

Role of HMGB1 and its associated signaling pathways in human malignancies

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ARTICLE INFO

Keywords:

HMGB1
Signaling pathways
cancer therapy
Immune checkpoint blockade
Clinical applications

ABSTRACT

The High-Mobility Group Box-1 (HMGB1), a non-histone chromatin-associated protein, plays a crucial role in cancer growth and response to therapy as it retains a pivotal role in promoting both cell death and survival. HMGB1 has been reported to regulate several signaling pathways engaged in inflammation, genome stability, immune function, cell proliferation, cell autophagy, metabolism, and apoptosis. However, the association between HMGB1 and cancer is complex and its mechanism in tumorigenesis needs to be further elucidated. This review aims to understand the role of HMGB1 in human malignancies and discuss the signaling pathways linked to this process to provide a comprehensive understanding on the association of HMGB1 with carcinogenesis. Further, we will review the role of HMGB1 as a target/biomarker for cancer therapy, the therapeutic strategies used to target this protein, and its potential role in preventing or treating cancers. In light of the recent growing

Abbreviations: ACE2, Angiotensin-converting enzyme 2; AGER, advanced glycosylation end product-specific receptor; AKT, serine/threonine-protein kinase; ALL, acute lymphoblastic leukemia; ATM, ataxia-telangiectasia mutated; BNCT, Boron neutron capture therapy; BRG1, Brahma-Related Gene 1; CA19–9, contrary carbohydrate antigen; CD, cluster of differentiation; CEA, carcinoembryonic antigen; CRP, C-reactive protein; CSCs, cancer stem cells; CTCL, Cutaneous T-cell lymphoma; CXCR4, C-X-C chemokine receptor type 4; DAMP, damage-associated molecular pattern; DC, dendritic cells; DOX, doxorubicin; ELISA, enzyme-linked immunosorbent assay; EMT, epithelial-mesenchymal transition; ERK1/2, extracellular signal-regulated kinase 1/2; ERKs, Extracellular signal-regulated kinases; ETS, E-twenty-six; GS, guggulsterone; HCC, hepatocellular carcinoma; HMG, high mobility group; HMGB1, The High-Mobility Group Box-1; hrHMGB1, anti-HMGB1 antibody; HSCT, Hematopoietic stem cell transplantation; ICAM-1, intracellular adhesion molecule 1; ICLs, immune checkpoint inhibitors; IHC, Immunohistochemistry; JAK, Janus Kinase; MAPK, mitogen activated protein kinase; MAPK, mitogen-activated protein kinase; MDR1, multidrug resistance protein 1; MDSC, myeloid-derived suppressor cells; MM, multiple myeloma; MMP-9, matrix metalloproteinase 9; mTORC2-AKT-C-MYC, mammalian target of rapamycin Complex 2-serine/threonine kinase - c-myelocytomatosis; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; NK, neutrophils, and natural killer; NSCLC, non-small-cell lung carcinoma; PAMPs, pathogen-associated molecular patterns; PDAC, pancreatic ductal adenocarcinoma patients; PI3K, phosphoinositide-3-kinase; RAGE, receptor for advanced glycation end-products; rhTM, recombinant human soluble thrombomodulin; SCLC, small cell lung carcinoma; SDF-1, stromal cell-derived factor-1; SIRT4, sirtuin 4; SLE, systemic lupus erythematosus; STAT, Signal Transducer and Activator of transcription; TIMER, tumor immune estimation resource; TISID, tumor and immune system interaction; TLR, Toll-like receptors; TME, tumor microenvironment; UBC, urothelial bladder carcinoma; VCAM-1, vascular adhesion molecule 1; VCP, Valosin-containing protein; VEGF, Vascular Endothelial Growth Factor.

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<https://doi.org/10.1016/j.cellsig.2023.110904>

Received 7 July 2023; Received in revised form 11 September 2023; Accepted 22 September 2023

Available online 25 September 2023

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evidence linking HMGB1 to cancer progression, we think that it may be suggested as a novel and emergent therapeutic target for cancer therapy. Hence, HMGB1 warrants paramount investigation to comprehensively map its role in tumorigenesis.

1. Introduction

The high mobility group (HMG) is a superfamily of proteins representing the most abundant non-histone chromatin-associated proteins [1,2]. These proteins contain a unique DNA binding domain known as HMG-Box (HMGB) that can effectively bind to non-B-type DNA structures such as triplexes (H-DNA), hairpins, Z-DNA, and distort DNA by forming loops or bends [3,4]. In mammals, there are four HMGBs (HMGB1–4) [1]; HMGB1 is the most abundant and the first HMGB protein discovered by Goodwin and Johns in 1973 [5,6]. HMGB1 is a ubiquitous nuclear protein existing in all types of mammalian cells, and available in high concentrations inside the thymus, lymphoid organs, testis, and newborn livers [7,8]. Under normal physiological conditions, HMGB1 is involved in various biological functions including DNA repair, transcription, replication, and genome stability [9]. HMGB1 could be transported to other sites and released towards the extracellular space by passive or active release [10]. Apoptotic cells retain HMGB1 linked to chromatin, while necrotic cells passively release this protein into the extracellular milieu through simple diffusion [7,11]. In response to diverse stimuli, HMGB1 could be secreted extracellularly through a range of immune and non-immune cells such as dendritic cells (DC), monocytes, neutrophils, macrophages, and natural killer (NK) cells [11–13]. Furthermore, HMGB1 works as a damage-associated molecular pattern (DAMP), since it contributes to the induction of pathogenesis of many diseases such as sepsis, liver diseases, autoimmune diseases, and cancer [14]. HMGB1's extracellular effects augment after interacting with pathogen-associated molecular patterns (PAMPs), chemokines, and cytokines depending on their redox state [15]. For instance, extracellular HMGB1 could bind to Toll-like receptors (TLR) such as TLR2 and activates the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) pathway, and thus promoting severe inflammatory storm and triggering the progression of infections [16]. HMGB1 is constantly expressed by quiescent macrophages, mainly in the nucleus [17,18]. However, HMGB1 is released in a time-dose dependent manner when stimulated by *exo*- or endogenous pro-inflammatory cytokines and macrophages [10]. Therefore, HMGB1 is acetylated by activated macrophages at nuclear localization sequences to allow its translocation from the nucleus towards the cytoplasm, and thus its release in extracellular environment [19]. HMGB1 is released rapidly following ischemia or reperfusion injury, and thereby, it can act as a tissue injury initial inflammatory mediator [20]. Moreover, hemorrhagic shock or other stimuli can also trigger HMGB1 release [21]. For instance, in a patient with hemorrhagic shock, serum HMGB1 levels surged considerably before returning to baseline as the patient's condition recovered [22]. Additionally, during hemorrhagic shock, HMGB1 release mechanism is potentially attributed to its liberation from the active immune cells and its passive outflow from the injured cells [6,23].

HMGB1 possesses several roles in the etiology of renal illness as a possible inflammatory cytokine [18]. In renal disease, many studies have reported elevated levels of HMGB1 in the cytoplasm and extracellular compartments, in renal tissue, as well as in blood and urine [18,24,25]. Similarly, high serum levels of HMGB1 have been reported in sepsis, rheumatoid arthritis, atherosclerosis, systemic lupus erythematosus (SLE), Alzheimer's disease as well as in cancer [26,27]. Interestingly, HMGB1 has also been linked to Corona virus disease 2019 (COVID-19) [28]. An *in vitro* study in human lung epithelial cells showed that HMGB1 promotes angiotensin-converting enzyme 2 (ACE2) expression, a receptor for SARS-CoV-2, through binding to the Receptor for Advanced Glycosylation End-product (RAGE) [29]. Therefore, HMGB1/RAGE inhibitors such as glycyrrhizin could effectively limit

COVID-19 infection [28]. HMGB1 has also been reported to be upregulated in patients with type 2 diabetes. Interestingly, the use of metformin, the first-line drug treatment of diabetes, has shown to decrease HMGB1 expression in diabetic patients [18,30]. Furthermore, HMGB1 plays a role in facilitating the cellular uptake of DNA through different inflammatory signaling pathways. For instance, HMGB1 could modulate the inflammatory response to infections through TLR4 receptor signaling or through binding to cluster of differentiation (CD) membrane proteins expressed by immunocytes, leading to the inhibition of the nuclear translocation of NF- κ B which is specifically induced by HMGB1-mediated TLR4 activation. [21]. In this regard, this review will:

1. Discuss the oncogenic potential of HMGB1
2. Review HMGB1 effect on immune checkpoint inhibition,
3. Discuss the HMGB1-associated pathways in cancer development and progression,
4. Outline HMGB1 as a target/biomarker for cancer therapy.

2. The mechanism of activity of HMGB1 in cancer development and progression

RAGE is an inflammatory type I transmembrane receptor involved in HMGB1-induced intracellular signaling of inflammation, chemotaxis, and NF- κ B activation [31]. The binding of HMGB1 with RAGE stimulates mitogen-activated protein kinase (MAPK) and NF- κ B, consequently activating the expression of pro-inflammatory cytokines [32–34]. Two explanations supported RAGE's fundamental function in HMGB1-induced cytokine production. First, it was observed that RAGE-neutralizing antibodies significantly reduced HMGB1-induced production of the tumor necrosis factor (TNF) (i.e. 40 to 50%), and second, inhibition of RAGE expression reduced the generation of pro-inflammatory cytokines induced by HMGB1 [9]. Further, it has been shown that HMGB1 activates macrophages, monocytes, and neutrophils to generate pro-inflammatory cytokines such as IL-1, IL-6 and macrophage inflammatory protein in a p38 and MAPK-dependent mechanism [35,36]. Moreover, *in vitro* studies in human microvascular endothelial cells have demonstrated that HMGB1 stimulation leads to upregulation of intracellular adhesion molecule 1 (ICAM-1), vascular adhesion molecule 1 (VCAM-1), TNF and IL-8, which could rise the invasion and metastasis of cancer cells through inducing the adhesion between cancer cells and vascular or lymphatic endothelial cells [37,38]. Thus, this suggests that HMGB1 is a potential inflammatory promotor of injury or tissue damage. Moreover, various cellular activities ranging from inflammation to reparative responses are mediated by HMGB1 [39,40]. In activated monocytes, HMGB1 accumulates in secretory lysosomes and is released into the extracellular compartment [41]. Consequently, extracellular HMGB1 acts as a pro-inflammatory mediator and promotes the migration of monocytes towards injury sites [42]. HMGB1 has a crucial role in cancer biological processes and is an integral constituent of the unstable tumor microenvironment [43,44]. Tumor cells secrete HMGB1 and many other intracellular factors in response to anti-cancer therapies such as radio- and chemotherapy [45]. However, the role of HMGB1 is paradoxical in tumors [46]. Studies have reported that HMGB1 levels were upregulated in various cancers such as melanoma, colon, pancreatic, and breast cancers and linked this observation to increased neoangiogenesis in tumors [47–50]. In prostate cancer patients, the co-expression of HMGB1 and RAGE was associated with poor prognosis [51]. Moreover, in lung cancers, HMGB1 expression could activate the expression of transcription factors such as extracellular signal-regulated kinase (ERK1/2) and p38, which are implicated in

tumor development and cell proliferation [52,53]. Additionally, HMGB1 plays a major role in multiple metastatic tumors [54–56]. Indeed, HMGB1 stimulates the TLR4 and RAGE signaling pathways, leading to caspase-1 activation and producing a cascade of inflammatory mediators promoting cancer invasion and metastasis [57,58]. Thereby, HMGB1 could be a novel therapeutic target for cancer treatment. Conversely, HMGB1 can also protect against tumor growth and the effects of chemoradiotherapy and immunotherapy by activation of a protective anti-cancer T-cell response [45,48]. Therefore, it is important to understand the intracellular behavior of HMGB1 and its associated pathways involved in various malignancies. Interestingly, the immunohistochemistry of normal and neoplastic breast tissues has demonstrated two types of staining for HMGB1 [59]. The normal breast tissues display nuclear expression of HMGB1, whereas most of the neoplastic breast tissues exhibited cytoplasmic staining. The cytoplasmic staining of HMGB1 in cancerous tissues was correlated with unfavorable outcomes and increased expression of CD206+ M2 macrophages and regulatory T lymphocytes. These cells are involved in developing and progressing cancer and inhibiting antitumor immunity, and they are thereby considered as poor prognostic factors [60]. Moreover, colon cancer tissues exhibiting increased cytoplasmic HMGB1 expression also displayed decreased infiltration of CD3+ and CD45RO+ T lymphocytes [61]. Thus, targeting HMGB1 would unleash the immune response and enhance the clinical outcome of immunotherapeutic strategies.

3. HMGB1 effect on immune checkpoint inhibition

Circulating HMGBs may promote inflammation and modulate the immune responses [62]. Although growing evidence suggested that

HMGB1 is involved directly and indirectly in cancer progression, its potential role in cancer immunotherapy is still poorly discussed [63]. Recent studies investigated the impact of combining HMGB1 blockers with immune checkpoint inhibitors (ICIs) immunotherapy. Fig. 1 highlights the impact of combining HMGB1 blockers with ICIs on the tumor microenvironment (TME). It has been shown that HMGB1 inhibition enhanced anti-PD-1 cancer immunotherapy efficacy in patient with different cancer types including invasive breast, lung and cervical cancer, and modulated tumor immune microenvironment components [59,64]. For instance, HMGB1 blockade reduced myeloid-derived suppressor cells (MDSC) and regulatory T lymphocytes. In addition it increased M1/M2 ratio of macrophages and dendritic cells activation [59]. Interestingly, HMGBs are suggested as promising predictive biomarkers for patients prognosis and response to immunotherapy in multiple cancers since they are upregulated in most human cancers including leukemia, lymphoma, and sarcoma [63,65]. Using the tumor immune estimation resource (TIMER) and tumor and immune system interaction (TISID) platform, a significant correlation has been observed between HMGBs and tumor infiltration of T helper 2 cells as well as MDSCs, and particularly between HMGB1 expression and the infiltration of CD8+ and CD4+ T lymphocytes [65]. Furthermore, it was reported that docetaxel stimulates the recruitment of CD8+ T cells in the tumor microenvironment in non-small-cell lung carcinoma (NSCLC) through inducing the secretion of both CXCL11 and HMGB1, leading to an improved therapeutic response. These findings indicate that the modulation of the HMGB1-CXCL11 complex could be useful in treating NSCLC [66]. Moreover, HMGB1 has been reported as a novel predictive biomarker for patients who may benefit from the ipilimumab therapy [67]. For instance, serum HMGB1 levels increased in melanoma patients

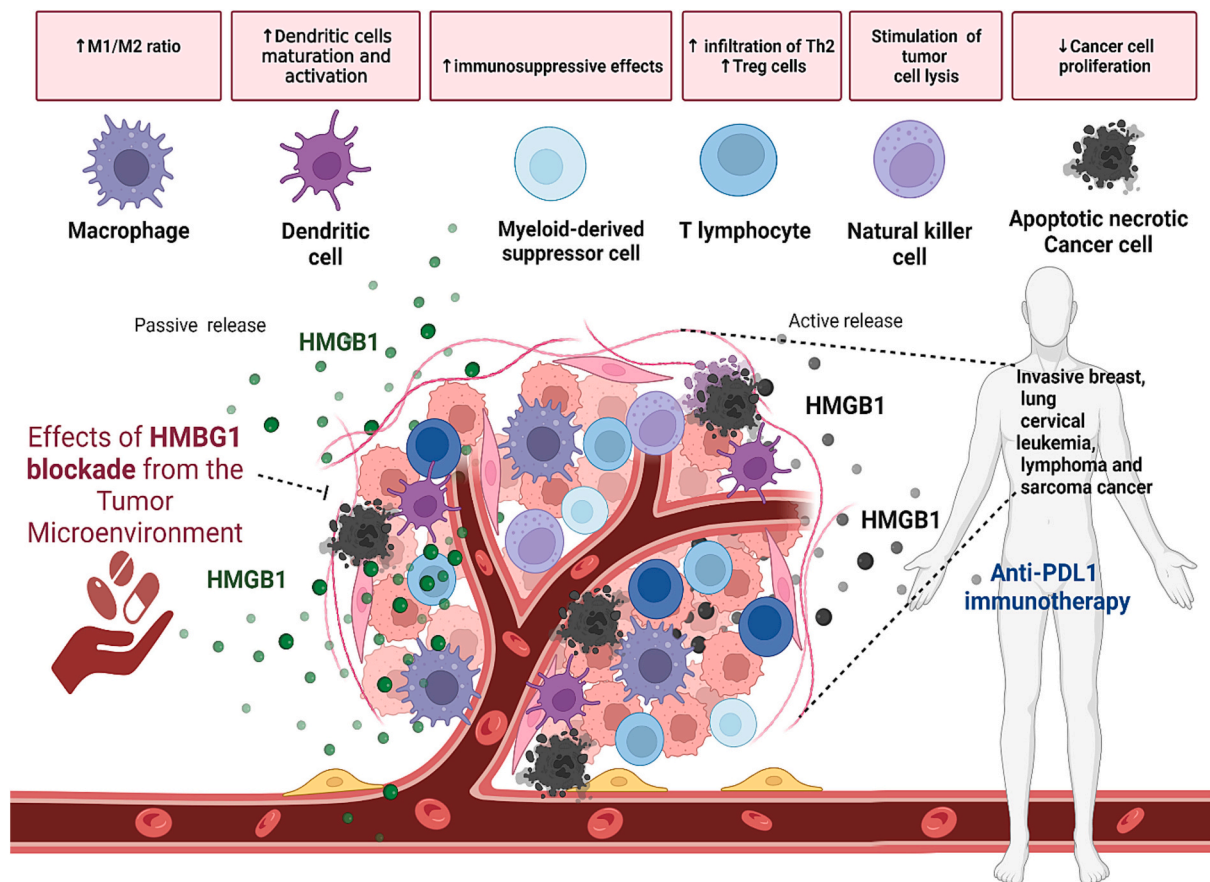


Fig. 1. Impact of combination of HMGB1 blockers with immune checkpoint inhibitors (ICIs). This combination decreases myeloid-derived suppressor cells (MDSC) and regulatory T lymphocytes (Treg). In addition, the M1/M2 macrophages ratio increases and contributes to dendritic cells maturation and activation in several types of cancer.

who did not respond to ipilimumab, compared to responding patients [68]. Similarly, Li et al. showed a significant overexpression of HMGB1 in melanoma samples compared to normal skin and nevi tissues [69]. However, for human melanoma, there are currently no available therapeutic strategy that specifically target HMGB1. A more recent study highlights that miR-429 has significantly inhibited HMGB1 expression, suppressed the proliferation and increased the apoptosis of colorectal cancer cells [70]. Furthermore, HMGB1 facilitated the stemness characteristics and the tumorigenesis of hepatocellular carcinoma by promoting glutamine metabolism via two mechanisms; either via activation of rapamycin *Complex 2*-serine/threonine kinase-c-myelocytomatosis (mTORC2-AKT-C-MYC) leading to increased expression of glutamine synthetase, or through prompting mTORC1 signaling causing a down-regulation of sirtuin 4 (SIRT4) on glutamate dehydrogenase [71]. Interestingly, this effect could inhibit the efficacy of immunotherapy via stimulation of PD-L1 production and upregulation of PD-L1+ exosomes [71]. In addition, increased secretion of type II interferons, such as IFN- γ , eventually promoting the response to PD-L1 antitumor immunotherapy [72], was enhanced following an upregulation of HMGB1 expression in the tumor microenvironment [44]. A recent study explored the carcinogenic role of HMGB1 expression in forty tumors using the TCGA, GEO, and OncoMine datasets. This study showed a high expression of HMGB1 in several types of cancers and reported that HMGB1 level significantly correlated with cancer-associated fibroblasts and intratumoral infiltration of CD8+ T cells [44]. Moreover, this study suggested that HMGB1 might impact immunotherapy efficacy in cancer

[44]. Overall, further investigations are required to broaden our knowledge of the role of HMGB1 in the context of cancer immunotherapy and of the potential clinical outcome of HMGB1 blockade as a treatment strategy for inhibition of cancer growth and metastasis.

4. HMGB1 associated pathways

The list of receptors of HMGB1 is quite extensive. Still RAGE and TLR are established as the most common and most important HMGB1 receptors [32,73]. HMGB1 is also associated with signaling pathways including phosphoinositide-3-kinase (PI3K)/RAC- α serine/threonine-protein kinase (AKT), mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase 1/2 (ERK1/2), and Janus Kinase (JAK)/Signal Transducer and Activator of transcription (STAT) pathway (Fig. 2). We will briefly describe the key signaling pathways playing a pivotal role in HMGB1 pathogenic effect.

4.1. RAGE and TLR

The activation of key signaling pathways is triggered by HMGB1 binding to RAGE or TLR [73]. RAGE is a multiligand cell surface protein that belongs to the immunoglobulin superfamily and is mainly expressed by leukocytes and activated endothelial cells. It has various and different classes of binding molecules. For example, it binds to HMGB1 when it is released during cellular stress leading to inflammatory responses such as NF- κ B activation and release of inflammatory cytokines [74]. Many

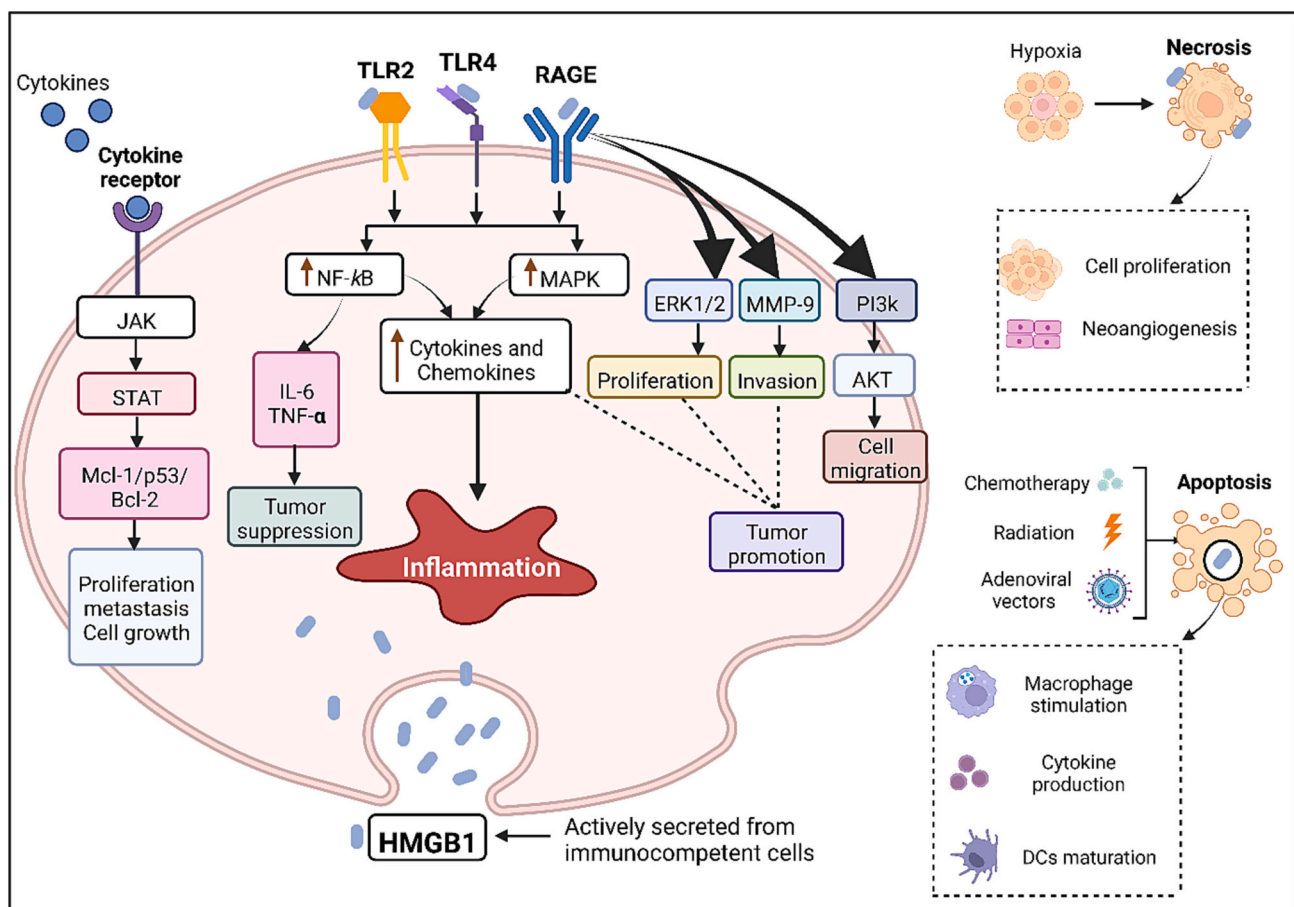


Fig. 2. A schematic representation of HMGB1 signaling pathways in cancer cells. HMGB1 is released towards the extracellular space in response to cancer therapy (i.e. chemotherapy and radiotherapy) or hypoxia active secretion from immunocompetent cells or passive release from apoptotic or necrotic cells. Inside the cytoplasm, HMGB1 prevents apoptosis, and controls the mitochondrial functions. The interaction of HMGB1 with RAGE, TLR2, and TLR4 will transduce cellular signals that stimulate NF- κ B and MAPK pathways, subsequently promoting the nuclear HMGB1 acetylation and secretion. JAK/STAT activation induces the translocation of HMGB1 from the nucleus towards the cytoplasm and its subsequent release into the extracellular space.

studies have reported RAGE to play a central role in inflammatory disorders [75,76]. In addition, TLR is a transmembrane protein expressed by innate immune cells including dendritic cells and macrophages, and by non-immune cells including epithelial and fibroblast cells, and it is responsible for activating the innate immune system [77]. HMGB1 induces inflammation by binding to RAGE and TLR receptors via the NF- κ B pathway leading to subsequent cytokines formation [78]. Nonetheless, it has been reported that macrophages that express both RAGE and TLR4 have not been able to produce cytokines upon HMGB1 stimulation if TLR4 is inactive or absent [79]. Moreover, the interaction of HMGB1 with RAGE activates the expression of matrix metalloproteinase 9 (MMP-9) via triggering NF- κ B and PI3K/AKT signaling pathways, resulting in tumor invasion and metastasis. Yet, a positive correlation was observed between HMGB1 and MMP-9 induction in lung cancers metastatic tumors [52]. Additionally, in breast cancer, NF- κ B activation, promoted by HMGB1/TLR2 axis, affected the cancer stem cells ability to tumor-generation and self-renewal [52,80]. HMGB1/RAGE axis also promotes other types of malignancies including prostate cancer and hepatocellular carcinoma (HCC). Chen et al. have observed increased expressions of mRNAs encoding both HMGB1 and RAGE in three different HCC cell lines and demonstrated that blockade of HMGB1-RAGE interactions was correlated with the survival of HCC cells [81]. In murine models of experimental tumorigenesis, blockade of HMGB1/RAGE interaction reduced the tumor spread and growth [82]. This effect results from the interference between several downstream targets, intracellular and signaling pathways, including NF- κ B and MAPKs, that are linked to cell growth and proliferation.

4.2. MAPK

Mitogen-activated protein kinases (MAPKs) are proteins that control cell mitosis, apoptosis, survival, differentiation, and metabolism [83]. The extracellular signal-regulated kinases (ERKs), a part of MAPKs, are activated in response to mitogenic stimuli [84]. MAPK signaling pathways are also activated when HMGB1/RAGE complex is formed [85]. Moreover, when TLR4 is activated by HMGB1, the MAPK expression levels increase and promote inflammatory genes responsible for the proliferation, invasion, and metastasis of tumor cells. However, deregulating MAPK signaling would result in inappropriate responses and might induce abnormal gene expression [84]. The activated MAPK signaling pathway is also involved in upregulating MMP-9 expression at the transcriptional level [86]. Thus, MMPs expression is mainly controlled by MAPK. Several studies have validated this correlation, by demonstrating that the effect of anti-cancer medications against invasion and metastasis takes place through the downregulation of the MAPK signaling pathway, followed by reduced expression of MMPs [87,88].

4.3. JAK/STAT

The Signal Transducer Activator of Transcription (STAT) is a major intracellular signaling protein that regulates tissue invasion, metastasis, proliferation, cell survival, and angiogenesis [89]. Janus Kinases (JAK) are classified as an exclusive class of tyrosine kinases comprising a catalytic and kinase-like domain [90]. It was reported that the JAK/STAT signaling pathway could control the expression of HMGB-1 in several situations [91]. Moreover, activation of JAK/STAT initiates the translocation of HMGB-1 from the nucleus towards the cytoplasm and its consequent release to the extracellular space. Indeed, the pharmacological suppression of JAK/STAT inhibits the translocation of HMGB-1 [92]. Also, during JAK/STAT mediated acetylation, HMGB1 is relocated and accumulated in the cytoplasm [93]. Additionally, C-X-C chemokine receptor type 4 (CXCR4), and its ligand chemokine stromal cell-derived factor-1 (SDF-1), known to promote invasion and cell migration by JAK/STAT activation, have been recently shown to form a complex with HMGB1 [94]. This HMGB1-CXCR4 complex is responsible

for recruiting inflammatory cells to damaged tissues [95]. To sustain the production of CXCL12/SDF-1 for the cells' migration towards HMGB1, NF- κ B is another critical signaling pathway [96]. Wu et al. demonstrated that the inhibition of JAK/STAT activity resulted in the downregulation of HMGB1, subsequently inhibiting the growth of lung tumors in vitro [97]. Interestingly, in HCC cells, treatment with HMGB1 induced IL-6 which in turn activated STAT3 via JAK signaling, further resulting in the stimulation of miR-21 expression and repression of the MMP inhibitors RECK (reversion-inducing cysteine-rich protein with Kazal motifs) and TIMP3 (tissue inhibitor of metalloproteinase), leading to increased tumor progression [98]. Similarly, HMGB1 has been reported to promote melanoma growth via IL6/STAT3 pathway [99].

4.4. PI3k/AKT

The PI3K/AKT pathway is an intracellular pathway over-activated in multiple cancer types and it contributes to survival, growth, proliferation, metastasis, and migration of tumors cells [100,101]. This pathway is involved in various cellular impairment mechanisms including mutations and genetic modifications, phosphorylation cascades and miRNA regulations. Moreover, the PI3K/AKT pathway counteracts common therapeutic strategies and contributes to multidrug resistance [102,103]. HMGB1 is an important regulator of the PI3k/AKT signaling pathway in different normal cells including fibroblast-like cells [104], mouse mesangial cells [105], human endothelial cells [106] and human dendritic cells [107]. Similarly, in cancer cells, HMGB1 was also described to mediate different cancer-related signal paths including the PI3K/AKT/mTOR pathway [108,109]. Recently, Amornsupak et al. indicated that HMGB1-RAGE interaction stimulates breast cancer cell invasion via the PI3K/AKT signaling pathway, but also abrogates PD-L1 expression resulting in effector T cell deactivation. Thus, targeting HMGB1-RAGE-PI3K/AKT pathway might restrain aggressive phenotypes of breast cancer cells [110]. The valosin-containing protein (VCP) is a key factor in several cellular activities including protein degradation, autophagy, cell cycle regulation, and NF- κ B pathway activation [111,112]. It was demonstrated that inhibition of HMGB1 in vitro in HCC cells significantly counteracted the ability of valosin-containing protein (VCP) in enhancing cell invasiveness. Additionally, the knock-down of HMGB1 significantly downregulated the levels of phosphorylated AKT, mTOR and PI3K that were upregulated following VCP overexpression [113]. Furthermore, in prostate cancer cells, HMGB1 promoted cancer cells growth through activation of AKT signaling pathway and increased tumor migration and invasion by regulating BRG1-dependent epithelial-mesenchymal transition (EMT) [108]. Moreover, by regulating PI3K/AKT pathway, HMGB1 can also affect radio-sensitivity in esophageal squamous cell carcinoma (ESCC) [114]. For instance, Zhang et al. showed that ESCC patients with high expression of HMGB1 and ataxia-telangiectasia mutated (ATM) have a poor prognosis after chemo-radiotherapy. This study also demonstrated that decrease of HMGB1 expression promoted radio-sensitivity in ESCC cells by regulating PI3K/AKT/ATM pathway [114]. Similarly, Du and colleagues observed that the increase of plasma HMGB1 levels in ESCC patients was associated with radio-resistance [115]. Yet, they reported that exosomal HMGB1 induced G2/M phase arrest and apoptosis via decrease of Bax and Bcl2 expression through the activation of PI3K/AKT/FOXO3 signaling pathway. Moreover, they showed that HMGB1 contributed to DNA damage repair via regulation of γ H2AX expression [115]. In pancreatic ductal adenocarcinoma, lucidone treatment blocked HMGB1/RAGE interaction through PI3K/AKT/ multidrug resistance protein 1 (MDR1) signaling and consequently promoted Gemcitabine chemo-sensitivity [116]. Zhou and colleagues demonstrated that Vitexin decreased HMGB1 protein levels in a dose-dependent fashion in prostate cancer cells. Additionally, HMGB1 interacts with BRG1 and activates the AKT signaling pathway to promotes the progression and metastasis of prostate cancer cells [117]. Overall, the HMGB1-induced PI3K/AKT pathway regulates tumors progression,

autophagy and chemoresistance by activating different upstream/downstream molecules.

4.5. Pathways involved in HMGB1 pro-autophagic role

HMGB1 protein plays a crucial role in various cellular processes, including autophagy [118–121]. Once HMGB1 is released from stressed or dying cells, it will bind to RAGE and TLRs receptors, activate them and consequently trigger downstream signaling pathways which initiate cell autophagy. One of these downstream mechanisms is the phosphorylation of Bcl2 leading to the disruption of Bcl2-Beclin1 interaction and subsequent induction of sustained autophagy [122,123]. Beclin1 is a Bcl-2-homology BH3-only domain protein known as a key regulator of autophagy and apoptosis [122]. In cytoplasm, HMGB1 can initiate autophagy by directly interacting with Beclin1 [121], consequently promoting the activation of the Beclin1-class III phosphatidylinositol 3-kinase complex (Beclin 1-PI3KC3), which is an essential initiator of autophagosomes formation [122–125]. Furthermore, HMGB1 plays a role in modulating inflammation, which can indirectly affect autophagy [118,126,127].

5. HMGB1 as a target/biomarker for cancer therapy

5.1. Preclinical studies

There is growing evidence linking the upregulation of HMGB1 and the development of several malignant diseases [128,129]. For instance, in vitro studies in gastric adenocarcinoma cell lines revealed that increased levels of HMGB1 were followed by cells metastasis [130]. Moreover, in vivo knockdown of HMGB1 using shRNA has suppressed the development and invasion of gastric adenocarcinoma cells through the NF- κ B pathway, showing that HMGB1 might act as a therapeutic biomarker for gastric adenocarcinoma [131]. Similarly, downregulating HMGB1 expression inhibited growth and metastasis of HCC cells and prevented the development of xenograft tumors by downregulating the PI3k/AKT-mediated pathway [54]. In another study, HMGB1 was employed as a predictive biomarker for radiotherapy outcomes in bladder cancer [132]. For instance, a positive association between the high expression of HMGB1 and the resistance to radiotherapy has been reported in vitro in several bladder cancer cell lines [133]. However, once the HMGB1 protein was knocked down, an increase in the tumor sensitivity to radiotherapy was observed and autophagy levels was decreased [134]. Moreover, we discussed in section 4.4 how the inhibition of HMGB1 had significantly reduced the VCP-mediated hepatocellular carcinoma growth and induced a downstream activation of AKT signals, thus representing a valuable therapeutic target for precise intervention and improving the survival outcomes in cancer patients [113]. Similarly, the downregulation of HMGB1 was associated with the suppression of tumor growth and metastasis of lung, hepatocellular, and prostate cancer cells both in vivo and in vitro [135–138]. Preclinical studies also supported the evidence of using HMGB1 as a biomarker in detecting cancer using dogs diagnosed with canine lymphoma, where HMGB1 serum levels were measured at different time intervals. It was reported that preliminary high levels of HMGB1 and their increase during chemotherapeutic interventions might represent adverse prognostic parameters in dogs diagnosed with lymphoma [139]. It has also been shown that tumor invasion and migration could be repressed using miR-200c and HMGB1 as putative biomarkers for breast cancer progression [140]. Recently, HMGB1 and CD62L^{dim} neutrophils were suggested as potential biomarkers for lung metastasis in patients with triple-negative breast cancer [141]. Boron neutron capture therapy (BNCT) is considered one of the promising therapeutic techniques to cure malignancies [142]. In this regard, a study intended to assess HMGB1 as a potential biomarker of BNCT therapeutic response by investigating the early responses of cancer cells [143]. Interestingly, increased levels of HMGB1 after BNCT irradiation were noticed even after tumor reduction

in size, indicating that the extracellular release of HMGB1 takes place at early stages, and thus, it could be used as a potential biomarker to assess the therapeutic responses of BNCT [143].

5.2. Clinical observations

High levels of HMGB1 are known to correlate with poor clinical prognosis showing that it is a potential prognostic biomarker for cancer. A meta-analysis and systematic review showed an overexpression of HMGB1 in patients with various types of cancer particularly in inflammation-associated cancers, such as hepatocellular carcinoma and colorectal cancer [144]. Table 1 summarizes the clinical implications investigating the potential role of HMGB1 as a cancer biomarker. Indeed, HMGB1 levels have been used to diagnose urothelial bladder carcinoma (UBC) as an alternative to cystoscopy which was found to be invasive and was associated with false negative results [145]. Moreover, a randomized controlled trial demonstrated that HMGB1 expression was higher in UBC patients than control subject. Additionally, it has been found that 60% of prostate cancer patients had increased HMGB1 levels [146]. Furthermore, HMGB1 levels correlated positively with the cancer stages and with the Gleason grade of prostate cancer. In prostate cancer cells, extracellular HMGB1 interacts with RAGE receptors to enhance cells' proliferation. In addition, HMGB1 interacts with the E-twenty-six (ETS) transcription factors and significantly enhance their DNA binding potential [147]. In lung cancer patients, HMGB1 levels increased in accordance with the stage of cancer and were highly associated with metastasis to lymph nodes and distal organs [148]. Furthermore, high HMGB1 levels correlated with shorter overall survival in NSCLC patients [149]. Similar survival outcomes were also demonstrated in Squamous cell carcinoma of uterine cervix patients [150]. In contrast, Naumnik et al. illustrated that patients with NSCLC possessing high serum concentration of HMGB1 and Vascular Endothelial Growth Factor (VEGF), which is a key mediator of angiogenesis in cancer, had similar surviving correlation with healthy individuals [151]. Moreover, in malignant mesothelioma, HMGB1 levels were high in both tissues and serum samples. A positive correlation between the stage of the mesothelioma tumor and HMGB1 cytoplasmic staining was also found [148]. Serum HMGB1 levels were approximately four times higher in patients with mesothelioma when compared with control patients [152]. HMGB1 has also shown evidence to be used as a biomarker in pancreatic ductal adenocarcinoma patients (PDAC) [153]. Indeed, HMGB1 levels can help to detect PDAC. Importantly, HMGB1 as a biomarker was not affected by the high alkaline phosphatase (ALP) levels caused by biliary obstruction, contrary to carbohydrate antigen (CA19–9) and carcinoembryonic antigen (CEA) which was highly expressed when this marker was increased [152]. Therefore, HMGB1 can be a better biomarker than CA19–9 and CEA to detect PDAC when biliary obstruction is present. Similarly, HMGB1 was also suggested as a potential biomarker in gastric and colorectal carcinomas [154–159].

The pivotal role of HMGB1 in the pathogenesis of hematopoietic malignancies has been also reported [5]. Kang et al. showed that in acute lymphoblastic leukemia (ALL) patients HMGB1 serum levels were increased compared to healthy controls. However, HMGB1 levels between healthy controls and ALL children patients in complete remission is no significant, suggesting that serum HMGB1 could be a robust biomarker to evaluate the prognosis of ALL in children [160]. Furthermore, in leukemia cells, HMGB1 was released to promote inflammation by secreting TNF- α through a MAPK-dependent mechanism. Therefore, HMGB1 may be related to hemocyte differentiation and maturation stage [160]. In many primary lymphomas, the HMGB1 expression level is higher than the average level in normal lymph nodes. However, HMGB1 expression and grading were not correlated [161]. In multiple myeloma (MM), Guo et al. indicated that high expression of HMGB1 is negatively associated with the 3-year survival of MM patients [162]. Interestingly, it was also demonstrated in vitro that HMGB1 participated in DNA damage repair and autophagy. Thus, HMGB1 downregulation

Table 1

Summary of clinical implications of HMGB1 as predictive biomarker in cancer therapy. Abbreviations: ELISA: enzyme-linked immunosorbent assay; IHC: Immunohistochemistry.

| Study Reference | Type of Malignancy | Tissue or serum expression | Quantification Assay | Study outcome |
|-----------------|--|------------------------------|------------------------------|---|
| [145] | Urothelial Carcinoma of Bladder (UCB) | Elevated in Serum and Tissue | ELISA and IHC | HMGB1 is suggested as a diagnostic biomarker in UCB |
| [148] | Non-small cell lung cancer (NSCLC) | Elevated in Serum | Western blot | HMGB1 is suggested as a powerful biomarker to evaluate NSCLC progression. |
| [149] | Advanced lung cancer, small cell lung carcinoma (SCLC), and Mesothelioma | Elevated in Serum | ELISA | High HMGB1 levels correlated with shorter overall survival in NSCLC patients. |
| [151] | Non-small cell lung cancer | Elevated in Serum | ELISA | No correlation was found between HMGB1, survivin and VEGF concentrations. |
| [152] | Malignant Mesothelioma | Elevated in Serum and Tissue | ELISA, IHC, and Western blot | HMGB1 induces migration and proliferation of malignant mesothelioma cells. Secreted HMGB1 plays a role in survival and motility of mesothelioma cells. |
| [153] | Pancreatic ductal adenocarcinoma (PDAC) | Elevated in Serum | ELISA | HMGB1 is a better diagnostic biomarker for PDAC compared with pre-existing PDAC biomarkers such as carbohydrate antigen (CA) 19-9 or carcinoembryonic antigen (CEA) CA19-9 and CEA. |
| [154] | Colorectal cancer | Elevated in Serum and Tissue | ELISA, IHC and western blot | HMGB1 recruits MDSC in tumor microenvironment and induces metastasis through CXCR4/CXCL12 |
| [155] | Gastric cancer | Elevated in Serum and Tissue | ELISA and IHC | HMGB1 increase is correlated with progression of gastric carcinogenesis. HMGB1 expression correlated with CEA levels. |
| [164] | Breast cancer | Elevated in Serum | ELISA | HMGB1 represents a powerful biomarker to predict the response to chemotherapy in breast patients. |
| [165] | Breast cancer | Elevated in Serum | ELISA | Higher HMGB1 levels correlated with increased overall survival in early breast cancer patients receiving neoadjuvant chemotherapy. It is suggested as a potential early prognosis biomarker |
| [150] | Squamous cell carcinoma of uterine cervix | Elevated in Serum | ELISA and IHC | HMGB1 level inversely correlated with overall survival and disease-free survival. |
| [167] | Advanced pancreatic cancer | Elevated in Serum | ELISA | HMGB1 expression correlated with cancer progression stage and overall survival. |
| [160] | Childhood Acute Lymphocytic Leukemia (ALL) | Elevated in Serum | ELISA | HMGB1 promotes inflammation and stimulates TNF-alpha secretion via activating MAPK pathways in leukemia cells. HMGB1 levels are suggested as prognostic factor in Childhood with ALL |
| [158] | Colorectal cancer | Elevated in Serum | ELISA | After radio-embolization therapy, serum HMGB1 was significantly higher in progressive compared to non-progressive patients |
| [168] | Chronic Lymphocytic Leukemia (CLL) | Elevated in Serum | Immunofluorescence ELISA | HMGB1 was significantly associated with shorter overall survival in CLL patients. |
| [102] | Cutaneous T-cell lymphoma (CTCL) | Elevated in Serum | ELISA and IHC | HMGB1 and DNA play important roles in differentiation of nurse-like cells. Increase of HMGB1 expression contributes to the CTCL angiogenesis and cancer progression via Th2 polarization |
| [166] | Liver cancer | Elevated in Serum | ELISA | HMGB1 levels increased already 24 h after trans-arterial chemoembolization. |
| [159] | Rectal cancer | Elevated in Serum | ELISA | Increased levels of HMGB1 following neoadjuvant chemotherapy were associated with lower incidence of metastatic disease and death |
| [163] | Esophageal cancer | Elevated in Tissue | IHC | Overexpression of HMGB1 induced cell migration, proliferation, and radio-resistance. It also reduces the cell cycle arrest at the G0/G1 phase induced by irradiation. |

sensitizes MM cells to dexamethasone via activation of the mTOR pathway to impede autophagy and promote apoptosis [155].

In esophageal cancer, the overexpression of HMGB1 has promoted the cell migration, proliferation, and radio-resistance, and reduced the cell cycle arrest at the G0/G1 phase induced by irradiation, which means that the HMGB1-positive expression would correlate with adverse clinical outcomes [163]. In breast cancer, high levels of HMGB1 was positively correlating with increased overall survival in early breast cancer patients who received neoadjuvant chemotherapy and was suggested as a potential early prognosis biomarker to predict the response to chemotherapy in breast cancer patients [164,165]. In liver cancer, HMGB1 was a potential predicting biomarker for estimating the prognosis and therapy responses of liver cancer patients to transarterial chemoembolization therapy [166].

5.3. The potential clinical application of HMGB1 in human malignancies

Several approaches have been developed to control the translocation and secretion of HMGB1, or to neutralize extracellular HMGB1 to treat

various inflammatory diseases and cancers [169–171]. For example, suppressing HMGB1 secretion was categorized into three groups: inhibiting HMGB1 release, neutralizing HMGB1 itself and blocking HMGB1 receptors [172]. Fig. 3 describes the different strategies to target HMGB1 expression in cancer research studies.

5.3.1. Hematopoietic stem cell transplantation

Hematopoietic stem cell transplantation (HSCT) is an anti-cancer therapeutic strategy that implies intravenous infusion of multipotent hematopoietic stem cell progenitors for treatment of hematological malignancies such as myeloma or leukemia [173]. An ongoing clinical trial (NCT02044185) is studying the clinical implications of HMGB1 in patients with myeloablative conditioning regimen and acute graft-versus-host disease treated with chemotherapy or HSCT [174]. This study attempted to correlate HMGB1 and acute graft-versus-host disease and oral mucositis which is devastating side effect in HSCT settings in human high-dose chemotherapy [172]. In addition, a study showed that patients with disseminated intravascular coagulation, which is caused by complications of allo-HSCT have significantly decreased expression

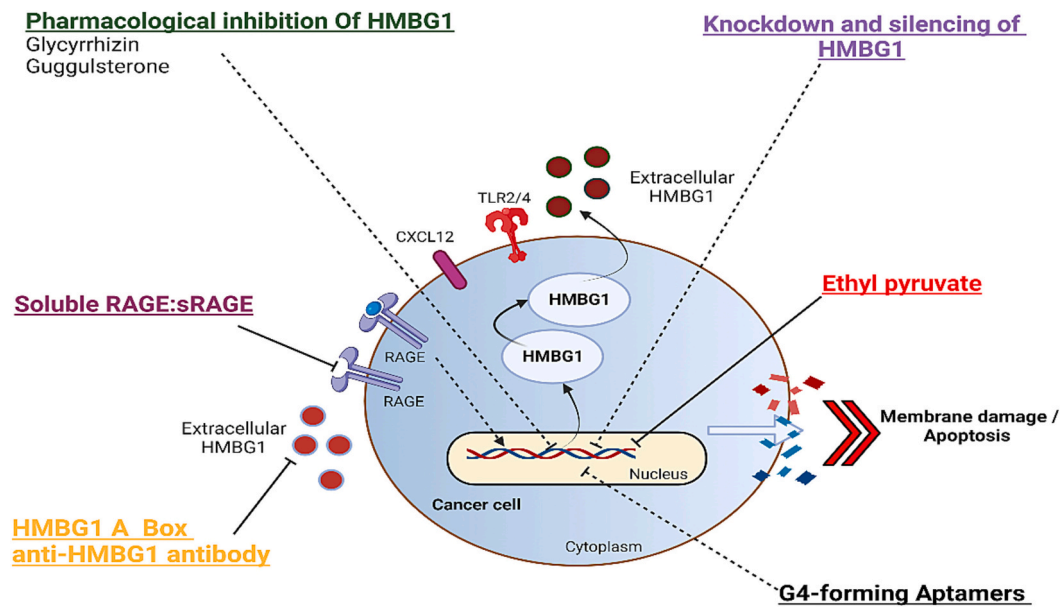


Fig. 3. Therapeutic strategies to target HMGB1 in cancer studies. In addition to the inhibition of HMGB1 by HMBG1 A Box and anti-HMBG1 antibodies or inhibition of its receptors by soluble RAGE, pharmacological inhibition of HMGB1 (glycyrrhizin and guggulsterone), HMGB1 silencing and knockout, as well as small-molecule inhibitors (such as ethyl pyruvate), have been used in a wide range of cancer research experiments and resulted in a reduction of HMGB1 expression.

of HMGB1 after treatment with recombinant human soluble thrombomodulin (rhTM) [175].

5.3.2. Anti-HMGB1 antibodies

Treatment with HMGB1-neutralizing antibody increased chemosensitization of leukemia cells and inhibited HMGB1-induced autophagy [45]. Napolitano E. and colleagues identified novel aptamers (G4-forming aptamers) which specifically target and inhibit HMGB1-induced leukemia cells migration [176]. Moreover, an in silico study showed that glycyrrhizin binds to HMGB1 protein and inhibits its release from the nucleus [177]. Further, Doxorubicin (DOX) induced the release of HMGB1 in breast cancer cells. It has been shown that treatment with anti-HMGB1 antibody (rHMGB1) and DOX significantly increased breast cancer cells viability compared to Dox alone. Nevertheless, the addition of rHMGB1 induced autophagy by converting LC3B-I to LC3B-II [178]. Moreover, hrHMGB1 impedes liver metastasis of colorectal cancer, indicating that HMGB1 could be a potential target for metastasis inhibition [179].

5.3.3. Inhibition of the soluble form of HMGB1

Several pharmacological inhibitors have been used to impede HMGB1 secretion. The first described pharmacological inhibitor was Ethyl Pyruvate (EP) [180]. EP diminishes HMGB1 release by malignant mesothelioma cells and decreases RAGE expression and NF- κ B activation. Additionally, serum HMGB1 levels was reduced by EP in mice subsequently resulting in inhibition of the growth of malignant mesothelioma xenografts [181]. Moreover, Glycyrrhizin is also utilized to inhibit HMGB1 secretion. It has been shown that HMGB1 expression is associated with autophagic activity via AMPK/mTOR signaling pathway activation in hepatocellular carcinoma patients [182]. Moreover, HMGB1 induced muscle atrophy through TLR4/NF- κ B pathway. The administration of glycyrrhizin relieved muscle wasting in vitro and decreased the progression of cachexia in vivo in colon cancer [183]. We have recently studied the effect of guggulsterone (GS), a plant extracted phytosteroid, on HMGB1 expression in multiple myeloma (MM) [184]. We showed that GS induced apoptosis via activation of caspases and cleavage of poly-(ADP-ribose) polymerase. In addition, GS treatment downregulated HMGB1 expression in MM cells via the JAK/STAT pathway [184].

5.3.4. Targeting receptors

Targeting HMGB1 receptors could be a potential strategy to inhibit HMGB1 activity and might be a hope for treating HMGB1-related disorders including inflammation and cancer. Soluble RAGE (s-RAGE) is an isoform generated by the proteolytic cleavage of RAGE at the membrane cell surface. Indeed, inhibition of HMGB1-RAGE interaction using s-RAGE repressed the activation of MAP kinases which play primordial role in tumor progression and metastasis in lung cancer model [185]. Additionally, s-RAGE blocks the HMGB1-RAGE signaling pathway in vivo [185,186]. Recent study also showed that using the anti-HMGB1 mAb, the HMGB1 antagonist box A, and cholinergic agonists inhibits HMGB1/RAGE-mediated endocytosis in cultured macrophages, resulting in restrained inflammation [187].

6. Future perspectives

HMGB1 acts as a potential chromatin-binding factor that binds to DNA and induces the assembly of proteins on specific DNA targets enabling the transcription process of several genes. Moreover, it possesses a high binding affinity to RAGE and is considered as a potent inflammatory mediator. During tumor progression, HMGB1 acts as a pro-cancer protein that promotes the expression of chemokines, cytokines, and growth factor activities. On the other hand, during cancer therapy, HMGB1 acts as an anti-cancer protein and the downregulation of HMGB1 levels can improve the efficacy of anti-cancer treatments. Unfortunately, there are no approved treatments to specifically target HMGB1.

Nevertheless, ongoing research and clinical trials are conducted for several cancer types to develop anti-cancer therapeutics targeting-HMGB1. Consequently, the approaches targeting HMGB1 for preventing and treating cancer are emerging as potential strategies for cancer therapy. In this regard, HMGB1 could be used to design targeted tumor-selective modulators. Furthermore, HMGB1 can induce immune responses, and thus, further efforts are required in order to elucidate the clinical implications and the role of HMGB1 as an anti- and pro-cancer protein agent, and to establish HMGB1-based tumor models. Moreover, additional basic research and clinical studies are required to confirm the importance of targeting HMGB1 in cancer therapy. Furthermore, recent multi-cancer analysis demonstrated that HMGB1 is

also associated with high number of mutations and deletions for example microsatellite instability (MSI) and tumor mutational burden (TMB) leading to immunotherapy resistance and showed a worse clinical prognosis between cancer patients [188]. Therefore, the combination of HMGB1 blockade and ICIs such as PD-L1 might influence the immunotherapy efficiency in diverse cancers, **particularly in patients who fail to respond to immunotherapy because of the highly aggressive phenotype and poor prognosis.**

Authors contribution

SU and MM conceived the idea and the design of the manuscript. SI, TB and MM wrote the manuscript and prepared figures and tables. SP, SA, ME and IA participated to manuscript writing. SU, MM, SP, and SD provided intellectual and scientific contribution. All authors contributed to the revision of this review and approved it for publication.

Funding statement

Medical Research Center, Grant number MRC-01-18-120 (SU), Hamad Medical Corporation, Doha, Qatar.

Declaration of Competing Interest

The authors declare that this work was conducted in the absence of any financial relationships that could be construed as a potential conflict of interest.

Data availability

No data was used for the research described in the article.

Acknowledgment

The Open Access funding is provided by Qatar National Library, Doha, Qatar.

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