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Review Article

Research advances in single-molecule multi-target strategies targeting ferroptosis for colorectal cancer treatment

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Abstract: Colorectal cancer (CRC) is a highly prevalent malignancy worldwide, with its incidence and mortality continuing to rise, and with an emerging trend toward younger-onset disease. The efficacy of current treatment modalities, including surgery, chemotherapy, targeted therapy, and immunotherapy, is often limited by the development of drug resistance. Ferroptosis, an iron-dependent form of regulated cell death driven by lipid peroxidation, is governed by a sophisticated regulatory network comprising core pathways and bypass systems in CRC, offering numerous potential targets for therapeutic intervention. The single-molecule multi-target strategy employs a single compound to simultaneously act upon multiple key nodes within this network, circumventing the resistance commonly associated with single-target agents while avoiding the pharmacokinetic interactions and additive toxicities of drug combinations. This review systematically delineates the key pathways and core targets of ferroptosis in CRC and summarizes recent progress across three classes of single-molecule multi-target compounds: natural products, synthetic small molecules, and "one-drug multi-modal death" inducers. We further propose a drug development and design framework integrating structural optimization, target integration, and delivery efficiency. Finally, we discuss current challenges and future directions, aiming to provide a theoretical foundation for developing novel CRC treatment strategies.

Keywords: Colorectal cancer, ferroptosis, single-molecule multi-target strategy, multi target drugs, immune microenvironment, drug resistance

Introduction

Colorectal cancer (CRC) ranks as the third most common malignancy globally, accounting for over 1.8 million new cases and approximately 850,000 deaths annually. Both its incidence and mortality continue to increase, with a concomitant shift toward younger age at diagnosis [1]. At present, the clinical treatment of CRC is mainly surgical resection, supplemented by chemotherapy, targeted therapy and immunotherapy [2]. Chemotherapy based on 5-fluorouracil and oxaliplatin combined with targeted or immune checkpoint inhibitors [anti-programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1)] has become a standard protocol, but the efficacy is limited due to drug resistance [3]. Notably, CRC drug resistance can be divided into primary resistance and acquired resistance, with complex molecular mechanisms including enhanced DNA damage repair, overexpression of ATP-binding cassette (ABC) drug efflux pumps, dysregulation of apoptotic pathways, epithelial-mesenchymal transition (EMT) and metabolic reprogramming. Traditional anti-tumor therapies mostly rely on inducing apoptosis, and tumor cells often develop cross-resistance to multiple apoptotic inducers through Bcl-2 family protein overexpression, p53 mutation and caspase pathway inactivation. This underscores the urgent clinical need for novel cell death modalities that operate independently of apoptotic pathways.

Due to the limitations of conventional therapies, increasing research has focused on novel forms of regulated cell death, among which fer-

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Table 1. Comparison of naturally occurring and rationally designed single-molecule multi-target compounds

Category	Origin/Design principle	Key characteristics	Examples
Naturally occurring multi-target compounds	Isolated from natural sources (plants, microorganisms, animals)	Complex chemical structures; multi-target effects discovered through screening rather than rational design; often act on multiple unrelated targets via different mechanisms	Berberine, luteolin, ursolic acid
Rationally designed single-molecule multi-target drugs	Intentionally designed and synthesized based on disease mechanisms and target structures	Simultaneously act on two or more preselected, functionally related targets; optimized for balanced activity against all intended targets	GPX4/SLC7A11 dual inhibitors, EGFR-GPX4 PROTACs

roptosis has attracted particular attention because of its unique regulatory mechanisms. Ferroptosis is a form of regulated cell death officially named in 2012. Its core feature is the irreversible accumulation of iron dependent lipid peroxidation products, which is morphologically different from classical cell death modes such as apoptosis, autophagy, and pyroptosis [4]. The occurrence of ferroptosis depends on three core pathways: glutathione (GSH) - glutathione peroxidase 4 (GPX4) axis in amino acid metabolism, polyunsaturated fatty acid phospholipid (PUFA-PL) synthesis and oxidation pathway in lipid metabolism, and iron metabolism steady-state regulation pathway [5]. Ferroptosis inducers can specifically kill CRC cells, especially on chemotherapy resistant cells. GPX4 inhibitor RSL3 can effectively trigger ferroptosis in CRC cells and inhibit tumor growth, but excessive ferroptosis may induce the release of inflammatory factors, accelerate tumor invasion and metastasis, and intestinal microbial metabolites (such as indole-3-acetic acid) can inhibit ferroptosis and weaken the therapeutic effect [6]. Importantly, drug-resistant CRC cells often exhibit increased iron uptake, enhanced lipid metabolism, and higher levels of reactive oxygen species (ROS), making them inherently more sensitive to ferroptosis induction than their drug-sensitive counterparts. This unique characteristic makes ferroptosis a particularly promising therapeutic target for overcoming CRC drug resistance.

The single-molecule multi-target strategy refers to the use of a single compound to simultaneously act on multiple key targets or pathways involved in tumorigenesis and progression. This strategy can be divided into two categories based on the origin and design principle of the compounds. See **Table 1**.

Compared with traditional single target drugs and combination drugs, this strategy can synchronously inhibit the compensatory pathway of tumor cells, avoid the tumor cells' resistance through bypass activation after single target inhibition, and a single compound can avoid the pharmacokinetic interaction and dose superposition toxicity when combined drugs are used [7]. Combination therapy, although theoretically effective, faces significant clinical challenges: different drugs often have mismatched pharmacokinetic profiles (e.g., different half-lives, tissue distribution and metabolic rates), making it difficult to achieve optimal therapeutic concentrations at the tumor site simultaneously; dose-limiting toxicities often prevent the administration of each drug at its optimal dose; and patient compliance decreases with the number of medications. Single-molecule multi-target drugs address these limitations by integrating multiple therapeutic activities into a single chemical entity, ensuring synchronized pharmacokinetics and simplified dosing regimens. Since ferroptosis is precisely regulated by multiple pathways such as amino acids, lipids and iron metabolism, the design of single-molecule multi-target drugs with ferroptosis as the core provides a new paradigm with great potential for the treatment of CRC. This paper aims to systematically describe the research progress, design concept and future direction of this strategy. Distinct from previous reviews that focus primarily on single-target ferroptosis inducers or the general role of ferroptosis in colorectal cancer, this review offers several unique contributions. First, it systematically summarizes, for the first time, the emerging application of PROTACs (proteolysis-targeting chimeras) in ferroptosis research, including dual-degraders targeting GPX4/FSP1 and EGFR/GPX4, which represent a paradigm shift from functional inhibition to tar-

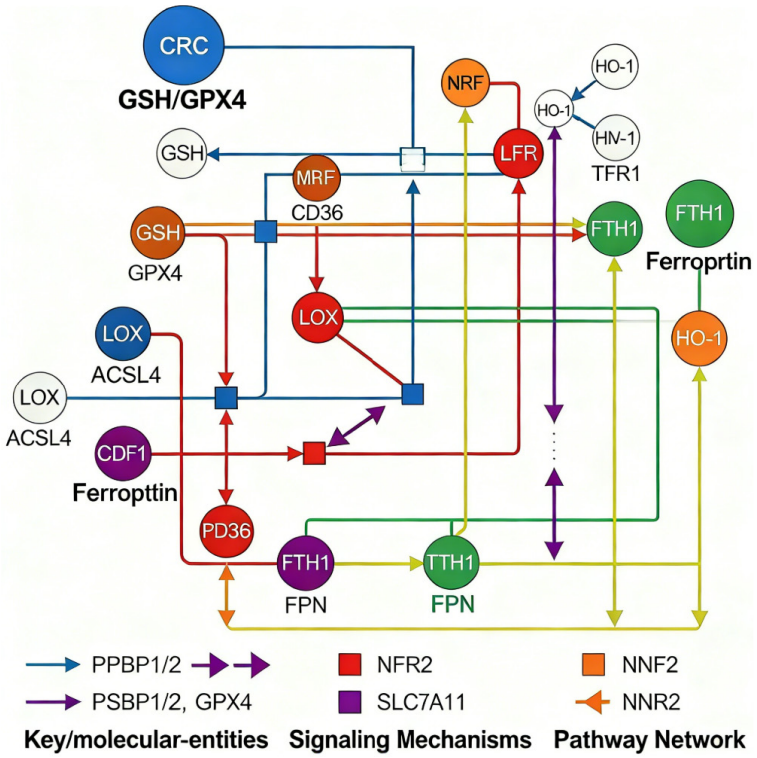

Figure 1. Schematic diagram of key regulatory pathways and core targets of ferroptosis in colorectal cancer (CRC). Abbreviations: GSH, glutathione; GPX4, glutathione peroxidase 4; LOX, lipoxygenase; ACSL4, acyl-CoA synthetase long-chain family member 4; SLC7A11, solute carrier family 7 member 11; FPN, ferroportin; NRF2, nuclear factor erythroid 2-related factor 2.

geted protein degradation. Second, it proposes a novel "structure-target-delivery" trinity design concept ("structure optimization - target integration - delivery efficiency") for single-molecule multi-target drugs, integrating medicinal chemistry, network pharmacology, and nano-delivery strategies. Third, it provides a comprehensive analysis of the "double-edged sword" effect of ferroptosis in CRC and the current challenges in clinical translation, including resistance mechanisms, off-target toxicity, and the lack of validated biomarkers, which have been inadequately addressed in prior literature. Together, these distinctions position this review as a forward-looking framework for the rational design and clinical development of next-generation multi-target ferroptosis-based therapies for CRC.

Key pathways and core targets of ferroptosis in CRC

The regulatory network of ferroptosis in CRC involves three core pathways of amino acid, lipid and iron metabolism and multiple bypass systems. There are cross regulatory nodes in each pathway, which provides rich targets for single-molecule multi-target strategy (**Figure 1**).

The amino acid/GSH-GPX4 axis

The amino acid/GSH-GPX4 axis constitutes the core defense pathway against ferroptosis and represents the primary target for single-molecule multi-target drugs [8]. The System Xc^- transporter is composed of solute carrier family 7 member 11 (SLC7A11) and solute carrier family 3 member 2 (SLC3A2). Its core function is to mediate the transmembrane transport of cystine into cells and provide raw materials for GSH biosynthesis. GPX4 utilizes GSH to specifically reduce lipid hydroperoxides, thereby maintaining intracellular redox homeostasis and supporting cell survival [9]. In CRC, SLC7A11 and GPX4 are frequently overexpressed. They form a synergistic defense mechanism, which is an important reason for the drug resistance of tumor cells. At the same time, targeting SLC7A11 and GPX4 can completely block this pathway and enhance the effect of ferroptosis induction. Studies have found that natural product acevaltrate (ACE) can directly bind and degrade GPX4, and indirectly inhibit the expression of *SLC7A11* [10]. Notably, the GSH-GPX4 axis is regulated not only at the transcriptional level but also at the post-translational level. For example, GPX4 can be degraded through the ubiquitin-proteasome pathway or autophagy-lysosome pathway, and its activity can be modulated by post-translational modifications such as phosphorylation and acetylation. These regulatory mechanisms provide additional targets for the design of multi-target ferroptosis inducers.

The lipid metabolism pathway

Lipid metabolism provides the "substrate" for ferroptosis, and its key enzymes acyl-CoA syn-

thase long chain family member 4 (ACSL4), lysophosphatidylcholine acyltransferase 3 (LPCAT3), and lipoxygenase (LOXs) are closely related to the GSH-GPX4 axis [11]. ACSL4 is responsible for activating polyunsaturated fatty acids (PUFAs), and LPCAT3 integrates the activated PUFAs into polyunsaturated fatty acid phospholipids (PUFA-PL), while LOXs further catalyzes the oxidation of PUFA-PL to produce lipid peroxides [12]. High expression of ACSL4 and LOXs in CRC cells enhances their sensitivity to ferroptosis, and the up regulation of LPCAT3 may provide a substrate for ferroptosis by promoting PUFA-PL synthesis, and may also enhance the survival ability of tumor cells by regulating lipid metabolism reprogramming. Such targets are often combined with GPX4 to be targeted by single-molecule drugs to achieve the synergistic effect of "synthesis enhancement + clearance inhibition" of lipid peroxidation. Recent studies have revealed that the composition of PUFA-PL in cell membranes also plays a critical role in ferroptosis sensitivity. Specifically, phospholipids containing arachidonic acid (AA) and adrenic acid (AdA) are the most susceptible to peroxidation, and their abundance in CRC cell membranes is positively correlated with ferroptosis sensitivity. This suggests that modulating the fatty acid composition of cell membranes could be a novel strategy to enhance ferroptosis induction.

Iron metabolism and oxidative balance pathway

Disruption of iron homeostasis is a prerequisite for ferroptosis initiation. The core regulatory targets include transferrin receptor 1 (TfR1, mediating iron uptake), ferroportin (FPN, mediating iron efflux), nuclear receptor coactivator 4 (NCOA4, regulating iron autophagy) and nuclear factor E2 related factor 2 (Nrf2, regulating oxidative stress balance) [13]. TfR1 increased the content of labile iron pool (LIP) by mediating iron ion influx, and NCOA4 released iron ion by degrading ferritin, both of which promoted the occurrence of ferroptosis; While FPN maintains iron homeostasis by excreting intracellular iron ions, thereby inhibiting ferroptosis [14]. Nrf2 can regulate the expression of SLC7A11, HO-1 and other genes at the same time, balance the cellular oxidative stress response, and indirectly participate in the regulation of ferroptosis. Single-molecule drugs often amplify the ferroptosis effect by synchronously regulating iron uptake and antioxidant targets (such as TfR1 and Nrf2) [15]. It is worth noting that iron metabolism in CRC is significantly reprogrammed compared with normal intestinal epithelial cells. CRC cells often upregulate TfR1 and downregulate FPN to increase intracellular iron levels, which not only supports their rapid proliferation but also makes them more susceptible to ferroptosis. This metabolic vulnerability provides a therapeutic window for the development of iron-dependent ferroptosis inducers with tumor selectivity.

Bypass anti ferroptosis system

When GSH-GPX4 axis is inhibited, CRC cells can maintain cell survival by activating two bypass pathways: ferroptosis inhibitory protein 1 (FSP1) - coenzyme Q10 (CoQ10) and guanosine triphosphate cyclic hydrolase 1 (GCH1) - tetrahydrobiopterin (BH4). FSP1 scavenges intracellular lipid peroxides by reducing CoQ10, and BH4 catalyzed by GCH1 can inhibit the oxidation process of PUFA-PL, which together constitute a bypass defense system against ferroptosis in CRC cells. This bypass system is a major contributor to resistance to single-target ferroptosis inducers. Therefore, multi-target drugs often take GPX4 and FSP1 as joint targets, and avoid compensatory resistance of tumor cells by blocking the core pathway and bypass system at the same time [16].

In addition to these two well-characterized bypass pathways, several novel anti-ferroptosis mechanisms have been identified in recent years, further expanding the complexity of the ferroptosis regulatory network. Dihydroorotate dehydrogenase (DHODH), a key enzyme in de novo pyrimidine synthesis, has been shown to localize on the outer surface of the inner mitochondrial membrane where it reduces CoQ10 to ubiquinol, thereby inhibiting lipid peroxidation independently of GPX4. In cancer cells with low GPX4 expression, DHODH becomes the primary defense against ferroptosis, and DHODH inhibitors significantly enhance the anti-tumor activity of GPX4 inhibitors. Another emerging anti-ferroptosis pathway involves inducible nitric oxide synthase (iNOS), which is highly expressed in tumor-associated macrophages (TAMs) in the CRC microenvironment.

iNOS produces nitric oxide (NO), which can react with lipid peroxyl radicals to terminate the lipid peroxidation chain reaction, protecting tumor cells from ferroptosis. Additionally, other proteins such as glutathione peroxidase 2 (GPX2), thioredoxin reductase 1 (TXNRD1) and stearoyl-CoA desaturase 1 (SCD1) have been reported to exert anti-ferroptosis effects in CRC through distinct mechanisms, further illustrating the redundancy and complexity of the ferroptosis defense network. The intricate regulatory network described above, comprising the core SLC7A11-GSH-GPX4 axis, the lipid metabolism pathway, iron homeostasis, and multiple bypass systems (FSP1-CoQ10, GCH1-BH4, DHODH, iNOS, GPX2, TXNRD1, and SCD1), provides a rich repertoire of pharmacological nodes for potential intervention [16]. The therapeutic implications of targeting these pathways, including their interplay with conventional treatments such as chemotherapy and radiotherapy, are discussed in detail in the following section.

Among these, GPX2, a gastrointestinal tract-specific glutathione peroxidase, exhibits significant tissue-specific overexpression in CRC, and its expression level is positively correlated with tumor stage and poor prognosis. Unlike GPX4, which is ubiquitously expressed and primarily localizes to the mitochondria and cytoplasm to scavenge lipid peroxides, GPX2 is predominantly localized in the cytoplasm and endoplasmic reticulum, with a preference for clearing water-soluble peroxides. However, recent studies have revealed that GPX2 indirectly participates in ferroptosis resistance by regulating the stability and activity of GPX4. Specifically, GPX2 inhibits endoplasmic reticulum stress-mediated PERK-eIF2α pathway, reducing the ubiquitination and proteasomal degradation of GPX4, thereby enhancing the ferroptosis defense capacity of CRC cells. Furthermore, GPX2 modulates the intracellular glutathione redox state, indirectly upregulating the expression and function of SLC7A11, forming a synergistic antioxidant network. This discovery uncovers the unique role of gastrointestinal-specific antioxidant enzymes in ferroptosis regulation in CRC, providing a novel target for the development of tissue-selective ferroptosis inducers [17].

Multiple therapeutic strategies targeting ferroptosis

Synergy of traditional therapy and ferroptosis

Radiotherapy and certain chemotherapeutic drugs (e.g., oxaliplatin and sorafenib) can indirectly induce ferroptosis and enhance its antitumor effects. Relevant studies have found that oxaliplatin can enhance the sensitivity of CRC cells to ferroptosis by consuming intracellular GSH or inducing oxidative stress [18]. However, other studies have pointed out that some traditional therapies may weaken the ferroptosis induction effect by activating Nrf2 and other protective pathways, thus reducing the therapeutic effect [19]. Therefore, it is of great significance to clarify the mutual regulation mechanism between traditional therapy and ferroptosis pathway for optimizing the combination therapy.

The interaction between chemotherapy and ferroptosis is complex and drug-specific, with different chemotherapeutic agents inducing ferroptosis through distinct mechanisms. Oxaliplatin, a first-line chemotherapeutic agent for CRC, not only depletes intracellular GSH but also upregulates ACSL4 expression, increasing the synthesis of peroxidation-susceptible PUFA-PLs. Furthermore, oxaliplatin-induced DNA damage activates the ATM-p53 pathway, and p53 transcriptionally represses SLC7A11 expression, further promoting ferroptosis [6]. In contrast, irinotecan, another commonly used CRC chemotherapeutic agent, exerts dual effects on ferroptosis. Its active metabolite SN-38 inhibits topoisomerase I and induces DNA damage, which upregulates TfR1 expression and increases intracellular iron levels, promoting ferroptosis. However, SN-38 also activates the Nrf2 pathway, which upregulates antioxidant genes and inhibits ferroptosis, leading to acquired resistance [13]. This dual effect explains why combining irinotecan with Nrf2 inhibitors significantly enhances its anti-tumor efficacy.

Radiotherapy, a cornerstone of CRC treatment, also induces ferroptosis through multiple mechanisms. Ionizing radiation directly generates ROS, which initiate lipid peroxidation. Additionally, radiotherapy upregulates ACSL4

and LOX expression, increasing the substrate pool for lipid peroxidation, and inhibits System Xc^- activity, reducing GSH synthesis. Radiation-induced DNA damage also activates the p53 pathway, contributing to ferroptosis induction. However, similar to chemotherapy, radiotherapy can activate the Nrf2 pathway as a protective response, limiting ferroptosis efficacy. Combining radiotherapy with Nrf2 inhibitors or ferroptosis inducers has shown promising synergistic effects in preclinical CRC models, highlighting the potential of this combination strategy in clinical practice.

Regulation of targeted therapy and immunotherapy on ferroptosis

Epidermal growth factor receptor (EGFR) or B-Raf proto-oncogene (BRAF) inhibitors can enhance the sensitivity of CRC cells to ferroptosis inducers by down regulating the expression levels of Nrf2 or SLC7A11 [20]. The combination of immune checkpoint inhibitors (e.g., anti-PD-1) and ferroptosis inducers has shown significant synergistic anti-tumor activity. Part of the mechanism is that ferroptosis can enhance the immunogenicity of tumor cells and improve the tumor immunosuppressive microenvironment, so as to improve the response rate of immunotherapy [21].

Beyond EGFR and BRAF inhibitors, other targeted therapies also interact with the ferroptosis pathway. MEK inhibitors, which are used in combination with BRAF inhibitors for BRAF-mutant CRC, downregulate Nrf2 expression through the MAPK pathway, enhancing ferroptosis sensitivity. Preclinical studies have shown that MEK inhibitors synergize with GPX4 inhibitors to induce robust ferroptosis in BRAF-mutant CRC cells, overcoming resistance to single-agent targeted therapy. PI3K/AKT/mTOR inhibitors, another class of targeted agents, modulate ferroptosis through autophagy regulation. Inhibition of mTOR activates autophagy, which promotes ferritinophagy (the autophagic degradation of ferritin), increasing intracellular labile iron levels and promoting ferroptosis. However, PI3K inhibition can also activate the Nrf2 pathway, creating a complex regulatory network that requires careful optimization of combination regimens.

The interaction between immunotherapy and ferroptosis is bidirectional and multifaceted. On one hand, immune cells actively regulate tumor cell ferroptosis. $CD8^+$ T cells, the key effectors of anti-tumor immunity, secrete interferon-γ (IFN-γ), which downregulates SLC7A11 expression in tumor cells, reducing cystine uptake and GSH synthesis, thereby sensitizing tumor cells to ferroptosis. Conversely, immunosuppressive cells in the tumor microenvironment, such as regulatory T cells (Tregs) and M2-type TAMs, secrete cytokines like IL-10 and TGF-β, which upregulate GPX4 and FSP1 expression in tumor cells, inhibiting ferroptosis. On the other hand, ferroptosis profoundly shapes the tumor immune microenvironment. Ferroptotic cells release damage-associated molecular patterns (DAMPs) such as ATP, HMGB1 and heat shock proteins, which activate dendritic cells and promote anti-tumor T cell responses. However, excessive ferroptosis can also release large amounts of pro-inflammatory lipid mediators and prostaglandin E2 (PGE2), which recruit immunosuppressive cells and inhibit $CD8^+$ T cell function. This dual role of ferroptosis in immunomodulation highlights the need to precisely control the magnitude and duration of ferroptosis induction to maximize therapeutic benefit.

Regulation of natural products on ferroptosis

Natural products have become important lead compounds in the development of single-molecule multi-target drugs due to their multi-target regulatory characteristics and low toxicity. In addition to ace, berberine can simultaneously regulate ROS generation, mitochondrial function, inflammatory and immune pathways and ferroptosis process, and inhibit the occurrence and development of CRC from multiple dimensions [22]. Luteolin induces ferroptosis by inhibiting GPX4 activity, while enhancing $CD8^+$ T cell infiltration and improving tumor immune microenvironment [23]. Ursolic acid can directly inhibit SLC7A11/System Xc^- function while simultaneously regulating ferroptosis signaling through the miR-214-3p/STAT3/GPX4 axis, achieving a dual inhibitory effect [24]. The multi-target mode of action of these natural products provides a natural template for the development of single-molecule drugs.

Resistance mechanisms to ferroptosis inducers in CRC and counter-strategies

Resistance to ferroptosis inducers in CRC arises from multiple molecular and cellular mecha-

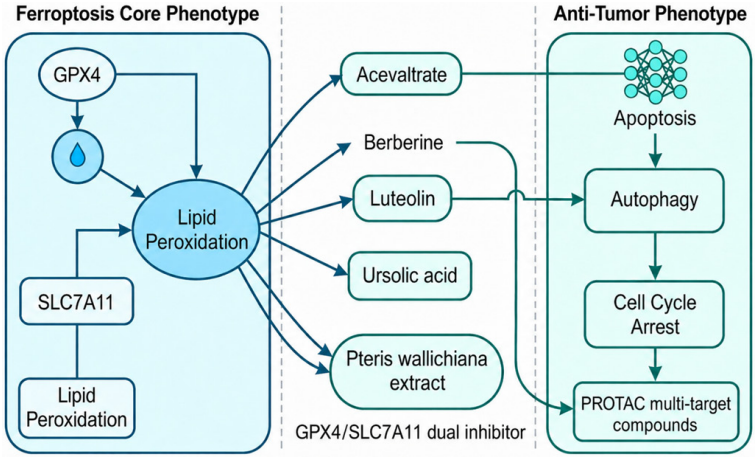

Figure 2. Typical mechanism of single-molecule multi-target regulation of ferroptosis. Abbreviations: GPX4, glutathione peroxidase 4; SLC7A11, solute carrier family 7 member 11; PROTAC, proteolysis-targeting chimera.

nisms. First, missense mutations (e.g., U46C) or transcriptional upregulation of GPX4 reduce drug binding affinity and enhance lipid peroxide scavenging capacity [25, 26]. Second, compensatory activation of the FSP1-CoQ10 bypass pathway, which is frequently upregulated upon GPX4 inhibition, provides an alternative glutathione-independent antioxidant system [16]. Third, constitutive activation of Nrf2 due to Keap1 or Nrf2 mutations drives over-expression of multiple antioxidant genes (SLC7A11, HO-1, NQO1), collectively blunting ferroptosis induction [27]. Fourth, the tumor microenvironment (TME) contributes to ferroptosis resistance. Cancer-associated fibroblasts (CAFs) secrete TGF-β and IL-6, upregulating SLC7A11 and GPX4 expression in CRC cells while promoting ferritin synthesis to reduce the labile iron pool. Tumor-associated macrophages (TAMs) secrete arginase-1 (ARG-1), depleting arginine and inhibiting nitric oxide synthesis, thereby reducing termination of lipid peroxidation chain reactions. Hypoxic conditions activate HIF-1α signaling, upregulating FSP1 and GCH1 expression [28]. To overcome these resistance mechanisms, dual-target inhibition strategies (e.g., simultaneous targeting of GPX4 and FSP1) or combination with Nrf2 inhibitors have shown preclinical efficacy.

Research progress of single-molecule multi-target regulation of ferroptosis

The single-molecule multi-target strategy can effectively kill CRC by integrating ferroptosis pathway and other anti-tumor pathways. According to the type of compounds, it can be divided into the following three categories (**Figure 2**).

Natural product single-molecule multi target compound

Natural products are an important source of single-molecule multi-target drugs. Their multi-target activities are derived from complex chemical structures, which can simultaneously regulate ferroptosis and immune and metabolic pathways.

ACE is a small-molecule compound identified from natural product libraries that specifically induces ferroptosis in CRC cells by dual-targeting polypyrimidine tract-binding protein 1/2 (PCBP 1/2) and GPX4 [29]. On the one hand, ACE can directly combine with pcbp1/2 and induce its degradation, promote the release of divalent iron ions (Fe^{2+}) in cells, and mediate the generation of a large number of reactive oxygen species (ROS) through Fenton reaction; On the other hand, ACE can directly bind to the selenocysteine (U46) site of GPX4, inhibit its enzyme activity and promote its ubiquitination degradation, blocking the clearance of lipid peroxide [30]. In vivo experiments show that ACE has better inhibitory effect on CRC xenograft tumor than capecitabine, sorafenib and other commonly used drugs, and has no obvious toxicity. Its multi-target mode of action can effectively avoid the pathway compensation after single target inhibition [31].

Berberine, an alkaloid widely found in traditional Chinese medicine such as Coptis chinensis and Phellodendron amurense, can simultaneously regulate ROS generation, mitochondrial function, inflammatory/immune pathways and ferroptosis, and improve CRC progression in multiple dimensions [32]. Studies have found that berberine can promote ROS accumulation by inhibiting the activity of mitochondrial complex I, while down regulating the expression of SLC7A11, reducing GSH synthesis and enhancing GPX4 inactivation mediated ferroptosis [33]. In addition, other studies have found that it can inhibit the NF-κB inflammatory pathway,

improve the tumor immune microenvironment, and enhance the synergistic effect of anti-tumor immunity and ferroptosis [34].

Luteolin is a natural flavonoid compound with both ferroptosis regulation and immune enhancement functions [35]. Studies have demonstrated that luteolin induces ferroptosis in colon cancer by directly targeting GPX4 or through HIC1-mediated inhibition of GPX4 expression [36]. At the same time, it can inhibit NF-κB inflammatory pathway, activate $CD8^+$ T cell infiltration, enhance anti-tumor immune response, realize the dual regulation of "ferroptosis + immunity", improve the inhibitory effect on CRC, and alleviate the immunosuppression caused by chemotherapy drugs [37].

Curcumin, a polyphenol compound extracted from Curcuma longa, is another promising natural multi-target ferroptosis inducer with excellent safety and anti-tumor activity. In CRC cells, curcumin exerts its ferroptosis-inducing effect through multiple synergistic mechanisms: it directly binds to the active site of GPX4 and inhibits its enzymatic activity, while downregulating SLC7A11 expression at the transcriptional level by inhibiting the Nrf2 pathway, reducing cystine uptake and GSH synthesis. Furthermore, curcumin promotes ferritinophagy by upregulating NCOA4 expression, increasing the intracellular labile iron pool and enhancing Fenton reaction-mediated ROS generation. Notably, curcumin also modulates the CRC immune microenvironment by inhibiting the polarization of M2-type TAMs and promoting the infiltration of $CD8^+$ T cells, achieving the triple regulatory effect of "ferroptosis induction + immune activation + TME remodeling". Preclinical studies have shown that curcumin significantly enhances the anti-tumor efficacy of oxaliplatin and anti-PD-1 antibodies in CRC xenograft models, with no obvious systemic toxicity [38].

Ursolic acid is a triterpenoid compound existing in hawthorn, Ligustrum lucidum and other plants, which regulates ferroptosis and related signals through two pathways [39]. On the one hand, ursolic acid directly inhibited the activity of SLC7A11/System Xc^- and reduced cystine uptake and GSH synthesis; On the other hand, by regulating miR-214-3p/STAT3/GPX4 axis, it can down regulate STAT3 expression, indirectly inhibit GPX4 transcription, double block the anti-ferroptosis pathway, effectively inhibit the proliferation of CRC cells and reverse chemotherapy resistance [40].

Pteris wallichiana extract can act on the SLC7A11-GSH-GPX4 AXIS with multiple targets. It can effectively reverse the chemotherapy resistance of CRC cells to oxaliplatin and 5-FU by inhibiting the expression of SLC7A11, reducing the content of GSH, and directly inhibiting the activity of GPX4. Its multi-target characteristics can avoid the compensatory increase of GSH synthesis caused by single node inhibition [41].

Small molecule targeted drugs or synthetic compounds

Through precise structural design, synthetic compounds can achieve the coordinated regulation of ferroptosis pathway and traditional targeting pathway, and some of them have shown good application potential.

MP-HJ-1b, a novel colchicine-binding-site microtubule inhibitor, has been shown to promote ferroptosis by downregulating SLC7A11 and GPX4 expression, accompanied by glutathione depletion and increased iron-dependent lipid peroxidation. Although this mechanism has been demonstrated in cervical cancer cells, its applicability to CRC remains to be experimentally validated [42]. These compounds show stronger killing activity than single inhibitors in CRC cell lines and lower cytotoxicity to normal cells. Their design idea is "dual node blocking of core pathway" [43]. Beyond GPX4/SLC7A11 dual inhibitors, GPX4/FSP1 dual inhibitors have emerged as a promising new class of ferroptosis inducers. By simultaneously inhibiting the core GSH-GPX4 axis and the FSP1-CoQ10 bypass pathway, these compounds completely abrogate the cellular antioxidant defense system, resulting in robust ferroptosis induction even in drug-resistant CRC cells. Preclinical studies have shown that a rationally designed GPX4/FSP1 dual inhibitor exhibits 10-fold higher potency than RSL3 in CRC cell lines and significantly reduced toxicity to normal intestinal epithelial cells.

Protein degradation targeting chimera (PROTAC) multi-target compounds are new anti-tumor compounds designed based on PROTAC technology, which can couple ferroptosis tar-

gets with traditional oncogene targets [44]. For example, the bifunctional PROTAC targeting ROS and EGFR simultaneously promotes GPX4 ubiquitination and proteasome degradation by binding EGFR at one end and recruiting ubiquitin ligase at the other, thereby blocking tumor proliferation signals while inducing ferroptosis [45]. Although there are few studies on CRC at present, this design concept provides a new direction for the single-molecule integration of "ferroptosis + targeted therapy". Recent advances in PROTAC technology have led to the development of dual-target PROTACs that can simultaneously degrade two different proteins. For instance, a PROTAC that degrades both GPX4 and FSP1 has been shown to induce potent ferroptosis in hepatoma cells with minimal off-target effects. Additionally, PROTACs targeting SLC7A11 and Nrf2 are under development, offering the potential to simultaneously block multiple anti-ferroptosis pathways. Covalent PROTACs, which form irreversible bonds with their target proteins, represent another promising direction, offering prolonged duration of action and lower required doses.

"One drug multimodal death" inducer

Certain single-molecule can simultaneously induce multiple programmed cell death modalities, including ferroptosis, apoptosis, autophagy, pyroptosis, thereby enhancing CRC cell killing efficiency and effectively circumventing tumor resistance induced by single cell death pathway [46]. For example, some natural product derivatives can activate the ferroptosis and apoptosis pathways at the same time: by inhibiting SLC7A11/GPX4 to induce ferroptosis and activating caspase-3/caspase-9 mediated apoptosis pathway, CRC cells can be doubly killed; Moreover, it can induce the transformation from protective autophagy to lethal autophagy by regulating autophagy related proteins such as beclin-1 and LC3, and further enhance the anti-tumor effect [47]. These molecules still have high killing activity in CRC resistant cells. Because their multimodal effects can cover the compensatory pathway of drug-resistant cells, they provide a new direction for the treatment of drug-resistant CRC.

Different combinations of cell death modalities exhibit distinct synergistic mechanisms and therapeutic advantages. Ferroptosis-pyroptosis combination, for example, is particularly effective in enhancing anti-tumor immunity. Ferroptosis-induced ROS and lipid peroxidation products activate the NLRP3 inflammasome, leading to caspase-1-mediated pyroptosis. Pyroptotic cells release large amounts of pro-inflammatory cytokines and DAMPs, which potently activate dendritic cells and prime anti-tumor T cell responses. This immunostimulatory effect makes ferroptosis-pyroptosis inducers ideal candidates for combination with immune checkpoint inhibitors. Ferroptosis-necroptosis combination, on the other hand, is highly effective against apoptosis-resistant CRC cells. Necroptosis is a caspase-independent form of cell death mediated by the RIPK1/RIPK3/MLKL pathway, and ferroptosis can activate RIPK3 through ROS-mediated mechanisms. Simultaneous induction of ferroptosis and necroptosis ensures that tumor cells cannot escape cell death by downregulating apoptotic pathways [47].

The design of "one drug multimodal death" inducers follows several strategic approaches. The multi-target design approach involves creating a single-molecule that binds to key regulators of different cell death pathways, such as a compound that inhibits both GPX4 (ferroptosis) and Bcl-2 (apoptosis). The prodrug approach involves designing a single prodrug that is activated in the tumor microenvironment to release two or more active moieties, each inducing a different cell death modality. The nano-delivery approach involves encapsulating multiple cell death inducers within a single nanoparticle, enabling synchronized release and synergistic action at the tumor site.

Single-molecule multi-target drug development and design concept with ferroptosis as the core

Based on the existing research results, the development of single-molecule multi-target drugs with ferroptosis as the core should follow the design concept of "structure optimization target integration delivery efficiency", and combine the pathological characteristics of CRC and the regulation law of ferroptosis to achieve the balance between efficacy and safety.

Structural transformation led by natural products

Natural products serve as important lead templates for the development of single-molecule

multi-target drugs. The core of their structural transformation is to optimize affinity for core ferroptosis targets (e.g., GPX4, SLC7A11, ACSL4, PCBP1/2), while retaining or enhancing regulatory capacity over immune, metabolic, and inflammatory pathways [48-50]. As described in detail in Section 3.1, several natural products (such as Ace, luteolin, berberine, and ursolic acid) exhibit multi-target ferroptosis-regulating activities. Based on these lead compounds, structural modification strategies - such as core structure optimization, functional group substitution, and enhanced metabolic stability - are employed to improve target selectivity and in vivo efficacy [51]. During structural transformation, techniques including molecular docking and micro-scale thermophoresis (MST) should be used to accurately predict the binding mode between the molecule and its targets, thereby ensuring the synergy of multi-target regulation [49].

Integrated design strategy of "site + pathway"

Single-molecule multi-target drug design focuses on the core pathway network of ferroptosis regulation in CRC, and adopts the integrated design idea of "site + pathway" to optimize the comprehensive effect of compounds on multiple key regulatory nodes. For the core axis of SLC7A11-GSH-GPX4, molecules that can simultaneously act on the two key sites of SLC7A11 and GPX4 are designed to block the pathway compensation [38]. For the cross network of ferroptosis and immune escape, the nanogel conjugate targeting GPX4 and PD-L1 are designed to achieve the dual effect of "ferroptosis induction + immune activation" [52]. In addition, it is necessary to combine bioinformatics and machine learning technology to screen ferroptosis related hub genes (e.g., NOX4, TFR2, ALOXE3) in CRC, and give priority to the cross path where the hub gene is located as the core of multi-target design, so as to improve the pertinence and efficacy of drugs [53].

Functional synergy of nano delivery/prodrug forms

Nano delivery system and prodrug technology can endow single-molecule multi-target drugs with "multi-target" characteristics at the functional level, and realize precise enrichment and multi-channel regulation of drugs in CRC tissues through tumor microenvironment (TME) triggering, multi-stage release and other mechanisms [54, 55]. Studies have found that the construction of pH sensitive nano carrier loaded with ace can trigger drug release in the CRC acidic microenvironment, and the carrier material can remove immunosuppressive factors in the tumor microenvironment, and enhance the ferroptosis induction effect and anti-tumor immune response of ACE [56, 57]. The prodrug based on the activation of tumor specific enzymes (such as matrix metalloproteinases) is designed to release ferroptosis inducing group and immune regulatory group at the same time after activation in tumor tissue, which can achieve multi-target synergy at the functional level [58, 59]. Such delivery systems can significantly reduce the off-target toxicity of drugs and improve the therapeutic effect on metastatic CRC. For example, bispecific antibody drug conjugates (bsADC) deliver rsl3, which can target CDH17/GUCY2C receptors, and reduce the tumor volume by 82% in CRC model without hepatotoxicity [60].

Optimization directions based on existing research experience

Drug development needs to learn from the research experience and lessons of existing ferroptosis drugs: avoid the activation of bypass anti ferroptosis pathway caused by single inhibition of GPX4, and give priority to the design of multi-target molecules that simultaneously inhibit the core pathway and bypass system (such as FSP1-CoQ10 axis); In view of the toxicity of ferroptosis inducers, structural modification can enhance tumor tissue selectivity, or nano delivery system can be used to reduce the damage to normal intestinal epithelial cells; For new molecules such as PROTACs, it is necessary to optimize their degradation efficiency and pharmacokinetic characteristics to solve the toxicity problem caused by off-target degradation [61, 62].

Structure-activity relationships and molecular design insights

For ACE, the cyclopentane ring and α,β-unsaturated lactone moiety are critical for binding to PCBP1/2 (Cys54) and GPX4 (Sec46). Methylation of the lactone ring reduces binding affinity by > 70%, highlighting the importance of the Michael acceptor for covalent interac-

tion. The C-1 hydroxyl group on the cyclopentane ring forms a hydrogen bond with the backbone carbonyl of Gly53 in PCBP1/2, and its removal results in a 4-fold decrease in binding affinity. The C-6 methyl group enhances lipophilicity and cell membrane permeability, but substitution with larger alkyl groups introduces steric hindrance and reduces target binding. The glycosyl moiety of ACE, although not directly involved in target binding, is essential for intestinal absorption and oral bioavailability. Deglycosylated ACE exhibits increased lipophilicity but significantly reduced oral absorption due to poor solubility in intestinal fluids.

For Luteolin, the 5,7-dihydroxy groups on ring A and the 3',4'-catechol structure on ring B are essential for Nrf2 inhibition and ferroptosis induction. The 5,7-dihydroxy groups on ring A fit into the hydrophobic pocket of Keap1, disrupting the Keap1-Nrf2 interaction and promoting Nrf2 degradation. Methylation of either the 5- or 7-hydroxyl group abolishes Keap1 binding and Nrf2 inhibitory activity. The 3',4'-catechol structure on ring B is responsible for ROS scavenging and GPX4 inhibition. Oxidation of the catechol group to a quinone forms a covalent adduct with the selenocysteine residue of GPX4, irreversibly inhibiting its activity. The 2,3-double bond and 4-carbonyl group on ring C maintain the planar conformation of the flavonoid skeleton, which is critical for optimal binding to both Keap1 and GPX4 [35].

For ursolic acid, the pentacyclic triterpene backbone with a carboxyl group at C-17 is responsible for SLC7A11 inhibition. The C-17 carboxyl group forms ionic interactions with Arg137 in the extracellular domain of SLC7A11, blocking cystine transport. Esterification or amidation of the C-17 carboxyl group significantly reduces SLC7A11 inhibitory activity but improves lipophilicity and oral bioavailability. The C-3 hydroxyl group is essential for STAT3 inhibition, forming a hydrogen bond with Tyr705 in the SH2 domain of STAT3, preventing its phosphorylation and dimerization. Oxidation of the C-3 hydroxyl group to a ketone abolishes STAT3 inhibitory activity. The double bonds between C-12-C-13 contribute to the rigidity of the triterpene backbone, and their reduction leads to decreased target binding affinity and anti-tumor activity [39, 40].

Several rational drug design approaches have been successfully applied to the development of multi-target ferroptosis inducers. Fragment-based drug design involves identifying small molecular fragments that bind to individual targets, then linking or merging these fragments to create a single-molecule with multi-target activity. Pharmacophore fusion combines the essential pharmacophoric features of different target ligands into a single-molecule, ensuring that it satisfies the binding requirements of all intended targets. Structure-based rational design guided by co-crystal structures is the core technology to solve the problem of imbalanced activity of multi-target drugs. In recent years, the high-resolution co-crystal structures of GPX4, SLC7A11 and FSP1 have been successively resolved respectively, providing atomic-level insights for the rational design of multi-target molecules. For example, by analyzing the co-crystal structure of GPX4 and RSL3, researchers identified an unutilized hydrophobic extension region in its active pocket, which can be used to introduce specific pharmacophores that bind to FSP1, thus achieving precise balanced inhibition of both targets. This structure-based pharmacophore fusion strategy not only significantly improves the target selectivity of molecules but also effectively reduces off-target toxicity, and has become the key mainstream method for the development of next-generation multi-target ferroptosis drugs.

Challenges and future perspectives

Current challenges

Despite the promising preclinical landscape, translating single-molecule multi-target ferroptosis-based therapies into clinical practice for CRC faces several significant challenges.

Challenges in controlling the double-edged sword effect of ferroptosis: Excessive induction of ferroptosis may cause intestinal inflammation, immunosuppression, and even promote tumor progression, whereas insufficient induction fails to overcome drug resistance. In preclinical CRC liver metastasis models, excessive ferroptosis has been shown to cause severe liver inflammation and tissue damage, which may paradoxically promote tumor cell seeding [63].

The detrimental effects of excessive ferroptosis are mediated through several distinct molecular and cellular mechanisms. First, ferrop-

totic cells release damage-associated molecular patterns (DAMPs) such as ATP, high-mobility group box 1 (HMGB1), and heat shock proteins, which activate the NLRP3 inflammasome in macrophages and dendritic cells. NLRP3 activation triggers caspase-1-mediated cleavage of pro-IL-1β and pro-IL-18, leading to the release of mature IL-1β and IL-18, which potentiate local and systemic inflammation. In the CRC microenvironment, IL-1β promotes the recruitment of myeloid-derived suppressor cells (MDSCs) and M2-type tumor-associated macrophages (TAMs), which secrete immunosuppressive cytokines such as IL-10 and TGF-β, thereby inhibiting $CD8^+$ T cell-mediated antitumor immunity [64].

Second, lipid peroxidation products generated during ferroptosis, including 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA), can act as chemoattractants for immunosuppressive cells. 4-HNE has been shown to upregulate the expression of CCL2 and CXCL8 in CRC cells, promoting the recruitment of MDSCs and regulatory T cells (Tregs) into the tumor microenvironment. These recruited immunosuppressive cells further secrete factors that protect residual tumor cells from ferroptosis, creating a vicious cycle of inflammation-induced immune evasion [65]. Third, excessive ferroptosis can damage intestinal epithelial barrier function, leading to increased intestinal permeability and translocation of bacterial lipopolysaccharide (LPS). LPS activates Toll-like receptor 4 (TLR4) signaling on immune cells, which not only amplifies systemic inflammation but also upregulates GPX4 and FSP1 expression in tumor cells through NF-κB-mediated transcriptional activation, paradoxically conferring resistance to further ferroptosis induction [66].

To mitigate these adverse effects, several regulatory strategies have been proposed and are under active investigation:

Intermittent dosing regimens. Preclinical studies in CRC xenograft models have demonstrated that intermittent administration of ferroptosis inducers achieves comparable antitumor efficacy to continuous dosing while significantly reducing intestinal inflammation and liver toxicity. Intermittent dosing allows normal tissues to replenish their antioxidant defenses between treatment cycles, minimizing collateral damage [67].

Targeted delivery systems. Nanoparticle-based delivery systems, such as pH-sensitive liposomes and tumor-targeting peptide-conjugated nanocarriers, can selectively deliver ferroptosis inducers to CRC tissues while sparing normal intestinal epithelial cells. For example, bispecific antibody-drug conjugates (bsADCs) targeting CDH17 and GUCY2C have been shown to deliver the ferroptosis inducer RSL3 specifically to CRC cells without detectable hepatotoxicity or intestinal damage [60]. Similarly, hyaluronic acid-based nanoparticles targeting CD44-overexpressing CRC cells have demonstrated enhanced tumor accumulation and reduced systemic toxicity of GPX4 inhibitors [68].

Combination with anti-inflammatory agents. Co-administration of ferroptosis inducers with anti-inflammatory drugs, such as NLRP3 inhibitors or IL-1β neutralizing antibodies, has been shown to prevent ferroptosis-induced inflammation without compromising anti-tumor efficacy. In a CRC liver metastasis model, combination of a GPX4 inhibitor with an IL-1β antibody significantly reduced liver inflammation and metastatic outgrowth compared with the ferroptosis inducer alone [69].

Ferroptosis inhibitors as antidotes. For severe off-target ferroptosis, small-molecule ferroptosis inhibitors such as ferrostatin-1 and liproxstatin-1 can be administered as antidotes to limit tissue damage. These inhibitors scavenge lipid peroxyl radicals and prevent the propagation of lipid peroxidation, effectively rescuing normal tissues from ferroptotic damage [70].

Lack of clinical data and validated biomarkers: Most studies remain at the preclinical stage. Although some ferroptosis inducers have entered clinical trials for solid tumors, specific data for CRC are scarce. No validated biomarkers exist for patient stratification or efficacy monitoring [71, 72]. Failed trials (e.g., sulfasalazine, artesunate) highlight the need for rational drug design, patient selection, and combination strategies [73, 74].

Difficulty in achieving balanced multi-target activity: An ideal multi-target drug requires potent and balanced activity against all intended targets while minimizing off-target effects. In practice, many putative multi-target com-

pounds exhibit highly imbalanced affinities, resulting in efficacy comparable to single-target agents. Increasing the number of targeted pathways also raises the risk of toxicity. Balancing efficacy, selectivity, and safety remains a major technical hurdle.

Clinical translation status and challenges

Ongoing clinical trials of ferroptosis-targeting agents in CRC: At present, several ferroptosis-related agents have entered clinical trials for the treatment of CRC, most of which are in phase I or phase II stages. These trials mainly evaluate the safety, tolerability, and preliminary efficacy of ferroptosis inducers alone or in combination with chemotherapy, targeted therapy, or immunotherapy (**Table 2**).

Failed clinical attempts and lessons learned: Despite promising preclinical results, several ferroptosis-targeting agents have failed in clinical trials for CRC. Among the available clinical studies, sorafenib combined with SBRT represents one of the most clinically advanced ferroptosis-related strategies for CRC. The phase II study linked high SLC7A11 expression with radioresistance and showed that sorafenib could enhance SBRT-induced ferroptosis. However, the evidence was derived from a single-arm study of colorectal liver metastases, and its findings cannot yet be generalized to the broader CRC population [73].

Cetuximab represents a combination strategy with potential translational value. Clinically, cetuximab is mainly used for RAS-wild-type metastatic CRC, whereas its ferroptosis-sensitizing effect was demonstrated in KRAS-mutant CRC cells and xenograft models treated with RSL3 [74]. Therefore, cetuximab combined with RSL3 should be regarded as a preclinical strategy for overcoming treatment resistance rather than evidence that ferroptosis contributes to the established clinical mechanism of cetuximab.

These limitations highlight the importance of rational drug design, patient stratification, and combination therapy strategies in the clinical development of ferroptosis-targeting agents.

Biomarker development for ferroptosis in CRC: Biomarker development is critical for the clinical translation of ferroptosis-targeting therapies. Potential biomarkers for ferroptosis in CRC can be divided into three categories:

Tissue biomarkers: These include the expression levels of ferroptosis core regulators (GPX4, SLC7A11, ACSL4, FSP1, Nrf2), lipid peroxidation products (4-HNE, MDA), and iron metabolism markers (TfR1, ferritin). High expression of GPX4 and SLC7A11 is associated with poor prognosis and resistance to ferroptosis inducers [75].

Circulating biomarkers: These include serum levels of iron, ferritin, MDA, and circulating tumor DNA (ctDNA) mutations in ferroptosis-related genes. Recent studies have shown that serum ferritin levels > 300 ng/mL are associated with better response to ferroptosis-inducing chemotherapy in CRC patients [76].

Imaging biomarkers: Magnetic resonance imaging (MRI) techniques such as T2*-weighted imaging and chemical exchange saturation transfer (CEST) can non-invasively detect iron accumulation and lipid peroxidation in tumor tissues, providing real-time monitoring of ferroptosis induction [77].

However, there is currently no validated biomarker for clinical use. Future research should focus on developing multi-biomarker panels that can accurately predict patient response to ferroptosis-targeting therapies.

Future perspectives

Combined with the development of multi-target strategy of intestinal microorganisms ferroptosis axis: intestinal microorganisms can regulate the ferroptosis pathway of CRC through metabolites, such as DCA secreted by C. scindens inhibits the function of immune cells, and IDA secreted by P. anaerobius activates the anti ferroptosis axis. In the future, single-molecule multi-target drugs targeting both ferroptosis pathway and intestinal microbial metabolism can be designed, or the efficacy of ferroptosis inducers can be enhanced by adjusting the composition of intestinal microorganisms, so as to build a trinity treatment system of the microbiota-ferroptosis-immunity axis.

Develop “one drug multi pathway” comprehensive treatment scheme: use single-molecule

Table 2. Clinical-stage ferroptosis-targeting agents for colorectal cancer

Agent name	Mechanism of action	Trial phase	Trial number	Primary endpoint	Status	Main limitations
Sorafenib + SBRT	Inhibits SLC7A11-mediated antioxidant defence and enhances SBRT-induced ferroptosis	II	Not stated in the PubMed record	Efficacy and safety; primary endpoint not specified	Completed; results published	Small single-arm study limited to CRC liver metastases; sorafenib is not SLC7A11-selective
Artesunate	Inhibits the CDK5/NRF2/GPX4 pathway and induces ferroptosis	Randomized pilot study	ISRCTN05203252	TUNEL-positive apoptotic cells (>7%)	Completed; results published	Only 23 patients were included; apoptosis rather than ferroptosis was assessed clinically
Trifluridine/tipiracil, (TAS-102)	Activates the p53–SLC7A11 axis to induce ferroptosis	III	NCT01607957	Overall survival	Completed; approved for previously treated metastatic CRC	Ferroptosis was not evaluated in the pivotal trial and is supported mainly by preclinical
Oxaliplatin/FOLFOX	Promotes oxidative stress and ferroptosis partly through NRF2 inhibition	III	MOSAIC; NCT number not reported in the publication	Disease-free survival	Completed; established standard treatment for CRC	Ferroptosis was not assessed clinically and remains a secondary preclinical mechanism
Regorafenib	Induces ferroptotic stress; the MYLK4-p53-SCD1 axis contributes to resistance	III	NCT01103323	Overall survival	Completed; approved for refractory metastatic CRC	Clinical trials did not assess ferroptosis; mechanistic evidence remains preclinical
Cetuximab	Enhances RSL3-induced ferroptosis by suppressing the NRF2/HO-1 pathway	III	NCT00154102	Progression-free survival	Completed;approved for RAS-wild-type metastatic CRC	Based on KRAS-mutant models with RSL3; clinical use is limited to RAS-wild-type CRC

Abbreviations: CRC, colorectal cancer; SBRT, stereotactic body radiotherapy; GSH, glutathione; NRF2, nuclear factor erythroid 2-related factor 2; GPX4, glutathione peroxidase 4; ORR, objective response rate; DCR, disease control rate; DFS, disease-free survival; PFS, progression-free survival; OS, overall survival.

multi-target drugs, immune checkpoint inhibitors, radiotherapy and chemotherapy to construct comprehensive treatment scheme. For example, ferroptosis induced multi-target drugs can reshape the tumor microenvironment and enhance the response rate of PD-1/PD-L1 inhibitors; Combined with oxaliplatin can synergistically inhibit the progression of CRC and reduce the dose and toxicity of chemotherapy. At the same time, it is necessary to develop personalized treatment plans based on the patient's genetic characteristics and intestinal microbial composition with the help of precision medical technology.

Strengthen translational medicine research and improve the clinical evaluation system: accelerate the preclinical research of single-molecule multi-target drugs and optimize the pharmacokinetics and toxicity characteristics of drugs; Carry out early clinical trials, explore the safe dose and efficacy evaluation index of drugs, and establish the detection system of ferroptosis related biomarkers (such as MDA, Fe^{2+} level, GPX4 expression) for clinical patient screening and efficacy monitoring. In addition, it is necessary to strengthen interdisciplinary cooperation and promote clinical transformation in this field by combining technological breakthroughs in structural biology, nanomedicine, microbiology and other fields.

Artificial intelligence (AI) is poised to revolutionize the development of single-molecule multi-target ferroptosis drugs. Machine learning algorithms can analyze large-scale omics data from CRC patients to identify novel ferroptosis-related targets and predict optimal target combinations for multi-target therapy. Generative AI models can automatically design novel molecular structures with predicted multi-target activity, significantly accelerating the lead discovery process. AI models can also predict the pharmacokinetic properties, toxicity and in vivo efficacy of candidate compounds, reducing the number of compounds that need to be synthesized and tested experimentally.

Patient-derived organoids (PDOs) and organ-on-a-chip technologies represent another promising direction for advancing ferroptosis drug development. CRC PDOs retain the genetic and phenotypic heterogeneity of the original patient tumors, providing a more physiologically relevant model for drug screening than traditional cell lines. PDOs can be used to identify patient subpopulations that are most likely to respond to ferroptosis-based therapies and to evaluate the efficacy of multi-target drugs in a personalized manner. Organ-on-a-chip systems, which mimic the structure and function of human organs, can more accurately predict the pharmacokinetics and organ-specific toxicity of candidate drugs, reducing the reliance on animal models and improving the success rate of clinical translation.

Conclusion

Ferroptosis, as a novel form of regulated cell death, provides promising therapeutic targets and strategies for colorectal cancer treatment. Single-molecule multi target drugs, by simultaneously acting on multiple key nodes within the ferroptosis regulatory network, effectively overcome the resistance issues associated with traditional single target agents and combination therapies, exhibiting significant synergistic anti-tumor effects.

Importantly, this review proposes a "site + pathway" integrated design concept for ferroptosis-based multi-target drugs, which prioritizes simultaneous blockade of core nodes (e.g., SLC7A11-GPX4) and key bypass systems (e.g., FSP1-CoQ10) within the same molecule. This concept, together with the "structure optimization - target integration - delivery efficiency" trinity framework, offers a practical roadmap for rational drug design.

Looking forward, several actionable directions should be prioritized to accelerate clinical translation. AI-assisted drug design can predict optimal target combinations, generate novel molecular structures with balanced multi-target activities, and forecast pharmacokinetic and toxicity profiles, significantly reducing the number of compounds requiring synthesis and experimental testing. PDO models and organ on a chip technology can recapitulate the genetic and phenotypic heterogeneity of CRC, enabling personalized efficacy evaluation and more accurate prediction of organ specific toxicity before clinical trials. Additionally, integrating multi target ferroptosis inducers with existing immunotherapies and leveraging intestinal microbiota modulation represent promising

combination strategies. Strengthening translational research and establishing validated biomarker panels for patient stratification will be essential to translate these preclinical advances into clinical benefit for CRC patients.

Disclosure of conflict of interest

None.

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