

Mechanisms involved in the HMGB1 modulation of tumor multidrug resistance (Review)

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Received March 5, 2023; Accepted June 22, 2023

DOI: 10.3892/ijmm.2023.5272

Abstract. Tumor multidrug resistance (MDR) remains one of the most challenging barriers to successful cancer treatment. Several previous studies have suggested that high mobility group box 1 (HMGB1) may be a promising therapeutic target for overcoming cancer drug resistance. Emerging evidence has indicated that HMGB1 functions as a 'double-edged sword' that plays both pro- and anti-tumor roles in the development and progression of multiple types of cancer. HMGB1 has also been found to be a key regulator of several cell death and signaling pathways, and is involved in MDR by mediating cell autophagy and apoptosis, ferroptosis, pyroptosis and multiple signaling pathways. Additionally, HMGB1 is regulated by a variety of non-coding RNAs (ncRNAs), such as microRNAs, long ncRNAs and circular RNAs that are involved in MDR. Thus far, studies have been conducted to identify strategies with which to overcome HMGB1-mediated MDR by the targeted silencing of HMGB1 and the targeted interference of HMGB1 expression using drugs and ncRNAs. Therefore, HMGB1 is closely associated with tumor MDR and is a promising therapeutic target.

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1. Introduction

With an ever-increasing aging population, the incidence of cancer is rising. Malignant tumors have high mortality rates and severely endanger human health. The drug resistance and metastasis of malignant tumors are the primary causes of mortality among cancer patients and are the major obstacles to cancer treatment at present (1). The initial solution to the problem of resistance to single-agent chemotherapy was a combination of drugs with non-overlapping mechanisms of action or combination chemotherapy. After almost 50 years of the application of combination chemotherapeutic regimens, the role of combination chemotherapy has largely stalled. Surgery, radiotherapy and combination chemotherapy are not sufficient to cure multiple tumors (2). Targeted therapies and immunotherapies represent a major advancement and breakthrough in the field of chemotherapy. However, studies have demonstrated that despite the notable efficacy of targeted therapies and immunotherapy in the treatment of tumors, drug resistance still emerges (3-5). Drug resistance remains a major limiting factor in achieving a cure for patients with cancer (6). That is, overcoming multidrug resistance (MDR) in patients with cancer remains a significant challenge.

MDR occurs in tumor cells during chemotherapy, and is a phenomenon in which tumor cells become resistant to one chemotherapeutic drug and then become resistant to other unexposed chemotherapeutic drugs of different origins, structures and mechanisms of action. Tumor MDR is mediated by multiple genes and factors, the mechanisms of which are complex and diverse. The MDR phenotype is characterized by cross-resistance to multiple anticancer drugs with different

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Key words: tumor multidrug resistance, high mobility group box 1, apoptosis and autophagy, pyroptosis, ferroptosis, non-coding RNA, traditional Chinese medicine, nanoparticles

structures and mechanisms of action. The multiple factors mediating MDR may include host factors, tumor factors as well as tumor-host interactions (7). More accurately, tumor cells develop MDR during chemotherapy. MDR can occur as both primary and acquired resistance, with the former being the phenomenon of insensitivity when first exposed to the drug, while acquired resistance refers to the phenomenon of a tumor being sensitive to the drug and only becoming insensitive following a period of treatment with chemotherapy (8). The acquisition of drug resistance is mediated by mutations, changes in gene expression, selective splicing and post-translational protein modifications, etc. (9). Acquired drug resistance is a common type of MDR. The most common mechanism of drug resistance relies on drug efflux from cancer cells mediated by ATP-binding cassette (ABC) transport proteins (10). Non-transport protein mechanisms, such as the persistence of cancer stem cells (CSCs) (11), interactions of the tumor microenvironment and epithelial-mesenchymal transition (12), enhanced DNA damage repair (13), epigenetic alterations (14), and the suppression of apoptosis (15) are also common causes of treatment failure.

A large number of discovered drugs and methods have the potential to reverse or antagonize resistance to MDR by various resistance mechanisms. These reversal agents include both chemically synthesized small molecules and large polymers, as well as natural products such as traditional Chinese medicines (TCMs) (16). Inhibitors studied for P-glycoprotein (ABCB1) include verapamil, dexverapamil, zosuquidar and elaquidar amongst others (17,18), although with limited efficacy. TCMs, including compound preparations and the screening of natural active ingredients with resistance to MDR, primarily including flavonoids (19,20), saponins (21,22) and alkaloids (23) have exhibited some success in overcoming tumor drug resistance, but have not been widely adopted. Nanodrug delivery systems are discoveries in technology for overcoming MDR. Nanoparticles (NPs) can enhance the therapeutic efficacy of anticancer drugs at the target site of action, which can limit the adverse systemic effects of chemotherapeutic drugs and reduce drug resistance. In addition, other innovative strategies include RNA interference as a biological process used to inhibit or knockdown the expression of specific genes, natural products such as MDR modulators with minimal systemic toxic effects, interference with the function of proteins involved in drug efflux, and physical approaches such as combinations also highlighting conventional drug administration using thermal, ultrasound and photodynamic strategies (24). Due to their tumor-targeting ability, NPs are a novel means of enhancing the therapeutic effects of anticancer drugs at the target site of action, which can limit the adverse systemic effects of chemotherapeutic drugs and reduce drug resistance. NPs that allow multi-target and multi-pathway combination therapies, the delivery of a stable dosage, or easy utilization by the organism are considered promising means of overcoming drug resistance and are under further investigation.

High mobility group box 1 (HMGB1) has been shown to be involved in inflammation, angiogenesis, DNA repair, tumor invasion, progression, metastasis and resistance to treatment (25-27). In the present review, the association between HMGB1 and MDR is described with an emphasis on MDR mechanisms, in an aim to provide a theoretical foundation

for exploring novel strategies with which to overcome drug resistance.

2. HMGB1 and its roles in tumors

HMGB family of proteins. HMGB protein family members include HMGB1, HMGB2, HMGB3 and HMGB4 (28). HMGB1, HMGB2 and HMGB3 have similar biochemical structures and share similar biochemical properties, including two HMG box structural domains and an acidic tail. HMGB4 contains two HMG boxes, but lacks an acidic tail (29). HMGB proteins are small structural DNA-binding proteins that regulate several genomic processes, such as DNA damage repair, nucleosome sliding, telomere homeostasis and transcription (30-32). Previous studies have reported that the HMGB family members are involved in various pathological processes in the human body, including inflammation (33), multiple immune system disorders (34) and multiple types of cancer (35-44). The HMGB family members are extensively involved in cellular processes in tumor cells, including proliferation, metastasis, autophagy, apoptosis and drug resistance (32).

HMGB1 structure, distribution and function. HMGB1 is a non-histone chromatin-associated protein that is widely distributed in eukaryotic cells and consists of 215 amino acids, including the DNA-binding region A-box (amino acid sequence 1-79), B-box (amino acid sequence 89-163) and the hydroxyl-terminal domain (C-tail) (amino acid sequence 186-215). Residues 7-74 bind to the suppressor gene p53 to regulate the transcription of target genes; residues 89-108 bind to Toll-like receptor (TLR)4 to promote the inflammatory response of the body; and residues 150-183 bind to the receptor for advanced glycation end products (RAGE) to promote cell migration. The overexpression of HMGB1 in cells with C-tail deletion can affect the transcription, translation and expression of downstream genes (45), through the regulation of DNA damage repair and genome stability maintenance (46). HMGB1 is active both intracellularly and extracellularly and the biological functions of the pro- and antitumor effects of HMGB1 are closely related to its expression levels and subcellular distribution. In the nucleus, HMGB1 can function as a DNA molecular chaperone to participate in DNA replication, binding and damage repair, maintaining nuclear homeostasis and exerting antitumor effects through a series of regulatory transcriptional pathways. In the cytoplasm, HMGB1 participates in the immune response by increasing autophagy, inhibiting apoptosis and regulating mitochondrial function (47). HMGB1 is secreted extracellularly as an immune signal; through interactions with ligand-receptors, extracellular HMGB1 functions as a typical damage-associated molecular pattern (DAMP) that functions as a cytokine directly or indirectly on TLRs, the major receptors of HMGB1, and on RAGE, thereby regulating immune cells and specific signaling pathways in the tumor microenvironment, including inflammation, proliferation, metastasis, autophagy and specific signaling pathways (such as RAGE-PI3K/AKT, HMGB1/RAGE/IL-8 pathway, etc.) (41,46,48-50). The aberrant expression of HMGB1 can function as a double-edged sword, exerting both pro- and antitumor effects during tumorigenesis and development.

Evidence of HMGB1 involvement in tumors. HMGB1 is involved in tumorigenesis and development. A high expression of HMGB1 has been detected in several types of tumors, suggesting that HMGB1 is closely associated with tumor progression. With the aid of the GEPIA database (<http://GEPIA.cancer-pku.cn>), HMGB1 has been found to be highly expressed in colon adenocarcinoma, diffuse large B cell lymphoma, glioblastoma (GBM), low-grade glioma, pancreatic adenocarcinoma, rectum adenocarcinoma, stomach adenocarcinoma and thymoma. HMGB1 has been found to be involved in a variety of malignancies, including liver cancer (37,51,52), breast cancer (50,53), multiple myeloma (MM) (25), thyroid cancer (38), rectal cancer (54), cutaneous melanoma (55), lung cancer (56), gastric cancer (57) and leukemia (58). In studies on hepatocellular carcinoma (HCC), HMGB1 and the RICTOR 3'untranslated region (UTR) epigenetically promote malignant proliferation, self-renewal and tumorigenesis (37), and hypoxia-induced HMGB1 and mitochondrial DNA mediate tumor growth via TLRs (59). In breast cancer, HMGB1 expression levels have been shown to be associated with sensitivity to chemotherapy, with a higher HMGB1 expression in adriamycin-resistant breast cancer cells than in parental cells (60). HMGB1 has also been found to activate fibroblast-promoted breast cancer cell metastasis through RAGE/aerobic glycolysis (61). Lee *et al* (62) found that cytoplasmic HMGB1 expression was associated with the levels of tumor-infiltrating lymphocytes, and it has also been found to be a key factor in tamoxifen treatment resistance (53). HMGB1 and RAGE may be used to predict and assess the efficacy of breast cancer treatment (62). It has been suggested that HMGB1 is a key regulator of hematopoietic malignancies and that the dysfunction of HMGB1 may contribute to the development of hematological malignancies by interfering with the hematopoietic function of bone marrow (63). MM cell lines and primary MM samples express high levels of HMGB1, which is negatively associated with the 3-year survival of patients with MM (25). During the development of acute myeloid leukemia (AML), HMGB1 is secreted to induce the production of TNF- α and subsequently, IL-1 β , which stimulates the release of stem cell factor from endothelial cells, and also induces the secretion of angiogenic vascular endothelial growth factor (VEGF), which further promotes the proliferation of AML cells (64). Another study found that HMGB1 induced cell proliferation and myeloid differentiation blockade, inhibited the apoptosis of AML cells, and that chidamide, a selective histone deacetylase inhibitor, exhibited good therapeutic efficacy in AML by downregulating HMGB1 expression (65). In chronic myeloid leukemia (CML), cytoplasmic HMGB1 has been found to reduce the sensitivity of CML cells to anticancer drugs by upregulating the autophagic pathway. HMGB1 overexpression increases the transcriptional activity of JNK, ERK and Beclin-1 to regulate autophagy (66).

The upregulation of HMGB1 is commonly observed in thyroid cancer tissues and is strongly associated with worse overall lymph node metastasis and clinical staging. HMGB1 knockdown significantly inhibits autophagy, sodium/iodide symporter (NIS) degradation and iodine uptake in Hank's balanced salt solution (HBSS)-treated cells. In addition, HBSS enhances reactive oxygen species (ROS)-maintained autophagy and promotes the cytoplasmic translocation of

HMGB1. HMGB1 knockdown inhibits LC3-II transactivation and NIS degradation via AMP-activated protein kinase (AMPK)/mTOR-dependent signaling pathways by regulating ROS production, but not adenosine triphosphate (ATP) (38), and HMGB1 knockdown has been shown to inhibit cell migration and invasion (67). The nuclear expression of HMGB1 has been found to be significantly higher in colorectal cancer (CRC) and colorectal adenoma tissue samples (84.0 and 92.6%, respectively) than in normal colorectal tissue (15.0%), and a positive cytoplasmic expression of HMGB1 is significantly higher in CRC tissues (25.2%) compared with colorectal adenoma (11.8%) and normal colorectal tissue (0.0%). A positive cytoplasmic expression of HMGB1 is associated with high-grade CRC and a poor prognosis, and negatively associated with a strong positive nuclear HMGB1 expression in CRC tissue specimens. Patients with CRC with a strong positive nuclear HMGB1 expression exhibited an improved prognosis compared with other patients with CRC (68). HMGB1 is involved in the tumorigenesis of colitis-associated CRC via the ERK1/2 pathway (54). Furthermore, HMGB1 exposure has been shown to lead to CRC cell proliferation and CRC stem cell expansion (69). The low expression of HMGB1 inhibits cell proliferation and migration in CRC (70). In lung cancer, the overexpression of HMGB1 has been shown to promote lung cancer invasion and metastasis by promoting matrix metalloproteinase (MMP)-2 mediated-invasion and metastasis through an NF- κ B-dependent mechanism; thus, HMGB1 is a potential prognostic marker for lung cancer (71). HMGB1 expression has also been shown to be upregulated in gastric cancer tissues, and an increased HMGB1 expression is associated with a poorer prognosis of patients with gastric cancer (57). Gastric cancer cell-derived exosomes induce autophagy and pro-tumor activation via HMGB1/TLR4/NF- κ B signaling, and induce neutrophil autophagy and pro-tumor activation (57). RAGE and HMGB1 may regulate polypyrimidine tract-binding protein 1 expression and inhibit cellular glycolysis, thereby affecting gastric cancer cell proliferation and migration (72). Taken together, HMGB1 is closely related to the development and progression of a variety of tumors.

Potential mechanisms of HMGB1 in cancer. In a review summary study on the biological functions and therapeutic potential of HMGB family members in human cancer (32), several key points of the role of HMGB1 in carcinogenesis were summarized, including two primary aspects: Angiogenesis and migration. HMGB1 promotes the expression of neurofibrillin-1, VEGFA, VEGF receptors-1 and -2 and platelet-derived growth factor (73), which induces angiogenesis, and also binds to RAGE to activate NF- κ B (74). In terms of tumor migration, HMGB1 binds to RAGE and mediates epithelial-mesenchymal transition (EMT) via MMP-7, p-NF- κ B and Snail (75); HMGB1 binds to RAGE and mediates EMT via NF- κ B, p65, inducible nitric oxide synthase and MMP-9 production, and the phosphorylation of Rac-1, ERK1 and AKT (76); HMGB1 binds to TLR4 and upregulates downstream signaling and PI3K signaling pathways (77); secreted HMGB1 targets other stromal cells and release factors, which leads to the hydrolytic degradation of ECM proteins (78). In addition, a number of microRNAs (miRNAs/miRs), such as miR-200-c (79) and miR-325-3p (80) inhibit HMGB1 expression and translocation.

In summary, HMGB1 is involved in the development of a variety of tumors by regulating tumorigenesis via several mechanisms.

3. Mechanisms of HMGB1 in tumor MDR signaling

A study on the role of the induction of secretory clusterin (sCLU) by HMGB1 in chemoresistance in human prostate tumor cells found that a variety of chemotherapeutic agents currently in use can result in the release of HMGB1 from tumor cells (81). The acquisition of chemoresistance may be achieved through the regulation of an HMGB1/TLR4-RAGE/sCLU axis triggered by dead cells, thus providing a survival advantage to residual living tumor cells. That study suggested a link between HMGB1 and the development of drug resistance in tumor cells. Cell death is the outcome of successful chemotherapeutic action (82). The authors then found numerous studies (as described below) to confirm that HMGB1 is associated with apoptosis, necroptosis, autophagy, pyroptosis and ferroptosis in tumors.

HMGB1 participates in tumor MDR via autophagy and apoptosis. One of the well-known mechanisms of chemoresistance is the mitochondrial death pathway, which is activated when cells are exposed to increased levels of stress, such as during treatment with chemotherapy. Mitochondrial autophagy or mitochondrial selective autophagy is essential for cell quality regulation, as it effectively breaks down, removes and recycles defective or damaged mitochondria. Cancer cells use mitophagy to rapidly remove damaged mitochondria to mediate their drug resistance, which affects the efficacy of tumor chemotherapy and the degree of drug resistance (83). The activation of autophagy by chemotherapeutic agents contributes, at least in part, to the development of MDR (84). Therefore, the combination of chemotherapeutic drugs with appropriate autophagy inhibitors has been proposed as an effective method with which to reverse the transformation of tumor cells from chemotherapy-resistant to sensitive. Chloroquine is an effective autophagy blocker that has been shown to enhance chemotherapy sensitivity in cancer (85).

Apoptosis is a programmed cell death (PCD) process that usually occurs through one of two pathways, the endogenous and exogenous pathways. The intrinsic pathway of apoptosis involves the mitochondria and is activated by a decrease in mitochondrial membrane potential, the release of cytochrome *c* from the mitochondria into the cytoplasm, and the activation of the performer cysteine protease (86). Cancer chemotherapy generates stress signals that act on mitochondria to initiate apoptosis. Significantly reduced apoptosis in MDR tumor cells acquired in children with relapsed neuroblastoma (87) suggests that mitochondria-associated apoptosis is involved in the mechanism of tumor MDR.

Both apoptosis (self-killing) and autophagy (self-eating) are evolutionarily conserved processes whose interactions affect anticancer drug sensitivity and cell death. The inhibition of the PARP1/HMGB1 pathway reduces autophagy and increases apoptosis. HMGB1 is a significant upstream regulator of autophagy, maintaining a homeostatic balance between apoptosis and autophagy (88). The interaction between apoptosis and autophagy has been shown to affect anticancer drug

sensitivity and cell death in HCC cells and tumor models, and HepG2 cells exhibit an enhanced sensitivity to cisplatin when HMGB1 inhibitors and autophagy inhibitors are used (89). The REDOX status of HMGB1 can regulate the autophagy or apoptosis of tumor cells. The reduced state of HMGB1 induces Beclin-1-dependent autophagy by acting on the RAGE receptor, thereby promoting the resistance of colon cancer cells to radiation and chemotherapy. By contrast, the oxidized state of HMGB1 increases the cytotoxicity of the drug, thereby inducing apoptosis via the mitochondrial pathway (90). Endogenous HMGB1 is a key pro-autophagic protein that enhances cell survival and limits programmed apoptotic cell death. HMGB1 induces resistance to chemotherapy by upregulating autophagy through three different mechanisms: Nuclear HMGB1 upregulating autophagy through HSPB1, cytoplasmic HMGB1 binding Beclin-1 and extracellular HMGB1, leading to advanced glycosylation end-product specific receptor (AGER)-mediated class III PI3K activation (91,92).

HMGB1-mediated autophagy and apoptosis have been demonstrated in several tumor MDR studies, by promoting autophagy and inhibiting apoptosis induced by anticancer drugs, which has been identified as a key mechanism in the development of MDR. In liver cancer, the HMGB1-mediated activation of autophagy has been found to be involved in the development of cisplatin resistance in HepG2 cells (93). It has been found that morin hydrate enhances the sensitivity of HCC cells and xenografts to cisplatin chemotherapy by downregulating PARP-1-HMGB1-mediated autophagy (89). In hepatoma cells, HepG2, HMGB1 and p53 have been found to jointly provide a delicate balance between autophagy and apoptosis (94). In breast cancer, the inhibition of autophagy has been found to increase paclitaxel-induced apoptosis and enhance the sensitivity of MCF-7 cells to paclitaxel (95). HMGB1 is a target gene and autophagy regulator of miR-129-5p, and interference with HMGB1 expression enhances the chemosensitivity of paclitaxel by inhibiting autophagy and inducing the apoptosis of MCF-7 cells (95). In a previous study, the overexpression of HMGB1 in doxorubicin (DOX)-resistant MCF-7 breast cancer cells significantly reversed apoptosis promotion and autophagy inhibition mediated by miR-142-3p upregulation (60). Zhang *et al* (96) found that pediatric AML bone marrow and cell lines exhibited a high expression of HMGB1, and miR-451 exerted tumor suppressive effects by targeting and modulating HMGB1 to enhance cell death and reduce autophagy in AML cells. In a study on thyroid cancer, the higher expression of HMGB1 was observed in vemurafenib-resistant thyroid cancer BCPAP-R cells (97). The overexpression of HMGB1 attenuated the sensitivity of BCPAP cells to vemurafenib by increasing cell viability and decreasing apoptosis and caspase-3 activity. HMGB1 targeting inhibited vemurafenib-induced autophagy. Blocking the autophagy pathway with the autophagy inhibitor, 3-methyladenine, or knocking out HMGB1, sensitized BCPAP-R cells to vemurafenib (97). In a study on skin cancer, autocrine HMGB1 was found to regulate autophagy via a RAGE/HMGB1/ERK1/2-dependent pathway, thereby protecting keratinocytes from apoptosis upon UV irradiation (98). GBM exhibits a high autophagic activity, where YAP overexpression enhances autophagy in glioma cells, and the downregulation of HMGB1 eliminates the effects of

YAP on autophagy and glioma growth, suggesting that YAP promotes glioma progression by enhancing HMGB1-mediated autophagy (39). It has been shown that HMGB1-inducible p62 overexpression promotes EMT in glioblastoma cells (99). In their study on the chemosensitization of rectal cancer, Liu *et al* (100) found that oxaliplatin administration significantly enhanced the expression of HMGB1, which regulated the autophagic response and negatively regulated apoptosis. Following HMGB1 knockdown in rectal cancer cells, the cells were treated with oxaliplatin, and the autophagy response decreased, whereas apoptosis increased (100). In a study on pancreatic cancer, triphorone inhibited autophagy and MDR1 expression in pancreatic cancer cells through an HMGB1/RAGE/PI3K/Akt axis (101). The results of another study on the resistance mechanisms of sunitinib, a multi-kinase inhibitor approved for multiple cancer indications, suggested that HMGB1 controlled TP53 autophagic degradation through the regulation of its nucleus-to-cytoplasm translocation, thereby inhibiting sunitinib resistance (102).

In summary, HMGB1 functions as an immune signal and can be considered an autophagy inducer, regulating various autophagic pathways to inhibit or promote tumor progression. The interaction between autophagy and apoptosis affects cell death and anticancer drug sensitivity in various cancer cell lines, and HMGB1-mediated autophagy and apoptosis are involved in MDR.

Ferroptosis is involved in HMGB1-related tumor MDR. Ferroptosis is a newly discovered form of regulated cell death that can be induced by small molecule compounds or drugs. First proposed in 2012 by Dixon *et al* (103), ferroptosis is an iron-dependent and peroxide-driven form of cell death associated with multiple metabolic disorders and imbalances in body homeostasis. The primary biochemical features of ferroptosis are iron accumulation and lipid peroxidation. Glutathione peroxidase 4 (GPX4) activity prevents the accumulation of lipid ROS, and ferroptosis can be triggered by the inhibition of glutathione (GSH) or GPX4 biosynthesis (104). Ferrous ions generate large quantities of ROS through the Fenton reaction, leading to lipid peroxidation. If GPX4 activity decreases, the cellular antioxidant capacity is reduced and the excessive accumulation of ROS is not removed in a timely manner, which leads to oxidative stress, causing oxidative damage to the cell and consequently ferroptosis (105).

It has been shown that ferroptosis is involved in a variety of diseases, including neurodegenerative diseases (such as Alzheimer's disease and Parkinson's disease, amongst others), strokes, tumors and other diseases, and that ferroptosis plays a crucial role in the development and progression of these diseases (106). Compared to normal cells, cancer cells are more iron-dependent than normal cells for maintaining cell proliferation and promoting cell expansion, and this increased need for iron renders cancer cells more susceptible to ferroptosis (107). A review article on studies using iron death as a therapeutic target in oncological disease focused on two primary areas for intervention: On the one hand, the use of ferroptosis inhibitors (primarily ferrostatin-1, liproxstatin-1, vitamin E and iron chelators) and the upregulation of GPX4 are effective in inhibiting ferroptosis to prevent the accumulation of lipid ROS, attenuating progression and improving clinical

symptoms; on the other hand, the inhibition or promotion of GPX4 degradation, as well as the reduction of coenzyme Q10, achieved through peroxide, iron, or polyunsaturated fatty acid overload, and the induction of lipid peroxidation, improve the clearance of specific cell populations (e.g., specific tumor types) (108). In cancer cells, metabolic rates, the levels of ROS and iron content are higher than those in normal cells (109). Tumor cells usually contain large quantities of H₂O₂, and ferrous/iron ions react with excessive H₂O₂ to produce hydroxyl radicals in the cells and induce ferroptosis in tumor cells (110). Based on these features, ferroptosis in cancer cells can inhibit tumor growth (106).

Ferroptosis is associated with HMGB1 in disorders, including inflammation and neoplasia. Extracellular HMGB1 generally functions as a DAMP molecule following active secretion or passive release, controlling inflammatory and immunological responses via various receptors or direct absorption. A variety of variables influence HMGB1 secretion and release, including post-translational changes (acetylation, ADP-ribosylation, phosphorylation and methylation) and PCD (apoptosis, pyroptosis, necrosis, alkalosis and ferroptosis) (111). Ferroptosis activators induce the release of HMGB1, and autophagy promotes the acetylation of HMGB1 in ferroptosis cells to promote the release of HMGB1. HMGB1 mediates the inflammatory response in ferroptosis through the HMGB1/AGER pathway. HMGB1 inhibition or AGER deficiency attenuates the iron-dependent cell-induced inflammatory response in macrophages, suggesting that targeting HMGB1 release can limit the iron inflammatory response during ferroptosis (112). By constructing a model of induced ferroptosis, three stages of iron death have been identified: i) The 'initial' stage related to lipid peroxidation; ii) the 'intermediate' stage related to ATP release; and iii) the 'terminal' stage is characterized by the release of HMGB1 and the loss of plasma membrane integrity (113). In another study, HMGB1 was shown to be passively released during ferroptosis, where it serves as a signal associated with early ferroptosis immunogenicity in cancer cells (114). In a study on skin inflammation induced by ferroptosis in keratinocytes following UV-B radiation, the inhibition of ferroptosis prevented the release of HMGB1 from human epidermal keratinocytes and blocked necroinflammation in the skin of UV-B radiation-exposed mice (115). In another study on the role and mechanisms of dexamethasone in adriamycin-induced ferroptosis and cardiomyopathy in rats, molecular experiments were performed to detect ferroptosis in adriamycin-treated rats with the down-regulation or overexpression of the HMGB1 gene (116). The overexpression of HMGB1 promoted adriamycin-induced ferroptosis and cardiotoxicity in rats, while the silencing of HMGB1 resulted in the opposite effect. Dexamethasone had a protective effect on ferroptosis and cardiomyopathy in rats by regulating HMGB1 (116).

It has been found that HMGB1 and ferroptosis are associated with tumor MDR, and its drug-resistance mechanism has emerged as a possible therapeutic target. Friedman Angeli *et al* (117) argued that ferroptosis is present at the crossroads of cancer-acquired resistance and immune evasion, that ferroptosis may act as a double-edged sword in tumors, and that it is critical to identify the difference between ferroptosis that inhibits tumor growth and ferroptosis that drives

cancer progression. Metabolic reorganization is critical for the persistence, dedifferentiation and expansion of cancer cells, and in certain cases, this metabolic reorganization is associated with acquired ferroptosis. The ferroptosis-sensitive state is what allows cancer cells to produce lipid-derived mediators that regulate intracellular and intercellular signaling pathways, including receptor tyrosine kinase (RTK) signaling, leading to cancer cell growth. Furthermore, the complex interactions between different lipid oxidases (such as LOXs and PTGS2) highlight novel possibilities to bind and regulate them at the tumor site, thus allowing an effective immune response and enhancing the immunogenicity of ferrophilic cells. A study on leukemia found that HMGB1 plays a critical role in both leukemia pathogenesis and chemotherapy resistance. Ferroptosis agonists sensitize chemotherapy by enhancing ROS levels, thereby promoting the cytoplasmic translocation of HMGB1 and enhancing ferroptosis, and HMGB1 is a novel modulator of iron death through the RAS-JNK/p38 pathway and a potential drug target for therapeutic intervention in patients with leukemia (58). Lipocalin 2 is a siderophore-binding protein that regulates iron homeostasis. Lipocalin 2 can promote tumor growth and chemoresistance by inhibiting ferroptosis in CRC. In a previous study, the inhibition of Lipocalin 2 function by monoclonal antibodies reduced chemoresistance in the xenograft mouse model (118). In another study, cell death significantly increased in paclitaxel-resistant persistent cancer cells compared to parental cells when exposed to ferroptosis inducers inhibiting xCT: Erastin, sulfasalazine and cyst(e)ine deprivation (119). Ferroptosis is relatively insensitive in cisplatin-resistant head and neck cancer cells, and ferroptosis agonists are expected to exhibit a chemosensitizing effect (120).

In summary, ferroptosis as a new mode of PCD, is closely related to tumor pathogenesis and drug resistance mechanisms. The release of HMGB1 is closely related to ferroptosis. The interaction mechanism between HMGB1 and ferroptosis is a potential therapeutic target for tumor therapy, which is worthy of further investigations.

Pyroptosis is involved in HMGB1-related tumor MDR. Pyroptosis is a unique form of PCD characterized by DNA fragmentation, chromatin condensation, cell swelling with the appearance of large bubbles and the leakage of cell contents, accompanied by inflammation and membrane disruption (121). Pyroptosis is divided into a typical pathway triggered by caspase-1 and an atypical pathway independent of caspase-2. In general, the pyroptosis process can be divided into four main stages: i) The capture of the stimulus signal; ii) transmission of the stimulus signal; iii) the activation of the pyroptosis actuator; and iv) the execution of pyroptosis. Pyroptosis plays a crucial role in cancer initiation, progression and metastasis, and it also influences immunotherapy outcomes by affecting immune cell infiltration (122).

Pyroptosis is related to the sensitivity of tumor chemotherapy in liver cancer, gastric cancer, non-small cell lung cancer (NSCLC) and rectal cancer. Sorafenib is a kinase inhibitor with direct effects on cancer cells and angiogenesis, inducing the pyroptosis of macrophages and releasing pro-inflammatory cytokines. Natural killer cells are then activated to ultimately eliminate HCC cells (123). As

previously demonstrated, lipopolysaccharide (LPS) from Gram-negative bacterial outer membranes enhances sensitivity to oxaliplatin in rectal cancer by inducing the gasdermin D (GSDMD)-mediated pyroptosis of HT29 cells (124). The campothecin analog, FL118, has been shown to inhibit rectal cancer growth and metastasis by inducing NLR family pyrin domain containing 3 (NLRP3)/caspase-1-mediated pyroptosis (125). It has been shown that gasdermin E (GSDME) mediates the lobaplatin-induced pyroptosis downstream of ROS/JNK/Bax-mitochondrial apoptosis pathway and caspase-3/-9 activation in colon cancer cells (126). The activation of the NLRP3 inflammasome and caspase-1 by simvastatin can stimulate pyroptosis activation through the canonical pathway and inhibit the migration of NSCLC (127). It is hypothesized that pyroptosis plays a 'double-edged sword' role in tumors. On the one hand, pyroptosis alters the tumor microenvironment and inhibits tumor growth by releasing inflammatory factors, such as IL-1 β and IL-18 (128). On the other hand, pyroptosis reduces the immune response of the body to tumor cells and accelerates the growth rate of different types of cancers (129). In the treatment of malignant tumors, appropriate chemotherapeutic drugs can be selected according to the expression levels of DFNA5/GSDME, such that it can be upregulated in tumor cells, thereby increasing the sensitivity to chemotherapeutic drugs and reducing drug resistance. Thus, induced pyroptosis may play a major role in the treatment of cancer (130). It is important to determine the balance between the induction or inhibition of pyroptosis and the precise improvement of chemotherapy sensitivity in different types of cancer.

HMGB1 interacts with pyroptosis and is involved in the pathogenesis of several diseases. GSDMD indirectly regulates the release of HMGB1 in cases where HMGB1 is not released when pyroptosis is suppressed, inflammatory vesicle activation and IL-1 β secretion (131). The depletion of hepatocyte HMGB1, the inhibition of hepatocyte HMGB1 release, and the neutralization of extracellular HMGB1 or RAGE deficiency prevent caspase-11-dependent pyroptosis and death from endotoxemia and bacterial sepsis (132). These findings suggest that HMGB1 interacts with LPS to mediate caspase-11-dependent focal death in lethal sepsis (132). As previously demonstrated, in a rat model of chronic liver failure aggravation, the percentage of hepatocyte pyroptotic cells was significantly increased, and the expression levels of pyroptosis-related genes and proteins in liver tissue and serum were significantly increased (133). However, these phenomena were attenuated by the inhibition of HMGB1, and the dual inhibition of HMGB1 and caspase-1 exerted a more potent effect. GSDME-mediated cellular pyroptosis promotes CRC development through the release of HMGB1. Previous *in vivo* experiments using mice demonstrated that the number and size of tumors in mice were reduced by interfering with HMGB1, and *in vitro* experiments also revealed that HMGB1 induced CT26 colon cancer cell proliferation and proliferating cell nuclear antigen expression through the ERK1/2 pathway (54).

The search for solutions to tumor chemoresistance by intervening in HMGB1 and pyroptosis has identified partially positive outcomes. GSDME-enhanced cisplatin sensitivity in NSCLC (134). miR-556-5p has been found to be significantly upregulated in tumor tissues of patients with cisplatin-resistant NSCLC, and its knockdown inhibits tumor cell viability and

induced pyroptosis, while miR-556-5p downregulation induces NLRP3-mediated cell pyroptosis, which effectively enhances cisplatin sensitivity in NSCLC, providing a novel therapeutic strategy to overcome resistance to chemotherapy in patients with NSCLC (135). In a previous study on the pyroptosis regulation of the tumor immune microenvironment, the expression of pyroapoptotic gene sets was positively associated with the percentage of tumor response to target therapy, and the pyroptosis signal upregulated during the process of tumor drug resistance (136). The release of HMGB1 and GSDME cleavage were inhibited in melanoma BRAFi + MEKi-resistant cells, and targeting this PCD pathway is a potential strategy for salvage therapy in patients with BRAFi + MEKi-resistant melanoma (136).

In conclusion, pyroptosis is a form of inflammatory necrosis of cells triggered by inflammasomes, which are present in a variety of tumor cells. HMGB1 can affect tumor proliferation, invasion, metastasis, and MDR through pyroptosis. Therefore, HMGB1 is a promising target therapeutic target for overcoming MDR, highlighting a novel basis for the diagnosis and treatment of cancer and the development of new drugs.

HMGB1 interacts with non-coding RNAs (ncRNAs) involved in MDR in tumors. ncRNAs are RNAs that do not code for proteins and include miRNAs, long ncRNAs (lncRNAs), circular RNAs (circRNAs), small nuclear RNAs (snRNAs); miRNAs, lncRNAs and circRNAs are widely recognized as universal regulators of a variety of cancer features, such as proliferation, apoptosis, invasion, metastasis and genomic instability. ncRNAs also play crucial roles in resisting different cancer treatments by rewiring important signaling pathways (137). RNAs in the circulatory system are primarily secreted by cells and can be indicative of disease and biological processes, including response to therapy. Exploiting the role of certain ncRNAs in intrinsic and acquired therapeutic resistance highlights their value as biomarkers that can predict the outcome of a particular patient before, during, and/or following treatment. This association relies in part on the properties of ncRNAs that play a role in intercellular communication (138-140).

miRNAs regulate gene expression at the transcriptional level by binding to the mRNA 3'UTR region of target genes and inhibiting their translation through degradation of the mRNA (141). miRNAs in tumors can be divided into oncogenic and suppressor miRNAs. Oncogenic miRNAs suppress their target genes through overexpression, leading to the occurrence of tumors, while suppressor miRNAs can also induce tumorigenesis when their target genes (oncogenes) are overexpressed when their expression is decreased or absent. Several miRNAs are involved in drug resistance in cancer therapy through complex underlying regulatory mechanisms, and knowledge of these may assist clinicians in tailoring treatments and thus improve a patient's prognosis (142). Research on bladder cancer (BC) has recently identified miRNAs as potential regulators of the oncogenic potential of BC cells (143). A variety of miRNAs, including miR-23a-3p and miR-141-3p, were found to be abnormally expressed in BC tissues, and in the peripheral, blood, or urine samples from patients with BC. These miRNAs promote the oncogenic potential of BC by regulating epithelial-mesenchymal transition or PI3K/AKT, JAK/STAT and NF- κ B/Snail signaling pathways (143). In addition, several

tumor suppressor miRNAs were found to be downregulated in BC samples, leading to the enhanced proliferation, invasion and metastasis of these cells (143). miRNAs are also involved in regulating the response of cancer cells to chemotherapeutic agents. The role of miR-193a-3p in enhancing multi-chemoresistance in BC cells was identified in BC treatment; the miR-193a-3p/LOXL4 axis was found to be a possible target for enhancing the response of BC tissues to chemotherapy (144). The upregulation of miR-204-5p and miR-211-5p following treatment with vemurafenib in melanoma leads to the emergence of drug resistance (145). This indicates that miRNAs are associated with tumor development, drug resistance and the assessment of therapeutic efficacy.

lncRNAs are a class of endogenous ncRNAs >200 nt in length (146), which play key roles in biological processes such as tumor proliferation, differentiation, invasion, inflammatory response, metabolism and angiogenesis. ARHGAP5-AS1 was previously identified as an upregulated lncRNA in chemoresistant gastric cancer cells (147). The impaired autophagic degradation of lncRNA ARHGAP5-AS1 in chemoresistant cancer cells promoted chemoresistance, and its knockdown reversed this increase in chemoresistance (147). Moreover, a high ARHGAP5-AS1 expression was associated with a poor prognosis of patients with gastric cancer, and the ARHGAP5-AS1/ARHGAP5 axis was a possible target for overcoming chemoresistance in gastric cancer (147). In another study, lncRNA (lncRNA) EIF3J-DT induced chemotherapeutic resistance in gastric cancer through autophagy activation in *in vivo* and *in vitro* experiments (148). A previous study also demonstrated that the long-stranded ncRNA DLGAP1-AS2 promoted Wnt1 transcription and drove malignancy in gastric cancer through physical interaction with Six3, promoting cell proliferation, migration and invasion (149). Colon cancer research identified DLGAP1-AS2, a lncRNA that promotes human CRC progression, to be significantly increased in CRC tissues and cell lines. The knockdown of DLGAP1-AS2 inhibited CRC cell proliferation, migration, invasion *in vitro*, and tumor growth *in vivo* (150). In colon cancer, lnc-RP11-536 K7.3 was recently found to promote proliferation, glycolysis, angiogenesis and chemoresistance via the SOX2/USP7/HIF-1 α signaling axis (151). The knockdown of lnc-RP11-536 K7.3 inhibited proliferation, glycolysis and angiogenesis in colon cancer. However, it enhanced the chemosensitivity of resistant organoids and colon cancer cells both *in vitro* and *in vivo* (151).

circRNAs are single-stranded ncRNAs with an increased stability and a longer half-life compared to linear RNAs due to the secondary closed-loop structure of the phosphodiester bond between the 3' and 5' ends and the absence of the 3' polyadenosine tail (152). circRNAs can play oncogenic or tumor suppressor roles in a variety of cancer types and affect cancer phenotypes via a variety of mechanisms. Singh *et al* (153) found that circRNAs could be used as diagnostic and prognostic biomarkers for AML. circRNAs regulate gene expression and various steps of leukemia development and progression, including differentiation, proliferation, cell cycle transition, adhesion and apoptosis. A previous study on gastric cancer found that circDLG1 was significantly upregulated in distant metastatic lesions and in anti-programmed cell death protein 1 (PD-1)-treated gastric cancer tissue, and was associated with an aggressive tumor phenotype and a poorer prognosis

of patients with gastric cancer treated with anti-PD-1 (154). The ectopic expression of circDLG1 promoted the proliferation, migration, invasion and immune escape of gastric cancer cells. Mechanistically, circDLG1 interacted with miR-141-3p, acting as a miRNA sponge to increase CXCL12 expression, thereby promoting gastric cancer progression and resistance to anti-PD-1-based therapy (154). In a study on HCC, it was found that the knockdown of circMRPS35 expression in HCC cells inhibited proliferation, migration, invasion, colony formation and cell cycle progression *in vitro*, and tumor growth *in vivo* (155). Furthermore, a peptide encoded by circMRPS35 (circMRPS35-168aa) was significantly induced by chemotherapeutic agents and promoted cisplatin resistance in HCC (155).

The regulation of HMGB1 expression by ncRNAs is frequently observed in studies to overcome chemoresistance in tumors. For example, miR-451 was found to play an oncogenic role in pediatric AML (96). Pediatric AML bone marrow and cell lines exhibited a low miR-451 expression and a high HMGB1 expression, and HMGB1 was identified as a functional target of miR-451. miR-451 overexpression significantly enhanced apoptosis and reduced autophagy in both AML cell lines, which was reversed by pcDNA-HMGB1 transfection (96). In addition, exogenous miR-451 significantly enhanced the sensitivity of HL-60 cells to chemotherapeutic agents. miR-451 played a tumor suppressor role by enhancing cell death and reducing autophagy in AML cells by targeting HMGB1 (96). In another study on leukemia, the upregulation of miR-142-3p was found to improve drug sensitivity in AML by reducing P-glycoprotein and inhibiting autophagy by targeting HMGB1 (156). Similarly, Liang *et al* (60) demonstrated that miR-142-3p was significantly downregulated in DOX-resistant breast cancer cell lines, and that miR-142-3p negatively regulated HMGB1 expression. Furthermore, the overexpression of HMGB1 significantly reversed the increase in apoptosis and inhibition of autophagy mediated by miR-142-3p upregulation (60). miR-142-3p overexpression may inhibit autophagy and promote drug sensitivity to DOX in breast cancer cells by targeting HMGB1. The miR-142-3p/HMGB1 axis may thus serve as a novel target for regulating drug resistance in breast cancer patients (60). The most common type of thyroid cancer is papillary thyroid carcinoma (PTC) (157). The overexpression of miR-let-7e or the knockdown of HMGB1 has been found to inhibit cell migration and invasion (67). miR-let-7e has been shown to downregulate HMGB1 expression by directly targeting the HMGB1 3'-UTR. In addition, the reintroduction of HMGB1 has been found to reversed the anti-proliferative, anti-migratory and anti-invasive effects of miR-let-7e. miR-let-7e may thus exert tumor suppressive effects via HMGB1 in PTC (67). The RNA interference-mediated knockdown of HMGB1 reduces lung cancer cell viability, induced apoptosis and partially restores sensitivity to gefitinib (158).

In summary, ncRNAs have a wide impact on tumor development, treatment, drug resistance, and efficacy assessment. ncRNAs can be transmitted between cells as cellular signals, including ncRNAs which imbue drug resistance. ncRNAs are often specific for diagnosis, and there is a significant potential that ncRNAs can be used as biomarkers for clinical applications. Given the widespread involvement of ncRNAs in tumor and chemotherapy resistance, the prospect of different ncRNA

intervention strategies to inhibit tumor growth and overcome drug resistance is promising.

HMGB1 is involved in MDR in tumors mediated by multiple signaling pathways. In a previous study, when mouse bone marrow mesenchymal stem cells pre-treated with oxidized HMGB1 were co-cultured with homologous cancer cells, the cell proliferation and stemness of the cancer cells increased, and tumorigenesis and drug resistance increased (159). It has been found that extracellular HMGB1 promotes the release of cytokines, such as IL-6 and IL-8 through the activation of MAPK and via MyD88-dependent NF- κ B pathways, which in turn stimulates tumor cell proliferation, angiogenesis, EMT, invasion and metastasis. Nuclear and cytoplasmic HMGB1 promotes phagocytosis and inhibits tumor cell apoptosis to induce chemoresistance (63). HMGB1 is involved in the tumorigenesis of colitis-associated CRC via the ERK1/2 pathway (54). HMGB1-mediated autophagy regulates sodium/iodine transporter degradation in thyroid cancer cells, and the knockdown of HMGB1 inhibits LC3-II transactivation and sodium/iodine cotransporter degradation through AMPK/mTOR-dependent signaling pathways by regulating ROS production, but not ATP (38). Zha *et al* (41) found that neutrophil extracellular traps produced tumor-infiltrating neutrophils-mediated crosstalk between glioma progression and the tumor microenvironment by regulating the HMGB1/RAGE/IL-8 axis. The autophagic secretion of HMGB1 by cancer-associated fibroblasts promotes metastasis of NSCLC cells via NF- κ B signaling (160). Cancer-associated fibroblast autophagy secretes HMGB1 to promote the metastasis of NSCLC cells via NF- κ B signaling (160). HMGB1 regulates NF- κ B in MM; that is, HMGB1 regulates drug resistance in MM cells by modulating the NF- κ B signaling pathway (161). HMGB1 and the PI3K/Akt signaling pathways are involved in tumor chemotherapy sensitization research, and gemcitabine resistance in pancreatic ductal adenocarcinoma involves HMGB1/RAGE-initiated PI3K/Akt/MDR1 signaling (101). In breast cancer, HMGB1/RAGE has been found to promote not only breast cancer cell invasion, but also PD-L1 expression through PI3K/AKT signaling, leading to the destruction of effector T-cells (50). In gastric cancer, the HMGB1-mediated activation of the PI3K/Akt/HIF-1 α signaling pathway is associated with gastric cancer growth and metastasis (162). As observed in HCC, the interaction of VCP with HMGB1 promotes HCC cell proliferation, migration and invasion through the activation of the PI3K/AKT/mTOR pathway (163). In esophageal squamous cell carcinoma, patients with an increased expression of HMGB1 and p-ATM have been shown to have a poorer prognosis following radiotherapy; the downregulation of HMGB1 may promote the radiosensitivity of esophageal cancer cells by regulating the PI3K/Akt/ATM pathway (164).

In the search for methods with which to overcome tumor resistance, it has also been found that chemotherapy sensitization can be achieved by targeted intervention in HMGB1-related pathways (165). Autocrine and paracrine active signaling-mediated NF- κ B signaling-mediated PD-L1/PD-1 upregulation is a key response to stress in lung cancer cells and their tumor-associated macrophages (TAMs), which can be

induced by nanodiamond-doxorubicin coupling (Nano-DOX). The blockade of Nano-DOX-induced PD-L1 in cancer cells and TAM enhances the activation of TAM-mediated antitumor responses (165).

In summary, the signaling pathways regulated by HMGB1 include PI3K/AKT/mTOR, AMPK/mTOR, NF- κ B and ERK1/2, amongst others. HMGB1 binds to a variety of receptors, such as RAGE and TLRs to induce downstream biological effects, thereby mediating drug resistance. The clear division of labor and mutual relationship between each pathway increases the complexity of drug resistance mechanisms. Thus, determining the core targets for intervention is of utmost importance to better understand and overcome drug resistance.

4. Advances in HMGB1 modulation to overcome MDR in tumors

Targeted silencing of HMGB1 gene expression to enhance sensitivity to chemotherapy. HMGB1 is involved in tumor resistance to chemotherapy through the regulation of multiple pathways. Given the various mechanisms of drug resistance, several methods have been experimented with. Silencing the HMGB1 gene is the most direct method; silencing of HMGB1 expression in tumor cells can enhance the sensitivity of tumor cells to chemotherapeutic drugs. In MM, HMGB1 knockdown has been shown to increase the vulnerability of MM cells by regulating autophagy and DNA damage repair. HMGB1 knockdown in MM cells enhances the inhibitory effects of dexamethasone chemotherapy through the induction of apoptosis. The downregulation of HMGB1 activates the mTOR pathway by regulating the expression of related genes, inhibiting autophagy and increasing dexamethasone-induced DNA damage. *In vivo* experiments using xenograft models have demonstrated that HMGB1 knockdown in mice leads to a reduced tumor load following dexamethasone treatment compared with the control mice (25). HMGB1 has also been found to regulate drug resistance in MM cells by modulating the NF- κ B signaling pathway, and HMGB1 knockdown inhibits MM cell viability (161). In leukemia, it has been found that HMGB1 overexpression attenuates the sensitivity of leukemia cells to adriamycin, vincristine and cytarabine, while HMGB1 knockdown enhances this effect. The overexpression of HMGB1 induces autophagy through the PI3K/Akt/mTORC1 pathway to induce drug resistance in leukemic cells, whereas the knockdown of HMGB1 inhibits autophagy and enhances the drug sensitivity of leukemic cells by increasing the phosphorylation of Akt and p70S6k (166). The expression levels of HMGB1 positively correlate with NLRP3 mRNA levels in patients with AML. Chronic stress promotes the progression of AML through an HMGB1/NLRP3/IL-1 β signaling pathway. The knockdown of HMGB1 significantly reduces the expression of NLRP3 and IL-1 β in AML cell lines, and the secretion of IL-1 β in AML cell culture supernatant, while the stimulation of HMGB1 expression results in the opposite effect (167).

Application of TCM in regulating HMGB1 expression. The essence of tumor drug resistance is 'the stronger the tumor's defensive ability' the more likely the tumor cells are likely

to survive. When the combined application of multiple antagonists exerts poor therapeutic effects and increases the toxic and side-effects of drugs, TCMs for antitumor therapy have been shown to exhibit positive clinical effects. TCMs exhibit low toxicity, multiple targets, multi-components, and multiple antitumor effects, overcoming the drug resistance to chemotherapy, and thus have significant prospects for reversing tumor resistance. TCMs and modern medicines synergistically inhibit the development of liver cancer, improve sensitivity after chemoresistance, ameliorate the adverse effects of chemotherapeutic drugs and molecularly target drugs, and prolong the survival after surgery or interventional treatment (168). TCMs primarily consist of compounded formulas and extract preparations (monomers, active ingredients, compounding, capsules, granules and injections). The primary types of monomers in Chinese medicine are alkaloids, flavonoids and saponins, amongst others. Wei *et al* (169) found that TCMs can overcome tumor MDR primarily by regulating ABC transporters, regulating autophagy, regulating cell cycle progression, regulating key signaling pathways, regulating CSC and regulating hypoxia.

The role of compound formulas in overcoming MDR in tumors has also been shown. Shenling-baizhu Powder is a classic Chinese herbal formula that has been used for decades in the treatment of patients with malignancies of the gastrointestinal tract (170). When combined with cytoxan (CTX) in a mouse model of HCC, the combined treatment reduced NF- κ B expression and promoted apoptosis, thereby inhibiting tumor growth, compared to the untreated or treated group (170). Shengbai decoction, which consists of *Codonopsis*, *astragalus*, licorice and other Chinese herbs, has been shown to reduce the levels of inflammatory factors in the serum of mice following treatment with CTX, promote apoptosis of HCC cells, and prolong survival through regulation of the p53 pathway (171). A previous study demonstrated that Baosheng combined with the Lomb II formula enhanced the antitumor effects of 5-fluorouracil by clearing appetite regulators in the hypothalamic central nervous system and feeding zone and improving chemotherapy-induced anorexia and gastrointestinal damage in ruminant mice (172).

TCM monomers can likewise overcome tumor MDR. Artesunate (an artemisinin derivative derived from *Artemisia annua*) significantly enhances the inhibitory effects of sorafenib on HCC *in vitro* and *in vivo*, attributed to the synergistic effects of lysosome-activated oxidation, the induction of iron sagging, and the enhancement of the sensitivity of HCC cells to sorafenib (173). Fucoxanthin (FX) is a major bioactive component extracted from kelp. It inhibits the cancerous behaviors of not only human lung cancer PC9 cells. but also of gefitinib-resistant PC9/G cells. FX inhibits EMT-related factors (Snail, Twist, fibronectin, N-cadherin, and MMP-2) and sensitizes drug-resistant cancer cells to gefitinib (174). Baicalein (BAI) is an herbal monomer that has been found to improve cognitive impairment and protect microglia from neuroinflammation induced by LPS via the SIRT1/HMGB1 pathway in -BV2 cells (175). BAI inhibits LPS-induced inflammation in RAW264.7 cells via a miR-181b/HMGB1/TRL4/NF- κ B axis (176). Curcumin overcomes primary resistance to gefitinib in NSCLC cells

by inducing autophagy-associated cell death (177). The proteasomal degradation of HMGB1 by lignocaine inhibits MEK-ERK activation, thereby decreasing the phosphorylation of Bcl-2 and leading to the constitutive binding of Bcl-2 to Beclin-1. It has been found that compounded herbal preparations or herbal monomers achieve therapeutic effects by interfering with HMGB1, such as auxin injection and its active ingredient, lignocaine, prevent sepsis in part by inhibiting the HMGB1/TLR4/NF- κ B/MAPKs signaling pathway (178). Gegen Qinlian pills have been shown to attenuate carrageenan-induced thrombosis in mice by modulating the HMGB1/NF- κ B/NLRP3 signaling pathway (179). In addition, it has been observed that the high expression of HMGB1 in bortezomib-resistant cells and the combination of bortezomib with lithophane is very effective in *in vitro* and *in vivo* myeloma models and re-sensitizing drug-resistant cells to bortezomib (180).

On the whole, the use of TCM monomers and compounds by the targeted intervention of HMGB1 can reduce invasion and metastasis, and reverse tumor drug resistance, improve the tolerance of patients to chemotherapy, reduce the adverse reactions to chemotherapy, reduce the recurrence of cancer and prolong the survival of patients.

ncRNAs interfere with HMGB1 expression. RNA interference technology is one of the most effective post-transcriptional gene suppression methods, as it can specifically eliminate or suppress gene expression, and has several advantages, including being cost-effective, fast, efficient, exhibiting high stability and easy to produce, and has been widely used to explore gene function and the treatment of tumors and infectious diseases (181). In recent years, it has been found that ncRNAs play a critical and complex role in human carcinogenesis and tumor metastasis. Common ncRNAs include shRNAs, siRNAs, miRNAs, circRNAs and lncRNAs, amongst others (182). circRNAs can function as a competitive endogenous RNAs (ceRNAs) to specifically bind to miRNAs, which in turn inhibits the function of miRNAs and thus indirectly regulates the expression of the miRNA target gene (182). siRNAs have a defined as the precise mode of action with which to achieve protein knockdown. siRNA-based therapies are advantageous in breast cancer treatment for inhibiting metastasis, overcoming drug resistance and immune evasion (183). In a previous study, shRNA or miR-142-3p was used to target HMGB3, and the suppression of HMGB3 expression inhibited colony formation and induced apoptosis, including increased ROS accumulation, and decreased MMP, p-mTOR and STAT3 (184). In another study, following the simultaneous targeting of HMGA1, HMGA2, HMGB1 and HMGB3 using shRNAs or miR-142-3p, apoptosis was induced, and cell viability and the clonogenic capacity of human cervical cancer cells were inhibited. miR-142-3p induced apoptosis by binding to the 3'UTR of HMGA1, HMGA2, HMGB1 and HMGB3, and the proliferation, migration and invasion of human cervical cancer cells were inhibited (185). Similar and experimental findings have been observed in human osteosarcoma cells; the siRNA-mediated knockdown of HMGB1, HMGB2, or HMGB3 in human osteosarcoma cells increased their sensitivity to chemotherapy (186).

5. Conclusions and future perspectives

Tumor drug resistance to chemotherapy is very common and the mechanisms by which tumor resistance arises are complex. The overexpression of drug efflux pumps and MDR-associated proteins, mutations in drug targets, enhanced cell repair function and reduced apoptosis can all lead to drug resistance in tumor cells. The complex mechanisms of drug resistance in tumor cells have not yet been fully elucidated. PCD is regulated by a complex mechanism that is closely associated with anticancer therapy and drug resistance. Members of the HMGB protein family, including HMGB1, HMGB2, HMGB3 and HMGB4 are extensively involved in cellular processes in tumor cells, including proliferation, metastasis, autophagy, apoptosis and drug resistance. HMGB1 is closely associated with the development and progression of a variety of tumors. HMGB1 is involved in tumor MDR through a variety of mechanisms (Fig. 1), including mediating multiple cell death modes and signaling pathways, and several ncRNAs are involved in tumor drug resistance by regulating or promoting the function of HMGB1. Several ncRNAs are involved in tumor drug resistance by regulating or promoting the function of HMGB1, and various drug resistance mechanisms are clearly regulated upstream and downstream, but can also crosstalk with each other, which contributes to the complexity of tumor drug resistance mechanisms. In a previous meta-analysis on 18 studies from 11 different tumor types, including gastric cancer, CRC, HCC, pancreatic cancer, nasopharyngeal cancer, head and neck squamous cell carcinoma, esophageal cancer, malignant pleural mesothelioma, BC, prostate cancer and cervical cancer, higher HMGB1 protein levels indicated a lower overall survival and lower progression-free survival rates (187). Given that the HMGB1 gene is involved in tumor chemotherapy resistance through multiple pathways, reducing HMGB1 gene expression is the most direct strategy with which to address drug resistance and has been demonstrated in several cellular and animal studies; however, such experiments cannot be performed in clinical trials. The targeted intervention of HMGB1 expression can be used in cellular, animal and clinical trials to identify solutions to unblock drug resistance. TCM has a long history and has long been widely accepted. Chinese herbal medicines alone and in combination with Western medicines can inhibit tumor invasion, metastasis and reverse drug resistance, and can also be used in combination with chemical drugs to inhibit tumor cell invasion and metastasis and thus reverse drug resistance. Research on TCM to interfere with HMGB1 expression to overcome drug resistance has achieved some success and is a promising method that warrants further investigations. The use of RNA interference technology to specifically eliminate or inhibit the expression of genes has been very fruitful in targeting and regulating HMGB1 expression, chemotherapy sensitization and therapeutic efficacy due to its several advantages such as economic, speed, efficiency, high stability and proliferation.

HMGB1 is associated with multiple PCD modalities including apoptosis, autophagy, apoptosis, pyroptosis and ferroptosis. Of note, regards tumor development and drug resistance, it is hypothesized that HMGB1 may also be associated with the newly discovered cell death modality, cuproptosis. A previous review of the literature revealed that cuproptosis is

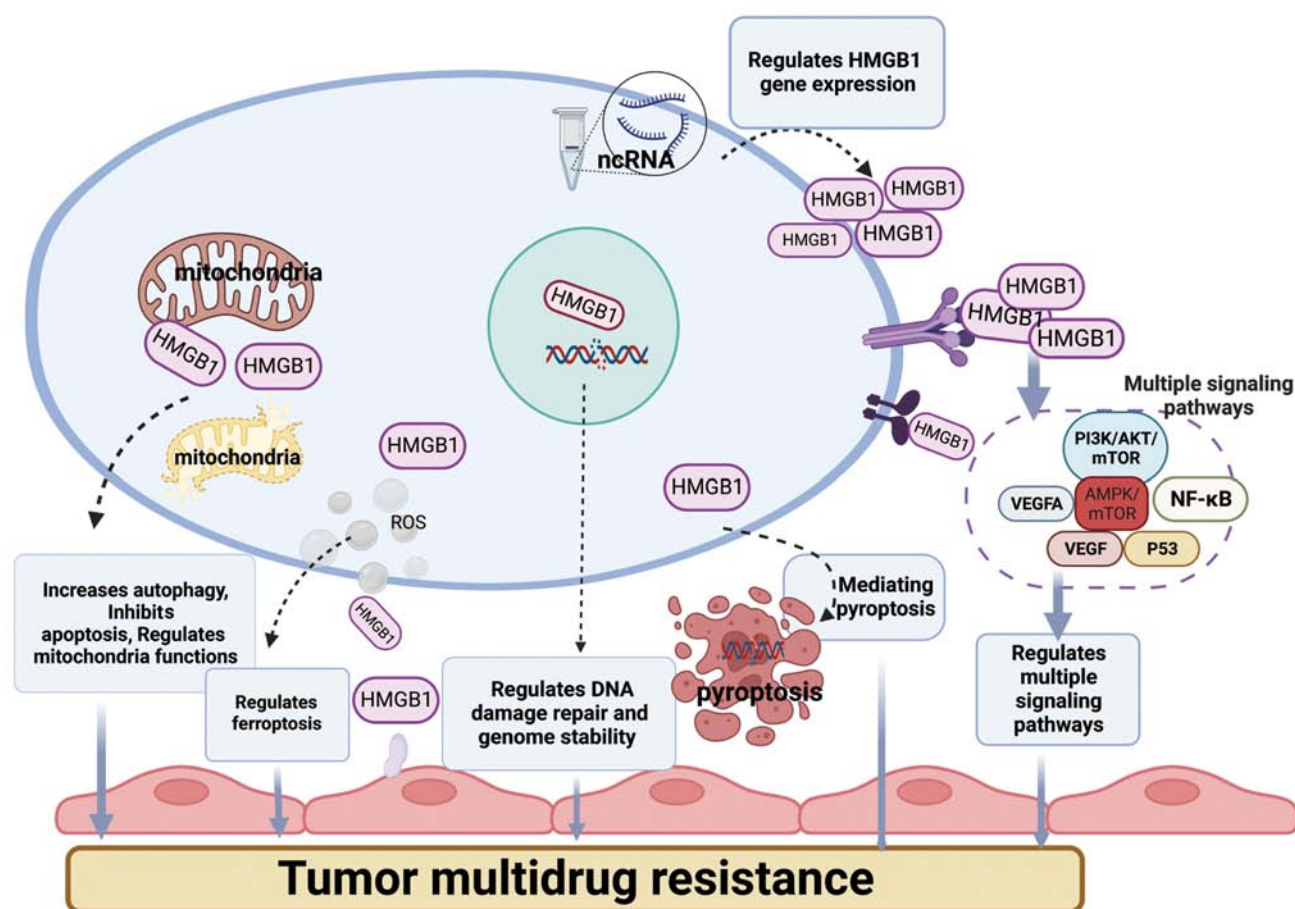


Figure 1. Mechanistic diagram of the roles of HMGB1 in MDR. HMGB1 regulates DNA damage repair and genome stability in the nucleus. In the cytoplasm, HMGB1 increases autophagy, inhibits apoptosis and plays a regulatory role in mitochondrial functions, regulating ferroptosis and pyroptosis, thereby mediating MDR. Extracellular HMGB1 can regulate multiple signaling pathways and induce downstream biological effects, thereby mediating drug resistance. A variety of ncRNAs can regulate the expression of HMGB1 and promote MDR. HMGB1, high mobility group box 1; MDR, multidrug resistance; ncRNA, non-coding RNA; mTOR, mammalian target of rapamycin.

a recently recognized form of cell death driven by intracellular copper-dependent mitochondrial stress (188). HMGB1, a molecular pattern associated with injury, is released by copper apoptotic cells to trigger inflammation. Copper accumulation-induced ATP depletion activates AMPK to promote HMGB1 phosphorylation, leading to increased extracellular release (189). By contrast, the genetic (using RNA interference) or pharmacological (using dorsomorphin) inhibition of AMPK activation limits copper sagging and HMGB1 release. Functionally, the ability of HMGB1-deficient copper apoptotic cells to promote late glycosylation end-product-specific receptor (AGER, also known as RAGE)-dependent inflammatory cytokine production is significantly reduced. Thus, HMGB1 is a key immune mediator of aseptic inflammation triggered by copper sagging (189). As a following step, exploring whether HMGB1 and cuproptosis are involved in tumor MDR and identifying chemotherapy sensitization regimens based on their mechanisms may facilitate a multi-pathway solution to the issue of tumor chemotherapeutic resistance.

Nanomedicines are the latest promising area of research and development. Compared to conventional chemotherapeutic drugs, NPs as drug delivery systems have several unique properties. NP surface binding to hydrophobic nuclei can overcome drug solubility issues. NPs can be modified by

a variety of molecules (peptides, small molecule ligands) for effective cell type and tissue targeting to improve therapeutic efficacy (190). Newly developed iron apoptosis inducers have now been combined with nanotechnology-based tumor cell targeting to demonstrate their advantages in overcoming drug resistance (190), and NP-mediated iron death enhances natural killer cell antitumor activity, achieving promising preliminary results in the treatment of prostate cancer (191). The combination of conventional chemotherapeutic drugs with other drugs in the area of nanomedicines has also shown some success in treatment. The biomimetic co-assembled nanomedicine of DOX and berberine not only effectively inhibits breast tumor growth with limited side-effects, but also significantly inhibits lung metastasis by blocking the HMGB1-TLR4 axis (192). Nanodelivery and self-cellular drug delivery platforms are considered effective strategies with which to overcome drug resistance due to their tumor-targeting ability, controlled release and consistent pharmacokinetic profile, particularly with the combined application of novel technologies (including CRISPR systems) (193). Combining ncRNA interference mechanisms with NP-based technologies has shown promising results and potential in tumor therapy. siRNA-loaded NPs for GBM, when loaded with temozolomide (TMZ) as a model, achieve

effective synergistic therapeutic effects by targeting key genes in the TMZ resistance STAT3 pathway (194). Given the several advantages of NPs and the understanding of the numerous mechanisms of targeted intervention of HMGB1 to overcome drug resistance, the two could be effectively combined in the future to develop NPs that target the HMGB1 gene. The advantages of pure drug nanocomponents based on the self-assembly or co-assembly of pure drug molecules over conventional NPs are promising and challenging for cancer therapy (195). According to different tumorigenesis, development and drug resistance mechanisms, autophagy agonists (or autophagy inhibitors), ferroptosis agonists (or ferroptosis inhibitors), pyroptosis agonists (or pyroptosis inhibitors), Chinese herbal medicines with significant therapeutic effects, and ncRNAs targeting HMGB1 regulation are prepared as pure drug nano-components, which are precisely delivered to the target site and are rapidly released to exert their effects in a targeted manner. The drug can regulate several downstream signaling pathways, inhibit tumor cell proliferation, induce apoptosis, inhibit invasion and metastasis, inhibit tumor vascularization, regulate body immunity and induce programmed tumor cell death, to overcome tumor MDR. This may serve as a novel approach for the development of a low-toxicity, high-efficiency and multi-target reversal strategy for tumor drug resistance using Chinese medicines and their active ingredients.

Acknowledgements

Not applicable.

Funding

The present study was funded by the National Natural Science Foundation of Gansu Province (grant no. 21JR7RA579), and by the Guiding Projects of the Enshi Tujia and Miao Autonomous Prefecture Science and Technology Plan of Hubei Province (grant no. E20220033).

Availability of data and materials

Not applicable.

Authors' contributions

LHS and LZ were involved in the conception of the review and in the writing of the manuscript. MW, YN and FQC were involved in the preparation of the figure and in revising the manuscript. XQG and CTY were involved in the literature search. HWW and HLL reviewed the manuscript. All authors have read and agreed to the final version of the manuscript. Data authentication is not applicable.

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.

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