Published in final edited form as:

Cancer Res. 2020 June 01; 80(11): 2075–2082. doi:10.1158/0008-5472.CAN-19-3066.

Targeting chromosomal architectural HMGB proteins could be the next frontier in cancer therapy

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Abstract

Chromatin-associated architectural proteins are part of a fundamental support system for cellular DNA-dependent processes and can maintain/modulate the efficiency of DNA replication, transcription, and DNA repair. Interestingly, prognostic outcomes of many cancer types have been linked with the expression levels of several of these architectural proteins. The High Mobility Group Box (HMGB) architectural protein family has been well studied in this regard. The differential expression levels of HMGB proteins and/or mRNAs and their implications in cancer etiology and prognosis present the potential of novel targets that can be explored to increase the efficacy of existing cancer therapies. HMGB1, the most studied member of the HMGB protein family, has pleiotropic roles in cells including an association with nucleotide excision repair, base excision repair, mismatch repair, and DNA double-strand break repair. Moreover, the HMGB proteins have been identified in regulating DNA damage responses and cell survival following treatment with DNA-damaging agents, and as such, may play roles in modulating the efficacy of chemotherapeutic drugs by modulating DNA repair pathways. Here, we discuss the functions of HMGB proteins in DNA damage processing, and their potential roles in cancer etiology, prognosis and therapeutics.

Keywords

High mobility group box (HMGB) proteins; drug resistance; cisplatin; DNA damage repair; cancer prognosis

Introduction

The HMGB proteins are chromatin-associated DNA binding proteins that can bend DNA (1,2). Such a function is fundamental for efficient genome organization and execution of DNA replication, DNA repair, and transcription (3). Cancer cells often have higher levels of DNA replication and DNA repair (compared to normal cells) to support their growth and survival; thus, these ubiquitously expressed proteins may play important roles in cancer etiology at a very basic level. Because of their ubiquitous presence and lack of enzymatic

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Conflict of interest: The authors declare no potential conflicts of interest.

function, they have not gained much attention as therapeutic targets in cancer therapy. However, more recent studies have suggested an association between expression levels of the HMGB proteins in various cancers. In this review, we discuss potential roles of the HMGB proteins in cancer etiology, and in the response to and repair of chemotherapeutic DNA-damaging agents.

The chromatin associated HMGB proteins, HMGB1, HMGB2, HMGB3, and HMGB4, were identified more than 40 years ago (4) [reviewed in (5)]. The HMGB proteins contain two conserved box domains; Box A, which facilitates DNA binding, and Box B, which assists in binding and bending DNA. In addition, HMGB1, HMGB2, and HMGB3 contain a C-terminal acidic tail that is lacking in HMGB4 (6). The C-terminal acidic tail has been shown to fold in between the two basic box domains and can regulate DNA binding and bending (7–9). Because HMGB4 does not contain a C-terminal acidic tail, its mode of interaction with DNA may differ from the other members of the family, and thus here we will focus on HMGB1–3.

HMGB proteins are largely localized in the nucleus with some cytoplasmic and extracellular distribution (10), which is in part regulated by posttranslational modifications (11). HMGB1 and HMGB2 have been shown to bind structurally distorted DNA in a sequence-independent manner and can topologically modify the DNA by introducing supercoiling and stabilizing DNA loops (12,13). Through DNA bending, HMGB1 has been shown to facilitate recruitment of other proteins to their DNA targets (14–16). Interestingly, some chemotherapeutic drug-induced DNA distortions/lesions are also high-affinity targets of HMGB1 (17,18), and perhaps of HMGB2 and HMGB3. Of relevance to cancer therapy, HMGB binding to structurally distorted DNA can modulate the processing of chemotherapeutic drug-induced DNA damage in cancer cells (19–25). Of note, the functions of HMGB1 have been the most studied among the HMGB family members and it is evident that HMGB1 has pleiotropic roles in cells, which will be discussed in a later section. In addition, several of the HMGB proteins have been found to play roles in various aspects of inflammation and immunity (26), though here we will focus on DNA damage responses and DNA repair in cancer etiology, prognosis, and therapeutic outcome.

Cancer etiology and prognosis correlate with HMGB mRNA and protein levels

With the accessibility of cancer genome databases, many gene products are emerging as potential cancer-associated genes/proteins. For example, an inverse relationship has been found between HMGB expression levels and overall survival of cancer patients. Correlations of the HMGB proteins with cancer etiology and prognosis have been supported by studies that measured the HMGB expression levels via immunohistochemistry and RT-qPCR from patient samples (27–29). In a meta-analysis of 18 studies with 11 different tumor types, including gastric cancer, colorectal cancer, hepatocellular carcinoma, pancreatic cancer, nasopharyngeal carcinoma, head and neck squamous-cell carcinoma (HNSCC), esophageal cancer, malignant pleural mesothelioma, bladder cancer, prostate cancer, and cervical carcinoma, higher HMGB1 protein levels indicated poor overall survival and poor

progression-free survival (27). A similar correlation was demonstrated in ovarian cancer (28) and in these cancers, HMGB1 was found to upregulate the ERK1/2, MAPK, NF-kβ and Akt signaling pathways via its binding to the receptor for advanced glycation end products (RAGE), contributing to the reprogramming of cancer cells. HMGB1 upregulation in squamous cell carcinoma has been shown to promote chromatin modification and increase the phosphorylation of CHK1 to activate DNA damage responses (DDR), contributing to radio-resistance (29). Although targeting of HMGB1 for cancer therapy is a matter of debate due to its pleiotropic roles in cells (30), it has shown promising results in prostate cancer cells (31) and in HNSCC (32). Similar to HMGB1, HMGB2 expression levels appear to be positively correlated with HNSCC (33), breast cancer (34,35), colorectal cancer (36), gastric cancer (37), and ovarian cancer (38), largely by modulating the glycolytic pathway. In colorectal cancer cells, HMGB2 was found to modulate DNA damage repair in a TP53 dependent manner (36). HMGB3 follows a similar trend of poor prognosis with high expression levels in lung cancer (39), NSCLC (39,40), colorectal cancer (41), urinary bladder cancer (42), gastric adenocarcinoma (43), breast cancer (44), and in esophageal squamous cell carcinoma (ESCC) (45). We have shown that siRNA targeting of HMGB3 sensitizes chemoresistant human ovarian cancer cells to low doses of cisplatin by attenuating the ATR/CHK1 DNA damage checkpoint signaling pathway (46). Although it is not fully understood why the overexpression of HMGB proteins correlates with poor prognosis, based on their known roles in facilitating DNA repair, one could speculate that their overexpression may contribute to more efficient removal of chemotherapeutic DNA adducts. These observations are summarized in Table 1.

An analysis of HMGB mRNA expression levels and copy number alterations using the cBioPortal (47,48) in patient cancer samples from 32 TCGA PanCancer Atlas studies indicated a 4- to 16-fold increase in their mRNA levels when compared to the surrounding non-cancerous tissues (49). We plotted the top 10 HMGB1–3 expressing cancers based on their median mRNA expression levels (Figure 1A) (50–52), which revealed that not all HMGB proteins are equally overexpressed in each cancer type. In addition, the expression of different HMGB mRNAs varied among the individual patient samples within the same cancer type. For example, mRNA expression analysis from 398 ovarian serous cystadenocarcinoma patient samples indicated a selective, non-overlapping expression pattern of HMGB1, HMGB2, and HMGB3 (Figure 1B) (52).

HMGB proteins are involved in cellular responses to chemotherapeutic DNA-damaging agents

Cytotoxic therapy has been a mainstay of cancer treatment and these regimens often include DNA interstrand crosslink (ICL)-inducing platinum drugs (e.g. carboplatin, oxaliplatin, and cisplatin), DNA double-strand break (DSB)-inducing drugs (e.g. doxorubicin, mitoxantrone, etoposide, and PARP inhibitors), radiation therapy, alkylating agents (e.g. cyclophosphamide), and antimetabolites (e.g. gemcitabine, clofarabine, cytarabine) that induce DNA damage and repair synthesis and/or inhibit DNA synthesis. Such damage is processed by DNA repair proteins from different repair pathways (53). It has been found that

the HMGB proteins play roles in several DNA repair mechanisms. Below we summarize the roles of HMGB1 in processing ICLs by different DNA repair pathways.

HMGB1 as a modulator of ICL processing by nucleotide excision repair (NER) proteins

The NER mechanism processes bulky DNA adducts, including those induced by many chemotherapeutic drugs, such as the ICL-inducing agents mentioned above. In NER, the damage-induced local distortion of the DNA is identified by the XPC-RAD23B protein complex in global-genome NER, and by stalled RNA polymerase II in transcription-coupled NER (54–58). In subsequent steps, a pre-initiation complex is formed by further recruitment of TFIIH, XPA, and RPA (59,60), and the DNA is unwound by the helicase activities of the XPB and XPD subunits of TFIIH. The open complex is stabilized by XPA binding on the single-stranded and double-stranded region of the DNA (61). In the stabilized open-complex, the lesion is removed by dual incision on one strand of the DNA surrounding the lesion. The ERCC1-XPF structure-specific nuclease complex cleaves the DNA on the 5′-side of the lesion, and XPG cleaves the DNA on the 3′-side of the lesion (62), releasing the nucleotides surrounding the lesion.

We found that HMGB1 functions as an NER co-factor, as it facilitated the error-free processing of lesions by the NER mechanism (63). It has been found that HMGB1 binds to 1,2 GG intrastrand cisplatin crosslinks (64) and site-specific psoralen ICLs with higher affinity compared to non-damaged DNA (18). Further, HMGB1 binds to ICLs in a positive cooperative fashion with the NER damage recognition complexes, XPC-RAD23B and XPA-RPA, to form higher order DNA-protein complexes (20), indicating its association with and facilitation of NER protein binding to DNA lesions. The physiological relevance of the binding interactions of HMGB1 with NER proteins on ICLs was studied by using cell viability and mutagenesis assays. In HMGB1 knockout mouse embryonic fibroblasts, induction of psoralen ICLs or UVC-mediated DNA adducts (canonical NER substrates) were more cytotoxic and mutagenic than in wild-type cells (63), in part, due to less efficient NER-mediated lesion processing (63). Similarly, in human osteosarcoma cells, HMGB1 promoted the error-free processing of psoralen ICLs by associating with the lesions and by assisting in the recruitment of XPA to the damaged sites (19). HMGB1 also induced more negative supercoiling preferentially in a damaged DNA substrate compared to a lesion-free DNA substrate (19), which may facilitate NER-mediated lesion removal.

HMGB1 as a modulator of ICL processing by mismatch repair (MMR) proteins

MMR repairs mismatches and small loops in DNA caused primarily by replication errors. In human cells the mismatch is recognized by the MSH2-MSH6 heterodimer and subsequently processed by the MLH1-PMS2 heterodimer, PCNA, 5′→3′ EXO1 exonuclease, RPA, DNA polymerase δ, and DNA ligase I [reviewed in (65)]. Helix-distorting ICLs can also be recognized and processed, in part, by MMR proteins in human cells (66), as well as in cell-free extracts from *Xenopus* egg extracts (67). In *Xenopus* egg extracts that do not support

replication and transcription, ICLs were identified by the MSH2-MSH6 heterodimer and subsequently excised by MLH1-PMS2 and EXO1 (67). In human cells, MSH2 plays a role in processing of psoralen ICLs (66). In addition, we have shown that MSH2-MSH3 can bind to site-directed psoralen ICLs with the NER proteins, XPC-RAD23B and XPA-RPA (68).

The capacity of HMGB1 to modulate the MMR process has been reported. HMGB1 was shown to interact with MSH2 and MLH1 to identify the mismatched bases (69). Additionally, HMGB1 can substitute for RPA in the EXOI-mediated excision step in MMR (70). However, results from studies using HMGB1 knockout mouse embryonic fibroblasts suggested that HMGB1 was dispensable for MMR (71). These studies indicated that HMGB1 may be involved in the MMR-associated removal of ICLs, although further studies are warranted for a conclusive understanding of the role(s) of HMGB1 in MMR-mediated ICL processing.

HMGB1 as a modulator of ICL processing by base excision repair (BER) proteins

BER removes endogenous DNA lesions by initiation of a glycosylase followed by 3′→5′ apurinic/apyrimidinic endonuclease 1 (APE1)-mediated cleavage of the DNA backbone, and then subsequent strand displacement and synthesis of DNA by Polβ, and Ligase III, or in long-patch BER by Polβ, Fen1, Pol λ, PCNA, and Ligase I [reviewed in (72)]. *In vitro* studies have demonstrated that the BER glycosylases, NEIL1 and NEIL3, can excise a psoralen ICL from a three or four-stranded DNA structure (73), and APE1 can incise cisplatin ICL-containing DNA (74). There are also indications of epistatic roles of BER and MMR in the processing of cisplatin-induced DNA lesions (75). However, psoralen ICLs and cisplatin ICLs may be processed differently by BER proteins (74,76).

Interestingly, HMGB1 has been found to be associated with BER via mass spectrometry analyses, which identified associations of HMGB1 with BER intermediates in mouse embryonic fibroblast extracts. In addition, HMGB1 was found to stimulate the activities of APE1 and FEN1 (77,78).

HMGB1 as a modulator of ICL processing by DNA double-strand break (DSB) repair proteins

The repair of ICLs is complex and is thought to involve proteins from several DNA repair pathways, including NER, MMR, BER, translesion synthesis (TLS), homologous recombination (HR), and Fanconi Anemia (FA) proteins [reviewed in (53,79)]. The structure-specific endonucleases, ERCC1-XPF and FAN1, can assist in the resolution of ICLs (80–84). Subsequently, RAD51, RAD52, RAD54, RPA, BRCA1 and FA proteins can generate intermediate structures that can be resolved by the MUS81-EME1 complex (85–88). In addition to these proteins, multiple TLS polymerases can bypass “unhooked” ICLs, often in a mutagenic fashion (89–91). In S-phase, unrepaired DNA damage induced by many chemotherapeutic drugs, including ICLs, can stall replication forks (91–93). Such stalled

replication forks can lead to fork collapse generating DSBs resulting in repair processing by homology-directed repair (HDR) (94,95).

How do the HMGB proteins modulate this complex process? Although detailed interactions are not clear, there are several studies that have associated HMGB1 and HMGB2 with DSB processing. In mouse brain tissues, accumulation of DSBs were inversely correlated with the expression of HMGB1, as assessed by immunostaining and immunoblotting (96). Similarly, HMGB1 depletion in MCF7 breast cancer cells resulted in inefficient repair of strand breaks caused by ionizing radiation due to downregulation of the ATM and ATR signaling pathways, and alterations in telomere-binding protein levels (97). HMGB1 depletion in ESCC cells impaired radiation-induced DNA damage repair as indicated by increased γ-H2AX foci and reduced PARP1 expression (98). Colorectal cancer cells were sensitized to radiation when HMGB2 was downregulated, likely due to unresolved DSBs as evidenced by prolonged γ-H2AX foci (36).

The role of HMGB1 and HMGB2 in facilitating V(D)J recombination is well documented. During V(D)J recombination, the RAG1 and RAG2 proteins bind to the conserved recombination signal sequences adjacent to the V, D, and J sequences and bring them together into a synaptic complex, which is then cleaved by the RAG1 protein (99–101). Although HMGB proteins are not essential for V(D)J recombination, they have been shown to enhance the affinity of the RAG complexes for DNA and increased the cleavage up to 100-fold by stabilizing the required DNA bending (26,102–106).

These studies clearly indicated an association of HMGB1 with various DNA damage processing pathways. However, the roles of HMGB2 and HMGB3 in processing DNA ICLs are not yet clearly defined. Because of the structural similarities between the HMGB1, HMGB2, and HMGB3 proteins and their abundance in cancer cells (Figure 1), further studies to determine the extent to which these proteins have functional redundancy or whether they have distinct and unique roles in the response to and the repair of genome-destabilizing chemotherapeutic and carcinogenic lesions may provide a better understanding of DNA lesion processing in cells.

HMGB3 inhibition as a potential neoadjuvant therapy

Recently, we have discovered that siRNA-mediated depletion of HMGB3 can sensitize chemoresistant human ovarian cancer cells to cisplatin treatment (46). This sensitization, among other possibilities, could be due to less efficient cisplatin-DNA adduct removal (Mukherjee & Vasquez, unpublished observation) in the absence of HMGB3. Therefore, the idea of a small molecule that can selectively inhibit the DNA binding properties of HMGB3 resulting in less efficient chemotherapeutic lesion removal has potential for increasing chemotherapeutic efficacy. However, HMGB1, HMGB2 and HMGB3 have similar sequences and domain structures, which may present a challenge in developing HMGB3-specific small molecules that inhibit only the DNA binding function of HMGB3. Although HMGB3 has not yet been implicated in modulating pro-inflammatory cytokine functions, HMGB1 has been shown to act as a pro-inflammatory cytokine/mediator by interacting with TLR (Toll-like receptors) (107), RAGE receptors (108), and by stimulating the synthesis of

Myeloid Derived Suppressor Cells (MDSCs) (109), all of which contribute to chronic inflammation in a tumor microenvironment [reviewed in (110)]. These pro-inflammatory properties of HMGB1 are mediated through the B-Box (111), which also possess DNA binding properties. Therefore, at least for HMGB1, a small molecule that interacts with the B-Box to inhibit its DNA binding properties may also inhibit its pro-inflammatory functions, which might increase the efficacy of chemotherapy by reducing the cancer-associated chronic inflammation burden.

For HMGB1, this approach has a significant paradox. In a non-tumor microenvironment, HMGB1 is released from necrotic cells and acts as a proinflammatory cytokine and induces the immune system to protect against infections (112). Free cytosolic DNA resulting from intracellular pathogens can bind HMGB1 and stimulates the activity of cyclic GMP-AMP (cGAMP) synthase (cGAS), and subsequently the stimulator of interferon genes (STING) complex to induce synthesis of proinflammatory cytokines (113). Loss of the pro-inflammatory cytokine functions of HMGB1 in a non-tumor microenvironment may increase the risk of infection and lead to autophagy deficiency (114), contributing to inflammation. In addition to its involvement in inflammation, HMGB1 has antitumor roles mediated by its interactions with tumor suppressors, such as RB (115) and TP53 (116). Further, HMGB1 mediates genomic stability by facilitating error-free DNA repair (19,63), and maintaining chromosomal telomere length via interactions with Topo IIα (117). Interestingly, unlike HMGB1, HMGB3 is not ubiquitously expressed and has not yet been shown to have pro-inflammatory cytokine properties. Although careful evaluation is warranted, HMGB3 may provide a more favorable target for neoadjuvant therapy than HMGB1. There are many described strategies to inhibit HMGB1, which include recombinant A-Box-mediated inhibition of RAGE receptor-mediated signaling, small molecule inhibitors derived from naturally-occurring molecules and steroids, anti-HMGB1 antibodies, peptide and protein inhibitors, and oligonucleotide-based inhibitors [reviewed in (118)]. Although these approaches show promise, they are not yet under clinical evaluation. Reports of the development of inhibitors or strategies to inhibit HMGB3 binding to DNA are lacking. Although there are structural similarities between the different HMGB proteins, there are also differences between them that may allow for specific targeting. For example, in cells HMGB1, HMGB2, and HMGB3 can be targeted distinctly with siRNAs, and there are antibodies that interact with separate and distinct epitopes of HMGB1, HMGB2, and HMGB3 (46). In addition, depending on the cancer type, not all HMGB proteins may be expressed equally (Figure 1C). Therefore, targeting the DNA binding function of HMGB3 may be possible without significantly disrupting the functions of other HMGB proteins, though further studies are warranted.

Conclusions

The involvement of the HMGB proteins in various DNA damage repair processing pathways, such as NER, BER, MMR and HR are evident. We have recently shown that siRNA-mediated depletion of HMGB1, HMGB2, or HMGB3 in human osteosarcoma cells increases their sensitivity to chemotherapeutic ICL-inducing agents. In addition, we have shown that targeting HMGB3 can sensitize chemoresistant ovarian cancer cells to lower doses of cisplatin by modulating the response to and repair of cisplatin-DNA adducts.

Whether these effects of HMGB3 depletion are specific for ovarian cancer cells or if they can be extended to other cell types needs to be experimentally determined. Moreover, the extent to which HMGB1 and/or HMGB2 play similar roles in cisplatin sensitivity is not known; thus, we are currently investigating this possibility. Nonetheless, the HMGB proteins, when targeted individually or in combination, may open new possibilities for therapeutic intervention to treat recurrent and/or chemoresistant cancers and may increase survival and improve the quality of life for cancer patients.

Acknowledgements

This work was supported by NIH/NCI grants to K.M.V. (CA193124 and CA093729) to KMV. The results shown here are in whole or in part based upon data generated by the TCGA Research Network: https://www.cancer.gov/tcga.

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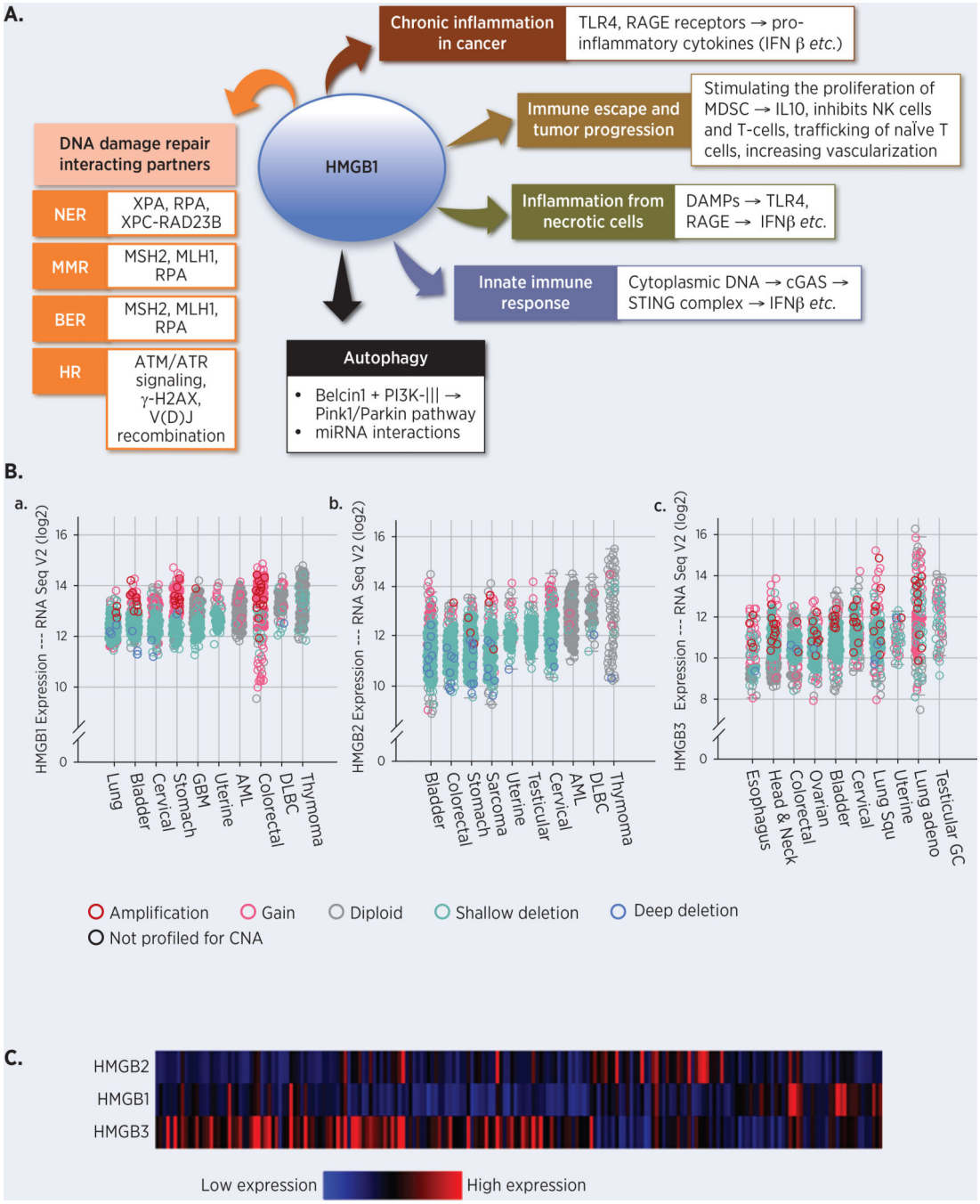

Figure 1.

A. Pleiotropic roles of HMGB1 in cells. HMGB1 has been found to be involved in DNA repair, chronic inflammation, immune responses, autophagy, DNA damage responses etc. Please see text for detailed description. **B.** Expression levels of *HMGB* mRNAs are higher in cancerous tissues when compared to the normal surrounding tissues as measured by Illumina RNA Seq V2 of cancer patient samples from 158 studies. The fold increase in expression levels as a function of mRNA in cancer samples are plotted in an increasing order of median values of the expression level. Samples with mutations are also identified in the same plot.

The copy number and expression levels are not always linearly correlated. A gain in copy number can also be accompanied by missense mutations or small truncating mutations, resulting in lower expression levels in those particular samples. **a,** *HMGB1* expression levels and copy number alterations data from 42,049 samples. The *HMGB1* gene was mutated in 263 patients. **b,** *HMGB2* expression levels and copy number alterations from 42,049 samples. The *HMGB2* gene was mutated in 285 of the queried patients. **c,** *HMGB3* expression levels and copy number alterations from the 42,049 samples. The *HMGB3* gene is altered in 351 of the queried patients. The data was procured, analyzed, and the graphs were prepared using cBioPortal. The copy number level per gene was derived from copy number analysis algorithms. Amplification = many additional gene copies, local; Gain = a few additional copies, broad; Diploid = two complete sets of chromosomes; Shallow deletion = possible heterozygous deletion; Deep deletion = possible homozygous deletion. CNA = Copy Number Alteration; GBM = Glioblastoma; AML = Acute Myeloid Leukemia; DLBC = Diffuse large B cell lymphoma; Lung Squ = Lung squamous cell carcinoma; Testicular GC = Testicular Germ Cell. **C.** HMGB mRNAs are expressed differentially in different ovarian serous cystadenocarcinoma patients. Heat maps representing the mRNA levels from 398 patient samples were generated from the TCGA Next-Generation Clustered Heat Map (NG-CHM) Compendium (https://bioinformatics.mdanderson.org/TCGA/NGCHMPortal/).

Table 1.

Association of HMGB proteins with cancer outcome.

Protein	Cancer outcome	DNA damage processing modulation	Ref.
HMGB1	• Gastric cancer • Hepatocellular cancer • HNSCC • Nasopharyngeal cancer • Colorectal cancer • ESCC • Mesothelioma • Bladder cancer • Prostate cancer • Cervical cancer • Ovarian cancer • NSCLC	• Promotes error-free repair via NER • Binds with high affinity to chemotherapeutic DNA lesions • Positive cooperative binding with NER damage recognition proteins on DNA lesions • Assists in recruitment of XPA to damaged DNA • Introduces negative supercoiling preferentially to damaged DNA • HMGB1 depletion increases sensitivity to DNA crosslinking agents • HMGB1 depletion results in increased DSBs	27–31 54–64 84–105
HMGB2	• HNSCC • Breast cancer • Colorectal cancer • Ovarian cancer • Gastric cancer	• Increases γ-H2AX foci formation after damage, and delays repair	33–38
HMGB3	• Ovarian cancer • NSCLC • Colorectal cancer • Gastric cancer • ESCC • Urinary bladder cancer	• HMGB3 depletion downregulates the ATR/CHK1 signaling pathway	39 – 46

HNSCC = Head and neck squamous cell carcinoma, NSCLC = Non-small cell lung cancer, ESCC = Esophageal squamous cell carcinoma