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REVIEW

HMGB1 as Double-Edged Regulator of Cancer Therapy: Mechanistic Roles in Chemotherapy Resistance and Immunotherapy Response

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Abstract: High-mobility group box 1 (HMGB1) is a ubiquitous non-histone nuclear protein with multifaceted roles in cancer biology. Emerging evidence suggests that the biological effects of HMGB1 are highly context-dependent, being determined by its subcellular localization, redox state, and release kinetics. Nuclear HMGB1 regulates chromatin structure and genome stability, whereas cytoplasmic HMGB1 controls autophagy and cell survival. When released extracellularly during cellular stress or therapy-induced immunogenic cell death, HMGB1 functions as a damage-associated molecular pattern that activates innate and adaptive immunity through pattern-recognition receptors such as Toll-like receptor 4. In this narrative review, we synthesize recent mechanistic and translational studies to clarify how HMGB1 regulates tumor proliferation, metastasis, and therapeutic responses under different treatment modalities. We particularly discuss the dual roles of HMGB1 in chemotherapy and emerging immunotherapies. Collectively, these insights highlight HMGB1 as a potential biomarker of treatment response and a therapeutically modifiable node for optimizing chemo-immunotherapy combination strategies.

Keywords: HMGB1, cancer, treatment, chemotherapy, immunotherapy

Introduction

Since HMGB1 was discovered and isolated from the thymus of calves in 1973, it has been a subject of extensive research for over half a century. Subsequently, these proteins were named "high mobility group" (HMG) proteins because of their high mobility in the polyacrylamide gel electrophoresis system and the absence of aggregation signs.[1–3] Furthermore, HMGB1 is a widespread sensor of cellular stress, and its balance between cell homeostasis and tissue maintenance is necessary for cell death and survival responses. In the early review on the relationship between HMGB1 and tumor treatment, its function is often summarized as a key framework determined by three factors: cellular localization, redox state, and release kinetics. HMGB1 in the nucleus participates in DNA repair and transcriptional regulation, while in the cytoplasm, after oxidation modification, its pro-inflammatory activity changes. The HMGB1 that is passively released or actively secreted then mediates the functions of immune cells, exerting complex and often contradictory regulatory effects in the tumor microenvironment.[2] Compared with other DAMPs, HMGB1 has a stronger bidirectional regulatory ability, a longer response time to ATP signals, a stronger receptor-related property, and is closely related to chemotherapy and immunotherapy. It has a good prognostic value.

From a clinical translational perspective, HMGB1 has emerged as a highly promising biomarker, particularly in the assessment of immune therapy responses, chemotherapy resistance, and prognosis determination. Current studies suggest that its expression levels in gastric cancer, colorectal cancer, and liver cancer are significantly correlated with patient survival. In

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terms of treatment strategies, HMGB1, as a target or regulatory factor, may be combined with immune checkpoint inhibitors, radiotherapy, and certain chemotherapy drugs to enhance anti-tumor immunity or overcome treatment resistance.

Methods/Literature Search Strategy

This review was conducted based on a structured literature search strategy. Electronic databases, including PubMed, Web of Science, and Embase, were systematically searched for relevant studies published from January 2000 to December 2025. The following keywords and their combinations were used: "HMGB1", "high mobility group box 1", "chemotherapy", "cisplatin", "etoposide", "radiotherapy", "immune checkpoint inhibitor", "RAGE", "TLR4", "oncolytic virus", "immunogenic cell death", "drug resistance", and "tumor microenvironment".

Inclusion Criteria

1. Original research articles investigating the role of HMGB1 in cancer biology or cancer therapy;
2. Studies reporting mechanistic, translational, or clinical outcome data;
3. Articles published in English.

Exclusion Criteria

1. Case reports, conference abstracts, editorials, or non-peer-reviewed studies;
2. Studies lacking primary data;
3. Duplicate publications.

HMGB1

The HMGB1 gene is located on chromosome 13q12 and consists of 4 intron sequences and 5 exon sequences. The human HMGB1 protein is a highly conserved nuclear protein with 215 amino acids.[4] HMGB1 consists of three domains: two positively charged DNA-binding domains (A-box and B-box) and a negatively charged C-terminal. The N-terminal region of it is rich in positively charged lysine residues, while the C-terminal region is mainly composed of negatively charged aspartic acid and glutamic acid, collectively referred to as the acidic tail.[1] Box A (9–79) and Box B (residues 95–163) recognize specific DNA structures, and on these structures, there are three cysteine residues, Cys23, Cys45, and Cys106, which can serve as redox modification sites for the translocation of HMGB1.[4] The two DNA-binding domains of A box and B box are composed of three α helices (helix-I, -II, and -III) that form a L-shaped structure and two rings (ring-I and-II). The B box of HMGB1 induces pro-inflammatory signals upon extracellular stimulation, while the A box induces antagonistic effects. The A box can also combine with the B box to inhibit the function of HMGB1. The acidic C-terminal domain of HMGB1 also functions as a transcriptional activator. HMGB1 contains two essential nuclear localization signals (NLS), specifically located at amino acids 28–44 (NLS 1) and 179–185 (NLS 2). These NLSs are responsible for the nuclear localization of HMGB1; moreover, they regulate the translocation of HMGB1 between the nucleus and the cytoplasm during post-translational modifications (such as phosphorylation and acetylation). The two nuclear export signals (NES) are located within the DNA domain, and in quiescent cells, the balance tilts towards nuclear accumulation, which also indicates the nuclear localization of HMGB1.[5] Therefore, by observing the changes in NLS and NES, the translocation situation of HMGB1 can be confirmed. HMGB1 utilizes various membrane receptors in its signal cascade reaction. The binding with advanced glycation end product receptor (RAGE) occurs at residues 150 to 183, while the binding with Toll-like receptor 4 (TLR4) takes place at residues 89 to 108 within the B box of the HMGB1 molecule.[2] Like other nuclear proteins, HMGB1 undergoes various post-translational modifications, including acetylation, N-glycosylation, ADP-ribosylation, phosphorylation, methylation, oxidation-reduction, and so on. The balance between histone acetyltransferase (HAT) and histone deacetylase (HDAC) determines the acetylation state of HMGB1, which in turn affects its subcellular localization.[6] The structure of HMGB1 and its common modification sites are shown in the following figure (Figure 1): In macrophages, lactate treatment significantly increased the acetylated lysine (Kac) in the HMGB1 immune complex, indicating that lactate promotes the acetylation of lysine in HMGB1.[7] Using a specific anti-acetylated HMGB1 antibody, after lactate stimulation, the acetylation levels of lysine 12 and 29 residues in HMGB1 increased. HMGB1 undergoes post-translational modification in monocytes. The migration pattern of the modified

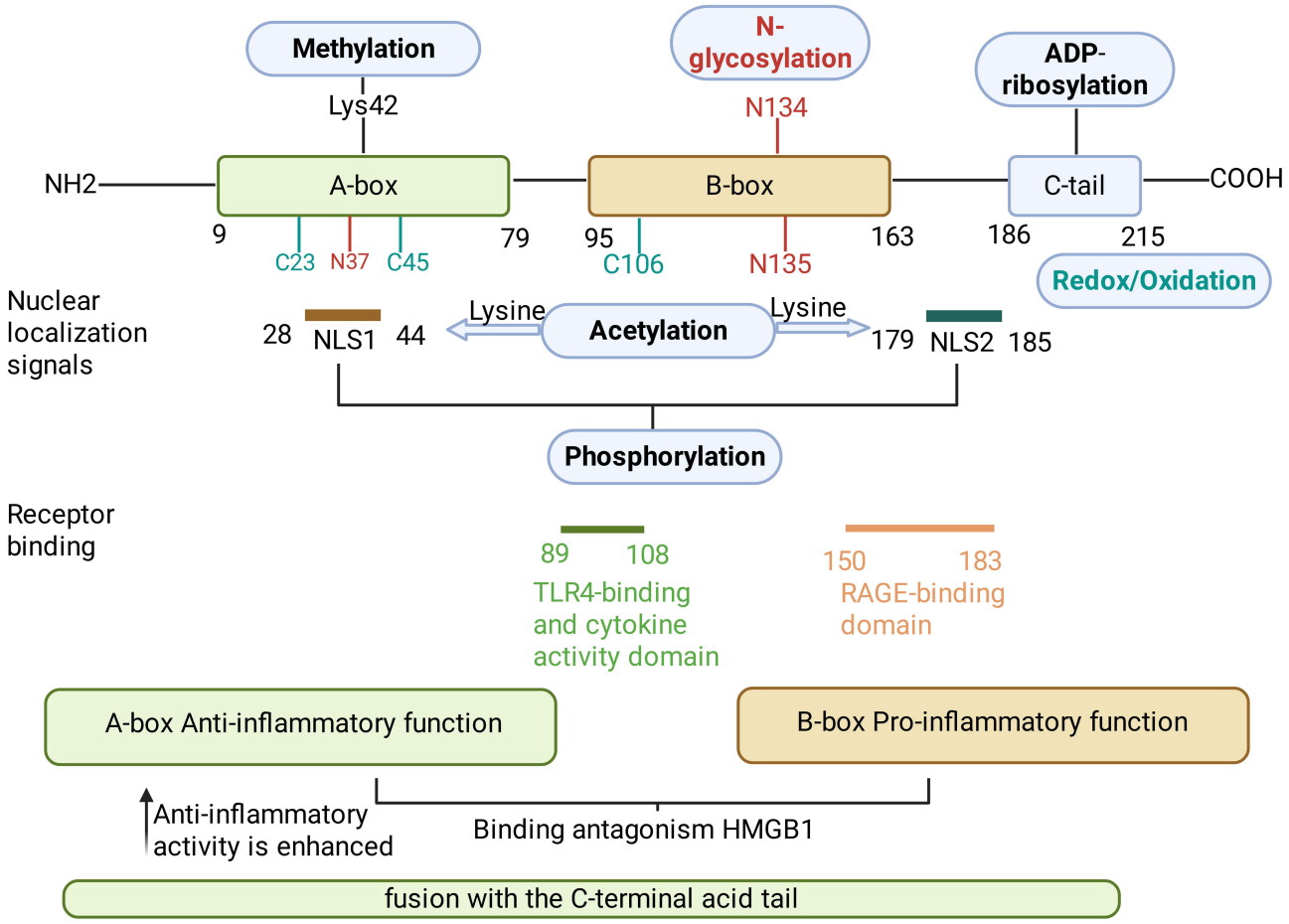

Figure 1 The structure of HMGB1 and its common modification sites. Created with biorender.com.

HMGB1 from monocytes is compatible with multiple lysine acetylation. Acetylation promotes the transport of HMGB1 between the nucleus and cytoplasm. It has been reported that in clear cell renal cell carcinoma (ccRCC), the single post-translational methylation at lysine 42 in neutrophils of HMGB1 alters its conformation and weakens its DNA binding activity.[8] This leads to its passive diffusion out of the nucleus and its translocation into the cytoplasm. In ccRCC, the cytoplasmic distribution of HMGB1 is related to the post-translational methylation of Lys112. After HMGB1 is phosphorylated by the protein kinase C (cPKC) family, its DNA binding affinity is significantly reduced, and then it binds to the nuclear export protein CRM1[9] and migrates to the cytoplasm. In alcoholic liver disease (ALD), the phosphorylation of the two NLSs is an important mechanism for the nuclear-to-cytoplasmic transport and secretion of HMGB1. Among the 14 potential phosphorylation sites, 6 are located within the NLS, but only serine 35 is phosphorylated in ALD.[10] In HMGB1, the phosphorylation of serine in NLS1 is crucial for the translocation of HMGB1 into the cytoplasm. The release of HMGB1 into the extracellular environment requires not only direct protein interaction with PARP-1, but also the enzymatic activity of PARP-1, which leads to the poly-ADP-ribosylation of HMGB1.[11] Macrophages lacking the C-tail are unable to carry out the corresponding PTM.[12] Among them, the N-glycosylation of HMGB1 occurs at positions N37, N134, and N135, which will weaken the binding of HMGB1 to DNA and promote the release of HMGB1.[13] Under mild conditions, cysteine residues 23 and 45 can form intramolecular disulfide bonds, which depend on the concentration of reactive oxygen species (ROS) and the environmental conditions for the binding of HMGB1 to its ligand. Cysteine residue 106 usually exists in its reduced form.[14] The immunogenicity of oxidized HMGB1 is inhibited, which affects its stability. Its main function is to lose activity or induce apoptosis. The reduced state (with three SH groups) of HMGB1 counteracts the oxidative effect of ROS to maintain its stability and binds to the receptor RAGE. Its main functions are promoting autophagy, drug resistance, and cancer cell migration. It also has

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a disulfide bond state (S-S), which binds to the receptor TLR4. It can induce inflammation, activate anti-tumor immunity, and activate the apoptotic pathway (caspase-3/9).[15,16] The structure of HMGB1 is crucial for its pro-inflammatory and anti-inflammatory activities. Its modifying function enables HMGB1 to shuttle between the nucleus and the cytoplasm of cells. As a DAMP, it combines with the corresponding receptors RAGE and TLR2/4 to trigger a series of physiological effects.[17] In tumors, the active secretion and passive release of HMGB1 are closely related to the occurrence and development of the tumor.

HMGB1 in Cancer

Tumors are a long-standing problem faced by humanity, posing a serious threat to human life and health. HMGB1, as a typical DAMP molecule, plays an extremely complex and often dualistic role in the pathological processes of various malignant tumors. After being stimulated and secreted outside the cells, it will activate multiple downstream signaling pathways, thereby profoundly influencing the proliferation, apoptosis, autophagy, metastasis, drug resistance, and shaping of the tumor microenvironment (TME) of tumor cells. Its function is highly dependent on the context, as it varies significantly depending on the type of cancer, cell background, and microenvironment.

The Function of HMGB1 in the Nucleus

HMGB1's role in the nucleus under physiological conditions is to facilitate DNA repair and transcription. However, in tumor cells, it may make proto-oncogenes more prone to mutations or promote unconventional DNA recombination. HMGB1 serves as a transcriptional co-factor for p53, p73, retinoblastoma protein, NF-κB, and nuclear hormone receptors, including estrogen receptor. In colorectal cancer, high expression of nuclear HMGB1 is associated with lower tumor grade and better survival prognosis.[16] In the early stage of tumor progression, HMGB1 helps maintain genomic stability and may have a certain tumor suppressive effect; in established tumors, overly active nuclear HMGB1 instead aids tumor cell survival, accumulation of beneficial mutations, and acquisition of treatment resistance. In the KCH mouse model, nuclear HMGB1 can prevent the accumulation of abnormal DNA structures and reduce chromosomal breaks, while its deficiency accelerates tumor progression and promotes the tumor microenvironment.[18] Overall, the role of nuclear HMGB1 in tumor progression shows significant context dependence. (Figure 2) In highly genomically unstable tumors such as pancreatic cancer, HMGB1 mainly exerts tumor suppressive effects by maintaining chromatin structure and inhibiting inflammatory imbalance; while in established tumors or under treatment pressure, its nuclear DNA repair function may be exploited by tumor cells to enhance survival and drug resistance.

The Tumor-Promoting Mechanism of HMGB1: From Proliferation to Treatment Resistance

HMGB1 has been implicated in tumor invasion, metastasis, and angiogenesis, although most supporting evidence derives from in vitro studies and animal models. In terms of tumor cell proliferation and survival, in vitro studies have suggested that HMGB1 may maintain the malignant phenotype by activating multiple key signaling pathways. For instance, in prostate cancer cell models, HMGB1 has been reported to activate the PI3K/Akt pathway, promote the phosphorylation and degradation of Rb protein, thereby weakening the inhibition of the cell cycle process and being associated with enhanced cell proliferation.[19] This thereby removes the inhibition on the cell cycle process and promotes cell proliferation. In gastric cancer cells, the HMGB1/RAGE axis can simultaneously activate the Akt/mTOR and ERK pathways,[20] synergistically promote the proliferation and migration of tumor cells. In glioma, oral cancer, and non-small cell lung cancer-related cells and in vitro experiments,[21–23] HMGB1, by binding to RAGE or TLRs, efficiently activates conserved survival-promoting pathways such as PI3K/Akt, NF-κB, and MAPK. These signal changes are associated with the continuous enhancement of proliferation and survival signals (Figure 3).

It is reported that one of its core mechanisms is to induce epithelial-mesenchymal transition (EMT) and upregulate the expression of matrix metalloproteinases (MMPs). In HCC cells, HMGB1 inhibits the transfer of inhibitory factors RECK and TIMP3, thereby activating MMPs[29] promote the degradation of the extracellular matrix and the spread of cancer cells. Regarding the experiment on colon cancer cells using the new drug C6, the activation of the HMGB1-RAGE-

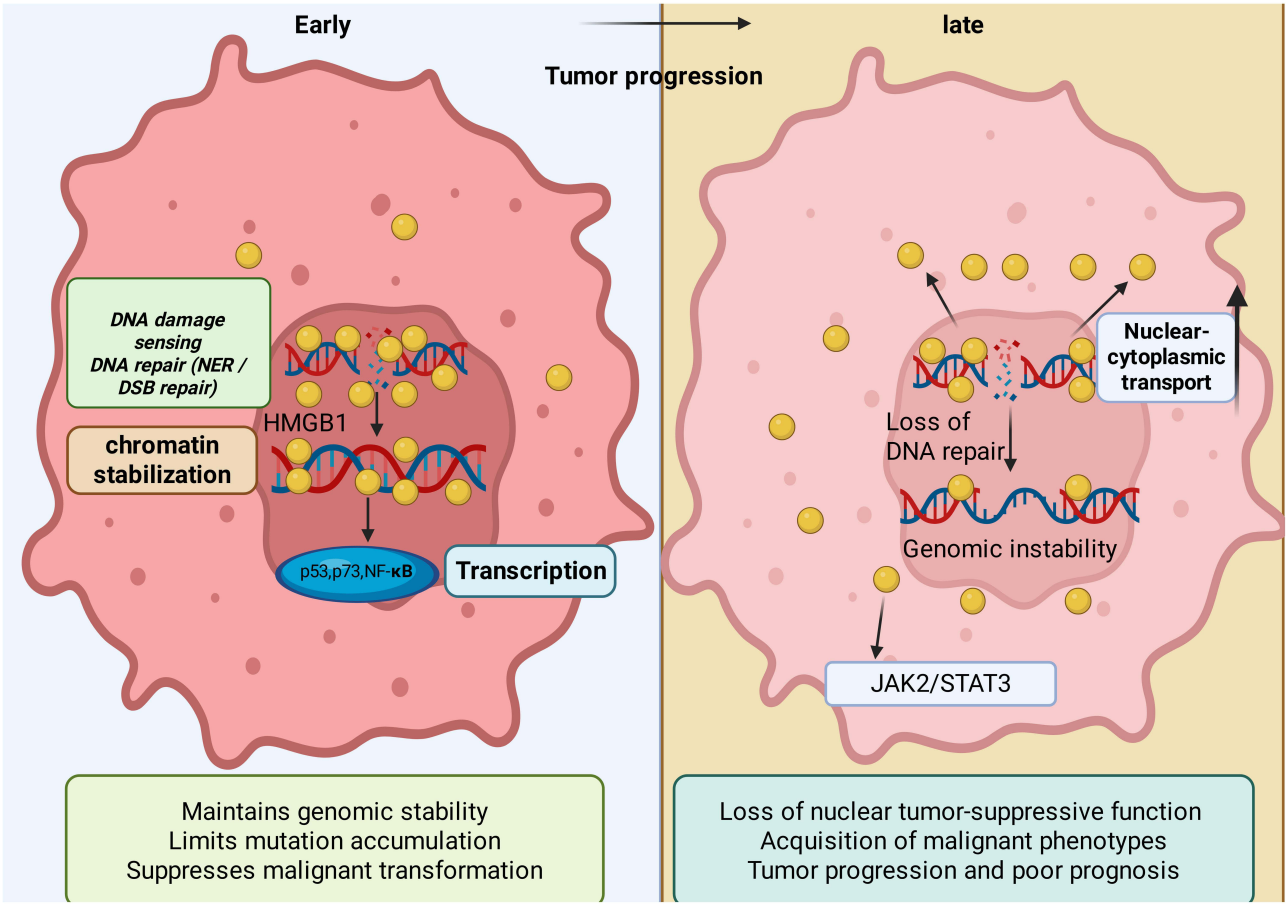

Figure 2 As the tumor progresses, HMGB1 may exert different functions within the nucleus. In the early stage of the tumor, HMGB1 promotes DNA damage and repair to maintain chromatin stability. However, in the advanced stage of the tumor, the nuclear-cytoplasmic exchange is enhanced, HMGB1 moves from the nucleus to the cytoplasm, its repair ability weakens, and it activates downstream pathways, resulting in a weakened anti-tumor effect, even promoting tumor progression.

ERK1/2 pathway can upregulate the transcription factors Snail and MMPs,[30] enhancing the migration and invasion capabilities of cells. Additionally, this pathway can also upregulate vascular endothelial growth factor (VEGF),[16] and with the melanoma suppressive activity protein (MIA), it promotes the formation of tumor blood vessels and lymphatic vessels, providing pathways for metastasis. In the Bare mouse pancreatic tumor model, the HMGB1 released by radiotherapy can drive the EMT process through the Wnt/p-GSK-3β axis,[31] promoting tumor recurrence and metastasis. In the hypoxic environment, HMGB1 secreted by breast cancer can activate the TLR2/6 pathway,[32] polarized $CD11b^{+}$ neutrophils form neutrophil extracellular traps (NETs), thereby promoting lung metastasis (Figure 3).

In terms of treatment resistance, the potential molecular mechanisms underlying the failure of HMGB1 chemotherapy, radiotherapy, and targeted therapy. Its mechanism of inducing drug resistance is diverse: Firstly, it activates protective autophagy. In the triple-negative breast cancer cell lines (MDA-MB-231, MCF-7), HMGB1 translocates and activates through the IGF1R/STAT3 pathway,[33] inducing autophagy and upregulating ATP-binding cassette transporter G2 (ABCG2), which mediates drug efflux, leading to chemotherapy resistance. Secondly, directly upregulating drug efflux pumps. In human-derived gastric cancer cells, HMGB1 released by necrotic cells interacts with surviving cells, promoting the expression of the MDR1 gene and increasing the level of P-gp protein.[34] Drug efflux leads to a decrease in the intracellular concentration of the drug, enhancing resistance to doxorubicin (ADM) and vincristine (VCR).[35] Third, it mediates radiotherapy resistance. In esophageal squamous cell carcinoma cells (ESCC), HMGB1 activates the PI3K/AKT/ATM pathway,[20] which leads to resistance to radiotherapy. Fourth, in targeted therapy, such as for thyroid cancer, the sensitivity of BRAF V600E mutant cells to vemurafenib is negatively correlated with the level of HMGB1.[36] Overexpression of HMGB1 can reduce caspase-3 activity by inducing excessive autophagy, thereby inhibiting apoptosis and leading to drug resistance.

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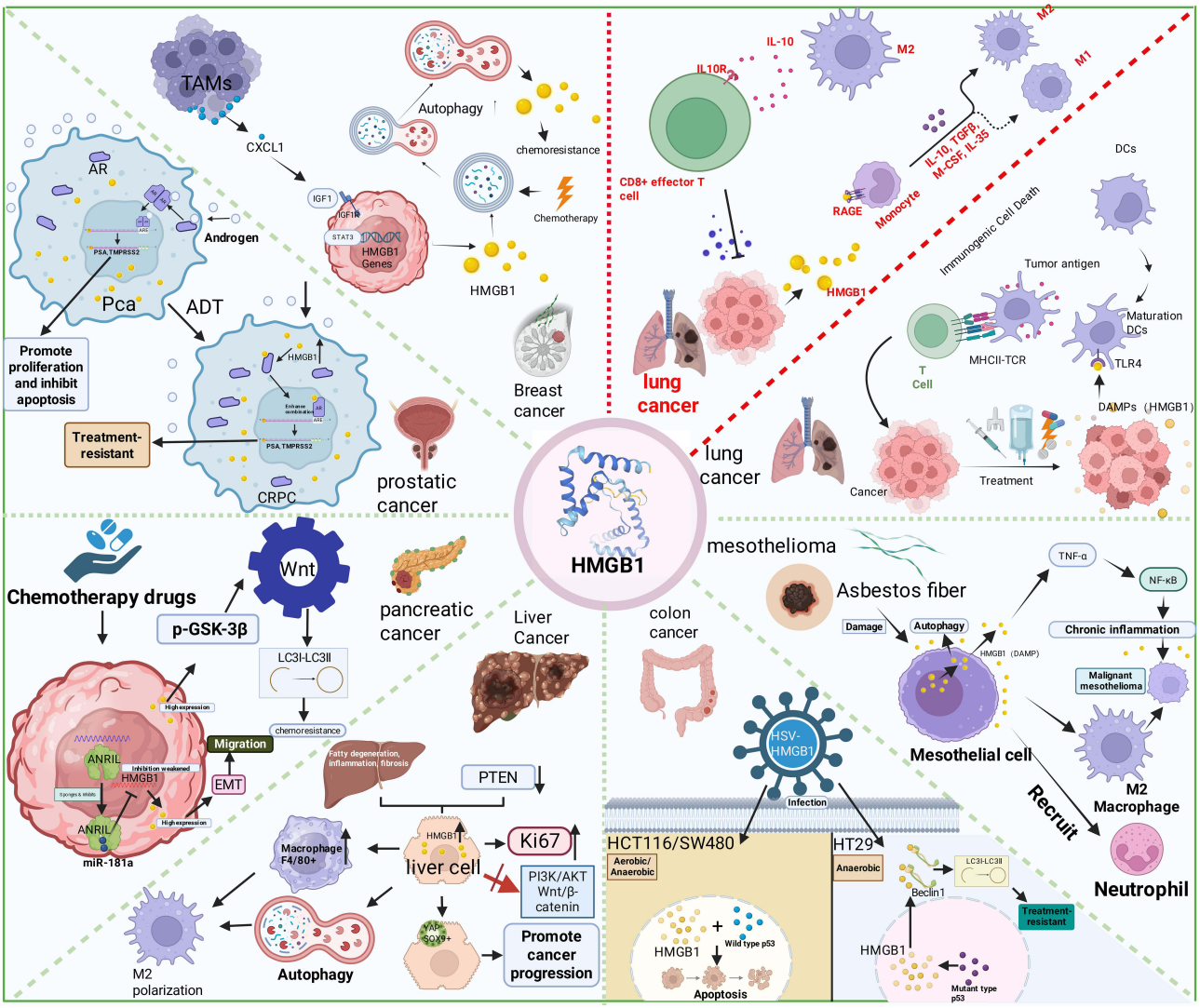

Figure 3 The expression of HMGB1 in different types of cancers. In breast cancer, TAMs secrete C-X-C motif chemokine ligand 1 (CXCL1) to activate the insulin-like growth factor 1 (IGFR1)/signal transducer and activator of transcription 3 (STAT3) signaling pathway, promoting the release of HMGB1 and autophagy to enhance chemotherapy resistance; In early prostate cancer, androgen enters the cell and binds to the AR receptor, promoting the dimerization of AR receptors to bind to ARE on mRNA and promoting the proliferation of cancer cells. However, after a period of androgen deprivation therapy (ADT), androgen cannot enter the cell, and HMGB1 binds to AR to bind to ARE, promoting drug resistance;[24] In PC, lncRNA ANRIL is affected by chemotherapy and acts as a sponge to adsorb miR-181a, thereby relieving the inhibition on HMGB1. The high expression of HMGB1 promotes cell autophagy through p-GSK-3β/Wnt, leading to chemotherapy resistance;[25] In liver cancer, steatosis, inflammation, fibrosis and PTEN deficiency lead to high expression of HMGB1 in cells, promoting macrophage infiltration/M2 transformation and YAP/SOX9 activation to facilitate tumor progression; in lung cancer cells, HMGB1 affects immune function by altering polarization status and binding to the corresponding TLR4;[26] In colorectal cancer, after HSV-HMGB1 virus invades tumor cells (HCT116/SW480), HMGB1 binds to wild-type p53 to promote apoptosis. In HT29, due to the hypoxic environment and the action of mutant p53, HMGB1 binds to Beclin1 to promote autophagy, resulting in treatment resistance;[27] In mesothelioma, due to the long-term effect of asbestos fibers, HMGB1 in mesothelial cells is transported from the nucleus to the cytoplasm, promoting autophagy. The HMGB1 that leaves the cell attracts neutrophils and activates TNF-β/NF-κB, leading to the occurrence of chronic inflammation. Eventually, its high expression interacts with this phenomenon, causing malignant transformation of mesothelioma.[28] Created with biorender.com.

The Tumor-Suppressing and Immune-Activating Effects of HMGB1

Although the oncogenic effect is the mainstream, under different conditions, HMGB1 can also exert a tumor-suppressing effect, which is mainly related to the immunogenic cell death (ICD) it triggers and the activation of the adaptive immune response. The most representative mechanism is tumor cell pyroptosis.[37] When tumor cells undergo pyroptosis, they actively release DAMP molecules such as HMGB1. These extracellular HMGB1 act as "alarm signals", which can promote the maturation and antigen-presenting function of dendritic cells (DCs), thereby activating tumor-specific T cell immune responses and exerting a powerful anti-tumor effect. This process provides a theoretical basis for using chemotherapy or radiotherapy to induce immunogenic cell death (ICD) to enhance the efficacy of immunotherapy.

Additionally, in certain specific circumstances, HMGB1 itself can directly induce cell apoptosis. For instance, in the presence of specific antioxidants, HMGB1 can instead induce cell apoptosis through the p38 mitochondrial pathway. In the mouse TNBC model, nuclear HMGB1 has been found to combine with the tumor suppressor gene Rb protein.[32] This suggests that it may be involved in inhibiting the cell cycle process in certain circumstances, and exerting its inherent tumor-suppressing function (Figure 2).

The Profound Shaping of the Tumor Microenvironment (TME) by HMGB1

HMGB1 is closely related to the regulation of the tumor microenvironment. It mainly achieves this by recruiting and polarizing various immune cells, creating an immunosuppressive environment conducive to tumor growth and metastasis. HMGB1 is a powerful chemoattractant for immunosuppressive cells. In colon cancer cells, the HMGB1-RAGE signaling pathway can recruit myeloid-derived suppressor cells (MDSCs),[16] which can significantly inhibit the anti-tumor activities of T cells and macrophages. In melanoma cells, HMGB1 binds to TIM-3, inducing the secretion of VEGF and the polarization of M2-type macrophages, and promoting the secretion of IL-10.[38] This inhibits the proliferation and function of CD8+ T cells.

The regulation of tumor-associated macrophages (TAMs) by HMGB1 is particularly complex and has a bidirectional potential. Usually, HMGB1 tends to promote the polarization of TAMs towards the pro-tumor M2 phenotype. In esophageal cancer cells[20] (Figure 3), the HMGB1 released through exosomes can induce high expression of programmed death receptor-1 (PD-1) in TAMs, significantly correlated with the inhibition of CD8+ T cell activity. However, it is worth noting that in cancers such as non-small cell lung cancer, studies have shown that under the stimulation of specific drugs, HMGB1 may potentially promote the transformation of TAMs from the M2 type to the anti-tumor M1 type.[39,40] This reveals the plasticity of its regulation and its potential as a therapeutic target.

HMGB1 can also promote the formation of the inflammatory microenvironment. In PC cell, the S100P-HMGB1-RAGE axis can strongly activate NF-κB,[41] it generates a large amount of inflammatory factors, forming a "cytokine storm", which promotes tumor development. In mesothelioma, the cell death caused by asbestos fibers leads to the release of HMGB1, which acts as a DAMP to activate TLR signaling,[42,43] recruit macrophages and neutrophils, and secrete pro-inflammatory factors such as reactive oxygen species (ROS), leading to chronic inflammation and ultimately driving the malignant transformation of cells.

The Potential Transformation of HMGB1 as a Therapeutic Target

The pleiotropic effects of HMGB1 in various cancer types and its central role in the tumor microenvironment make it an extremely attractive therapeutic target. Current strategies mainly focus on inhibiting its release, blocking its signals, or regulating its modifications. Direct targeting of HMGB1 itself or its receptors is the main direction. For instance, the new compound C6 has been reported to antagonize the HMGB1-RAGE-ERK1/2 pathway through dual actions, exerting a synergistic anti-inflammatory and anti-cancer effect. Using neutralizing antibodies or antagonists to block the interaction between HMGB1 and RAGE/TLRs shows inhibitory effects on tumor growth and metastasis in preclinical models. Regulating the post-translational modifications of HMGB1 is another precise strategy. The cytoplasmic translocation and pro-inflammatory activity of HMGB1 are highly dependent on its acetylation status.[6] The deacetylase SIRT1 can inhibit the migration and inflammatory ability of HMGB1. On the contrary, in cervical cancer, the valproic acid derivative HO-AAVPA inhibits the histone deacetylase HDAC1,[44] increasing the acetylation of HMGB1 and promoting its nuclear translocation to the cytoplasm, which may induce immunogenic cell death, which provides a possible approach for the combination of epigenetic drugs and immunotherapy.

Combined treatments targeting the downstream pathways of HMGB1 also demonstrate great potential. The most notable example is in thyroid cancer cells, where the resistance to vemurafenib is associated with autophagy mediated by HMGB1.[36] The combined use of autophagy inhibitors (such as 3-MA) can significantly reverse drug resistance and restore the sensitivity of cancer cells to targeted drugs.

Time Shapes the Role: HMGB1 plays different roles at different stages of tumor evolution. In the early stage of tumor development, it may act as a tumor suppressor by maintaining genomic stability; in the advanced stage, it promotes

tumor growth by facilitating angiogenesis and metastasis; during the treatment stress period (such as immunogenic cell death induced by radiotherapy and chemotherapy), it can transform into an "alarmin" that activates anti-tumor immunity.

HMGB1 In Chemotherapy

Chemotherapy is an important method for treating tumors, but its efficacy is often limited due to the emergence of drug resistance. HMGB1, as an important nuclear protein and DAMP, plays a complex and crucial role in the response to various chemotherapy drugs. It can mediate drug resistance through mechanisms such as participating in DNA damage repair, inducing protective autophagy, and promoting drug efflux, and it can also act as a key signaling molecule for immune-induced cell death (ICD) to activate anti-tumor immunity. This section will systematically elaborate on the molecular mechanisms of the interaction between HMGB1 and commonly used chemotherapy drugs, and deeply explore its potential value as a therapeutic target or prognostic marker.

HMGB1 and Platinum-Based Drugs: A Dual Role From DNA Damage Protection to Immune Activation

Cisplatin and other platinum-based drugs cause DNA-platinum adduct formation, resulting in intramolecular and intermolecular cross-linking of DNA strands. This blocks DNA replication and transcription, activates the DNA damage response (DDR), and ultimately induces apoptosis of cancer cells.[45] HMGB1 can specifically recognize and bind to these platinum-DNA adducts within the nucleus. The Phe37 and Asn53 residues in its A-box domain directly interact with the platinum atoms. This binding has a dual effect: on the one hand, the high expression of HMGB1 can mask the DNA damage sites, preventing the repair pathways, such as nucleotide excision repair (NER) from recognizing and removing the adducts, thereby enhancing the cytotoxicity of cisplatin.[46] On the other hand, it may also protect the adducts from being repaired;[47] in some cases, this phenomenon actually reduces the effectiveness of the drug. This occurs in rhabdomyosarcoma (RMS) and is associated with cisplatin resistance (with an increase in IC50). In terms of clinical relevance, tissue sample and serum analyses revealed that high expression of HMGB1 or elevated serum levels were associated with poorer clinical outcomes following cisplatin treatment. Retrospective survival analysis indicated that patients with high HMGB1 expression had significantly shorter overall survival (OS) and progression-free survival (PFS). Multivariate Cox regression analysis suggested that HMGB1 might be an independent adverse prognostic factor (Table 1).

Table 1 The Different Ways in Which Various Chemotherapy Drugs Affect HMGB1 in Different Types of Cancers

Drug Type	Mode of Action (HMGB1)	Type of Cancer	Result
Platinum	Transported outside the cell via XPO1	Adenocarcinoma of lung	Activate ICD
	Regulation of autophagy	Ovarian cancer/lung cancer	Chemotherapy resistance
Etoposide	Regulation of DNA damage and cell apoptosis	Embryonic stem cell	Chemotherapy resistance
Nab-paclitaxel	Nuclear-cytoplasmic transport	Lung cancer	Activate ICD
Cyclophosphamide	DAMP, Increase VEGF	Lung cancer	Promote tumor angiogenesis, Promote the transfer
	DAMP	Lymphoma	Chemotherapy resistance
Doxorubicin	Nuclear-cytoplasmic transport induces autophagy and affects apoptosis	Liver cancer	Chemotherapy resistance
	Promote EMT/ Activate T cells	Breast cancer	Promote metastasis and ICD
	Autophagy and upregulation of P-gp	Leukemia	Mediating multi-pathway drug resistance

(*Continued*)

Table 1 (Continued).

Drug Type	Mode of Action (HMGB1)	Type of Cancer	Result
Vincristine	Induction of autophagy	Oral cancer, leukemia	Inhibit the mitochondrial apoptosis pathway to protect cancer cells
	Increase P-gp	Adenocarcinoma of stomach	Mediating multi-pathway drug resistance
Gemcitabine	Promote autophagy and inhibit apoptosis	Pancreatic cancer	Chemotherapy resistance
	Protective autophagy	Carcinoma of urinary bladder	Chemotherapy resistance
Tamoxifen	DAMP	Breast cancer	Suppress anti-tumor immunity and promote metastasis

In addition to the intranuclear action, it was also found in the lung adenocarcinoma model that cisplatin can also actively transport HMGB1 from the nucleus to the cytoplasm through the nuclear export protein XPO1 (CRM1) and secrete it outside the cell.[48] This process does not rely on common post-translational modifications (such as acetylation, phosphorylation). It is worth noting that the HMGB1 secreted by cisplatin induction is mainly in a fully reduced state (all cysteines are not oxidized), giving it strong chemotactic activity. It can bind to receptors such as RAGE/TLR, recruit and activate immune cells such as dendritic cells (DCs) (Figure 4), enhance antigen presentation ability, and stimulate effective anti-tumor immune responses - this is the core feature of immune-induced cell death (ICD). In contrast, the oxidized HMGB1 released during DMSO-induced apoptosis is more likely to promote inflammation and tumor progression.[15] For instance, it promotes metastasis by binding to CXCL12, or causes drug resistance by continuously activating the RAGE/PI3K/Akt pathway.

Furthermore, HMGB1 is also related to autophagy regulation. Cisplatin can induce the intracellular translocation of HMGB1, thereby activating pathways such as AMPK/mTOR to promote protective autophagy, helping cancer cells eliminate damaged organelles and maintain metabolic homeostasis, thereby resisting apoptosis induced by platinum and mediating drug resistance. Inhibiting HMGB1 or its downstream autophagy pathways can significantly enhance the cytotoxicity of cisplatin. Recent studies have shown that the regulatory role of HMGB1 in platinum resistance is tissue-specific. In ovarian cancer cells, HMGB1 affects the sensitivity of cancer cells to cisplatin by regulating autophagy flow and mitochondrial function; while in lung cancer cells, its extracellular secretion form is more related to immune regulation. This tissue specificity suggests that when developing therapeutic strategies targeting HMGB1, we need to consider the differences in tumor types and microenvironment characteristics.

HMGB1 and Topoisomerase Inhibitors as Well as Microtubule-Targeted Drugs: Regulation of Cell Death Patterns and Immune Microenvironment

Etoposide as a topoisomerase II inhibitor, it can cause DNA double-strand breaks (DSBs) and induce cell apoptosis.[49] Research finding, during this process, HMGB1 is oxidized and tightly binds to the chromatin, thereby inhibiting its passive release.[50] This helps to reduce the inflammatory response related to necrosis/pyroptosis and promotes the smooth progression of apoptosis.[51] Studies have confirmed that in embryonic stem cells lacking HMGB1 (Figure 4), [52] the sensitivity to etoposide increased, manifested by a more severe G1 phase cell arrest, accumulation of 53BP1 foci (a marker of DNA damage), and activation of the caspase-3/PARP apoptotic pathway, indicating that HMGB1 plays an important role in regulating the DNA damage response and apoptotic threshold.[53]

Albumin-bound paclitaxel (nab-Paclitaxel) kills tumors by stabilizing microtubules and inhibiting mitosis. Its effects go beyond simple cytotoxicity. In lung cancer models, paclitaxel modified with IL4 receptor-targeting peptides (IL4R-Abx) can be efficiently internalized by M2-type macrophages,[54] inducing the outbreak of ROS, thereby causing the nuclear-to-cytoplasmic translocation and release of HMGB1.[54] The extracellular HMGB1, acting as a DAMP, binds to

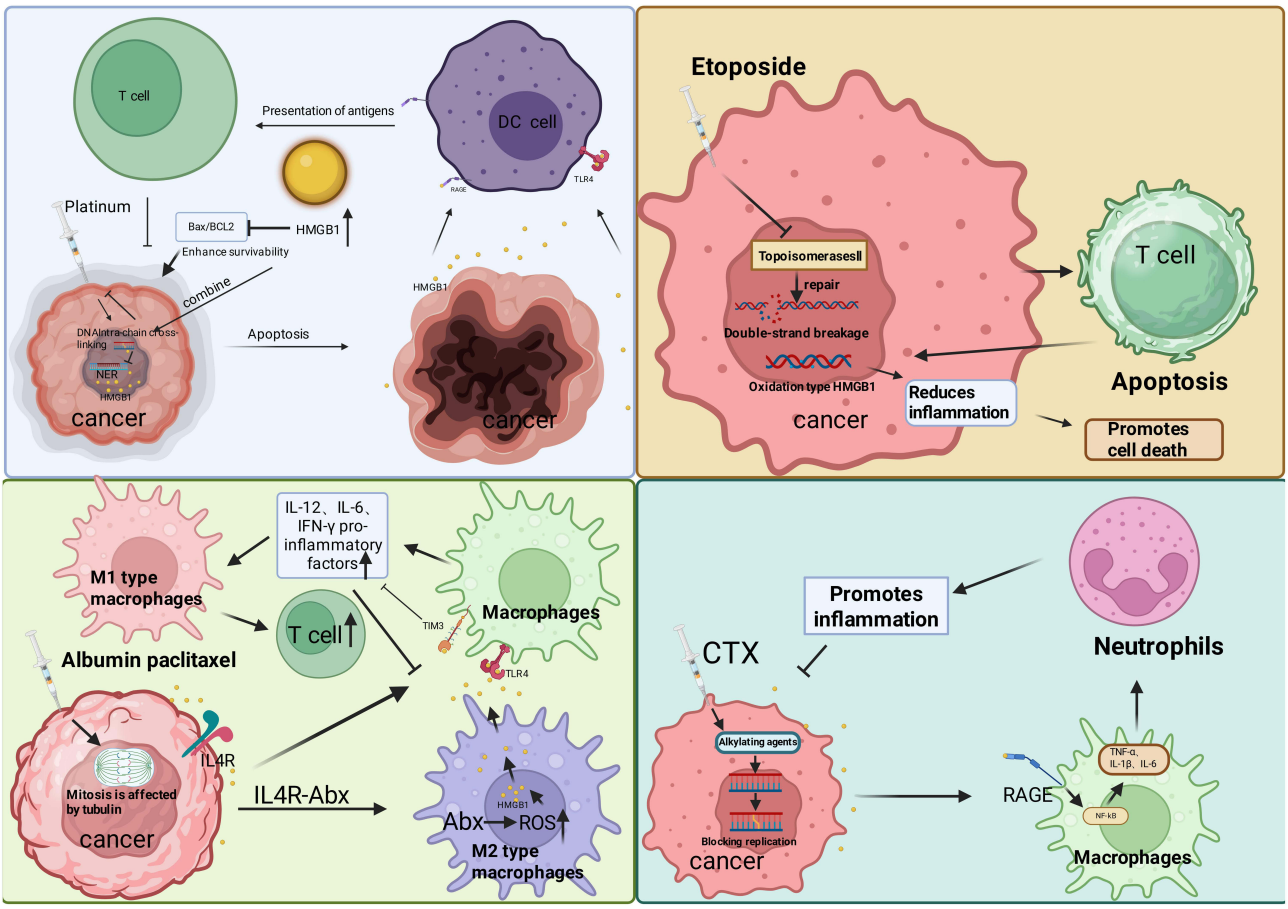

Figure 4 The impact of four chemotherapy drugs on HMGB1 on tumor progression. Created with biorender.com.

TLR4, triggering the upregulation of inflammatory factors (such as IL-12, IL-6, IFN-γ), and promoting the transformation of M2 type macrophages into M1 type macrophages (Figure 4).

Polarization, and increasing the infiltration of $CD8^+$ T cells,[55] reducing Treg and MDSC significantly improves the immune microenvironment. However, the ICD induced by paclitaxel may also be counteracted by the tumor immune escape mechanism: the VISTA protein on the surface of cancer cells interacts with the VISTA of tumor-associated macrophages (TAMs).[56] Moreover, HMGB1 binds to TIM-3, which together can block the response of TAMs to IFN-β and inhibit their pro-inflammatory (M1) polarization. The combined use of anti-TIM-3/VISTA antibodies can restore the tumor-killing function of TAMs, bypassing T cells to directly kill cancer cells, highlighting the background-dependent nature of HMGB1 in immune regulation.

The latest research has found that paclitaxel drugs can regulate the function of HMGB1 by influencing its spatial conformational changes. The fully reduced form of HMGB1 mainly exerts an immune-stimulating function,[56] while the partially oxidized type tends to promote inflammation and angiogenesis, the fully oxidized type loses almost all of its biological activity. The precise regulation of this redox state provides a basis for developing new therapeutic strategies, such as modulating the function of HMGB1 by regulating the redox state in the tumor microenvironment.

HMGB1 and Alkylating Agents, Anthracycline Drugs and Antimetabolites: A Convergence Point for Multiple Resistance Mechanisms

Cyclophosphamide (CTX), as an alkylating agent, can directly damage DNA and trigger inflammatory responses.[57] After lung tissue is damaged, HMGB1 is released as a DAMP and activates NF-κB by binding to RAGE,[58] promotes the release of pro-inflammatory factors such as TNF-α, IL-1β, and IL-6 (Figure 4), and recruits neutrophils,[59] it exacerbates

tissue inflammation and oxidative stress (by inhibiting the Nrf2 antioxidant pathway). On the contrary, in the case of bone marrow suppression, CTX can hinder DNA repair by inhibiting the expression of HMGB1,[60] promoting cell apoptosis demonstrates the tissue specificity of HMGB1's function.

Doxorubicin (DOX) induces cell death and ICD through multiple mechanisms (such as DNA damage, ROS generation, and calcium overload).[61,62] In liver cancer cells, DOX upregulates HMGB1 and promotes its cytoplasmic translocation, activating the AMPK/mTOR pathway-mediated protective autophagy.[63] This leads to inhibition of apoptosis and development of drug resistance. In breast cancer cells, HMGB1 released by DOX induction is upregulated through the TLR4/MyD88/NF-κB pathway and downregulated for E-cadherin, promoting epithelial-mesenchymal transition (EMT) and lung metastasis. However, it can also activate DC cells through TLR4 and promote T cell response (Figure 5), once again highlighting its dual nature.[64] In leukemia cells, HMGB1 enhances autophagy through the ERK pathway and upregulates various drug-resistant proteins such as P-gp through the NF-κB pathway. It mediates drug resistance through multiple pathways.[4]

Vincristine (VCR) blocks mitosis by inhibiting microtubule polymerization.[65] Among gastric cancer, oral cancer and leukemia cell,[4,66] VCR can induce autophagy (manifested as LC3-II conversion and p62 degradation) and stimulate HMGB1 secretion. The extracellular HMGB1 binds to RAGE (not TLR2/4) (Figure 5), enhances the transcription of MCL-1 (a key anti-apoptotic protein), inhibits the mitochondrial apoptotic pathway, and protects cancer cells.[35] In gastric adenocarcinoma cells, HMGB1 also causes multidrug resistance by upregulating P-gp-mediated drug efflux.[35]

Gemcitabine (GEM) is a first-line chemotherapy drug for PC. It achieves this by integrating into the DNA chain and terminating replication.[67] In pancreatic ductal adenocarcinoma (PDAC), the TGF-β1 secreted by TAMs can inhibit the transcriptional repressor Gfi-1[68] (Figure 5). This thereby removes the inhibition on HMGB1 transcription, leading to its

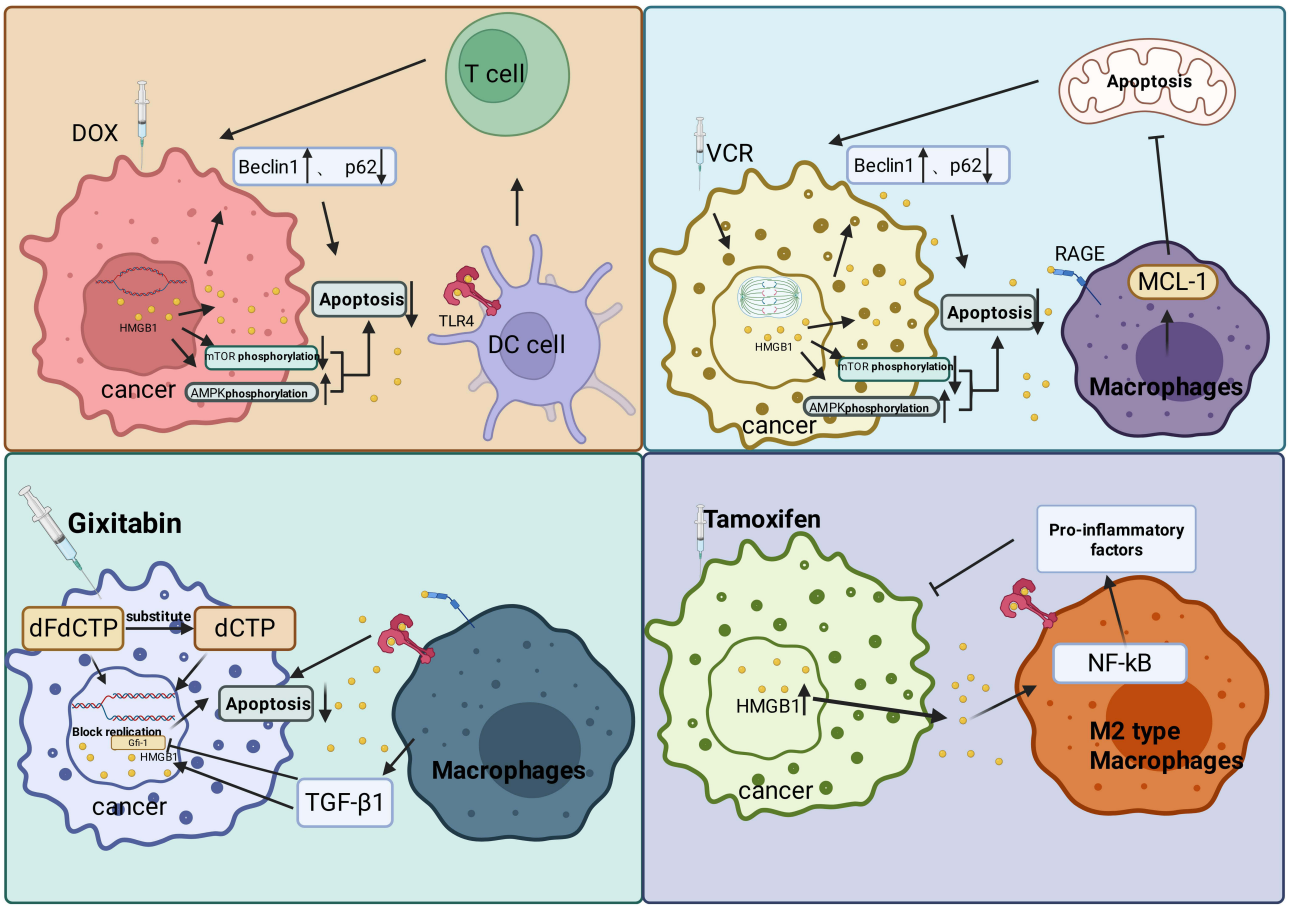

Figure 5 The effects of the other four chemotherapy drugs on HMGB1 and their impact on tumor progression. Created with biorender.com.

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high expression. HMGB1 promotes autophagy and inflammation through the TLR/RAGE pathway, inhibits apoptosis, and mediates GEM resistance. In pancreatic cancer cell lines, it is worth noting that the m6A methyltransferase (METTL3) can degrade HMGB1 mRNA through the YTHDF2-dependent pathway,[69] inhibit its expression, thereby inhibiting ferroptosis (a type of cancer-promoting death regulator), and enhancing the survival of cancer cells - this indicates that HMGB1 may also be an inducer of ferroptosis in specific contexts. In bladder cancer cells, GEM activates HMGB1-mediated protective autophagy through the JNK/ERK pathway, and knocking down HMGB1 can enhance the killing effect of GEM[70] (Table 1).

Recent studies have also revealed that HMGB1 plays a significant role in regulating the characteristics of tumor stem cells (CSCs).[4] Among various tumor types, HMGB1 enhances the self-renewal ability and drug resistance of tumor stem cells by activating signaling pathways such as NF-κB and STAT3 (Figure 5), providing a new perspective for understanding chemotherapy resistance.

HMGB1 and Hormone Therapy: The Inflammatory Driver in Tamoxifen Resistance

Tamoxifen (TAM) inhibits the growth of breast cancer by antagonizing the estrogen receptor (ER) signaling pathway.[71] However, TAM treatment can lead to high expression of HMGB1, which, through the TLR4-NF-κB pathway, promotes the release of inflammatory factors, induces the polarization of M2-type macrophages, thereby inhibiting anti-tumor immunity, enhancing tumor survival, proliferation and metastasis ability, and participating in the formation of drug resistance. The study indicates that CDK4/6 inhibitors can reverse TAM resistance by inhibiting HMGB1 and its downstream pathways[72] It provided a strategy for combined treatment.

It is worth noting that the expression level of HMGB1 in hormone receptor-positive breast cancer is significantly correlated with prognosis. Patients with high expression of HMGB1 tend to have shorter progression-free survival and overall survival, making it a potential prognostic biomarker. Moreover, HMGB1 may also affect the sensitivity to endocrine therapy by regulating the transcriptional activity of estrogen receptors.[73]

The Strategy of Targeting HMGB1 to Reverse Chemotherapy Resistance

HMGB1 plays a typical "double-edged sword" role in chemotherapy responses: On one hand, it drives drug resistance through multiple mechanisms such as DNA damage protection, induction of protective autophagy, upregulation of anti-apoptotic proteins (such as Bcl-2, MCL-1), promotion of drug efflux (such as P-gp), and EMT; on the other hand, as a key DAMP molecule of ICD, it can enhance anti-tumor immunity by activating DC, promoting T-cell responses, and polarizing M1 macrophages. Its functional outcome highly depends on its cellular localization (nucleus/ cytoplasm/ extracellular), redox state (reduced/oxidized), tumor type, and microenvironment background.

The therapeutic strategies targeting HMGB1 have great potential, here are a few hypothetical scenarios proposed: ① Develop neutralizing antibodies or antagonists to block its interaction with RAGE/TLR; ② Use small molecule inhibitors to target the autophagy or DNA repair pathways mediated by it; ③ Regulate its post-translational modifications (such as using SIRT1 agonists to promote deacetylation, or using HO-AAVPA, etc. to promote acetylation to induce immunogenic cell death); ④ Combine immune checkpoint inhibitors (such as anti-TIM-3/VISTA) to overcome its immunosuppressive effect; ⑤ Downregulate its expression based on m6A modification (such as METTL3 agonists).

HMGB1 in Immunotherapy

Immunotherapy is a major focus in cancer treatment and is a unique approach. The goal of immunotherapy is to activate the host's immune system to recognize and eliminate tumors, ranging from killing the tumors to altering the tumor microenvironment (TME) for long-lasting immune surveillance.[74] Tumors evade immune attack by down-regulating MHC molecules and expressing immune checkpoints (such as PD-L1), among other mechanisms,[75] Immunotherapy can restore T-cell activity by blocking relevant pathways.[76] The main immunotherapeutic drugs currently include immune checkpoint inhibitors (ICIs), such as CTLA-4 and PD-1/PD-L1; cancer vaccines, such as cell vaccines and nucleic acid vaccines; and adoptive cell therapy (ACT)[76](Table 2), such as CAR-T cells, new cell therapies; oncolytic viruses; cytokine therapies, such as IL-2, IFN-α, etc.[77] HMGB1 plays a dual role in immunotherapy,[78] under the influence of radiotherapy and chemotherapy, tumor cells will release HMGB1, which acts as a DAMP to activate the TLR-4-MyD88

Table 2 How Immunotherapy Affects Tumor Progression Through HMGB1

Immunological Drugs	Drug Effects	HMGB1	Function	Result
ICI	Enhance autoimmune function against cancer cells	DAMP	Binding DC Reduced M2 type	Enhances anti-tumor effect[82]
		Recruiting MDSCs Promote IL-10, TGF-β, ROS	Inhibition of T cell activity	Promote immune resistance[83]
Cell vaccines	Induce tumor regression	Immune adjuvants Recruit pro-inflammatory cells	Activate DC- Activates $CD8^+$T cells Strengthen the CTL effect	Inhibits tumor growth and development[84]
		DAMP	Induce DC maturation	Avoid nonspecific immune tolerance[85]
Oncolytic virus	Selective infection destroys tumor cells	DAMP	Promote DC cell maturation	Enhance anti-tumor immunity[86]
ACT	Synthesized to kill tumor cells	DAMP	TLR4-cDC1	Anti-tumor effect[87]

pathway of dendritic cells, promoting antigen presentation and T cell activity. The lung injury induced by cyclophosphamide is mediated by HMGB1, which activates NF-κB through RAGE and synergistically promotes the activation of NLRP3 inflammasome with TXNIP, thereby amplifying the innate immune inflammatory response, leading to excessive release of cytokines and tissue damage, ultimately disrupting immune homeostasis. Only when HMGB1 is in its reduced form (red-HMGB1) and forms a complex with CXCL12, and both of these conditions need to be met simultaneously, a fully functional thioredoxin system (Trx/TrxR1) is required. With this system, the HMGB1-RAGE axis activates DC migration (dependent on CCR7/CXCR4) without relying on ICD, and recruits T cells to the tumor site. Under oxidative stress or ICD conditions, HMGB1 forms disulfide bonds and instead induces inflammatory immune responses through TLR4, no longer through CXCR4.[75] In the tumor microenvironment (TME) with hypoxia or high oxidative stress, it will promote the polarization of M2-type macrophages, inducing $TIM1^+$ regulatory B cells (Breg) through the HMGB1-TLR2 /4 pathway, secreting IL-10 to inhibit the function of $CD8^+$ T cells, forming a complex with C1q/LAIR1, and driving single cells to transform into immunosuppressive M2-like phenotypes. In vitro experiments and mouse tumor models have shown that HMGB1 is closely related to TIM-3,[76] by inhibiting nucleic acid recognition and TLR signaling pathways, anti-tumor immunity is weakened. Targeting the HMGB1-TIM-3 axis can reverse immunosuppression, but there is still insufficient experimental evidence to prove the direct association between HMGB1 and TIM3, and when combined with PD-1/PD-L1 inhibitors, it has the potential for synergistic enhancement.[79] Meanwhile, the level of HMGB1 release may serve as a biomarker for predicting the response to immunotherapy. HMGB1 is a key recruiter for MDSC (myeloid-derived suppressor cells), and it promotes the infiltration of MDSC into the tumor microenvironment through the TLR4/RAGE signaling pathway.[80] MDSCs secrete inhibitory factors such as IL-10, TGF-β, and ROS, significantly affecting the activity of T cells and inducing the expansion of regulatory T cells (Treg), forming an immunosuppressive TME. Based on the results of the known experiments, the use of ICI alone has no significant effect on HMGB1. However, when combined with other treatments, it can significantly enhance the ability of T cells and the anti-tumor effect. In melanoma, HMGB1-mediated MDSC infiltration leads to ICI resistance, and the prognosis of patients is poor. Extracellular HMGB1 is a chemoattractant for $CD8^+$ T cells, and insufficient secretion of it results in reduced infiltration of $CD8^+$ cytotoxic T lymphocytes (CTL) in the tumor microenvironment. Low infiltration of $CD8^+$ CTL is a key factor for ICI (such as anti-PD-1) resistance[81](Table 2).

Cellular Vaccines, the Immunoadjuvant Function of HMGB1

In cellular vaccine therapy, HMGB1 is a highly expressed protein in various tumors, including liver cancer and can be recognized by the immune system as a tumor-associated antigen.[88] And as an immune adjuvant, it can promote the maturation, migration and antigen-presenting ability of DCs (through the TLR9 signaling pathway), thereby activating $CD8^+$ T cells,[85] the released HMGB1 recruits pro-inflammatory cells (such as macrophages), enhances the adaptive immune response, and increases the secretion of Th1-type cytokines like IFN-γ and TNF-α, strengthens the CTL effect, and promotes the generation of memory T cells, thereby inhibiting tumor growth and recurrence. The derivative peptide H_{100} of HMGB1, where C106 remains in the reduced state, can only bind to the TLR4/MD-2 complex,[84] after oxidation, it loses its activity. Activating the relevant pathways can induce the maturation of DC cells. When fused with antigens, it ensures that the same antigen-presenting cell simultaneously takes in the antigen and the adjuvant, avoiding non-specific immune tolerance.[89] Design non-oxidizable HMGB1-derived peptides (such as stable reduced-state H_{100} analogues), or develop TLR4/RAGE-specific gender-specific agonists, to enhance the efficacy of vaccines or cell therapies.

Oncolytic Viruses, the Release of Classic DAMPs

Oncolytic viruses, as a new treatment method in recent years, release HMGB1 by lysing tumor cells, which acts as a damage-associated molecular pattern (DAMP) to activate the immune system. HMGB1 binds to the TLR2/4 receptors of DCs, (Table 2) promoting antigen presentation and T cell activation, and enhancing anti-tumor immune responses.[90] In the T-VEC virus therapy,[86] the release of HMGB1 acts in concert with ATP, driving the maturation of DCs and the recruitment of tumor antigen-specific $CD8^+$ T cells, establishing long-term immune memory. Viruses with strong replication capacity (such as T-VEC) cause continuous replication and lead to late cell lysis,[91] release more ATP and HMGB1, induce stronger immunogenic cell death, activate the cGAS-STING pathway, upregulate IFN-β, enhance the innate immune response, and eliminate defective viruses (such as HSV-1 d106S),[92] early on, it rapidly kills tumor cells through apoptosis, but the release efficiency of HMGB1 is relatively low. Acute release (after treatment) is the key to immune activation and promotes anti-tumor immunity. Chronic high levels (baseline) indicate immunosuppression and predict a poor prognosis. Oncolytic virus CVA-1[93] can directly induce apoptosis and necrosis, promoting the release of HMGB1 and amplifying the immune effect. The virus can directly damage tumor blood vessels, alleviate hypoxia, and the release of HMGB1 reverses immunosuppression. The combination of oncolytic virus CVA21 with chemotherapy can enhance viral replication and the release of HMGB1,[94] synergistically enhancing therapeutic efficacy. Pre-treat bladder cancer cells with low-dose mitomycin C, upregulate the viral receptor ICAM-1, promote CVA21 infection and replication, significantly increase HMGB1 release, and targeting the HMGB1 pathway is expected to optimize the clinical strategy of oncolytic virus therapy. Construct a "virus-host" feedback-type oncolytic virus, whose replication and HMGB1 release are regulated by the oxidative state of the tumor microenvironment (such as hypoxia response elements), achieving precise immune activation and avoiding immune suppression.

ACT, a New Method for Modifying T Cells

In adoptive cell therapy (ACT), the application of CAR-T is the most common method. CAR-T therapy involves genetically engineering the patient's own T cells to express an artificially synthesized chimeric antigen receptor (CAR), enabling them to specifically recognize and kill tumor cells.[95] CAR-T cells kill tumor cells through the granzyme/perforin pathway, releasing HMGB1. HMGB1 binds to TLR4 on the surface of DCs, promoting DC maturation (Table 2), cross-presentation of endogenous tumor antigens, and BATF3-dependent cDC1-type dendritic cells are the key population that performs this function.[87] They are responsible for presenting tumor antigens to new $CD8^+$ T cells. Through the HMGB1-TLR4-cDC1 axis, the ICD induced by CAR-T cells not only eliminates the original target cells but also activates the T cell response against endogenous tumor antigens (non-CAR-T targeted antigens). During this process, the CAR-T-induced ICD and HMGB1 release do not rely on the mitochondrial apoptosis pathway, but caspase-3 activity is necessary: if tumor cells express caspase-3 mutants (DN-C3), even if HMGB1 is normally released, the immune protective effect is completely lost, indicating that caspase-3 is a key node in the integration of ICD signals. Through the epitope diffusion mediated by HMGB1, after CAR-T cells eliminate the original target cells, the newly activated T cells can recognize other antigens of the

residual tumor cells, reducing the risk of recurrence. Even if tumor cells downregulate the CAR-T target antigens, the newly generated T cells can still control the tumor through endogenous antigens.[96]

HMGB1 is a highly environment-dependent core regulatory factor in immunotherapy. Its functional diversity profoundly affects the initiation, maintenance, and exhaustion of anti-tumor immune responses. As a DAMP, HMGB1 is released during radiotherapy, chemotherapy, oncolytic virus, or CAR-T therapy-induced immunogenic cell death (ICD), and promotes the maturation of DC cells, cross-antigen presentation, and activation of $CD8^+$ T cells, even facilitating site spread and expanding the anti-tumor immune range. Especially in oncolytic virus therapy, HMGB1 works in synergy with ATP and the cGAS-STING pathway to enhance innate and adaptive immune responses and establish long-term immune memory. However, in chronic inflammation, hypoxia, or oxidative stress microenvironments, HMGB1 transforms into an immunosuppressive factor: by recruiting MDSC, inducing M2-type macrophages, and TIM-3^+ T cell exhaustion, it promotes immune escape and ICI resistance. The functional differences mainly depend on the redox state (reduced form has immunomodulatory function, while oxidized form loses activity), release kinetics (acute vs. chronic), and receptor interaction preferences (such as TLR2/4/9, RAGE, TIM-3). Therefore, the release level of HMGB1 is expected to become a biomarker for predicting the response to immunotherapy, and targeting the HMGB1-TIM-3 axis in combination with PD-1/PD-L1 inhibitors may have synergistic therapeutic potential.

Conclusion

This article systematically reviews the multiple biological functions and molecular mechanisms of HMGB1 in tumor occurrence, development, treatment resistance, and immune regulation. Within the nucleus, HMGB1 exerts a dynamic influence and can act as a transcriptional cofactor for tumor suppressor genes. In a mouse model of pancreatic cancer, HMGB1 can stabilize chromatin in the early stage of tumors and assist in DNA repair. However, in the later stage of tumors, the repair ability weakens, promoting nuclear-cytoplasmic transfer and reducing chromosomal stability, leading to an increase in malignant phenotypes. In previous studies, the role of HMGB1 in chemotherapy and immunotherapy was mainly based on evidence obtained from preclinical models. A large number of in vitro experiments and animal models have shown that tumor cell death induced by chemotherapy or radiotherapy can be accompanied by the passive release or active secretion of HMGB1. HMGB1, as a multifunctional DAMP, interacts with receptors such as TLR4 and RAGE, promoting the maturation of dendritic cells, antigen presentation, and T-cell-mediated anti-tumor immune responses, constituting the key molecular basis of immunogenic cell death (ICD). Additionally, in studies related to immunotherapy, HMGB1 has been proven to reshape the tumor immune microenvironment and enhance the efficacy of immune checkpoint inhibitors under certain conditions. However, these findings mainly come from highly controlled experimental systems, and the results still show significant heterogeneity among different tumor types, treatment regimens, and forms of HMGB1 release.

At the preclinical level, it is necessary to further distinguish the functional differences of HMGB1 under various release methods, oxidation states, and subcellular localizations, in order to clarify its dual mechanism of action in anti-tumor immune activation and immune suppression. At the same time, by combining single-cell sequencing, multi-omics analysis, spatial transcriptomics and other technologies, it will be helpful to more precisely analyze the tumor-immune microenvironment interaction network mediated by HMGB1 and identify its key regulatory nodes in different tumor types and treatment modalities. At the clinical research level, in the future, prospective and large-sample clinical studies should be designed to systematically evaluate the feasibility of HMGB1 as a predictive or companion biomarker, especially in the context of chemotherapy combined with immunotherapy, whether its dynamic changes can reflect treatment response or the occurrence of drug resistance. Moreover, standardizing the detection methods of HMGB1 and differentiating its functional forms will be the key to improving the research reproducibility and clinical interpretability. Further, intervention strategies targeting HMGB1 or its downstream signaling pathways are expected to enhance the efficacy of existing treatments.

Abbreviations

HMGB1, High Mobility Group Box 1; DAMP, damage-associated molecular pattern; RAGE, Receptor for Advanced Glycation End products; TLR, Toll-like Receptor; CXCL, C-X-C Motif Chemokine Ligand; Cys, Cystine; NLS, nuclear

localization signals; NES, nuclear export signals; HAT, histone acetyltransferase; HDAC, histone deacetylase; ROS, reactive oxygen species; ccRCC, clear cell renal cell carcinoma; cPKC, Conventional protein kinase C; ALD, alcoholic liver disease; CRM1, Chromosomal Region Maintenance 1; PARP1, Poly(ADP-ribose) Polymerase 1; PTM, Post-Translational Modification; NSCLC, non-small cell lung cancer; TME, Tumor microenvironment; PI3k, Phosphatidylinositol 3-Kinase; Akt, Ak strain transforming; NF-κB, Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells; MAPK, Mitogen-Activated Protein Kinase; EMT, epithelial-mesenchymal transition; MMPs, matrix metalloproteinases; VEGF, vascular endothelial growth factor; PC, pancreatic cancer; MIA, Melanoma Inhibitory Activity; MDR1, Multidrug resistance protein 1; BRAF, v-Raf murine sarcoma viral oncogene homolog B; ANRIL, Antisense Noncoding RNA in the INK4 Locus; VISTA, V-domain Ig Suppressor of T cell Activation; Gfi-1, Growth Factor Independent 1; P-gp, P-glycoprotein; YTHDF2, YTH Domain Family 2; LAIR1, Leukocyte-Associated Immunoglobulin-like Receptor-1; cGAS, cyclic GMP-AMP Synthase; STING, Stimulator of Interferon Genes; BATF3, Basic Leucine Zipper ATF-Like Transcription Factor 3.

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