

The progression of HMGB1-induced autophagy in cancer biology

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Abstract: Autophagy is an important process of cellular degradation and has been proven to contribute to tumorigenesis. High-mobility group box 1 (HMGB1) is an abundant nonhistone protein that has been widely reported to play a central role in the induction of autophagy. In nucleus, HMGB1 upregulates the expression of HSP27 to induce autophagy. In cytoplasm, the Beclin-1/PI3K-III complex can be activated by HMGB1 to promote autophagy. Extracellular HMGB1 binds to the receptor for advanced glycation end products to induce autophagy. Recent studies have shown that HMGB1-induced autophagy exerts multiple functions in various cancers like proliferation. Moreover, inhibition of HMGB1-induced autophagy can reverse chemoresistance, which is regulated by noncoding RNAs such as microRNAs and lncRNAs. Here, we provide a brief introduction to HMGB1 and HMGB1-induced autophagy in cancer. We also discuss the challenges associated with performing further investigations on this issue. HMGB1-induced autophagy exerts significant functions in cancer and has potential utility for new strategy to reverse drug resistance.

Keywords: HMGB1, autophagy, cancer, noncoding RNA, drug resistance

Introduction

Autophagy is a mechanism of degradation that alters the flow of materials to regulate cellular homeostasis. Following the establishment of the concept of autophagy in 1963, it attracted increasing attention¹ and its importance in health and disease was highlighted by the Nobel Prize being awarded for work in this field in 2016. Although autophagy is known to be strongly involved in different aspects of cancer,² such as metabolism,^{3,4} metastasis,^{5,6} and therapy,^{7,8} the details of this remain obscure. Conflicting evidence on the association of autophagy with cancer has been presented, with some findings showing that an increase of autophagy promoted the survival of tumor cells, whereas in other cases, it prevented cancer development.⁹ The induction of autophagy is also a double-edged sword during the treatment of cancer due to its ability to participate in both cell death and cell survival.¹⁰ Therefore, it is extremely important to determine the specific cellular elements and mechanisms behind the role of autophagy in cancer.

Autophagy is an intricate process that requires the involvement of autophagy-related genes (ATGs) to accomplish the formation of an autophagosome, a double-membraned vesicle.¹¹ It is regulated by a series of factors and signaling pathways.¹² Among these elements, Sun et al¹³ proposed that high-mobility group box 1 (HMGB1) plays a key role in autophagy and believed in the potential for exploiting HMGB1-induced autophagy in cancer therapy. HMGB1 is an evolutionarily conserved nonhistone DNA-binding protein present in all vertebrate cells.¹⁴ Substantial evidence has revealed the abnormal expression of HMGB1 in different tumors including non-small cell

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lung cancer (NSCLC),¹⁵ glioma,¹⁶ pancreatic cancer,¹⁷ and epithelial ovarian tumors.¹⁸ Here, we elaborate how HMGB1 induces and influences autophagy in cancer and discuss its significance in clinical applications.

General overview of HMGB1

As an abundant nonhistone chromosomal protein encoded by a single gene located on chromosome 13q12, HMGB1 contains 215 amino acid residues, which are organized into three individual domains: two tandem DNA-binding HMG box domains (A box [aa 9–79] and B box [aa 89–162]) and an acidic C-terminal tail (aa 186–215), which contains numerous glutamic and aspartic acid residues.¹⁹ Sanchez et al²⁰ found that HMG box A binds to an AT-rich DNA fragment. The Phe37 residues of two HMG box A domains stack together and intercalate the same CG base pair, generating highly kinked DNA. HMG-B box has also been identified as a functional zone identifiable by toll-like receptor 4 (TLR-4).²¹ In addition, the A box could compete with the B box since it contains a site antagonistic to the B box.²² The C-terminal tail contains a number of glutamic and aspartic acid residues, whereas the N-terminal is composed of lysine. In other words, the C-terminal tail is negatively charged and the N-terminal is highly positively charged, giving the protein a bipolar nature²³ (Figure 1).

HMGB1 was considered to be a housekeeping gene because it is widely detected in most cells as the most highly expressed protein in the HMG family.²⁴ However, Muller et al²⁵ disagreed with this and summarized the data on HMGB1 expression in different tissues. They described that the expression of HMGB1 is high in lymphoid tissues

and testis, but low in brain and liver. The difference between these sites was ~100-fold, suggesting the correlation between the expression of HMGB1 and the differentiation of tissues. Similar results have been obtained in skeletal myogenic cell lines²⁶ and blood cells.²⁷ In addition, the level of HMGB1 is apparently higher in most tumor samples than in their normal counterparts.²⁵ Furthermore, HMGB1 expression has been reported to be higher in metastasizing tumors.²⁸

HMGB1 is a nuclear protein that alters DNA transcriptional regulation.²⁹ It can also act as a cytokine outside of the nucleus.²⁵ The lysine residues located in the A box (aa 28–44) and the B box (aa 179–185) can form nuclear localization sites (NLSs). HMGB1 can shuttle from the nucleus into the cytoplasm under the control of NLSs. The monomethylation of lysine 42 can inhibit the DNA binding ability of HMGB1³⁰ and set HMGB1 free. Bonaldi et al³¹ also reported that the nuclear-to-cytoplasmic shuttling of HMGB1 depends on the acetylation of NLSs. Immunofluorescence analysis showed that a large amount of fluorescent protein concentrated in the cytoplasm after the acetylation of HMGB1–GFP. At the same time, a mutant form of HMGB1 (whose lysines in NLSs cannot be acetylated) maintained its localization in the nucleus. Further investigation revealed that the JAK/STAT1³² and PARP-1³³ signal pathways mediate the acetylation process. Apart from acetylation, Zhang et al³⁴ demonstrated that the phosphorylation of HMGB1 by calcium/calmodulin-dependent protein kinase (CaMK) IV also plays a role in its nuclear-to-cytoplasmic translocation. Although HMGB1 lacks a leader sequence, which is essential in the classical secretion pathway, it can be released into extracellular space

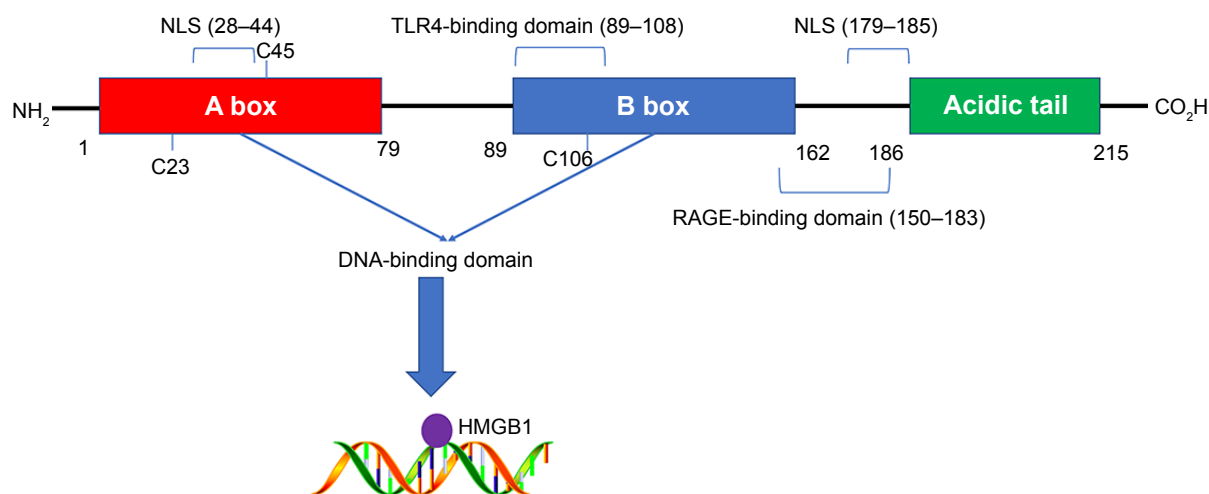


Figure 1 The structure of HMGB1.

Notes: The HMGB1 protein is composed of 215 amino acid residues and can be divided into three parts. Each part contains various function domains and exerts corresponding functions like DNA binding.

Abbreviations: HMGB1, high-mobility group box 1; NLS, nuclear localization sites; TLR, toll-like receptor; RAGE, receptor for advanced glycation end products.

both actively and passively. The HMGB1 in the cytoplasm can be concentrated by secretory lysosomes and released into the extracellular environment.³¹ HMGB1 can also be passively released by necrotic cells, but this phenomenon does not occur in apoptotic cells. Moreover, immune cells such as macrophages can also actively secrete HMGB1 after the engulfment of dying cells.³⁵ This indicates the potential involvement of a link between dying cells and immune cells in the induction of HMGB1 release.

Due to its extensive distribution, HMGB1 exerts a great influence on cellular activity both inside and outside of cells. As mentioned above, nuclear HMGB1 can bind to and bend DNA to regulate gene expression.³⁶ Different posttranslational modifications (PTMs) such as acetylation, methylation, and phosphorylation are involved in the distribution of HMGB1 and endow it with various functions. Ugrinova et al³⁷ revealed that the acetylation of HMGB1 at lysine 2 can promote its affinity to distorted DNA structures. Moreover, Yu et al³⁸ believed that oxidative stress plays a central role in regulating HMGB1 translocation, release, and functions. The redox state of three cysteines (C23, C45, and C106) in extracellular HMGB1 is of great importance in the regulation of cell activities. Entirely reduced HMGB1, which has three reduced cysteines, shows chemotactic activity, but this can be abolished by partial or full oxidation.³⁷ The redox state is also a checkpoint between autophagy and apoptosis after the binding of receptor for advanced glycation end products (RAGE).^{39,40} Although the mechanisms by which PTMs exert effects on the cell have not been comprehensively revealed, the evidence obtained thus far suggests that they play an important role in the functions of HMGB1.

Typical receptors such as RAGE, toll-like receptors (TLRs), and T cell immunoglobulin domain and mucin domain-3 (TIM3), which directly or indirectly bind with HMGB1, also play roles in the pathological and physiological functions of HMGB1³⁶ (Table 1). As the first reported receptor of HMGB1, RAGE is a transmembrane receptor that has high affinity for HMGB1.⁴¹ Numerous recent reports^{23,35,36} have asserted that RAGE plays an indispensable role in HMGB1-induced cell activities such as autophagy. In addition, RAGE can interact with other receptors such as TLR9⁴² and Mac-1⁴³ to impact immune responses, adhesion, and migration of cells. The mechanisms underlying this could involve the activation of downstream factors such as MAPK,⁴⁴ nuclear factor (NF)-κB,⁴⁵ and mTOR.⁴⁶ TLRs expressed on innate immune cells can induce and regulate adaptive immune responses. TLRs are also expressed on tumor cells. HMGB1 released by dying tumor cells activates the TLRs–MyD88 signaling

Table 1 Typical receptors of HMGB1

Receptors	Signaling pathways	Functions	Reference
RAGE	MAPK, NF-κB, mTOR	Autophagy, adhesion, immune responses, migration	44–46
TLRs	MyD88	Adaptive immune responses	47
TIM3	Inhibit the recruitment of nucleic acids to the endosome	Inhibitory on efficacy of antitumor treatment	48
CXCR4	NF-κB	Inflammatory cell recruitment	50, 51
TREM-1	NF-κB	Immune responses	52, 53

Abbreviations: CXCR4, C-X-C chemokine receptor type 4; HMGB1, high-mobility group box 1; NF-κB, nuclear factor κB; RAGE, receptor for advanced glycation end products; TIM3, T cell immunoglobulin domain and mucin domain-3; TLR, toll-like receptor; TREM-1, triggering receptor expressed on myeloid cells-1.

pathway to confer anti- or protumor effects.⁴⁷ TIM3 is a biomarker for activation and maturation of natural killer (NK) cells. The interaction between HMGB1 and TIM3 interferes with the recruitment of nucleic acids into endosomes. This reduces the immunogenicity of nucleic acids from dying tumor cells and weakens the efficacy of antitumor treatment such as chemotherapy.⁴⁸ C-X-C chemokine receptor type 4 (CXCR4) has been proved to be related to tumor aggressiveness, metastasis and recurrence.⁴⁹ Evidence has shown that HMGB1 can promote the migration of inflammatory cells via CXCR4.⁵⁰ The NF-κB signaling pathway plays a critical role in inflammatory cell recruitment.⁵¹ TREM-1 belongs to the immunoglobulin superfamily and induces the inflammatory response. HMGB1 can activate TREM-1 in various cell types.⁵² HMGB1 upregulates the production of cytokines via the NF-κB signaling pathway after binding with TREM-1, which participates in the inflammatory response.⁵³ At present, few partners of HMGB1 have been identified, but they are assumed to be involved in many novel signaling pathways to participate in the functions of HMGB1.³⁶ Further investigation is needed to obtain a comprehensive understanding of these receptors.

The mechanism of HMGB1-induced autophagy

As mentioned above, HMGB1 is widely distributed inside and outside the cell. Numerous studies have reported that HMGB1 can induce autophagy through various pathways in different intra- and extracellular locations.¹³ We also reviewed the mechanism of HMGB1-induced autophagy based on the distribution of this molecule (Figure 2).

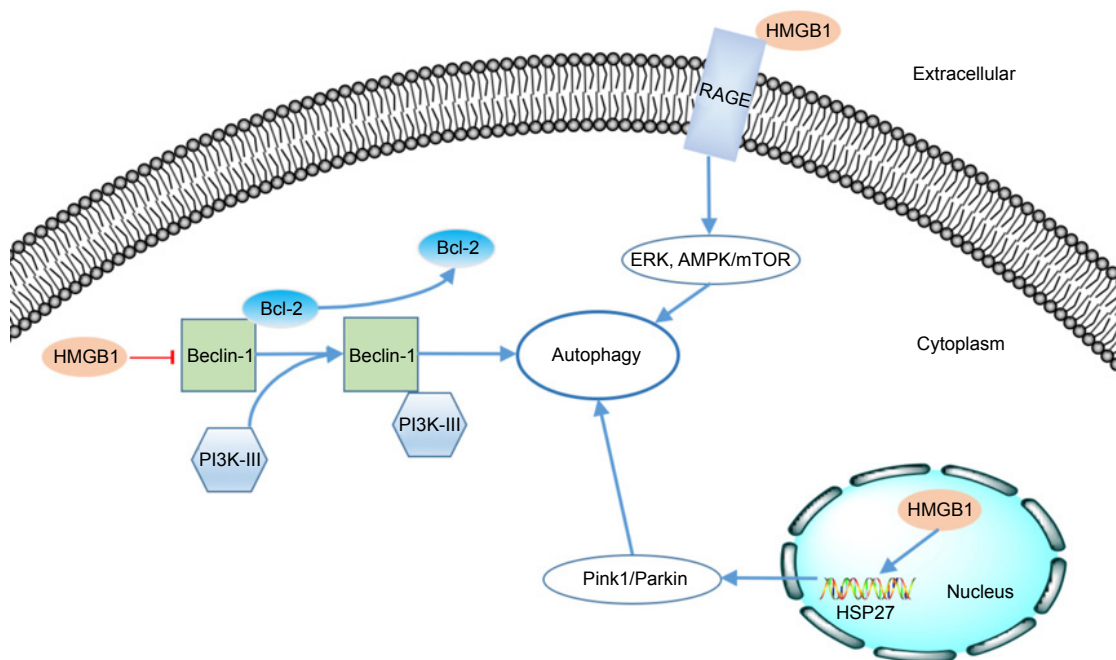


Figure 2 The mechanism of HMGB1-induced autophagy.

Notes: In extracellular, reducible HMGB1 could bind to RAGE receptor to activate ERK and AMPK/mTOR pathways. In cytoplasm, HMGB1 could induce the dissociation of Beclin-1-Bcl-2 complex. It contributed to the formation of Beclin-1/PI3K-III complex, which can start the autophagy; In nucleus, HMGB1 could promote the transcription of HSP27 and lead to the autophagy through Pink1/Parkin pathway.

Abbreviations: HMGB1, high-mobility group box 1; RAGE, receptor for advanced glycation end products.

As a kind of cargo-specific autophagy, mitophagy is a selective form of autophagy of mitochondria^{54,55} and is strongly correlated with tumorigenesis.⁵⁶ Kuramitsu et al⁵⁷ confirmed that the expression of HMGB1 and MAPKAPK2 was upregulated in gemcitabine-resistant pancreatic cancer cells. HMGB1 can act as a transcription factor in the nucleus. Tang et al⁵⁸ proved that HMGB1 can upregulate the transcription of the heat-shock protein 27 (HSP27) gene. Consequently, nuclear HMGB1 can activate the HSP27 pathway in autophagy. HSP27 phosphorylated by MAPKAPK2 has the ability to modulate actin polymerization and reorganization and then participates in mitophagy.⁵⁹ The Pink1/Parkin pathway plays a key role in mitochondrial health and quality control.⁶⁰ One of its major roles is in the mediation of mitophagy.⁵⁴ As a kinase of outer mitochondrial membranes, PINK can mediate the mitochondrial translocation of Parkin, which leads to ubiquitination of the voltage-dependent anion channel 1 (VACD1). This information can be identified by performing analyses using p62, the autophagic adaptor. After the abovementioned translocation, p62 binds directly to LC3 to accelerate the formation of the autophagosome. Kang et al⁵⁹ observed that the HMGB1/HSP27 signal pathway participates in the translocation of Parkin and the ubiquitination of VACD1. Furthermore, knockdown of Pink1

or Parkin prevents the HSP27-induced functional recovery of mitochondria in HMGB1-deficient cells, indicating that the Pink1/Parkin pathway is required for HMGB1/HSP27-dependent mitophagy. We know that the HSP27 pathway is a potential mechanism by which nuclear HMGB1 regulates autophagy.

Beclin-1 was identified as an ortholog of the Atg6/vacuolar protein sorting (Vps)-30 protein and was proven to be important in the initiation of autophagy in the cytoplasm.^{61,62} Beclin-1 can form a complex with class III phosphatidylinositol-3 kinase (PI3K-III).⁶³ This Beclin-1/PI3K-III complex initiates the recruitment of Atg proteins to the phagophore.⁶⁴ The Beclin-1/PI3K-III complex can be reduced by the binding between Beclin-1 and Bcl-2.⁶⁵ HMGB1 can induce dissociation of the Beclin-1-Bcl-2 complex through the ERK/MAPK pathway.⁶⁶ Kang et al⁶⁷ found that HMGB1 may promote the phosphorylation of Bcl-2 by ERK/MAPK to inhibit formation of the Beclin-1-Bcl-2 complex. Formation of the Beclin-1/PI3K-III complex could be promoted by HMGB1-induced dissociation of the Beclin-1-Bcl-2 complex. Consequently, autophagy would be promoted.

As mentioned above, extracellular HMGB1 released by cancer cells could bind to several receptors such as RAGE and induce autophagy activity in other cells.⁶⁸ Tang et al³⁹

reported that Beclin-1-dependent autophagy can be activated by the binding of RAGE and extracellular HMGB1. They also demonstrated that HMGB1 may play a role as a checkpoint between autophagy and apoptosis. Reducible HMGB1 leads to the activation of autophagy, while oxidized HMGB1 increases the apoptosis in cancer cells. Su et al⁶⁹ found that the induction of autophagy by the HMGB1/RAGE axis can be reduced after treatment with Erk1/2 inhibitor in Lewis cells. Moreover, Zhang et al⁷⁰ also proved that the HMGB1/RAGE axis promoted the phosphorylation of ERK1/2 and consequently induced autophagy in gastric cancer cells. Substantial evidence has implicated the AMPK/mTOR signaling pathway in the process of autophagy in cancer.^{71,72} Furthermore, Li et al⁷³ also reported that the AMPK/mTOR signaling pathway may be the downstream mechanism through which the HMGB1/RAGE axis affects hepatocellular carcinoma (HCC).

The role of HMGB1-induced autophagy in tumors

Autophagy has been widely acknowledged to be an important biological process in cancer.⁷⁴ It contributes to various aspects of cancer,⁹ especially drug resistance.^{75,76} HMGB1-induced autophagy is part of this phenomenon, as discussed below.

Lung cancer

Non-small cell lung cancer (NSCLC) is a devastating form of cancer with high morbidity and mortality.⁷⁷ As an approved therapeutic for NSCLC, pemetrexed can interact with sildenafil to enhance the death of NSCLC cells; factors such as Beclin-1, ULK-1, and mTOR, which are involved in the autophagy, may be involved in the mechanism underlying this.^{78,79} Booth et al⁸⁰ found that treatment with pemetrexed+sildenafil in vitro led to the release of HMGB1 and that the subsequent autophagy could participate in regulating the response of NSCLC cells to immunotherapy. Zhang et al⁸¹ demonstrated that interference with HMGB1 can increase the sensitivity of NSCLC to chemotherapy via HMGB1-induced autophagy. The expression of HMGB1 in different NSCLC cell lines increased greatly after treatment with chemotherapeutic drugs. The drug-resistant A549 had higher levels of HMGB1 than the drug-sensitive A549. In addition, interference with endogenous HMGB1 by HMGB1-specific shRNA could reverse the drug resistance in drug-resistant A549. At the same time, the autophagy in drug-resistant A549 was inhibited along with the interference of endogenous HMGB1. Further investigation by Chen et al⁸² showed that the knockdown of HMGB1 could increase PI3K, Akt, and

mTOR phosphorylation to restrain the autophagy in NSCLC. In addition, luciferase reporter assay results demonstrated the interaction between miR-142-3 p and HMGB1-induced autophagy. miR-142-3 p can directly suppress HMGB1-induced autophagy by targeting the 3'-UTR of HMGB1 in NSCLC. Thus, the miR-142-3 p/HMGB1 signaling pathway is involved in the chemosensitivity of NSCLC via HMGB1-induced autophagy. Pan et al⁸³ reported a similar result obtained in an analysis of human lung adenocarcinoma (LAD). From both in vivo and in vitro results, HMGB1-induced autophagy contributes to docetaxel resistance in LAD cells. Mechanistic investigations revealed that formation of the Beclin-1/PI3K-III complex could be promoted by HMGB1 through activation of the MEK/ERK signaling pathway, consequently promoting autophagosome formation.

Hematological malignancy

Autophagy is commonly believed to play a pivotal role in hematological malignancy.⁸⁴ Research focused on HMGB1-induced autophagy has also indicated the importance of HMGB1 in autophagy in hematological malignancy.^{85,86} Kong et al⁸⁷ recruited 30 children with B-cell acute lymphoblastic leukemia (ALL) and 8 control subjects to evaluate the correlation between the levels of HMGB1 and clinical stages of ALL. The results showed that HMGB1 was upregulated in ALL patients with primary, relapsed, or recurrent disease, while its level was equal to that at baseline in those with complete remission. Yu et al⁸⁵ concluded that HMGB1 acts as a proautophagic protein in leukemia and has the potential to be a therapeutic target for leukemia. Liu et al⁸⁸ found that HMGB1 released from leukemia cell lines in response to chemotherapy could render these cells more resistant to chemotherapy via regulating autophagy. Yang et al⁸⁹ also proved that endogenous HMGB1 could act as an intrinsic regulator of autophagy to promote drug resistance in leukemia. We know that both exogenous and endogenous HMGB1 can regulate autophagy to promote the drug resistance of leukemia.

HMGB1-induced autophagy is also involved in childhood chronic myeloid leukemia (CML). Zhao et al⁹⁰ found that autophagy induced by HMGB1 could decrease the sensitivity of CML cells to chemotherapy drugs. In addition, Kong et al⁸⁷ asserted that targeting the autophagic complexes of HMGB1-like HMGB1-Beclin1 complex may inhibit HMGB1-induced autophagy and overcome drug resistance in leukemia. Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia (AML) characterized by distinctive morphology. All-trans retinoic acid, a specific drug capable of curing APL,

can induce the differentiation of leukemia cells. Yang et al⁹¹ demonstrated the vital role of HMGB1-induced autophagy in this process. They reported that HMGB1-induced autophagy can be activated by the ROS induced by ATAR in APL. The HMGB1-induced autophagy can directly promote the degradation of PML/RAR α , an oncogene in APL, to mediate APL cell differentiation.

MicroRNAs play an important role in the pathogenesis of AML.⁹² Liu et al⁹³ found that miR-34a acts as a tumor suppressor gene in AML, one of the regulatory mechanisms of which may involve HMGB1-induced autophagy. A dual luciferase reporter system confirmed HMGB1 as a potential target of miR-34a and it was shown that overexpression of HMGB1 significantly reversed the inhibition of autophagy mediated by miR-34a. Zhang et al⁹⁴ reported that miR-142-3 p negatively regulated HMGB1 expression to repress autophagy in AML and promoted the chemosensitivity of AML. In addition, Gao et al⁹⁵ claimed that HMGB1-induced autophagy is involved in the proliferation of multiple myeloma (MM) cells. Tumor growth was greatly inhibited in tumor-bearing mice that had reduced expression of HMGB1, LC3B, and Beclin-1 in tumor tissues. In addition, the overexpression of HMGB1 reversed the repression of LC3B and Beclin-1 mediated by LV-si-MALAT-1 and consequently promoted the viability of MM cells. MALAT-1 can prevent degradation of HMGB1 by modification of the ubiquitination of HMGB1. This indicated that HMGB1-induced autophagy can suppress apoptosis and promote the survival of MM tumor cells.

Breast cancer

Estradiol (E2) is believed to play a crucial role in mediating autophagy in breast cancer.⁹⁶ Wang et al⁹⁷ reported that the knockdown of HMGB1 can attenuate E2-induced autophagosome formation in BT474 breast cancer cells. Western blot showed that the knockdown of HMGB1 inhibited the expression of LC3-II and Beclin-1 mediated by E2. Ladoire et al^{98,99} investigated the expression of nuclear HMGB1 and the occurrence of cytoplasmic LC3B (microtubule-associated protein 1 light chain 3B)-positive puncta, which is an immunohistochemical sign of autophagy, in tumor tissues from breast cancer patients who were treated with adjuvant chemotherapy. The results showed that the combination of nuclear HMGB1 and positivity for LC3B(+) puncta was an independent prognostic marker significantly associated with prolonged metastasis-free survival and improved breast cancer-specific survival. HMGB1(+) LC3B(+) double-positive tumors exhibited better prognosis than breast cancer that lacked one or both of these markers. In other words, the

combined analysis of HMGB1 and the level of autophagy is of great value in determining the prognosis of breast cancer. Further investigation demonstrated that the mechanism behind these results may involve the loss of HMGB1 and the blockage of autophagy having a negative impact on anticancer immunosurveillance.¹⁰⁰ Based on this we know that HMGB1 is related to autophagy in breast cancer and that HMGB1-induced autophagy plays a vital role in the progression of breast cancer. Moreover, HMGB1-induced autophagy participates in the chemoresistance and radioresistance of breast cancer.

Amornsupak et al¹⁰¹ found that the promotion of HMGB1 induced a degree of resistance to doxorubicin in the human breast cancer cell line MDA-MB-231, whereas anti-HMGB1 neutralizing antibody reduced this effect. MDA-MB-231 showed an increase in doxorubicin resistance and the induction of LC3B after the treatment of recombinant HMGB1. HMGB1-specific antibody also reversed the effect of rHMGB1 on autophagy and doxorubicin resistance. This indicates that HMGB1 can lead to autophagy in breast cancer and that HMGB1-induced autophagy contributes to doxorubicin resistance. Radiotherapy is an important adjuvant treatment after breast-conserving surgery. Luo et al¹⁰² focused on the impact of autophagy induced by the miR-129-5 p/HMGB1 axis on the radioresistance of breast cancer. The knockdown of HMGB1 suppressed irradiation-induced autophagy and substantially enhanced radiosensitivity in breast cancers. Online prediction revealed potential binding sites between miR-129-5 p and HMGB1. Further study showed that miR-129-5 p could be an upstream regulator of HMGB1-induced autophagy and consequently participate in the radioresistance of breast cancer.

Urogenital cancer

Bladder cancer is the most common malignancy of the genitourinary system.¹⁰³ Radiation therapy can preserve urinary and sexual function and predict a high quality of life in patients.¹⁰⁴ Liao et al¹⁰⁵ showed that a decreased level of HMGB1-induced autophagy in bladder urothelial carcinoma (BUC) cells significantly inhibited the viability of BUC cells. Shrivastava et al¹⁰⁶ reported the important role of HMGB1 as a predictive marker in bladder cancers subjected to radiation therapy and its correlation with autophagy. Higher expression of HMGB1 had a positive correlation with radiation resistance, while HMGB1 knockdown led to the inhibition of autophagy by more than three-fold ($P < 0.01$) and a better response to radiation treatment in *in vitro* and *in vivo* studies. These findings highlight the value of HMGB1 for radiation

therapy in bladder cancer and that HMGB1-induced autophagy plays a vital role in this process. As another alternative treatment of bladder cancer, chemotherapy also occupies a position in bladder cancer treatment.¹⁰⁷ Yin et al¹⁰⁸ focused on the function of HMGB1 in bladder cancer cells treated with gemcitabine. The results showed that gemcitabine induced an increase of HMGB1 in a dose- and time-dependent manner and an increase of LC3-II, which is a marker of autophagy, at the same time in bladder cancer cells. Moreover, Western blotting showed the activation of JNK and ERK in this process, while knockdown of HMGB1 attenuated the JNK and ERK activation. It has been asserted that the MAPK signal is involved in autophagy induction. It has also been demonstrated that HMGB1-induced autophagy induced the chemoresistance of bladder cancer and that targeting this process could improve the anticancer efficacy of chemotherapeutics. Moreover, Lin et al¹⁰⁹ proved that cytolethal distending toxin (CDT) could enhance radiosensitivity in prostate cancer via HMGB1-induced autophagy. CDT could reduce the expression of HMGB1, thereby inhibiting the formation of the Beclin-1/PI3K-III complex and restraining autophagy. Moreover, HMGB1-induced autophagy leads to chemoresistance to gemcitabine in hormone-independent prostate cancer.¹¹⁰

Xu et al¹¹¹ investigated the role of LC3 and HMGB1 in squamous cervical cancer (SCC). Their results showed that both HMGB1 and LC3 are associated with the prognosis of SCC. In addition, they found a negative correlation between nuclear HMGB1 and LC3, which means that HMGB1-induced autophagy plays a role in SCC. Xia et al¹¹² successfully reversed the cisplatin resistance in HeLa cells by inhibiting the nuclear-to-cytoplasmic translocation of HMGB1. Studies also showed that cisplatin resistance was reestablished by the administration of recombinant HMGB1. Further research revealed that the autophagy induced by HMGB1 via the phosphorylation of ERK contributed to cisplatin resistance in HeLa cells. Therefore, HMGB1-induced autophagy can represent a therapeutic target for chemotherapy-resistant cervical cancer. Ran et al¹¹³ reported similar results in endometrial carcinoma (EC) cells. In paclitaxel-resistant EC cells, HMGB1 was upregulated and mediated the autophagy contributing to chemoresistance. The inhibition of HMGB1-induced autophagy by miR-218 could protect against chemotherapy resistance in EC cells.

Digestive system carcinoma

Hsieh et al¹¹⁴ reported that the autophagy-related release of HMGB1 plays a key role in the protection of oral cancer cells

treated with vincristine. Their results showed that the blockade of autophagy abolished the release of HMGB1-induced by vincristine in SCC9 and OECM-1 cells. At the same time, they found that the knockdown of HMGB1 substantially increased apoptosis. Further investigation demonstrated that the HMGB1 released by autophagy inhibited the expression of Mcl-1 by binding to RAGE. Consequently, the apoptosis was inhibited by HMGB1-induced autophagy. Notably, Luo et al⁶⁸ revealed a novel relationship in energy production between cancer and its host tissues. Colorectal cancer could lead to the increase of HMGB1, along with the increase of autophagy, in mouse muscle tissues. The autophagy induced by HMGB1 provided glutamine to the cancer cells by the degradation of host muscle tissues. Liu et al¹¹⁵ also reported the vital role of HMGB1-induced autophagy in the chemoresistance of CRC. HMGB1 could induce autophagy to reduce the sensitivity of CRC to oxaliplatin via the MEK/ERK pathway.

Research has suggested the importance of autophagy in the process of development of pancreatic tumors.¹¹⁶ For example, Søreide et al¹¹⁷ asserted that autophagy plays an important role in tumor growth and the suppression of pancreatic tumors; their findings also suggested that the HMGB1–RAGE pathway, which can induce autophagy, is also involved in the process of pancreatic tumor development. Moreover, Xiong et al¹¹⁸ demonstrated that miR-410-3 p could alleviate the resistance to gemcitabine in pancreatic ductal adenocarcinoma by reducing HMGB1-induced autophagy. As a member of the TNF family, TNFSF10/TRAIL is considered to be of great value in cancer therapy. For example, Yang et al¹¹⁹ discovered that the suppression of HMGB1-induced autophagy reduced the resistance of the pancreatic cancer cell line PANC-1 to the drug TNFSF10/TRAIL.

Chemically modified tetracycline 3 (CMT-3) is recognized as a potential anticancer drug for its ability to inhibit matrix metalloproteinases. Zhao et al¹²⁰ showed that CMT-3 reduced the growth and proliferation of HepG2 cells through the inhibition of HMGB1-induced autophagy. Moreover, Wu et al¹²¹ also reported that HMGB1-induced autophagy could enhance the resistance of HepG2 cells to irradiation. The autophagy triggered by irradiation could inhibit p53 expression by degrading HMGB1. They suggested that HMGB1-induced autophagy would have great value in the treatment of hepatocellular carcinoma with irradiation. Li et al⁷³ also reported that HMGB1 induces autophagy through interaction with RAGE in HCC. The HMGB1-induced autophagy contributes to the proliferation and sorafenib

resistance of HCC. This finding may provide a novel target for the treatment of HCC.

Other tumors

The most common bone tumor in adolescents, osteosarcoma, is associated with a high rate of mortality.¹²² Studies^{123,124} have indicated the importance of HMGB1-induced autophagy in the proliferation, migration, and drug resistance of osteosarcoma. HMGB1 binds to Beclin-1 and regulates the formation of the Beclin-1/PI3K-III complex to mediate autophagy in osteosarcoma, consequently contributing to drug resistance.¹²⁴ Li et al¹²⁵ revealed the relationship between miR-22 and HMGB1-induced autophagy. miR-22 can directly target the 3'-UTR of HMGB1. Therefore, the overexpression of miR-22 can suppress the HMGB1-induced autophagy against drug resistance. Guo et al¹²³ proved that the interaction between miR-22 and HMGB1 also blocks autophagy in normal osteosarcoma cells and inhibits osteosarcoma cell proliferation, migration, and invasion. In addition, the inhibition of macrophage migration inhibitory factor (MIF), which is an inflammation-related cytokine implicated in the chemoresistance of cancer, can enhance chemosensitivity by decreasing the level of HMGB1-induced autophagy.¹²⁶ The increase of HMGB1 also facilitates autophagy in human synovial sarcoma cells and consequently decreases the sensitivity to chemotherapy.¹²⁷ miR-34A is regarded as a tumor suppressor and it was proved to bind with HMGB1 3'-UTR

in retinoblastoma cells.¹²⁸ This leads to the inhibition of autophagy in retinoblastoma cells under stress and promotes the death of tumor cells. In medulloblastoma, miR-let-7f-1 has similar functions in cisplatin resistance.¹²⁹ Neuroblastoma is another common tumor in childhood. Liu et al¹³⁰ demonstrated that HMGB1-induced autophagy, which mostly depends on the activation of TLR4, promoted the proliferation of neuroblastoma cells. Wang et al¹³¹ further proved that HMGB1 is a critical regulator of autophagy in neuroblastoma and promotes resistance to doxorubicin. In other words, HMGB1-induced autophagy plays a vital role in the development of chemoresistance and tumorigenesis in neuroblastoma.

Discussion

We have reviewed the roles of HMGB1-induced autophagy in human malignancies. HMGB1 is an abundant nonhistone protein that is distributed both inside and outside of cells. It can induce autophagy through various pathways depending on its location. HMGB1-induced autophagy also contributes to tumorigenesis, such as through proliferation and migration. It has been highlighted that HMGB1-induced autophagy plays a vital role in drug resistance in numerous types of cancer, such as lung cancer, hematological malignancies, and breast cancer. This process can also be regulated by several noncoding RNAs which has been summarized in Table 2. Noncoding RNA can be divided into housekeeping RNA and regulatory RNA. MirRNA and

Table 2 Noncoding RNAs regulating the HMGB1-induced autophagy in cancer

Noncoding RNAs	Mechanisms	Effect	Functions	Cancer	Reference
miR-142-3 p	3'-UTR of HMGB1	Inhibition	Decrease chemoresistance	Non-small cell lung cancer Acute myeloid leukemia	82, 94
miR-34a	3'-UTR of HMGB1	Inhibition	Promote apoptosis, decrease chemoresistance	Acute myeloid leukemia Retinoblastoma	93, 128
MALAT-1	Modification of the ubiquitination of HMGB1	Promotion	Promote proliferation	Multiple myeloma	95
miR-129-5 p	3'-UTR of HMGB1	Inhibition	Decreases radioresistance	Breast cancer	102
miR-218	3'-UTR of HMGB1	Inhibition	Decrease chemoresistance	Endometrial carcinoma	113
miR-22	3'-UTR of HMGB1	Inhibition	Decrease proliferation, migration, chemoresistance	Osteosarcoma	123, 125
miR-410-3P	3'-UTR of HMGB1	Inhibition	Decrease chemoresistance	Pancreatic ductal adenocarcinoma	118
miR-let-7f-1	3'-UTR of HMGB1	Inhibition	Decrease chemoresistance	Medulloblastoma	129

Abbreviation: HMGB1, high-mobility group box 1.

lncRNA are typical regulatory RNAs that are strongly involved in carcinogenesis.^{132,133} LncRNA plays a major role in the autophagy in cancer.¹³⁴ LncRNA MALAT-1 regulates chemotherapy-induced autophagy in gastric cancer via miR-23b-3p sequestration.¹³⁵ In our review, lncRNA MALAT-1 was also shown to prevent the degradation of HMGB1 via modification of the ubiquitination of HMGB1.⁹⁵ Hence, it could upregulate HMGB1-induced autophagy and promote the proliferation of MM. Several studies have revealed the interplay between miRNA and autophagy in cancer.¹³⁶ MirRNA participates in various steps of autophagy from upstream induction to later stages of autophagosome maturation and lysosome fusion. We summarized that several miRNAs can suppress autophagy through HMGB1 in cancer. Dual-luciferase reporter assay suggested that miRNAs can target 3'-UTR of the HMGB1 gene to inhibit the expression of HMGB1 and reduce the HMGB1-induced autophagy. This effect leads to the promotion of apoptosis and decrease of radioresistance and chemoresistance.

As mentioned above, HMGB1-induced autophagy plays an important role in tumorigenesis, especially in resistance to chemoradiotherapy. Autophagy inhibitors such as hydroxychloroquine have now been proved to improve clinical outcomes of cancer in various clinical trials.¹² We also have some strategies to regulate HMGB1 directly or indirectly for cancer treatment. Liver metastasis of colorectal cancer can be prevented by the administration of anti-HMGB1 antibody.¹³⁷ Soluble RAGE can also act as a decoy to block the HMGB1/RAGE axis and suppress tumor growth and metastasis.¹³⁸ We believe that sites such as 3'-UTR and ubiquitination of HMGB1 can act as targets for clinical treatment. HMGB1-induced autophagy can be regulated by noncoding RNAs, which may help us with resistance to cancer treatment such as chemoradiotherapy.

However, we still know little about the complex regulatory network underlying HMGB1-induced autophagy. As mentioned above, there is a close relationship between HMGB1 and autophagy in cancer. HMGB1 is an undisputed regulator of autophagy.¹³⁹ An increasing number of studies have proved that autophagy also regulates HMGB1 release to exert corresponding functions.¹⁴⁰ Thorburn et al¹⁴¹ revealed that autophagy in dying tumor cells could induce the selective release of HMGB1 without classical necrosis or damage to the cell membrane. Then, HMGB1 could function as an immune modulator. Moreover, Zhan et al¹⁴² reported that the release of HMGB1 occurred as a consequence of autophagy in gastric cancer cells and it is essential for the autophagy-mediated inhibition of apoptosis induced by

vincristine. Zhang et al⁷⁰ reported that the autophagy-related release of HMGB1 could induce the proliferation of gastric cancer cells.

Cancer-associated fibroblasts (CAFs) as the major components of the niche of breast cancer initiating cells play a vital role in the progression of breast cancer. CAFs with high autophagy activity can release HMGB1, which activates the TLR4 receptor on luminal breast cancer cells and enhances the stemness and tumorigenicity of these cells.¹⁴³ In addition, Luo et al⁶⁸ reported an interesting phenomenon regarding energy metabolism induced by the autophagy-released HMGB1 in the context of cancer. HMGB1 was increased in serum and colonic mucosa in a mouse model of colon carcinogenesis, along with increases in autophagy and glutamine, and a decrease in PKM1 levels. The autophagy-released HMGB1 from cancer cells induced the transfer of ¹³C-glutamine of muscle into cancer cells and the consolidation of ¹³C-glutamine into acetyl-CoA. This effect was proved to be associated with RAGE and TLR4 receptors. HMGB1 could decrease the level of active mTOR via RAGE and active Beclin-1 through TLR4. The autophagy in tumor-hosting tissue was induced by the autophagy-released HMGB1 and consequently glutamine was recruited to cancer cells as an energy source. Su et al⁶⁹ also proposed the existence of positive feedback of the RAGE-HMGB1-Erk1/Erk2 pathway in HMGB1-induced autophagy in Lewis cells. Hence, HMGB1 can also be involved downstream of autophagy in cancer. In addition, the autophagy-released HMGB1 has the ability to induce further autophagy in other cells. There may be positive feedback between autophagy and HMGB1 in tumors, which warrants further investigation. An understanding of this is necessary for further clinical applications of HMGB1-induced autophagy.

Conclusion

In this review, we have summarized regulatory networks known to be behind the HMGB1-induced autophagy. HMGB1-induced autophagy plays an important role in cancer biology, such as proliferation, migration and chemoresistance. Further investigation of novel molecular mechanisms involved in this is needed because there is clearly great potential to exploit HMGB1-induced autophagy in efforts to combat cancer from different perspectives, especially in terms of its drug resistance. A better understanding of HMGB1-induced autophagy should provide additional insight into ways of reversing drug resistance in cancer therapy.

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Disclosure

The authors report no conflicts of interest in this work.

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