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Review Article

Ferroptosis in Regulating Treatment Tolerance of Digestive System Tumors

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Abstract

Among all tumors worldwide, digestive tract tumors have a higher incidence rate and a significant disease burden. Esophageal cancer, gastric cancer, liver cancer, and colorectal cancer are often diagnosed at an advanced stage, and the prognosis remains poor. Currently, tumor treatment resistance is a major global challenge, with many underlying mechanisms. Ferroptosis has been shown to reverse drug resistance. This article reviews the mechanisms and recent advancements in ferroptosis related to reversing treatment resistance in gastrointestinal tumors, aiming to provide theoretical insights and research directions for the diagnosis and treatment of digestive tract tumors.

Introduction

Cancer has become the most serious public health issue in the world.[1,2] The incidence of digestive tract tumors accounts for 50% of all malignant tumors. Although new endoscopic techniques have improved the diagnosis and treatment rates for early gastrointestinal cancer, most patients with gastrointestinal tumors are diagnosed at an advanced stage and have a high mortality rate.[3] For these patients, medication is often the only option, but it can lead to treatment tolerance. While there are many mechanisms involved, the details are still unclear. Recent studies have shown that ferroptosis plays a key role in tumor suppression and offers new perspectives for tumor treatment. Inducing ferroptosis can reverse tumor treatment resistance,[4–7] but the mechanisms by which ferroptosis influences treatment resistance remain unclear. This article clarifies the relationship between ferroptosis and treatment resistance in various digestive tract tumors and explores the connection between ferroptosis-related mechanisms and treatment resistance, aiming to provide new research directions for the future treatment of gastrointestinal tumors.

Ferroptosis and tumor treatment resistance

Ferroptosis is a unique form of cell death driven by iron-dependent phospholipid peroxidation. It is regulated by multiple cellular processes, including redox balance, iron metabolism, and lipid metabolism.[8] The primary mechanism of ferroptosis involves the peroxidation of polyunsaturated fatty acid-containing phospholipids in the cell membrane under conditions rich in iron, reactive oxygen species (ROS), and lipid peroxidation.[9,10] The accumulation of lipid peroxides in the cell membrane eventually disrupts membrane integrity, leading to cell death. The molecular mechanisms of ferroptosis can be roughly divided into three pathways: the deletion or activation of glutathione peroxidase 4 (GPX4), iron metabolism, and lipid peroxidation (Fig. 1).[11]

Tumor cells can significantly enhance their defense against oxidative stress by regulating ferroptosis, which leads to treatment resistance.[12–14] Drug resistance in tumor cells is a major cause of cancer treatment failure. Currently, all tumor treatment drugs used in clinical practice can induce tumor cell resistance, resulting in tumor recurrence, metastasis, and ultimately, patient death. Studies have found that tumor resistance is primarily related to the activation of endogenous stress relief pathways by oncogenic stressors (e.g., starvation, DNA damage, dietary toxins, infection, or cancer therapy).[15,16] These pathways enable cells to better cope with stressors during development and renewal. Radiation therapy, chemotherapy, targeted therapy, and immunotherapy increase oncogenic stress, leading to further dependence of cancer cells on stress relief pathways. Cancer cells, as well as cells in the tumor microenvironment, rapidly adapt to relieve the stress caused by cancer treatments. These factors ultimately contribute to the resistance mechanisms of tumor treatment and provide new therapeutic targets,[17] with ferroptosis playing a key role in therapeutic resistance.[18] In tumor cell treatment resistance, persister cells (PCs) are particularly important.[19] PCs are tumor cells that survive after several rounds of chemotherapy and represent a treatment-resistant state.[20] The survival of PCs criti-

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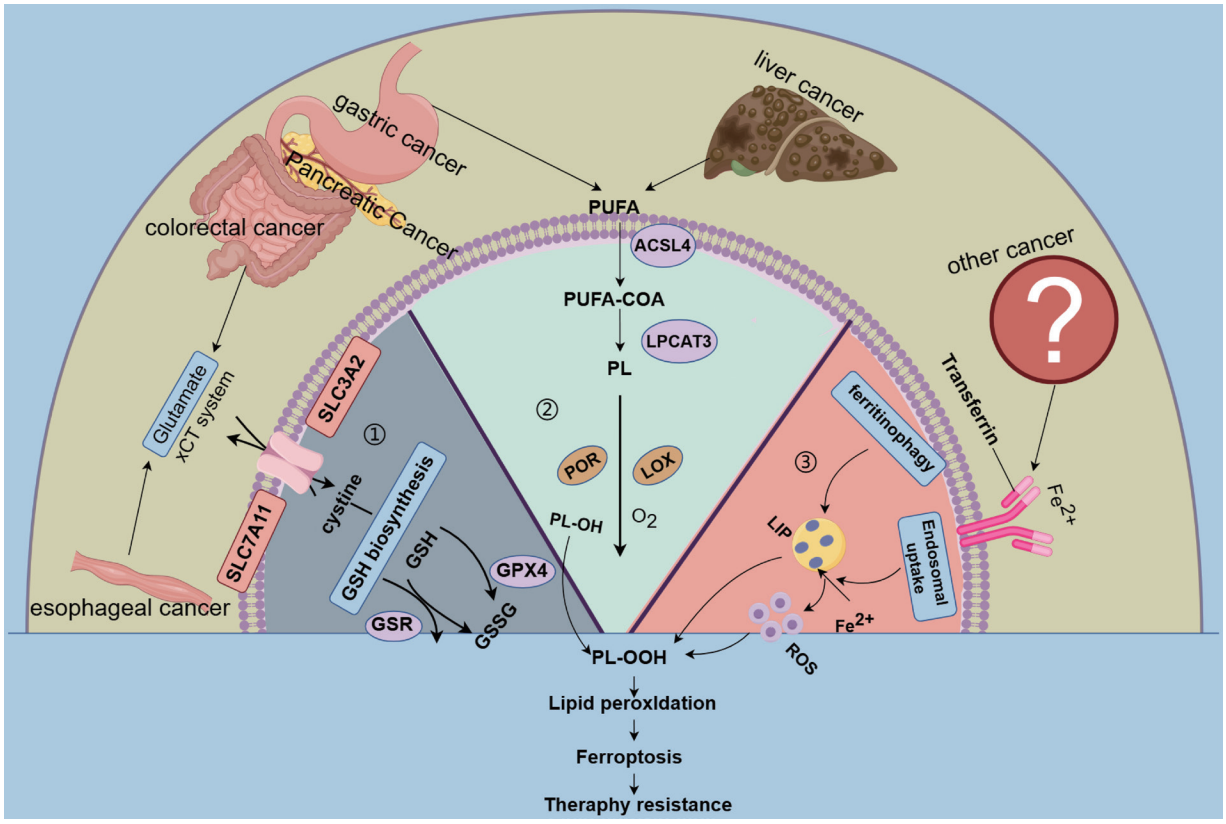

Fig. 1. The mechanism of gastrointestinal tumors involved in the ferroptosis pathway. ① Antioxidant pathway: Cysteine is imported into cells to synthesize GSH through the SLC7A11/SLC3A2 complex. GPX4 uses GSH as a substrate to reduce membrane phospholipid hydroperoxides to harmless lipid alcohols, thereby preventing the accumulation of lethal lipid ROS and inhibiting ferroptosis. ② Lipid peroxidation pathway: ACSL4 catalyzes the connection of long-chain polyunsaturated fatty acids to coenzyme A, and LPCAT3 promotes esterification and the incorporation of these products into membrane phospholipids (PL). PUFA-containing PL is oxidized by the iron-dependent enzymes LOX or POR, leading to lipid peroxidation, membrane damage, and subsequent ferroptosis. ③ Overexpression of nuclear receptor coactivator 4 increases intracellular LIP by increasing ferritin degradation. The increased intracellular LIP can generate free radicals (hydroxyl radicals) through the Fenton reaction and participate in the peroxidation reaction of phospholipids to generate PLOOH. Most intracellular production of reactive oxygen species is iron-catalyzed. The production of ROS triggers lipid peroxidation and ultimately leads to ferroptosis. ACSL4, acyl-CoA synthetase long chain family member 4; CoA, coenzyme A; GPX4, glutathione peroxidase 4; GSH, glutathione; GSR, glutathione-disulfide reductase; GSSG, glutathione oxidized; LIP, labile iron pool; LOX, lipoxygenase; PL, phospholipid; PLOH, phospholipid alcohol; PLOOH, phospholipid hydroperoxide; POR, cytochrome P450 oxidoreductase; PUFA, polyunsaturated fatty acid; ROS, reactive oxygen species; xCT, cystine/glutamate antiporter.

cally depends on GPX4, and the downregulation of GPX4 levels can selectively induce ferroptosis in PCs. Additionally, ferroptosis can selectively target the unique metabolic and signaling pathways of cancer stem cells (CSCs), playing an important role in treatment resistance.[21,22] Erastin, an inhibitor of the cystine/glutamate transporter (SLC7A11), also known as xCT, is a component of the cystine/glutamate antitransporter (system Xc-).[23] SLC7A11 has a significant cytotoxic effect on CSCs and can reduce chemotherapy resistance in CSCs.[24] Therefore, ferroptosis offers hope for overcoming treatment resistance by modulating PCs and CSCs. Numerous studies have found that ferroptosis is involved in the treatment resistance of gastrointestinal tumors (Table 1).[6,9,10,21,24–34] This article will next introduce the relationship between ferroptosis and digestive tract tumors, focusing on colorectal cancer, gastric cancer, pancreatic cancer, and liver cancer (Fig. 1).[11,23,35,36]

Ferroptosis and gastric cancer treatment resistance

Studies have found that inducing ferroptosis may be a key strategy to address gastric cancer treatment resistance. ROS interferes with the cellular oxidative environment and induces cell death. The antioxidant enzyme peroxiredoxin 2 significantly increases cell sensitivity to cisplatin treatment by regulating ROS levels.[29] Silva found that resistance to chemotherapy in gastric cancer is associated with gene mutations that regulate apoptosis and elevated levels of glutathione (a substance that inhibits ferroptosis in cells),[37] and that ferroptosis inducers (FINS) can help overcome this resistance.[30] Another potential target for gastric cancer treatment is to block the ROS-activated general control nonderepressible 2 (GCN2)-eukaryotic initiation factor 2α subunit (eIF2α)-activation transcription factor 4 (ATF4)-xCT pathway, which causes mitochondrial dysfunction and enhances cisplatin tolerance.[29] Sorafenib, a tyrosine kinase inhibitor, plays an important anti-tumor role in gastric cancer as a FINS. Activating transcription factor 2 (ATF2), a member of the ATF/CREB transcription factor family, is associated with various cancer-related biological functions. Studies have shown that ATF2 is activated during sorafenib-induced ferroptosis in gastric cancer cells. ATF2 knockdown promotes sorafenib-induced ferroptosis, whereas ATF2 overexpression shows the opposite effect in gastric cancer cells.

Table 1. Specific mechanisms of cell ferroptosis and treatment tolerance in gastrointestinal tumors

Tumor type	Key pathways to ferroptosis	Mechanism	Tolerance type	Medicine	References
Gastric cancer	Lipid peroxidation	GCN2-eIF2α-ATF4-xCT	Chemotherapy	Cisplatin	Wang *et al*., 2016[29]
	Lipid peroxidation	Antioxidase peroxiredoxin 2	Chemotherapy	Cisplatin	Wang *et al*., 2016[29]
	Lipid peroxidation; Inhibit GPX4 activity	SIRT6	Targeted therapy	Sorafenib	Cai *et al*., 2021[34]; Xu *et al*., 2022[24]
	Lipid peroxidation	SLC7A11	Targeted therapy	Sorafenib	Wang *et al*., 2016[9,10]; Xu *et al*., 2023[10]
Colorectal cancer	Inhibit GPX4 activity	KIF20A/NUAK1/PP1β/GPX4	Chemotherapy	Oxaliplatin	Yang *et al*., 2021[31]
	GPX4	FAM98A	Chemotherapy	5-fluorouracil	Chen *et al*., 2020[21]
Liver cancer	Lipid peroxidation	Metallothionein-1G (MT-1G)	Targeted therapy	Sorafenib	Sun *et al*., 2016[30]
	Iron metabolism	miR-23a-3p	Targeted therapy	Sorafenib	Lu *et al*., 2022[33]
Pancreatic Cancer	Inhibit GPX4 activity	Activate p22-phox expression	Chemotherapy	Gemcitabine	Sporn *et al*., 2012[32]
	Lipid peroxidation	Nuclear translocation of NRF2 stimulates the production of partially encoded enzymes to catalyze glutathione (GSH) production	Chemotherapy	Gemcitabine	Sporn *et al*., 2012[32]

ATF4, activation transcription factor 4; eIF2α, eukaryotic initiation factor 2α subunit; FAM98A, family with sequence similarity 98 member A; GCN2, general control nonderepressible 2; GPX4, glutathione peroxidase 4; KIF20A, kinesin family member 20A; NUAK1, NUAK family kinase 1; PP1β, protein phosphatase 1 beta; SIRT6, recombinant Sirtuin 6; xCT, SLC7A11 (solute carrier family 7, (cationic amino acid transporter, y+ system) member 11).

Furthermore, results from tumor xenograft models indicate that ATF2 knockdown can effectively enhance sorafenib sensitivity *in vivo*.[24] Heat shock protein (HSP) overexpression inhibits erastin-mediated ferroptosis by reducing cellular iron uptake and lipid ROS production.[38] HSP regulates GPX4 degradation by inducing chaperone-mediated autophagy and plays a role in necroptosis and ferroptosis.[39] At the same time, HSP can negatively regulate ferroptosis by inhibiting GPX4 degradation.[40] Studies have shown that heat shock protein family member 1 (HSPH1) is a direct target of ATF2 and mainly acts as a molecular chaperone to prevent the aggregation of misfolded or unfolded proteins, thus maintaining protein homeostasis.[41] HSPH1 can also affect sorafenib-induced ferroptosis by regulating SLC7A11 stability. Further experiments have shown that knocking down HSPH1 can partially negate the effect of ATF2 overexpression on sorafenib-induced ferroptosis. Both ATF2 and HSPH1 are closely related to chemotherapy resistance in tumor cells. ATF2 knockdown or loss-of-function mutations in HSPH1 significantly increase the sensitivity of colorectal cancer and melanoma to oxaliplatin and 5-fluorouracil.[24] These findings suggest potential targets for overcoming drug treatment resistance in gastric cancer. Pathways such as GPX4 and lipid metabolism involved in ferroptosis are relevant to the treatment resistance of gastric cancer.

The role of ferroptosis in treatment resistance in colorectal cancer

The prognosis for patients with advanced colorectal cancer is poor due to resistance to anticancer drugs. Studies have found that interfering with the lipid metabolism involved in ferroptosis in colorectal cancer cells disrupts the metabolic balance of iron in these cells and enhances the chemosensitivity of drug-resistant cancer cells.[42–44] Ferroptosis plays a crucial role in both chemotherapy and targeted therapy.

The role of ferroptosis in chemotherapy resistance in colorectal cancer

Research has revealed that cysteine desulfurase (NFS1) deficiency synergizes with oxaliplatin to induce ferroptosis, increase intracellular ROS levels, and enhance the sensitivity of colorectal cancer cells to oxaliplatin. The KIF20A-NUAK1-PP1β-GPX4 signaling pathway can directly or indirectly inhibit ferroptosis in colorectal cancer cells,[45] playing an important role in reversing colorectal cancer resistance to oxaliplatin. FAM98A, a microtubule-associated protein involved in cell proliferation and migration, enhances the expression of xCT in stress granules, inhibits ferroptosis in colorectal cancer cells, and improves the tolerance of colorectal cancer to 5-fluorouracil.[31] Therefore, inducing ferroptosis through various mechanisms may be an effective strategy to overcome resistance to colorectal chemotherapy.

The role of ferroptosis in resistance to targeted therapy in colorectal cancer

Resistance to epidermal growth factor receptor (EGFR) therapy limits the effectiveness of EGFR-targeted treatments in colorectal cancer. Cetuximab, a monoclonal antibody targeting EGFR, can promote RAS-selective lethal 3 (RSL3)-induced ferroptosis by inhibiting the nuclear factor erythroid 2-related factor 2/heme oxygenase-1 (Nrf2/HO-1) signaling pathway in kirsten rats arcomaviral oncogene homolog (KRAS) mutant colorectal cancer cells.[46,47] Additionally, β-elemene, a compound with broad-spectrum anticancer effects and a new type of FINs, can induce ferroptosis and inhibit epithelial-to-mesenchymal transition when combined with cetuximab, thereby improving treatment resistance in KRAS-

mutant colorectal cancer cells.[48] Vitamin C, an antioxidant that can induce oxidative stress at pharmacological doses, disrupts iron homeostasis and further increases ROS levels, ultimately leading to ferroptosis. The combination of cetuximab and Vitamin C can induce ferroptosis and reduce acquired resistance to anti-EGFR antibodies.[49] Therefore, modulating ferroptosis can reverse the treatment resistance effects of cetuximab.

The role of ferroptosis in treatment resistance in pancreatic cancer

Pancreatic cancer is often accompanied by lymph node invasion or distant organ metastasis at an early stage, with less than 20% of patients being eligible for surgical treatment once diagnosed.[50] For patients with unresectable pancreatic cancer, chemotherapy and radiotherapy are currently the main treatments. However, conventional chemotherapy regimens are prone to tumor cell resistance and strong chemotherapy side effects in the short term.[51] Consequently, the overall effectiveness of pancreatic cancer treatment has not improved obviously.[52] Previous studies have shown that FINS can inhibit pancreatic cancer growth by inducing cellular ferroptosis and, when combined with chemotherapy drugs, can increase tumor cell sensitivity to these drugs.[53]

Gemcitabine induces ROS accumulation during treatment.[54] In addition, knocking down GPX4 can increase lipid ROS production and induce ferroptosis. Gemcitabine can also induce ferroptosis by activating p22-phox expression in pancreatic ductal adenocarcinoma cells, which leads to NF-kB activation and NADPH oxidase (NOX) derived ROS accumulation. This may further enhance sensitivity to chemotherapy drugs. NRF2 is a major regulator of antioxidant molecules in cells. The nuclear translocation of NRF2 stimulates the production of enzymes that catalyze glutathione production, thereby reducing ROS levels. This mechanism can improve tumor cell resilience.[32] Therefore, combining NRF2 inhibitors with FINS may be a feasible strategy to reduce the resistance of pancreatic cancer cells to gemcitabine treatment. In summary, inducing ferroptosis through GPX4 and ROS accumulation may reverse resistance to chemotherapy drugs, providing a promising theoretical basis for the development of new treatments for pancreatic cancer. However, the role of ferroptosis in chemotherapy resistance in pancreatic cancer still requires further research.

The role of ferroptosis in treatment resistance in cholangiocarcinoma

Cholangiocarcinoma (CCA) is the second most common primary liver tumor after hepatocellular carcinoma.[55] Ferroptosis has been found to be closely related to the occurrence and development of various cancers, including CCA.[11,56,57] Therefore, it is important to further explore the role of ferroptosis in CCA. Studies have found that abnormal expression of iron regulatory proteins is key to the development of CCA. Increased iron deposits correlate with a worse prognosis. Artemisinin can induce both cell apoptosis and ferroptosis in cancer cells by promoting ferritin autophagy and increasing intracellular free iron ions. Research by Wanna *et al*. demonstrated that dihydroartemisinin has a strong toxic effect on CCA cells, offering a new strategy for treating CCA.[58]

The role of ferroptosis in treatment resistance in liver cancer

Sorafenib is the first systemic treatment approved for patients with advanced liver cancer who are not suitable for surgical resection.[59] However, resistance to sorafenib can affect its efficacy in treating liver cancer. Compared with apoptosis inducers, the combined use of FINS and sorafenib can induce ferroptosis in liver cancer cells, thereby increasing the sensitivity of liver cancer to chemotherapy drugs. This ferroptosis mechanism is unique to sorafenib and is independent of its kinase inhibitory activity.

Lu *et al*.[33] found that miR-23a-3p negatively regulates sorafenib-induced ferroptosis by reducing iron overload and lipid peroxidation. Knockout or downregulation of miR-23a-3p significantly improved the responsiveness of orthotopic hepatocellular carcinoma (HCC) tumors and HCC cells to sorafenib treatment. Sun *et al*.[60] discovered that upregulating metallothione-1G (MT-1G) expression could protect HCC cells from the effects of sorafenib and promote cancer progression by inhibiting lipid peroxidation-mediated ferroptosis. This study suggests that regulating MT-1G expression is a potential therapeutic strategy to overcome the acquired resistance of HCC cells to sorafenib. These findings provide a promising therapeutic strategy for improving tolerance to sorafenib treatment in the future.[60,61]

The role of ferroptosis in treatment resistance in esophageal cancer

Patients with advanced esophageal cancer usually receive concurrent chemoradiotherapy and surgery. However, repeated use of chemotherapy drugs often leads to the development of treatment resistance in tumor cells, resulting in poor prognosis for these patients. Addressing therapy resistance in esophageal cancer can involve promoting ferroptosis in cells by targeting the system Xc-,[62] GPX4,[62] and NRF2, thereby inhibiting tumor proliferation and differentiation. Currently, there are few reports on the mechanism of ferroptosis in immunotherapy for esophageal cancer. As research on immunotherapy progresses, programmed death 1 (PD-1) and programmed cell death-ligand 1 (PD-L1) targeted inhibitors have been used in the treatment of various tumors, including digestive tract tumors such as esophageal cancer, gastric cancer, colorectal cancer, and liver cancer. Liu J. *et al*. concluded that anti-PD-L1 antibodies can promote ferroptosis in tumor cells through the lipid peroxide pathway. Combining anti-PD-L1 antibodies with FINS can greatly inhibit tumor growth, with the mechanism related to cytotoxicity. T cells release interferon-γ, activate STAT1, inhibit xCT expression, and subsequently induce ferroptosis.[63] Few studies have explored the immunogenicity of esophageal cancer cells. Inducing ferroptosis in tumor cells can enhance their immunogenicity, thereby boosting the anti-cancer activity of immune cells.[64] These mechanisms of ferroptosis and treatment resistance in esophageal cancer offer new options and methods for the further treatment of patients with advanced esophageal cancer.

Limitations and future perspectives

Current research on ferroptosis and tumors has also been explored in other systemic tumors, such as non-small cell lung cancer,[65] and breast cancer.[66–68] The treatment of these tumors primarily utilizes ferroptosis-related mechanisms and pathways, including: (1) inhibiting the XC-glutathione/GPX4 axis by regulating antioxidants; (2) modulating the p62-Keap1-NRF2 pathway and NRF2 downstream antioxidant gene expression; (3) activating the ferroptosis axis by regulating the functions of lysosomes, ferritin, transferrin, and ferrophagosomes. Therefore, ferroptosis plays a crucial role in killing tumor cells and inhibiting tumor growth. Targeted induction of

ferroptosis may be a novel strategy to overcome tumor treatment resistance. However, clinical understanding of the factors involved in regulating cellular ferroptosis and treatment resistance remains limited. As alternative therapeutic targets, a deeper understanding of the initiation and transformation of ferroptosis and treatment resistance mechanisms in gastrointestinal tumors is needed.

Currently, ferroptosis represents a new clinical treatment direction and has garnered increasing attention in cancer therapy. Despite the growing research on ferroptosis, several issues remain: (1) Further exploration is needed to understand the unknown and regulatory mechanisms of ferroptosis in tumor treatment resistance; (2) Different tissues exhibit varying sensitivities to ferroptosis, making the correct application of ferroptosis in tumor treatment an important research direction; (3) Anti-tumor drugs are often used in combination, but the antagonistic or synergistic effects of these combinations are not yet fully understood, and substantial theoretical research support is still required; (4) While some drugs and compounds can induce ferroptosis, and new drug delivery systems such as exosomes and nanotechnology are being explored, clinical application remains a challenge. Further exploration and effort from scholars are needed.

The detection and application of ferroptosis in tumor drug resistance are crucial. Ongoing research and detection methods related to ferroptosis provide valuable tools for understanding and intervening in this process. For example, measuring the levels of specific lipid peroxides within cells, such as malondialdehyde and 4-hydroxynonenal, can help assess ferroptosis.[69] Additionally, detecting the activity of enzymes associated with ferroptosis, such as GPX4, is an important indicator of ferroptosis occurrence. The release of cytochrome C, changes in mitochondrial membrane potential,[70] and increases in intracellular iron ion levels are also key events in ferroptosis, detectable through biochemical experiments.[71] Techniques such as flow cytometry, fluorescence microscopy,[72] and Western blotting are widely used for detecting ferroptosis.[73,74] Although there is currently no single gold standard for detecting ferroptosis, combining these methods can provide a more comprehensive assessment. Future research may uncover new biomarkers and detection technologies, further improving the accuracy of ferroptosis detection and its clinical application feasibility.

Conclusions

We anticipate seeing more meaningful clinical and basic research in the near future. These studies will enhance our understanding of resistance mechanisms to ferroptosis reversal therapy and lead to more effective cancer treatments, thereby reducing the disease burden on patients and improving their quality of life.

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Conflict of interest

The authors have no conflicts of interest related to this publication.

Author contributions

Manuscript drafting (XQ), study concept and design (XQ, HW, MXZ), figures and tables (XQ, MXZ), English polishing (HL), critical revision of the important intellectual content for the manuscript (MXZ). All authors read and approved the final manuscript.

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