Published in final edited form as:
Biochim Biophys Acta. 2010 ; 1799(1-2): 131. doi:10.1016/j.bbagrm.2009.11.014.

High-mobility Group Box 1 [HMGB1] and Cancer

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Abstract

High-mobility group box 1 protein (HMGB1), a chromatin associated nuclear protein and extracellular damage associated molecular pattern molecule (DAMP), is an evolutionarily ancient and critical regulator of cell death and survival. Overexpression of HMGB1 is associated with each of the hallmarks of cancer including unlimited replicative potential, ability to develop blood vessels (angiogenesis), evasion of programmed cell death (apoptosis), self-sufficiency in growth signals, insensitivity to inhibitors of growth, inflammation, tissue invasion and metastasis. Our studies and those of our colleagues suggest that HMGB1 is central to cancer (abnormal wound healing) and many of the findings in normal wound healing as well. Here, we focus on the role of HMGB1 in cancer, the mechanisms by which it contributes to carcinogenesis, and therapeutic strategies based on targeting HMGB1.

"The total high-mobility group proteins are only about 3%, by weight of the histone or DNA content, and they are therefore a small group of proteins compared to the histones. However, this quantity of proteins is still relatively large when compared to the quantity of protein one might expect if they were specific gene derepressors where only a few molecules per structural gene would be required." Graham H. Goodwin, C Live Sanders and Ernest W. Johns; Institute of Cancer Research, Royal Cancer Hospital, Chester Beatty Research Institute, London (Received May 21; Accepted June 21, 1973) [1]

Introduction

The high-mobility group box 1 protein (HMGB1) is present in almost all metazoans and plants. It was first identified as one of a group of chromatin-associated protein with high acidic and basic amino acid content [1]. HMGB1 is a highly conserved nuclear protein, acting as a chromatin-binding factor that bends DNA and promotes access to transcriptional protein assemblies on specific DNA targets (Figure1) [2,3]. In addition to its nuclear role, HMGB1 also functions as an extracellular signaling molecule during inflammation, cell differentiation, cell migration, and tumor metastasis [2–5]. HMGB1 is passively released from necrotic cells and is actively secreted by inflammatory cells, binding with high affinity to several receptors including the receptor for advanced glycation end products (RAGE), Toll-like receptors (TLR)-2, TLR-4, TLR-9, and, as a negative signaling molecule, CD24, mediating the response to infection and injury, thereby promoting inflammation (Figure1) [2,4,6–8]. HMGB1 has been implicated in disease states, including sepsis [9], ischemia-reperfusion [10], arthritis [11],

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meningitis [12], neurodegeneration [13], aging [14], and cancer [5,15,16]. Overexpression of HMGB1 is associated with all of the central hallmarks of cancer. HMGB1, along with other intracellular factors released from tumor cells induced by chemotherapy or radiotherapy, is an important component of the disordered tumor microenvironment. As such HMGB1 is the prototypic Damage Associated Molecular Pattern Molecule, or DAMP, associated with both acute inflammatory responses and driving much of the biology of chronic inflammation and wound repair [17][18]. Here we review current knowledge concerning the role of HMGB1 in the development of cancer and as a potential target for therapy.

HMGB1 Structure, Modification And Expression

HMGB1 is composed of two homologous DNA-binding domains (termed A box and B box, each 75 amino acids in length) and a highly negatively charged C-terminal domain consisting of a continuous stretch of glutamate and aspartate residues [1,19]. It is highly conserved with >99% amino acid identity when comparing rodent and human molecules. It is extensively modified posttranslationally in several ways: by glycosylation, acetylation, methylation, oxidation, and phosphorylation [2,3,20]. Only the acetylated form of HMGB1 protein apparently forms a specific complex with homologous DNA polymerase-α and stimulates its activity [21]. Acetylation and phosphorylation induce translocation of HMGB1 from the nucleus to the cytoplasm and increase HMGB1 secretion from macrophages and colon cancer cells [6,22,23]. Posttranslational methylation of HMGB1 causes its cytoplasmic localization in neutrophils [24]. A calcium- or reactive oxygen species (ROS)-dependent mechanism was confirmed to induce HMGB1 release [25,26]. Overexpression as well as cytoplasmic localization of HMGB1 has been observed in most tumor cells including gastrointestinal stromal tumors [27], colon [28], and cervical carcinomas [29]. Higher HMGB1 mRNA expression is increased in prostate cancer when compared with normal prostate tissue [30]. HMGB1 is upregulated in malignant melanoma cells and further activated by hypophosphorylation [31]. Estrogen treatment increases HMGB1 mRNA levels in breast cancer MCF-7 cells [32]. Advanced skin tumors have increased HMGB1 levels as do most epithelial malignancies [33]. The expression of HMGB1 is regulated by transcription factors such as p53 [34], c-Myc [35], and Kruppel-like factor (KLF)-4 [36] in various cell types (Figure1).

Nuclear Function of HMGB1

HMGB1 proteins are constitutively expressed in the nucleus of both cancer and normal cells. HMGB1's affinity for a number of different DNA structures has been measured. In addition to supercoiled, single-stranded, B- and Z-DNA, it binds preferentially to DNA mini-circles, four-way junctions, looped structures, hemicatenated DNA, and triplex DNA [37–40]. Native HMGB1 extracted from tumor cells inhibits DNA replication and this effect is reduced following acetylation and completely abolished upon removal of the acidic C-terminal tail. Recombinant HMGB1, however, fails to inhibit replication but it acquires this property following *in vitro* phosphorylation by protein kinase C (PKC) [41]. HMGB1 also interacts with and enhances the activities of a number of transcription factors implicated in cancer development (Figure1), including p53 [42–46], p73 [34,47], the retinoblastoma protein [48, 49], members of the Rel/NF-κB family [50,51], and nuclear hormone receptors including the estrogen receptor [52–55]. A nuclear protein complex containing HMGB1 and HMGB2, heat shock protein 70 (Hsp70), ERp60, and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) is involved in the cytotoxic response to DNA modified by incorporation of anticancer nucleoside analogues [56], suggesting that HMGB1 plays a critical role in DNA repair.

HMGB1 and p53

p53 family members are important in multicellular organisms, regulating cell cycle progression and functioning as a tumor suppressor. Recombinant His-tagged HMGB1 enhances p53 DNA binding *in vitro*, interacting directly with this molecule [42]. Interaction between HMGB1 and p53 requires expression of the A box [C-terminal domain] of HMGB1 [44] and the amino terminus (amino acids 363–376) of p53 [57]. HMGB1 provides the optimal DNA structure for p53 binding through its bending/binding effects [43]. Borna disease virus is a noncytolytic, neurotropic RNA virus that represses p53-mediated transcriptional activity by interference with HMGB1 [58]. Phosphorylation of p53 at Ser12 (corresponding to Ser9 in human p53) and Ser18 (corresponding to Ser15 in human p53), as well as phosphorylation of histone H2AX following 5-fluorouracil, cytosine arabinoside, and mercaptopurine treatment, is reduced in HMGB1-deficient mouse embryonic fibroblasts and the human carcinoma cell lines, A549 and UO31 [59,60].

HMGB1 and p73

p73, was the first identified homologue of p53. DNA damage that is elicited either by cisplatin, ultraviolet irradiation or γ-irradiation triggers a p73 pathway that is mediated by Mut L homologue-1 (MLH1) and c-ABL [61]. HMGB1 physically interacts with the two splicing variants of p73 (p73α and p73β), and enhances binding of p73 to specific cognate DNA sites. Both HMGB1 A box and B box, interact with p73α. Association of HMGB1 with p73, like the demonstrated ability of HMGB1 to stimulate p73 binding to different p53-responsive elements, requires the oligomerization region and/or region between the DNA-binding domain and oligomerization domain of p73 (residues 312–381) [47].

HMGB1 and RB

The retinoblastoma protein (RB) is a tumor suppressor protein that is dysfunctional in many types of cancer. HMGB1 associates with RB via an LXCXE motif-dependent interaction mechanism [49]. HMGB1 enhances the ability of RB to repress both E2F and cyclin-A transcription. Increased expression of HMGB1 confers an altered phenotype characterized by suppression of cell growth. G1 arrest and apoptosis is induced in the human breast adenocarcinoma MCF-7 containing the wild-type RB gene, but has no activity in the human breast carcinoma cell line, BT-549 containing an RB gene deletion [49].

HMGB1 and Rel/NF-κB

Transcription factors of the Rel/NF-κB family are activated in response to signals that lead to cell growth, differentiation, apoptosis, and these proteins are critical elements involved in the regulation of cancer. Drosophila protein DSP1, an HMGB1-like protein, binds DNA highly cooperatively with three members of the Rel family of transcriptional regulators (NF-κB, the p50 subunit of NF-κB, and the Rel domain of Dorsal) [50]. HMGB1 enhances DNA binding by p65/p50 and p50/p50, but reduces binding by p65/p65, c-Rel/c-Rel, p65/c-Rel, and p50/c-Rel [51]. In pull-down assays, HMGB1 interacts directly with the p50 subunit via its HMG boxes and this interaction is weakened by the presence of the acidic tail [51].

HMGB1 and Estrogen Receptor

The estrogen receptor (ER) belongs to a family of ligand-inducible nuclear receptors that exert their effects by binding to cis-acting DNA elements in the regulatory region of target genes. ER is over-expressed in around 70% of breast cancer cases. HMGB1 interacts with ER and promotes estrogen response element (ERE) binding in a concentration- and time-dependent manner [54,55]. Moreover, HMGB proteins facilitate strong ER binding to ERE consensus

half-sites, exhibiting binding affinities with comparable ER binding to consensus ERE in the absence of HMGB proteins [53].

Extracellular Function of HMGB1 in Cancer

Tumor cell stress and death can be induced by a panoply of distinct triggers including hypoxia, nutrient deprivation, absence of essential growth factors or application of conventional anticancer treatments (i.e. radiation and chemotherapy) [62]. HMGB1 presence in the extracellular medium indicates that some cells are stressed or have died and alert other cells to the clear and present, immediate danger [63,64] (Figure 1). Cells that undergo necrosis or tumor cells treated with chemotherapy release HMGB1, which has proinflammatory properties [6,65,66]. Cytolytic cells, both NK and specific T-cells, induce HMGB1 release from melanoma cell lines [67]. It has been thought that HMGB1 release would be a specific marker of necrosis. Nonetheless, both apoptotic and autophagic cells release HMGB1, at least under certain circumstances [68–72]. Recently, the redox status of HMGB1 has been discovered to be important for its immunological potential during apoptotic release [73]. *In vitro*, apoptotic cells activate macrophages to release HMGB1 [74]. In the case of tumors, HMGB1 recognition has a paradoxical dual effect. It both promotes tumor neoangiogenesis and also triggers protective anti-neoplastic T-cell responses [75]. HMGB1, released from dying tumor cells, stimulates mature dendritic cells (mDC) tumor antigen processing through its interaction with TLR-4 [76]. Neutralization or knockdown of HMGB1 or knockout of TLR-4 abolishes the capacity of dying tumor cells to elicit anticancer immune responses both *in vitro* and *in vivo* [77]. HMGB1 mediates endogenous TLR-2 activation and thereby brain tumor regression [78]. Moreover, ethyl pyruvate, a potent inhibitor of HMGB1 release, inhibits hepatic tumor growth and induces a so-called ‘field effect’ in HMGB1 distribution in hepatocytes [79]. Recently, CD24 and Siglec-G have been found to negatively regulate immune responses to HMGB1, but not to lipopolysaccharide (LPS) *in vivo* and *in vitro* [80]. HMGB1 interacts with RAGE on endothelial cells causing activation and leukocyte recruitment [16]. Blockade of RAGE-HMGB1 signaling suppresses tumor growth and metastases [81].

HMGB1 and the Hallmarks of Cancer

In 2000, Hanahan and Weinberg [82] proposed a model to define the six properties that a tumor acquires (Figure 2). These are unlimited replicative potential, ability to develop blood vessels (angiogenesis), evasion of programmed cell death (apoptosis), self-sufficiency in growth signals, insensitivity to inhibitors of growth, and tissue invasion and metastasis. Increasing evidence suggests that inflammation is the seventh feature [83–85]. All of these have been associated with alterations in HMGB1 location, abundance, or levels, thereby placing HMGB1 in the center of our modern understanding of cancer biology.

HMGB1 and Apoptosis

HMGB1 plays a major role in apoptosis, dependent on the cell type and antecedent stress. HMGB1 is an inhibitor of yeast cell death induced by the pro-apoptotic Bcl-2 family member, Bak. HMGB1 is also a suppressor of ER-associated apoptotic death due to calnexin overexpression in yeast [86]. HMGB1 protects mammalian cells against several death stimuli including ultraviolet radiation, CD95-, TRAIL-, Casp-8-, and Bax-induced apoptosis [87]. Down-regulation of HMGB1 expression results in apoptosis in LNCaP prostate cancer cells via caspase-3-dependent pathways [88]. Overexpression of HMGB1 in K562 leukemia cells sustains Bcl-2 protein expression and inhibits adriamycin (ADM)-induced activation of Caspase-3 and -9 [89]. Suppression of HMGB1 by siRNA in K562/A02 leukemia cells results in reversal of the resistance to ADM, and significantly promotes ADM-induced Smac/DIABLO release from the mitochondria to the cytoplasm, increasing the activation of Caspase-3 [90]. HMGB1 protein levels that are significantly elevated in human colon

carcinomas, when compared with control matched normal tissues, are also associated with increased expression of the antiapoptotic protein c-IAP2 [28]. IAP proteins bind and inhibit caspases limiting the downstream increase in cytochrome C release in mitochondria and thereby complete inhibition of the apoptotic pathway [28]. Targeted knockdown of RAGE in pancreatic tumor cells, leads to increased apoptosis, diminished autophagy and decreased tumor cell survival [91]. Furthermore, depletion of HMGB1 by shRNA in pancreatic tumor cell renders them significantly more sensitive to melphalan-induced apoptotic cell death [91]. These findings demonstrate a critical role for the HMGB1/RAGE pathway in the regulation of apoptosis in pancreatic tumors.

Steroid hormones induce HMGB1 overexpression and sensitize breast cancer cells to cisplatin and carboplatin treatment [32]. *bis*-estrogen-*cis*-diamminedichloroplatinum-3 selectively induces overexpression of HMGB1 in MCF-7 tumor cells and enhances their sensitivity to the compound [92]. HMGB1 promotes the radiosensitivity of breast cancer cell lines including both the MCF-7 and BT-549 cell lines [49]. Chemosensitivity experiments with 5-fluorouracil, cytosine arabinoside, thiopurines, and mercaptopurine demonstrate that HMGB1−/− mouse embryonic fibroblasts (MEFs) are more resistant to these drugs when compared with HMGB1 wild type MEFs [56,59]. However, HMGB1−/− MEFs are hypersensitive to DNA damage induced by psoralen plus UVA irradiation (PUVA) or UVC radiation [93]. This suggests that HMGB1 usually protects cells from apoptosis.

HMGB1 and Angiogenesis

The rapid growth of tumors is accompanied by a 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 also attract macrophages, which also produce a number of potent angiogenetic cytokines and growth factors. In an endothelial-sprouting assay, exogenous HMGB1 induces endothelial cell migration and sprouting *in vitro* in a dose-dependent manner [94]. Activation of HMGB1 and its receptor RAGE results in the activation of NF-κB, which upregulates leukocyte adhesion molecules and the production of proinflammatory cytokines and angiogenic factors in both hematopoietic and endothelial cells, thereby promoting inflammation and angiogenesis [95]. HMGB1 in complex with heparin also induces angiogenesis [96]. Treatment with HMGB1 increases the secretion of VEGF but not that of VEGF-C in human oral squamous cell carcinoma cells. The effect of HMGB1 is abrogated by RAGE down-regulation by antisense molecules [97]. Antibody targeting HMGB1 inhibits angiogenesis *in vitro* and *in vivo* [98].

HMGB1 and Replicative Potential

Three acquired capabilities: growth signal autonomy, insensitivity to antigrowth signals, and resistance to apoptosis, all lead to an uncoupling of a cell's growth program from signals within it's environment. HMGB1 regulates the proliferation of lymphocytes in a time- and dose-dependent manner [99]. *In vitro*, HMGB1 induces migration and proliferation of both adult and embryonic mesoangioblasts, and disrupts the barrier function of endothelial monolayers [100]. Colon cancer cell-derived HMGB1 induces growth inhibition and apoptosis in macrophages [101]. Telomere maintenance is clearly a key component of the capability for unlimited replication [82]. Telomeres are repetitive DNA sequences located at the termini of linear chromosomes of most eukaryotic organisms, and a few prokaryotes [102,103]. Telomere shortening in humans can induce replicative senescence which in turn blocks cell division. This mechanism appears to limit genomic instability and development of cancer in aged human cells by limiting the number of cell divisions. Malignant cells which bypass this arrest become immortalized by telomere extension, mostly due to the activation of telomerase, the reverse

transcriptase enzyme responsible for synthesis of telomeres [102,103]. HMGB1, is essential because knock-out mice die shortly after birth [104]. HMGB1 dissociates from chromosomes during mitosis [105] and takes part in telomere maintenance. Plants lacking HMGB1-like proteins display telomere shortening and, consistently, overexpression of HMGB1 leads to telomere elongation. However, it is not clear what the relationship is between HMGB1 and telomere biology in mammalian cells.

HMGB1 and Invasion and Metastasis

Expression of RAGE is closely associated with the invasive and metastatic activity of gastric cancer [106], and colorectal cancer [107]. Inhibition of the RAGE-HMGB1 interaction suppresses activation of p44/p42, p38 and SAP/JNK MAP kinases. These molecular effector mechanisms are linked to tumor proliferation, invasion and expression of matrix metalloproteinases (MMPs) [81]. Tiam1 (T lymphoma invasion and metastasis-1), a guanine nucleotide exchange factor that activates Rac, was recently identified as a novel colorectal cancer metastasis-related gene. Tiam1 transfection in colorectal cancer cells upregulates the expression of Fascin-1, heat shock protein 27, HMGB1, and glutathione S-transferase omega 1 [108]. Trophinin is a unique adhesion molecule expressed by human trophoblastic cells, and high trophinin expression is closely associated with colon cancer patient's poor prognosis. HMGB1 and RAGE were coexpressed in 65.6% of trophinin-positive patients [109]. These results suggest that trophinin promotes invasion through a mechanism involving HMGB1/RAGE. Moreover, cell growth, migration and invasion were inhibited significantly in Colo320 and WiDr carcinoma cells treated with RAGE and HMGB1 antisense S-oligodeoxynucleotide (S-ODNs) compared with sense-treated cells [110]. Infiltration of the phorbol 12-myristate 13-acetate (PMA)-treated human leukemic monocyte lymphoma cell line, U937 through the monolayer of the human colon cancer cell line, KM12SM was increased by pretreatment of the KM12SM cells with HMGB1 S-ODNs. Moreover, extracted HMGB1 inhibited PMA-U937 monocyte infiltration in a dose-dependent manner. Thus, HMGB1 may play an important role in the inhibition of macrophage infiltration into colon cancer [111]. Suppression of DCs by HMGB1 is associated with lymph node metastasis of human colon cancer [112].

HMGB1 and the Inflammatory Microenvironment

The role of the immune system during cancer development is complex involving extensive reciprocal interactions between genetically altered cells, adaptive and innate immune cells, their soluble mediators and structural components present within the tumor microenvironment. Each stage of cancer development in most adult tumors is regulated by the immune system. Whereas full activation of adaptive immune cells at the overt, invasive tumor stage may result in eradication of malignant cells, chronic activation of innate immune cells at sites of premalignant growth may actually enhance tumor development. In addition, the balance between desirable antitumor immune responses and undesirable pro-tumor chronic inflammatory responses largely depends on the context in which a malignancy is developing [113]. HMGB1 alerts the innate immune system to stress and excessive or unregulated cell death [114,115]. To act as a danger signal and inflammatory mediator, HMGB1 must be transported extracellularly. This occurs in two fundamentally different manners: active secretion from living inflammatory cells or passive release from necrotic or stressed cells. Anticancer treatments (e.g. radiotherapy and chemotherapy) cause cell death and promote HMGB1 passive release. Activated leukocytes actively secrete HMGB1 in the microenvironment. Cytolysis of human melanoma cells by immune effectors (both NK and T cells) is associated with release of HMGB1 [67]. Extracellular HMGB1 mediates a number of important functions including stimulating the release of tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and other inflammatory products, endothelial cell activation, stromagenesis, recruitment and activation of innate immune cells, and also dendritic cell

maturation that, in the setting of cancer, lead to a chronic inflammatory response [65]. Two HMGB1-related peptides, denoted as pHMGB-89 and pHMGB-106, were explored for their ability to enhance the immunogenicity of Ag-containing liposomes [116]. Importantly, vaccination of mice with B16-OVA-derived plasma membrane vesicles (PMVs) engrafted with pHMGB-89 and pHMGB-106 inhibited tumor growth and metastasis, in syngeneic mice challenged with highly metastatic B16-OVA melanoma [116]. Moreover, HMGB1 inhibits phagocytosis of apoptotic neutrophils through binding to phosphatidylserine [117]. The importance of this observation is unclear

HMGB1 and Anti-Growth Signals

Antigrowth signals can block proliferation by two distinct mechanisms [82]. Cells may be forced out of the active proliferative cycle into the quiescent (G0) state from which they may reemerge on some future occasion when extracellular signals permit. Alternatively, cells may be induced to permanently relinquish their proliferative potential by being induced to enter into postmitotic states, usually associated with acquisition of specific differentiation-associated traits. There are few changes in the cell cycle phase distribution following HMGB1 overexpression in MCF-7 cells [118]. Following estrogen treatment, cells progressed through the cell cycle in both the HMGB1 overexpressed MCF-7 and the mock-treated cells. However, a larger proportion of HMGB1 overexpressing MCF-7 cells progressed to either the S or G2 phase than the mock-treated cells [118]. The enhanced expression of HMGB1 caused suppression of growth of MCF-7 tumor xenografts in nude mice, while LXCXE-defective HMGB1 completely lost antitumor growth activity [49]. HMGB1-deficient MEFs demonstrate decreased caspase activity and compromised cell cycle arrest following genotoxic stress induced by antimetabolite drugs [59]. When in a hypophosphorylated state, pRb blocks proliferation by sequestering and altering the function of the E2F family of transcription factors [82]. HMGB1 interacts with many apparently unrelated proteins incuding pRb by recognizing short amino acid sequences [48]. An HMGB1-RB interaction is critical for the HMGB1-mediated E2F and cyclin A transcriptional repression, cell growth inhibition, G1 cell cycle arrest, apoptosis induction, and tumor growth suppression, but is not required for radiosensitization [49]. Moreover, the HMG box-containing transcription factor UBF is the primary target for pRb-induced transcriptional repression [119].

HMGB1 and Growth Signals

HMGB1 activates signaling pathways involving protein kinase B (AKT), mitogen-activated protein kinases (MAPKs), and NF-κB, which play important role in tumor growth. AKT, a key regulator of cell proliferation and survival, is commonly dysregulated in human cancers. HMGB1 mediates phosphatidylinositol 3-kinase/Akt pathway activation in neutrophils [120] and colon cancer cells [110]. *In vitro* stimulation of neutrophils with recombinant HMGB1 caused TLR4-dependent activation of NAD(P)H oxidase as well as increased ROS production through both MyD88-IRAK4-p38 MAPK and MyD88-IRAK4-AKT signaling pathways [121]. HMGB1 binding to RAGE leads to activation of NF-κB and ERK1/2, p38 and SAPK/JNK kinases [122]. HMGB1 also binds to TLR-2 and TLR-4, both of which leads to a MyD88-dependent activation of NF-κB [123]. This suggests that MAPKs and NF-κB pathways are important signal pathways involving in HMGB1's pro-inflammatory function. Morover, inhibitors of MEK1/MEK2, protein kinase C, and PI-3/AKT inhibit cytokine-induced HMGB1 secretion [124]. Overexpression of heat shock protein 72 (Hsp72) strongly inhibits HMGB1-induced cytokine (TNF-α, IL-1β) expression and release which correlates closely with inhibition of the MAP kinases (p38, JNK, and ERK) and inhibition of the NF-κB pathway with elevated Hsp72 [125–127].

Clinical Studies of HMGB1 in Cancer

Colon Cancer

Macrophage infiltration into colon cancer and HMGB1 expression in cancer cells was examined in 42 human colon cancers invading the subserosa. HMGB1 expression was detected at heightened amounts in both Dukes' B and C cases ($p=0.0684$). In macrophage-depleted cases, HMGB1 expression is significantly higher than that in non-depleted cases ($p=0.0015$) [111]. Another study of clinical relevance of RAGE and HMGB1 expression was in 119 non-diabetic patients with colorectal carcinoma [128]. RAGE expression is observed in 55% (64/119) of the cases. RAGE positivity in Dukes' B, C and D cases is 19, 81 and 100%, respectively ($p<0.0001$). HMGB1 is expressed in most patients' tumors regardless of tumor stage. Survival analysis of Dukes' B and C cases showed a significantly poorer prognosis for patients with co-expression of RAGE and HMGB1 than for patients without co-expression. The results suggest that co-expression of RAGE and HMGB1 is closely associated with invasion and metastasis of colorectal cancer [128]. To confirm the HMGB1-induced inhibitory effect on dendritic cells, 16 cases of human colon cancer invading into the subserosal layer were examined [112]. The 8 nodal metastasis-positive cases showed higher nodal HMGB1 concentrations (74 ± 23 vs. 41 ± 15 μg/ml, $p = 0.0116$) in lymph node tissues and lower CD205-positive nodal dendritic cell numbers (86 ± 22 vs. $137 \pm 43/mm^2$, $p=0.0224$) than those in the 8 metastasis-negative cases [112]. In addition, individual serum samples from 43 patients with colorectal cancer and 40 patients with no cancer on colonoscopy were profiled on a 37,830-clone recombinant human protein array. Using a sex- and age-matched training set, 18 antigens associated with cancer and 4 associated with the absence of cancer ($p < 0.05$) were identified. These antigens included those associated with cellular accumulation (p53), aberrant cellular expression (HMGB1) and overexpression (TRIM28, p53, HMGB1, TCF3, LASS5, ZN346) in colorectal cancer tissues when compared to normal colorectal mucosa [129].

Breast Cancer

Northern blot analyses of the 1.4 kb and the 2.4 kb transcripts of HMGB1 in 13 breast cancer samples revealed a strong intertumoral variation by a factor of 8.5 and 14.5, respectively. This variation may contribute to altered responses, of estrogen receptor-positive breast tumors to endocrine therapy [130].

Lung Cancer

The mean value of serum HMGB1 levels in 145 patients with lung cancer was 76.1 ± 37.0 ng/ml and was significantly higher than that found in 77 patients chronic obstructive pulmonary disease (COPD) patients (39.8 ± 10.8 ng/ml), and 49 healthy control (7.7 ± 6.1 ng/ml, $p<0.0001$, respectively). The serum HMGB1 levels were 30.2 ± 5.9 ng/ml, 60.9 ± 22.5 ng/ml, 99.0 ± 23.1 ng/ml and 133.4 ± 18.9 ng/ml in patients with non-small cell lung cancer (NSCLC) of TNM stages I, II, III, and IV. There were significant differences among the four groups ($p<0.0001$). Moreover, there was a significant positive correlation between the levels of serum HMGB1 and the size of the tumor ($r=0.799$, $p<0.001$). The serum HMGB1 levels were 57.2 ± 28.8 ng/ml in patients with NSCLC before operation, and 26.5 ± 14.7 ng/ml one month following operation ($p<0.0001$) [131]. However, the HMGB1 expression in NSCLC tissue was lower than that in matched normal lung tissue as assessed by mRNA levels ($p<0.001$) and the down-regulation in stage III–IV patients was also significantly greater than those in stage I–II ($p=0.005$). At the protein level, HMGB1 expression was also down-regulated in NSCLC tissue [132].

Prostate Cancer

Expression of HMGB1 and RAGE was examined in prostatectomy specimens from 40 patients with pT3 prostate cancer (18 non-metastatic and 22 metastatic) preoperatively treated with a lutenizing hormone-releasing hormone (LH-RH) agonist [133]. HMGB1 was detected in tumor cells of 6 (27%) metastatic and 0 non-metastatic cases ($p<0.0001$). HMGB1 was also detected in prostatic stromal cells of 14 (63%) metastatic cases and 2 (11%) non-metastatic cases ($p=0.0010$). RAGE expression was also detected in cancer cells of 16 (73%) metastatic and 6 (33%) non-metastatic cases ($p=0.0244$). A total of 2 (22%) non-metastatic and 16 (73%) metastatic cases co-expressed HMGB1 and RAGE in tumor cells or in tumor cells and stromal cells ($p=0.0001$). In untreated prostate cancer tissue and hormone-refractory prostate cancer, higher RAGE and HMGB1 mRNA expression was observed when compared with normal prostate tissue [30].

Cervical Cancer

The expression of HMGB1 in sixty cervical squamous epithelial carcinomas (CSEC) samples and paraneoplastic tissues was similar ($p>0.05$), but higher when compared to 30 normal cervical tissues ($p<0.05$). Overexpression of HMGB1 in the CSEC tissues was significantly correlated with tumor ($p<0.05$), and the presence of metastasis ($p<0.01$), but not correlated with either the tumor diameter or tumor grade [29]. Serum HMGB1 levels in patients with recurrent CSEC were significantly higher than in patients with non-recurrent disease and healthy controls [134]. Of the factors analyzed, HMGB1 had the greatest specificity and positive correlation ratio (78.0% and 3.25, respectively) [134].

Gastric Cancer

A total of 227 subjects were classified into 5 disease groups according to the 'gastritis-dysplasia-carcinoma' sequence of gastric carcinogenesis and serum levels of HMGB1 were analyzed. Serum HMGB1 levels were significantly different among the disease groups ($p<0.05$) analyzed. HMGB1 levels tended to increase according to the progression of gastric cancer. Serum HMGB1 levels were significantly associated with depth of invasion, lymph node metastasis, tumor size, and poor prognosis ($p<0.05$). However, HMGB1 levels were not associated with patient gender or age, differentiation of tumor cells, or lymphatic, vascular and perineural invasion, nor the existence of distant metastasis in patients with advanced cancer ($p>0.05$). The sensitivity and specificity of serum HMGB1 was 71% and 67% (cut-off value of 5 ng/ml) for the diagnosis of early gastric cancer, and 70% and 64% (cut-off value of 4 ng/ml) for the diagnosis of high-risk lesions, respectively. These values were greater than those for carcinoembryonic antigen (30–40% sensitivity) [135].

Hepatocellular Carcinoma

The serum HMGB1 levels in patients with hepatocellular carcinoma (84.2 ± 50.4 ng/ml) was significantly higher than those with chronic hepatitis (39.8 ± 10.5 ng/ml), liver cirrhosis (40.2 ± 11.6 ng/ml) or healthy controls (7.0 ± 5.9 ng/ml, $p<0.0001$, respectively), and positive correlated with alpha-fetoprotein levels ($r = 0.952$, $p<0.0001$), and the size of the tumor ($r = 0.904$, $p<0.0001$). HMGB1 also correlated with Edmondson grades I, II, III, IV and TNM stages I, II, III, IV ($p<0.0001$) [136].

Leukemia

HMGB1 expression was analysed in 18 patients with non-Hodgkin lymphoma. 11/18 primary lymphomas expressed HMGB1 mRNA at a level exceeding the amount found in normal lymph nodes. Immunohistochemistry showed that HMGB1 increases were confined to lymphoma cells [137]. In addition, the serum levels of HMGB1 were significantly higher in childen with acute lymphocytic leukemia (ALL) in the initial treatment group ($n = 15$, 43.78 ± 4.62 μg/ml)

than those in the healthy control group (n = 15, 0.60 ± 0.48 μg/ml, $p < 0.01$) and ALL complete remission group (n = 15, 0.89 ± 0.62 μg /ml, $p < 0.01$) [138]. No significant difference was found between the healthy control group and ALL complete remission group in HMGB1 levels ($P > 0.05$) [138].

Potential Therapies Targeting HMGB1 in Cancer

Targeting the HMGB1 ligand or its receptor represents an important potential application in cancer therapeutics, given its widespread overexpression, as well as that of its receptor in virtually every tumor type carefully examined [16,115].

HMGB1-neutralizing Antibodies

Administration of anti-HMGB1 antibody before and shortly after endotoxin exposure increases the survival of exposed mice [8]. This response is dose dependent, with a higher survival rate correlating with increased frequency of administration of the anti-HMGB1 antibody [8]. Neutralizing anti-HMGB1 antibodies inhibit release of TNF-α and IL-6 by blocking extracellular HMGB1 but does not prevent HMGB1 secretion. Neutralizing antibodies to HMGB1 decrease tumor incidence and size in colitis-associated cancer models [139].

sRAGE and RAGE-HMGB1 Blocking Strategies

Blockade of RAGE signaling pathways could also result in attenuation of tumor development and growth. Several strategies that block HMGB1-RAGE signaling have been reported, such as the administration of extracellular ligand binding domain of sRAGE, administration of blocking Fab fragments derived from anti-RAGE and/or anti-HMGB1 IgG, and generation of stably transfected C6 glioma expressing sRAGE [5]. sRAGE acts as a decoy to prevent RAGE signaling and has been used successfully in animal models [140]. Human sRAGE generated by alternative splicing of the RAGE transcript is able to bind heparin, enabling distribution in the extracellular matrix and at the cell surface (43). sRAGE administration blocks endogenous growth of many tumors, including murine papillomas [81]. Serum levels of sRAGE are higher in patients with advanced breast cancer (stage III), lower grade and positive estrogen receptors, and intermediate positivity of Her2/neu receptors and are also influenced genetically by the Gly82Ser and 2184 AG polymorphisms of the RAGE gene. Decreased sRAGE levels in patients with breast cancer may contribute to the progression of the disease [141]. However, recently sRAGE has been shown to have effects other than simply blocking cell surface RAGE function [142].

Ethyl Pyruvate

Ethyl pyruvate (EP) inhibits the release of TNF and HMGB1 from endotoxin-stimulated RAW 264.7 murine macrophages, as well as attenuates activation of both the p38 mitogen-activated protein kinase and NF-κB signaling pathways. Ethyl pyruvate treatment of septic mice decreases circulating levels of HMGB1 [143]. Pretreatment with ethyl pyruvate also prevents endotoxin lethality and inhibits the release of TNF and HMGB1 [143]. Ethyl pyruvate decreases HMGB1 release and ameliorates murine colitis [144] and renal ischemia and reperfusion injury [145]. In a liver tumor model, pretreatment with EP 30 min prior to infusion of tumor cells and continuing daily for 9 days inhibited tumor growth significantly in a dose-dependent manner, with 80 mg/kg EP achieving >70% reduction in the number of tumor nodules when compared with untreated animals [79]. Delayed treatment with EP also suppresses tumor growth significantly, although to a lesser extent. Tumors had early, marked leukocytic infiltrates, and EP administration decreased innate (NK cells, monocytes) and adaptive (T and B cell lymphocytic) immune cell infiltrates acutely and significantly in the liver. Serum IL-6 and HMGB1 levels, which are elevated following tumor injection, are

decreased significantly in EP-treated animals [79]. Moreover, EP induces necrosis-to-apoptosis switch and inhibits HMGB1 release in A549 lung adenocarcinoma cells [146].

Platinum Therapy

Platinum therapy characteristically creates two adducts: a 1, 2 intrastrand dGpG crosslink and a minor 1,3 intrastrand dGpTpG adduct. Both of these adducts are reparable by an excision repair system. HMG domain motifs bind specifically to the major platinum DNA dGpG adducts, creating a shield against the human excision nucleases accomplished through the HMGB1 acidic domain [147]. One well-known side effect of platinum therapy is ototoxicity, and HMGB1 has been shown to play a role in cisplatin-induced ototoxicity in rats [148]. Tumor cells incubated with the platinating agent oxaliplatin, retain HMGB1 within the nucleus for significantly longer periods than other agents used at comparable cytotoxic concentrations or even with potent cytolytic cells [65]. Oxaliplatin also retains HMGB1 intranuclearly and ameliorates collagen type II-induced arthritis [149], at least transiently. In the initial stages of cisplatin treatment of skin tumors, HMGB1 is still bound to the nucleus. However, extended treatment of skin tumors with cisplatin caused necrosis and showed significantly increased levels of HMGB1 [150]. Similarly, *in vitro* studies in primary cultured rat hepatocytes show that nontoxic concentrations of cisplatin can sequester HMGB1 inside the nucleus of hypoxic cells, and *in vivo* prevent liver damage [71].

Quercetin

As an antioxidant, quercetin (3,3’,4’,5,7-Pentahydroxyflavone dihydrate) has anti-inflammatory effects, regulating NO, IL-6 and TNF-α release [151,152], thereby alleviating oxidative damage in the tissue [151,153], and inhibiting the LPS-induced delay in spontaneous apoptosis and activation of neutrophils [154]. Quercetin treatment significantly reduces circulating levels of HMGB1 in animals with established endotoxemia [70]. In macrophage cultures, quercetin inhibits release as well as the cytokine activities of HMGB1, including limiting the activation of MAPK and NF-κB, two signaling pathways that are critical for HMGB1-induced subsequent cytokine release. Quercetin and the autophagic inhibitor wortmannin inhibit LPS-induced type II LC3 production and aggregation as well as HMGB1 translocation and release [70]. A number of quercetin’s actions make it a potential anti-cancer agent, including cell cycle regulation, interaction with type II estrogen binding sites, and tyrosine kinase inhibition [155]. Quercetin mediates the down-regulation of mutant p53 and activation of mitochondrial- and caspase-3-dependent pathways in the human breast cancer cell line MDA-MB468 [156,157].

Other Agents

Several agents such as anticoagulants, endogenous hormones, vagus nerve stimulation, Chinese herbal components, stearoyl LPC, and the truncated forms of HMGB1 A box, are protective in the setting of experimental sepsis, partly through attenuating systemic HMGB1 accumulation [158], inhibiting HMGB1 release in inflammation. Further investigation is needed to evaluate these therapies and their possible role in cancer therapeutics.

Conclusions

HMGB1 is both a nuclear factor and a secreted protein. In the cell nucleus it acts as an architectural chromatin-binding factor that bends DNA and promotes protein assembly on specific DNA targets. Outside the cell, it binds with high affinity to RAGE and is a potent mediator of inflammation. HMGB1 clearly plays a role in cancer development and metastasis, with RAGE-HMGB1 signaling promoting spread of most tumor types. Further basic and clinical studies are warranted to confirm the important and central role played by HMGB1 in cancer and to identify means to exploit this therapeutically.

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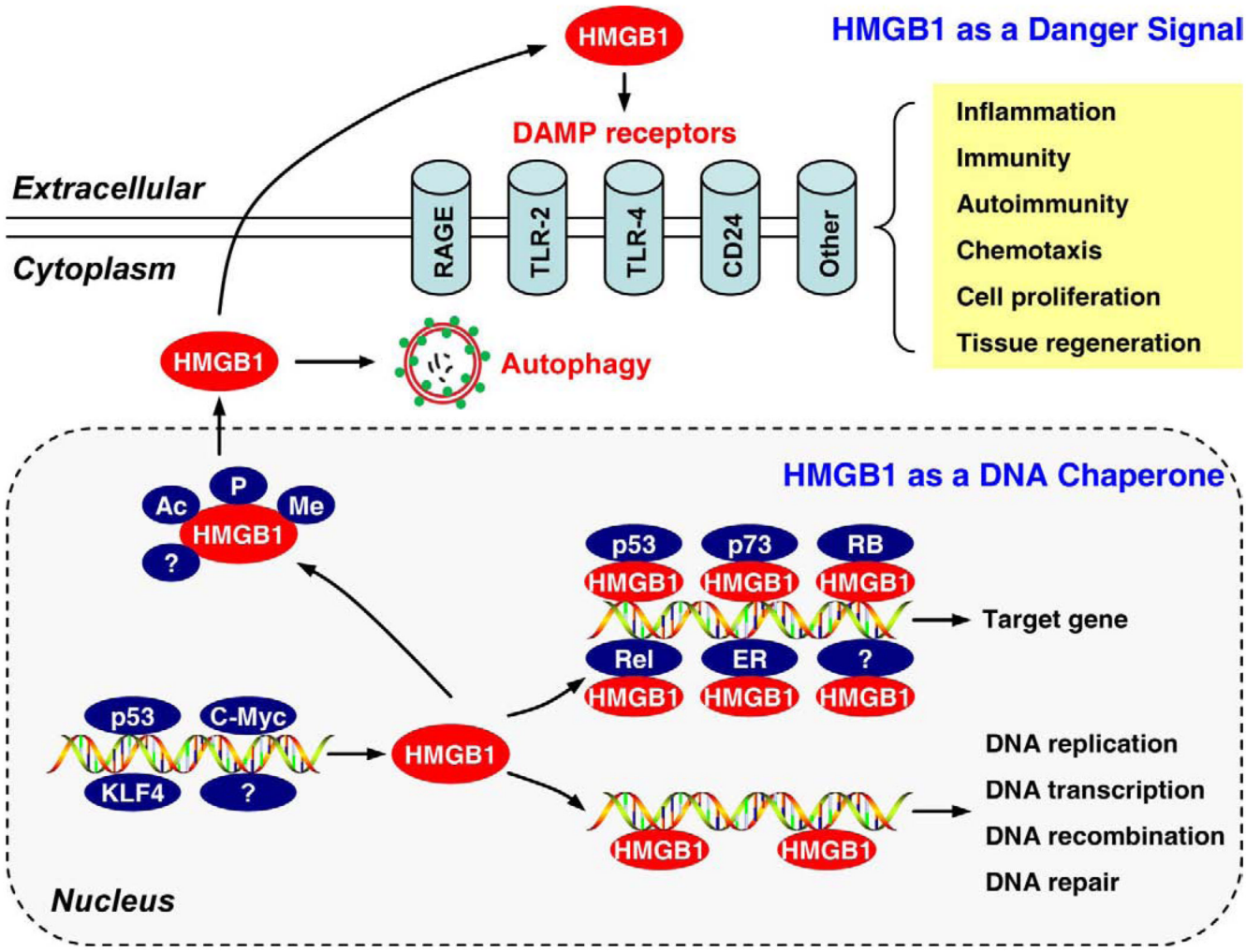

Figure 1. Intranuclear and Extranuclear Functions of HMGB1

The high-mobility group box 1 protein (HMGB1) is present in almost all metazoans and plants. The expression of HMGB1 is regulated by transcription factors including p53, c-Myc, and KLF4 in individual cell types. As a DNA chaperone, HMGB1 participates in DNA replication, recombination, transcription and repair. HMGB1 also been interacts with and enhances the activities of a number of transcription factors implicated in cancer development, including p53, p73, the retinoblastoma protein (RB), members of the Rel/NF-κB family, and nuclear hormone receptors including the estrogen receptor (ER). Cytosolic HMGB1 promotes autophagy and, in particular, mitophagy. HMGB1 is passively released from necrotic cells and is actively secreted by inflammatory cells, binding with high affinity to several receptors including the receptor for advanced glycation end products (RAGE), Toll-like receptors (TLR)-2, TLR-4, TLR-9, and, as a negative signaling molecule, CD24, mediating the response to infection, immunity, autoimmunity, chemotaxis, cell proliferation and tissue regeneration.

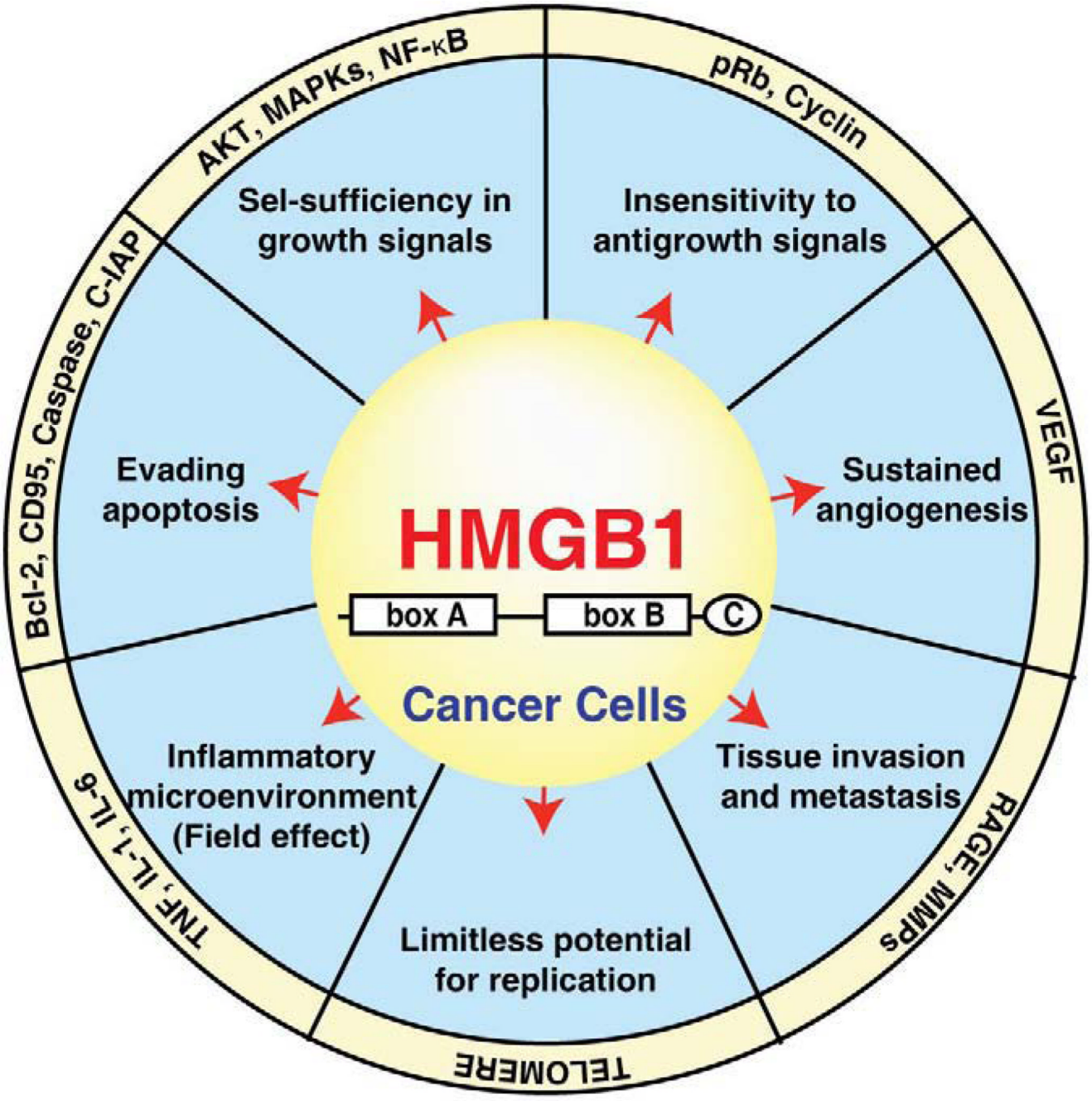

Figure 2. Role of HMGB1 in Cancer

In cancer, overexpression of HMGB1 is associated with each of the hallmarks of cancer including unlimited replicative potential, ability to develop blood vessels (angiogenesis), evasion of programmed cell death (apoptosis), self-sufficiency in growth signals, insensitivity to inhibitors of growth, inflammation, tissue invasion and metastasis.