Medicine Insights

Review

Research Progress on Ferroptosis in Drug Resistance in Multiple Myeloma

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Abstract: Multiple myeloma (MM) as a hematological malignant tumor remains incurable,and drug resistance continues to pose a core obstacle that urgently needs to be overcome in clinical practice.Ferroptosis is a novel programmed cell death that is driven by iron-dependent form of the excessive accumulated lipid peroxides,and it has become a research hotspot for reversing tumor drug resistance due to its unique mechanism of action.Numerous studies have confirmed that ferroptosis-related signaling pathways participate in the occurrence, progression, and drug resistance in MM. This paper reviews the association between death regulatory mechanisms and multiple myeloma (MM) drug resistance, and briefly describes the links between genetic subtypes such as t(4;14), 1q21 amplification, and del(17p) in multiple myeloma and ferroptosis. We also elaborate on the regulatory role of the bone marrow microenvironment in MM ferroptosis. These findings may provide new insights for future research into combined therapeutic strategies targeting ferroptosis for the treatment of myeloma.

Keywords: Multiple myeloma; Ferroptosis; Drug resistance; Cytogenetics; Bone marrow microenvironment

1. Introduction

Multiple myeloma (MM) is characterized primarily by the uncontrolled proliferation of clonal plasma cells in the bone marrow and the massive secretion of monoclonal immunoglobulins; it subsequently causes target-organ damage, including hypercalcemia, anemia, renal injury, and osteolytic bone disease, making it the second most common hematologic malignancy [1]. According to GBD 2021 data, in 2021, China reported 17,250 new cases of MM and 12,984 deaths; furthermore, the disease burden of MM in China has risen significantly from 1990 to2021, and as the countrys population ages, the domestic disease burden of MM will be further increased [2]. Proteasome inhibitors, immunomodulatory drugs, CAR-T therapy, and other interventions have significantly extended patient survival; however, some patients still inevitably face disease progression or relapse and drug resistance, and multiple myeloma remains incurrable. There is therefore an urgent need to identify novel targets and pathways for intervening in drug resistance [3].

Ferroptosis can sensitize various tumors to chemotherapy and reverse drug resistance [4]. Studies have shown that resistance in multiple myeloma (MM) is often associated with the inhibition of ferroptosis pathways [5]. MM cells exhibit high metabolic activity and increased iron demand, and long-term transfusion therapy-induced local or systemic iron overload further exacerbates this situation [6]. This provides favorable conditions for inducing ferroptosis, indicating that targeting ferroptosis holds significant therapeutic potential for overcoming MM resistance. A detailed analysis of the association

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between ferroptosis and MM resistance will provide reference for developing combined therapeutic intervention strategies targeting ferroptosis in the future.

2. Overview of Ferroptosis

In 2012, Dixon first proposed the concept of ferroptosis [7]. Ferroptosis is a novel form of programmed cell death driven by iron-dependent lipid peroxidation, characterized primarily by excessive accumulation of free iron within cells, excessive accumulation of lipid peroxicles, and inactivation of the antioxidant system [8]. The metabolically active pools within cells that handle iron utilization, storage, excretion, and exchange are referred to as the labile iron pool (LIP). Unstable iron overload in LIP can generate large amounts of reactive oxygen species(ROS) through the Fenton reaction. These ROS attack polyunsaturated fatty acids (PUFAs) on the cell membrane, triggering a chain reaction of lipid peroxidation. It causes cell membrane rupture leading to cell death, known as ferroptosis. The antioxidant system can protect cells from ferroptosis by eliminating lipid peroxides [8]. The ferroptosis regulatory network mainly involves three major aspects: iron metabolism, lipid metabolism, and the antioxidant system. Any abnormality in one of these areas may affect the occurrence of ferroptosis.

3. Upstream Regulation of Ferroptosis: Iron Homeostasis Remodeling and MM Drug Resistance

The available free iron in LIP is a key factor driving the Fenton reaction to triggers ferroptosis. Research has shown that drug-resistant MM cells block ferroptosis-mediated resistance by remodeling intracellular iron distribution to reduce the availability of free iron in LIP. This mainly involves processes such as iron autophagy, uptake, sequestration, and excretion.

Ferritin is the primary intracellular iron storage form. It can be degraded via selective autophagy-mediated by Nuclear Receptor Coactivator 4 (NCOA4), releasing free Fe^{2+} to increase LIP [8]. In sensitive MM cells, bortezomib inhibits proteasome function, thereby suppressing the ubiquitinated degradation of NCOA4 and promoting iron autophagy; consequently, it exerts a synergistic cytotoxic effect with the ferroptosis inducer RSL3 [9]. The natural Chinese herbal compound lithospermic acid promotes ferroptosis in MM cells by activating iron autophagy via GOT1, and significantly inhibits tumor growth in a mouse xenograft model [10]. Furthermore, targets in the iron autophagy pathway in drug-resistant MM cells are generally abnormal and are closely associated with poor MM prognosis. The autophagy-related protein ATG5 is a starting target of autophagy and can regulate downstream iron autophagy flux. Studies have found that low expression of the E3 ubiquitin ligase TRIM21, overexpression of the ubiquitin-like protein SDE2, and overexpression of the DNA methyltransferase DNMT3B in bone marrow plasma cells from patients with relapsed, drug-resistant MM are all closely asociated with poor rognosis in these patients [11,13]. In the study by Chen J et al., knockdown of TRIM21 expression increased bortezomib resistance in MM cells, whereas overexpression produced a synergistic effect with bortezomib [11].Studies on infection in macrophages have demonstrated that TRIM21 enhances NCOA4-mediated iron autophagy by targeting HERC2 for proteasomal degradation [12].In the study by Xia L et al., knockout of SDE2 promotes iron autophagy via the ATG5-NCOA4 axis, sensitizing MM cells to ferroptosis; the combined use of an SDE2 inhibitor and an autophagy agonist synergistically inhibits tumor growth in mice [13]. Studies have found that the DNMT family is closely associated with multidrug resistance in multiple myeloma. Knockdown of DNMT3B or the use of DNMT3B inhibitors exert a cytotoxic effect on primary MM cells from both newly diagnosed and relapsed patients; furthermore, DNMT3B inhibitors can reverse resistance to multiple first-line MM agents, including bortezomib, melphalan, and daratumumab [14]. A study on diabetic myocardial ischemia-reperfusion injury demonstrated that knockdown of DNMT1 within the DNMT family transcriptionally suppresses the expression of NCOA4, thereby reducing iron autophagy and blocking ferroptosis [15].

Furthermore, research by Zhang Rui et al. found that the iron autophagy-related gene ELAVL1 is upregulated in MM, and its expression level can serve as a biomarker for the diagnosis of MM and poor prognosis [16].

Iron uptake and efflux systems are also key mechanisms that influence the availability of iron in LIP.Transferrin Receptor 1 (TFR1) mediates the influx of transferrin-bound iron, while Ferroportin 1 (FPN1) is currently the only known iron efflux transporter; together, under the coordination of Iron Regulatory Protein 1/2(IRP1/IRP2), they maintain the balance of iron entry and exit from the cell [17]. Serine/threonine kinaseSTK17B is a recently identified iron homeostais regulator that is highly expressed in drug-resistant MM and serves as an independent risk factor for poor prognosis. Studies have shown that STK17B is highly expressed in bortezomib-resistant MM cells; its phosphorylation stabilizes IREB2, which regulates iron homeostasis reprogramming, simultaneously upregulates TFR1 and inhibits FPN1, resulting in abnormal intracellular accumulation of total iron. However, the elevated LIP also rapidly compensatorily activates the Nuclear factor erythroid 2-related factor 2(Nf2)-Ferritin Heavy Chain 1(FTH1) axis, efficiently sequestering Fe^{2+} and ensuring that the level of available iron in LIP remains low, thereby enabling escape from the Fenton reaction; targeting STK17B can disrupt abnormal iron homeostasis and induce ferroptosis, thereby reversing drug resistance [18].

4. Core Mechanisms of Ferroptosis: Lipid Peroxidation and MM Drug Resistance

Irreversible lipid peroxidation induced by PUFA is a core step in the execution of ferroptosis. In LIP, Fe^{2+} catalyzes the generation of reactive oxygen species via the Fenton reaction; these species attack membrane PUFA, initiating a chain oxidation that disrupts membrane integrity and leads to cell death [8]. The intensity of lipid peroxidation directly determines whether ferroptosis occurs; this process is precisely regulated by lipid metabolism enzymes and transcriptional pathways.

Free PUFAs must be activated via the Acyl-CoA Synthetase Long-Chain Family Member 4 (ACSL4)-lyso phosphatidylcholine acyltransferase 3 (LPCAT3) axis and incorporated into cell membrane phospholipids before they can serve as substrates for lipid peroxidation. Studies have shown that ACSL4 exhibits a dual role in promoting both tumorigenesis and ferroptosis in MM cells. Aberrantly high expression of ACSL4 in most MM cases is significantly associated with poor prognosis in MM patients. Theoretically, high ACSL4 increases the reserve of ferroptosis substrates, making ferroptosis more likely to be induced; in MM, ACSL4 drives proliferation by regulating pro-tumorigenic signaling pathways such as c-Myc and sterol regulatory element-binding proteins (SREBPs). However, MM cells can simultaneously activate multiple antioxidant pathways, thereby counteracting the lethal effects of lipid peroxidation; consequently, high ACSL4 levels are instead associated with poor prognosis and drug resistance. Knockdown of ACSL4 can inhibit MM proliferation [19-20]. Although MM cells with t(4;14) translocation are closely associated with poor prognosis, studies have found that this MM cell subtype exhibits high ferroptosis susceptibility [21].

The ratio of PUFA to monounsaturated fatty acids (MUFA) within the membrane determines oxidative susceptibility: PUFA, which contain abundant double bonds, are more prone to oxidation, whereas MUFA, with fewer double bonds, are less susceptible to oxidation [5]. Drug-resistant MM escapes ferroptosis by remodeling lipid metabolism and reprogramming lipid composition: it reduces PUFA levels and enriches MUFA levels. SREBP1 is a core transcription factor for de novo MUFA synthesis. In drug-resistant MM cells, the transcription factor ATF4 is activated and synergistically activates SREBP1 together with c-Myc, upregulating lipogenic enzymes to promote the extensive synthesis of MUFA; simultaneously, it upregulates CD36-mediated uptake of exogenous fatty acids and activates the membrane-bound O-acyltransferase domain-containing proteins 1 and 2 (MBOAT1/2), which replace membrane PUFA; this multilevel approach reduces the supply of peroxidizable substrates and thereby inhibits ferroptosis [22-24]. In summary, drug-resistant MM downregulates ACSL4 and activates SREBP1, thereby remodeling

membrane lipid composition, blocking the lipid peroxidation chain reaction, and conferring resistance to ferroptosis.

Activation of the Ferroptosis Antioxidant Defense System Promotes Multidrug Resistance in MM: The dynamic balance between the capacity of cells to scavenge lipid peroxides and the level of peroxide accumulation determines whether ferroptosis occurs; drug-resistant MM activates multiple antioxidant pathways, establishes a multilayered defense barrier, resists ferroptosis, and mediates drug resistance.

The cystine/glutamate antiporter (Xc^-)-glutathione (GSH)-glutathione peroxidase 4 (GPX4) pathway constitutes the core mechanism for clearing lipid peroxides. SLC7A11 (the Xc- subunit) takes up cystine to synthesize GSH. GPX4 uses GSH as a cofactor to detoxify toxic lipid peroxides, keeping lipid peroxide levels within a safe threshold and preventing ferroptosis. Research found that MM patients with high HSPA9 expression exhibit poorer responses to chemotherapy and shorter progression-free survival, suggesting that there is a close association between HSPA9 and MM drug resistance [25]. Drug-resistant multiple myeloma cells overexpress HSPA9 which binds to SLC7A11, preventing SLC7A11 degraded by the proteasome, thereby continuously activating antioxidant pathways to inhibit ferroptosis [26].

Various upstream mechanisms or auxiliary pathways can influence the function of the GPX4 pathway. The CLEC2/HIF-1a is a novel upstream mechanism regulating this pathway. MM cells generally exhibit low expression of CLEC2. Loss of CLEC2 leads to sustained activation of HIF-1a to upregulates GPX4, inhibits ferroptosis and promotes drug resistance [27]. Nrf2 is an upstream regulator for GPX4, its activation upregulates the expression of GPX4 and other antioxidant pathways to enhance antioxidant capacity [18]. In addition, MM cells can also counteract ferroptosis through multiple antioxidant pathways, such as the FSP1-CoQ10, GCH1-BH4, and DHODH [5].

5. Cytogenetic Subtypes and Heterogeneity in Ferroptosis Sensitivity in MM

t(4;14),1q21 amplification, del(17p), and t(14;16) are high-risk cytogenetic abnormalities in MM and serve as core reference indicators for risk stratification. Patients with these mutations have a significantly increased risk of drug resistance and relapse [28]. Multiple studies have revealed a close link between these mutations and ferroptosis.

MMSET overexpression is the core driver of high-risk in t(4;14). MMSET upregulates ACSL4 transcription by binding to the its promoter. ACSL4 increases PUFA reserves in MM cells, ensuring an adequate supply of substrates for ferroptosis. Research found that the antioxidant defense primarily relies on the Xc-GPX4 pathway in this subtype, making it highly sensitive to GPX4 inhibitors. Bortezomib(BTZ) combined with a GPX4 inhibitor can counteract the xCT upregulation caused by treatment, preventing excessive antioxidant capacity from inhibiting ferroptosis, thereby leading to drug resistance. This combination exhibits a synergistic effect and has demonstrated favorable efficacy in mouse models [21].

1q amplification is a common genetic abnormality in relapsed or refractory MM [28]. Studies have found that NR5A2 in the 1q32 region is closely associated with the dexamethasone resistance of MM cells. NR5A2 amplification drives phospholipid remodeling, significantly downregulating ACSL4 expression to reduce the synthesis of PUFA. PUFA is a substrate for ferroptosis, and its reduction decrease the occurrence of ferroptosis [24]. MM plasma cells are continuously exposed to oxidative stress and endoplasmic reticulum protein toxicity due to the massive synthesis of immunoglobulins. Research has found that the TXNIP gene in the 1q21 amplicon is involved in the regulation of oxidative stress homeostasis. TXNIP can regulate ROS clearance to reduce ROS levels. In addition, its upstream regulatory factor CREB1 participates in the regulation of antioxidant pathways such as NRF2 and GPX4 [29].

del(17p), accompanied by complete inactivation of both p53 alleles, is one of the high-risk markers associated with a poor prognosis in MM [28]. Studies have found that TP53 can promote the ferroptosis sensitivity in cells [30], and its inactivation can reduce the efficacy of BTZ [31]. PRMT1, a downstream target of TP53, is highly expressed in drug-

resistant MM cells. PRMT1 can inhibit ferroptosis by downregulating the expression of ACSL1 [32].

6. Bidirectional Regulation of MM Cells Ferroptosis by the Bone Marrow Microenvironment

The bone marrow microenvironment (BMME) comprises stromal cells, adipocytes, cytokines, extracellular vesicles, and other components; it interacts bidirectionally with MM cells and drives proliferation and stromal-dependent drug resistance [33]. The microenvironment exerts a bidirectional regulatory effect on MM cells-promoting ferroptosis while inhibiting it-with the direction of this effect influenced by multiple factors.

Bone marrow mesenchymal stem cells (BMSCs) are core scaffold cells within the microenvironment that can bidirectionally regulate the ferroptosis susceptibility of drug-resistant MM cells through CD40/CD40L membranecontact. Studies have found that direct contact between BMSCs and MM cells can activate the CD40/CD40L-Tf/TFRC-linolenic acid pathway, leading to the massive accumulation of linolenic acid, which induces lipid peroxidation and promotes ferroptosis; simultaneously, the CD40/CD40L membrane-contact signal can upregulate SENP3, mediate the removal of SUMO modification from GPX4, enhance protein stability, and strengthen antioxidant capacity to inhibit ferroptosis and thereby protect MM cells. The same CD40/CD40L membrane-contact signal can simultaneously initiate two mutually antagonistic pathways; consequently, the ferroptosis susceptibility of MM cells may depend on the balance between these two pathways. In the study, knockdown of SENP3 or the addition of exogenous linolenic acid favored the pro-ferroptotic pathway, thereby sensitizing the killing effect of the ferroptosis inducer RSL3 on drug-resistant cells; conversely, knockdown of HMGCR, a key rate-limiting enzyme in the linolenic acid synthesis pathway, or the addition of the ferroptosis inhibitor fer-1 to suppress the pro-ferroptotic pathway reversed the killing effect of RSL3 on drug-resistant cells. Targeting the CD40-CD40L membrane-related pathway holds promise for reversing BMSC-mediated MM drug resistance [34-35].

Cancer-associated fibroblasts (CAFs) are activated and generated from BMSCs and secrete a variety of factors that regulate MM resistance [36]. Senescent CAFs (senCAFs) have been shown in solid tumors to establish a matrix iron reservoir via theRELA-FTH1 pathwvay, thereby sequestering free ferrous ions in the microenvironment and inhibiting the Fenton reaction; silencing FTH1 or inhibiting NF-KB can disrupt this iron sequestration effect [37]. The NF-KB pathway is abnormally activated in MM and represents one of the key pro-survival signaling pathways in MM [38]. Studies have found that MM cells can induce senescence in bone marrow mesenchymal stem cells (MSCs) through paracrine signaling (via the NF-kB pathway) and drive their transdifferentiation into CAFs. The senescent phenotype of bone marrow MSCs in MM patients is markedly enhanced, and this stromal reprogramming is involved in the pathological process of myeloma [39]. The above studies suggest that senescent CAFs in the bone marrow microenvironment may establish a matrix iron reservoir via the RELA-FTH1 pathway, thereby regulating ferroptosis and influencing resistance to MM therapy.

In drug-resistant MM, the content of adipose tissue in bone marrow is significantly increased. Lipid breakdown in adipocytes releases large amounts of free fatty acids (FFAs); MM cells can uptake FFAs by upregulating the fatty acid transport proteins FATP and FATP4. FFAs exert a concentration-dependent bidirectional regulatory effect on MM cells: low concentrations of FFAs promote the proliferation of MM cells and support tumor survival; where as high concentrations of FFAs trigger a lipid peroxidation cascade, producing lipid peroxides that attack the cell membrane and disrupt its integrity, thereby promoting ferroptosis [40].

7. Summary and Outlook

The mechanisms underlying multidrug resistance in MM are highly complex. Ferroptosis, a novel mode of cell death driven by iron-dependent lipid peroxidation, has opened a new avenue for the treatment of drug-resistant MM. Drug-resistant MM cells remodel iron metabolism to reduce LIP, reprogram lipid metabolism to decrease peroxidizable substrates, and simultaneously activate multilayered redundant antioxidant networks; together with protection from the bone marrow microenvironment, these mechanisms enable them to evade ferroptosis. Genetic subtypes such as t(4;14),1q21 amplification, and del(17p) exhibit heterogeneity in ferroptosis regulation, necessitating stratified and differentiated targeted interventions.

Small-molecule ferroptosis inducers (RSL3 and others) and individual compounds derived from traditional Chinese medicine (andrographolide and others) can induce ferroptosis in MM cells, thereby exerting an antitumor effect and demonstrating strong potential for clinical translation [19,41]. Currently, related research has largely been confined to in vitro cell models and mouse models; numerous bottlenecks remain in the translation of targeted ferroptosis-based combination therapies into clinical practice. Understanding the relationship between ferroptosis mechanisms and MM resistance, as well as identifying optimal combination strategies under different genetic backgrounds and microenvironmental conditions, will provide valuable insights for promoting the clinical translation of ferroptosis-targeted strategies into the individualized treatment of relapsed or refractory MM.

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