLR4-mediated cytokine production (Velegraki et al., 2013).

4.1.15 Lysosome-Dependent Mechanism—Christian de Duve first identified lysosomes in 1949 via cell fractionation as the organelles responsible for protein degradation within cells. In addition to lysosome-mediated degradation, a subset of lysosomes, namely secretory lysosomes, are found in different cells of the immune system and are responsible for lysosome exocytosis in response to external stimuli. Secretory lysosomes are Ca^{2+}-regulated secretory organelles displaying features of both lysosomes and secretory granules. The best candidate for a molecular marker of secretory lysosomes is Rab27a. Lysosome exocytosis has been proposed to mediate secretion of leaderless cytokines such as IL-1β and HMGB1 (Gardella et al., 2002). There is a significant colocalization between HMGB1 and lysosomal marker LAMP1, but not early endosome marker EEA1, in activated monocytes after LPS treatment. The release kinetics of IL-1β and HMGB1 is significantly different in activated monocytes. IL-1β is rapidly released in response to ATP and LPS, whereas HMGB1 release is a late event in response to lysophosphatidylcholine (LPC) and LPS (Gardella et al., 2002). Like HMGB1, the release of the enzyme phosphatidylcholine sPLA2, responsible for the generation of extracellular LPC in the site of inflammation, is also a late event (Gardella et al., 2002). Gamma-interferon inducible lysosomal thiol reductase (GILT) can reduce protein disulfide bonds, which facilitate the complete unfolding of proteins destined for lysosomal degradation. Several studies reveal that NF-κB and STAT1 play direct roles in the regulation of LPS and IFN-γ-inducible GILT expression, respectively (Lackman and Cresswell, 2006; O'Donnell et al., 2004). Loss of GILT in immune cells such as T cells and monocytes has diminished cytokine production following Ag exposure or LPS

(Lackman and Cresswell, 2006; Rausch and Hastings, 2012). Interestingly, loss of GILT increases mitochondrial oxidative damage and cytosolic HMGB1 accumulation (Chiang and Maric, 2011), suggesting a potential role of GILT in the regulation of secretory lysosome-mediated HMGB1 release (Lackman et al., 2007).

4.1.16 Other—In addition, ATF3$^{-/-}$ (Lai et al., 2013), CCR7$^{-/-}$ (Kawakami et al., 2012), IL-17A$^{-/-}$ (Ogiku et al., 2012), SLPI$^{-/-}$ (Nakamura et al., 2003), C5l2$^{-/-}$ (Rittirsch et al., 2008), C3$^{-/-}$ (Cai et al., 2010), and ADAMTS13$^{-/-}$ (Fujioka et al., 2012) mice increase HMGB1 release in response to sterile and infectious threat.

4.2 Passive Release of HMGB1

In addition, HMGB1 can be passively released in cell death (e.g., necrosis, apoptosis, lysosomal cell death, and autophagic cell death) and injury following various stimuli such as chemotherapy, irradiation, hypoxia, hyperthermia, hyperpressure (Fucikova et al., 2014), glucose deprivation (Lee et al., 2011a), bacillus Calmette-Guerin (Zhang et al., 2013c), virus (Whilding et al., 2013), free fatty acids (FFA) (Rockenfeller et al., 2010), toxin (Kennedy et al., 2009; Radin et al., 2011), foreign matter (Yang et al., 2010b), ATP (Kawano et al., 2012), ubiquitin isopeptidase inhibitor (Fontanini et al., 2009), and cytolytic cells (Ito et al., 2007b). Multiple signaling pathways regulate passive HMGB1 release as discussed below (Figure 6).

4.2.1 PARP1 Dependent Mechanism—PAR polymerases (PARPs) are a family of enzymes responsible for poly (ADP)-ribosylation reactions. PARP catalyzes the transfer of ADP-ribose moieties from NAD+ onto acceptor proteins in response to several stress responses such as DNA damage, heat shock, and the unfolded protein response. Among them, PARP-1 is the best-characterized and master regulator for poly (ADP)-ribosylation reactions in the mammalian cell. Extensive DNA damage-mediated PARP-1 overactivation leads to excessive consumption of NAD+, ATP depletion, and subsequent necrotic cell death (Zong et al., 2004). In addition to inducing necrosis by energy deletion, nuclear PARP-1 also interacts with transcriptional factors such as p53 and NF-Kb to regulate expression of several genes (e.g., TNF-α) which are involved in the cell death and inflammatory response (Jog et al., 2009). HMGB1 has generally been considered a necrosis marker to stimulate inflammation. A recent study indicated that PARP1 is responsible for DNA-damaging agent-induced HMGB1 release during necrosis. Compared with wild type cells, loss of PARP1 in MEFs or using PARP inhibitor significantly inhibits alkylating DNA damage-induced HMGB1 translocation and release. These findings suggest that targeting PARP can inhibit HMGB1 release and the necrosis-associated inflammatory response. Interestingly, endogenous HMGB1 regulates the DNA damage response and PARP1 activity. Loss of intracellular HMGB1 leads to PARP-1 over activation (Huang et al., 2013a).

4.2.2 RIP3-Dependent Mechanism—Necroptosis, also termed programmed necrosis, is an alternative form of programmed cell death that occurs when cells lack the capacity to activate caspase-8 following ligation of death receptors (e.g., TNF-α), the same ligands that activate apoptosis. Two members of the receptor-interacting serine-threonine kinase (RIP)

family, RIP1 and RIP3, have recently been implicated in necroptosis due to their interaction to generate necrosomes (Li et al., 2012b; Vandenabeele et al., 2010). RIP1 and RIP3 interact via their RIP homotypic interaction motif (RHIM) domains. Compared with RIP1, RIP3 is more specific to the regulation of necroptosis. Overexpression of RIP3 *in vitro* increases necroptosis, whereas knockout of RIP3 *in vitro* or *in vivo* inhibits necroptosis in response to various stressors, especially inflammatory stimuli. For example, $RIP3^{-/-}$ mice are protected against sepsis and donor kidney inflammatory injury partly by inhibition of release of DAMPs, including HMGB1 (Lau et al., 2013). In addition, RIP3-mediated necroptosis has also been proposed to be required for dsRNA/poly (I:C)-induced HMGB1 release, which is important for the inflammatory response during retinal degeneration (Murakami et al., 2014). In contrast, IPS-1, an adaptor molecule for RIG-I-like receptors (RLRs) may be critical for poly (I:C)-induced necroptosis and HMGB1 release in DCs.

4.2.3 Cathepsin-Dependent Mechanism—Lysosomal cell death is a form of cell death mediated by lysosomal cathepsin proteases. Lysosomal membrane permeabilization is increased in response to several stressors such as chemotherapy and pathogens, which result in the release of cathepsins and other hydrolases from the lysosome to the cytosol. Lysosomal cell death has necrotic, apoptotic, or apoptosis-like features depending on the extent of the leakage and the cellular context (Aits and Jaattela, 2013). A recent study indicated that cathepsin B, a lysosomal cysteine protease, promotes *L. pneumophila*-induced lysosomal cell death and HMGB1 release (Morinaga et al., 2010). An early study indicated that minute amounts of cathepsin B are transferred abruptly to the nuclear compartment, including histone and HMGB1, in a variety of activated cells (Seeler et al., 1988). Cathepsin B may interact with histones and HMGB1 in pre-treatment with a specific cathepsin B inhibitor, CA074Me, inhibited *L. pneumophila*-induced cell death as well as HMGB1 release. The pattern of cathepsin B activation was important for subsequent PARP cleavage and type of cell death (Morinaga et al., 2010). In addition, cathepsin B is also involved in inflammasome activation and HMGB1 release (Duncan et al., 2009; Willingham et al., 2007). Moreover, cathepsin D is required for necroptosis-mediated HMGB1 release in DCs. These findings suggest that cathepsin plays a critical role in the regulation of HMGB1 release while cells undergo mixed cell death.

4.2.4 Antioxidant Enzyme-Dependent Mechanism—ROS affect cellular physiology in multiple ways, whereas excessive ROS can trigger death. ROS not only induce HMGB1 secretion, but also promote HMGB1 release during cell death such as necrosis, apoptosis, and necroptosis. Although there are multiple sources of ROS in the cell, mitochondria have been considered a major source of ROS production. Mitochondrial ROS (mtROS) are produced by increasing mitochondrial damage. Superoxide dismutases (SOD) are a class of metalloenzymes that catalyze the dismutation of superoxide (O_2^-) into O_2 and H_2O_2 and play a critical role in protecting cells against oxidative injury. In humans, SOD1 (CuZn-SOD) is located in the cytoplasm, whereas SOD2 (Mn-SOD) is located in the mitochondria. SOD3 (EC-SOD) exists as a copper and zinc-containing tetramer and is located in extracellular spaces. Dysfunction of SOD1 and SOD2 is involved in the regulation of HMGB1 release in cell death (Kang et al., 2011b; Lo Coco et al., 2007; Tang et al., 2011d; Vezzoli et al., 2011; Yao and Brownlee, 2010). In addition, other antioxidant enzymes such

as glutathione reductase (Chiang and Maric, 2011; Hoppe et al., 2006), thioredoxin (Vezzoli et al., 2011; Xiang et al., 2011; Xu et al., 2013a), and peroxiredoxins (Shichita et al., 2012) can regulate HMGB1 release.

4.2.5 DNase-Dependent Mechanism—Deoxyribonuclease (DNAse) is an enzyme for degrading DNA to fragmentation by catalyzing the hydrolytic cleavage of phosphodiester linkages in the DNA backbone. DNA is degraded during cell death that accompanies a number of diseases. DNA in apoptotic cells is specifically degraded into nucleosomal units by DNA endonuclease (DNase-gamma), whereas DNA in necrotic cells is usually degraded randomly by extracellular DNAse I from the pancreas or by lysosomal acid DNAse II (Nagata et al., 2003). An early study indicated that HMGB1 is released only by necrotic cells, but not apoptotic cells. We now know that apoptotic cells also release HMGB1 and nucleosome to mediate inflammatory and immune responses. The release of HMGB1 in apoptosis is triggered by DNase-gamma-mediated nucleosomal DNA fragmentation (Yamada et al., 2011a, b). Thus, DNase gamma inhibitors such as DR396 can limit HMGB1 release from apoptotic cells (Yamada et al., 2011a, b).

4.2.6 Caspase-Dependent Mechanism—Caspases are a group of intracellular cysteine-aspartic proteases that mediate apoptosis and other types of cell death such as pyroptosis. Caspases exist as inactive proenzymes that are activated by proteolytic cleavage. Caspase 8 is implicated in the death receptor-mediated apoptosis pathway and cytokine processing. Caspase 9 has been linked to the mitochondrial death pathway by triggering the release of cytochrome c from mitochondria. Caspase 3 and caspase 7 share similar substrate specificities and function as effector caspases through amplified initiation signals from caspase 8 and caspase 9. Recent studies indicate that caspase3/7 induce mitochondrial complex 1 protein p75 NDUFS1 cleavage, which in turn increases mitochondrial ROS production and subsequent HMGB1 release during apoptosis. This finding provided an explanation for the apoptosis-mediated HMGB1 release mechanism. Pyroptosis is an inflammatory cell death and is typically triggered by caspase 1 after its activation by various inflammasomes. Inhibition of caspapse 1 activity can diminish HMGB1 release and the inflammatory response during pyroptosis (Kamo et al., 2013; Lu et al., 2012b). In addition, a recent study indicated that HMGB1 at the sites of aa67, aa158, and aa169 can be directly cleaved by caspase 1, but not other caspases (-2, -3, -5, -7, -9 or -11) (Leblanc et al., 2014). Different from full length HMGB1, A box with anti-inflammatory activity, the caspase-1 generated A-box fragment (especially residues 23–50) binding to RAGE can rescue apoptosis-induced immune tolerance in a sepsis model (Leblanc et al., 2014). These findings suggest that caspase 1 regulates both the release and processing of HMGB1 in inflammation and immunity.

4.2.7 ATG-Dependent Mechanism—Autophagy is a lysosome-mediated, dynamic process including induction, cargo recognition, phagophore formation, autophagosme formation, autolysosme formation, and substrate degradation. This process is tightly regulated by ATG proteins that were first identified in yeast. Several ATG homologs have subsequently been identified in mammalian cells, suggesting that autophagy is a highly-conserved process from the evolution of prokaryotes to eukaryotes. Although autophagy is

generally considered a survival mechanism against harmful stress, excessive autophagy can lead to cell death, namely autophagic cell death. In response to epidermal growth factor receptor (EGFR)-targeted diphtheria toxin (DT-EGF), epithelial and glioblastoma tumor cells can release HMGB1 in an autophagy-dependent way (Thorburn et al., 2009). Knockdown of ATG5, ATG7, or ATG12 by RNAi decreases autophagy and HMGB1 release in response to DT-EGF (Thorburn et al., 2009). In addition, the ATG5-mediated autophagy pathway is also involved in HMGB1 secretion from fibroblasts and macrophages in response to starvation and lipopolysaccharide (LPS) (Dupont et al., 2011; Tang et al., 2010c). This process requires ROS signaling (Tang et al., 2010c).

5. HMGB1 Receptors (Figure 7)

5.1 RAGE

RAGE, a member of the immunoglobulin gene superfamily, is a transmembrane receptor with an extracellular domain, a short transmembrane domain, and a 43-amino acid cytoplasmic tail. The gene is localized on chromosome 6p21.3 near the HLA locus in the vicinity of the class III region of the major histocompatibility complex in humans and mice. This locus is in close proximity to the homeobox gene HOX12 and the human counterpart of the mouse mammary tumor gene int-3. A recent study indicated that RAGE is evolved from a cell adhesion molecule family and acts as an adhesion molecule in mammalian cells (Sessa et al., 2014). Extracellular domain, containing one “V”- type domain and two “C”-type-domains, is responsible for ligand binding, whereas a cytoplasmic tail is required for intracellular signaling transduction such as NF-κB signaling. There are multiple spliced transcript variants of RAGE which encode different isoforms, as well as non-protein-coding variants. In addition, the soluble form of RAGE (sRAGE) can be generated by ADAM10 or matrix metalloproteinase- mediated proteolysis (Raucci et al., 2008; Zhang et al., 2008a). RAGE was recognized as a receptor for AGEs and is now known as a multi-ligand receptor. In addition to AGE, RAGE binds HMGB1, S100, amyloid-β peptide, DNA, RNA, and other molecules to regulate multiple physiological and pathological processes. A number of studies demonstrate that RAGE is required for HMGB1-induced cell migration (Degryse et al., 2001; Fages et al., 2000; Palumbo and Bianchi, 2004; Palumbo et al., 2004), proliferation (Kang et al., 2010), regeneration (Degryse et al., 2001; Sorci et al., 2004), inflammation (He et al., 2012b; Lv et al., 2009; Treutiger et al., 2003; Wu et al., 2013c), autophagy (Kang et al., 2012a; Weiner and Lotze, 2012), injury (Huang et al., 2012c; Wolfson et al., 2011), metabolism (Kang et al., 2014; Luo et al., 2014), and immunity (Leblanc et al., 2014). In addition, extracellular HMGB1 can stimuli RAGE expression in several cell types (Li et al., 1998). Knockout of RAGE *in vitro* or *in vitro* decreases tumor growth and metastasis (Gebhardt et al., 2008; Heijmans et al., 2012; Kang et al., 2010; Taguchi et al., 2000), and increases chemotherapy resistance (Tang et al., 2011d). Currently, the HMGB1-RAGE signaling axis represents an important potential target for diseases such as diabetes (Manigrasso et al., 2014), neurogeneration (Li et al., 1998), cancer (Sims et al., 2010), and inflammatory (Liliensiek et al., 2004) and autoimmune diseases (Ullah et al., 2014).

5.2 TLR

The Toll-like receptors (TLRs) are an evolutionarily-conserved type I transmembrane superfamily that contain extracellular leucine-rich repeat (LRR) domains and a cytoplasmic Toll/IL-1 receptor (TIR) domain. TLRs recognize several danger signals, including PAMPs and DAMPs, to activate the innate immunity response for defense against infection and injury (Akira and Takeda, 2004). There are two major signal transduction pathways involved in TLR activation. The MyD88-dependent pathway is required for the production of inflammatory cytokines, whereas the MyD88-independent pathway is required for the production of type I IFN and the maturation of DCs. HMGB1 can interact with TLRs (TLR2, TLR4, and TLR9) to activate the NF-κB and IRF pathways and then produce cytokines and chemokines for the inflammation and immunity response. Of these, the structural basis for activation of the HMGB1-TLR4 pathway is well studied, and both an intra-molecular C23–C45 and a C106 amino acid of HMGB1 is required for TLR4 binding and activation (Yang et al., 2010a; Yang et al., 2012d). In addition, a lipid-bound HMGB1 may bind to CD14 and/or MD2 on the cell surface and induce signaling through TLR4 (Kim et al., 2013d). In addition to activating inflammatory responses, the interaction between HMGB1 and TLR4 mediates anti-cancer immunity during radio- or chemotherapy (Apetoh et al., 2007). Knockout of TLR4 *in vitro* or *in vivo* decreases HMGB1-induced tissue injury (Laird et al., 2014; Yang et al., 2013e; Ye et al., 2013a), cell migration and adhesion (Bauer et al., 2013) (Furlani et al., 2012; Wang et al., 2013m), angiogenesis (Lin et al., 2011), and the inflammation (Lv et al., 2009; Tadie et al., 2012b; Zong et al., 2013) and immunity responses (Apetoh et al., 2007). In addition to TLR4, TLR2 is required for tissue injury (Herzog et al., 2014; Kim et al., 2012h; Kruger et al., 2010; Leemans et al., 2009; Li et al., 2009), cell migration and adhesion (Furlani et al., 2012), inflammation (Park et al., 2006; Yu et al., 2006b), and self-renewal of stem cells (Conti et al., 2013). TLR9 is generally responsible for HMGB1-DNA complex-induced nucleotide immunity and RAGE can enhance this process (Bamboat et al., 2010; Hirata et al., 2013; Ivanov et al., 2007; Tian et al., 2007; Yanai et al., 2009).

5.3 Integrin

Integrins are adhesion proteins that play critical roles in leukocyte recruitment, a well-defined cascade immunological process enabling leukocytes to leave the microvasculature and migrate into inflamed tissue (Herter and Zarbock, 2013). Mac-1, also called αMβ2, ITGB2 and CD11b/CD18, is a leukocyte integrin involved in inflammatory cell recruitment and pathogen recognition by neutrophil phagocytosis. Previous studies have demonstrated that endothelial RAGE and sRAGE interact with Mac-1 on leukocytes (Chavakis et al., 2003; Pullerits et al., 2006), suggesting a potential role of Mac-1 in the regulation of HMGB1 activity. Indeed, HMGB1 not only enhances Mac-1 expression by activation of p47 NADPH oxidase and the NF-κB pathway, but also promotes subsequent interaction between Mac-1 and RAGE, which is required for HMGB1-mediated neutrophil recruitment (Gao et al., 2011a; Orlova et al., 2007). These findings suggest that HMGB1-mediated inflammatory cell recruitment is mediated by crosstalk between RAGE and Mac-1. In addition, the expression of Mac-1 in neutrophils is regulated by Rac1, a small G-protein (Hwaiz et al., 2013). Inhibition of Rac1 signaling by blocking Mac-1 expression and HMGB1 release in an

animal sepsis model (Hwaiz et al., 2013) suggests an important role for Rac1 in the regulation of neutrophil activation and recruitment. In addition to Mac-1, HMGB1 inhibits macrophage activity in efferocytosis through binding to $\alpha_V\beta_3$ integrin (Friggeri et al., 2010).

5.4 α-synuclein Filaments

Deposition of α-synuclein aggregates as filaments in Lewy bodies and Lewy neurites represent a hallmark of Parkinson's disease and dementia with Lewy bodies. HMGB1 is identified as α-synuclein filament-binding protein and its direct interaction can inhibit HMGB1-mediated autophagy, which contributes to the neurodegenerative process (Lindersson et al., 2004; Song et al., 2014).

5.5 Proteoglycans

Proteoglycans are glycosylated proteins with covalently attached, highly anionic glycosaminoglycans (Yanagishita, 1993). Different types of proteoglycans are found in the extracellular matrices of connective tissues. Heparan sulfate, a linear polysaccharide, binds multiple protein ligands (e.g., cyclophilin A, cyclophilin B, and hepatoma-derived growth factor) and regulates a wide variety of biological activities. Using heparin-sepharose chromatography, HMGB1 was originally isolated from rat liver (Bianchi, 1988), suggesting its ability to bind cell surface proteoglycans. Indeed, some proteoglycans, including heparan sulfate (Xu et al., 2011a), syndecan (Salmivirta et al., 1992), neurocan (Milev et al., 1998), and phosphacan/PPTP-ζ/β (Milev et al., 1998), are identified as HMGB1 receptors. In addition, RAGE may be required for HMGB1 binding to heparan sulfate (Xu et al., 2011a), suggesting an interaction between RAGE and proteoglycan to mediate HMGB1 activity. However the functional significance of such interaction remains largely unknown *in vivo*.

5.6 CD24

CD24, first identified as a B cell differentiation marker, is a cell surface GPI-anchored mucin-like glycoprotein expressed by a variety of hematopoietic, neuronal, and epithelial cell types (Fang et al., 2010). Accumulating evidence shows that CD24 is involved in several physiological and pathological processes such as lymphocyte maturation, tissue regeneration, neuronal development, tumor development, and tumor metastasis. A recent study demonstrated that CD24 functions as a positive PAMP regulator, but serves as an important negative DAMP regulator. Upon recognizing HMGB1, CD24 inhibits HMGB1-induced NF-κB activation and subsequent pro-inflammatory cytokine production (Chen et al., 2009). Thus, $CD24^{-/-}$ mice exhibit increased susceptibility to DAMPs but not PAMPs (Chen et al., 2009). These findings provide a receptor switch to distinguish the immune response from intracellular and extracellular danger signals. In addition, CD24 expressed in $CD103^+$ DCs is required for generation of effector $CD8^+$ T cells by presenting HMGB1 to $RAGE^+$ T cells (Kim et al., 2014).

5.7 TIM-3

TIM-3 is a member of the TIM (T-cell immunoglobulin domain and mucin domain) family. It was first identified as an immune checkpoint receptor that suppresses the activation of T_H1 cells (Monney et al., 2002) thorough binding ligand galectin-9 (Zhu et al., 2005).

TIM-3 is also expressed on other immune cells such as DCs (Anderson et al., 2007), monocytes and macrophages (Nakayama et al., 2009), and NK cells (Ndhlovu et al., 2012) to regulate inflammation, efferocytosis, and cytotoxicity, respectively (Tang and Lotze, 2012). In addition, TIM3 suppresses the activation of tumor-associated DCs in response to DNA vaccines and chemotherapy by binding to HMGB1 (Chiba et al., 2012a). As a negative receptor, TIM-3 impairs HMGB1-mediated recruitment of nucleic acids into the endosome, a key step in nucleic acid-mediated antitumor immunity (Chiba et al., 2012a). Therefore, blockade of TIM-3 by neutralizing antibody could improve therapeutic responses in combination with DNA vaccines and chemotherapy.

5.8 CXCR4

CXCR4, a member of the G protein-coupled receptors, is widely expressed by hematopoietic cells. In addition, CXCR4 is expressed lower in normal tissues, but expressed significantly higher in tumor tissues, indicating a critical role in tumor biology, including tumor proliferation and metastasis. After binding its ligands (e.g. CXCL12/SDF-1), the major function of CXCR4 is promoting cell migration and invasion by activation of downstream signaling pathways such as RAS/MAPKs, AKT/PI3K and JAK/STAT. In addition, acting as a chemokine receptor, CXCR4 acts as an HIV co-receptor for entry into T cells, which facilities T cell-mediated HIV clearance. Recent evidence demonstrates that ubiquitin and HMGB1 are also ligands of CXCR4. HMGB1 forms a heterocomplex with CXCL12 and then binds to CXCR4, but not RAGE and TLR4, to induce the recruitment of inflammatory cells to damaged tissues (Schiraldi et al., 2012). The NF-κB noncanonical pathway is required for CXCL12 production for cells to migrate toward HMGB1 (Kew et al., 2012), whereas the NF-κB canonical pathway is required for RAGE expression for cells to migrate toward HMGB1 (Penzo et al., 2010). These findings indicate that HMGB1-mediated cell migration is regulated by the NF-κB pathway and binding partner.

5.9 NMDAR

N-Methyl-D-aspartate receptor (NMDAR), a member of post-synaptic ionotropic glutamate receptors (iGluRs), is a heteromeric ligand-gated calcium ion channel mainly in the central nervous system. NMDAR mediates glutamate-induced calcium influx and sustains synaptic plasticity and neural excitatory. In contrast, excessive opening of NMDARs results in calcium overload and ultimately neuron death. Interestingly, NMDAR activation also causes HMGB1 cytoplasmic translocation and release. Cytosolic HMGB1 can bind to Beclin-1 to limit death by upregulated autophagy (Perez-Carrion and Cena, 2013), whereas extracellular HMGB1 plays both negative and positive roles in the regulation of neuronal cell death (Kim et al., 2010a; Kim et al., 2012c; Kim et al., 2006; Kim et al., 2012d; Kim et al., 2011b). A recent coimmunoprecipitation study demonstrated that HMGB1 physiologically interacts with GluN1 and GluN2B subunits of NMDAR via a specific region of HMGB1 localized in the B box upstream from the RAGE and downstream from the TLR4 binding sites (Pedrazzi et al., 2012). This interaction between HMGB1 and NMDAR on synaptosomes and cells of neuronal and non-neuronal origin promotes calcium influx and NO synthesis, which results in neuroblastoma cell motility and neurite outgrowth (Pedrazzi et al., 2012). Other studies indicate that activation of TLR4, but not RAGE, is required for the functional interaction between HMGB1 and NMDAR in neuronal cells (Balosso et al., 2014; Maroso et al., 2010).

HMGB1 only in its disulfide form binds TLR4 to enhance neuronal calcium influx, which facilitates neuronal hyper excitability in seizures (Balosso et al., 2014; Maroso et al., 2010).

5.10 TREM1

The triggering receptor expressed on myeloid cells-1 (TREM-1) is a member of the immunoglobulin superfamily including three domains: extracellular domain (194aa), a membrane-spanning domain (29aa), and a short cytoplasmic tail (5 aa). The extracellular Ig-like domain contains the motif DxGxYxC, which corresponds to the V-type Ig-domain. The cytosolic domain of TREM-1 associates with the adaptor DAP12 that is required for intracellular signaling transduction. Soluble TREM-1 (sTREM-1) is created by cleavage of extracellular domain, namely TREM-1 shedding. TREM-1 mediates the inflammatory response initiated by TLRs in neutrophils, monocytes, and macrophages (Bouchon et al., 2001). Recent studies indicate that HMGB1 is a ligand of TREM1. Upon binding to TREM1, HMGB1 promotes cytokine production via the NF-κB pathway (El Mezayen et al., 2007), which plays a critical role in sepsis (Bouchon et al., 2001; El Mezayen et al., 2007) and tumor growth (Wu et al., 2012b).

6. HMGB1 Transcriptional Regulation (Figure 8)

6.1 CTF2

The CCAAT-binding transcription factor (CTF)/nuclear factor I (NF-I) group of site-specific DNA-binding proteins that recognize the sequence TTGGC (N_5)-GCCAA and are required for both viral DNA replication and various cellular gene expressions (Gronostajski, 2000). Human HMGB1 promoter is regulated by a silencer and an enhancer-containing intron (Lum and Lee, 2001). The sequence of HMGB1 promoter is TATA-less but contains three different CCAAT boxes (Nagatani et al., 2001). HMGB1 levels correlate with the anticancer activity of cisplatin. CTF2, one of the splice variants of CTF/NF-I, is overexpressed in cisplatin-resistant cells (KB-CP20) and is responsible for HMGB1 transactivation and DNA replication following cisplatin treatment (Nagatani et al., 2001).

6.2 p53/p73

The tumor suppressor p53 and its homologue p73 play opposite roles in the regulation of HMGB1 promoter activities by their physical interaction with CTF/NF-I. p53 binding to CTF2 downregulates the activity of the HMGB1 gene promoter, whereas p73a binding to CTF2 upregulates the HMGB1 gene promoter (Uramoto et al., 2003). In contrast, CTF2 has an opposite role in the regulation of p53/p73-dependent activation of the p21 promoter. CTF2 binding to p53 upregulates the p21 gene promoter, whereas CTF2 binding to p73 downregulates the p21 gene promoter (Uramoto et al., 2003). These findings suggest that interaction between same transcriptional factors play different roles in the regulation of different genes.

6.3 KLF4

KLF4, a member of the erythroid Kruppel-like factor (EKLF) multigene family, is widely expressed in a number of cells and tissues. KLF4 plays a critical role in proliferation, differentiation, development, inflammation, and cell death. KLF4 clearly acts as both a

repressor and activator of gene transcription depending on target genes and cofactors. KLF4 can induce HMGB1 expression in activated macrophages by binding to the KLF4-binding element in the promoter of HMGB1 (Liu et al., 2008b). Overexpression of KLF4 increases HMGB1 expression and release, whereas suppression of KLF decreases HMGB1 expression and release in macrophages following treatment with LPS (Liu et al., 2008b).

6.4 C-myc

c-Myc, a member of the transforming Myc oncoprotein family, is overexpressed in many human cancers. c-Myc regulates a number of genes that are involved in the regulation of cell cycle, protein synthesis, cell adhesion, metabolism, cell death, and genomic integrity. Although c-Myc is a proto-oncogene and stimulates proliferation, downregulation of c-Myc promotes cancer cell survival under oxygen- and glucose-deprived conditions (Okuyama et al., 2010). This process occurs partly through deregulated intracellular levels of ATP and HMGB1 (Okuyama et al., 2010), suggesting c-myc acts as a positive regulator for HMGB1 expression.

6.5 C/EBP

CCAAT-enhancer-binding proteins (C/EBPs) are a family of transcription factors that are characterized by a leucine zipper motif that mediates dimerization and a basic DNA binding domain. The viral Tax protein encoded from human T-cell leukemia virus type-I (HTLV-1) is considered to play a central role in the process leading to adult T-cell leukemia. Tax acts as a transcriptional activator by associating with specific DNA-bound protein and transcript factors. A recent study indicated that Tax can interact with C/EBPs in HMGB1 promoter and promote subsequent HMGB1 expression in CD4+ T-cells (Zhang et al., 2013b). These findings suggest that HMGB1 may be involved in HTLV-1-mediated adult T-cell leukemia.

6.6 STAT3

Signal transducer and activator of transcription 3 (STAT3) is a transcription factor which was first described as a DNA-binding activity from IL-6-stimulated hepatocytes. In addition to IL-6, Stat3 is also activated by multiple stimuli such as growth factors, cytokines, oncogenes, hypoxia, and oxidative stress. Human HMGB1 promoter has a STAT3 binding site that has located 872 base pairs from the transcription start site. Importantly, inhibition of STAT3 expression decreases HMGB1 upregulation during excessive mechanical stress in lung microvascular endothelial cells (Wolfson et al., 2013).

6.7 ErbB3

ErbB3, also called Her3, is a member of the ErbB receptor protein tyrosine kinase family that includes ErbB1 (EGFR), ErbB2 (Her2), ErbB3, and ErbB4. ErbB3 lacks tyrosine kinase activity, whereas ErbB2 is a ligand-less receptor. However, some ligands (e.g., neuregulin-1) can activate the ErbB3 pathway by inducing ErbB2/ErbB3 heterodimer formation. A recent study indicated that nuclear ErbB3 in Schwann cells significantly inhibits the transcriptional activity of HMGB1 promoters in response to neuregulin-1 (Adilakshmi et al., 2011).

6.8 HSF1

HSF1, a member of the heat shock factors (HSF), is activated under various stressors (e.g. hypoxia and high temperature) and subsequently induces up-regulation of heat shock genes (e.g., Hsp72) through binding to heat shock sequence elements (HSE) in promoters. Previous studies have demonstrated that HSP72 inhibits HMGB1 release in activated macrophages by direct protein-protein interaction in the nucleus. A recent study indicated that HSF1 overexpression inhibits the expression of HMGB1 and H_2O_2-induced cardiomyocyte death (Yu et al., 2012b). These findings suggest that HSF1 acts as a negative regulator of HMGB1 expression.

6.9 NAC1

Nucleus accumbens-1 (NAC1) is a transcription repressor that belongs to the BTB/POZ gene family. Knockdown of NAC1 inhibits cisplatin-induced HMGB1 expression, translocation, and release in ovarian cancer cells, which will limit autophagy and increase apoptosis (Zhang et al., 2012d; Zhang et al., 2011e).

6.10 microRNA

Several microRNAs (miR34A, miR218, miR181, and miR1192) are identified to function as negative regulators of HMGB1 gene expression by directly targeting its 3'-untranslated region. miR34A inhibits HMGB1 expression in retinoblastoma cells and leads to a decrease in autophagy under starvation conditions or chemotherapy treatment (Liu et al., 2014a). miR218 inhibits HMGB1 expression in lung cancer cells and leads to a decrease in cell migration and invasion (Zhang et al., 2013a). miR181b/c inhibits HMGB1 expression in astrocytes and leads to a decrease in the inflammatory response (Hutchison et al., 2013). miR181a inhibits HMGB1 expression in T- and B-Acute Lymphoblastic Leukemia (ALL) cells and leads to a decrease in cell proliferation and metabolic activity (Dahlhaus et al., 2013). miR-1192 inhibits HMGB1 expression in muscle cells and leads to a decrease in myogenesis, which is regulated by RNA-binding protein HuR (Dormoy-Raclet et al., 2013).

6.11 Other

$CCR2^{-/-}$ mice are protected against sepsis partly through downregulation of ERK-dependent HMGB1 expression (Alves et al., 2013). $CXCR3^{-/-}$, but not $CCR1^{-/-}$, $CCR5^{-/-}$ mice and NK cell-depleted mice display severe liver damage after CCl4 injection partly through increased HMGB1 expression in the liver (Zaldivar et al., 2012); $HO1^{-/-}$ mice show increased mortality in sepsis partly through increased HMGB1 expression in response to LPS or IL-1β (Garcia-Arnandis et al., 2010a; Takamiya et al., 2009); $PI3K\gamma^{-/-}$ mice ameliorated the LPS-induced decrease in myocardial contractility and HMGB1 mycocardial expression (Xu et al., 2010); Single-Ig-interleukin-1 related receptor $(SIGIRR)^{-/-}$ mice show cognitive deficiencies and hippocampal dysfunction with enhanced expression of HMGB1 (Costello et al., 2011); Metalloproteinase $Zmpste24^{-/-}$ mice exhibit lipodystrophy with upregulated HMGB1 expression (Peinado et al., 2011).

7 HMGB1 Post-translational Modification

HMGB1 can undergo several post-translational modifications including acetylation ADP-ribosylation, methylation, phosphorylation, glycosylation, and oxidation as shown by studies with HPLC, gel electrophoresis, ion-exchange chromatography, and isoelectric focusing. These modifications and regulations are critical for HMGB1 localizations and functions (Figure 9A).

7.1 Acetylation

HMGB1 acetylation at Lys2 and Lys11 has been known for about 35 years (Sterner et al., 1979; Sterner et al., 1978), studies on the properties of HMGB1 acetylation started much later (Wong et al., 1991). *In vivo* acetylation of HMGB-1 at Lys 2 by histone acetyltransferases CBP (CREB-binding protein), but not PCAF, and Tip60 significantly enhanced its affinity to distort DNA structures (e.g., UV damaged- and cisplatinated DNA and with synthetic four-way junctions) (Pasheva et al., 2004; Ugrinova et al., 2001). In addition, removal of the highly charged C-terminal tail creates an additional acetylation site of HMGB1 at Lys81 *in vitro* by CBP, which has no effect on DNA binding affinity but increases DNA bending activity (Pasheva et al., 2004), suggesting that Lys-81 is critical for the DNA bending ability of truncated HMGB1 (Elenkov et al., 2011). There is a direct interaction between the acetylation and phosphorylation of HMGB1 lacking the C terminus *in vitro*. Phosphorylation by PKC prior to acetylation inhibits CBP activity, whereas acetylation by CBP has a stronger effect on the subsequent phosphorylation than the PKC modification (Pelovsky et al., 2009). Acetylated HMGB1 in cancer cells is tetrameric and interacts with homologous DNA polymerase alpha, which is involved in DNA replication (Alexandrova and Beltchev, 1987, 1988; Dimov et al., 1990). In addition to serving as a fine modulator of its “architectural” abilities, HMGB1 acetylation limits nuclear import of HMGB1 and mediates HMGB1 release in response to several stimuli such as LPS (El Gazzar, 2007), IFN (Lu et al., 2014), sodium butyrate (Carneiro et al., 2009) and I/R injury (Dhupar et al., 2011). Upregulation of pyruvate kinase M2 (PKM2) expression enables a metabolic switch to aerobic glycolysis, leading to excessive production of lactate. By inhibiting histone deacetylases activity, lactate in turn increases HMGB1 hyperacetylation, cytoplasmic translocation and release in systemic inflammatory response syndrome (Yang et al., 2014b).

7.2 ADP-ribosylation

ADP-ribosylation is the process of adding one or more ADP-ribose moieties to a protein by ADP-ribosyl transferases. ADP-ribosylation reactions can be divided into four groups: mono-ADP-ribosylation, poly-ADP-ribosylation, ADP-ribose cyclization, and formation of O-acetyl-ADP-ribose (Hassa et al., 2006). HMGB1 is a target of mono-ADP-ribosylation in intact cultured cells with or without DNA damage (Tanuma and Johnson, 1983; Tanuma et al., 1985a, 1986; Tanuma et al., 1985b). ADP-ribosylated HMGB1 does not change during aging, but increases in cancer cells (Alexandrova and Beltchev, 1987; Thakur and Prasad, 1990). Since ADP-ribosylation is generally inversely related to transcription, hyper ADP-ribosylation of HMGB1 downregulates gene transcription. In addition to mono-ADP-ribosylation, PARP1-mediated poly-ADP-ribosylation reactions are required for the nuclear

export and release of HMGB1 during cell death, especially necrosis (Ditsworth et al., 2007; Zong et al., 2004). After release, hyper poly (ADP-ribosyl)ated HMGB1 enhances inhibition of efferocytosis by binding to PS and RAGE (Davis et al., 2012a). Lack of intracellular HMGB1 leads to excessive PARP1 activation and injury (Huang et al., 2013a). These findings suggest cross talk between HMGB1 and PARP1 in ADP-ribosylation reaction to regulate cell death.

7.3 Methylation

HMGB1 in neutrophils is mono-methylated at Lys42 during end differentiation from myelocytic cells. The DNA binding activity of methylated HMGB1 is significantly decreased by altering the conformation of box A. This change will cause HMGB1 to translocate from the nucleus to the cytoplasm in neutrophils (Ito et al., 2007a). In clear cell renal cell carcinoma, HMGB1 is mono-methylated at Lys112, which also contributes to HMGB1 relocation to the cytoplasm (Wu et al., 2013a). Thus, HMGB1 is a target for methylating agents in chromatin (Boffa and Bolognesi, 1985).

7.4 Phosphorylation

Phosphorylation of HMGB1 is mediated by several kinases such as PKC, casein kinase I (CK-I), CKII, and cyclin-dependent kinase 5 (Cdk5) in insect, chironomus, and vertebrates (Alami-Ouahabi et al., 1996; de Abreu da Silva et al., 2011; Kang et al., 2009; Kimura et al., 1985; Oh et al., 2009; Okano et al., 2001; Palvimo et al., 1987; Ugrinova et al., 2011; Ugrinova et al., 2012; Wisniewski et al., 1994; Wisniewski et al., 1999). *In vitro*, HMGB1 extracted from livers of young, but not old rats, is more sensitive to spermine and sodium butyrate-induced phosoporation (Prasad and Thakur, 1990b). Phosphorylated HMGB1 affects both its DNA binding/bending affinity and nucleocytoplasmic distribution and release (Alami-Ouahabi et al., 1996; Kang et al., 2009; Oh et al., 2009; Youn and Shin, 2006). PKC-phosphorylated HMGB1 increases DNA binding activity to cis-platinated DNA (Ugrinova et al., 2012) as well as HMGB1 release in cancer and by immune cells (Lee et al., 2012a). Cdk5-mediated HMGB1 phosphorylation regulates DNA end-joining activity, but not its ability to recognize distorted DNA structures (Ugrinova et al., 2011). Multiple HMGB1 serine residues (35, 39, 42, 46, 53, and 181) are phosphorylated within both NLSs in macrophages following TNF-α and OA treatments (Youn and Shin, 2006). Phosphorylated HMGB1 decreases its binding to nuclear import protein KAP-α1, which in turn promotes HMGB1 cytoplasmic relocation and its eventual secretion (Youn and Shin, 2006). This process is Ca^{2+} and PDK1- dependent (Oh et al., 2009). PDK1 is the downstream target of PI3K and regulates many PKC isoenzyme activities.

7.5 Glycosylation

HMGB1 is also able to undergo glycosylation, although the amount is insignificant and the function is unclear (Chao et al., 1994).

7.6 Oxidation

Increasing evidence indicates that changes in HMGB1 location and function largely depends on redox states (Tang et al., 2011e). Human HMGB1 contains three cysteines (C23, C45,

and C106). Cys23/Cys45 in Box A can rapidly form an intramolecular disulfide bond; the cellular glutathione system alone is not enough to keep HMGB1 completely reduced within the cell (Sahu et al., 2008). C106 in Box B is required for HMGB1 nuclear location because C106 mutation, but not C23 and C45 mutations, promotes HMGB1 translocation from the nucleus to the cytosol. The native state of HMGB1 is rapidly lost via oxidation of sulfhydryl groups during storage (Kohlstaedt et al., 1986). Compared with oxidized HMGB1, reduced HMGB1 exhibits a stronger affinity for distorted DNA structures (Park and Lippard, 2011). Indeed, ROS significantly promote HMGB1 translocation and release in activated immune cells or injured cells (Tang et al., 2011e; Tang et al., 2007e). These findings suggest that ROS is a major signal that decreases nuclear HMGB1 DNA binding activation, which in turn promotes cytoplasmic translocation and release. In addition to location and release, the redox status of HMGB1 directly influences its extracellular activity, including immunity and autophagy (Venereau et al., 2012). The first research finding on HMGB1 redox and immunity was that oxidized HMGB1 released from apoptotic cell leads to DC immune tolerance (Kazama et al., 2008). However, this process can be reversed if HMGB1 is cleaved by caspase 1 and then binds to RAGE (Leblanc et al., 2014). Later, reduced HMGB1, but not oxidized HMGB1, promotes autophagy and cell proliferation by binding to RAGE in cancer cells (Tang et al., 2010a). Recent reports from several laboratories indicate that fully-reduced HMGB1 (also called all-cysteine-reduced HMGB1) acts as a chemokine by forming a heterocomplex with CXCL12 to bind CXCR4; disulfide HMGB1 with a disulfide bond connecting C23 and C45 acts as a proinflammatory cytokine by binding to TLR4 or NDMAR; sulfonyl HMGB1 (also called oxidized HMGB1) has no activity in cell migration or cytokine induction (Figure 9B) (Balosso et al., 2014; Liu et al., 2012a; Schiraldi et al., 2012; Venereau et al., 2012; Yang et al., 2010a). However, other reports indicate that oxidized HMGB1 still has the ability to activate neutrophils, vascular inflammation, and age-associated inflammation (Davalos et al., 2013; Maugeri et al., 2014). The different HMGB1 redox forms can be identified in serum, saliva, and cell culture medium by mass spectrometry (Balosso et al., 2014; Liu et al., 2012a; Schiraldi et al., 2012; Venereau et al., 2012; Yang et al., 2010a) and nuclear magnetic resonance (NMR) spectroscopy (Zandarashvili et al., 2013), although currently there is no convenient method. A systematic nomenclature for the redox states of HMGB1 and other HMGB proteins has been proposed by Marco E. Bianchi and colleagues (Antoine et al., 2014).

8 HMGB1 Cleavage and Degradation

Thrombin-thrombomodulin complexes, chlamydial-protease-like activity factor (CPAF), dipeptidyl peptidase IV, autophagic pathway, and caspase 1 have been identified as being involved in HMGB1 proteolytic cleavage and/or degradation under some conditions such as DIC (Ito et al., 2008) and infection with *C. trachomatis* (Yu et al., 2010) (Figure 10).

8.1 Thrombomodulin

Thrombomodulin (TM) (also called CD141 or BDCA-3) is an integral membrane protein expressed on the surface of endothelial cells and composed of three domains: an N-terminal lectin-like domain, followed by an EGF-like domain consisting of six EGF-like repeats, and an O-glycosylation–rich domain. The major function of TM is as a cofactor for thrombin.

An early study demonstrated that TM can bind HMGB1 thorough N-terminal lectin-like domain, which in turn prevents interaction between HMGB1 and RAGE during the inflammatory response (Abeyama et al., 2005). A recent study indicated that thrombin can directly cleave HMGB1 at the Arg10-Gly11 bond, and TM enhanced thrombin-mediated cleavage of HMGB1 to a less pro-inflammatory form (Ito et al., 2008). This cleaved HMGB1 form can be detected in serum from septic patients and animal models (Ito et al., 2008), suggesting that serum HMGB1 levels in patients in fact reflect active and inactive forms (Urbonaviciute et al., 2007). In addition, other thrombosis regulators such as activated protein C (Bae and Rezaie, 2011) and heparin (Wake et al., 2009a) have different roles in the regulation of HMGB1 degradation. Activated protein C promotes degradation of HMGB1 and other nDAMPs such as histone (Bae and Rezaie, 2011; Xu et al., 2009), whereas heparin inhibits the degradation of HMGB1 by plasmin (Wake et al., 2009a).

8.2 CPAF

During infection of epithelial cells, the obligate intracellular pathogen *Chlamydia trachomatis* secretes the serine protease Chlamydia protease-like activity factor (CPAF) into the host cytosol to regulate a range of host cellular processes through targeted proteolysis. A recent study indicated that CPAF mediated the cleavage and degradation of both HMGB1 and PARP-1 in *C. trachomatis*-infected HeLa cells (Yu et al., 2010). In contrast, lactacystin, an inhibitor of the 26S proteasome, can decrease CPAF activity and prevent HMGB1 degradation (Yu et al., 2010). These findings suggest that HMGB1 degradation contributes to immune tolerance during pathogen infection.

8.3 Autophagy

Autophagy plays a central role in the regulation of the cellular traffic, secretion, and degradation of HMGB1 in response to various stressors. Use of natural products including Chinese herbs is a novel way to inhibit HMGB1 release during sepsis; potential mechanisms of action are involved in promoting autophagy-mediated HMGB1 degradation. For example, Tanshinone IIA sodium sulfonate, a famous Chinese medicine which has been used in the treatment of cardiovascular disorders, induces clathrin- or caveolin-dependent endocytosis of exogenous HMGB1 and subsequently, autophagy-dependent degradation in macrophages (Zhang et al., 2012e). Green tea and its major constituent epigallocatechin gallate inhibit HMGB1 release in macrophages by stimulating its autophagic degradation (Li et al., 2011e).

8.4 DPP4

Dipeptidyl peptidase-4 (DPP4) (also called ADCP2 and CD26), a type II transmembrane glycoprotein, is a serine exopeptidase belonging to the S9B protein family that cleaves X-proline dipeptides from the N-terminus of polypeptides, such as chemokines, neuropeptides, and peptide hormones (Matteucci and Giampietro, 2009). A recent study indicated that HMGB1 is cleaved at its N-terminal region by DPP4, which in turn diminishes HMGB1's angiogenic activity *in vitro* and *in vivo* (Marchetti et al., 2012). In contrast, diprotin A, a DPP-IV inhibitor, prevented HMGB1 degradation. The N-terminal truncated form of HMGB1 is detected in the serum of type 2 diabetic patients, which may affect diabetes-associated vascular complications.

8.5 Caspase-1

HMGB1 released from necrotic cells is immunogenic, whereas that released from apoptotic cells is tolerogenic. A recent study indicated that caspaspe1-mediated HMGB1 cleavage reversed apoptosis-induced tolerance through binding to RAGE in DCs (Leblanc et al., 2014). HMGB1 can be specifically processed to create an active A-box peptide by caspase-1, but not other caspases (-2, -3, -5, -7, -9 or -11) (Leblanc et al., 2014). These findings provide a new mechanism by which to regulate immune tolerance by HMGB1 cleavage and receptor recognition.

9 Regulation of Extracellular HMGB1 Activity

Extracellular HMGB1 plays multiple roles in the pathogenesis of human disease. The extracellular actions of HMGB1 depend on its forms (e.g., reduced or oxidized, dimer or multimer, full length or cleaved, single or partner), concentrations (e.g., high dose or low dose), receptor types (e.g., positive receptor or negative receptor) and downstream signaling (e.g., NK-κB, IRF, and STAT). Of note, ultra-pure HMGB1 (free from contaminating bacterial proteins and nucleic acids) at a low dose fails to trigger the inflammatory response. In contrast, HMGB1 is very “sticky” and can bind to various PAMPs (e.g., LPS), DAMPs (e.g., DNA), and other molecules (e.g., cytokines, chemokine and IgG) to regulate inflammatory and immune responses (Table 3) (Urbonaviciute et al., 2007). In many disease conditions, the oxidizing nature of the extracellular environment differs from the intracellular compartment’s highly reducing nature. In addition, normal and disease tissue (e.g., cancer) microenvironments also have a number of significantly different, even opposite properties regarding level of pH, O_2, electrolytes, and glucose. These factors will determine HMGB1 activity and make HMGB1 biology extremely complex.

10 Anti-inflammatory and Anti-injury Activity of Intracellular HMGB1

It is clear that extracellular HMGB1 is generally a mediator of sterile inflammation and infection. Inhibition of HMGB1 release and activity has been demonstrated to prevent several inflammatory diseases such as sepsis and reperfusion injury. However, intracellular HMGB1 may function as an anti-inflammatory and anti-injury protein in these diseases, based on recent studies with HMGB1 conditional knockout mice. For example, conditional knockout of HMGB1 in the pancreas, liver, and myeloid cells decreases protection against experimental pancreatitis, liver ischemic reperfusion, and sepsis, respectively (Figure 11) (Huang et al., 2013a; Kang et al., 2013b; Yanai et al., 2013). The mechanism is involved in intracellular HMGB1-mediated nuclear hemostasis and autophagy. Loss of HMGB1 increases nuclear injury-mediated nucleosome release (Huang et al., 2013a; Kang et al., 2013b). In addition, loss of HMGB1 causes autophagy deficiency, which will increase oxidative stress and subsequent inflammasome signaling pathway activity, including proinflammatory IL-1β rerelease (Yanai et al., 2013). Nucleosome release from local tissue with HMGB1 deficiency will activate and recruit immune cells (e.g., macrophages and neutrophils) to increase systemic serum HMGB1 levels (Kang et al., 2013b). These findings provide a novel mechanism to explain why local injury causes systemic inflammation. Overexpression of HMGB1 in cardiac tissue by transgenic knockin methods significantly

increases animal survival and protects mice against myocardial infarction by enhancing angiogenesis and cardiac function (Kitahara et al., 2008).

11 HMGB1 and Cell Death (Figure 12)

11.1 Necrosis

The term “necrosis” was first used by morphologists to describe irreversible tissue damage in pathological circumstances lacking the morphological characteristics of apoptosis or autophagy (Zong and Thompson, 2006). Necrosis is not only accidental, but is also a specific form of programmed cell death, namely necroptosis (Galluzzi et al., 2012). Necroptosis refers to death-receptor-initiated cell death under conditions where cells lack the capacity to activate caspase-8. In response to TNFa, kinase receptor-interacting protein 1 (RIP1)/RIP3 form “necrosomes” to initiate necroptosis, which can be inhibited by necrostatin 1 (Degterev et al., 2008; Degterev et al., 2005; Li et al., 2012b; Vandenabeele et al., 2010). Morphologically, necrosis is characterized by cell swelling, cell rupture, and breakdown of cell organelles. The fundamental causes of necrosis include calcium overload, ROS generation, cellular energy depletion, membrane lipid injury, lysosomal destabilization, and release of lysosomal enzymes to digest liberated cellular components (Zong and Thompson, 2006). These factors can often cause HMGB1 release; therefore, HMGB1 is widely-used as a necrosis marker (Jeon et al., 2013). In addition to release from RIP3, PAPR1, and cathepsin-mediated necrotic cells (Zou et al., 2013), loss of intracellular HMGB1 also prompts necrosis in response to cytotoxic agents and inflammatory stimulus. Our unpublished data suggest that loss of HMGB1 causes necroptosis to switch to apoptosis, suggesting a potential role of HMGB1 in balancing different cell deaths.

11.2 Apoptosis

Apoptosis is activated through specific signaling pathways that result in a series of well-defined biochemical (e.g., activation of pro-apoptotic Bcl-2 family members, caspase activation, and substrate cleavages) and morphological (e.g., apoptotic bodies formation) changes. The two central apoptosis pathways include the extrinsic pathway triggered by cell death receptors (e.g., FasR, TNFR1, lymphotoxin receptor, DR3, and DR4/DR5) and the intrinsic pathway mediated by mitochondria and ER (Igney and Krammer, 2002). Although caspase activation is critical for apoptotic cell death, the caspase-independent pathway has been discovered by translocation of apoptosis-inducing factor (AIF) (Daugas et al., 2000; Susin et al., 1999) and endonuclease G (ENDOG) (Li et al., 2001) from the mitochondria to the nucleus, thereby mediating large-scale DNA fragmentation. HMGB1 not only regulates endonuclease activity, but is also a component of apoptotic body (Arends et al., 1990; Cockerill and Goodwin, 1983). Crosstalk between HMGB1 and apoptosis has been studied in many cancer cells. On one hand, HMGB1 can be released by apoptotic cancer cells at the late stage; on the other hand, extracellular oxidized HMGB1 can induce caspase-dependent apoptosis in cancer cells. Moreover, intracellular HMGB1 is generally an anti-apoptosis protein in response to several apoptotic stimuli such as ultraviolet radiation, CD95, TRAIL, Casp-8, and Bax (Brezniceanu et al., 2003). HMGB1 plays transcriptional-dependent (e.g., regulation of Bcl-2 family protein expression) and -independent roles (e.g., regulation of autophagy and p53 location) in the regulation of apoptosis. In some cases, overexpression of

HMGB1 renders cells sensitive to apoptosis, suggesting that HMGB1 plays dual roles in the regulation of apoptosis (Guerin et al., 2008). The precise molecular mechanisms for this effect remain largely unknown.

11.3 Autophagy

Autophagy is a highly-conserved process in many species. It is a lysosomal-mediated degradation pathway that includes multiple steps such as phagophore, autophagosome, and autolysosome formation and progression. This dynamic process is primarily controlled by members of the autophagy related gene (Atg) family and share regulators derived from other cell processes such as trafficking, proteasome, and cell death pathways (Yang and Klionsky, 2010b). In contrast to bulk autophagy, selective autophagy involves targeted removal of damaged organelles, cellular debris, microorganisms, and pathogens (Reggiori et al., 2012). These special targets include mitochondria (mitophagy) (Youle and Narendra, 2011), peroxisomes (pexophagy) (Dunn et al., 2005), lysosomes (lysophagy) (Hung et al., 2013), lipid droplets (lipophagy) (Singh et al., 2009), secretory granules (zymophagy) (Grasso et al., 2011), the ER (reticulophagy) (Bernales et al., 2007), nucleus (nucleophagy) (Park et al., 2009), RNA (RNautophagy) (Fujiwara et al., 2013), pathogens (xenophagy) (Levine, 2005), ribosomes (ribophagy) (Kraft et al., 2008), and aggregate-prone proteins (aggrephagy) (Overbye et al., 2007).

Autophagy plays dual roles in cell death depending on the response context. In many cases, upregulated autophagy increases the ability to resist cell death, whereas autophagy deficiency contributes to cell death (Kroemer and Levine, 2008). In contrast, autophagy mediates cell death under specific circumstances such as apoptosis deficiency (Klionsky and Emr, 2000; Yang and Klionsky, 2010a). Autophagy dysfunction plays a critical role in human health and disease. Currently, autophagy is a hot research field and is thought to be involved in multiple physiological and pathological processes including HMGB1 release, secretion, and degradation. In many cases, autophagy inhibition prevents HMGB1 release, secretion, and degradation (Dupont et al., 2011; Li et al., 2011e; Liu et al., 2011b; Tang et al., 2010a; Tang et al., 2010c; Thorburn et al., 2009; Zhan et al., 2012; Zhang et al., 2012e). Autophagy is also regulated by HMGB1 at multiple levels. For example, Nuclear HMGB1 as a transcriptional cofactor regulates the expression of heat shock protein β-1 (HSPB1) (Tang et al., 2011c), which in turn sustains dynamic intracellular trafficking during autophagy and mitophagy (Tang et al., 2011c). Cytosolic HMGB1 competes with Bcl-2 for interaction with Beclin-1 by intra-molecular disulfide bridge (C23/45) of HMGB1, which in turn promotes Beclin-1-mediated autophagosomes (Tang et al., 2010b). The interaction between HMGB1 and Beclin-1 is positively regulated by ULK1 (Huang et al., 2012a), MAPK (Tang et al., 2010b), and NAC (Cheng et al., 2013), but negatively regulated by p53 (Livesey et al., 2012a) and synuclein (Song et al., 2014). Extracellular HMGB1 in its reduced form promotes autophagy through binding to RAGE (Tang et al., 2010a), which may contribute to lactate production and glutamine metabolism for tumor growth (Luo et al., 2014). Indeed, RAGE is a positive regulator of autophagy and a negative regulator of apoptosis during chemotherapy, oxidative stress, DNA damage, and hypoxia (Kang et al., 2011d; Kang et al., 2010). HMGB1-mediated autophagy increases chemoresistance in cancer cells, including colon cancer, pancreatic cancer, osteosarcoma, leukemia, gastric

cancer, and ovarian cancer (Huang et al., 2012a; Kang et al., 2010; Liu et al., 2011c; Livesey et al., 2012b; Yang et al., 2012e; Zhan et al., 2012; Zhang et al., 2012d; Zhao et al., 2011a). In addition, HMGB1-mediated autophagy *in vitro* and/or *in vivo* prevents polyglutamine aggregates in Huntington's disease (Min et al., 2013), systemic inflammation during sepsis (Hagiwara et al., 2012; Yanai et al., 2013), N-methyl-D-aspartate-induced excitotoxicity (Perez-Carrion and Cena, 2013), hepatic ischemia-reperfusion injury (Fang et al., 2013b; Shen et al., 2013), and sustains T cell survival in myositis (Zong et al., 2014). Conditional knockdown of HMGB1 in the liver or heart cannot change baseline autophagy level and mitochondrial quality (Huebener et al., 2014).

11.4 Pyroptosis

Pyroptosis is an inflammation-associated cell death characterized by rapid plasma-membrane rupture and release of pro-inflammatory intracellular molecules that occurs primarily with macrophages. Caspase 1 is not involved in apoptosis, but plays a central role in pyroptosis. In contrast, caspases 3, 6, and 8 are important for apoptosis, but not involved in pyroptosis. Unlike apoptosis, loss of mitochondrial integrity and release of cytochrome c and the cleaved PARP and ICAD are not observed in pyroptosis. Caspase-1 is activated during pyroptosis by inflammasome, a large supramolecular complex largely composed of dimers of the adaptor protein ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain). Increasing evidence indicates that HMGB1 released during pyroptosis is regulated by classical components of inflammasome as well as the recently-identified PKR (Van Opdenbosch et al., 2014). Thus, inhibition of inflammasome activation decreases serum HMGB1 level and protects against liver ischemic injury (Kamo et al., 2013).

11.5 NETosis

NETosis is a regulated, antimicrobial cell death that occurs primarily in neutrophils, the first cells recruited to the site of infection (Remijsen et al., 2011). In 2004, Volker Brinkmann, Arturo Zychlinsky, and colleagues first reported that neutrophils release DNA-protein structures called neutrophil extracellular traps (NETs) to kill pathogens (Brinkmann et al., 2004). Indeed, pro-inflammatory stimuli (e.g., LPS, IL-8, and TNF) and infections (e.g., microorganisms and pathogens) induce NET formation, which is regulated by ROS production, the activation of NADPH oxidase, and peptidylarginine deiminase 4 (PD4)-mediated histone citrullination. Increasing evidence indicates that NETs are released in the context of cell death, called NETosis (Steinberg and Grinstein, 2007). NETs are composed of DNA, histones, granule components, and some cytoplasmic proteins, as well as HMGB1. The release of HMGB1 during NETosis is regulated by autophagy (Kambas et al., 2012; Mitroulis et al., 2011), which may be implicated in inflammatory and autoimmune diseases (Branzk and Papayannopoulos, 2013).

12 HMGB1 and Disease

12.1 Sepsis

Severe sepsis and septic shock represent major clinical problems and are the leading causes of death in patients in intensive care units worldwide (Angus and van der Poll, 2013), with

an overall mortality rate of 30% in the United States (Dombrovskiy et al., 2007). This medical problem results from an exuberant and excessive host response associated with a deleterious and non-resolving systemic inflammatory response syndrome, often caused by Gram-negative bacterial infection (Vincent et al., 2009). As the major component of Gram-negative bacteria, LPS can induce the secretion and release of multiple pro-inflammatory cytokines such as TNF-α (Tracey et al., 1987), IL-1β (Dinarello and Thompson, 1991), and HMGB1 (Wang et al., 1999). Early cytokines (e.g., TNF-α and IL-1β) peak within the first hours after infection, then circulatory levels revert to near baseline in three to four hours (Tracey and Cerami, 1993). This kinetic characteristic of "early" cytokines provides a narrow therapeutic time window for clinical intervention. In resting cells, most of the HMGB1 resides in the nucleus and functions as a DNA chaperone to regulate chromosomal structure and DNA biology (Malarkey and Churchill, 2012). When actively secreted by immune cells or passively leaked from necrotic or injured cells (Scaffidi et al., 2002; Tsung et al., 2005; Wang et al., 1999), HMGB1 functions as a DAMP to mediate innate immune responses (Lotze and Tracey, 2005). HMGB1 is one of the delayed cytokines secreted by macrophages 20 hours after activation with LPS (Wang et al., 1999). *In vivo*, HMGB1 is first detectable in the circulation eight hours after the onset of lethal endotoxemia and sepsis, subsequently increasing to plateau levels from 16 to 32 hours (Wang et al., 1999). Meanwhile, tissue HMGB1 mRNA levels are increased in various tissues (e.g., muscle, liver, and lung) during endotoxemia (Lang et al., 2003) or thermal injury-induced sepsis (Fang et al., 2002). Administration of recombinant HMGB1 to mice recapitulates the characteristic organ dysfunction of severe sepsis, including derangement of intestinal barrier function, acute lung injury, and lethal multiple organ failure (Andersson and Tracey, 2011; Wang et al., 2001). In addition, we and others have demonstrated that administration of anti-HMGB1 antibodies (Qin et al., 2006; Valdes-Ferrer et al., 2013; Wang et al., 1999; Yang et al., 2004a), inhibitors (e.g. ethyl pyruvate (Ulloa et al., 2002), nicotine (Wang et al., 2004a), stearoyl lysophosphatidylcholine (Chen et al., 2005), quercetin (Tang et al., 2009), chloroquine (Yang et al., 2013d), spermine (Zhu et al., 2009) and Chinese herbal extracts such as *Angelica sinensis* (Wang et al., 2006) and *Salvia miltiorrhiza* (Li et al., 2007b)) or endogenous hormones (e.g., insulin (Hagiwara et al., 2008b), vasoactive intestinal peptide (Chorny and Delgado, 2008), and ghrelin (Chorny et al., 2008; Wu et al., 2009)) protect mice against lethal endotoxemia and rescue mice from cecal ligation and puncture-induced lethal experimental sepsis even when the first doses are given 24 hours after the onset of sepsis. Taken together, these results suggest that HMGB1 is released in a delayed manner and functions as a late mediator of lethal sepsis and thus as a therapeutic target with a wider time window for clinical intervention (Andersson and Tracey, 2003, 2011; Huang et al., 2010; Wang et al., 2009a; Wang et al., 2004b; Wang et al., 2008a; Waterer, 2007). HMGB1 also causes endotoxin tolerance, suggesting another face for HMGB1 in immunity (Li et al., 2013d).

12.2 Ischemia Reperfusion Injury

Ischemia reperfusion (I/R) injury is a pathophysiologic process whereby hypoxic organ damage is accentuated following return of the blood supply, triggering a sterile inflammatory response. The ischemia is due to either arterial or venous occlusion. Such pathology occurs during solid organ transplantation, trauma, stroke, hypovolemic shock,

myocardial infarction, and elective liver resection. I/R injury results in leukocyte recruitment and oxidative stress at the site of injury, which in turn promote inflammatory mediator release and complement activation. These events are thought to contribute to the local tissue damage and end-organ injury during I/R in various organs. Increasing evidence suggests that HMGB1 is an important mediator of I/R injury in the liver (Kamo et al., 2013; Liu et al., 2011a; Liu et al., 2014b; Tsung et al., 2007a; Tsung et al., 2005; Watanabe et al., 2005; Yang et al., 2013e), heart (Andrassy et al., 2008; Huang et al., 2007; Kaczorowski et al., 2009a; Oozawa et al., 2008; Zhai et al., 2012), kidney (Chen et al., 2011b; Chung et al., 2008; Rabadi et al., 2012; Wu et al., 2007; Wu et al., 2010), spinal cord (Esposito et al., 2009; Gong et al., 2012; Huang et al., 2011c; Wang et al., 2009c; Zhai et al., 2012; Zhou et al., 2013b), brain (Hayakawa et al., 2008a; Huang et al., 2013b; Kim et al., 2008a; Qiu et al., 2008; Schulze et al., 2013; Tang et al., 2013a), and intestine (Hagiwara et al., 2010a; He et al., 2012a; Kojima et al., 2012b; Tetteh, 2013) and triggers a potentially injurious innate immune response (Kaczorowski et al., 2009b). HMGB1 is also a biomarker of injury in human liver and kidney transplantation (Ilmakunnas et al., 2008; Kruger et al., 2009). HMGB1 levels were increased during mice liver I/R as early as one hour after reperfusion and then increased in a time-dependent manner for up to 24 hours (Tsung et al., 2005). Inhibition of HMGB1 activity with neutralizing antibody significantly decreased liver damage following I/R (Pardo et al., 2008), whereas administration of recombinant HMGB1 worsened I/R injury (Tsung et al., 2005). The release of HMGB1 during I/R is involved in ROS and Ca2+ signaling (Tsung et al., 2007a), whereas the activity of HMGB1 is mediated by several receptors such as TLR4 (Chen et al., 2011b; Kruger et al., 2009; Tsung et al., 2005; Wu et al., 2007; Zhang et al., 2013i), TLR-9 (Bamboat et al., 2009), and RAGE (Zeng et al., 2009). Treatment with HMGB1-neutralizing antibody remarkably ameliorates hepatic, kidney, and brain infarction (Levy et al., 2007; Liu et al., 2007c; Muhammad et al., 2008; Tsung et al., 2005; Watanabe et al., 2005; Wu et al., 2007). Like ischemic preconditioning, pretreatment of mice with HMGB1 can decrease I/R injury (Du et al., 2014; Izuishi et al., 2006; Wu et al., 2013b) and promote tissue regeneration (Biscetti et al., 2011). The protection observed in mice pretreated with HMGB1 partly depends on expression of IL-1R-associated kinase-M, a negative regulator of TLR4 signaling (Izuishi et al., 2006).

12.3 Central Nervous System

12.3.1 Aging—HMGB1 was initially recognized as a heparin-binding protein abundantly expressed in rat brain neurons promoting neurite outgrowth (Rauvala and Pihlaskari, 1987). In the early phase (E14.5-E16), HMGB1 is widely expressed throughout the brain; in the late phase (E18), HMGB1 is expressed in the cortical plate and thalamic area; in the adult, HMGB1 has limited expression in the regions of neurogenesis (Guazzi et al., 2003). Total HMGB1 expression is the highest in the brains of young adults and gradually decreases during aging in the mouse brain, which is a cause for the accumulation of DNA double-strand breaks in the aged brain (Enokido et al., 2008). HMGB1 is downregulated in the neurons of the aged brain, whereas it is upregulated in astrocytes, suggesting that HMGB1 expression during aging is differentially regulated between neurons and astrocytes (Enokido et al., 2008). Once released from neuronal death, HMGB1 binds to several receptors such as RAGE, TLR-2, TLR-4, and Mac1 in microglia, which in turn accelerates neuroinflammation, injury, and further HMGB1 release (Gao et al., 2011a). In addition to

nervous system development, ischemia (e.g., stroke), and injury we discussed above, HMGB1 dysfunction plays dual roles in several neurodegenerative diseases, which are primary caused by polyglutamine (polyQ) expansions in diverse proteins (Fang et al., 2012).

12.3.2 Huntington's Disease—Huntington's disease is a progressive brain disorder caused by an expanded trinucleotide repeat (CAG)n, encoding glutamine, on chromosome 4p16.3. The aggregates formed by polyQ induce neuronal cell toxicity. Huntington's disease affects muscle coordination and leads to uncontrolled movements, psychiatric problems, and cognitive decline. The expression of HMGB1 is decreased when mutant polyQ proteins are expressed in Huntington's disease (Qi et al., 2007). In addition, downregulation of HMGB1 in the nucleus is associated with the DNA double-strand break (DDSB)-mediated neuronal damage in Huntington's disease (Qi et al., 2007). In addition to DDSB, HMGB1 is the cofactor of base excision repair by increasing activity of apurinic/apyrimidinic endonuclease (APE1) and 5´-flap endonuclease-1 (FEN1) (Goula et al., 2009; Liu et al., 2009; Prasad et al., 2007). APE1 and FEN1 can prevent the neuronal CAG repeat expansion associated with Huntington's disease. In addition, HMGB1 can direct bind to polyQ aggregates and then promote degradation by autophagy or lysosomal pathways (Min et al., 2013). These findings suggest that HMGB1 regulates somatic CAG expansion via two different mechanisms.

12.3.3 Alzheimer's Disease—Alzheimer's disease is the most common form of dementia in which the death of brain cells causes memory loss and cognitive decline. One of the pathological characteristics of Alzheimer's disease is the formation of extracellular senile plaques with global neuronal loss, which is caused by the production and deposition of the amyloid-beta peptide (Aβ) and the presence of intracellular tau protein tangles. RAGE is a receptor for Aβ in Alzheimer's disease (Yan et al., 1996). The secreted HMGB1 impairs memory by RAGE and TLR4 (Mazarati et al., 2011). In addition, the secreted HMGB1 can aggregate to neurotic plaques and then bind Aβ, which in turn inhibits the phagocytosis and degradation of Aβ by microglial cells (Takata et al., 2003; Takata et al., 2012).

12.3.4 Parkinson's Disease—Abnormal accumulation of alpha-synuclein filaments in Lewy bodies is a neuropathological hallmark of Parkinson's disease and sequestration of cellular protein into these protein aggregates may contribute to the degenerative process. The alpha-synuclein can bind to HMGB1 in Lewy bodies, but the significance remains unknown (Lindersson et al., 2004). The interaction between HMGB1 and alpha-synuclein inhibits HMGB1 cytosolic translocation and subsequent HMGB1-Beclin-1 interaction, therefore limiting autophagy (Song et al., 2014). In contrast, corynoxine B inhibits the interaction between HMGB1 and alpha-synuclein and rescues the impaired autophagy (Song et al., 2014). These findings indicate that alpha-synuclein impairs the autophagy pathway by binding to HMGB1 in Parkinson's disease.

12.3.5 Multiple Sclerosis—Multiple sclerosis, also known as disseminated sclerosis or encephalomyelitis disseminata, is a chronic inflammatory central nervous system disease involving the brain, spinal cord, and optic nerves. HMGB1 and its receptors are increased in the brains of patients with multiple sclerosis and mice with experimental autoimmune encephalomyelitis (Andersson et al., 2008). HMGB1-neutralizing antibody ameliorates

experimental autoimmune encephalomyelitis (Robinson et al., 2013; Uzawa et al., 2013b). These findings suggest a direct role of HMGB1 in the regulation of innate immune and inflammatory responses in the central nervous system (Das, 2012; Hoarau et al., 2011).

12.3.6 Amyotrophic Lateral Sclerosis—Amyotrophic lateral sclerosis is a progressive neurodegenerative disorder caused by loss of motor neurons and extensive astrogliosis and microglial activation in the motor cortex and spinal cord. HMGB1 and its receptors such as TLR2, TLR4, and RAGE are increased in reactive glia, whereas they are decreased in degenerating motor neurons in patients with amyotrophic lateral sclerosis, suggesting a possible role in the progression of inflammation and motor neuron degeneration (Casula et al., 2011; Lo Coco et al., 2007). In addition, serum HMGB1 autoantibody is increased in patients with amyotrophic lateral sclerosis compared with patients with Alzheimer's disease and Parkinson's disease (Hwang et al., 2013). These findings suggest that HMGB1 autoantibody may be a biomarker for amyotrophic lateral sclerosis (Hwang et al., 2013).

12.3.7 Neuromyelitis Optica—Neuromyelitis optica, also known as Devic’s disease, is a rare autoimmune disorder involving repeated clinical symptoms of optic neuritis or myelitis. This disease can lead to loss of vision, muscle strength, and coordination, sensory impairment, and paraplegia or even tetraplegia. Serum and cerebrospinal fluid HMGB1 levels are significantly greater in patients with neuromyelitis optica, suggesting that HMGB1 might be a diagnostic marker for neuromyelitis optica in the early stage (Uzawa et al., 2013a; Wang et al., 2013c; Wang et al., 2012a).

12.3.8 Epilepsy—Epilepsy, also known as seizure disorder, is a sudden change in behavior including loss of consciousness caused by increased electrical activity in the brain. Serum HMGB1 levels are increased in child febrile seizure patients (Choi et al., 2011). Early evidence in experimental models of seizures and in temporal lobe epilepsy indicates that HMGB1 promotes seizures in a TLR-4-dependent pathway by triggering tissue damage and the inflammatory response (Kleen and Holmes, 2010; Maroso et al., 2010). Recent studies indicate that this process requires other receptors such as IL-1 receptor, TLR2, RAGE, and NMDAR (Balosso et al., 2014; Iori et al., 2013; Maroso et al., 2011; Vezzani et al., 2011; Zurolo et al., 2011). These findings suggest that a complex receptor interaction is required for HMGB1-induced seizure.

12.3.9 Neuropathic Pain—HMGB1 is involved in pathophysiological pain from cancer (Tong et al., 2010), acute appendicitis (Albayrak et al., 2011), type 2 diabetes (Ren et al., 2012), bladder pain (Tanaka et al., 2014), and neuropathic pain (Maeda et al., 2013). Neuropathic pain is caused by nervous system injury and persistent alterations in pain sensitivity. HMGB1 is released from neurons and satellite cells after nerve injury and can enhance pain hypersensitivity via RAGE or TLR4 (Feldman et al., 2012; Kuang et al., 2012; Maeda et al., 2013). In contrast, HMGB1-neutralizing antibody inhibited pain onset in a neuropathic pain model (Otoshi et al., 2011; Shibasaki et al., 2010). A recent study indicated that Panx1 channel-mediated HMGB1 released from neurons is a mediator of migraine from spreading depression (Karatas et al., 2013). Blockade of panx-1 channels by carbenoxolone

inhibits HMGB1 release in neurons as well as macrophages, which may be involved in the PKR-signaling pathway (Karatas et al., 2013; Li et al., 2013e).

12.3.10 Meningitis—Meningitis is an acute inflammation of the protective membranes covering the brain and spinal cord. Meningitis may develop in response to a number of causes such as bacteria, viruses, physical injury, cancer, or drugs. HMGB1 in the cerebrospinal fluid sustains inflammation and brain damage in meningitis, including bacterial, aseptic, and tuberculous meningitis (Asano et al., 2011; Carrol et al., 2009; Eisenhut, 2008; Hohne et al., 2013; Tang et al., 2008a). Of them, HMGB1 levels are the highest in patients with bacterial meningitis (Tang et al., 2008a). These findings suggest that HMGB1 in the cerebrospinal fluid sustains biomarkers for neurological infection diseases.

12.4 Vascular Disease

The vascular system includes the arteries, veins, and capillaries that carry blood to and from the heart. Vascular disorders are diseases of the blood vessels. HMGB1 is implicated in vascular disorders, in particular systemic vasculitis and atherosclerosis (de Souza et al., 2012).

12.4.1 Systemic Vasculitis—Systemic vasculitis is thought to be an autoimmune disease characterized by inflammation of the blood vessel walls. Recent studies have found that serum HMGB1 levels are increased in patients with systemic vasculitis diseases such as Kawasaki syndrome (Eguchi et al., 2009; Hoshina et al., 2008), Churg-Strauss syndrome (Taira et al., 2007), Henoch-Schönlein purpura, and antineutrophil cytoplasmic antibody-associated vasculitis (Bruchfeld et al., 2011; de Souza et al., 2013a; Sato et al., 2008; Wibisono et al., 2010). Active immune cells as well as damaged cells are the sources of increased HMGB1 release in serum. These findings suggest that HMGB1 may be a biomarker for systemic vasculitis activity.

12.4.2 Atherosclerosis—Atherosclerosis is an inflammatory condition in which an artery wall thickens due to the accumulation of lipids. The pathogenesis of the atherosclerotic plaque in the vessel wall is a dynamic process that includes vascular injury, monocyte recruitment, macrophage activation, lipid deposition, platelet degranulation and aggregation, vascular smooth muscle cell migration, proliferation, and extracellular matrix synthesis (Caplice et al., 2003). In the normal human vessel wall, HMGB1 is expressed in endothelial cells, smooth muscle cells, and macrophages (Kalinina et al., 2004). In contrast, HMGB1 is overexpressed and released from several cell types in human atherosclerotic lesions including vascular smooth muscle cells, endothelial cells, foam cells, macrophages, and activated platelets (Inoue et al., 2007; Kalinina et al., 2004; Peng et al., 2006; Yao and Brownlee, 2009). Extracellular HMGB1 can stimulate vascular endothelial cells or smooth muscle cells to express and/or secrete adhesion molecules, cytokines, chemokines, plasminogen activator, vasoactive substances, lipid mediators, and matrix metalloproteinases, as well as the receptor RAGE (Fuentes et al., 2014; Jaulmes et al., 2006; Li et al., 2006b; Porto et al., 2006; Treutiger et al., 2003). In addition to unregulated HMGB1, RAGE was directly responsible for HMGB1 activity in atherosclerotic plaque formation in a transgenic mouse model of atherosclerosis (apolipoprotein E-deficient mice)

(Basta, 2008; Harja et al., 2008; Inoue et al., 2007; Kanellakis et al., 2011; Lee et al., 2013b; Liu et al., 2013c; Soro-Paavonen et al., 2008). Oxidative stress and NF-κB activation is involved in HMGB1-RAGE mediated atherosclerosis (Soro-Paavonen et al., 2008). Of note, other RAGE ligands such as S100A8/A9 and AGE also contribute to the development of atherosclerosis (Basta, 2008; Harja et al., 2008).

12.4.3 Abdominal Aortic Aneurysm—An abdominal aortic aneurysm (AAA) refers to an aortic diameter at least one and one-half times the normal diameter at the level of the renal arteries, which is approximately 2.0 cm (Aggarwal et al., 2011). HMGB1 expression is increased in the aortic wall of AAA patients. HMGB1-neutralizing antibody prevented disease progression and inflammatory cell infiltrations in a mouse AAA model (Kohno et al., 2012), indicating a pathogenic role of HMGB1 in AAA.

12.5 Heart Diseases

12.5.1 Heart Failure—Heart failure is a chronic condition with considerable morbidity and mortality that occurs when the heart's muscle becomes too damaged to adequately pump the blood through the body. Inflammation has emerged as a critical biological process contributing to nearly all aspects of cardiovascular diseases, including heart failure. HMGB1 and RAGE levels are increased in patients with heart failure (Volz et al., 2010b; Wang et al., 2011c) and serum HMGB1 is an independent predictor of death in heart failure from heart transplantation (Volz et al., 2012). The HMGB1-RAGE pathway sustains the inflammatory response in inflammatory cardiomyopathy, eventually leading to heart failure (Volz et al., 2010a). Thus, inhibition of HMGB1 activity and sustaining HMGB1 expression could prevent heart failure (Du et al., 2013; Funayama et al., 2013).

12.5.2 Myocardial Infarction—Myocardial infarction (MI), also known as heart attack, is the irreversible process of myocardial cell necrosis secondary to prolonged ischemia. HMGB1 plays dual roles in MI (Ding and Yang, 2010; Jiang and Liao, 2010; Li et al., 2006b; Volz et al., 2010b). On one hand, HMGB1 can enhance myocardial regeneration and repair by its angiogenic, vasculogenic, and stem cell self-renewal abilities (Germani et al., 2007; Limana et al., 2013; Limana et al., 2005; Rossini et al., 2008). Thus, administration of exogenous HMGB1 protein restores cardiac function and improves survival post-MI (Abarbanell et al., 2011; Kitahara et al., 2008; Takahashi et al., 2008). On the other hand, HMGB1 acts as a potent pro-inflammatory cytokine that accelerates MI and ischemic injury (Xu et al., 2011b; Zhai et al., 2012). Thus, elevated serum HMGB1 levels are associated with adverse clinical outcomes in patients with MI (Cirillo et al., 2009; Giallauria et al., 2010; Kohno et al., 2009; Sorensen et al., 2011b).

12.5.3 Acute Coronary Syndrome—Acute coronary syndrome refers to any condition brought on by sudden, reduced blood flow to the heart. Serum HMGB1 levels are higher in patients with acute coronary syndrome than in controls, suggesting that HMGB1 may be a potential and independent predictor of cardiovascular mortality in patients (Cirillo et al., 2009; Goldstein et al., 2006; Hashimoto et al., 2012; Peter and Bobik, 2012; Yamada et al., 2006).

12.5.4 Cardiac Hypertrophy—Cardiac hypertrophy is associated with many forms of heart disease, including ischemic disease, hypertensive heart disease, and valvular stenosis, and is a major risk factor for the development of heart failure and death (Funayama et al., 2013). Hypertrophic stimulation increases translocation of HMGB1 from the nucleus to the cytoplasm, which is associated with DNA damage and cardiomyocyte hypertrophy (Funayama et al., 2013). In contrast, activation of PPARα by fenofibrate inhibits HMGB1 cytoplasmic translocation and prevents cardiac hypertrophy development (Jia et al., 2014b). In addition, exogenous HMGB1 stimulates cardiac regeneration (Takahashi et al., 2008). These findings indicate that nuclear HMGB1 is a negative regulator of cardiomyocyte hypertrophy, whereas extracellular HMGB1 promotes cardiomyocyte hypertrophy.

12.6 Kidney Disease

12.6.1 Glomerulonephritis—Glomerulonephritis, also known as glomerular nephritis, is characterized by inflammation of the glomeruli, the basic filtration units of the kidney. HMGB1 is expressed in patients with glomerulonephritis (Sato et al., 2008). *In vivo*, the expression of HMGB1 and its receptors (RAGE and TLR4) are upregulated in granulomas in adenine-fed rat kidneys. Furthermore, HMGB1 increased the expression of monocyte chemoattractant protein-1 (MCP-1/CCL2) expression, which in turn recruited more macrophages to sustain HMGB1 release during granulomatous inflammation and injury (Oyama et al., 2010). These findings suggest that the HMGB1-RAGE/TLR4-MCP-1 pathway is involved in glomerulonephritis.

12.6.2 Lupus Nephritis—Lupus nephritis is kidney inflammation caused by systemic lupus erythematosus. Serum HMGB1, serum anti-HMGB1 antibodies, and urinary HMGB1 levels are increased in patients with lupus nephritis (Abdulahad et al., 2012; Abdulahad et al., 2011; Ma et al., 2012a; Zickert et al., 2012). In addition, HMGB1 expression positively correlates with MCP-1 expression, suggesting interplay between HMGB1 and MCP-1 in the pathogenesis of lupus nephritis (Pisetsky, 2012a; Zhou et al., 2011a). HMGB1 acts as a pro-inflammatory mediator by RAGE or TLR2/4 in antibody-induced kidney damage in systemic lupus erythematosus (Qing et al., 2008). In lupus-prone MRL/lpr mice, HMGB1 released by DCs participates in the autoimmunity response (Iwata et al., 2009). Thus, inhibition of HMGB1 expression and/or release can alleviate lupus nephritis in MRL/lpr mice (Gu et al., 2010). These findings suggest that HMGB1 plays an important role in lupus nephritis (D'Agati and Schmidt, 2010; Zhu et al., 2013b).

12.6.3 Diabetic Nephropathy—Diabetic nephropathy, also known as Kimmelstiel-Wilson syndrome, is the leading cause of chronic kidney disease in the world. Hyperglycemia-mediated HMGB1 release induces renal injury and tubulointerstitial inflammation through the RAGE/TLR4/TLR2 receptor and downstream NF-κB activation (Bierhaus et al., 2005; Kim et al., 2011a; Li et al., 2010a; Lin et al., 2013; Lin et al., 2012b; Penfold et al., 2010). However, serum HMGB1 levels are decreased in patients with diabetic nephropathy (Penfold et al., 2010). Further study is needed to explain this paradox finding in the future.

12.6.4 Autosomal Dominant Polycystic Kidney Disease—Autosomal dominant polycystic kidney disease is a genetic condition that causes multiple cysts to develop on the kidneys. Serum HMGB1 level is increased and correlates with oxidative stress status in autosomal dominant polycystic kidney disease (Nakamura et al., 2011a; Nakamura et al., 2012a).

12.6.5 Chronic Allograft Dysfunction—Chronic allograft dysfunction is associated with a variety of fibrosing and sclerosing changes in the allograft that cause a gradual worsening of renal function. HMGB1 promotes inflammation through the TLR4-MyD88-TRIF pathway in chronic allograft dysfunction, which leads to renal transplant loss (Wang et al., 2010e).

12.6.6 Chronic Kidney Disease—Chronic kidney disease is associated with inflammation and malnutrition that cause a loss of kidney function over time. Serum HMGB1 level is increased in patients with chronic kidney disease (Bruchfeld et al., 2008; Nakamura et al., 2009b). Through binding to TLR2 and RAGE, HMGB1 enhances the inflammatory response, immune-mediated epithelial-mesenchymal transition, and renal fibrosis in the development of chronic kidney disease (D'Agati and Schmidt, 2010; Leelahavanichkul et al., 2011; Leemans et al., 2009; Zakiyanov et al., 2013a).

12.6.7 Clear Cell Renal Cell Carcinoma—Renal cell carcinoma is the most common kidney cancer in adults. HMGB1 expression is increased in clear cell renal cell carcinoma, in which HMGB1 is methylated and translocates to the cytoplasm (Wu et al., 2013a). The HMGB1-RAGE pathway is involved in the progression of clear cell renal cell carcinoma through activation of ERK1/2 signaling (Lin et al., 2012a).

12.7 Autoimmune Disease

Autoimmune diseases arise from an abnormal immune response against healthy body tissue. HMGB1 plays a critical role in regulating innate and adaptive immune responses by itself as well as in association with other endogenous and exogenous molecules (Bianchi and Manfredi, 2007; Harris et al., 2012; Magna and Pisetsky, 2014). Dysfunction of HMGB1 has been implicated in several autoimmune diseases that may affect one or more organ or tissue types such as blood vessels, connective tissues, endocrine glands (e.g., thyroid or pancreas), joints, muscles, red blood cells, and skin (Voll et al., 2008a; Voll et al., 2008b). Here, we focus on the role of HMGB1 in arthritis, systemic lupus erythematosus, and myositis.

12.7.1 Arthritis—Rheumatoid arthritis is a chronic, systemic, inflammatory disease that triggers an autoimmune reaction, resulting in synovial hypertrophy and joint inflammation. Rheumatoid arthritis is the first confirmed autoimmune disease linking HMGB1 to immune-mediated conditions (Andersson and Erlandsson-Harris, 2004; Pisetsky et al., 2008). The expression of HMGB1 is increased at the site of joint inflammation, including the synovial tissue and synovial fluid (Hamada et al., 2008; Kokkola et al., 2002; Taniguchi et al., 2003). Serum HMGB1 level is increased in patients with rheumatoid arthritis (Pullerits et al., 2011). Importantly, injection of HMGB1 into a normal joint caused NF-κB activation, IL-1β

production, and the development of arthritis in 80% of animals in one study (Garcia-Arnandis et al., 2010b; Pullerits et al., 2003). HMGB1-triggered joint inflammation is not mediated through the TNF-α pathway (Goldstein, 2008; Pullerits et al., 2008; Sundberg et al., 2008). HMGB1 forms complexes with IL-1α, IL-1β, and LPS to enhance immune and inflammatory responses at the joint (Qin et al., 2014; Wahamaa et al., 2011). Moreover, therapeutic targeting of HMGB1 (e.g., HMGB1 neutralizing antibodies, recombinant A box, recombinant thrombomodulin, soluble RAGE, oxaliplatin, gold salts, and glucocorticoid) inhibits HMGB1 release and activity, which prevents the progression of arthritis in experimental animals (af Klint et al., 2005; Bossaller and Rothe, 2013; Goldstein et al., 2007; Hamada et al., 2008; Ostberg et al., 2010; Ostberg et al., 2008; Takahashi et al., 2013b; Yuan et al., 2008; Zetterstrom et al., 2008). These findings suggest that HMGB1 is an important target in the treatment of rheumatoid arthritis (Andersson and Harris, 2010).

12.7.2 Systemic Lupus Erythematosus—Systemic lupus erythematosus is a heterogeneous and multi-organ-involved autoimmune disease characterized by the production of a broad spectrum of autoantibodies directed to nuclear and cytoplasmic antigens. These autoantibodies can form immune complexes with other molecules, including nucleosome and HMGB1, to induce pro-inflammatory cytokine release in local tissue and whole body by RAGE and TLR9 receptors (Tian et al., 2007; Urbonaviciute et al., 2008). The expression of HMGB1 with translocation and release is increased in skin lesions in patients with systemic lupus erythematosus (Popovic et al., 2005). Ultraviolet radiation can enhance HMGB1 translocation and release, suggesting a mechanism for photosensitivity that flares disease (Barkauskaite et al., 2007). Serum HMGB1 is increased in patients with systemic lupus erythematosus and correlates with disease activity index and anti-dsDNA (Abdulahad et al., 2012; Abdulahad et al., 2011; Jiang and Pisetsky, 2008a; Ma et al., 2012a). HMGB1-nuclesome complex released from apoptotic cells can induce anti-DNA antibody production in mice, for which TLR2, MyD88, and microRNA-155 is required (Sanford et al., 2005; Urbonaviciute et al., 2008; Urbonaviciute et al., 2013; Wen et al., 2013). Interestingly, patients with systemic lupus erythematosus or other autoimmune diseases (e.g., arthritis) can create anti-HMGB1 autoantibodies (Abdulahad et al., 2011; Hayashi et al., 2009; Qing et al., 2008; Wittemann et al., 1990). Sadly, there is a clear lack of blocking the effects of HMGB1 in lupus animal models or in systemic lupus erythematosus patients (Pan et al., 2010; Pisetsky, 2010; Schaper et al., 2014).

12.7.3 Myositis—Myositis is a rare disease in which the immune system chronically inflames the body's own healthy muscle tissue. HMGB1 expression as well as HMGB1 cytoplasmic translocation and release are increased during myositis compared with control samples from healthy donors, suggesting a potential role of HMGB1 in mysitis (Ulfgren et al., 2004). Indeed, HMGB1 induced MHC-class I expression and muscle fatigue through binding to TLR4, but not RAGE (Grundtman et al., 2010; Zong et al., 2013). HMGB1-Beclin-1 complex-mediated autophagy may contribute to T cell survival in the muscles of patients with myositis (Zong et al., 2014). HMGB1 also has the ability to promote muscle fiber regeneration (De Mori et al., 2007; Vezzoli et al., 2011), suggesting a dual role of HMGB1 in the regulation of inflammatory myopathy.

12.8 AIDS

Acquired immunodeficiency syndrome (AIDS) is a disease of progressive human immune system failure caused by infection with human immunodeficiency virus (HIV) at advanced stage. Despite advances, HIV remains a major public health challenge since it was discovered in the early 1980s. Plasma HMGB1 levels are elevated and related to viral load and MD2/TLR4 in patients with HIV infection (Nowak et al., 2007; Troseid et al., 2013; Troseid et al., 2010). Intracellular HMGB1 inhibits long terminal repeat (LTR)-mediated HIV transcription (Naghavi et al., 2003), whereas extracellular HMGB1 has a dual role in the regulation of HIV transcription, depending on the stage of infection and type of cell (Cassetta et al., 2009; Nowak et al., 2006). HMGB1 can be passively released by virus-infected cells such as CD4 T (Barqasho et al., 2010), which is required for HIV-1-induced impairment of NK-DC crosstalk and subsequent viral persistence (Gougeon and Bras, 2011; Melki et al., 2010; Saidi et al., 2008). HMGB1 also forms a complex with PAMPs (e.g., LPS) to amplify inflammatory loops and increase viral replication in HIV disease (Troseid et al., 2010). These findings suggest that HMGB1 has an important role in HIV infection (Gougeon and Bras, 2011; Gougeon et al., 2012; Troseid et al., 2011).

12.9 Diabetes

Diabetes is a group of metabolic diseases associated with high blood sugar, either because of lack of insulin (Type 1), or insulin resistance (Type 2). Type 1 diabetes, also known as autoimmune or juvenile diabetes, is an autoimmune disease. Cytokine-mediated inflammatory damage is believed to contribute to the loss of β-cell mass and function during the development of autoimmune diabetes. IL-1β-induced β-cell necrosis and HMGB1 release in a nitric oxide-dependent manner may contribute to insulitis progression and diabetes onset (Han et al., 2008; Steer et al., 2006). Hyperglycemia-mediated oxidative stress promotes HMGB1 and RAGE expression (Yao and Brownlee, 2010). Loss of RAGE and TLR4 inhibits diabetes onset (Li et al., 2012c; Soro-Paavonen et al., 2008). During islet transplantation for the treatment of type 1 diabetes mellitus, the HMGB1-mediated inflammatory response can cause early islet loss through TLR2 and TLR4 (Itoh et al., 2012c; Kruger et al., 2010; Matsuoka et al., 2010; Tamura et al., 2011). In addition to type 1 diabetes, HMGB1-mediated inflammation and angiogenesis also facilitate the onset of type II diabetes (Biscetti et al., 2010; Skrha et al., 2012).

12.10 Lung Disease

12.10.1 Asthma—Asthma is a chronic obstructive lung disease characterized by chronic inflammation of the respiratory tract. Asthma is more commonly associated with Th2-mediated eosinophilic airway inflammation, although neutrophil inflammation also exists. Serum or sputum HMGB1 levels are increased in patients with asthma and are related to disease severity (Hou et al., 2011a; Shim et al., 2012; Watanabe et al., 2011; Zhou et al., 2012c). These findings suggest that HMGB1 plays a role in the pathogenesis of asthma and may be a useful marker for assessing the degree of airway obstruction.

12.10.2 Chronic Obstructive Pulmonary Disease—Chronic obstructive pulmonary disease (COPD), a leading cause of morbidity and mortality worldwide, is associated with

chronic inflammation predominantly in the small airways and lung parenchyma, which causes progressive airway obstruction (Barnes, 2013). Macrophages, neutrophils, and T lymphocytes can release cytokines, including IL-1β and HMGB1, which are responsible for sustaining inflammation and remodeling during COPD. Serum or sputum HMGB1 as well as other RAGE ligands are increased in COPD patients, suggesting that the RAGE pathway is critical in the pathophysiology of COPD (Ferhani et al., 2010; Hou et al., 2011a; Kanazawa et al., 2012; Ko et al., 2013; Pouwels et al., 2014; Sukkar et al., 2012).

12.10.3 Acute Respiratory Distress Syndrome—Acute respiratory distress syndrome, a potentially devastating form of acute inflammatory lung injury, is a major cause of morbidity and mortality in critically ill patients. HMGB1 released by dying or dead cells is a mediator of lung inflammation and acute injury (Lutz and Stetkiewicz, 2004). Injection of HMGB1 in the lung, but not HMGB2, can cause acute respiratory distress syndrome in mice (Ueno et al., 2004). In addition, serum HMGB1 level is increased and related to death in patients with acute lung injury (Nakamura et al., 2011b; Ueno et al., 2004). *In vivo*, inhibition of HMGB1 release and activity prevents acute lung injury in animal studies (Gong et al., 2008; Hagiwara et al., 2008a; Hagiwara et al., 2008b; Hagiwara et al., 2008c; Hagiwara et al., 2008d; Hagiwara et al., 2007; Kim et al., 2005; Kudo et al., 2013; Lin et al., 2005). These findings suggest that HMGB1 is a therapeutic target for acute respiratory distress syndrome.

12.10.4 Cystic Fibrosis—Cystic fibrosis is a genetic disease that causes thick, sticky mucus to form in the lungs, digestive tract, and other organs. In the lung, mucus causes progressive obstruction of the airways, lung damage, neutrophil-predominant airway inflammatory response, as well as acute pulmonary exacerbations (Gaggar et al., 2010). HMGB1 expression in the sputum contributes to the inflammatory response and lung matrix degradation in cystic fibrosis airway disease (Rowe et al., 2008) and is a potential biomarker for predicting clinical outcome and treatment response (Liou et al., 2012). Moreover, inhibition of the HMGB1-TLR4 signaling pathway prevents development of cystic fibrosis airway disease partly through enhancing phagocytic activity and bacterial clearance (Enomoto et al., 2008; Entezari et al., 2012; Griffin et al., 2013).

12.10.5 Pneumonia—Pneumonia is an inflammatory condition of the lung caused by bacteria, a virus, or fungi. Community-acquired pneumonia is pneumonia acquired infectiously from normal social contact, as opposed to being acquired during hospitalization (termed hospital-acquired pneumonia). Increased serum HMGB1 level is caused by bacteria or virus in both community-acquired and hospital-acquired pneumonia (Achouiti et al., 2013; Angus et al., 2007; Entezari et al., 2012; Ito et al., 2011; Kosai et al., 2008; Sharma et al., 2013; Tasaka et al., 2010; van Zoelen et al., 2008; Zhou et al., 2011d). Both RAGE and TLR4 play roles in the regulation of HMGB1-mediated inflammatory response during pneumonia (Achouiti et al., 2013; Entezari et al., 2012; Ramsgaard et al., 2011).

12.10.6 Lung Cancer—Lung cancer, one of the most common cancers, is a leading cause of cancer death in the world. About 85–90% of lung cancer is non-small-cell lung cancer (NSCLC). Mutations in epidermal growth factor receptor (EGFR), K-RAS, and anaplastic

lymphoma kinase (ALK) have been proposed as the initiating genetic lesions in NSCLC. Cigarette smoking is the number one risk factor for lung cancer. HMGB1 expression is increased in the lungs of patients with NSCLC and correlates with disease development, invasion, and metastasis (Liu et al., 2010a; Shen et al., 2009a; Zhang et al., 2013a; Zhang et al., 2013g). Moreover, serum HMGB1 may be a biomarker for NSCLC (Shang et al., 2009). miR-218 functions as a tumor suppressor in lung cancer partly thorough downregulation of HMGB1 expression and subsequently, metastasis (Zhang et al., 2013a). HMGB1 regulates MMP-9 expression and cellular metastatic ability in lung cancer cells thorough active PI3K-Akt and NF-κB pathways (Liu et al., 2010a).

12.11 Pancreas Disease

12.11.1 Pancreatitis—Acute pancreatitis (AP) is an inflammatory process of the pancreatic gland that exhibits a broad clinical spectrum; its severity may vary from mild and edematous to a serious, necrotizing disease with high morbidity and mortality (Whitcomb, 2006). AP is involved in a complex cascade of immunological events, including inflammatory mediator production, which affects not only the pathogenesis but also the course of the disease. Some of these inflammatory mediators are initially released by pancreatic acinar cells and result in the recruitment and activation of neutrophils, monocytes, and macrophages (Gea-Sorli and Closa, 2010; Satoh et al., 1998; Shrivastava and Bhatia, 2010; Sugita et al., 1997), which lead to further acinar cell injury. When released, these mediators gain access to the systemic circulation and play a central role in the progression of SIRS and multisystem organ failure (Hegyi et al., 2011). In patients and animals with AP, serum levels of HMGB1 are significantly elevated and positively correlate with the severity of this disease (Kocsis et al., 2009; Yasuda et al., 2007; Yasuda et al., 2006). Importantly, inhibiting the release or cytokine activity of HMGB1 (e.g., HMGB1 neutralizing antibody, ethyl pyruvate, danaparoid sodium, cisplatin, A box, antithrombin III, and pyrrolidine dithiocarbamate) confers protection against experimental AP (Cheng et al., 2007; Hagiwara et al., 2009g; Jo et al., 2013; Luan et al., 2013a; Luan et al., 2012; Luan et al., 2013b; Sawa et al., 2006; Weng et al., 2012; Yan et al., 2012a; Yang et al., 2009b; Yang et al., 2008; Yuan et al., 2009; Zhang et al., 2010). However, intracellular HMGB1 in the pancreas protects against acute pancreatitis (Kang et al., 2013b). Loss of endogenous HMGB1 within the injured pancreatic acinar cell worsens the severity of experimental AP with increased DNA damage, cell death, nDAMP release, and inflammatory response (Kang et al., 2013b). These findings suggest that HMGB1 plays dual roles in AP.

12.11.2 Pancreatic Cancer—Pancreatic cancer is a major, unsolved, public health problem in the world. It ranks as the fourth leading cause of cancer death in USA (Siegel et al., 2011), with advanced stage at diagnosis and poor response to current treatments (Hidalgo, 2010; Mazur and Siveke, 2011). Pancreatic ductal adenocarcinoma (PDAC), the most common type of pancreatic cancer, progresses from non-invasive pancreatic lesions termed pancreatic intraepithelial neoplasias (Hruban and Adsay, 2009). Mutations of the K-RAS gene occur in over 90% of pancreatic carcinomas and are proposed to be the initiating genetic lesion in PDAC (Bardeesy and DePinho, 2002; Hong et al., 2011; Maitra and Hruban, 2008; Morris et al., 2010b). In addition, PDAC commonly displays reactivation of embryonic signaling pathways in the early stage (Morris et al., 2010a; Thayer et al., 2003;

Wang et al., 2009b). Serum HMGB1 is increased in pancreatic cancer patients with or without chemotherapy (Dong Xda et al., 2007; Wittwer et al., 2013a). HMGB1 release from necrotic or inflammatory cells promotes ATP production and pancreatic cancer growth through RAGE (Kang et al., 2014). Knockdown of HMGB1 or its receptor RAGE by RNAi or antisense nucleotide inhibits pancreatic cancer cell invasion and enhances chemotherapy sensitivity partly by downregulation of autophagy (Huang et al., 2004; Kang and Tang, 2012; Kang et al., 2011d; Kang et al., 2011e; Kang et al., 2010; Tang et al., 2010e). Moreover, loss of RAGE inhibits oncogenic K-RAS driven pancreatic tumorigenesis (Kang et al., 2012b). These findings suggest that the HMGB1-RAGE pathway is an important regulator of pancreatic cancer growth and therapy.

12.12 Stomach

12.12.1 Gastritis—*Helicobacter pylori*, discovered by Barry Marshall and Robin Warren, is a Gram-negative bacterium that infects over half of the world's population (1983). *H. pylori* infection causes gastric mucosal inflammation, which is an established risk factor for the development of peptic ulcer disease and gastric cancer. *H. pylori* and its active component VacA can induce HMGB1 release in gastric epithelial cells (Radin et al., 2011). This process is regulated by PARP-1-dependent necrosis (Radin et al., 2011).

12.12.2 Gastric Mucosal Injury—Gastric mucosal injury occurs when causative agents such as gastric acid, ethanol, and drugs (e.g., nonsteroidal anti-inflammatory drugs) overwhelm the mucosal defense. Recent studies indicate that HMGB1 is an important mediator of gastric mucosal injury by activation of RAGE and the TLR4-dependent inflammatory pathway (Nadatani et al., 2013; Ye et al., 2013a; Ye et al., 2013b). Inhibition of the HMGB1signaling pathway decreases gastric mucosal injury.

12.12.3 Gastric Cancer—Gastric cancer is the second most common cause of cancer-related death in the world and is most frequently discovered in advanced stages. The mRNA and protein expression levels of HMGB1 are increased and associated with inflammatory status in gastric cancer (Akaike et al., 2007; Xiang et al., 1997). Serum HMGB1 is a potential early diagnostic marker for gastric cancer (Chung et al., 2009). In addition to HMGB1, expression of RAGE is highly related to the invasive and metastatic activity of gastric cancer by enhancing NF-κB activity (Kuniyasu et al., 2002; Oue et al., 2005; Zhang et al., 2014a; Zhang et al., 2012a). During chemotherapy, HMGB1-mediated autophagy decreases vincristine-induced apoptosis in gastric cancer partly through upregulation of Mcl-1, a Bcl-2 family member (Zhan et al., 2012). However, overexpression of HMGB1 may mark good prognosis of gastric cancer after anticancer therapy (Bao et al., 2010). These findings suggest that HMGB1 plays different roles in the different gastric cancer stages.

12.13 Intestine

12.13.1 Intestinal Inflammation Disease—Inflammatory bowel disease refers to two chronic intestinal inflammation diseases: ulcerative colitis and Crohn's disease. In the gastrointestinal tract, increased levels of HMGB1 have positively correlated with intestinal barrier dysfunction and colonic inflammation in mice (Dave et al., 2009; Liu et al., 2006; Luan et al., 2010; Maeda et al., 2007; Sappington et al., 2002; Wu et al., 2009; Yang et al.,

2009a). Moreover, fecal HMGB1 is a novel biomarker of intestinal mucosal inflammation in patients with inflammatory bowel disease (Vitali et al., 2011), whereas serum HMGB1 is diagnostic marker in patients with acute appendicitis (Albayrak et al., 2011; Soreide, 2011; Wu et al., 2012a). TLR4 and TLR2 are required for the HMGB1-mediated inflammatory response and injury in inflammatory bowel disease, as well as necrotizing enterocolitis (Dai et al., 2010; Downard et al., 2011; Lu et al., 2013b; McDonnell et al., 2011; Zamora et al., 2005).

12.13.2 Colorectal Cancer—Colorectal cancer is the second leading cause of cancer-related mortality in men and women in the United States. Gene mutations (e.g., APC, K-RAS, and p53), chromosomal instability, DNA-repair defects, and aberrant DNA methylation have been identified as molecular genetic bases of colorectal cancer. Nuclear HMGB1 may be an important regulatory factor for these molecular genetic bases (Balasubramani et al., 2006; Breikers et al., 2006; Yu et al., 2006a). HMGB1 expression is increased in patients with colorectal cancer and correlates with tumor progression and poor prognosis (Liu et al., 2008c; Wiwanitkit, 2010; Yao et al., 2010). Interestingly, anti-HMGB1 autoantibody is increased in serum from patients with colorectal cancer, although the significance of this change remains unclear (Kijanka et al., 2010). E-selectin promotes HMGB1 release in metastatic colorectal carcinoma cells, which in turn enhances E-selectin expression by endothelial cells, suggesting a novel mechanism regulating HMGB1 release and cancer metastasis. An early study indicated that extracellular HMGB1 induces macrophage apoptosis and inhibits macrophage infiltration into colon cancer, which might affect host immunity against cancer (Aychek et al., 2008; Kuniyasu et al., 2003a; Kuniyasu et al., 2004; Sasahira et al., 2005b). Recent studies indicate that phosphorylated HMGB1 released from colon cancer cells can promote tumor cell migration (Kang et al., 2009) by RAGE (Harada et al., 2007). Knockdown of HMGB1 increases chemotherapy sensitivity in clone cancer cells partly by regulating p53-mediated autophagy and apoptosis (Livesey et al., 2012c; Livesey et al., 2012d). HMGB1 released from chemotherapy (e.g., oxaliplatin)-induced cell death could increase antitumor immunity in colon cancer cells (Tesniere et al., 2010).

12.14 Liver Disease

In addition to liver I/R (Bamboat et al., 2010; Cai et al., 2013; Cardinal et al., 2009; Dhupar et al., 2011; Evankovich et al., 2010; Huang et al., 2013a; Izuishi et al., 2006; Kang et al., 2011a; Li et al., 2013a; Liu et al., 2013b; Nace et al., 2013; Ogiku et al., 2011; Oishi et al., 2012; Tsung et al., 2005; Watanabe et al., 2005; Zeng et al., 2009), transplantation (Ilmakunnas et al., 2008; Kao et al., 2008) and hepatocyte regeneration (Ogiku et al., 2011; Yang et al., 2012g; Zhou et al., 2011b) (discussed above), HMGB1 is implicated in several liver diseases (discussed below) (Chen et al., 2013c).

12.14.1 Viral Hepatitis—Viral hepatitis is inflammation of the liver caused by viruses, including hepatitis A-E. Viral hepatitis infection may eventually develop into liver cirrhosis and hepatocellular carcinoma (Albayrak et al., 2010). HMGB1 serum levels are increased in patients with chronic hepatitis B virus (HBV) and are related to the disease stage (Cheng et al., 2008). In response to HCV or HBV infection, HMGB1 translocates to the cytoplasm and

is then released into the extracellular space. Extracellular HMGB1 is an important mediator for the inflammatory and immune responses through activating a TLR4-dependent antiviral response (Jung et al., 2011; Zhou et al., 2011b). HMGB1 also inhibits regulatory T-cell activity that contributes to liver failure in chronic HBV patients (Wang et al., 2010d). These findings shed light on the pathogenesis of viral hepatitis, which is mediated by HMGB1.

12.14.2 Nonalcoholic Fatty Liver Disease—Nonalcoholic fatty liver disease (NAFLD), one of the most common causes of chronic liver disease, is an inflammation of the liver characterized by an accumulation of lipid deposits, which can result in liver damage, including steatosis, nonalcoholic steatohepatitis, fibrosis, and cirrhosis (Day and James, 1998). Extracellular HMGB1 enhances the inflammatory response and liver damage at the early stage of NAFLD. This process requires the TLR4-MyD88 signaling pathway; $TLR4^{-/-}$ and $MyD88^{-/-}$ mice showed impaired HMGB1-induced liver dysfunction after high fat treatment (Li et al., 2011d). Inhibition of HMGB1 activity by neutralizing antibody decreased production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) and protected against experimental NAFLD (Li et al., 2011d). These findings indicate that HMGB1 functions as a novel mediator linking acute damage and the inflammatory response in NAFLD.

12.14.3 Liver Fibrosis—Liver fibrosis, the final common pathway of chronic liver diseases, is characterized by the accumulation of excess extracellular matrix, including collagen (Guo and Friedman, 2007). *In vitro* evidence indicates that HMGB1 is involved in liver fibrosis through single stimulating hepatic stellate cell proliferation (Kao et al., 2008) or combining with transforming growth factor β1 to induce fibrogenic protein expression (Zhang et al., 2012f). Moreover, the TLR4-MyD88 and MAPK-NF-κB pathways are required for HMGB1-mediated liver fibrosis (Wang et al., 2013b; Zhang et al., 2012f). An *in vivo* hepatic fibrosis animal study showed that HMGB1 expression closely correlates with collagen deposition. Knockdown of HMGB1 by siRNA significantly decreases expression of α-SMA and collagen (type I and III) in hepatic stellate cells (Ge et al., 2011). These studies have demonstrated that both intracellular and extracellular HMGB1 are positive regulators for liver fibrosis (Albayrak et al., 2010).

12.14.4 Hepatocellular Carcinoma—Hepatocellular carcinoma (HCC), the fifth most common form of cancer in the world, is a typical inflammation-related carcinoma, characterized by extensive inflammation and fibrosis. Serum HMGB1 levels are increased in patients with HCC and expression of HMGB1 in the liver closely correlates with pathological grade, distant metastases, and drug resistance of liver cancer (Dong et al., 2013; Jiang et al., 2012a; Kawahara et al., 1996; Liu et al., 2012b; Xiao et al., 2014). In addition, serum HMGB1 levels were significantly higher in HCC patients with HCV or HBV infection (Cheng et al., 2008; Jiang et al., 2012a). HMGB1 released from the hypoxic tumor microenvironment can bind to TLR4 and RAGE, which in turn mediate HCC invasion and metastasis by activating inflammasome, NF-κB, and AKT pathways (Chen et al., 2014c; Cheng et al., 2014; Kostova et al., 2010; Yan et al., 2012b; Yaser et al., 2012). Interestingly, p53 may be a positive regulator for HMGB1 release in hepatocarcinogenesis (Yan et al., 2013b). Moreover, therapeutic targeting of HMGB1 (e.g., RNAi, ethyl pyruvate, and N-

acetylcysteine) inhibits HMGB1 expression, release, and activity, which in turn suppresses tumor growth in liver metastasis models of colon cancer (Cheng et al., 2014; Cheng et al., 2013; Jiang et al., 2012b; Liang et al., 2009). These findings suggest that HMGB1 plays a critical role in the pathogenesis and treatment of HCC.

12.14.5 Drug-induced Liver Injury—Drug-induced liver injury (DILI), the first cause of acute liver failure, refers to liver injury caused by drugs or chemical agents. Acetaminophen overdose is a well-known cause of DILI (Lee, 2004). A number of animal and human studies have demonstrated that serum HMGB1 is a diagnosis and severity-assessment biomarker of acute liver injury induced by acetaminophen, as well as other drugs (Antoine et al., 2013; Antoine et al., 2012a; Antoine et al., 2010; Dragomir et al., 2011; Gong et al., 2010a; Yang et al., 2012g; Zhou et al., 2011c). HMGB1 release during acetaminophen-mediated liver injury impairs the innate immune response and accelerates the inflammatory response (Scaffidi et al., 2002; Wang et al., 2007a; Wang et al., 2013m). The activity of HMGB1 after release in DILI depends on post translational modification. For example, oxidized HMGB1 diminishes the inflammatory response in mice treated with acetaminophen (Antoine et al., 2010), whereas acetylated HMGB1 is related to DILI prognosis (Antoine et al., 2012b; Antoine et al., 2009). Therapeutic targeting of HMGB1 (e.g., neutralizing antibody and ethyl pyruvate) prevents acetaminophen-induced hepatotoxicity, promotes regeneration, and restores liver function (Dragomir et al., 2011; Yang et al., 2012g).

12.15 Cancer

In 2011, Hanahan and Weinberg (Hanahan and Weinberg, 2011) updated their cancer hallmark model and outlined ten fundamental properties that drive tumor development and growth. These cancer hallmarks include: sustainment of proliferative signaling; evasion of growth suppressors; avoidance of immune destruction; enablement of replicative immortality; tumor-promoting inflammation; activation of invasion and metastasis; induction of angiogenesis; genome instability and mutation; resistance to cell death; and deregulation of cellular energetics. Over the past two decades, HMGB1 has been demonstrated as one of the major players in a number of cancers including colon, breast, lung, prostate, cervical, skin, kidney, stomach, pancreatic, liver, bone, and blood cancer (Ellerman et al., 2007; Lotze and DeMarco, 2003; Sims et al., 2010; Tang et al., 2010d). HMGB1 acts as both a tumor suppressor and an oncogenic factor in tumorigenesis and cancer therapy depending on the context and the study conditions, as well as HMGB1 location and modification (Kang et al., 2013c).

12.15.1 Oncogenic Roles in Tumorigenesis—The tumor microenvironment consists of tumor cells and nontumor cells, including several immune cells. HMGB1 can be released, including by autocrine from the tumor cells and the surrounding cells under hypoxia or other environmental stimuli (Jube et al., 2012; Tafani et al., 2011; van Beijnum et al., 2013; Yan et al., 2012b). Extracellular HMGB1 mediates communication between cells in the tumor microenvironment by several receptors (e.g., RAGE and TLR4), which contributes to tumor growth and spreads by several mechanisms including sustenance of the inflammatory microenvironment (Bald et al., 2014; Gebhardt et al., 2008; Mittal et al., 2010), fulfillment

of metabolic requirements (Kang et al., 2013a; Tang et al., 2011b), promotion of invasion and metastasis (Huttunen et al., 2002; Kuniyasu et al., 2002; Sasahira et al., 2005a; Taguchi et al., 2000), inhibition of antitumor immunity (He et al., 2012c; Kusume et al., 2009; Liu et al., 2011f), and promotion of angiogenesis (Sasahira et al., 2007; van Beijnum et al., 2012). Thus, inhibition of HMGB1 release and activity can block tumor growth and development.

12.15.2 Tumor Suppressor Roles in Tumorigenesis—Several studies indicate that intracellular HMGB1 may be a tumor suppressor. For example, nuclear HMGB1 binds to tumor suppressor RB, which leads to RB-dependent G1 arrest and apoptosis induction and prevents tumorigenicity in breast cancer cells *in vitro* and *in vivo* (Jiao et al., 2007). Nuclear HMGB1 is an important architectural factor with DNA chaperone activity. Loss of HMGB1 leads to genome instability with telomere shortening, which is major driving force in tumorigenesis (Celona et al., 2011; Giavara et al., 2005; Polanska et al., 2012). In addition, recent studies indicate that deficiencies of autophagy gene (e.g., Beclin-1, ATG5, UVRAG, Bif-1) increase tumorigenesis due to genome instability, inflammation, and organelle injury (Degenhardt et al., 2006; Mathew et al., 2007; Takahashi et al., 2013c; Zhao et al., 2012). Given that HMGB1 is a positive regulator of autophagy (Tang et al., 2010c; Tang et al., 2011b), HMGB1 deficiency leading to autophagy dysfunction may cause genome instability and inflammation, which promotes tumorigenesis. The translational potential of these findings still needs further investigation.

12.15.3 Sensitivity to Anticancer Therapy—Depending on the type of anticancer therapy, cancer cell death can be immunogenic or nonimmunogenic (Green et al., 2009; Hou et al., 2013; Krysko et al., 2012). HMGB1 can be released by dead or dying cells, which in turn mediate immunogenic cell death and subsequent anti-tumor immunity and tumor clearance by binding to TLR4 (Apetoh et al., 2007; Fucikova et al., 2011; Suzuki et al., 2012; Yamazaki et al., 2014). TLR2, but not TLR4 in DCs, mediates the T-cell-dependent antitumor immune response that induces brain tumor regression (Curtin et al., 2009). These findings suggest that HMGB1 release contributes to anticancer immunity. In contrast, HMGB1 released during cell death may mediate immunogenic tolerance if HMGB1 binds to TIM-3 or undergoes a redox change to oxidized form (Chiba et al., 2012b; Kazama et al., 2008). Furthermore, HMGB1 released during chemotherapy enhances the ability of remnant cancer cells to regrow and metastasize in a RAGE-dependent way (Luo et al., 2013). Inhibition of the HMGB1-RAGE pathway improves the effectiveness of chemotherapy (Kang et al., 2010). Collectively, many factors including receptor, death type, and redox state determine the activity of HMGB1 in the anticancer immune response.

12.15.4 Resistance to Anticancer Therapy—In addition to the important role of extracellular HMGB1 in anticancer therapy, intracellular HMGB1 is a general negative regular for the effectiveness of anticancer therapy. Several chemotherapy agents such as platinating agents can increase HMGB1 expression (Rabik and Dolan, 2007). HMGB1 is a novel therapeutic target for chemotherapy resistance. Downregulation of HMGB1 expression by RNAi increased the anticancer activity of cytotoxic agents, whereas upregulation of HMGB1 expression by gene transfection increased drug resistance (Huang et al., 2012a; Liu et al., 2011b; Livesey et al., 2012b). Increased HMGB1 expression in

cancer cells facilitates chemotherapy resistance partly through inhibition of apoptosis and promotion of autophagy, which determine cell fate in anticancer therapy (Huang et al., 2012a; Kang et al., 2010; Liu et al., 2014a; Liu et al., 2011c; Livesey et al., 2012b; Ni et al., 2013; Yang et al., 2012e; Zhan et al., 2012; Zhang et al., 2012d; Zhao et al., 2011a). Interestingly, HMGB1 differs in the regulation of chemotherapeutic agent toxicity in cancer cells and normal cells (Krynetskaia et al., 2008). The potential mechanisms for these differences need further study.

13 HMGB1-targeting Therapeutic Strategies

Currently, several strategies have been proposed from cell, animal, and human studies to inhibit HMGB1 expression, release, and activity in a direct or indirect manner. These strategies include antibodies, peptide, RNAi, anti-coagulant agents, endogenous hormones, chemicals including natural product, HMGB1-receptor and signaling pathway inhibition, artificial DNAs, physical methods (e.g., medical hydrogen gas), vagus nerve stimulation, and surgery. The details of these strategies and associated experimental models are listed in Table 4.

14 HMGB1 Measurements and Significance in Clinical Practice

Biomarkers are characteristics that are objectively measured and evaluated as indicators of normal biological processes, pathogenic processes, or pharmacologic responses to therapeutic intervention (Atkinson et al., 2001). A number of studies have indicated that the level of HMGB1 in samples (e.g., serum, plasma, cerebrospinal fluid, sputum, urine, fecal, and tissue) may be a biomarker of human disease which can be used for detection and diagnosis of disease, prediction of response to therapeutic interventions, and prognosis of outcome. Interestingly, circulating HMGB1 levels have been positively or inversely associated with sRAGE levels, suggesting that sRAGE not only regulates HMGB1 activity, but also eliminates circulating HMGB1 in human disease (Fukami et al., 2009). Currently, ELISA and Western blot have been used to detect HMGB1 in serum, plasma, and body fluid. Of note, HMGB1 levels in serum or plasma may be five times higher when analyzed by Western blot compared to ELISA because serum and plasma components (e.g., immunoglobulins, phospholipids, thrombomodulin, and proteoglycans) can interfere with the detection of HMGB1 by ELISA (Urbonaviciute et al., 2007). In contrast, perchloric acid-modified ELISA can detect masked forms of HMGB1 (Barnay-Verdier et al., 2011). However, currently, the only commercially available HMGB1 ELISA kit is from Shino-Test Corporation in Japan, first reported in 2006 (Yamada et al., 2006). In addition to ELISA (Lepp and Martinez, 1989; Urbonaviciute et al., 2007; Wahamaa et al., 2007; Yamada et al., 2003), several new techniques (e.g., DNA nanostructure-based assay) have been proposed to test HMGB1 concentration in serum or supernatants (Gaillard et al., 2008). Immunohistochemical staining is widely used in the assessment of HMGB1 expression and localization in tissues. RT-PCR and q-PCR are widely used to test HMGB1 mRNA expression in tissues. HMGB1 gene polymorphisms (Kornblit et al., 2007) are involved in several human disease such as chronic HBV infection (Deng et al., 2013), trauma (Zeng et al., 2012), allogeneic hematopoietic cell transplantation (Kornblit et al., 2010), and systemic inflammatory response syndrome (Kornblit et al., 2008). Serum anti-HMGB1 autoantibody

is increased in several autoimmune diseases (Urbonaviciute and Voll, 2011). The details of HMGB1 measurement and significance in clinical practice are listed in Table 5.

15 Concluding Remarks

In 1973, the discovery of HMGB1 as a non-histone chromosomal protein was reported. Nuclear HMGB1 regulates a number of DNA-related events such as replication, recombination, repair, and transcription (Goodwin et al., 1973). In 1999, with the discovery of HMGB1 as a late mediator of sepsis, a new research field was born (Wang et al., 1999). During the past 15 years, a number of HMGB1 receptors and posttranslational modifications have been identified, which enhance or diminish extracellular HMGB1activity in multiple cellular processes (Bianchi, 2009; Yang et al., 2013c). In addition to its receptors, HMGB1 endocytic uptake plays an important role in mediated HMGB1 activity and degradation (Kang et al., 2014; Xu et al., 2014; Zhang et al., 2012e). Intracellular and extracellular HMGB1 play significantly different roles in inflammation, injury, and cancer. A new function for HMGB1 is as an autophagy regulator, which has been linked to sterile inflammation, infection, neurodegenerative disease, and cancer (Kang et al., 2011c; Zhang et al., 2013d). These properties of HMGB1 make it an attractive biomarker and therapeutic target (Andersson and Tracey, 2011; Sims et al., 2010). Numerous strategies are being employed to inhibit HMGB1 release and activity in inflammation-associated diseases (Musumeci et al., 2014; Wang et al., 2014b). Several genetic animal models of HMGB1 have recently been created to examine the physiological and pathological roles of HMGB1 in health and disease. The phenotype of HMGB1 conditional knockout mice is complex and even paradoxical (Ge et al., 2014; Huang et al., 2013a, 2014; Huebener et al., 2014; Kang et al., 2013b; Tang et al., 2014; Yanai et al., 2013). Future work investigating the details of HMGB1 location, structure, modification, and partners will uncover the secrets of HMGB1's multiple functions.

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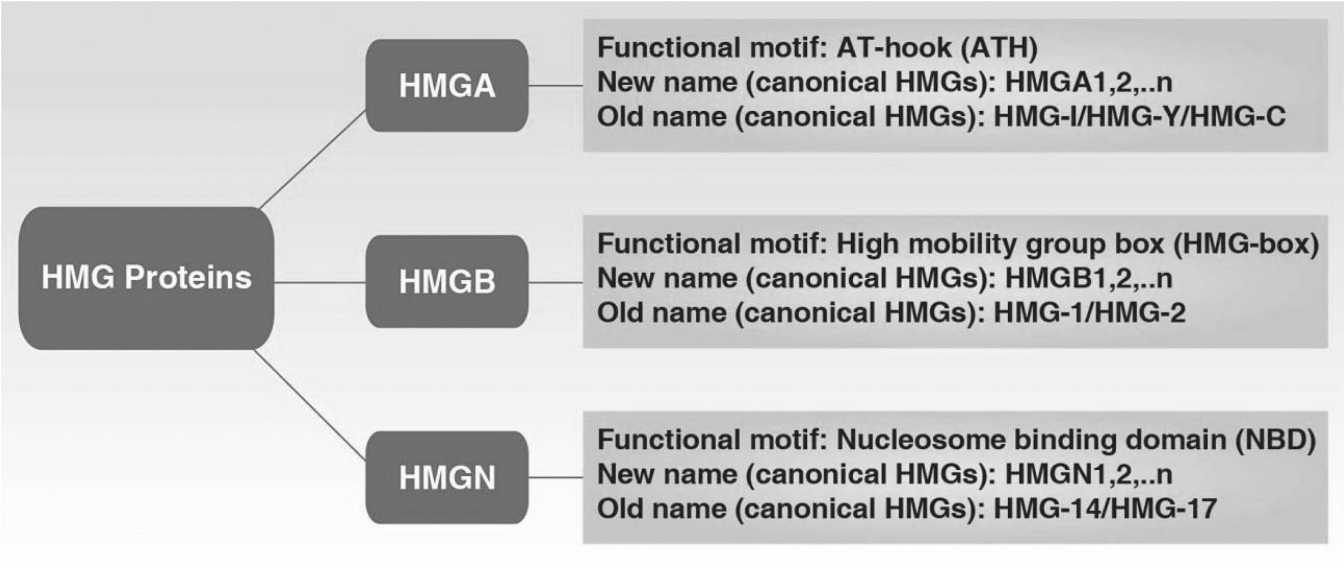

Figure 1.
Revised nomenclature for the HMG chromosomal proteins (Bustin, 2001)

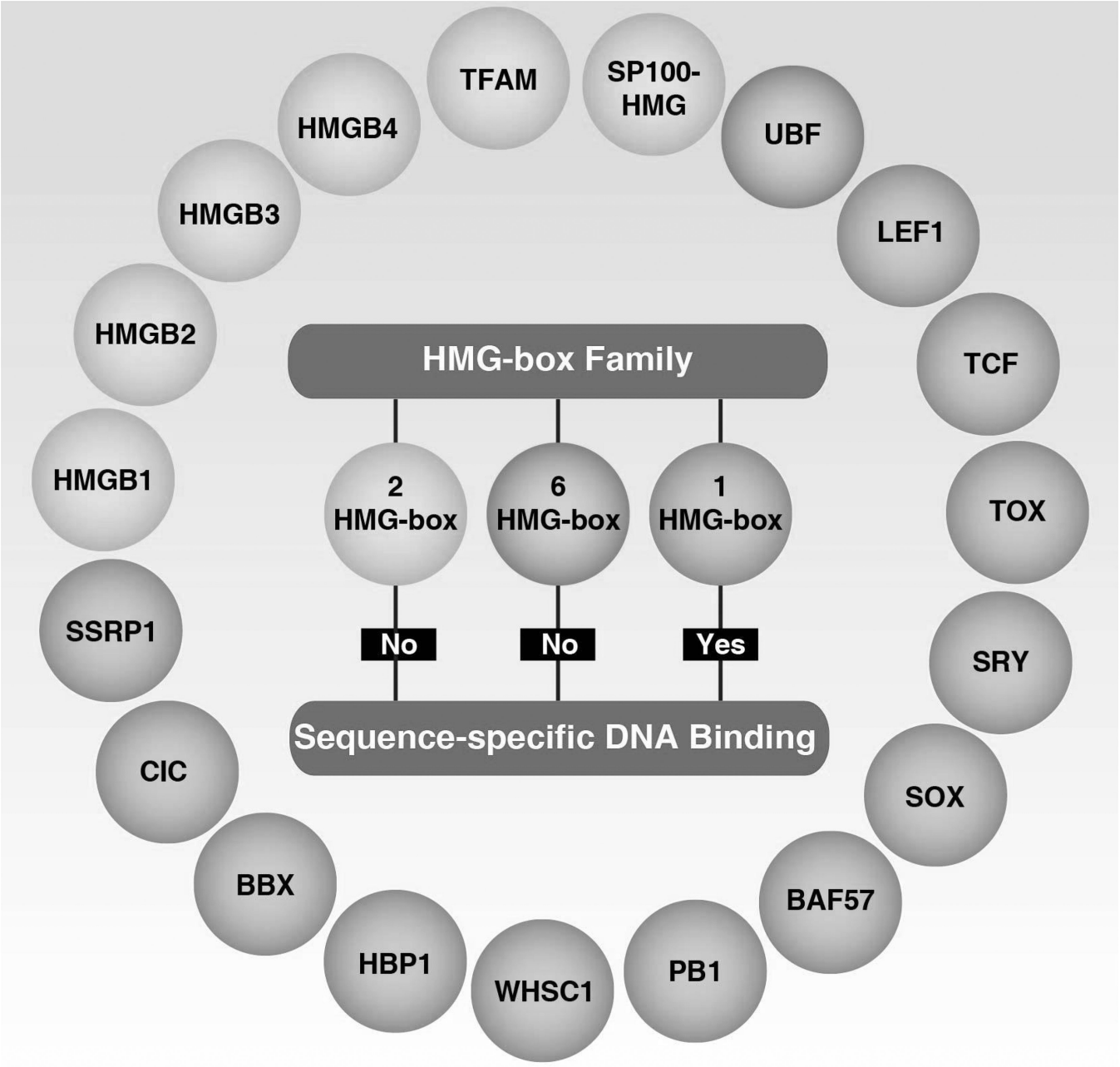

Figure 2.
The HMG-box proteins

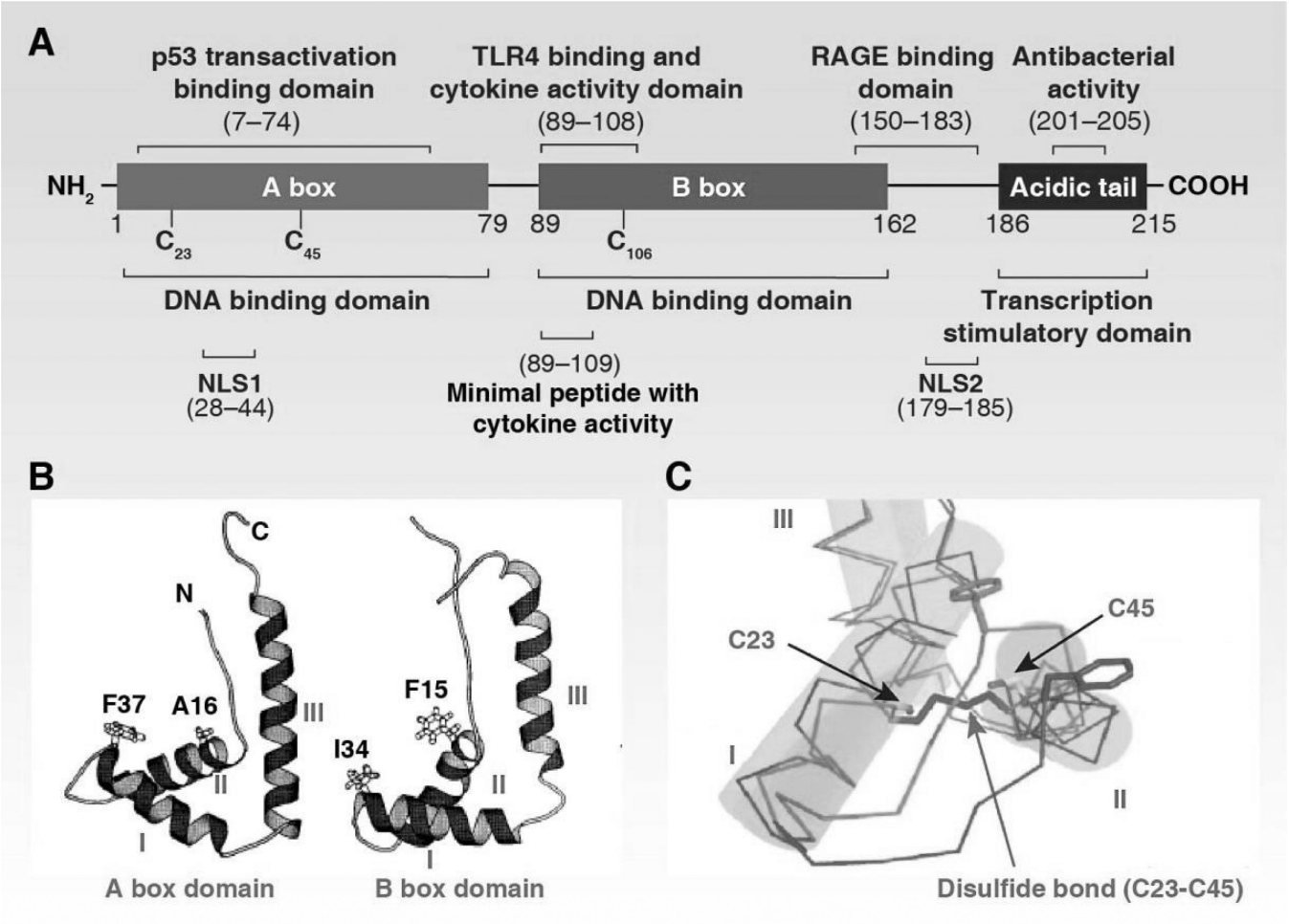

Figure 3.

Structure of the HMGB1 protein. (A) HMGB1 has two DNA-binding domains (A and B box) and an acidic C-terminal tail. (B) Helical secondary structure of A and B box domains (Thomas, 2001). (C) Intramolecular disulfide bond in the Adomain of HMGB1 (Wang et al., 2013e).

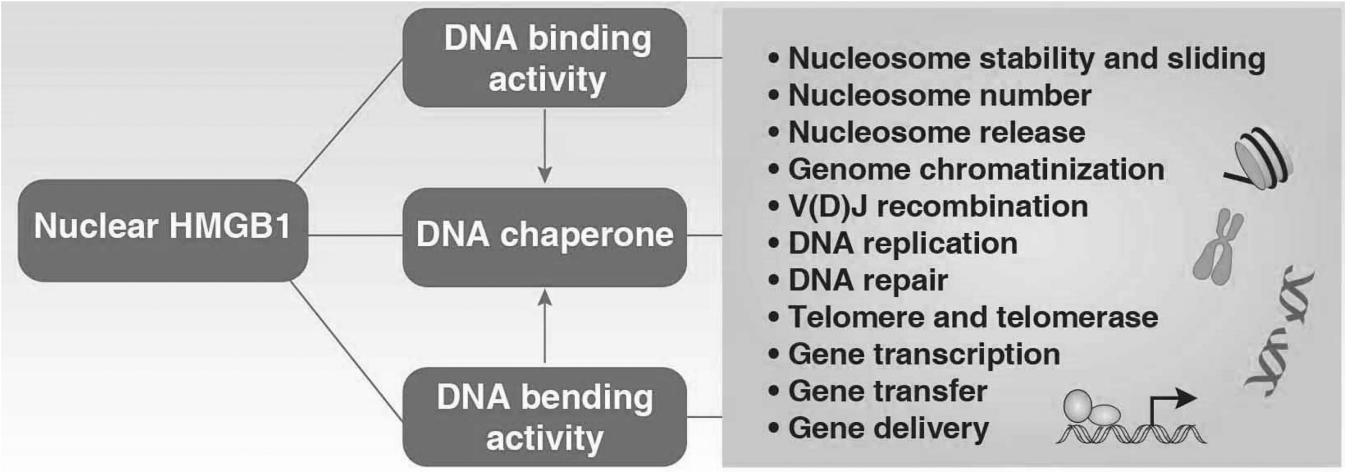

Figure 4.
Nuclear HMGB1 acts as a DNA chaperone with DNA binding and bending activities that regulate a number of nuclear events.

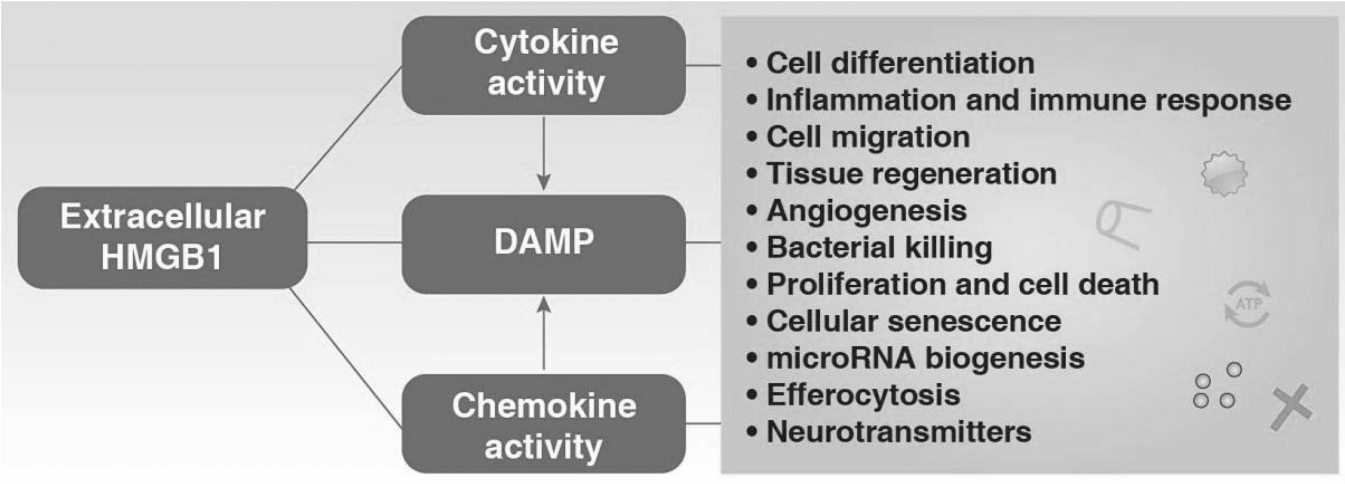

Figure 5.
Extracellular HMGB1 acts as a DAMP with cytokine and chemokine activities that regulate a number of cellular processes.

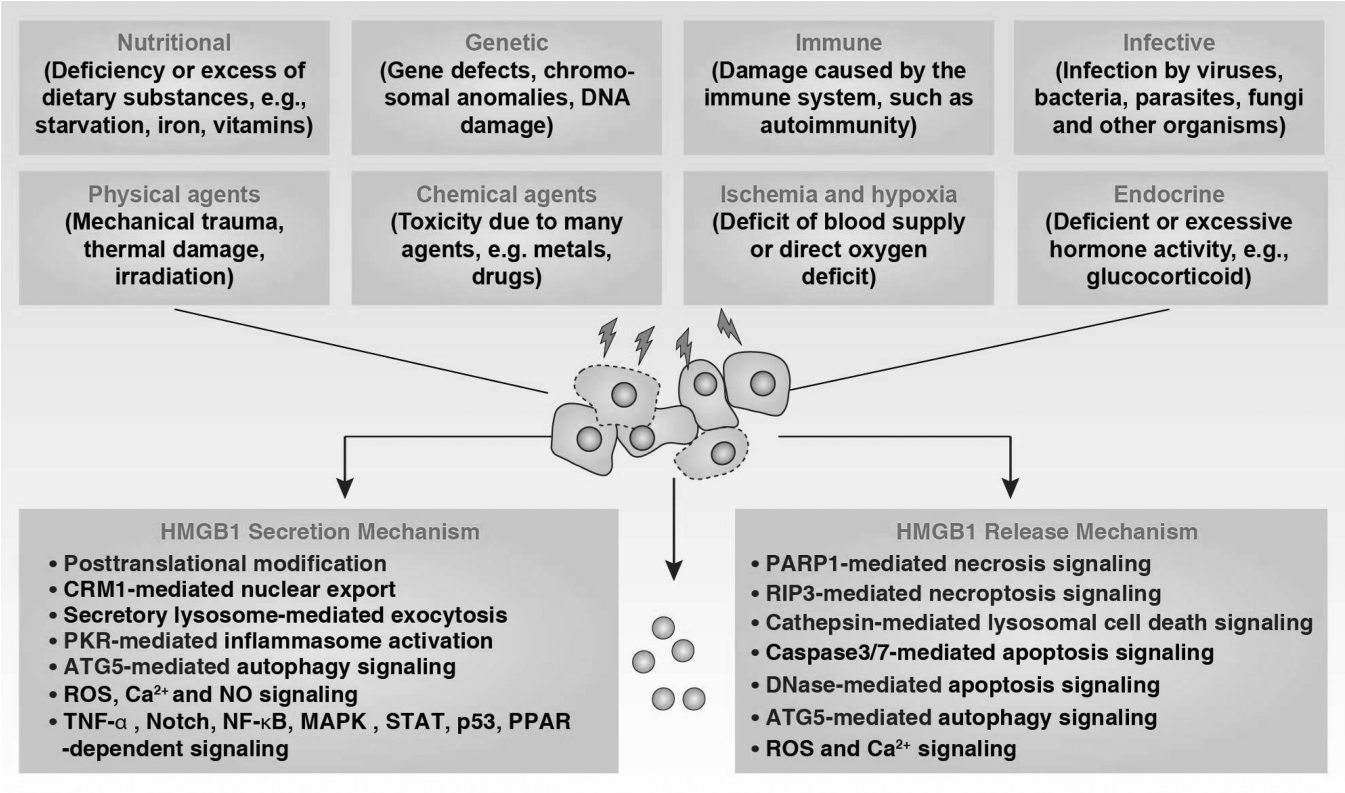

Figure 6.
HMGB1 is released in two different ways: active secretion and passive release.

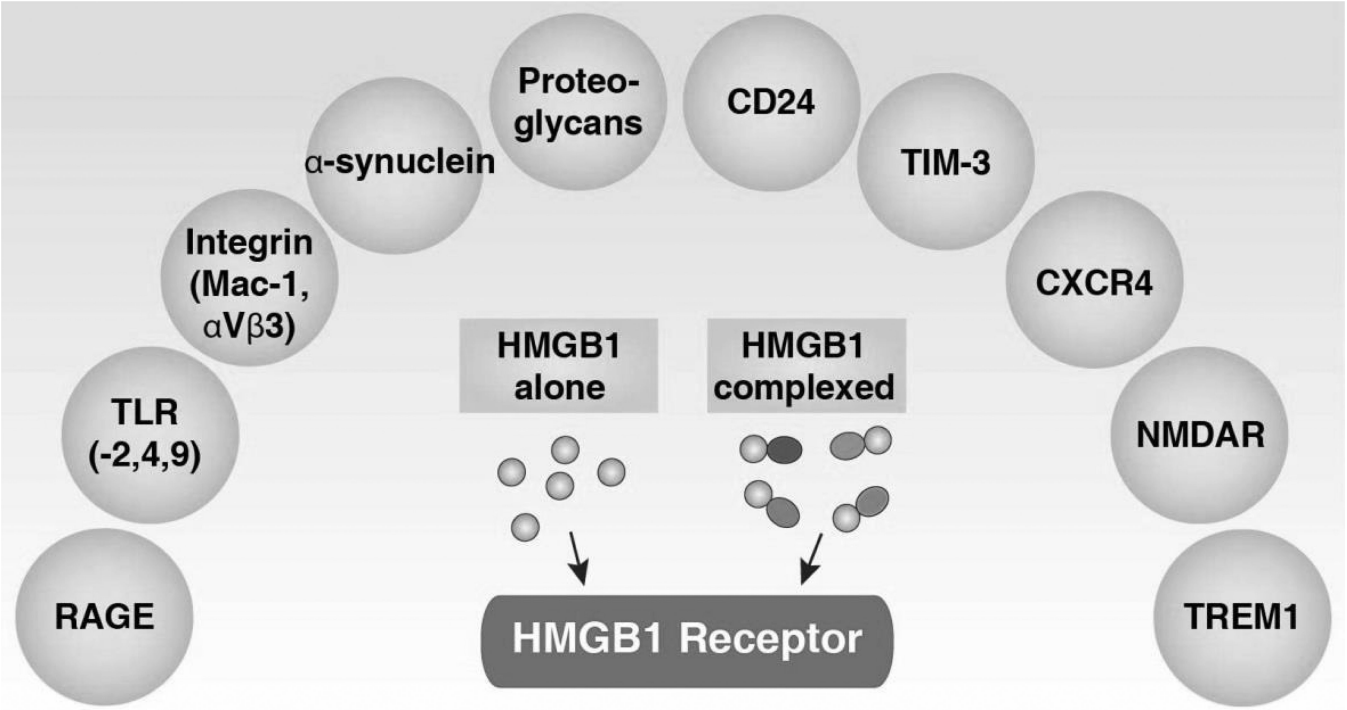

Figure 7.
HMGB1 signals through receptors.

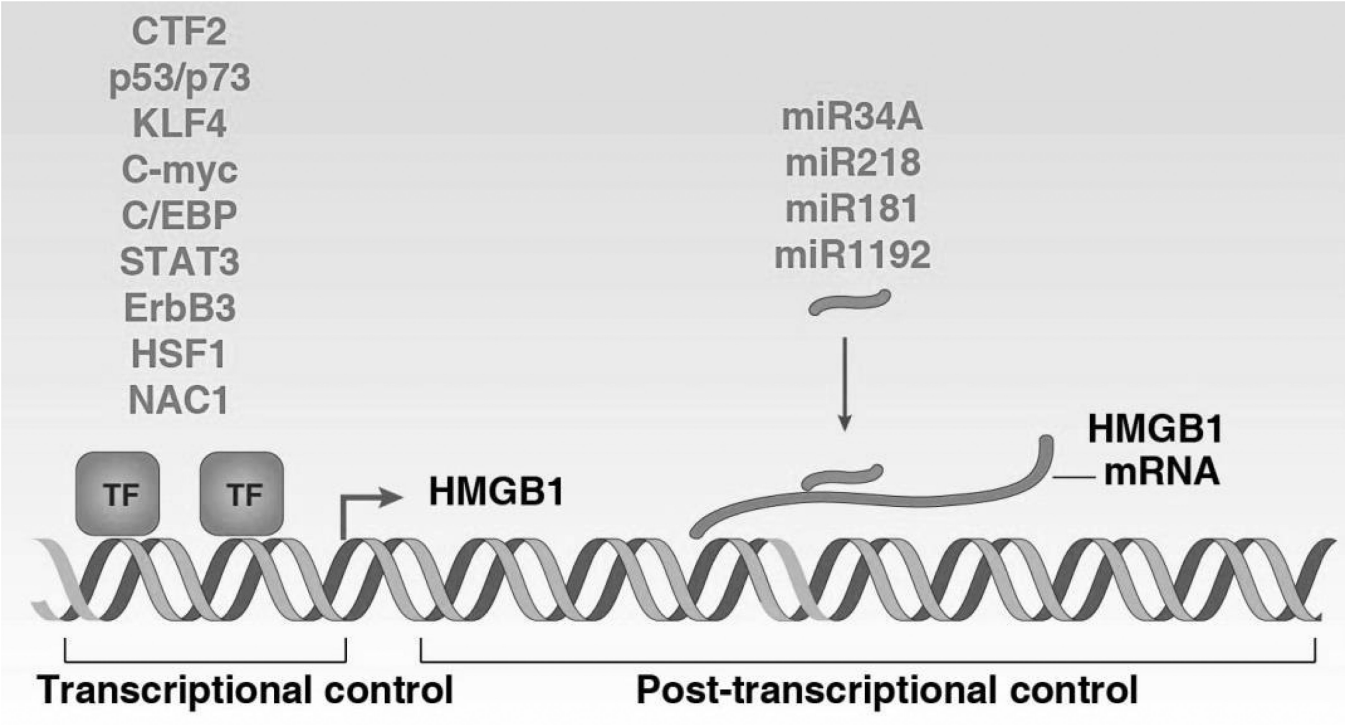

Figure 8.
HMGB1 transcriptional regulation.

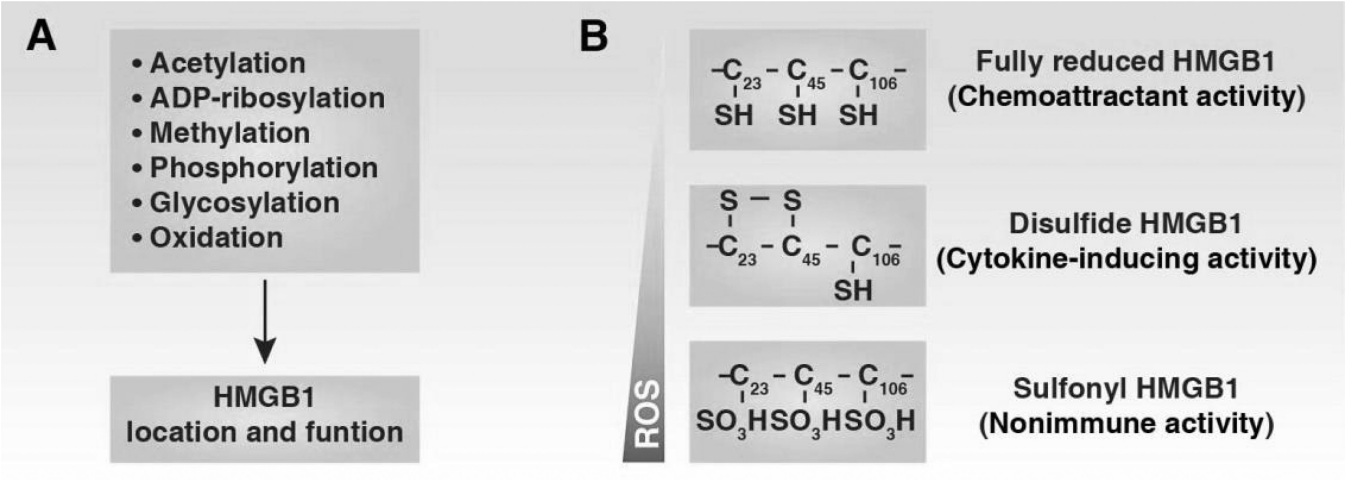

Figure 9.

HMGB1 post-translational modification. (A) These modifications and regulations are critical for HMGB1 location and function. (B) The redox status of HMGB1 regulates its cytokine-inducing and chemokine activities.

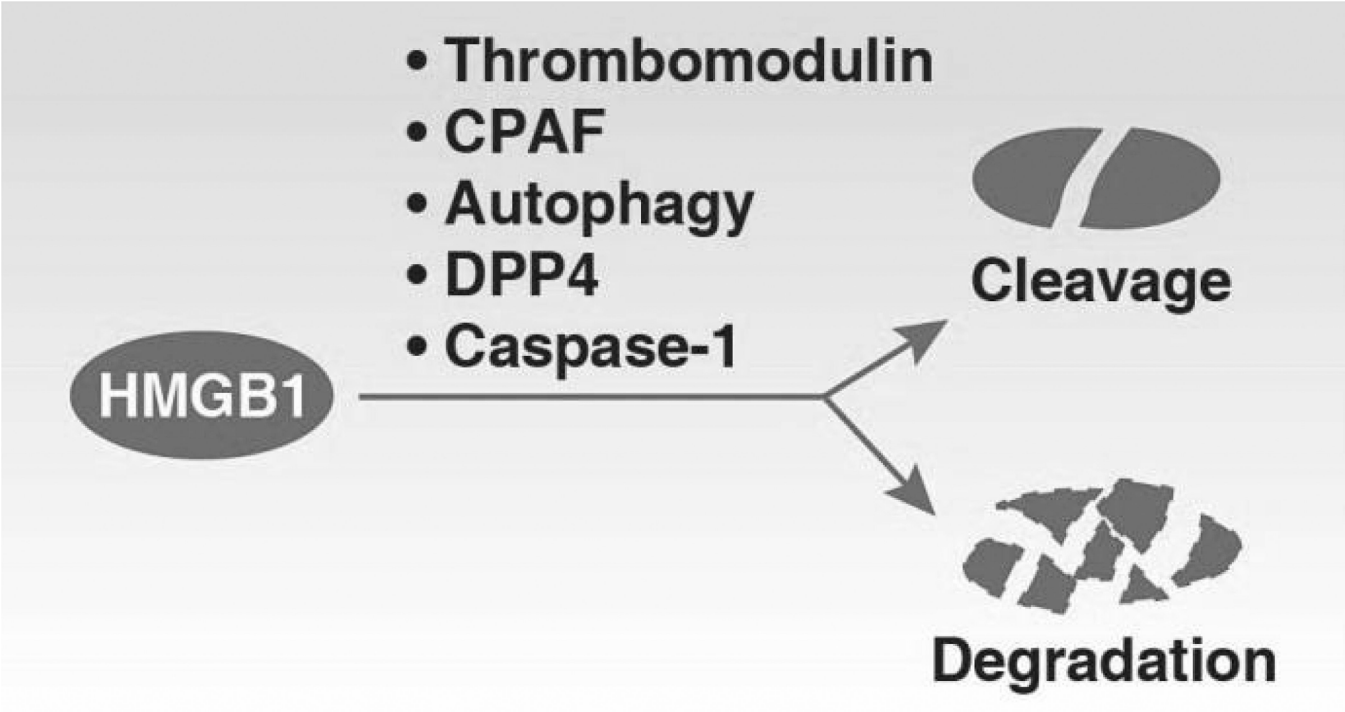

Figure 10.
HMGB1 cleavage and degradation.

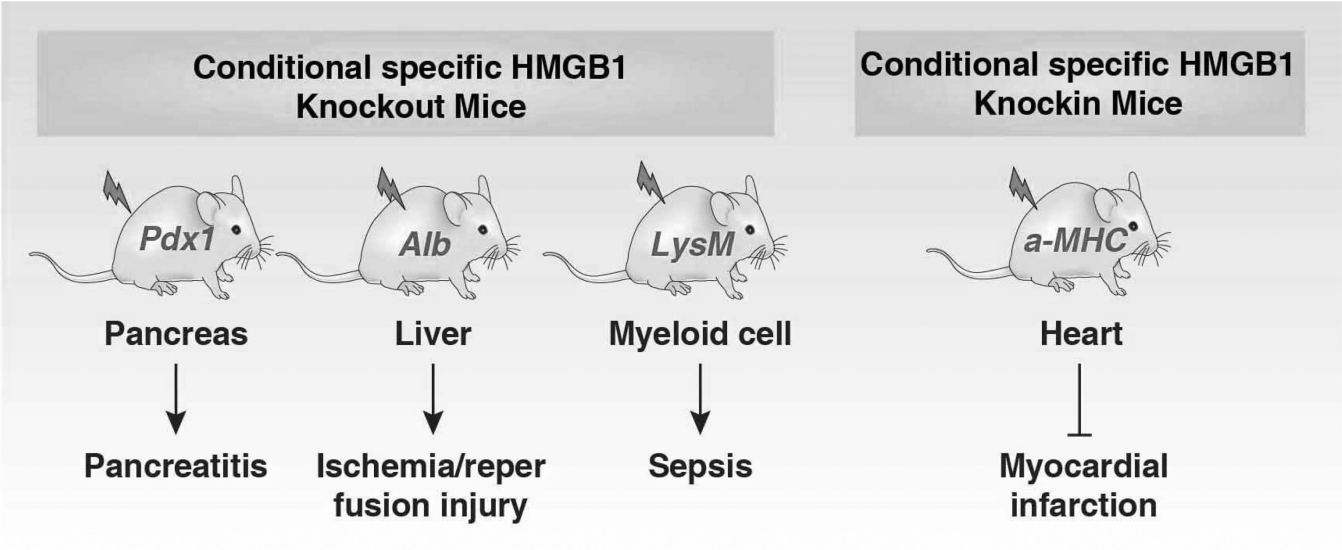

Figure 11.
Phenotype of the HMGB1 conditional knockout or knockin mouse in response to stress.

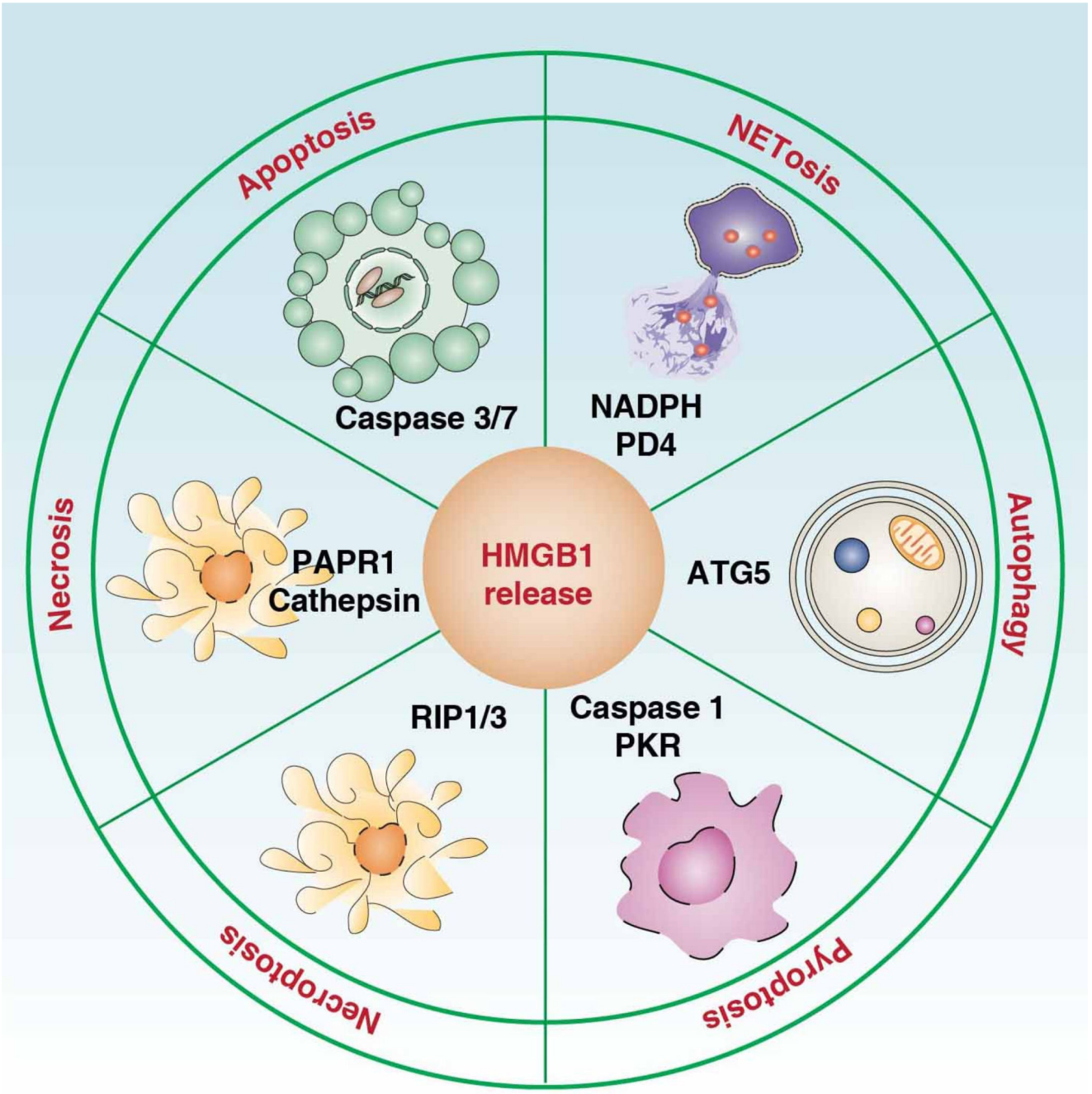

Figure 12.
HMGB1 release in cell death

Table 1

Multi-species Expression and Function of HMGB1

Species	Function	References
Goldfish (*Carassius auratus L.*)	Inflammatory and immune response	(Xie et al., 2014)
Chlamys farreri	DNA-binding ability and pro-inflammatory activity	(Wang et al., 2014d)
Adult zebrafish	Regeneration after spinal cord injury and brain development	(Fang et al., 2014; Moleri et al., 2011; Zhao et al., 2011b)
Grass carp (*Ctenopharyngodon idella*)	Innate immune response	(Yang et al., 2013a)
Saccharomyces cerevisiae	DNA repair	(Thongsroy et al., 2013)
Pacific oyster (*Crassostrea gigas*)	Innate defense	(Li et al., 2013c)
Nematode *Caenorhabditis elegans*	Hypoxia response	(Lee, 2013)
Wuchereria bancrofti and *Brugia malayi*	Lymphatic filariasis	(Thirugnanam et al., 2012)
Aedes aegypti	DNA bending	(Ribeiro et al., 2012)
Lampetra japonica	Innate immunity	(Pang et al., 2012)
Arabidopsis thaliana	Chromatin dynamics and telomere maintenance	(Schrumpfova et al., 2011)
Yeast	Genome stability; DNA binding; Antiapoptosis	(Giavara et al., 2005; Guerin et al., 2008; Labazi et al., 2009)
Plasmodium falciparum	Inflammatory immune responses	(Kumar et al., 2008)
Saccharomyces cerevisiae	Chromosomal rearrangement Gene transcription	(Diffley and Stillman, 1991, 1992; Kim et al., 2007; Sikdar et al., 2008)
Human blood flukes *Schistosoma mansoni* and *Schistosoma japonicum*	Schistosomiasis	(de Oliveira et al., 2006; Gnanasekar et al., 2006)
Pelodiscus sinensis	Unknown	(Zheng et al., 2005)
Plodia interpunctella	Unknown	(Aleporou-Marinou et al., 2003)
Drosophila	DNA binding and bending	(Lehming et al., 1998; Lehming et al., 1994; Ner et al., 1993; Wagner et al., 1992)
Saccharomyces cerevisiae	Nucleosome	(Perez-Martin and Johnson, 1998a, b)
Lamprey lampetra fluviatilis	Unknown	(Sharman et al., 1997)
Sea-urchin	Unknown	(Niemeyer et al., 1995)
Trout	Unknown	(Stros et al., 1994a)
Chironomus thummi (Diptera)	DNA binding and bending	(Wisniewski and Schulze, 1992; Wisniewski et al., 1994)
Tetrahymena thermophila	Gene transcription	(Schulman et al., 1991)

Table 2

Intracellular Binding Partners for HMGB1

Name	Function	Site	Reference
H1, H2a, 2b, H3, H4	Regulates nucleosome function	Nucleus	(Carballo et al., 1983; Kohlstaedt and Cole, 1994b; Smerdon and Isenberg, 1976; Stros and Kolibalova, 1987; Stros and Vorlickova, 1990; Totsingan and Bell, 2013; Watson et al., 1977)
Bric-a-brac	Inhibits HMGB1-induced oncogenesis	Nucleus	(Ko et al., 2014)
Sox9	Inhibits E-selectin expression	Nucleus	(Zhang et al., 2013h)
RAG1 and RAG2	Promotes V(D)J recombination	Nucleus	(Agrawal and Schatz, 1997; Ji et al., 2010; Little et al., 2013)
Gadd45a	Regulates DNA demethylation	Nucleus	(Li et al., 2013h)
p53	Regulate gene transcription	Nucleus	(Banerjee and Kundu, 2003; Imamura et al., 2001; Jayaraman et al., 1998; Livesey et al., 2012c; McKinney and Prives, 2002; Rowell et al., 2012; Zhang et al., 2003)
Influenza virus nucleoprotein	Promotes viral replication	Nucleus	(Moisy et al., 2012)
Viral ribonucleoprotein	Promotes viral replication	Nucleus	(Matsumoto et al., 2012)
Estrogen receptor	Regulates gene transcription	Nucleus	(Joshi et al., 2012)
DFF40	Regulates nuclease activity	Nucleus	(Kalinowska-Herok and Widlak, 2008; Ninios et al., 2010; Widlak and Garrard, 2005)
Oct1	Regulates Rta expression	Nucleus	(Harrison and Whitehouse, 2008)
PU.1	Regulates IL-1β expression	Nucleus	(Mouri et al., 2008)
Ets	Regulates transcription activity	Nucleus	(Shiota et al., 2008)
Mutant AT1 and Htt	Regulates genotoxic stress	Nucleus	(Qi et al., 2007)
Topoisomerase II alpha	Regulates catalytic activity	Nucleus	(Stros et al., 2007a)
Hsp72	Regulates inflammatory response	Nucleus	(Tang et al., 2007a; Tang et al., 2007d)
GR	Regulates transcription activity	Nucleus	(Agresti et al., 2005)
Sterol regulatory element-binding proteins	Regulates DNA-binding activity	Nucleus	(Najima et al., 2005)
Replication protein A	Regulates DNA damage response	Nucleus	(Reddy et al., 2005)
Estrogen receptor	Regulates transcription activity	Nucleus	(Borrmann et al., 2001; Chau et al., 1998; Das et al., 2004; Melvin et al., 2004; Verrier et al., 1997) (Romine et al., 1998)
Replication and transcription activator	Regulates DNA-binding activity	Nucleus	(Song et al., 2004)
MutSalpha	Regulates DNA repair	Nucleus	(Yuan et al., 2004)
Rel family	Regulates transcription activity	Nucleus	(Agresti et al., 2003; Brickman et al., 1999)

Name	Function	Site	Reference
HMGB1-HMGB2-HSC70-ERp60-glyceraldehyde 3-phosphate dehydrogenase complex	Regulates chemotherapy	Nucleus	(Krynetski et al., 2003)
Sleeping Beauty	Regulates transposition	Nucleus	(Zayed et al., 2003)
Groucho-related gene proteins 1	Unknown	Unknown	(Dintilhac and Bernues, 2002)
Dof2	Regulates transcription activity	Nucleus	(Krohn et al., 2002)
Steroid hormone subgroup of nuclear receptors (androgen, glucocorticoid, progesterone and mineralocorticoid receptors)	Regulates transcription activity	Nucleus	(Melvin et al., 2002; Onate et al., 1994; Verrijdt et al., 2002)
p73	Regulates transcription activity	Nucleus	(Stros et al., 2002)
TATA-binding protein/TATA complex	Regulates DNA-binding activity	Nucleus	(Das and Scovell, 2001; Sutrias-Grau et al., 1999)
Up-stream stimulatory factor 1	Regulates transcription activity	Nucleus	(Marmillot and Scovell, 1998)
SP100 nuclear bodies	Regulates transcription activity	Nucleus	(Seeler et al., 1998)
DNA-PKcs	Regulates DNA damage response	Nucleus	(Watanabe et al., 1994; Yumoto et al., 1998)
Transcription by RNA polymerase II	Regulates DNA binding activity	Nucleus	(Ge and Roeder, 1994)
Adeno-associated virus replication protein	Regulates virus replication	Nucleus	(Costello et al., 1997)
The conserved lymphokine elements-0	Regulates DNA-binding activity	Nucleus	(Marrugo et al., 1996)
Hox	Regulates transcriptional activation	Nucleus	(Zappavigna et al., 1996)
SNCA/alpha-synuclein	Inhibits HMGB1-induced autophagy	Nucleus and cytosol	(Song et al., 2014)
Beclin-1	Regulates autophagy	Cytosol	(Tang et al., 2010c)
Tubulin	Regulates cell skeleton	Cytosol	(Briolay et al., 1994)

Table 3

Extracellular Binding Partners for HMGB1

Name	Function	Receptor	Reference
Inorganic polyphosphate	Amplifies inflammatory signaling	RAGE, P2Y1	(Dinarvand et al., 2014)
CXCL12	Promoting inflammatory cell recruitment and activation	CXCR4	(Kew et al., 2012; Schiraldi et al., 2012)
DNA	Immunity regulation	TLR9, RAGE	(Jinushi, 2012; Pisetsky, 2012b; Tian et al., 2007)
Hemoglobin	Amplifies inflammatory signaling	TLR2, TLR4	(Lin et al., 2012c)
LPS	Amplifies inflammatory signaling	CD14, TLR4	(Hreggvidsdottir et al., 2012; Qin et al., 2009; Youn et al., 2008)
Pam(3)CSK(4)	Amplifies inflammatory signaling	TLR2	(Hreggvidsdottir et al., 2012)
Heparin	Diminishes inflammatory signaling	RAGE	(Ling et al., 2011)
Kinked oligonucleotide duplexes	Diminishes inflammatory signaling	Unknown	(Musumeci et al., 2011)
IL-1α	Amplifies inflammatory signaling	IL-1R	(Harris et al., 2012; Wahamaa et al., 2011)
IL-1β	Amplifies inflammatory signaling	IL-1R	(Garcia-Arnandis et al., 2010b; Harris et al., 2012; Leclerc et al., 2013; Sha et al., 2008; Wahamaa et al., 2011)
RNA substrates	Regulates RNA processing as well as transcription	Unknown	(Bell et al., 2008)
Nucleosome (histone)	Amplifies inflammatory signaling	TLR2 TLR9	(Huang et al., 2011a; Urbonaviciute et al., 2008)
Lipids	Amplifies inflammatory signaling	Unknown	(Rouhiainen et al., 2007)
Thrombomodulin	Diminishes inflammatory signaling	Unknown	(Abeyama et al., 2005)

Table 4

HMGB1-targeting Therapeutic Strategies

Therapeutic strategies	Inhibition of HMGB1	Model	References
Antibody			
Mouse anti-HMGB1 DPH1.1 antibody	Activity	Migration	(Venereau et al., 2012)
Mouse monoclonal anti-HMGB1 2G7 antibody	Activity	Sepsis	(Yang et al., 2010a)
Anti-HMGB1 chicken IgY polyclonal antibody	Activity	UV-induced inflammation	(Abeyama et al., 2005)
IFNγ antibody	Release	Sepsis	(Yin et al., 2005)
TNF-α antibody	Release	Acute-on-chronic liver failure	(Yang et al., 2014a)
Peptide and protein			
A box	Activity	Sepsis; thromboangiitis obliterans; postischemic brain; acute pancreatitis	(Jin et al., 2011; Kong et al., 2013; Yang et al., 2004b)
Fusion protein HMGB1 A box-TMD1	Activity	Macrophage activation	(Li et al., 2010d)
LPS-binding peptide regions within HMGB1	Activity	Sepsis	(Youn et al., 2011)
The fibrin-derived peptide Bbeta15–42	Release and activity	Liver ischemia-reperfusion injury	(Liu et al., 2013a)
Recombinant bactericidal/permeability-increasing protein (rBPI21)	Expression and activity	Sepsis	(Zhang et al., 2008b)
Cationic antibacterial polypeptide of 11-kDa	Release	Sepsis, phagocytosis	(Murakami et al., 2009; Shibusawa et al., 2009)
HMGB1 binding heptamer peptide (HBHP; HMSKPVQ)	Activity	Ischemic brain injury	(Kim and Lee, 2013)
Fetuin-A	Release	Sepsis; cerebral ischemia injury	(Li et al., 2011f; Wang et al., 2010a)
Recombinant kallistatin	Release and expression	Sepsis	(Li et al., 2014b)
HMGB1 mutant protein	Activity	Monocyte activation	(Yuan et al., 2008)
RNAi			
HMGB1 siRNA	Expression	Postischemic brain injury	(Kim et al., 2012b)
HMGB1 shRNA	Expression	Type 1 diabetes; cancer	(Livesey et al., 2012a; Wang et al., 2014f)
Physical method			
Hemoperfusion with a HMGB1 adsorption column	Activity	Liver ischemia-reperfusion injury; sepsis	(Yamamoto et al., 2010;

Therapeutic strategies	Inhibition of HMGB1	Model	References
			Yasuda et al., 2012)
Polymyxin B-immobilized fiber column	Activity	Patients with idiopathic pulmonary fibrosis with acute exacerbation; septic shock patient	(Abe et al., 2011; Nakamura et al., 2011c) (Sakamoto et al., 2006; Yamato et al., 2013)
Membranes for continuous hemofiltration (AN69ST)	Activity	Experimental hemofiltration *in vitro*	(Yumoto et al., 2011)
Calorie restriction	Release and expression	Sepsis	(Hasegawa et al., 2012)
Low temperature condition	Release	Hypoxia-induced islet cell damage	(Itoh et al., 2012b)
Xenon treatment	Release	Cold ischemia injury	(Zhao et al., 2013)
Controlled oxygen reperfusion	Release	Cardiopulmonary bypasses	(Rong et al., 2013)
Molecular hydrogen	Release	Sepsis; liver/spinal cord/ cerebral ischemia-reperfusion injury	(Huang et al., 2011c; Li et al., 2012a; Liu et al., 2014b; Xie et al., 2012; Xie et al., 2010; Zhou et al., 2013b)
Surgery			
Splenectomy	Release	Sepsis	(Huston et al., 2008)
Chemicals			
Carboxylated N-glycans	Activity	Neurite outgrowth	(Srikrishna et al., 2002)
Antileukinate (alpha-chemokine receptor inhibitor)	Release	Sepsis	(Lin et al., 2005)
Pyrrolidine dithiocarbamate (NF-κB inhibitor)	Release	Acute pancreatitis	(Zhang et al., 2010)
20-5,14-HEDGE	Expression	Lung ischemia-reperfusion injury	(Ali et al., 2012)
Glutamine	Expression	Sepsis	(Kwon et al., 2010b)
Endothelin receptor antagonist	Release	Sepsis	(Goto et al., 2010)
2-(2-N,N-dimethylaminoethylamine-1-carbonyl)-1H-quinolin-4-one hydrochloride (an analogue of Kynurenic acid)	Release	Monocyte activation	(Tiszlavicz et al., 2011)
Rosiglitazone (a PPAR-γ agonist)	Expression	Sepsis	(Wang et al., 2014a)
D-Ala2-D-Leu5-enkephalin (a delta-opioid receptor agonist)	Release	Sepsis	(Tang et al., 2011a)
Resolvin D1	Release	Sepsis	(Murakami et al., 2011)

Therapeutic strategies	Inhibition of HMGB1	Model	References
DR396 (an apoptotic DNase gamma inhibitor)	Release	Apoptosis	(Yamada et al., 2011a)
Farnesyltransferase inhibitor FTI-277	Release	Sepsis	(Yang et al., 2011)
TNF-α inhibitor	Release	Arthritis; sepsis	(Fei et al., 2011)
tricarbonylchloro(glycin ate) ruthenium (II) (CORM-3)	Expression	Arthritis	(Maicas et al., 2010)
JAK2 inhibition with AG490	Release	Sepsis	(Hui et al., 2009; Pena et al., 2010)
Glutamine	Expression	Sepsis	(Hu et al., 2012c)
Rosiglitazone (a specific ligand for PPAR-γ)	Release	Macrophage activation	(Hwang et al., 2012)
Alpha 2A-adreno receptor	Release and expression	Sepsis	(Ji et al., 2012a)
T-5224 (a selective inhibitor of c-Fos/activator protein-1)	Release	Sepsis	(Izuta et al., 2012)
Carbon monoxide from CORM-2 (Carbon monoxide-releasing molecule 2)	Release	Macrophage activation	(Tsoyi et al., 2010)
Galectin-9	Release	Sepsis	(Kadowaki et al., 2013)
PNU-282987 (a selective alpha7 nicotinic acetylcholine receptor agonist)	Release	Liver ischemia-reperfusion injury	(Li et al., 2013a)
Sodium butyrate	Expression	Severe burn injury	(Liang et al., 2013b)
Tolerization with bacterial lipoprotein	Expression and release	Sepsis	(Coffey et al., 2007)
Tetrahydroisoquinoline alkaloid THI-28	Release	Sepsis	(Kim et al., 2013b)
Exendin-4 (a glucagon-like peptide-1 receptor agonist)	Expression	Myocardial ischemia-reperfusion injury	(Hu et al., 2013)
4,4'-diphenylmethane-bis (methyl) carbamate	Activity	Endothelial cell activation	(Feng et al., 2013)
Ethyl pyruvate	Release and expression	Sepsis; postischemic brain;hepatitis;hepatoce llular carcinoma; liver and myocardial ischemia-reperfusion injury; acute pancreatitis; murine colitis	(Cheng et al., 2014; Dave et al., 2009; Hu et al., 2012b; Luan et al., 2012; Shen et al., 2014; Shin et al., 2014; Ulloa et al., 2002)
Troglitazone (a PPAR-γ agonist)	Expression	EA.hy926 cell activation	(Gao et al., 2011b)
Glucan phosphate	Release	Sepsis	(Ha et al., 2011a)
Heme oxygenase-1 inducer	Release	Sepsis	(Ha et al., 2011b)
Clopidogrel sulfate (a adenosine diphosphate receptor antagonist)	Expression	Sepsis	(Hagiwara et al., 2011a)

Therapeutic strategies	Inhibition of HMGB1	Model	References
Spermine	Release and activity	Sepsis	(Zhu et al., 2009)
Gold chloride	Release	Macrophage activation	(Zetterstrom et al., 2008)
Oroxylin-A	Release	Sepsis	(Tseng et al., 2012)
EPC-K1 (a vitamin E derivative)	Expression	Liver ischemia-reperfusion injury	(Oishi et al., 2012)
Geranylgeranylacetone	Expression	Myocardial ischemia-reperfusion injury	(Wang et al., 2012d)
Penehyclidine hydrochloride	Release	Sepsis	(Yang et al., 2014c)
Pyrrolidine dithiocarbamate (a NF-κB inhibitor)	Expression and release	Acute-on-chronic liver failure; chronic obstructive pulmonary disease	(Wang et al., 2013a; Yang et al., 2014a)
Dehydroxymethylepoxy quinomicin (a NF-κB inhibitor)	Activity	Islet transplantation	(Watanabe et al., 2013)
Probenecid (a pannexin 1 channel inhibitor)	Release	Middle cerebral artery occlusion	(Xiong et al., 2014)
AS605240 (a PI3Kgamma inhibitor)	Release	Sepsis	(Xu et al., 2010)
GW9662 (PPAR-γ antagonist)	Release	Cerebral ischemia injury	(Haraguchi et al., 2009)
Melatonin	Expression and release	Hemorrhage; hepatitis; liver ischemia-reperfusion injury	(Kang et al., 2011a; Laliena et al., 2012; Wang et al., 2013o)
Hemopexin	Activity	Macrophage activation	(Lin et al., 2012c)
Adiponectin	Release	Sepsis	(Li et al., 2012d)
Chymase	Degradation	Danger-induced inflammation	(Roy et al., 2014)
Glyceollins	Release	Sepsis	(Lee et al., 2014)
Prorenin receptor blocker	Release and expression	Sepsis	(Hirano et al., 2014)
Sodium hydrosulfide	Release	Hemorrhagic shock	(Xu et al., 2013a)
3-(3-chloro-phenyl)-5-(4-pyridyl)-4,5-dihydroisoxazole	Release	Sepsis	(Vicentino et al., 2012)
Natural chemicals			
Quercetin (a flavonoid)	Release and activity	Sepsis	(Tang et al., 2009)
An extract from Machilus zuihoensis	Release	Macrophage activity	(Mao et al., 2011)
Osthole (an active compound from Cnidium monnieri and Angelica pubescens)	Expression	Myocardial ischemia-reperfusion injury	(Wang et al., 2013n)
Tanshinone II A	Release and expression	Sepsis; cerebral ischemia-reperfusion injury	(Li et al., 2007b;

Therapeutic strategies	Inhibition of HMGB1	Model	References
			Wang et al., 2010b; Zhan et al., 2014)
An extract from Helleborus purpurascens	Release	Sepsis	(Apetrei et al., 2011)
Chloroquine	Release and activity	Sepsis	(Yang et al., 2013d)
Lycopene	Release and activity	Vascular inflammation	(Lee et al., 2012d)
Withaferin A (an active compound from Withania somnifera)	Release and activity	Leukocyte migration	(Lee et al., 2012c)
Pellitorine (an active amide compound from Asarum sieboldii)	Release	Sepsis	(Ku et al., 2013)
Persicarin (an active compound from Oenanthe javanica)	Release and activity	Sepsis	(Kim et al., 2013f)
Isorhamnetin-3-O-galactoside (I3G) (an active compound from O. javanica)	Release	Sepsis	(Kim et al., 2013e)
Omega-3 polyunsaturated fatty acids	Release	Liver ischemia-reperfusion injury	(Kim et al., 2013c)
Curcumin	Expression	Hepatitis; Cardiac ischemia-reperfusion injury	(Tu et al., 2013) (Kim et al., 2012h)
18alpha-glycyrrhetinic acid	Expression	Cancer	(Shetty et al., 2011)
Glycyrrhizin	Activity and release	Traumatic brain injury; Sepsis; hemorrhage-induced injury	(Gu et al., 2014; Mollica et al., 2007; Ohnishi et al., 2011; Vitali et al., 2013)
An extract of Prunus mume Sieb. et Zucc	Release	Macrophage activation	(Kawahara et al., 2009)
2-methoxycinnamaldehyde (one of active ingredients of Cinnamomum cassia)	Expression	Myocardial ischemia-reperfusion injury	(Hwa et al., 2012)
Astragaloside IV (an important component of astragalus mongholicus)	Activity	T cell activation	(Hwa et al., 2012)
Danggui (*Angelica sinensis*)	Release	Sepsis	(Wang et al., 2006)
Oleanolic acid	Release	Endothelial cell activation	(Yang et al., 2012b)
Protocatechuic aldehyde	Release	Sepsis	(Xu et al., 2012)
n-3 polyunsaturated fatty acids	Expression	Chronic vasculopathy of small bowel allografts	(Wei et al., 2013)
Mung bean (*Vigna Radiata*)	Degradation	Sepsis	(Wei et al., 2013; Zhu et al., 2012a)
Danshen (*Salvia miltiorrhiza*)	Release	Sepsis	(Li et al., 2007b; Wang et al., 2006)

Therapeutic strategies	**Inhibition of HMGB1**	**Model**	**References**
Green tea (*Camellia sinensis*)	Release and activity	Sepsis	(Li et al., 2007a; Li et al., 2011e)
Epi-sesamin (an active compound from *Asarum sieboldii* roots)	Release	Sepsis	(Lee et al., 2013e)
Berberine	Release	Macrophage activation	(Lee et al., 2013a)
18 beta-glycyrrhetic acid	Activity	Macrophage activation	(Cavone et al., 2011b)
Paeoniflorin	Expression and release	Endothelial cell activation	(Wan et al., 2013)
Saponins (an active compound from Dioscorea nipponica Makino)	Expression	Liver injury	(Yu et al., 2014)
Shikonin	Release	Sepsis	(Yang et al., 2014e)
Higenamine	Expression	Brain injury	(Ha et al., 2012b)
Asperosaponin X (an active compound from the roots of *Dipsacus asper*)	Release	Myocardial ischemia injury	(Jiang et al., 2012e)
Forsythoside B	Release	Sepsis	(Jiang et al., 2012d)
Tricin 7-glucoside	Expression	Cerebral ischemia	(Jiang et al., 2012c)
Vitamin E derivative, E-Ant-S-GS	Expression and release	Sepsis; liver ischemia-reperfusion injury	(Kono et al., 2012) (Koga et al., 2012)
EPCK1 (a vitamin C and E analogue)	Release	Sepsis	(Shingu et al., 2011)
Genipin (an aglycon of geniposide)	Release	Sepsis	(Kim et al., 2012g)
Phlorotannins (active compounds of *Eisenia bicyclis*)	Release	Leukocyte migration	(Kim et al., 2012f)
Kaempferol-3-O-sophoroside (active compounds from leaves of cultivated mountain ginseng)	Release	Endothelial cell activation	(Kim et al., 2012e)
Gelam honey	Release	Sepsis	(Kassim et al., 2012)
Matrine	Release	Sepsis	(Zhang et al., 2011a)
Acanthopanax gracilistylus-extracted Acankoreanogenin A	Release	Hepatitis	(Zhang et al., 2011b)
8-O-acetyl shanzhiside methylester (active compounds from leaves of Lamiophlomis rotata (Benth.) Kudo)	Expression	Myocardial ischemia injury	(Kang et al., 2012c)
Ethanol extract of Prunella vulgaris var. lilacina	Release and expression	Sepsis	(Jun et al., 2012)
Cannabidiol	Release and expression	Cerebral ischemia injury	(Hayakawa et al., 2008a)
Baicalin (the main active ingredient of the root from *Scutellaria*)	Release	Sepsis	(Wang and Liu, 2014)
Piperlonguminine (an active compound from Piper longum fruit)	Release and expression	Sepsis	(Ku et al., 2014)

Therapeutic strategies	**Inhibition of HMGB1**	**Model**	**References**
Astilbin (an active compound from the rhizome of Smilax china L.)	Expression	Cardiac ischemia-reperfusion injury	(Diao et al., 2014)
Luteolin	Release and activity	Macrophage activation	(Chen et al., 2014a)
Qinggan Huoxue Recipe (a traditional Chinese medicine)	Expression	Acute liver failure	(Zhu et al., 2013a)
Betaine	Expression	Liver injury	(Zhang et al., 2013f)
Fucoidan (a sulfated polysaccharide from brown algae)	Expression	Myocardial ischemia-reperfusion injury	(Li et al., 2011a)
Curculigoside A	Expression	Cerebral ischemia injury	(Jiang et al., 2011)
Emodin-6-O-beta-D-glucoside (an active compound from *Reynoutria japonica*)	Release and activity	Sepsis	(Lee et al., 2013f)
Rutin (an active flavonoid compound)	Release and activity	Sepsis	(Yoo et al., 2014)
Rosmarinic acid (an active compound from leaves of *Perilla frutescens*)	Expression and activity	Sepsis	(Yang et al., 2013b)
Fish oil	Expression	Chronic allograft vasculopathy	(Wei et al., 2013)
Anethole (a major component of *Foeniculum vulgare*)	Release	Liver ischemia-reperfusion injury	(Cho et al., 2013)
Ursolic acid	Expression and release	Sepsis	(Chen et al., 2013e)
Scolopendra subspinipes mutilans	Release	Acute pancreatitis	(Jo et al., 2013)
Clinical drugs			
Atorvastatin	Expression	Brains focal ischemia; patients with hyperlipidemia	(Jin et al., 2012; Wang et al., 2010c)
Bicyclol	Release	Sepsis	(Luo et al., 2011)
Carbenoxolone	Release	Sepsis	(Li et al., 2013e)
CKD712, (S)-1-(alpha-naphthylmethyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline	Release	Macrophage activation	(Oh et al., 2011)
CuZnSOD and MnSOD	Release	Tumor growth	(Lee et al., 2010b)
Cholinergic agonist physostigmine	Expression	Forebrain ischemia-reperfusion injury	(Kutsuna et al., 2010)
Cisplatin	Release	Liver ischemia-reperfusion injury; acute liver failure	(Cardinal et al., 2009; Li et al., 2013g)
Candesartan	Activity	Stroke	(Kikuchi et al., 2013)
Chloroquine	Release	Sepsis; monocyte activation; cancer	(Schierbeck et al., 2010)
Dobutamine	Release	Myocardial ischemia-reperfusion injury	(Wang et al., 2013g)
Dihydropyridine-type calcium-channel blocker--CV159	Release	Liver ischemia-reperfusion injury	(Hataji et al., 2010)

Therapeutic strategies	Inhibition of HMGB1	Model	References
Dexamethasone	Release	Monocyte activation	(Schierbeck et al., 2010)
DL-sulforaphane	Release	Macrophage activation	(Killeen et al., 2006)
Dexmedetomidine	Release	Macrophage activation; sepsis	(Chang et al., 2013; Xu et al., 2013b)
Daunomycin	Release	Cancer	(Lotfi et al., 2013)
Ethacrynic acid	Release	Macrophage activation	(Killeen et al., 2006)
Fluvastatin	Expression	Hyperlipidemia	(Haraba et al., 2011b)
Fluorocitrate	Release	Focal cerebral ischemia	(Hayakawa et al., 2010)
Edaravone	Release	Sepsis; cerebral infarction	(Kato et al., 2009; Kikuchi et al., 2009b)
Forsythoside B	Expression	Myocardial ischemia-reperfusion injury	(Jiang et al., 2010)
Enalapril (an angiotensin-converting enzyme inhibitor)	Release and expression	Sepsis	(Hagiwara et al., 2009e)
Etanercept	Expression	Chronic constriction injury	(Wang et al., 2013i)
Gold sodium thiomalate	Release	Monocyte activation	(Schierbeck et al., 2010)
Gabexate mesilate	Expression	Sepsis	(Hidaka et al., 2011)
Glucocorticoid	Expression	Obstructive jaundice model	(Huang et al., 2011d)
Intravenous immunoglobulin G	Release	Sepsis	(Hagiwara et al., 2008a; Yoshikawa et al., 2012)
Intravenous parecoxib	Release	Cerebral ischemia-reperfusion injury	(Wang et al., 2011d)
Irbesartan	Activity	Stroke	(Kikuchi et al., 2013)
Lidocaine	Release	Macrophage activation	(Wang et al., 2013d; Wang et al., 2011b)
Losartan (a type 1 angiotensin II receptor antagonist)	Release	Sepsis	(Hagiwara et al., 2009b)
Landiolol (an ultrashort-acting beta1-adrenoceptor antagonist)	Release and expression	Sepsis	(Hagiwara et al., 2009d)
Lercanidipine	Release	Vascular smooth muscle cell activation	(Yeh et al., 2013)
Labedipinedilol-A	Release	Vascular smooth muscle cell activation	(Yeh et al., 2013)
Minocycline	Expression	Myocardial ischemia-reperfusion injury; microglia	(Hayakawa et al., 2008b;

Therapeutic strategies	Inhibition of HMGB1	Model	References
			Hu et al., 2010)
Methotrexate	Release	Macrophage activation; cancer	(Kuroiwa et al., 2013)
Metformin	Release	Sepsis; Hyperglycemia-treated neonatal rat ventricular myocytes	(Tsoyi et al., 2011b; Zhang et al., 2014c)
Magnesium sulfate	Expression and release	Macrophage activation	(Liu et al., 2013d)
Niaspan	Release	Type-1 diabetes	(Ye et al., 2011)
Nafamostat mesilate	Expression and release	Sepsis	(Hagiwara et al., 2007)
Oxaliplatin	Release	Arthritis	(Ostberg et al., 2008)
Oltipraz	Release	Macrophage activation	(Killeen et al., 2006)
Polymyxin B	Release	Sepsis	(Morita et al., 2004)
Propofol	Expression	Gastric mucosal injury	(Ye et al., 2013a)
Rosuvastatin	Expression	Myocardial ischemia-reperfusion injury	(Du et al., 2014)
Sivelestat	Release	Liver resection injury; macrophage activation; sepsis	(Hagiwara et al., 2009c; Hagiwara et al., 2008e; Tsujii et al., 2012)
Statins	Activity	Endothelial cell activation	(Yang et al., 2010c)
Sodium butyrate	Release	Sepsis	(Zhang et al., 2007)
Stearoyl lysophosphatidylcholine	Release	Sepsis	(Chen et al., 2005)
Simvastatin	Release and expression	Sepsis; vascular inflammation and atherosclerosis	(Liu et al., 2013c; Zhang et al., 2012b)
Surfactant protein A	Release and activity	Dendritic cell maturation	(Ledford et al., 2010)
Sodium salicylate	Release	Cancer and necrosis	(Lim et al., 2008)
Tetrandrine (a bisbenzylisoquinoline alkaloid)	Release	Sepsis	(Lin et al., 2009)
Telmisartan	Activity	Stroke	(Kikuchi et al., 2013)
Ulinastatin (a human urinary trypsin inhibitor)	Release and expression	Sepsis; Forebrain ischemia-reperfusion injury	(Koga et al., 2010; Tanaka et al., 2010)
HMGB1-receptor and signaling pathway inhibition			

Therapeutic strategies	Inhibition of HMGB1	Model	References
sRAGE	Inhibition of HMGB1-RAGE pathway	Sepsis, cancer	(Liliensiek et al., 2004)
Anticoagulant agents			
Thrombomodulin	Activity and release	Sepsis	(Abeyama et al., 2005; Nagato et al., 2009)
Danaparoid sodium	Expression	Heat stroke; sepsis; acute pancreatitis	(Hagiwara et al., 2008c; Hagiwara et al., 2011b; Hagiwara et al., 2009g)
Activated protein C	Release and activity	Endothelial cell activation	(Bae and Rezaie, 2011)
Antithrombin III	Activity, expression and release	Innate immune rejection; acute pancreatitis; sepsis	(Hagiwara et al., 2008d; Hagiwara et al., 2009f, 2010b; Kojima et al., 2012a)
Low molecular weight heparin	Expression and activity	Sepsis	(Luan et al., 2014)
2-O, 3-O-desulfated heparin	Release	Airway inflammation	(Griffin et al., 2013)
Lower concentration thrombin	Release and activity	Endothelial cell activation	(Bae, 2012)
Endogenous hormones			
Insulin	Release	Sepsis; cardiopulmonary bypass	(Hagiwara et al., 2009a; Hagiwara et al., 2008b; Hasegawa et al., 2011; Liu et al., 2012c)
Neuropeptides	Release and activity	Sepsis	(Chorny and Delgado, 2008; Tang et al., 2008c)
Insulin-like growth factor 1	Release	ox-LDL-induced inflammation	(Yu et al., 2012a)
Ghrelin	Release	Sepsis	(Chorny et al., 2008; Wang et al., 2009d)
Glucagon-like peptide-1 (a gut incretin hormone secreted from L cells)	Expression	Cardiocyte injury	(Cai et al., 2012)
Vagus nerve stimulation			
Chemical (nicotine, GTS-21, choline) ; Electrical; Mechanical	Release	Arthritis; sepsis	(Huston et al., 2007; Li et al., 2010c; Ni et al., 2011; Parrish et al., 2008; Pavlov et al., 2007; Rosas-

Therapeutic strategies	Inhibition of HMGB1	Model	References
			Ballina et al., 2009; Wang et al., 2004a)
Artificial DNAs			
Kinked oligonucleotide duplexes	Activity	Sepsis	(Musumeci et al., 2011; Yanai et al., 2011)
Bent oligonucleotide duplexes	Activity	Cell free system	(Musumeci et al., 2007; Yanai et al., 2011)

Table 5

HMGB1 Measurements and Significance in Clinical Practice

Disease	Sample	Significance	References
Respiratory system			
Chronic rhinosinusitis with/without nasal polyposis	Nasal mucosa epithelial cells and inflammatory cells of patients	Expression and secretion markers of upper airway inflammatory diseases	(Bellussi et al., 2013)
Asthma	Sputum	HMGB1 plays a key role in the pathogenesis of clinical and experimental asthma characterized by eosinophilic airway inflammation	(Shim et al., 2012)
Acute respiratory distress syndrome (ARDS)	Plasma	Active involvement of HMGB1-RAGE axis in poor prognosis of ARDS	(Splichalov a et al., 2011)
Non-small cell lung cancer (NSCLC)	Serum	No clinical significance in the prognosis of the survival time in lung cancer	(Naumnik et al., 2009)
Community-acquired pneumonia (CAP)	Serum	HMGB1 is elevated in almost all CAP subjects, and higher circulating HMGB1 is associated with mortality of CAP	(Angus et al., 2007)
Chronic obstructive pulmonary disease (COPD)	Broncho-alveolar lavage	Elevated HMGB1 expression in COPD airways may sustain inflammation and remodeling through its interaction with IL-1β and RAGE	(Ferhani et al., 2010)
Non-small cell lung cancer (NSCLC)	Tissue	Diagnosis and prognosis of outcome	(Liu et al., 2010a)
Non-small cell lung cancer (NSCLC)	Serum	Useful clinical marker for evaluating NSCLC progression and potential prognostic value	(Shang et al., 2009)
Acute lung injury (ALI)	Plasma and lung epithelial lining fluid	Extracellular HMGB1 may play a key role in the pathogenesis of clinical and experimental ALI	(Ueno et al., 2004)
Cystic fibrosis (CF) with acute pulmonary exacerbations	Sputum	HMGB1 is potential CF reporting tools and treatment targets	(Liou et al., 2012)
Lung injury	Blood and Bronchoalveolar lavage (BALF), BALF macrophages	Diagnosis and prognosis of outcome	(Bitto et al., 2010)
Thoracic esophagectomy	Serum	A predictive marker for complications in this setting	(Suda et al., 2006)
Chronic obstructive pulmonary disease (COPD)	Plasma	In smokers, high expression of HMGB1 in the blood and lungs is related to lung function impairment and appears to be associated with the development of COPD	(Ko et al., 2013)
Asthma and chronic obstructive pulmonary disease (COPD)	Sputum	HMGB1 may contribute to airway inflammation through its higher expression in bronchial asthma and COPD patients	(Cheng et al., 2011b)
Chronic obstructive pulmonary disease (COPD)	Peripheral airways	A potentially interesting target for treatment	(Kanazawa et al., 2012)
Bronchial asthma	Sputum	Predictors of therapeutic effects	(Cheng et al., 2011a)
Asthma and chronic obstructive pulmonary disease (COPD)	Bronchial lavage fluid	Neutrophilic airway inflammation in asthma and COPD is associated with reduced sRAGE	(Sukkar et al., 2012)

Disease	Sample	Significance	References
Chronic obstructive pulmonary disease (COPD)	Sputum and plasma	A potential role for HMGB1 as a biomarker and diagnostic tool for the differential diagnosis of asthma and COPD	(Hou et al., 2011a)
Pneumonia	Serum	Differential diagnosis	(Zhou et al., 2011d)
Acute respiratory distress syndrome (ARDS)	Blood	HMGB1 and oxidative stress play a role in the pathogenesis of ARDS	(Nakamura et al., 2009a)
Cystic fibrosis airway disease	Sputum	HMGB1 expression contributes to pulmonary inflammation and lung matrix degradation in CF airway disease	(Rowe et al., 2008)
Urogenital system			
Bladder cancer (BC)	Tumor tissue	A new molecular marker to predict the prognosis of patients with BC	(Yang et al., 2012c)
Clear cell renal cell carcinoma (CCRCC)	Tissue	HMGB1 promotes the development and progression of CCRCC	(Lin et al., 2012a)
Recurrent squamous cell carcinoma of uterine cervix	Tissue and serum	A useful and specific marker for evaluating the disease recurrence and predicting prognosis	(Sheng et al., 2009)
Acute kidney injury	Serum	HMGB1 is related to inflammatory parameters	(Zakiyanov et al., 2013b)
Bladder cancer	Tissue	HMGB1 serves as a potential diagnostic and therapeutic target	(Wang et al., 2013j)
Prostate cancer	Tissue	HMGB1 presents as a novel prognostic factor	(Li et al., 2012e)
Kidney transplantation after donor brain death	Tissue	Prognosis of outcome	(Kaminska et al., 2011)
Clear cell renal cell carcinoma	Tissue	Relocation of HMGB1 to cytoplasm was correlated with tumor grades	(Wu et al., 2013a)
Renal clear cell cancer	Tissue	HMGB1 expressed in the cytoplasm may be an effective marker of tumor grade	(Takeuchi et al., 2013)
Renal diseases	Serum	Predictor of disease progression	(Sato et al., 2008)
Immune system			
Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV)	Serum	In contrast to systemic lupus erythematosus, HMGB1 is not a useful biomarker in AAV	(de Souza et al., 2013b)
Juvenile idiopathic arthritis (JIA)	Blood and synovial fluid	A mediator of JIA pathogenesis as well as a biomarker for inflammatory activity and as a target for therapy	(Schierbeck et al., 2013)
systemic lupus erythematosus (SLE)	Serum	HMGB1 contributes to the development of inflammatory lesions in the skin of SLE patients upon UVB exposure	(Abdulahad et al., 2013)
Systemic lupus erythematosus	Serum and urinary	Urinary HMGB1 might reflect both local renal inflammation as well as systemic inflammation	(Abdulahad et al., 2012)
Rheumatoid Arthritis (RA)	Peripheral blood mononuclear cells	Correlates with RA immunotherapy and pathogenesis	(Shi et al., 2012a)
Rheumatoid Arthritis (RA)	Serum	serum HMGB1 levels in postmenopausal women with RA could serve as a useful marker of inflammatory activity in these patients	(Pullerits et al., 2011)

Disease	Sample	Significance	References
Systemic lupus erythematosus (SLE)	Serum	HMGB1, HMGB1-anti-HMGB1 immune complexes play a role in the pathogenesis of SLE	(Abdulahad et al., 2011)
Rheumatoid Arthritis (RA)	Synovial biopsy specimen	Therapeutic target in RA	(Sundberg et al., 2008)
Systemic lupus erythematosus (SLE)	Tissue	HMGB1 is an important factor in the inflammatory autoimmune process of CLE	(Barkauskaite et al., 2007)
Alopecia areata (AA)	Serum	A promising predictor of prognosis and treatment response, a new potential therapeutic target for the treatment of AA	(Lee et al., 2013g)
Lupus nephritis (LN)	Tissue	This study clearly indicates a role for HMGB1 in LN	(Zickert et al., 2012)
Behçet's disease (BD)	Serum	extracellular HMGB1 may play an important role in the pathogenesis of BD	(Ahn et al., 2011)
Rheumatoid arthritis (RA)	PBMCs	HMGB1 plays a pivotal role in the pathogenesis of RA and may be a target of therapy as a novel cytokine	(Zuo et al., 2007)
Systemic sclerosis (SSc)	Serum	Associated with the disease severity and immunological abnormalities in SSc	(Yoshizaki et al., 2009)
Polymyositis and dermatomyositis	Endothelial cells and muscle fibers	Correlated with pathogenesis of polymyositis and dermatomyositis	(Ulfgren et al., 2004)
Juvenile SLE	Serum	A potential marker of disease activity	(Kanakoudi-Tsakalidou et al., 2014)
Fibromyalgia (FM)	Serum	HMGB1 protein might be a good laboratory-sourced candidate for the assessment of functional status and disease severity in patients with FM	(Li et al., 2014a)
Ankylosing spondylitis (AS)	Serum	HMGB1 might play an important role in the pathogenesis of AS as well as a new therapy option in AS	(Oktayoglu et al., 2013)
Neuromyelitis optica (NMO) and multiple sclerosis (MS)	Cerebrospinal fluid	Reflect the neuroinflammatory process in disease	(Wang et al., 2013c)
Neuromyelitis optical	Plasma	Serve as a surrogate marker for NMO disease activity and aid in differential diagnosis.	(Wang et al., 2012a)
Allergic rhinitis (AR)	Nasal lavage fluid	Nasal HMGB1 has significantly increased in children with AR and is significantly related to symptom severity	(Salpietro et al., 2013)
Systemic sclerosis	Serum	Contribute to disease progression	(Maugeri et al., 2012a)
Myasthenia gravis (MG)	Serum	Correlate with the pathophysiology of MG. Further studies are warranted to elucidate more about this immunological axis in patients with MG	(Moser et al., 2012)
Granulomatosis with polyangiitis	Serum	HMGB1 may be used as a marker of the burden of granulomatous inflammation in GPA	(Henes et al., 2011)
Systemic lupus erythematosus (SLE)	Plasma	HMGB1 associated with disease activity in SLE	(Ma et al., 2012a)
Wegener's granulomatosis (WG) and ANCA-associated vasculitis (AAV)	Serum	HMGB1 may be useful as a marker of disease activity in WG and as a discriminating marker between different forms of AAV	(Wibisono et al., 2010)

Disease	Sample	Significance	References
Systemic lupus erythematosus (SLE)	Serum	HMGB1 in SLE may be associated with lupus disease activity	(Li et al., 2010b)
(ANCA)-associated vasculitis (AAV)	Serum	HMGB1 is useful as a marker of disease activity and a predictor of outcome in AAV	(Bruchfeld et al., 2011)
Kawasaki syndrome	Serum	In conclusion, an elevated HMGB1 value could be a potential marker for poor-responders	(Eguchi et al., 2009)
Kawasaki disease (KD)	Serum	HMGB1 plays an important role in immune responses in KD patients	(Hoshina et al., 2008)
Rheumatoid arthritis (RA)	Serum	Correlated with disease progression	(Goldstein et al., 2007)
Churg-Strauss syndrome	Serum	HMGB1 might contribute to the pathogenesis of CSS	(Taira et al., 2007)
Circulatory system			
Cardiopulmonary bypass (CPB)	Serum	HMGB1 levels may be used as an indicator of inflammation and may be a novel target during CPB	(Zhang et al., 2013j)
Non-ST-segment elevation myocardial infarction (NSTEMI)	Serum	A potential and independent predictor of outcome	(Hashimoto et al., 2012)
ST-segment elevation myocardial infarction (STEMI)	Plasma	Plasma HMGB1 may be used as a new prognostic biomarker in STEMI patients	(Sorensen et al., 2011a)
Effects of exercise training on acute myocardial infarction	Serum	Prognosis of outcome	(Giallauria et al., 2011)
Acute myocardial infarction	Serum	Prognosis of outcome	(Giallauria et al., 2010)
ST-elevation MI	Serum	Predictor of adverse clinical outcomes	(Kohno et al., 2009)
Atrial fibrillation (AF)	Serum	Significant independent predictors of AF	(Wu et al., 2013d)
Coronary artery disease	Serum	The levels of HMGB1 were correlated with the levels of high-sensitivity C-reactive protein (hs-CRP) and cardiac troponin	(Yao et al., 2013)
Cardiomyopathy	Tissue	Correlated with disease outcome	(Funayama et al., 2013)
Abdominal aortic aneurysm (AAA)	Human AAA samples	These findings suggest a significant role for HMGB1 in the pathogenesis of AAA	(Kohno et al., 2012)
Cardiac arrest	Serum	Associated with outcome	(Oda et al., 2012)
Exertional Heatstroke	Plasma	An indicator of the severity of illness and a useful mortality predictor in exertional heatstroke	(Tong et al., 2011)
Cardiac surgery patient	Plasma	Contribute to disease progression	(Haque et al., 2011)
Heart failure	Serum	Related with disease progression	(Wang et al., 2011c)
Myocardial infarction (MI)	Serum	A highly valuable surrogate marker for infarct transmurality and for the prediction of residual left ventricular function after MI	(Andrassy et al., 2011)
Thoracic aortic aneurysm (TAA) repair	Serum	HMGB1 might play a key role in the pathogenesis of SIRS after surgical TAA repair	(Kohno et al., 2011)

Disease	Sample	Significance	References
Coronary artery stenosis	Serum	Correlated with disease severity	(Hu et al., 2009)
Coronary artery disease in nondiabetic and type 2 diabetic patients	Serum	Correlated with disease severity	(Yan et al., 2009)
Digestive system			
Pancreatic cancer (PC)	Serum	Courses of HMGB1 show prognostic relevance in PC patients undergoing chemotherapy	(Wittwer et al., 2013b)
Colorectal cancer after radioembolization	Serum	A valuable serum biomarker for early estimation of therapy response and prognosis in colorectal cancer patients	(Fahmueller et al., 2013)
Human primary liver cancer	Tissue	Represent a potential therapeutic target for this aggressive malignancy	(Dong et al., 2013)
Liver cancer patients receiving transarterial chemoembolization therapy	Serum	There was no difference with respect to treatment response for DNase and HMGB1	(Kohles et al., 2012)
Acetaminophen hepatotoxicity	Serum	HMGB1 represent blood-based tools to investigate the cell death balance clinical APAP hepatotoxicity. Acetylated HMGB1 was associated with worse outcome	(Antoine et al., 2012b)
Gastric cancer	Serum	HMGB1 appears to be a useful serological biomarker for early diagnosis as well as evaluating the tumorigenesis, stage, and prognosis of gastric cancer	(Chung et al., 2009)
Esophageal squamous cell carcinoma (ESCC)	Serum	HMGB1 may be used as a marker in diagnosis, prediction of prognosis and monitor of postoperative recurrence of ESCC	(Chen et al., 2013a)
Autologous islet transplantation	Serum	Therapeutic target	(Itoh et al., 2012a)
Esophageal squamous cell carcinoma (ESCC)	Serum	Related to clinical outcome after chemoradiation	(Suzuki et al., 2012)
Liver resection	Serum	Correlated with therapy effect	(Tsujii et al., 2012)
Acute appendicitis (AA)	Serum	HMGB-1 might be useful in the diagnosis of AA	(Albayrak et al., 2011)
Inflammatory bowel disease	Serum	Correlated with disease progression	(McDonnell et al., 2011)
Carcinoma of the thoracic esophagus who underwent transthoracic esophagectomy	Serum	Predictor of therapy effect	(Suda et al., 2007)
Severe acute pancreatitis (SAP)	Serum	These results suggest that HMGB1 may act as a key mediator for inflammation and organ failure in SAP	(Yasuda et al., 2006)
Hepatocellular carcinoma (HCC)	Tissue	An important pathogenetic factor in HCC	(Jiang et al., 2012a)
Gastrointestinal surgery	Serum	Correlated with disease progression	(Takahata et al., 2011)
Colorectal carcinoma	Tissue	Co-expression of RAGE and amphoterin is closely associated with invasion and metastasis of colorectal cancer	(Kuniyasu et al., 2003b)
Hepatocellular carcinoma (HCC)	Serum	A useful marker for evaluating the tumor stage and predicting prognosis in HCC, as well as therapeutic target.	(Cheng et al., 2008)
Acetaminophe n-induced acute liver injury	Plasma	The application of such a biomarker panel could improve the speed of clinical decision-making.	(Antoine et al., 2013)

Disease	Sample	Significance	References
Acute liver failure	Tissue	Cytoplasmic HMGB1 translocation contributes to the pathogenesis of liver inflammatory diseases	(Zhou et al., 2011b)
Malignant peritoneal mesothelioma	Serum	A useful serum marker for diagnosis	(Tabata et al., 2013a)
Esophageal squamous cell carcinoma	Carcinoma cells	HMGB1 might serve as the marker of progression and potential target for anti-lymphangiogenesis therapy	(Chuangui et al., 2012)
Acute-on-chronic liver failure (ACLF)	PBMCs and serum	HMGB1 plays a critical role in the systemic inflammation of ACLF and could be a potential therapeutic target in the treatment of ACLF	(Zhou et al., 2012b)
Gastric cancer	Tissue	Combined evaluation of HMGB1 and VEGF-C may serve as a valuable independent prognostic factor for GC patients	(He et al., 2013)
Malignant pleural mesothelioma (MPM)	Serum	A useful prognostic factor for MPM	(Tabata et al., 2013b)
Hepatocellular carcinoma (HCC)	Tissue	Contribute to disease progression and become useful prognosis factor	(Liu et al., 2012b)
Pancreatic ductal adenocarcinoma	Serum	A desirable diagnostic and prognostic biomarker for PDAC	(Chung et al., 2012)
Acute liver failure (ALF)	Plasma	HMGB1 levels were increased in patients with ALF	(Oshima et al., 2012)
Colorectal carcinoma	Serum	A supportive diagnostic marker for colorectal carcinomas	(Lee et al., 2012b)
Colon cancer	Tissue	Diagnosis value	(Soldevilla et al., 2011)
Pediatric inflammatory bowel disease	Fecal	A novel marker for intestinal inflammation	(Vitali et al., 2011)
Esophageal squamous cell carcinoma	Tissue	could be used as tumor-associated antigen (TAA) biomarkers in cancer diagnosis	(Zhang et al., 2011c)
Acute pancreatitis	Serum	Predictor for prognosis	(Lindstrom et al., 2009)
Colorectal cancer	Tissue	Contribute to disease progression	(Kijanka et al., 2010)
Acute pancreatitis	Serum	A complex study of the plasma levels of HMGB1, sRAGE and circulating DNA can be informative in evaluations of acute pancreatitis with different levels of severity	(Kocsis et al., 2009)
Human liver transplantation	Serum	A marker of hepatocellular injury in human liver transplantation	(Ilmakunnas et al., 2008)
Colon cancer	Tissue	HMGB1 might contribute to the progression of colon cancer via modulation of the local immune response	(Peng et al., 2010)
Colon carcinoma	Tissue	Contribute to disease progression	(Volp et al., 2006)
Gastrointestinal stromal tumors	Tissue	Contribute to disease progression	(Choi et al., 2003)
Colorectal	Macrophages in the lymph nodes of colorectal cancer	Contribute to disease progress	(Moriwaka et al., 2010)
Ear, Nose, and Throat			

Disease	Sample	Significance	References
Laryngeal squamous cell carcinoma	Tissue	HMGB1 contribute to disease development and may be an independent prognostic factor	(Tang et al., 2013b)
Laryngeal squamous cell carcinoma (LSCC)	Tissue	HMGB1 may become a valuable marker for the prediction of prognosis in patients with LSCC	(Liu et al., 2012d)
Laryngeal squamous cell carcinoma (LSCC)	Tissue	HMGB1 might play a critical role in the initiation and progression of LSCC	(Liu et al., 2011e)
Squamous-cell carcinoma of the head and neck (SCCHN)	Tissue	HMGB1 may contribute to the malignant progression of SCCHN, and present as a novel prognostic marker and a potential therapeutic target for patients with SCCHN	(Liu et al., 2010d)
Sasopharyngeal carcinoma (NPC)	Tissue	Predictor for clinical outcome	(Wu et al., 2008)
Laryngeal squamous cell carcinoma (LSCC)	Tissue	Correlated with tumor stage	(Guo et al., 2012)
Chronic rhinosinusitis with nasal polyposis	Tissue	HMGB1 may play a crucial role in the pathogenesis of chronic rhinosinusitis with nasal polyps	(Bellussi et al., 2012)
Chronic rhinosinusitis	Paranasal sinus mucosa	A possible contribution of HMGB1in the pathophysiology of CRS	(Hong et al., 2013)
Head and neck cancer	Serum and tumor cells	Contribute to disease progression	(Wild et al., 2012b)
Ophthalmology			
Conjunctivitis and Blepharitis	Tears	Contribute to disease progression	(Cavone et al., 2011a)
Children affected by vernal keratoconjunctivitis	Serum	Contribute to disease progression	(Zicari et al., 2013)
Proliferative vitreoretinopathy	Stromal cells	The HMGB1/RAGE/OPN/Egr-1 pathway may be involved in inflammatory, angiogenic and fibrotic responses in proliferative vitreoretinal disorders	(El-Asrar et al., 2011a)
Endophthalmitis	Tissue	Contribute to disease progression	(Arimura et al., 2008)
Hematology			
T-cell lymphoma	Tissue	Elevated expression of HMGB1 may be an important biomarker for the development and progression of T-cell lymphoma	(Mao et al., 2012)
Children with acute lymphocytic leukemia	Serum	Predictor of prognosis	(Kang et al., 2007)
Disseminated intravascular coagulation(DIC)	Plasma	A potentially suitable prognostic marker of DIC	(Hatada et al., 2005)
Chronic idiopathic neutropenia	Bone marrow cells	Contribute to disease progression	(Velegraki et al., 2012)
Non-Hodgkin lymphoma	Tissue	An interesting therapeutic target as well	(Meyer et al., 2008)
Nervous system			
Multiple sclerosis (MS)	Cerebrospinal fluids	HMGB1 in the CNS is a useful biomarker and may contribute to the chronicity of neuroinflammation	(Andersson et al., 2008)
Neuromyelitis optica (NMO)	Cerebrospinal fluids	HMGB1 could play a key role in central nervous system inflammation in NMO patients	(Uzawa et al., 2013a)

Disease	Sample	Significance	References
Ischemic stroke	Plasma	Plasma HMGB1 level represents a novel biomarker for predicting outcomes of ischemic stroke	(Huang et al., 2013c)
Aneurysmal subarachnoid hemorrhage	Plasma	HMGB1 level is a useful, complementary tool to predict functional outcome and mortality after aneurysmal subarachnoid hemorrhage	(Zhu et al., 2012b)
Traumatic brain injury (TBI)	Plasma	Plasma HMGB1 concentration emerges as a novel biomarker for predicting clinical outcomes of TBI	(Wang et al., 2012b)
Acute cerebral infarction (ACI)	Serum	Might be helpful to evaluate the severity and prognosis of ACI	(Zhou et al., 2012a)
Neonates with hypoxic-ischemic encephalopathy	The umbilical artery HMG B1	HMGB1 is a useful index of the inhibition of early stage inflammation.	(Nakamura et al., 2013)
Traumatic brain injury	Tissue	Might be a therapeutic target	(Gao et al., 2012)
Pediatric traumatic brain injury	Cerebrospinal fluids(CSF)	These data are also consistent with the designation of HMGB1 as a "danger signal"	(Au et al., 2012)
Intracranial inflammatory lesions	cytoplasm collapse	Contribute to disease progression	(Hirano et al., 2012)
Febrile seizure	Serum	Might be a therapeutic target	(Choi et al., 2011)
Several neurological diseases	Cerebrospinal fluids(CSF)	HMGB1 is a poor disease marker for acute encephalopathy	(Asano et al., 2011)
Acute intracerebral hemorrhage	Serum	Contribute to disease progression	(Zhou et al., 2010)
Stroke	Serum	Serum HMGB1 release are possible mediators in stroke induced activation of T cells	(Vogelgesang et al., 2010)
Subarachnoid hemorrhage (SAH)	Elisa	HMGB1 might play a key role in the inflammatory response in the CNS of SAH patients	(Nakahara et al., 2009)
Pediatric patients with meningitis	Spinal fluid	Contribute to disease progression	(Tang et al., 2008a)
Cerebral and myocardial ischemia	Serum	Systemic HMGB1 levels are elevated in human ischemic disease	(Goldstein et al., 2006)
Infectious diseases			
Acute liver failure	Serum	Correlate with disease pathogenesis	(Allonso et al., 2012)
Sepsis and septic shock	Serum	HMGB1is indeed a downstream mediator of inflammation	(Sunden-Cullberg et al., 2005)
2009 pandemic H1N1	Serum	Correlate with disease pathogenesis	(Momonaka et al., 2013)
Brucellosis	Serum	May be diagnostic markers for brucellosis	(Ayarci et al., 2013)
HIV-1	Serum	Contribute to disease progression	(Troseid et al., 2010)
Community acquired infections and bacteraemia	Serum	Whereas LBP, IL-6 and CRP seem to be good markers to detect patients with bacteraemia, HMGB1 seem to be of minor importance	(Pavare et al., 2010)
Severe infection	Plasma	Plasma HMGB1 was higher in HIV-infected children than in HIV-uninfected children	(Carrol et al., 2009)

Disease	Sample	Significance	References
Severe infection	Serum	Correlate with disease pathogenesis	(van Zoelen et al., 2007)
Multiple organ dysfunction syndrome, coupled plasma filtration adsorption (CPFA)	Serum	Predictor of therapy effect	(Hu et al., 2012a)
Sepsis-induced immunosuppression	Serum	Used for monitoring of monocytic function in immunostimulatory trials	(Unterwalder et al., 2010)
Septic shock	Serum	Predictor of therapy effect	(Sakamoto et al., 2007)
Pulmonary tuberculosis	Lung tissue and serum	The measurement of serum HMGB1 is useful to evaluate the severity of disease	(Yang and Yang, 2013)
HIV-infection	Plasma	Contribute to disease progression	(Troseid et al., 2013)
Malaria	Serum	Could offer a potential target for therapeutic intervention	(Angeletti et al., 2013)
Severe and fatal Plasmodium falciparum malaria	Plasma	An informative prognostic marker of disease severity	(Higgins et al., 2013)
M. tuberculosis infection	Serum	HMGB1 is secreted during active and latent tuberculosis in the highest amounts compared to other lung diseases	(Magrys et al., 2013)
2009 H1N1 influenza virus	Serum	HMGB1 could play an important role in the pathogenesis of severe pneumonia	(Ito et al., 2011)
Sepsis in severely burned patients.	Plasma	Dynamic measurements of circulating HMGB1 levels should be helpful to monitor the disease course and judge the prognosis of burned patients	(Dong et al., 2007)
Suspected community-acquired infections and sepsis	Serum	Levels of HMGB1 correlated only very weakly to other pro-inflammatory markers and did not correlate to the anti-inflammatory marker sCD163	(Gaini et al., 2007)
Septic shock	Serum	Contribute to disease progression	(Nakamura et al., 2011c)
Chronic hepatitis B	Serum	Serve as a therapeutic marker	(Wang et al., 2010d)
Severely burned patients	Serum	Correlated with disease progression	(Huang et al., 2011b)
Bacteraemia	Serum	Neither HMGB1 nor any of the proinflammatory markers were elevated in fatal cases compared to survivors	(Gaini et al., 2008)
Severe sepsis	Serum	Serum HMGB1 concentrations were elevated in patients with severe sepsis	(Karlsson et al., 2008)
Septic shock	Serum	Correlate with disease stage	(Gibot et al., 2007)
HEV	Serum	Contribute to disease progression	(Majumdar et al., 2013)
Falciparum malaria	Serum	Contribute to disease progression	(Alleva et al., 2005)
Severe sepsis and septic shock	Serum	Contribute to disease progression	(Sasahira et al., 2005a)
Hepatitis B	Serum	HMGB1 is a noninvasive, repeatable, and convenient marker for distinguishing advanced fibrosis from low fibrosis in chronic HBV patients	(Albayrak et al., 2010)

Disease	Sample	Significance	References
Chronic hepatitis B (HBV)	Serum	HMGB1 may play a key role in the pathogenesis of chronic severe hepatitis B and liver failure	(Liu et al., 2007b)
HBV-related ACLF	Serum	HMGB1 may be useful as a prognostic marker for development of ACLF	(Duan et al., 2013)
Dermatology			
Recessive dystrophic epidermolys is bullosa	Serum	HMGB1 levels may represent a new biomarker reflecting disease severity	(Petrof et al., 2013)
Psoriasis vulgaris (PV) and atopic dermatitis (AD)	Serum	HMGB1 might be involved in the pathogenesis of PV	(Chen et al., 2013d)
Epidermal tumors	Seborrheic keratosis	They also indicate that the TLR4 signaling pathway, rather than HMGB1, may be the principal mediator of inflammation in high-grade malignant epidermal tumors	(Weng et al., 2013)
Stevens-Johnson Syndrome	Serum	Would be a useful diagnostic tool	(Nakajima et al., 2011)
Psychiatry			
Autistic disorder	Serum	Compared with healthy subjects, serum levels of HMGB1 were significantly higher in patients with autistic disorder	(Emanuele et al., 2010)
Autism	Serum	EGF levels correlated with HMGB1 levels but not the other tested putative biomarkers	(Russo, 2013)
Endocrine system			
Type 1 and 2 diabetes mellitus	Serum	Reflect endothelial dysfunction developing in diabetes	(Skrha et al., 2012)
Proliferative diabetic retinopathy (PDR)	Serum	HMGB1 regulates the angiogenesis in PDR	(Abu El-Asrar et al., 2012)
Proliferative diabetic retinopathy (PDR)	Serum	Contribute disease progression	(El-Asrar et al., 2011b)
Proliferative diabetic retinopathy	Serum	Contribute disease progression	(Abu El-Asrar et al., 2013)
Type 1 diabetes	Serum	Associated with a higher risk of all-cause mortality	(Nin et al., 2012a)
Type 1 diabetes	Serum	Contribute disease progression	(Nin et al., 2012b)
Type 2 diabetes	Serum	Contribute disease progression	(Dasu et al., 2010)
Type 1 diabetes	Serum	Contribute disease progression	(Devaraj et al., 2009)
Gynecology and obstetrics			
Normal pregnancy and preeclampsia	Serum	Serum	(Naruse et al., 2012)
Preterm parturition	Amniotic fluid	Contribute disease progression	(Romero et al., 2011)
Early neonates	Plasma	Contribute disease progression	(Nakamura et al., 2012b)
Preeclampsia	Placental tissue	Contribute disease progression	(Wang et al., 2011a)
Inflammation-Induced Preterm Birth and Fetal Tissue Injury	Fetal circulation	Important mediators of cellular injury in fetuses delivered in the setting of inflammation-induced preterm birth	(Buhimschi et al., 2009)

Disease	Sample	Significance	References
Preterm and term cervix	Tissue	Contribute disease progression	(Dubicke et al., 2010)
Pre-eclampsia	Placenta	Contribute disease progression	(Gao et al., 2008)
Human endometrium	Endometrium	HMGB1 is expressed in the human endometrium, and its expression is modulated by E2, progesterone, and nitric oxide	(Zicari et al., 2008)
Human term placental	Placenta	Contribute disease progression	(Holmlund et al., 2007)
Chondrosarcoma	Tissue	The numbers of cells positive for HMGB1 expression are positively associated with histologic grade	(Takeuchi et al., 2007)
Breast cancer after the initial dose of epirubicin/doc etaxel	Plasma	HMGB1 could be a promising biomarker to predict the final response to therapy in breast cancer patients	(Arnold et al., 2013)
Breast cancer patients during neoadjuvant chemotherapy	Serum	Valuable for the diagnosis and early estimation of response to n therapy	(Stoetzer et al., 2013)
Ovarian cancer	Tissue	HMGB1 may serve as a new biomarker and a therapeutic target for ovarian cancer in the future	(Chen et al., 2012a)
Human epithelial ovarian cancer	Tissue	Contribute to disease progression and serve as a therapeutic target for ovarian cancer	(Zhang et al., 2013e)
Chorioamnionitis	Amniotic fluid	HMGB1are engaged in the process of clinical chorioamnionitis at term	(Romero et al., 2012)
Department of stomatology			
Periodontitis	Tissue	HMGB1 may be a potential target for the therapy of periodontitis	(Xie et al., 2011)
Metabolic disorders			
Obese children	Serum	HMGB1 may be an important diagnostic marker for obesity-related complications	(Arrigo et al., 2013)
Hyperlipidemia	Serum	Serum HMGB1 levels are increased in patients with hyperlipidemia which could be reduced by atorvastatin	(Jin et al., 2012)
Trauma			
Severe trauma	Serum	Serum HMGB1 of severe trauma patients can be used for the clinical indicator of prognosis	(Dang et al., 2011)
Multiple trauma	Serum	HMG-1 can be used as a warning indicator of the onset of MODS	(Fei et al., 2005)
Surgical/anesthesia trauma	Serum	Contribute to disease progression	(Manganelli et al., 2010)
Mechanical trauma	Plasma	A potential target for future therapeutics.	(Peltz et al., 2009)
Burn trauma	Plasma	Contribute to disease progression	(Lantos et al., 2010)
Extensively burned patient	Plasma	Might be involved in the pathogenesis of suppression of T cell-mediated immunity in these patients	(Dong et al., 2008)
Emergencies			
Emergent diseases	Serum	HMGB-1 is not significantly sensitive or specific for diagnosis of sepsis	(Gamez-Diaz et al., 2011)

Disease	Sample	Significance	References
Other			
Human malignant tumors	Tissue	Could have a prognostic meaning in carcinogenesis	(Kostova et al., 2010)
Cancerous and Inflammatory Effusions	Pleural and peritoneal effusions	A possible target for treatment in advanced cancer as well	(Winter et al., 2009)