HMGB3: A pivotal orchestrator of therapy resistance and cancer stemness in human malignancies (Review)

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Abstract. High mobility group box 3 (HMGB3) acts as an essential participator in fundamental biological processes, including transcriptional regulation, chromatin remodeling and DNA repair. HMGB3 is highly expressed and functionally essential during embryonic development, particularly in the hematopoietic and nervous systems, but it is significantly downregulated or silenced in most normal adult tissues. Its aberrant upregulation has been revealed in numerous human malignancies, such as leukemia, as well as breast, bladder, colorectal and gastric cancer, and its expression levels have been established to be closely associated with poor prognosis of specific patients. Accordingly, the present review systematically explores the central roles of HMGB3 in mediating resistance to cancer therapy. This review focuses on its multifaceted mechanisms of maintaining cancer stemness, enhancing DNA damage repair, modulating cell death pathways and remodeling the tumor microenvironment, thereby contributing to the resistance to chemotherapy, radiotherapy, targeted therapy and immunotherapy collectively. HMGB3 can be accepted as a key target in the development of highly promising therapeutic strategies, given its pivotal involvement in multidrug resistance, which may offer novel avenues for overcoming clinical treatment resistance and improving patient outcomes.

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Contents

1. Introduction

High mobility group (HMG) proteins, isolated initially from bovine thymus in 1973, are named according to their high electrophoretic mobility in polyacrylamide gels (1). The HMG family constitutes the second most abundant family of chromatin-associated proteins in the cell nucleus after histones. Based on structural characteristics, it consists of three major subfamilies: HMGA, HMGB and HMGN. HMGB1, HMGB2, HMGB3 and HMGB4 are the four major members of the HMGB subfamily. The former three members share high structural homology, each containing two tandem HMG-box domains (A- and B-box) and an acidic C-terminal tail, as illustrated in Fig. 1. These proteins can bind and bend DNA, in turn being involved in diverse cellular processes such as DNA repair, replication, recombination and transcription (2-4).

Critically, HMGB3 exhibits distinct spatiotemporal specificity, unlike the widely expressed HMGB1 and the more restricted HMGB2. Specifically, it may exhibit typical expression patterns, manifesting as high expression during embryonic development that is critical for maintaining stem cell pluripotency and self-renewal, while it is nearly silenced in most differentiated adult tissues (5-7). Therefore, the reactivation of HMGB3 may have an intimate association with cellular dedifferentiation and malignant transformation. Indeed, HMGB3 is aberrantly overexpressed in multiple cancers, such as breast cancer (8), ovarian cancer (9), lung cancer (10), colorectal cancer (CRC) (11) and bladder cancer (12), indicating a certain correlation with poor prognosis simultaneously. In addition

to driving malignant progression, this overexpression may be linked to therapy resistance, particularly to chemotherapy and tumor recurrence. For instance, HMGB3 is considered a key indicator in relapse and treatment failure of acute myeloid leukemia (AML) (13). Its knockdown in gastric cancer cells may inhibit cell proliferation and migration, and affect chemosensitivity (14). HMGB3 may also promote the repair of interstrand DNA crosslinks and double-strand breaks (DSBs), suggesting its potential role in resistance to DNA-damaging chemotherapeutic agents (3). In addition, this member may also be implicated in non-neoplastic diseases, including ulcerative colitis (15), silica-induced pulmonary inflammation (16) and myocardial infarction (17).

With respect to the above, the present work systematically reviews the multifaceted roles of HMGB3 in driving resistance to cancer therapy and explores its underlying molecular mechanisms. Based on the examination of its functions in cancer cell proliferation, invasion, metastasis and cancer stem cell (CSC) maintenance, this study continues to integrate its roles in DNA damage repair and autophagy, with the purpose to uncover its mechanism in synergistically promoting multidrug resistance through multiple pathways (14,18). Additionally, the clinical potential of HMGB3 as a diagnostic biomarker and therapeutic target was discussed, thereby offering novel strategies for overcoming resistance to cancer therapy. Overall, HMGB3 exhibits complicated expression and function across different cancers, and tumor heterogeneity may exert an impact on treatment response (19,20). Therefore, in the future, our understanding of the specific mechanisms of HMGB3 within a distinct tumor microenvironment (TME) should be refined to facilitate the development of targeted inhibitors or regulatory strategies, thereby advancing precision oncology.

2. Transcriptional and epigenetic regulation of HMGB3

Multi-level molecular mechanisms, covering transcription factors and epigenetic modifications, are involved in the co-regulation of the dysregulated HMGB3 expression in cancer, eventually forming an interconnected regulatory network (21). The expression of HMGB3, acting as a chromatin-associated protein, is directly regulated by the binding of multiple transcription factors. In gastric cancer, nine transcription factors, including GATA1/2/3 and MZF1, can directly bind to the promoter or enhancer regions of HMGB3, developing a 'HMGB3-target gene' axis that may further promote tumor progression (22). In AML, its expression may also be modulated by disease-specific transcription factors (13). Epigenetically, HMGB3 expression is shaped by histone modifications, non-coding RNAs (ncRNAs) and DNA methylation. For instance, the histone H3 lysine 27 trimethylation modification can be catalyzed by enhancer of zeste homolog 2 in glioma, further suppressing microRNA (miR)-142-3p, thereby relieving its inhibition of the long (l) ncRNA KCNQ1OT1, consequently enhancing the expression of HMGB3 by binding to LIN28B (23). Additional investigations on DNA methylation analysis support a negative correlation between DNA methylation and HMGB3 expression, as hypomethylation of the HMGB3 gene is frequent in tumors with HMGB3 upregulation, while its hypermethylation is associated with its downregulation (24-26).

Notably, HMGB3 also functionally synergizes with other transcription factors. In prostate cancer, the HMGB3 A-box domain can interact with SOX9, resulting in a co-activation of NANOG homeobox (NANOG), thereby enhancing tumor stemness and progression (27). Collectively, HMGB3 is critical within a complex regulatory network in cancer. Its expression can be dynamically balanced by direct transcriptional regulation and epigenetic modifications, ultimately determining its functional output in tumorigenesis and progression.

Post-transcriptional regulation. HMGB3 expression is finely regulated at the post-transcriptional level by a network of ncRNAs [miRNAs, lncRNAs and circular (circ)RNAs] through competitive endogenous RNA (ceRNA) mechanisms. It may eventually affect tumor progression and therapy resistance significantly, as summarized in Table I.

Multiple miRNAs (e.g., miR-101-5p, miR-142-3p, miR-205 and miR-758) may inhibit HMGB3 expression by directly targeting the corresponding 3'UTR. In this regard, it may effectively suppress cancer cell proliferation, migration and invasion in various tumor types, such as breast cancer, cervical cancer and non-small cell lung cancer (NSCLC) (12,28-30). In particular, beyond targeting HMGB3 directly, miR-142-3p can also induce mitochondrial dysfunction and promote apoptosis by inactivating the mTOR/STAT3 pathway (29).

In addition to direct regulation, lncRNAs (e.g., SNHG5, HOTTIP) and circRNAs (e.g., circFOXO3, circIGF1R, circN4BP2L2) can sequester corresponding miRNAs to upregulate HMGB3 expression directly, which may further promote the progression of malignancies such as nasopharyngeal carcinoma (NPC), NSCLC and CRC (31-37). In CRC, circIGF1R and circN4BP2L2 can remarkably stimulate tumor cell proliferation, invasion and glycolysis while inhibiting apoptosis through the activation of the HMGB3/Wnt/β-catenin signaling pathway (36,37). Under hypoxic conditions, downregulation of miR-200b-3p in cancer-associated fibroblast-derived exosomes can attenuate the suppression of HMGB3, in turn weakening the sensitivity of CRC cells to 5-fluorouracil (5-FU)-based chemotherapy (38).

Altogether, the multi-level regulation of HMGB3 expression by ncRNAs through ceRNA networks is essential in malignant progression and therapy resistance. Additional representative ncRNA-mediated regulatory axes involving HMGB3 across different cancers, including NSCLC, breast cancer, colorectal cancer, gastric cancer, and cervical cancer, are summarized in Table I (10,29,33,38-50).

Post-translational modifications (PTMs) of HMGB3 protein. Critically, despite less advanced research compared to that on HMGB1 and HMGB2, the function of HMGB3 from the HMG family may be dynamically regulated by PTMs (2,51,52). The current understanding of the PTMs of HMGB3 relies largely on homology-based inference. In particular, these modifications may play a role in cancer therapy resistance by affecting subcellular localization, DNA damage response (DDR) and extracellular release under stress conditions.

In HMGB1, acetylation and phosphorylation act as crucial regulators of nuclear-cytoplasmic trafficking and participation in DNA repair. Following these modifications,

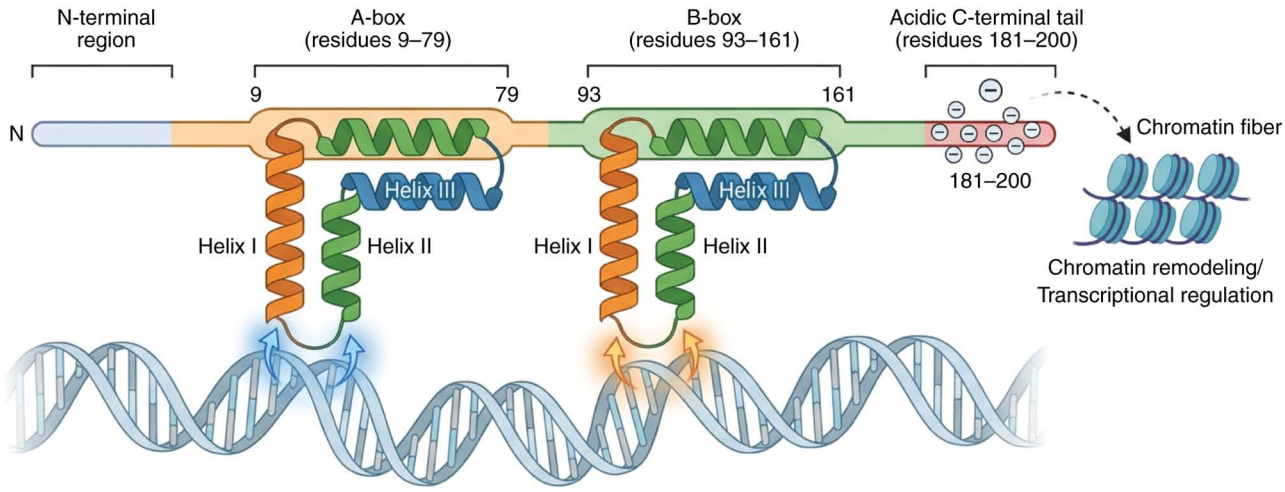

Figure 1. Schematic representation of the domain organization and functional modules of the human HMGB3 protein. The HMGB3 protein consists of an N-terminal region (residues 1-8), two conserved HMGB DNA-binding domains (A-box: Residues 9-79; B-box: Residues 93-161), and an acidic C-terminal tail (residues 181-200). Each HMGB comprises three characteristic α-helices (helix I, II and III, color-coded in orange, green and blue, respectively) that fold into a compact functional unit to facilitate DNA binding and architectural bending. The negatively charged C-terminal tail is primarily involved in modulating chromatin accessibility and regulating downstream transcriptional activity through its interaction with histones. HMGB, high mobility group box.

there may be reduced chromatin-binding stability, which may further boost the exposure of DNA damage sites and recruitment of repair factors, while driving nuclear export and extracellular release under conditions of severe stress, thereby influencing inflammatory signaling and cell survival (53-63). Similarly, the PTM status of HMGB3 may modulate DNA damage tolerance, replication stress response and post-chemotherapy or post-radiotherapy cell survival, considering that it retains highly conserved DNA-binding domains and regulatory regions (2). Furthermore, HMGB proteins may have a relationship with therapy resistance, given the redox regulation. To be specific, the oxidation state of cysteine residues in HMGB1 can determine the functional switch from a nuclear DNA chaperone to an extracellular signaling molecule, a process that is highly relevant under radiotherapy- or chemotherapy-induced oxidative stress (53,64-67). With the presence of conserved cysteine residues as well, HMGB3 may also have similar stress-induced functional reprogramming, potentially affecting DNA repair efficiency and TME-associated inflammatory responses, both of which are recognized to be key components of acquired therapy resistance (68). Additionally and significantly, there is so far limited research on the methylation and glycosylation of HMGB3. Furthermore, existing evidence indicates a negative correlation of HMGB3 DNA methylation with its expression in tumors (24). Despite the scarcity of direct experimental evidence, at the protein level, HMGB3 activity may be further modulated by lysine methylation and potential glycosylation sites within the B-box domain (69-72).

Collectively, even with limited direct experimental evidence for HMGB3 PTMs, PTMs may modulate HMGB3 activity during DDR and therapy-induced stress, as evidenced by homology- and structure-based functional insights. Consequently, it may participate in the modulation of tumor cell tolerance to radiotherapy, chemotherapy and targeted therapies potentially (2,51-53).

3. Core functional mechanisms of HMGB3: Bridging cancer stemness and treatment resistance

By coordinating multiple critical biological processes, HMGB3 can drive malignant progression and therapeutic resistance, thus forming an integrated regulatory network. These may include maintenance of CSC properties, modulation of the DDR, regulation of apoptosis-autophagy balance and remodeling of the TME. Therefore, these mechanisms may constitute the molecular foundation for resistance across diverse therapeutic modalities, as depicted in Fig. 2.

Maintenance of CSC properties. HMGB3 is a chromatin-associated protein overexpressed in multiple cancers, establishing an intimate association with CSC characteristics. CSCs represent a subpopulation of tumor cells that can undergo self-renewal and differentiation, exhibiting close relationships with tumor recurrence, metastasis and intrinsic therapeutic resistance (73-75).

Initially, HMGB3 was found to be preferentially expressed in hematopoietic stem cells, where it balances self-renewal and differentiation. For example, there are reduced common lymphoid progenitors and common myeloid progenitors in HMGB3-deficient mice, suggesting its potential role in maintaining primitive stem cell properties (76). Importantly, the proposed stemness-maintaining function appears to be conserved in malignancies. In solid tumors, HMGB3 can enhance spheroid formation, colony formation and the expression of pluripotency-associated transcription factors (e.g., NANOG, SOX2 and OCT4) to promote the formation of CSC-like phenotypes (27,77-79). In ovarian and breast cancer models, HMGB3 overexpression may indicate increased expression of stemness markers and unfavorable prognosis (77-80). Conversely, HMGB3 silencing can reduce self-renewal capacity and impair tumorigenicity. Its mechanisms may be related to the regulation of multiple stemness-associated signaling pathways. It can improve the expression of downstream

Table I. ncRNA-mediated regulation of HMGB3 in therapy resistance and apoptosis-associated tumor adaptation.

Tumor/cancer	CircRNA/lncRNA	Regulatory axis	Function and mechanism	(Refs.)
Non-small cell lung cancer	-	miR-758/ HMGB3	Inhibits the proliferation, migration and invasion of cancer cells and promotes their apoptosis.	(10)
	Circ_0060937	miR-195-5p/ HMGB3	Inhibits cancer cell proliferation, migration, invasion and glycolysis and triggers apoptosis.	(33)
	Circ_0020123	miR-1299/ HMGB3	Inhibits the proliferation, migration and invasion of cancer cells and promotes their apoptosis.	(39)
	-	miR-513b/ HMGB3	Activates the mTOR signaling pathway and promotes cancer cell proliferation, invasion, migration and apoptosis.	(40)
Breast cancer	-	miR-142-3p/ HMGB3	Modulates autophagy and induces apoptosis through reactive oxygen species accumulation and mitochondrial dysfunction.	(29)
	-	miR-27b/ HMGB3	Enhances cancer cell sensitivity to tamoxifen, inhibits invasion and reverses epithelial to mesenchymal transition-like phenotypes.	(41)
	-	miR-381-3p/ HMGB3	Exosome-delivered OIP5-AS1 confers resistance to trastuzumab in cancer cells via its competing endogenous RNA mechanism.	(42)
CRC	-	miR-200b-3p/ HMGB3	The loss of exosomal miR-200b-3p in hypoxic cancer-associated fibroblasts reduces sensitivity to 5-fluorouracil in CRC by targeting HMGB3.	(38)
	-	miR-429/ HMGB3	Inhibits cancer cell proliferation and induces apoptosis.	(43)
	-	miR-93/ HMGB3	Inhibits the activation of the PI3K/AKT pathway and promotes apoptosis in CRC cells.	(44)
Gastric cancer	-	miR-513b/ HMGB3	Inhibits cancer cell proliferation and migration, and promotes their apoptosis.	(45)
Prostate cancer	LncRNA SOX2-OT	miR-452-5p/ HMGB3	Inactivates the Wnt/β-catenin pathway and inhibits the proliferation and metastasis of prostate cancer cells.	(46)
Ovarian cancer	-	miRNA-374b-5p/HMGB3	Downregulates the Wnt/β-catenin pathway axis and inhibits the malignant progression of epithelial ovarian cancer.	(47)
Cervical cancer	LncRNA BCYRN1	miR-330-5p/ HMGB3	Disrupts the cisplatin resistance of cancer cells.	
	-	miR-758/ HMGB3	Downregulates the Wnt/β-catenin signaling pathway and inhibits cancer cell proliferation and metastasis.	(48,49)
Esophageal cancer	-	miR-216a/ HMGB3	Activates the Wnt/β-catenin pathway and promotes the progression of esophageal cancer.	(50)

HMGB, high mobility group box; miR, microRNA; lncRNA, long noncoding RNA; circRNA, circular RNA; CRC, colorectal cancer.

targets [e.g., c-Myc and MMP7] by boosting β-catenin nuclear accumulation and transcriptional activity. Its deficiency may also increase the level of E-cadherin while reducing that of mesenchymal markers (e.g., Snail and vimentin), indicating its role in driving epithelial-mesenchymal transition (EMT) and reinforcing invasive phenotypes (21,27,81,82). In addition, HMGB3 may also activate MAPK/ERK signaling and cooperate with transcriptional regulators (e.g., SOX9) to enhance the transcription of NANOG, thereby stabilizing the pluripotency network (80,83-85).

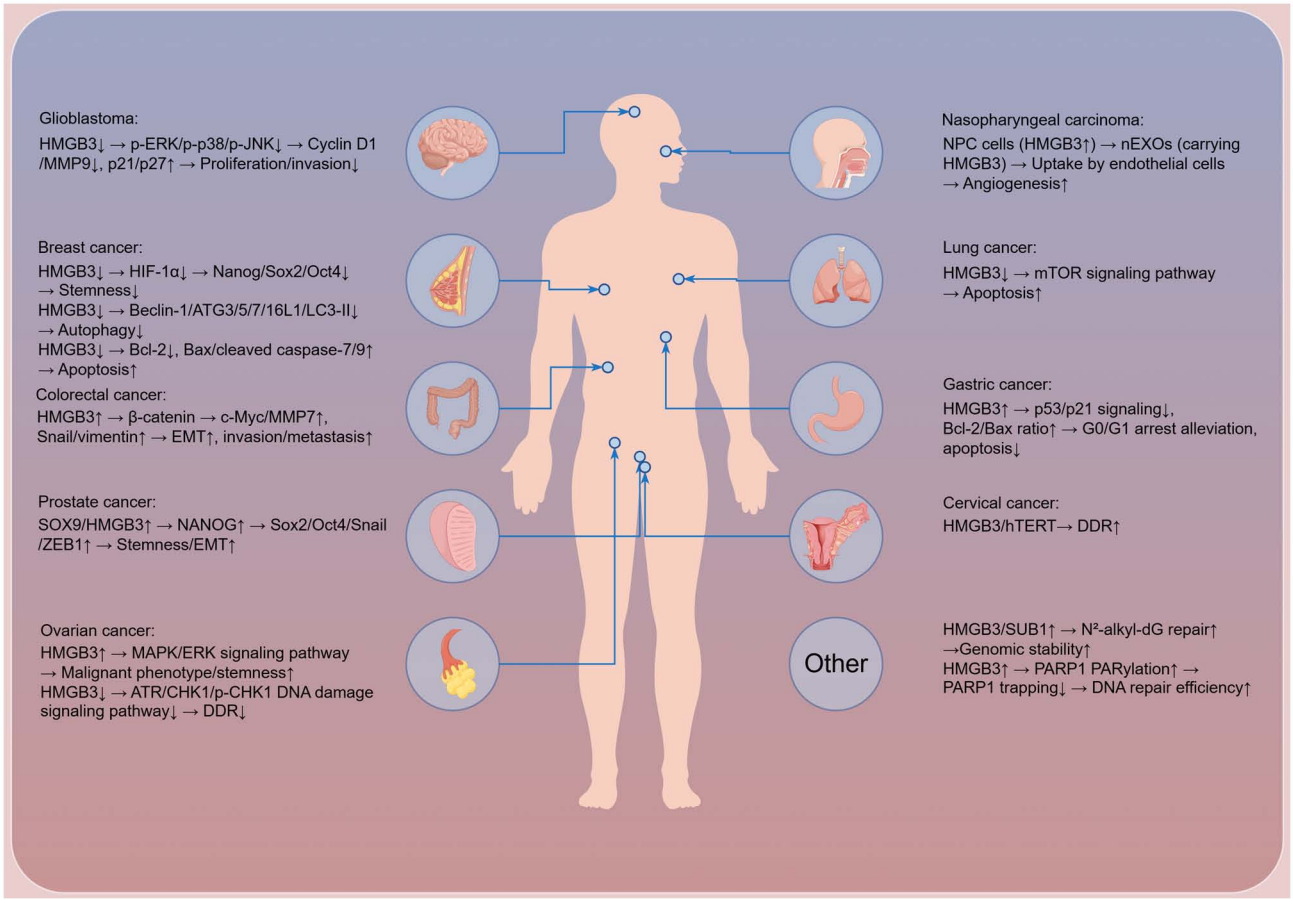

Figure 2. HMGB3 serving as a central driver of tumor malignancy. This schematic illustrates the mechanisms of HMGB3 in coordinating a multi-dimensional regulatory network, driving tumor progression and therapy resistance by sustaining cancer stemness, modulating DDR, inhibiting apoptosis, inducing autophagy and remodeling the tumor microenvironment. HMGB, high mobility group box; EMT, epithelial to mesenchymal transition; HIF, hypoxia-inducible factor; DDR, DNA damage response; p-CHK, phosphorylated checkpoint kinase; Nanog, Nanog homeobox; Oct4, octamer-binding transcription factor 4; ZEB1, Zinc finger E-box binding homeobox 1; ATR, Ataxia telangiectasia and Rad3-related; hTERT, human telomerase reverse transcriptase; SUB1, SUB1 regulator of transcription; PARP1, poly(ADP-ribose) polymerase 1.

HMGB3 can activate Wnt/β-catenin, MAPK/ERK and related regulatory axes collaboratively, thereby sustaining the CSC pool and enhancing tumor adaptability under therapeutic stress.

Regulation of the DDR pathway. Genomic instability is a hallmark of cancer. Sustained activation of DDR pathways may enable tumor cells to survive under endogenous and exogenous genotoxic stress. HMGB3 is a chromatin-associated architectural protein that may contribute to DDR regulation at multiple functional levels, including damage sensing, chromatin remodeling, transcriptional control of repair genes and coordination of complex DNA lesion repair.

At the early stage of the DDR, rapid lesion recognition and chromatin relaxation constitute the premise of efficient repair to permit the recruitment of repair complexes. Depending on its HMG box domains, HMGB3 can bind distorted DNA structures and modulate chromatin conformation, thereby facilitating access of repair machinery to damaged sites. HMGB3 can recognize specific DNA adducts, such as N^2-alkyl-2'-deoxyguanosine (dG) lesions induced by benzo[a]pyrene-7,8-dihydrodiol-9,10-epoxide (BPDE), and, together with SUB1 regulator of transcription, functions as a damage sensor exhibiting stereoselective repair activity toward trans-N^2-BPDE-dG adducts (86). Thus, HMGB3 exerts potential roles in early lesion recognition and damaged DNA stabilization. Following the recognition of damage, HMGB3 can further promote repair progression by interacting with key repair enzymes. Through a direct interaction with poly(ADP-ribose) polymerase 1 (PARP1), it can enhance its PARylation activity and potentially influence its retention at DNA damage sites (9,87). By modulating PARP1 activity, HMGB3 can support efficient repair of single-strand breaks and alkylation-induced lesions. Beyond its structural role, HMGB3 can transcriptionally regulate major DDR components. By binding to its promoter, it can activate human telomerase reverse transcriptase (hTERT), resulting in telomere maintenance and genomic stability under stress (88,89). HMGB3 can also activate the transcription of ATR checkpoint kinase (ATR) and checkpoint kinase 1 (CHK1) (90-92), which may further strengthen checkpoint signaling, replication fork stabilization and homologous recombination repair. Consistently, the depletion of HMGB3 may attenuate ATR/CHK1 signaling and impair the efficiency of interstrand crosslink repair (8). These coordinated functions converge on the repair of interstrand crosslinks (ICLs) and DSBs, two complex DNA lesions. However, its deficiency may impair the deficiency of ICL repair (3,93) and DSB repair (3,94,95). Accordingly,

HMGB3 can facilitate the recruitment or stabilization of core repair factors involved in homologous recombination and non-homologous end joining.

Collectively, HMGB3 works to maintain genomic stability by integrating chromatin remodeling, enzymatic activation and transcriptional amplification within the DDR network.

Inhibition of apoptosis and induction of autophagy. HMGB3 can modulate the balance between apoptosis and autophagy, serving as a critical indicator in tumor cell survival. There is growing evidence that HMGB3 can suppress apoptotic signaling while sustaining pro-survival autophagic activity, thereby promoting cellular adaptation under stress.

In breast cancer, there is an increased expression of Beclin-1, ATG family proteins and light chain 3-II, supporting the role of HMGB3 in maintaining protective autophagy (29). Suppression of HMGB3 by miR-142-3p can disrupt this autophagic program, leading to mitochondrial dysfunction, featured by the accumulation of reactive oxygen species (ROS) and the loss of mitochondrial membrane potential. These alterations may further activate the caspase cascade and shift cellular fate toward apoptosis, suggesting that HMGB3 can regulate autophagy through the preservation of mitochondrial integrity and prevention of cell death. Consistently, downregulation of HMGB3 can promote apoptotic signaling in multiple tumor types. For instance, in gastric cancer, reduced HMGB3 expression can induce G0/G1 cell cycle arrest and modulate the p53/p21 pathway, while decreasing the Bcl-2/Bax ratio to favor apoptosis (1). Similar HMGB3 silencing-induced pro-apoptotic effects have been reported in NSCLC (10,40), cervical cancer (96), ovarian cancer (47), CRC (37,44), thyroid cancer (97) and esophageal cancer (50), highlighting its broad role in sustaining tumor cell viability. Despite the scarcity of direct evidence linking HMGB3 to autophagy regulation, its structural similarity to HMGB1 suggests potential mechanistic parallels. HMGB1 can regulate autophagy by interacting with Beclin-1 (98), highlighting potential roles of HMGB3 in autophagosome formation or autophagy flux via related pathways. Of note, context-dependent effects were also noted. HMGB3 overexpression combined with selinexor can enhance apoptosis in myelodysplastic syndromes, possibly through the activation of cytoplasmic DNA-sensing pathways and interferon-related innate immune signaling (99). It underlines the complexity of HMGB3-mediated regulation of cell fate across different cellular contexts.

HMGB3-driven remodeling of the TME. In addition to intrinsic genetic alterations, tumor progression may also be determined by dynamic interactions between malignant cells and their surrounding microenvironment. Therefore, HMGB3 functions as a critical regulator linking tumor cell plasticity to microenvironmental remodeling. HMGB3 can regulate cellular behavior, intercellular communication and oncogenic signaling networks coordinately, thereby benefiting the reshaping of the structural and functional landscape of the TME.

Tumor cell plasticity as a driver of microenvironmental change. HMGB3 can enhance malignant cell plasticity, serving as a primary force in TME remodeling. Its overexpression may promote the proliferation and cell cycle progression across multiple tumor types. In leukemia, HMGB3 may enhance cell proliferation by activating MAPK/ERK signaling (13). In ovarian cancer, its overexpression may accelerate cell growth, whereas its silencing can induce G2/M arrest (80). In prostate cancer, depletion of HMGB3 may cause G0/G1 arrest by regulating cyclin D1, p21 and p27 (46). More importantly, HMGB3 may trigger EMT, a process that fundamentally alters tumor-stroma interactions. Its upregulation can escalate the expression of mesenchymal markers (e.g., N-cadherin, vimentin, β-catenin, snail and slug) (80), while its silencing may hinder cell migration and invasion in gastric cancer (14) and CRC (24). HMGB3 can strengthen EMT to disrupt tissue architecture, thereby facilitating dynamic cellular redistribution within the TME. Additionally, HMGB3 can also support CSC phenotypes. In breast cancer, it can increase mammosphere formation, while upregulating the expression of Nanog, SOX2 and OCT-4 (100), with similar effects observed in ovarian cancer (80). Maintenance of stem-like subpopulations can contribute to intratumoral heterogeneity and continuous microenvironmental adaptation. With respect to the above, HMGB3-driven cellular plasticity may offer a possible biological foundation for TME restructuring.

Intercellular communication and stromal remodeling. Beyond tumor cell-intrinsic changes, HMGB3 may also play a role in non-malignant components of the TME, among which angiogenesis represents a well-defined mechanism. In NPC, HMGB3, secreted via nuclear exosomes, may be internalized by endothelial cells to promote proliferation and tube formation (101). HMGB3-containing exosomes may increase microvascular density to facilitate the expansion of the vascular network within the TME. Furthermore, HMGB3 can modulate the immune microenvironment. Even with an insufficiency of the direct mechanistic data, its structural homology to HMGB1-an established damage-associated molecular pattern-may suggest potential immunoregulatory functions (18,102,103). In glioblastoma, the overexpression of HMGB3 may be related to reduced immune cell infiltration and an immunosuppressive microenvironment (104). Dysregulation of HMGB3 expression can also amplify ROS generation and activate the NF-κB signaling to mediate the production of cytokines such as VEGF and IL-6, thereby shaping the status of inflammation within the TME (1). The remodeling of extracellular matrix can further induce microenvironmental restructuring. HMGB3 can regulate MMPs, as evidenced by reduced MMP2 expression following HMGB3 knockdown in bladder cancer and decreased MMP2/MMP9 activity in gastric cancer, ultimately altering the physical and biochemical properties of the TME (1,105).

Integrated signaling networks underlying TME remodeling. Diverse effects of HMGB3 on TME architecture are mediated through interconnected oncogenic signaling pathways. HMGB3 can activate the MAPK/ERK signaling in leukemia and ovarian cancer (13,80), promote β-catenin nuclear accumulation and downstream target (e.g., MMP7 and c-Myc) transcription (44,46,80,105), and modulate PI3K/AKT signaling, as revealed by miR-93-mediated suppression of HMGB3 in CRC (44). The interaction between HMGB3 and hypoxia-inducible factor (HIF)-1α in breast cancer also establish a relationship of HMGB3 to hypoxia-associated microenvironmental adaptation (100).

By integrating these signaling cascades, HMGB3 can coordinate malignant cell plasticity, stromal reprogramming and microenvironmental adaptation, thereby reshaping the organization and function of TME.

4. HMGB3-mediated tumor therapy resistance

HMGB3 may induce resistance across multiple therapeutic modalities. As described above, the present study has systematically elucidated its roles in DDR, apoptosis regulation and microenvironmental remodeling. This chapter continues to unveil the manifestations of these biological functions in specific therapeutic contexts. Notably, HMGB3-mediated resistance appears to be treatment-dependent, highlighting the presence of mechanistic heterogeneity across varied anticancer therapies.

Chemotherapy resistance. Chemotherapeutic agents may produce cytotoxic effects through diverse mechanisms and HMGB3 has been reported to modulate resistance in a drug-specific manner. Platinum compounds, such as cisplatin, can induce cytotoxicity primarily through the formation of DNA adducts that distort the DNA helix and activate DNA damage signaling pathways (1,4). HMGB3 is predominantly involved in DNA damage processing, supporting its implication in platinum resistance. Through potential binding to cisplatin-DNA adducts, it may facilitate lesion recognition and subsequent repair (1). In cisplatin-resistant ovarian cancer models, the inhibition of HMGB3 may enhance drug sensitivity and attenuate the activation of the ATR/CHK1/p-CHK1 axis, suggesting its role in supporting sustained DDR signaling under platinum-induced genotoxic stress (8). HMGB3 may also influence the clearance rate of cisplatin-DNA adducts by interacting with the cisplatin resistance-associated protein (also known as LUC7L3). HMGB3 knockdown may reduce the efficiency of adduct removal, thereby altering cellular responses to cisplatin exposure (93). Of note, in gastric cancer cells, HMGB3 silencing may amplify the sensitivity to cisplatin and paclitaxel but reduce the sensitivity to oxaliplatin (14,106), indicating the possible compound- and cellular context-dependent HMGB3-mediated modulation of platinum response. Microtubule-targeting agents represent another major class of chemotherapeutics. For example, paclitaxel can stabilize microtubules and prevent their depolymerization (107), while vincristine can inhibit tubulin polymerization and disrupt spindle formation (108). Alterations in cell cycle regulation and apoptotic signaling thresholds have been proven to be strongly associated with resistance to these agents. In gastric cancer, HMGB3 knockdown can suppress cell proliferation, induce G0/G1 arrest and enhance paclitaxel sensitivity by modulating p53, p21 and the Bcl-2/Bax ratio (14). Similarly, in cervical cancer, given reduced IC50 values, its depletion may enhance the sensitivity to both paclitaxel and vincristine (88). Collectively, HMGB3 enables the modulation of cell cycle progression and apoptosis-related pathways to promote cell survival under mitotic stress eventually. HMGB3 has been proposed to be associated with resistance to antimetabolites and endocrine therapies, in addition to the aforementioned agents. In CRC, by activating Wnt/β-catenin signaling and EMT-associated transcriptional programs, HMGB3 may mediate the resistance to 5-FU (109). In breast cancer, HMGB3 expression is negatively regulated by miR-27b, and its overexpression is associated with resistance to tamoxifen (41). Currently, although there is still an incomplete definition of the mechanistic details, there is reason to believe that HMGB3 exerts a broader role in shaping chemotherapeutic responsiveness through transcriptional and signaling reprogramming.

Radiotherapy resistance. Radiotherapy induces cytotoxicity primarily through the induction of DSBs. Therefore, the efficiency of DNA repair and the propensity to undergo post-damage apoptosis remain the major determinants for cellular radiosensitivity. Current evidence suggests that HMGB3 may induce radioresistance by regulating the HMGB3/hTERT axis. HMGB3, a transcriptional regulator, can bind to the hTERT promoter and enhance its expression. Elevated hTERT levels may be related to increased DNA repair capacity and reduced radiation-induced apoptosis. Conversely, HMGB3 knockdown may contribute to accumulated γH2AX foci, impaired DSB repair, and enhanced radiosensitivity in both *in vitro* and *in vivo* models (88). As a result, HMGB3 may possibly promote repair competence and restrict apoptotic execution to sustain radiation tolerance.

Targeted therapy resistance. Targeted therapies frequently encounter resistance owing to pathway reactivation, compensatory signaling or DNA repair dynamic alterations. Via both protein-protein interactions and oncogenic signaling network modulation, HMGB3 appears to participate in these adaptive processes. Notably, HMGB3 can interact with PARP1 to affect its functional activity. Loss of HMGB3 can induce PARP1 'trapping' at sites of DNA damage and weaken the activity of PARylation, highlighting the regulatory role of HMGB3 in PARP1 DNA-binding kinetics. Such modulation can potentially attenuate the cytotoxic effect of olaparib and other PARP inhibitors (PARPi) (9,110). Besides, given the common function of the MAPK/ERK pathway as a bypass pathway in targeted therapy failure, HMGB3-mediated activation of the pathway-reported in multiple tumor types-may induce adaptive resistance (80,83-85). However, there is still an insufficiency of direct causal evidence linking HMGB3 to resistance against specific kinase inhibitors, necessitating further mechanistic studies to clarify this relationship.

Immunotherapy resistance. Immune checkpoint inhibitors (ICIs) may disrupt inhibitory signaling pathways that restrain T-cell activity to restore antitumor immunity. Emerging evidence indicates that, on the basis of both tumor-intrinsic signaling alterations and microenvironmental modulation, HMGB3 may boost immune evasion and reduce responsiveness to ICIs. In triple-negative breast cancer, HMGB3 can suppress interferon (IFN)-γ-induced STAT1 phosphorylation and IFN regulatory factor 1 expression while enhancing STAT3 activation. Concurrently, it can also upregulate ferroptosis-inhibitory proteins [e.g., solute carrier family 7 member 11 (SLC7A11), glutathione peroxidase 4 and SLC3A2] to accumulate lipid ROS and restrict IFN-γ-mediated ferroptotic cell death. These molecular changes are associated with the resistance to anti-programmed cell death 1 (PD-1) therapy (111). In glioblastoma, elevated expression of HMGB3 is associated

Table II. HMGB3-mediated mechanisms of therapy resistance in cancer.

Treatment modality	Classes of resistance mechanisms	Core mechanism	Tumor type	(Refs.)
Targeted therapy	PARPi resistance	HMGB3/PARP1	Ovarian cancer	(9)
Radiotherapy	Radioresistance	HMGB3/hTERT	Cervical cancer	(88)
Chemotherapy	Paclitaxel resistance	HMGB3/Bcl-2/Bax	Gastric cancer	(14)
		HMGB3/MMP2/MMP9		
	Tamoxifen resistance	miR-27b/HMGB3	Breast cancer	(41)
	Cisplatin/platinum resistance	ATR/CHK1/p-CHK1	Ovarian cancer	(8,93)
		CROP/LUC7L3	Gastric cancer	(106)
		miR-200b/HMGB3		
	5-FU resistance	miR-200b-3p/HMGB3	Colorectal cancer	(38)
		Wnt/β-catenin	Breast cancer	(109)
Immunotherapy	Anti-PD-1/PD-L1 therapy resistance	HMGB3/IFNγ/STAT1/ ferroptosis	Triple-negative breast cancer	(111)

HMGB, high mobility group box; PARPi, poly(ADP-ribose) polymerase inhibitor; PARP1, poly(ADP-ribose) polymerase 1; hTERT, human telomerase reverse transcriptase; Bcl-2, BCL2 apoptosis regulator; Bax, BCL2-associated X protein; MMP2/9, matrix metallopeptidase 2/9; miR, microRNA; ATR, Ataxia telangiectasia and Rad3-related; CHK1, checkpoint kinase 1; CROP, cisplatin resistance-associated-overexpressed protein; LUC7L3, LUC7 like 3 pre-mRNA splicing factor; 5-FU, 5-fluorouracil; PD-1, programmed cell death protein 1; PD-L1, programmed cell death 1 ligand 1; IFNγ, interferon gamma; STAT1, signal transducer and activator of transcription 1.

with a non-inflammatory, immune-excluded microenvironment characterized by reduced immune cell infiltration (104). Such an immunologically 'cold' tumor phenotype may compromise the efficacy of ICIs, further implicating HMGB3 in immunotherapy resistance.

Overall, HMGB3 can mediate the resistance to chemotherapy, radiotherapy, targeted therapy and immunotherapy in a context-dependent manner. Instead of functioning through a single dominant mechanism, HMGB3 may enhance tumor survival under therapeutic pressure by integrating DNA repair regulation, cell cycle control, apoptotic modulation, signaling pathway activation and immune adaptation. Nonetheless, in order to determine whether HMGB3 can serve as a predictive biomarker or actionable therapeutic target for overcoming treatment resistance, further mechanistic validation and clinical correlation are required. Representative HMGB3-mediated mechanisms contributing to resistance to chemotherapy, radiotherapy, targeted therapy and immunotherapy are summarized in Table II.

5. HMGB3-targeted therapeutic strategies and clinical prospects

HMGB3 features high embryonic expression, limited expression in normal adult tissues and aberrant overexpression in multiple malignancies (e.g., leukemia, breast cancer, CRC, lung cancer, glioma), underscoring its potential as an attractive therapeutic target.

Direct targeting strategies. Targeting HMGB3 directly is the best approach for precision therapy. Through antisense oligonucleotides (ASOs) or small interfering RNA (siRNA), the specific silencing of HMGB3 has been documented to possess significant antitumor activity in multiple cancer models, which can hinder the proliferation and invasion while enhancing chemosensitivity (24,80,88). Such findings provide proof-of-concept for developing ASO- or siRNA-based HMGB3-targeted therapeutics.

The function of HMGB3, a DNA-binding protein and transcription factor, depends on specific domains and protein interactions. Small-molecular compounds developed by targeting its key functional sites (e.g., the HMGB domain or protein-protein interaction interfaces) may block its pro-cancer activities. For example, HMGB3can promote PARPi resistance by interacting with PARP1 in ovarian cancer (9), enhance radioresistance by binding the hTERT promoter in cervical cancer (88) and promote breast cancer growth by interacting with HIF-1α (100). Developing inhibitors that specifically block these interactions can precisely suppress specific oncogenic functions of HMGB3.

HMGB3 may exist extracellularly, although it is primarily nuclear, offering antibody targets. In NPC, HMGB3 is secreted via nuclear exosomes, and circulating nuclear exosomes HMGB3 may link to angiogenesis and metastasis (101), suggesting the potential of neutralizing antibodies in impeding extracellular HMGB3 functions. The high expression of HMGB3, even without extracellular activity, in specific cancers warrants the development of antibody-drug conjugates targeting cell surface markers associated with HMGB3 expression, thereby enabling precise drug delivery.

Indirect targeting strategies. miRNAs are recognized as post-transcriptional regulators that may participate in HMGB3 regulation, which can be modulated to indirectly influence HMGB3 levels. In prostate cancer, HMGB3 can be negatively regulated by miR-205-5p and its elevated expression is associated with poor outcomes (112). In breast cancer, by targeting HMGB3, miR-27b is linked to tamoxifen resistance. Thus,

targeting miR-27b or HMGB3 may reverse the resistance to tamoxifen (109), indicating the miR/HMGB3 axis serving as a potential therapeutic target (113).

HMGB3 may activate or participate in multiple oncogenic signaling pathways. In ovarian cancer (92) and leukemia (13), HMGB3 can promote malignancy and stemness via MAPK/ERK. Significantly, MEK/ERK inhibitors (e.g., AZD6244, PD0325901) can effectively reverse HMGB3-induced pro-cancer effects (80). It may also promote disease progression by activating pathways such as Wnt/β-catenin, PI3K/AKT, hypoxia/HIF-1α (44,100,114,115). Inhibiting these pathways represents an effective indirect strategy targeting HMGB3.

Combination therapy. Given the central role in resistance and stemness, HMGB3 may be an ideal combination therapy target. Targeted HMGB3 inhibition combined with PARPi can restore sensitivity to PARPi, thereby overcoming resistance (9). When combined with chemotherapy, targeting HMGB3 can enhance the sensitivity to multiple agents (e.g., paclitaxel, cisplatin) (9,109). While combined with radiotherapy, it can enhance radiation response by blocking the HMGB3/hTERT axis. When used jointly with immunotherapy, it may overcome HMGB3-mediated anti-PD-1 resistance by inhibiting IFN-γ-driven ferroptosis in triple-negative breast cancer. In addition, HMGB3 can promote the stemness (80) and CSC-associated EMT in ovarian cancer via modulating the Wnt/β-catenin pathway (24). Accordingly, targeting HMGB3 may suppress or eliminate CSCs, reducing the risks of recurrence and metastasis.

Potential of HMGB3 as a prognostic biomarker and efficacy predictor. HMGB3 can also be regarded as a promising biomarker for diagnosis, prognosis and treatment response prediction, given its abnormal expression in multiple cancers and strong association with clinical outcomes. HMGB3 is overexpressed in various tumors (e.g., breast cancer, NSCLC, CRC, bladder cancer, prostate cancer), with elevated levels being associated with poor prognosis. Furthermore, its expression also exhibits a positive association with advanced clinicopathological features, such as tumor grade, size, stage and lymph node metastasis (105,109,114,116). In breast cancer, HMGB3 shows excellent diagnostic potential, with an area under the receiver operating characteristic curve of 0.932 (109). In NPC and thyroid cancer, circulating HMGB3 in exosomes or serum may imply metastasis, suggesting the potential of liquid biopsy (101,115). Elevated HMGB3 may predict resistance to radiotherapy, chemotherapy, targeted therapy and ICIs, as well as unfavorable survival, underscoring its role in treatment response prediction and prognostic assessment.

6. Conclusions and future perspectives

This review systematically summarizes the central roles of HMGB3 in resistance to cancer therapy and cancer stemness. HMGB3 is highly and specifically expressed during embryonic development, but remains largely silent in adult tissues. It may function significantly in malignant transformation, given its aberrant reactivation in various malignancies. HMGB3 can regulate tumor cell functions through a multi-level network, maintaining CSC properties, promoting DNA damage repair and cellular survival and further supporting therapy resistance via TME remodeling. Mechanistically, these functions are finely modulated by ncRNAs and PTMs, highlighting that HMGB3 may be a core molecular node linking cancer stemness, genomic instability, cellular survival and microenvironmental regulation.

Despite notable progress, there are significant deficiencies in existing research on HMGB3. Specifically, most functional validations are limited to *in vitro* models, with a lack of support from complex *in vivo* systems. Meanwhile, there is a poor interpretation of its roles and underlying molecular mechanisms within the tumor immune microenvironment. Additionally, its clinical translation is blocked owing to the absence of highly specific HMGB3 small-molecule inhibitors or neutralizing antibodies. In the future, there is a need to develop highly specific HMGB3-targeted tools and validate their therapeutic potential using patient-derived organoids and humanized models, and to conduct multicenter clinical cohort studies to systematically assess the correlation between HMGB3 expression and treatment response or prognosis. Besides, it is important to elucidate its dual roles within the tumor immune microenvironment and their molecular bases to provide a rationale for combination immunotherapy strategies. Overall, HMGB3 serves as a pivotal node connecting multiple oncogenic processes that exhibits substantial translational potential and may be a novel precision therapeutic target for overcoming the resistance of cancer therapy.

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Authors' contributions

NHF and JFS designed this study and provided clinical guidance as well as data interpretation. JZ and YFS prepared the figures for this study. JZ and LYW drafted the manuscript. JYG and YH supervised the study and revised the manuscript. Data authentication is not applicable. All authors reviewed the manuscript, provided comments and approved the final version.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Wen B, Wei YT and Zhao K: The role of high mobility group protein B3 (HMGB3) in tumor proliferation and drug resistance. Mol Cell Biochem 476: 1729-1739, 2021.
2. Chikhirzhina E, Tsimokha A, Tomilin AN and Polyanichko A: Structure and functions of HMGB3 protein. Int J Mol Sci 25: 7656, 2024.
3. Dangerfield J, Mukherjee A, Reh W, Battenhouse A and Vasquez KM: High-Mobility group box protein 3 (HMGB3) facilitates DNA interstrand crosslink processing and Double-strand break repair in human cells. Genes (Basel) 16: 1044, 2025.
4. Niu L, Yang W, Duan L, Wang X, Li Y, Xu C, Liu C, Zhang Y, Zhou W, Liu J, *et al*: Biological functions and theranostic potential of HMGB family members in human cancers. Ther Adv Med Oncol 12: 1758835920970850, 2020.
5. Vaccari T, Beltrame M, Ferrari S and Bianchi ME: Hmg4, a new member of the Hmg1/2 gene family. Genomics 49: 247-252, 1998.
6. Lv Y, Lv M, Ji X, Xue L, Rui C, Yin L, Ding H and Miao Z: Down-regulated expressed protein HMGB3 inhibits proliferation and migration, promotes apoptosis in the placentas of fetal growth restriction. Int J Biochem Cell Biol 107: 69-76, 2019.
7. Tang D, Kang R, Zeh HJ and Lotze MT: The multifunctional protein HMGB1: 50 years of discovery. Nat Rev Immunol 23: 824-841, 2023.
8. Mukherjee A, Huynh V, Gaines K, Reh WA and Vasquez KM: Targeting the High-mobility group box 3 protein sensitizes chemoresistant ovarian cancer cells to cisplatin. Cancer Res 79: 3185-3191, 2019.
9. Ma H, Qi G, Han F, Lu W, Peng J, Li R, Yan S, Yuan C and Kong B: HMGB3 promotes PARP inhibitor resistance through interacting with PARP1 in ovarian cancer. Cell Death Dis 13: 263, 2022.
10. Zhou GH, Lu YY, Xie JL, Gao ZK, Wu XB, Yao WS and Gu WG: Overexpression of miR-758 inhibited proliferation, migration, invasion, and promoted apoptosis of non-small cell lung cancer cells by negatively regulating HMGB. Biosci Rep 39: BSR20180855, 2019.
11. Zhou D, He S, Zhang D, Lv Z, Yu J, Li Q, Li M, Guo W and Qi F: LINC00857 promotes colorectal cancer progression by sponging miR-150-5p and upregulating HMGB3 (high mobility group box 3) expression. Bioengineered 12: 12107-12122, 2021.
12. Xie X, Pan J, Han X and Chen W: Downregulation of microRNA-532-5p promotes the proliferation and invasion of bladder cancer cells through promotion of HMGB3/Wnt/β-catenin signaling. Chem Biol Interact 300: 73-81, 2019.
13. Swenson SA, Dhir A, Weber IS, Dobish KK, Xiao P, Buckley SM and Hyde KT: HMGB3: A novel regulator of leukemia proliferation. Blood 144: 4112-4113, 2024.
14. Guo S, Wang Y, Gao Y, Zhang Y, Chen M, Xu M, Hu L, Jing Y, Jing F, Li C, *et al*: Knockdown of high mobility Group-Box 3 (HMGB3) expression inhibits proliferation, reduces migration, and affects chemosensitivity in gastric cancer cells. Med Sci Monit 22: 3951-3960, 2016.
15. Qiu C, Chen Y, Xia H, Duan J, Zhang L, Zhang Y, Chen Z and Zhang L: Hsa_circ_0004662 accelerates the progression of ulcerative colitis via the microRNA-532/HMGB3 signalling axis. J Cell Mol Med 29: e70430, 2025.
16. Qin X, Niu Z, Chen H and Hu Y: Macrophage-derived exosomal HMGB3 regulates silica-induced pulmonary inflammation by promoting M1 macrophage polarization and recruitment. Part Fibre Toxicol 21: 12, 2024.
17. Manhas A, Tripathi D and Jagavelu K: Involvement of HIF1α/Reg protein in the regulation of HMGB3 in myocardial infarction. Vascul Pharmacol 152: 107197, 2023.
18. Chen R, Zou J, Zhong X, Li J, Kang R and Tang D: HMGB1 in the interplay between autophagy and apoptosis in cancer. Cancer Lett 581: 216494, 2024.
19. Sethi N and Kang Y: Unravelling the complexity of metastasis-molecular understanding and targeted therapies. Nat Rev Cancer 11: 735-748, 2011.
20. Vemula S, Bonala S, Vadde NK, Natu JZ, Basha R, Vadde R and Ahmad S: Drug resistance and immunotherapy in gynecologic cancers. Life Sci 332: 122104, 2023.
21. Mirzaee F, Abbaszade-CheragheAli A and Khamoushi A: Overview of high mobility group box 3 (HMGB3] protein. Mol Genet Genomics 300: 59, 2025.
22. Gong Y, Cao Y, Song L, Zhou J, Wang C and Wu B: HMGB3 characterization in gastric cancer. Genet Mol Res 12: 6032-6039, 2013.
23. Zhang Y, Yu Y, Yuan L and Zhang B: EZH2 promotes glioma cell proliferation, invasion, and migration via Mir-142-3p/KCNQ1OT1/HMGB3 Axis: Running Title: EZH2 promotes glioma cell malignant behaviors. Mol Neurobiol 61: 8668-8687, 2024.
24. Gong W, Guo Y, Yuan H, Hu X, Chai R, Zheng B, Wan Z and Tu S: HMGB3 is a potential therapeutic target by affecting the migration and proliferation of colorectal cancer. Front Cell Dev Biol 10: 891482, 2022.
25. Zheng M, Wu L, Xiao R, Zhou Y, Cai J, Chen W, Chen C, Sun K and Shen S: Integrated analysis of coexpression and a tumor-specific ceRNA network revealed a potential prognostic biomarker in breast cancer. Transl Cancer Res 12: 949-964, 2023.
26. Moore LD, Le T and Fan G: DNA methylation and its basic function. Neuropsychopharmacology 38: 23-38, 2013.
27. Xu Y, Xu M, Li X, Weng X, Su Z, Zhang M, Tan J, Zeng H, Li X, Nie L, *et al*: SOX9 and HMGB3 co-operatively transactivate NANOG and promote prostate cancer progression. Prostate 83: 440-453, 2023.
28. Toda H, Seki N, Kurozumi S, Shinden Y, Yamada Y, Nohata N, Moriya S, Idichi T, Maemura K, Fujii T, *et al*: RNA-sequence-based microRNA expression signature in breast cancer: Tumor-suppressive miR-101-5p regulates molecular pathogenesis. Mol Oncol 14: 426-446, 2020.
29. Sharma P, Yadav P, Sundaram S, Venkatraman G, Bera AK and Karunagaran D: HMGB3 inhibition by miR-142-3p/sh-RNA modulates autophagy and induces apoptosis via ROS accumulation and mitochondrial dysfunction and reduces the tumorigenic potential of human breast cancer cells. Life Sci 304: 120727, 2022.
30. Elgamal OA, Park JK, Gusev Y, Azevedo-Pouly AC, Jiang J, Roopra A and Schmittgen TD: Tumor suppressive function of mir-205 in breast cancer is linked to HMGB3 regulation. PLoS One 8: e76402, 2013.
31. Liu D, Wang Y, Zhao Y and Gu X: LncRNA SNHG5 promotes nasopharyngeal carcinoma progression by regulating miR-1179/HMGB3 axis. BMC Cancer 20: 178, 2020.
32. Shi J, Wang H, Feng W, Huang S, An J, Qiu Y and Wu K: Long non-coding RNA HOTTIP promotes hypoxia-induced glycolysis through targeting miR-615-3p/HMGB3 axis in non-small cell lung cancer cells. Eur J Pharmacol 862: 172615, 2019.
33. Xi J, Xi Y, Zhang Z, Hao Y, Wu F, Bian B, Hao G, Li W and Zhang S: Hsa_circ_0060937 accelerates non-small cell lung cancer progression via modulating miR-195-5p/HMGB3 pathway. Cell Cycle 20: 2040-2052, 2021.
34. Zhou ZF, Wei Z, Yao JC, Liu SY, Wang F, Wang Z, Chen XF, Lin H, Ye Y and Zheng QF: CircRNA_102179 promotes the proliferation, migration and invasion in non-small cell lung cancer cells by regulating miR-330-5p/HMGB3 axis. Pathol Res Pract 216: 153144, 2020.
35. Yang M, Zheng E, Ni J, Xu X, Jiang X and Zhao G: Circular RNA circFOXO3 facilitate non-small cell lung cancer progression through upregulating HMGB3 via sponging miR-545-3p/miR-506-3p. Tissue Cell 75: 101702, 2022.
36. Gao S, Zhang X, Bai W, Wang J and Jiang B: Circ-IGF1R affects the progression of colorectal cancer by activating the miR-362-5p/HMGB3-Mediated Wnt/β-Catenin signal pathway. Biochem Genet 61: 1210-1229, 2023.
37. Yang K, Zhang F, Luo B and Qu Z: CAFs-derived small extracellular vesicles circN4BP2L2 promotes proliferation and metastasis of colorectal cancer via miR-664b-3p/HMGB3 pathway. Cancer Biol Ther 23: 404-416, 2022.
38. Yuan H, Chen B, Chai R, Gong W, Wan Z, Zheng B, Hu X, Guo Y, Gao S, Dai Q, *et al*: Loss of exosomal micro-RNA-200b-3p from hypoxia cancer-associated fibroblasts reduces sensitivity to 5-flourouracil in colorectal cancer through targeting high-mobility group box 3. Front Oncol 12: 920131, 2022.
39. Sun F, Yang X, Song W, Yu N and Lin Q: Tanshinone IIA (TSIIA) represses the progression of non-small cell lung cancer by the circ_0020123/miR-1299/HMGB3 pathway. Mol Cell Biochem 478: 1973-1986, 2023.
40. Wang J, Sheng Z and Cai Y: Effects of microRNA-513b on cell proliferation, apoptosis, invasion, and migration by targeting HMGB3 through regulation of mTOR signaling pathway in non-small-cell lung cancer. J Cell Physiol 234: 10934-10941, 2019.

41. Li X, Wu Y, Liu A and Tang X: MiR-27b is epigenetically down-regulated in tamoxifen resistant breast cancer cells due to promoter methylation and regulates tamoxifen sensitivity by targeting HMGB3. Biochem Biophys Res Commun 477: 768-773, 2016.
42. Yu Q, Li Y, Peng S, Li J and Qin X: Exosomal-mediated transfer of OIP5-AS1 enhanced cell chemoresistance to trastuzumab in breast cancer via up-regulating HMGB3 by sponging miR-381-3p. Open Med (Wars) 16: 512-525, 2021.
43. Tian X, Chang J, Zhang N, Wu S, Liu H and Yu J: MicroRNA-429 acts as a tumor suppressor in colorectal cancer by targeting high mobility group box 3. Oncol Lett 21: 250, 2021.
44. Gu M, Jiang Z, Li H, Peng J, Chen X and Tang M: MiR-93/HMGB3 regulatory axis exerts tumor suppressive effects in colorectal carcinoma cells. Exp Mol Pathol 120: 104635, 2021.
45. Chen X, Zhao G, Wang F, Gao F, Luo H, Wang Y, Du Y, Chen X, Xue C, Dong Z, *et al*: Upregulation of miR-513b inhibits cell proliferation, migration, and promotes apoptosis by targeting high mobility group-box 3 protein in gastric cancer. Tumour Biol 35: 11081-11089, 2014.
46. Song X, Wang H, Wu J and Sun Y: Long noncoding RNA SOX2-OT knockdown inhibits proliferation and metastasis of prostate cancer cells through modulating the miR-452-5p/HMGB3 axis and inactivating Wnt/β-Catenin pathway. Cancer Biother Radiopharm 35: 682-695, 2020.
47. Chen F, Sun F, Liu X, Shao J and Zhang B: Glaucocalyxin A inhibits the malignant progression of epithelial ovarian cancer by affecting the MicroRNA-374b-5p/HMGB3/Wnt-β-catenin pathway axis. Front Oncol 12: 955830, 2022.
48. Sun D, Cao R, Han L, Yu X, Wang H, Wang X and Chen X: Long noncoding RNA brain cytoplasmic RNA 1 induces Cisplatin-resistance of cervical cancer cells by sponging MicroRNA-330-5p and upregulating High-Mobility group Box 3. Gynecol Obstet Invest 87: 200-210, 2022.
49. Song T, Hou X and Lin B: MicroRNA-758 inhibits cervical cancer cell proliferation and metastasis by targeting HMGB3 through the WNT/β-catenin signaling pathway. Oncol Lett 18: 1786-1792, 2019.
50. Sun CX, Zhu F and Qi L: Demethylated miR-216a regulates high mobility group box 3 promoting growth of esophageal cancer cells through Wnt/β-Catenin pathway. Front Oncol 11: 622073, 2021.
51. Chen R, Kang R and Tang D: The mechanism of HMGB1 secretion and release. Exp Mol Med 54: 91-102, 2022.
52. Starkova T, Polyanichko A, Tomilin AN and Chikhirzhina E: Structure and functions of HMGB2 protein. Int J Mol Sci 24: 8334, 2023.
53. Kwak MS, Kim HS, Lkhamsuren K, Kim YH, Han MG, Shin JM, Park IH, Rhee WJ, Lee SK, Rhee SG and Shin JS: Peroxiredoxin-mediated disulfide bond formation is required for nucleocytoplasmic translocation and secretion of HMGB1 in response to inflammatory stimuli. Redox Biol 24: 101203, 2019.
54. Wei T, Liu J, Li C, Tan Y, Wei R, Wang J, Wu H, Li Q, Liu H, Tang Y and Li X: Revealing the extracellular function of HMGB1 N-terminal region acetylation assisted by a protein semi-synthesis approach. Chem Sci 14: 10297-10307, 2023.
55. Elenkov I, Pelovsky P, Ugrinova I, Takahashi M and Pasheva E: The DNA binding and bending activities of truncated tail-less HMGB1 protein are differentially affected by Lys-2 and Lys-81 residues and their acetylation. Int J Biol Sci 7: 691-699, 2011.
56. Pasheva E, Sarov M, Bidjekov K, Ugrinova I, Sarg B, Lindner H and Pashev IG: In vitro acetylation of HMGB-1 and -2 proteins by CBP: The role of the acidic tail. Biochemistry 43: 2935-2940, 2004.
57. He Y, Ding Y, Wang D, Zhang W, Chen W, Liu X, Qin W, Qian X, Chen H and Guo Z: HMGB1 bound to cisplatin-DNA adducts undergoes extensive acetylation and phosphorylation in vivo. Chem Sci 6: 2074-2078, 2015.
58. Zhou S, Lu H, Chen R, Tian Y, Jiang Y, Zhang S, Ni D, Su Z and Shao X: Angiotensin II enhances the acetylation and release of HMGB1 in RAW264.7 macrophage. Cell Biol Int 42: 1160-1169, 2018.
59. Pelovsky P, Pashev IG and Pasheva E: Interplay between in vitro acetylation and phosphorylation of tailless HMGB1 protein. Biochem Biophys Res Commun 380: 138-142, 2009.
60. Zhang X, Wheeler D, Tang Y, Guo L, Shapiro RA, Ribar TJ, Means AR, Billiar TR, Angus DC and Rosengart MR: Calcium/calmodulin-dependent protein kinase (CaMK) IV mediates nucleocytoplasmic shuttling and release of HMGB1 during lipopolysaccharide stimulation of macrophages. J Immunol 181: 5015-5023, 2008.
61. Youn JH and Shin JS: Nucleocytoplasmic shuttling of HMGB1 is regulated by phosphorylation that redirects it toward secretion. J Immunol 177: 7889-7897, 2006.
62. Lv WL, Arnesano F, Carloni P, Natile G and Rossetti G: Effect of in vivo post-translational modifications of the HMGB1 protein upon binding to platinated DNA: A molecular simulation study. Nucleic Acids Res 46: 11687-11697, 2018.
63. Liu Y, Song D, Li S, Guo Z and Zheng P: Click Chemistry-based force spectroscopy revealed enhanced binding dynamics of phosphorylated HMGB1 to cisplatin-DNA. J Am Chem Soc 146: 13126-13132, 2024.
64. Venereau E, Casalgrandi M, Schiraldi M, Antoine DJ, Cattaneo A, De Marchis F, Liu J, Antonelli A, Preti A, Raeli L, *et al*: Mutually exclusive redox forms of HMGB1 promote cell recruitment or proinflammatory cytokine release. J Exp Med 209: 1519-1528, 2012.
65. Taverna S, Tonacci A, Ferraro M, Cammarata G, Cuttitta G, Bucchieri S, Pace E and Gangemi S: High mobility group box 1: Biological functions and relevance in oxidative stress related chronic diseases. Cells 11: 849, 2022.
66. Kazama H, Ricci JE, Herndon JM, Hoppe G, Green DR and Ferguson TA: Induction of immunological tolerance by apoptotic cells requires caspase-dependent oxidation of high-mobility group box-1 protein. Immunity 29: 21-32, 2008.
67. Yang H, Hreggvidsdottir HS, Palmblad K, Wang H, Ochani M, Li J, Lu B, Chavan S, Rosas-Ballina M, Al-Abed Y, *et al*: A critical cysteine is required for HMGB1 binding to Toll-like receptor 4 and activation of macrophage cytokine release. Proc Natl Acad Sci USA 107: 11942-11947, 2010.
68. Raucci A, Di Maggio S, Scavello F, D'Ambrosio A, Bianchi ME and Capogrossi MC: The Janus face of HMGB1 in heart disease: A necessary update. Cell Mol Life Sci 76: 211-229, 2019.
69. Ito I, Fukazawa J and Yoshida M: Post-translational methylation of high mobility group box 1 (HMGB1) causes its cytoplasmic localization in neutrophils. J Biol Chem 282: 16336-16344, 2007.
70. Wu F, Zhao ZH, Ding ST, Wu HH and Lu JJ: High mobility group box 1 protein is methylated and transported to cytoplasm in clear cell renal cell carcinoma. Asian Pac J Cancer Prev 14: 5789-5795, 2013.
71. Vergoten G and Bailly C: N-glycosylation of high mobility group box 1 protein (HMGB1) modulates the interaction with glycyrrhizin: A molecular modeling study. Comput Biol Chem 88: 107312, 2020.
72. Kim YH, Kwak MS, Park JB, Lee SA, Choi JE, Cho HS and Shin JS: N-linked glycosylation plays a crucial role in the secretion of HMGB1. J Cell Sci 129: 29-38, 2016.
73. Bhavnagari H, Raval A and Shah F: Deciphering potential role of hippo signaling pathway in breast cancer: A comprehensive review. Curr Pharm Des 29: 3505-3518, 2023.
74. Zhao Q, Zong H, Zhu P, Su C, Tang W, Chen Z and Jin S: Crosstalk between colorectal CSCs and immune cells in tumorigenesis, and strategies for targeting colorectal CSCs. Exp Hematol Oncol 13: 6, 2024.
75. Lian JW, Li SY, Clarke RB, Howell SJ and Meng QJ: Can we utilise the circadian clock to target cancer stem cells? Cancer Lett 611: 217360, 2024.
76. Nemeth MJ, Kirby MR and Bodine DM: Hmgb3 regulates the balance between hematopoietic stem cell self-renewal and differentiation. Proc Natl Acad Sci USA 103: 13783-13788, 2006.
77. Gu J, Xu T, Zhang CM, Chen HY, Huang QH and Zhang Q: HMGB3 small interfere RNA suppresses mammosphere formation of MDA-MB-231 cells by down-regulating expression of HIF1α. Eur Rev Med Pharmacol Sci 23: 9506-9516, 2019.
78. Leis O, Eguiara A, Lopez-Arribillaga E, Alberdi MJ, Hernandez-Garcia S, Elorriaga K, Pandiella A, Rezola R and Martin AG: Sox2 expression in breast tumours and activation in breast cancer stem cells. Oncogene 31: 1354-1365, 2012.
79. Varisli L, Zoumpourlis P, Spandidos DA, Zoumpourlis V and Vlahopoulos S: ALDH1A1 in breast cancer: A prospective target to overcome therapy resistance (review). Oncol Lett 29: 213, 2025.
80. Ma H, Qi G, Han F, Gai P, Peng J and Kong B: HMGB3 promotes the malignant phenotypes and stemness of epithelial ovarian cancer through the MAPK/ERK signaling pathway. Cell Commun Signal 21: 144, 2023.
81. Wang LK, Xie XN, Song XH, Su T, Chang XL, Xu M, Liang B and Huang DY: Upregulation of miR-200b inhibits hepatocellular carcinoma cell proliferation and migration by targeting HMGB3 protein. Technol Cancer Res Treat 17: 1533033818806475, 2018.

82. Chen X and Zeng L: Ginkgo biloba extract 761 enhances 5-fluorouracil chemosensitivity in colorectal cancer cells through regulation of high mobility group-box 3 expression. Am J Transl Res 10: 1773-1783, 2018.
83. Zhang S, Liu J, Yuan T, Liu H, Wan C and Le Y: Circular RNA 0001313 knockdown suppresses non-small cell lung cancer cell proliferation and invasion via the microRNA-452/HMGB3/ERK/MAPK Axis. Int J Gen Med 13: 1495-1507, 2020.
84. Liu J, Wang L and Li X: HMGB3 promotes the proliferation and metastasis of glioblastoma and is negatively regulated by miR-200b-3p and miR-200c-3p. Cell Biochem Funct 36: 357-365, 2018.
85. Ji F, Yao Z, Liu C, Fu S, Ren B, Liu Y, Ma L, Wei J and Sun D: A novel lnc-LAMC2-1:1 SNP promotes colon adenocarcinoma progression by targeting miR-216a-3p/HMGB3. Heliyon 8: e12342, 2022.
86. Zhao T, He X, Liang X, Kellum AH Jr, Tang F, Yin J, Guo S, Wang Y, Gao Z and Wang Y: HMGB3 and SUB1 bind to and facilitate the repair of N2-Alkylguanine lesions in DNA. J Am Chem Soc 146: 22553-22562, 2024.
87. Ray Chaudhuri A and Nussenzweig A: The multifaceted roles of PARP1 in DNA repair and chromatin remodelling. Nat Rev Mol Cell Biol 18: 610-621, 2017.
88. Li Z, Zhang Y, Sui S, Hua Y, Zhao A, Tian X, Wang R, Guo W, Yu W, Zou K, *et al*: Targeting HMGB3/hTERT axis for radioresistance in cervical cancer. J Exp Clin Cancer Res 39: 243, 2020.
89. Masutomi K, Possemato R, Wong JM, Currier JL, Tothova Z, Manola JB, Ganesan S, Lansdorp PM, Collins K and Hahn WC: The telomerase reverse transcriptase regulates chromatin state and DNA damage responses. Proc Natl Acad Sci USA 102: 8222-8227, 2005.
90. Yang SF, Nelson CB, Wells JK, Fernando M, Lu R, Allen JAM, Malloy L, Lamm N, Murphy VJ, Mackay JP, *et al*: ZNF827 is a single-stranded DNA binding protein that regulates the ATR-CHK1 DNA damage response pathway. Nat Commun 15: 2210, 2024.
91. Saldivar JC, Hamperl S, Bocek MJ, Chung M, Bass TE, Cisneros-Soberanis F, Samejima K, Xie L, Paulson JR, Earnshaw WC, *et al*: An intrinsic S/G2 checkpoint enforced by ATR. Science 361: 806-810, 2018.
92. Liu Q, Guntuku S, Cui XS, Matsuoka S, Cortez D, Tamai K, Luo G, Carattini-Rivera S, DeMayo F, Bradley A, *et al*: Chk1 is an essential kinase that is regulated by Atr and required for the G(2)/M DNA damage checkpoint. Genes Dev 14: 1448-1459, 2000.
93. Mukherjee A, Benhamou LR and Vasquez KM: Abstract 1512: Architectural protein HMGB3 interacts with cisplatin resistance associated overexpressed protein (CROP/LUC7L3) in human cancer cells and modulates cisplatin-DNA adduct removal. Cancer Res 82: 1512, 2022.
94. Kok I, Bayraktar C, Durgun A, Aksu AC, Kayabolen A, Yedier Bayram O, Sur Erdem I and Bagci Onder T: P03.10.A identifying DNA damage response (DDR) related factors Essenti al for radiotherapy response in glioblastoma using a novel CRISPR/Cas9 library, ddrkol. Neuro Oncol 25: ii38, 2023.
95. Li J, Song C, Gu J, Li C, Zang W, Shi L, Chen L, Zhu L, Zhou M, Wang T, *et al*: RBBP4 regulates the expression of the Mre11-Rad50-NBS1 (MRN) complex and promotes DNA double-strand break repair to mediate glioblastoma chemoradiotherapy resistance. Cancer Lett 557: 216078, 2023.
96. Zhuang S, Yu X, Lu M, Li Y, Ding N and Ding Y: High mobility group box 3 promotes cervical cancer proliferation by regulating Wnt/β-catenin pathway. J Gynecol Oncol 31: e91, 2020.
97. Dong S, Pan J, Shen YB, Zhu LX, Chen L, Zhu F, Li H, Shen HX, Xia Q, Wu YJ and Xie XJ: SYT7 plays a role in promoting thyroid cancer by mediating HMGB3 ubiquitination. Endocr Relat Cancer 29: 175-189, 2022.
98. Wang X, Shao X, Li T, Zhang L, Yang Q, Ye W, Tong J, Li Z and Fang X: Pingchuanning Formula suppresses airway inflammation in a rat model of asthmatic cold syndrome by regulating the HMGB1/Beclin-1 axis-mediated autophagy. Nan Fang Yi Ke Da Xue Xue Bao 45: 1153-1162, 2025 (In Chinese).
99. Tong HY, Yang WL, Ma LY, Zhang YD, Wang W, Li KF, Lang W, Wang L, Yang WB and Huang H: HMGB3 as a cargo protein for XPO1: Implications for myelodysplastic syndromes prognosis and treatment. Blood 144: 4570-4571, 2024.
100. Gu J, Xu T, Huang QH, Zhang CM and Chen HY: HMGB3 silence inhibits breast cancer cell proliferation and tumor growth by interacting with hypoxia-inducible factor 1α. Cancer Manag Res 11: 5075-5089, 2019.
101. Zhang K, Liu D, Zhao J, Shi S, He X, Da P, You Y and You B: Nuclear exosome HMGB3 secreted by nasopharyngeal carcinoma cells promotes tumour metastasis by inducing angiogenesis. Cell Death Dis 12: 554, 2021.
102. Khambu B, Yan S, Huda N and Yin XM: Role of High-mobility group Box-1 in liver pathogenesis. Int J Mol Sci 20: 5314, 2019.
103. Patra S, Roy PK, Dey A and Mandal M: Impact of HMGB1 on cancer development and therapeutic insights focused on CNS malignancy. Biochim Biophys Acta Rev Cancer 1879: 189105, 2024.
104. Wang L, Xu P, Li X and Zhang Q: Comprehensive bioinformatics analysis identified HMGB3 as a promising immunotherapy target for glioblastoma multiforme. Discov Oncol 16: 478, 2025.
105. Li M, Cai Y, Zhao H, Xu Z, Sun Q, Luo M, Gu L, Meng M, Han X and Sun H: Overexpression of HMGB3 protein promotes cell proliferation, migration and is associated with poor prognosis in urinary bladder cancer patients. Tumour Biol 36: 4785-4792, 2015.
106. Ke Y, Mai J, Liu Z, Xu Y, Zhao C and Wang B: Interfering HMGB3 release from cancer-associated fibroblasts by miR-200b represses chemoresistance and epithelial-mesenchymal transition of gastric cancer cells. J Gastrointest Oncol 13: 2197-2218, 2022.
107. Zhu L and Chen L: Progress in research on paclitaxel and tumor immunotherapy. Cell Mol Biol Lett 24: 40, 2019.
108. Singh A, Srivastav S, Singh MP, Singh R, Kumar P and Kush P: Recent advances in phytosomes for the safe management of cancer. Phytomedicine Plus 4: 100540, 2019.
109. Zhou X, Zhang Q, Liang G, Liang X and Luo B: Overexpression of HMGB3 and its prognostic value in breast cancer. Front Oncol 12: 1048921, 2022.
110. Fu X, Li P, Zhou Q, He R, Wang G, Zhu S, Bagheri A, Kupfer G, Pei H and Li J: Mechanism of PARP inhibitor resistance and potential overcoming strategies. Genes Dis 11: 306-320, 2024.
111. Luo B, Zheng H, Liang G, Luo Y, Zhang Q and Li X: HMGB3 contributes to Anti-PD-1 resistance by inhibiting IFN-γ-Driven ferroptosis in TNBC. Mol Carcinog 64: 490-501, 2025.
112. Yamada Y, Nishikawa R, Kato M, Okato A, Arai T, Kojima S, Yamazaki K, Naya Y, Ichikawa T and Seki N: Regulation of HMGB3 by antitumor miR-205-5p inhibits cancer cell aggressiveness and is involved in prostate cancer pathogenesis. J Hum Genet 63: 195-205, 2018.
113. Zhong X, Zhang S, Zhang Y, Jiang Z, Li Y, Chang J, Niu J and Shi Y: HMGB3 is associated with an unfavorable prognosis of neuroblastoma and promotes tumor progression by mediating TPX2. Front Cell Dev Biol 9: 769547, 2021.
114. Zhang Z, Chang Y, Zhang J, Lu Y, Zheng L, Hu Y, Zhang F, Li X, Zhang W and Li X: HMGB3 promotes growth and migration in colorectal cancer by regulating WNT/β-catenin pathway. PLoS One 12: e0179741, 2017.
115. Zhao Y, Lv HJ, Deng XY, Chen P, Garstka MA, Shi BY and Fu J: Translocated HMGB3 is involved in papillary thyroid cancer progression by activating cytoplasmic TLR3 and transmembrane TREM1. Cell Cycle 22: 2584-2601, 2023.
116. Song N, Liu B, Wu JL, Zhang RF, Duan L, He WS and Zhang CM: Prognostic value of HMGB3 expression in patients with non-small cell lung cancer. Tumour Biol 34: 2599-2603, 2013.