Ferroptosis in colorectal cancer: Molecular mechanisms and regulatory crosstalk with therapeutic prospects (Review)

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Received March 18, 2026; Accepted May 7, 2026

DOI: 10.3892/or.2026.9143

Abstract. Colorectal cancer (CRC) is a common malignancy of the colonic and rectal epithelia. Numerous patients with CRC derive only limited and unsustained benefit from conventional chemotherapy or immunotherapy, underscoring the need for novel treatments. Ferroptosis is an iron-dependent, lipid peroxidation-driven form of regulated cell death, controlled by iron and lipid metabolism, as well as antioxidant defense pathways, which represent attractive therapeutic targets. Ferroptosis-related genes are closely linked to immune status, and metabolic reprogramming within the tumor microenvironment can modulate immune cell activation and antitumor immunity. Induction of ferroptosis suppresses CRC proliferation and overcomes resistance to cytotoxic drugs, whereas inhibition of ferroptosis may alleviate inflammatory bowel disease and limit CRC initiation in specific settings. This review summarizes the molecular basis and immunological relevance of ferroptosis in CRC, and discusses recent advances in combination strategies involving chemotherapy, immunotherapy, gut microbiota-based therapy and nanotherapy, as well as current clinical progress, potential biomarkers and translational challenges.

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Key words: ferroptosis, colorectal cancer, antitumor immunity, gut microbiota, nanotherapy

1. Introduction

Colorectal cancer (CRC) is a leading cause of mortality from cancer worldwide and is among the most frequent malignancies of the digestive tract. CRC has been calculated to be the third cancer type globally with regard to cancer incidence and second in relation to cancer mortality, with this imposing large economic and psychosocial burdens on patients, families and healthcare systems (1). The pathogenesis of CRC is multifactorial in origin, exhibiting a complex causative association with obesity, dietary patterns, physical inactivity, inherited susceptibility and chronic intestinal inflammation, including inflammatory bowel disease (IBD) (2). Standard management techniques rely on surgical resection, complemented by chemotherapy, molecularly targeted agents and immunotherapy (3). Despite this, high rates of postoperative relapse, a limited response to systemic therapy and a restricted set of actionable targets contribute to adverse outcomes; the 5-year survival estimate for patients with unresectable disease or distant metastases remains ~15% (4). These challenges emphasize the pressing need to formulate novel therapeutic strategies to better manage CRC and enhance patient survival.

Ferroptosis is a form of programmed cell death driven by iron-dependent lipid peroxidation (LPO), first proposed and explained by Dixon *et al* (5). Ferroptosis differs from apoptosis, autophagy and necroptosis in both morphological and biochemical characteristics. Ferroptosis is defined by the presence of shrunken mitochondria with increased membrane density, reduced mitochondrial volume and diminished or absent cristae (6,7). In the typical ferroptotic event, classical apoptotic hallmarks such as chromatin condensation or apoptotic body formation are absent. The initiation and execution of this pathway are orchestrated across multiple cellular organelles, namely the mitochondria, endoplasmic reticulum and Golgi apparatus, which collectively integrate the lipid metabolism, iron handling and antioxidant defenses of the cell. This integration defines the cellular vulnerability to ferroptosis (8). In the context of tumors, ferroptosis has been revealed as a crucial modulator of malignant phenotypes, exerting a notable

influence on processes such as proliferation and migration, while concomitantly shaping therapeutic resistance (9).

Accumulating evidence indicates that pharmacological induction of ferroptosis can significantly boost the therapeutic efficacy of conventional treatment regimens for CRC (10-13). However, ferroptosis inhibition has been reported to limit intestinal epithelial cells (IECs) injury and dampen inflammatory signalling, thus ameliorating IBD phenotypes, and potentially influencing CRC prevention and therapeutic outcomes (14,15). The present review aims to delineate the core molecular circuitry and principal signalling networks that govern ferroptosis. In addition, it highlights key recent advances and discusses emerging opportunities for CRC intervention through modulation of LPO, iron metabolism and antioxidant defense systems. Furthermore, it evaluates the translational potential of ferroptosis-oriented therapies, provides an overview of the current limitations in the extant evidence base and establishes a conceptual framework for the development of microbiota-informed and nanotechnology-enabled approaches.

2. Molecular mechanisms of ferroptosis

Enhanced iron accumulation and exacerbation of LPO are the core triggers of ferroptosis. To counter this, cells deploy antioxidant programs. These can be dependent on glutathione (GSH) peroxidase 4 (GPX4) or independent of it. The purpose of these programs is to detoxify lipid hydroperoxides and limit oxidative damage. When the ferroptotic drive overcomes these defenses, peroxidized phospholipids build up in cellular membranes. This accumulation breaches membrane integrity and leads to cell death (Fig. 1). Ferroptosis is thus a terminal outcome of compromised redox homeostasis.

Lipid metabolism. Lipid remodeling has been defined as a key feature of ferroptosis. In addition, peroxidation of polyunsaturated fatty acids (PUFAs) within membrane phospholipids is widely acknowledged as the proximal driver of ferroptotic death, whereas monounsaturated fatty acids (MUFAs) have been found to counteract ferroptosis initiation by diminishing the availability of oxidizable substrates (16). PUFA oxidation is a process that can take place through both enzymatic and non-enzymatic routes. In the non-enzymatic axis, acyl-CoA synthetase long-chain family member 4 (ACSL4) has been observed to display a marked preference for the stimulation of PUFAs, with a particular affinity for arachidonic acid (AA) and adrenic acid (AdA), which results in the formation of the corresponding acyl-CoA thioesters (17). These activated species are then esterified into phosphatidylethanolamine by lysophosphatidylcholine acyltransferase 3 (LPCAT3), producing PUFA-containing phospholipids that are vulnerable to peroxidative damage (18). On the phospholipid molecules, AA and AdA participate in LPO by forming acyl chains, becoming key substrates that trigger ferroptosis. In the enzymatic pathway, lipoxygenase and cytochrome P450 reductase (POR) are key enzymes that initiate LPO. Arachidonate lipoxygenases (ALOXs) participate in the catalysis of PUFAs through various mechanisms, including the generation of reactive oxygen species (ROS), lipid signalling, modification of the structure and function of complex lipid-protein complexes and regulation of cellular redox states (19). POR provides electrons to cytochrome P450 enzymes, activates molecular oxygen and inserts it into the PUFA chain, catalyzing the LPO reaction, which ultimately produces phospholipid hydroperoxides (20).

Conversely, saturated fatty acids can be desaturated by stearoyl-CoA desaturase 1, thereby generating MUFAs. Subsequent to activation by ACSL3, MUFAs are incorporated into membrane phospholipids by membrane-bound O-acyltransferase domain-containing 1/2, thus generating MUFA-containing phospholipids (21-23). MUFA-enriched lipids are relatively resistant to oxidation, a process that contributes to the conservation of the membrane architecture and the mitigation of oxidative injury. This results in the attenuation of ferroptosis through competitive dilution of peroxidation-prone substrates. Of note, the sensitivity of tumor cells to ferroptosis appears to be limited less by the total levels of intracellular PUFAs than by the efficiency with which highly unsaturated PUFAs are directed into vulnerable phospholipid pools (24). Accordingly, the equilibrium between PUFA- and MUFA-containing phospholipids within cellular membranes is a fundamental determinant of ferroptotic susceptibility.

Iron metabolism. Intracellular iron metabolism is a dynamic process involving the uptake, transport, storage and utilization of iron, and is tightly regulated by multiple signaling molecules at various levels. The core mechanism of cellular iron uptake relies on transferrin (TF) receptor 1 (TFR1), which mediates the transmembrane transport of TF-ferric iron complexes via endocytosis (25). TF ensures the stability of the Fe^{3+} oxidation state during transport into the cell, preventing ion displacement. Following endocytic internalization of the TF-receptor complex, the process of endosomal acidification promotes the dissociation of Fe^{3+}, which is subsequently reduced to Fe^{2+} by six-transmembrane epithelial antigen of prostate 3, which then channels the Fe^{2+} into the labile iron pool (LIP), thus facilitating the support of cellular metabolism. Cytosolic Fe^{2+} trafficking and buffering are complex processes involving several routes, including export from endosomes via divalent metal transporter 1 (DMT1), sequestration within ferritin and intercellular redistribution via multivesicular bodies and exosomes (26). DMT1 delivers Fe^{2+} into the cytoplasm, directly expanding the LIP and contributing to intracellular iron homeostasis. Pharmacological DMT1 inhibition or disruption of multivesicular body-exosome biogenesis can lead to iron accumulation by restricting iron efflux (27,28). Ferroportin 1 (FPN1) is the sole recognized iron exporter in mammalian cells and is subject to tight control by hepcidin. Under iron-replete conditions, hepatocyte-derived hepcidin binds FPN1 and prompts its internalization and degradation, blocking iron release to preserve systemic and cellular iron balance (29). Iron storage is regulated by ferritin, a heteropolymer composed of ferritin heavy (FTH1) and light chains. Nuclear receptor coactivator 4 (NCOA4) functions as a selective cargo receptor for ferritinophagy, targeting ferritin to autophagosomes for subsequent lysosomal degradation, resulting in the liberation of redox-active iron (30). As indicated by Liu *et al* (31), activation of the NCOA4-FTH1 axis instigates ferritinophagy and promotes ferroptosis in CRC. Fe^{2+} in the LIP catalyzes the generation of hydroxyl radicals and other ROS via the Fenton reaction. Excessive accumulation triggers

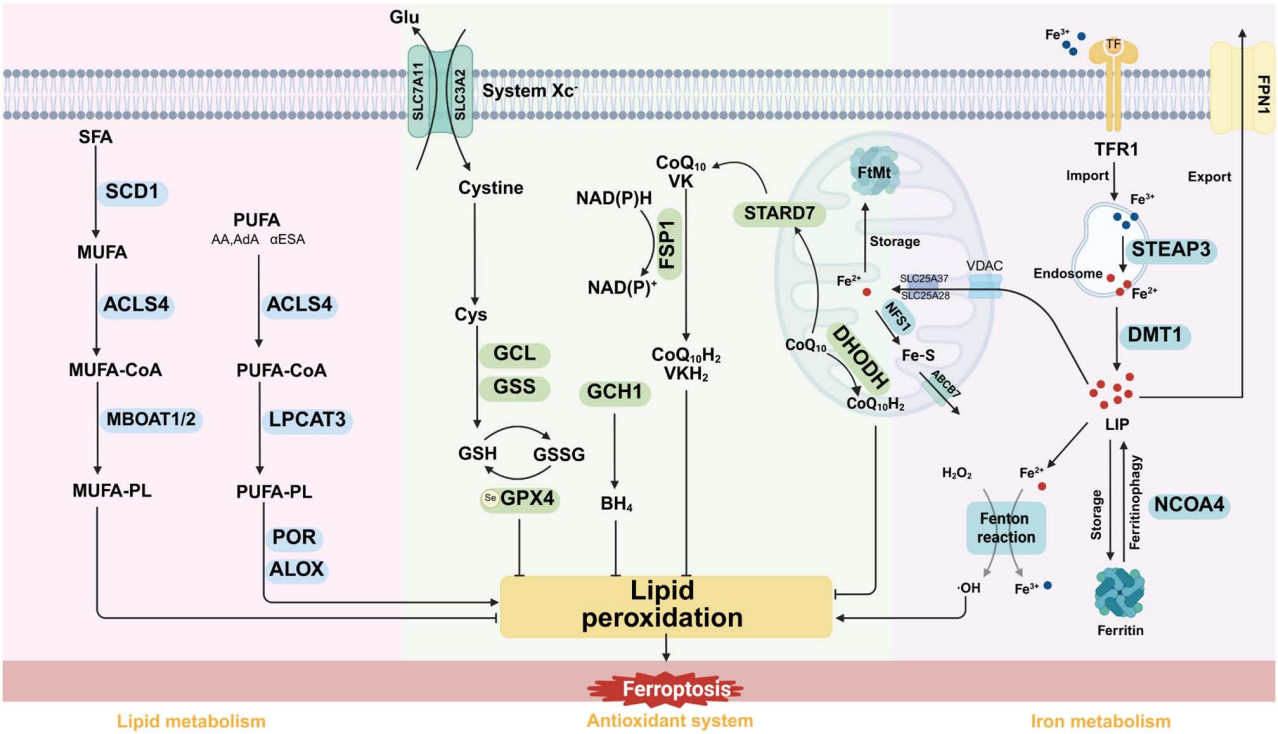

Figure 1. Molecular mechanisms of ferroptosis. Several key pathways are involved in regulating ferroptosis, interconnected through iron metabolism, lipid metabolism and antioxidant systems. Iron metabolism plays a dual regulatory role in ferroptosis, both promoting and inhibiting the process. Circulating Fe^{3+} ions bind to TF and TFR1 and are internalized. They then act through two mechanisms: i) Promoting the formation of the LIP, which activates the Fenton reaction, triggering ferroptosis; and ii) being stored in ferritin to limit free iron accumulation and reduce its redox activity, thereby inhibiting ferroptosis. In lipid metabolism, PUFAs are esterified by ACSL4 and incorporated into the cell membrane via LPCAT3. LOX catalyzes the oxidation of PUFA-PL into peroxide derivatives, leading to membrane instability. SFAs and MUFAs protect against ferroptosis by antagonizing LPO. In the antioxidant system, GPX4 effectively inhibits LPO by converting GSH to GSSG and reducing toxic lipid hydroperoxides to non-toxic phosphatidyl alcohols. Additionally, the FSP1/$CoQH_2$, DHODH/$CoQH_2$ and GCH1/BH_4 systems contribute to mitigating LPO in a GPX4-independent manner. TF, transferrin; TFR1, TF receptor 1; PUFAs, polyunsaturated fatty acids; ACSL4, acyl-CoA synthetase long-chain family member 4; LPCAT3, lysophosphatidylcholine acyltransferase 3; PUFA-PLs, PUFA-containing phospholipids; SFAs, saturated fatty acids; MUFAs, monounsaturated fatty acids; LPO, lipid peroxidation; GPX4, glutathione peroxidase 4; GSH, glutathione; GSSG, GSH disulfide; FSP1-CoQ_{10}, ferroptosis suppressor protein 1-coenzyme Q_{10}; DHODH-CoQ_{10}, dihydroorotate dehydrogenase-CoQ_{10}; GCH1-BH_4, guanosine triphosphate cyclohydrolase 1-tetrahydrobiopterin; SCD1, stearoyl-CoA desaturase 1; MBOAT1/2, membrane-bound O-acyltransferase domain-containing 1 and 2; POR, cytochrome P450 reductase; Glu, glutamate; Cys, cysteine; GSH, glutathione; GPX4, glutathione peroxidase 4; GCL, glutamate-cysteine ligase; GSS, glutathione synthetase; NAD(P)H, nicotinamide adenine dinucleotide phosphate; ALOXs, Arachidonate lipoxygenases; AA, arachidonic acid; AdA, adrenic acid; αESA, α-eleostearic acid; STARD7, StAR-related lipid transfer domain containing 7; FtMt, ferritin mitochondrial; SLC25A37, solute carrier family 25 member 37; $CoQ10H_2$, reduced coenzyme Q10; ABCB7, ATP binding cassette subfamily B member 7; NFS1, cysteine desulfurase 1; STEAP3, six transmembrane epithelial antigen of the prostate 3; DMT1, divalent metal transporter 1; LIP, labile iron pool; FPN1, ferroportin 1; NCOA4, nuclear receptor coactivator 4; VDAC, voltage-dependent anion channel.

a LPO chain reaction, ultimately leading to cellular damage or ferroptosis. Therefore, regulating the transmembrane transport of iron ions is a core strategy for maintaining LIP homeostasis.

Beyond the cytosol, mitochondria constitute an important source of ROS and represent a central node for iron utilization. The handling of iron is linked to electron transport chain activity and redox homeostasis in ferroptosis. Mitochondrial iron metabolism relies on a highly regulated transfer of iron across both the outer and inner mitochondrial membranes. On the outer membrane, the voltage-dependent anion channel enables the interchange of iron and other metabolites between the cytoplasm and the intermembrane space. The process of import across the inner membrane is predominantly mediated by solute carrier family 25 members 37 and 28, which function as dedicated mitochondrial iron importers to regulate matrix iron availability (32,33). Following delivery to the matrix, iron is predominantly utilized as a substrate for the biosynthesis of iron-sulfur (Fe-S) clusters. This process relies on the mitochondrial iron-sulfur cluster (ISC) system, which serves as the central hub for Fe-S cluster synthesis, coordinating both cluster assembly and transmembrane transport. Cysteine desulfurase 1 (NFS1), an Fe-S cluster biosynthesis enzyme, regulates ISC assembly. Downregulation of NFS1 impedes ISC assembly, leading to an iron starvation response, intracellular iron overload, ROS accumulation and ultimately ferroptosis (34). Mitochondrial ferritin, as an iron storage protein in mitochondria, converts free Fe^{2+} to a stable form through its ferrous oxidase activity, preventing iron-induced oxidative stress as well as damage to mitochondria and cells (35). Additionally, mitochondrial iron transporter ATP binding cassette subfamily B member 7 assists in transporting Fe-S clusters from mitochondria to the cytoplasm, thereby contributing to the regulation of iron transfer and its utilization within the mitochondria (36). Therefore, mitochondria play a central hub role in cellular iron homeostasis. Targeted disruption of mitochondrial iron metabolism can selectively induce cellular ferroptosis, providing novel intervention strategies for disease treatment.

Antioxidant system in ferroptosis

GPX4-dependent pathway. To mitigate the oxidative stress that drives ferroptosis, organisms employ antioxidant defense strategies. GPX4 is a crucial suppressor of ferroptosis across diverse cell types and in various tissues. GSH has been identified as a core redox metabolite within this network. In the ferroptosis context, GPX4 uses GSH as a substrate for the reduction of phospholipid and cholesterol hydroperoxides, with the subsequent conversion of the hydroperoxides to their corresponding alcohols. Simultaneously, GSH is oxidized to glutathione disulfide (GSSG). By limiting the accumulation of peroxidized PUFA-containing lipids, this biochemical reaction preserves membrane bilayer integrity and halts the self-propagating LPO cascade, thereby preventing ferroptotic death (37). In accordance with this mechanism, RAS-selective lethal 3 (RSL3), an archetypal ferroptosis inducer, covalently modifies the catalytic selenocysteine residue (Sec46) of GPX4, disabling its peroxidase activity and precipitating ferroptosis (38).

The Xc^-/GSH/GPX4 axis forms a core antioxidant defense pathway that effectively blocks LPO-driven ferroptosis by maintaining redox homeostasis. The system Xc^- consists of solute carrier family 7 member 11 (SLC7A11) and SLC3A2, also known as the light chain subunit xCT and the heavy chain partner protein CD98. System Xc^- is a sodium-independent antiporter that catalyzes the 1:1 equilibrium exchange of extracellular cystine for intracellular glutamate (Glu). Following importation, cystine is rapidly reduced to cysteine (Cys), which provides the rate-limiting substrate for GSH biosynthesis (39). Inhibition of system Xc^- depletes intracellular GSH reserves, reduces the antioxidant capacity of the cell and ultimately triggers membrane rupture and ferroptosis. Erastin, a reductive inducer of ferroptosis, promotes lipid ROS accumulation and triggers oxidative damage and ferroptosis by binding to SLC7A11, inhibiting Cys2 uptake, disrupting GSH synthesis and suppressing GPX4 enzyme activity (40). Notably, erastin inhibits system Xc^-, progressively depleting GSH reserves and promoting the accumulation of lipid ROS and mitochondrial ROS, ultimately leading to ferroptosis. By contrast, RSL3 inhibits the GPX4 active site, rapidly suppressing its ability to reduce phospholipid hydroperoxides, leading to a rapid accumulation of mitochondrial ROS and ultimately resulting in ferroptosis (41). Thus, both inducers directly or indirectly inactivate GPX4 function, highlighting its regulatory role in the ferroptosis pathway as a classic ferroptosis inducer. Additionally, GPX4 is a selenoprotein with a selenocysteine-containing catalytic center, and its activity depends on the biological availability of selenium. The addition of selenium to cells or its administration to animals can inhibit ferroptosis (42). Therefore, selenium may regulate GPX4 expression levels to dynamically control cellular sensitivity to ferroptosis. In addition to GPX4, other selenoproteins (such as selenophosphate synthetase 2 and selenophosphate) play roles in ferroptosis by scavenging free radicals or reducing mitochondrial oxidative stress (42). In summary, targeting the Xc^--GSH-GPX4 axis can induce ferroptosis by inhibiting either system Xc^- or GPX4. This dual strategy provides a new approach for treating ferroptosis-related diseases.

GPX4-independent pathway. GPX4 is a pivotal regulator of ferroptosis, safeguarding membrane integrity by reducing phospholipid hydroperoxides and consequently limiting lipid peroxide accumulation. In the same way, various GPX4-independent defense modules also restrain ferroptotic signalling, which includes the ferroptosis suppressor protein 1 (FSP1)-coenzyme Q_{10} (CoQ_{10}; ubiquinone) axis, the dihydroorotate dehydrogenase (DHODH)-CoQ_{10} pathway and the guanosine triphosphate cyclohydrolase 1 (GCH1) - tetrahydrobiopterin (BH_4) system. In essence, these programs act to impede the propagation of lipid radicals and the progression of the LPO cascade, consequently delaying or preventing ferroptotic collapse. FSP1, which resides within lipid droplets (LDs) and the plasma membrane, functions as an NAD(P)H-dependent oxidoreductase that catalyzes the reduction of CoQ_{10} to its oxidized form, $CoQ_{10}H_2$, also known as ubiquinol (43), which functions as a lipophilic radical-trapping antioxidant, exerting a direct quenching impact on lipid radicals and effectively terminating chain-propagating peroxidation processes.

Additionally, it enhances antioxidant function by reducing α-tocopherol, indirectly preventing ferroptosis. At the cell membrane, aldehyde dehydrogenase 7A1 generates NADH, which supports the antioxidant activity of FSP1. It also reduces membrane damage by consuming harmful aldehydes such as 4-hydroxynonenal (4-HNE) and malondialdehyde (44). Furthermore, FSP1 is involved in the reduction of vitamin K and mediates endosomal sorting complex required for transport-III-dependent membrane repair to inhibit ferroptosis (45). Similar to FSP1's strategy of scavenging lipid-free radicals, DHODH in mitochondria also reduces CoQ_{10} to ubiquinol, inhibiting ferroptosis (46). StAR-related lipid transfer domain protein 7 facilitates a mechanistic connection between the FSP1-CoQ_{10} and DHODH-CoQ_{10} antioxidant programs by acting as a shuttle for CoQ_{10} between the mitochondria and the plasma membrane, extending ubiquinone-based protection beyond the organelle (47). In the same manner, guanosine triphosphate GCH1 catalyzes the pivotal step in BH4 biosynthesis. BH4 functions as a radical-trapping antioxidant that suppresses lipid peroxyl radicals and LPO. It also plays an essential role as a cofactor for nitric oxide synthases, forming a GPX4-independent ferroptosis defense module (48). Through its actions in ROS control and membrane protection against autoxidation, the GCH1-BH4 axis offers resistance to ferroptotic stress; however, genetic or pharmacological blockade of GCH1 depletes BH4, increases peroxide accumulation and precipitates ferroptosis (49). Taken together, the human body harbors multiple antioxidant defense networks that attenuate iron-dependent oxidative stress via synergistic mechanisms, thereby sustaining cellular homeostasis.

3. Ferroptosis in tumor development and regulation

A broad range of tumor-associated stimuli and signaling pathways contribute to tumor development and cancer cell proliferation by regulating ferroptosis, either through its activation or suppression. These insights position ferroptosis at the forefront of cancer pathophysiology. The principal regulatory factors and signalling pathways that govern ferroptosis in cancer are described below.

p53. p53 is a pivotal tumor suppressor that orchestrates cell-cycle arrest, DNA repair and metabolic homeostasis,

constituting a paramount intrinsic barrier to malignant transformation. The available evidence also points to p53 as a context-dependent regulator of ferroptosis, with both pro- and anti-ferroptotic functions (50). From a mechanistic perspective, p53 is able to repress the transcription of SLC7A11, limiting cystine uptake and consequently constraining GSH biosynthesis and redox buffering. p53 can promote ferroptotic vulnerability by enabling ALOX12 activity, thereby driving ALOX12-dependent LPO and increasing the sensitivity of tumor cells to ferroptosis (51,52). In support of this axis, the DNA-replication factor GINS4 has been observed to antagonize p53 acetylation, leading to a reduction in p53 stability and an increase in SLC7A11 expression (53). In turn, this has been shown to diminish ferroptosis in cancer cells. Beyond its regulation of system Xc^-, p53 also induces the expression of spermidine/spermine N1-acetyltransferase 1 (SAT1), a rate-limiting enzyme in polyamine catabolism, further supporting a link between p53 signalling and metabolic pathways involved in ferroptosis. In various tumors, p53 promotes ferroptosis, and ALOX15 inhibitors can block SAT1-mediated ferroptosis (54). Notably, p53 also indirectly influences ferroptosis by regulating metabolic target genes such as glutaminase 2, prostaglandin-endoperoxide synthase 2 and ferredoxin reductase (55). However, under certain stress conditions, p53 exhibits an inhibitory effect on ferroptosis.

For illustrative purposes, p53 has been found to transcriptionally induce cyclin-dependent kinase inhibitor 1A, thus delaying GSH deficiency under cystine limitation and concomitantly diminishing the ferroptosis sensitivity of lung cancer cells (56). In CRC, p53 has furthermore been demonstrated to impede ferroptosis by attenuating dipeptidyl peptidase-4 (DPP4) activity and diminishing the DPP4-NADPH oxidase 1 interaction (57). In sum, these findings accentuate the context-dependent nature of p53 control over ferroptosis and highlight the necessity for meticulous, tumor-specific modification of p53-ferroptosis signalling in the development of ferroptosis-based anticancer therapies.

Nuclear factor E2-related factor 2 (Nrf2). Nrf2 was initially recognized as a crucial component in the process of cellular antioxidant responses. Further research has since revealed the vital function of Nrf2 in the regulation of iron metabolism and the antioxidant defense system, consequently counteracting ferroptosis (58). Nrf2 regulates iron metabolism by activating downstream target genes involved in iron metabolism, such as ferritin, FPN1 and ferrochelatase, which subsequently reduces the free iron levels in the LIP and inhibits the occurrence of ferroptosis (59). Heme oxygenase 1 (HO-1), an Nrf2-dependent inducible enzyme, protects tumor cells from ferroptosis by alleviating oxidative stress. However, the free iron produced by HO-1 can increase the cell's sensitivity to ferroptosis, with this dual effect depending on the dynamic balance between oxidative stress and ferroptosis (60). In the antioxidant system, activation of Nrf2 triggers the transcription of a series of downstream target genes. These genes encode enzymes such as SLC7A11, the catalytic subunit of glutamate-cysteine ligase and its regulatory subunit GCLM, which together regulate GSH synthesis and metabolism. These proteins facilitate the entry of Cys into the cell, and the resulting GSH maintains cellular redox homeostasis, enabling the cell to sustain GPX4 activity and inhibit ferroptosis (61).

The activity of Nrf2 is tightly regulated by Kelch-like ECH-associated protein 1 (KEAP1). Under normal conditions, KEAP1 binds to NRF2, inhibiting its nuclear translocation and promoting its ubiquitination and degradation, thereby limiting Nrf2 activity (62). The binding and dissociation of these two proteins regulate Nrf2 stability, thereby influencing the cellular redox balance. Notably, transmembrane protein 160, ring finger protein 217 and cathepsin S interact with KEAP1, promoting its ubiquitination and proteasomal degradation (63-65). On the other hand, DPP9 competes with NRF2 and can non-enzymatically bind to KEAP1 (66). These distinct interference mechanisms disrupt the normal binding of the KEAP1-NRF2 complex, maintaining Nrf2 stability and activating its downstream antioxidant responses, thereby inhibiting ferroptosis in tumor cells. Furthermore, protein arginine methyltransferase 5-mediated KEAP1 methylation enhances its stability, leading to negative regulation of Nrf2 activity (67). Therefore, exploring how Nrf2 selectively regulates specific target genes to prevent ferroptosis is crucial for developing novel cancer therapies and prevention strategies based on ferroptosis mechanisms.

Autophagy. Autophagy acts as a mediator of ferroptosis and interacts with various forms of autophagy, including ferritinophagy, lipophagy, mitophagy, clock autophagy and chaperone-mediated autophagy (CMA). These types of autophagy influence cellular iron metabolism, lipid metabolism and the redox system. Ferritinophagy is a selective autophagy process mediated by NCOA4. After forming a complex with ferritin, NCOA4 is transported to the lysosome for degradation, which increases the level of free iron within the cell (68). Previous studies have shown that ataxia telangiectasia mutated kinase phosphorylates NCOA4 and decreases HO-1 expression. Both mechanisms enhance the interaction between NCOA4 and ferritin, thereby inducing ferroptosis in tumor cells (69,70). On the other hand, the E3 ubiquitin ligases Deltex 2 and S-phase kinase-associated protein 2 promote the degradation of NCOA4 through ubiquitination, thereby inhibiting ferritinophagy and its associated ferroptosis (71,72).

Lipophagy reduces intracellular lipid reserves by degrading LDs, thereby increasing the sensitivity of cells to ferroptosis. Ras related protein Rab 7a, a member of the RAS oncogene family, is a key factor linking lipophagy to ferroptosis. It specifically recognizes and degrades LDs, promoting ferroptosis in tumor cells (73). By contrast, the p53 target gene phospholipid transfer protein promotes LD formation and inhibits lipophagy-dependent ferroptosis (74). Of note, clock autophagy further promotes ferroptosis by inhibiting lipid storage. This process is mediated by the autophagic cargo receptor sequestosome-1, which degrades brain and muscle ARNT-like 1 (BMAL1) (75). DDB1- and CUL4-associated factor 7 stabilizes BMAL1 through deubiquitination, preventing its degradation and thus inhibiting clock autophagy (76).

Mitophagy inhibits ferroptosis by removing damaged or excess mitochondria, thereby reducing ROS production. This process also helps maintain mitochondrial network stability (77). LPO-induced endoplasmic reticulum stress

activates ATF4, which upregulates the E3 ubiquitin ligase Parkin, initiating the transport of damaged mitochondria to autophagosomes, thereby effectively inhibiting mitochondria-associated ferroptosis (78). GPX4 interacts with chaperone heat shock cognate protein 70 (HSC70) and lysosomal membrane protein type 2A (LAMP2A), promoting GPX4 degradation in the lysosome via the CMA pathway, ultimately inducing ferroptosis (79). Notably, HSP90 has been found to enhance LAMP2A stability, thereby promoting GPX4 degradation and ferroptosis (80). On the other hand, prostaglandin E synthase 3 (also known as p23) competes with HSC70 for binding, while creatine kinase B phosphorylates GPX4, thus preventing its interaction with HSC70. Both mechanisms stabilize GPX4 protein levels, thereby inhibiting ferroptosis (81,82). Therefore, further investigation into the complex interplay between ferroptosis and autophagy will provide new intervention strategies for cancer treatment (Fig. 2).

4. Role of ferroptosis in the TME

The TME comprises neoplastic cells in addition to stromal and immune compartmental elements, whose dynamic interactions shape tumor growth, metastatic dissemination and therapeutic sensitivity in a coordinated manner. Within this biological system, reciprocal intercellular signalling is an important factor in the evolution of tumors, and it is progressively evident that ferroptosis is firmly incorporated into these bidirectional circuits. Non-malignant cells, particularly immune populations, can influence the susceptibility of cancer cells to ferroptosis via the secretion of cytokines, metabolites and lipid mediators. Conversely, ferroptotic cancer cells secrete signals that can reprogram neighbouring stromal and immune cells, thereby augmenting or diminishing antitumor immunity (83). Notably, TME-associated stresses and risk factors have the potential to induce ferroptosis within immune cells themselves, thereby compromising immunoregulatory capacity and fostering tumor progression. It is imperative to analyze these ferroptosis-centered crosstalk networks between tumor and non-tumor cells to achieve mechanistic insight and to develop rational therapies that exploit ferroptosis in cancer.

$CD8^+$ T cells. $CD8^+$ T cells primarily rely on secreting interferons (IFNs) and cytotoxic granules to eliminate infected or tumorigenic cells. IFN-γ secretion was found to promote ferroptosis through at least two complementary mechanisms: First, IFN-γ exerts a suppressive effect on the expression of the system Xc^- subunits SLC3A2 and SLC7A11, thereby constraining cystine import and depleting intracellular GSH. These effects consequently sensitize tumor cells to LPO-driven cell death. Second, in the occurrence of AA and related fatty acids, IFN-γ upregulates ACSL4, reshaping the tumor-cell lipid composition by means of facilitating AA incorporation into phospholipids bearing C16 or C18 acyl chains, which in turn increases the pool of peroxidation-prone substrates and ultimately precipitates ferroptosis (84,85). Recent studies indicate that, under the combined treatment of IFN-γ and AA, a small subset of resistant tumor cells use VPS33B-interacting protein as a regulatory factor to export ACSL4 via exosomes, thereby evading ferroptosis (86). Furthermore, the synergistic effect of AA and IFN-κ activates the transcription factor STAT1 signaling pathway, thus upregulating ACSL4 expression in tumor cells and ultimately increasing their susceptibility to ferroptosis (87). $CD8^+$ T cells not only initiate ferroptosis in tumor cells, but are also modulated by ferroptotic programs within the tumor, thereby establishing a bidirectional regulatory circuit. As tumor cells are subject to ferroptosis, they release damage-associated molecular patterns (DAMPs) that serve to promote the maturation and activation of dendritic cells (DCs). Activated DCs enhance the function of $CD8^+$ T cells, thereby reinforcing tumor cell killing and establishing a positive-feedback cycle that amplifies antitumor immunity (88).

Ferroptosis exhibits cell type dependence during tumor development. Inducing ferroptosis in tumor cells effectively inhibits tumor growth; however, ferroptosis in $CD8^+$ T cells significantly reduces their cytotoxic activity, potentially indirectly promoting tumor progression. Lipid accumulation is a common metabolic alteration in the TME, closely linked to immune suppression (89). Within the TME, elevated cholesterol can lead to CD36 upregulation in $CD8^+$ T cells, resulting in enhanced fatty-acid uptake and a greater susceptibility to ferroptosis. This lipid-driven susceptibility has been observed to attenuate the production of cytotoxic cytokines and compromise antitumor activity (90). Sickle cell disease has been observed to induce changes in the three-dimensional chromatin architecture of $CD8^+$ T cells, effectively repressing the ferroptosis-associated gene SLC7A11. Reductions in hydrogen sulfide levels concomitantly impede SLC7A11 recovery, thereby potentiating the risk of ferroptosis (91). Li *et al* (92) further elucidated that the loss of the epilepsy-susceptibility gene DEP domain-containing protein (DEPDC)5 increased mechanistic target of rapamycin signalling, elevated intracellular ROS and led to the sensitization of $CD8^+$ T cells to ferroptotic death. Notably, vitamin E supplementation or an iron-restricted diet restored peripheral CD8+ T-cell abundance in DEPDC5-deficient mice, improving cellular homeostasis and strengthening antitumor immunity. Collectively, these findings underscore a pivotal therapeutic challenge, namely, the need for selectively inducing ferroptosis in tumor cells while preserving the effector function of $CD8^+$ T cells, a prerequisite for precision immunotherapy.

Tumor-associated macrophages (TAMs). TAMs exist in two phenotypes: M_1 and M_2. M_1 macrophages primarily secrete pro-inflammatory factors with antitumor immune effects and molecules that inhibit angiogenesis, while M_2 macrophages produce factors that promote tissue remodeling and angiogenesis, facilitating tumor initiation and progression (93). In triple-negative breast cancer, the cytokine TGF-β_1 secreted by TAMs stimulates the synthesis of GSH in malignant cells, consequently increasing their tolerance to ferroptosis and inducing tumor progression (94). Furthermore, targeting ferroptosis not only directly affects tumor cells but also modulates the functional state of TAMs, influencing the overall antitumor immune response. Ferroptosis inducers can impair the ability of TAMs to clear ferroptotic tumor cells by inducing phospholipid peroxidation in TAMs, thereby promoting tumor resistance to ferroptosis-based therapy. Upregulating the expression of Toll-like receptor 2

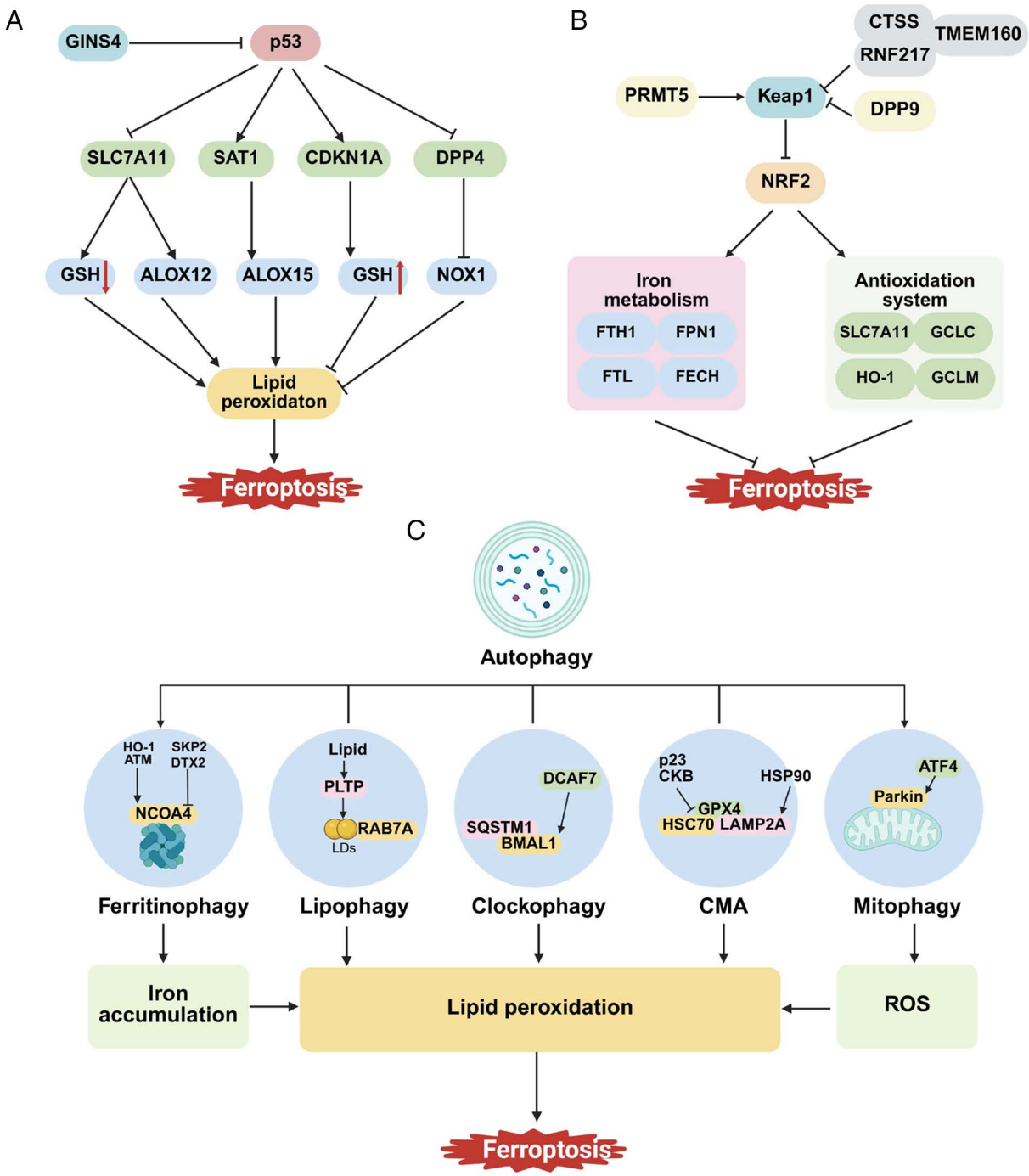

Figure 2. Cancer-related signaling pathways regulating ferroptosis. (A) GINS4 inhibits the stability of p53, affecting its function. p53 promotes ferroptosis by downregulating SLC7A11 and upregulating SAT1. Additionally, p53 inhibits ferroptosis by promoting CDKN1A or suppressing DPP4. (B) NRF2 inhibits ferroptosis by regulating components related to the antioxidant system and iron metabolism. During ferroptosis, NRF2 activity is regulated by target genes such as PRMT5, DPP9 and CTSS. (C) Interaction between autophagy and ferroptosis. Ferritinophagy, lipophagy, mitophagy, clock autophagy and CMA regulate ferroptosis by modulating iron accumulation, ROS levels and LPO. SLC7A11, solute carrier family 7 member 11; SAT1, spermidine/spermine N1-acetyltransferase 1; CDKN1A, cyclin-dependent kinase inhibitor 1A; DPP4, dipeptidyl peptidase-4; PRMT5, protein arginine methyltransferase 5; CTSS, cathepsin S; CMA, chaperone-mediated autophagy; GINS4, GINS complex subunit 4; GSH, glutathione; ALOXs, Arachidonate lipoxygenases; NOX1, NADPH oxidase 1; Keap1, Kelch-like ECH- associated protein 1; RNF217, ring finger protein 217; TMEM160, transmembrane protein 160; FTH1, ferritin heavy chain 1; FPN1, ferroportin 1; FTL, ferritin light chain; FECH, ferrochelatase; GCLC, glutamate-cysteine ligase catalytic subunit; GCLM, glutamate-cysteine ligase modifier subunit; HO-1, heme oxygenase 1; ATM, ataxia-telangiectasia mutated; SKP2, S-phase kinase-associated protein 2; DTX2, E3 ubiquitin ligase deltex 2; PLTP, phospholipid transfer protein; RAB7A, Ras related protein Rab 7a; SQSTM1, sequestosome 1; BMAL1, brain and muscle ARNT-like 1; DCAF7, DDB1- and CUL4-associated factor 7; CKB, Creatine kinase B; HSC70, heat shock cognate protein 70; HSP90, heat shock protein 90; LAMP2A, lysosomal membrane protein type 2A; ATF4, activation transcription factor 4; ROS, reactive oxygen species; LDs, lipid droplets.

in TAMs can restore their phagocytic function, representing a synergistic stratagem to enhance the efficacy of ferroptosis-inducing therapy (95).

In multiple settings, M_2-like macrophages are more predisposed to ferroptosis than their M_1-like counterparts, a discrepancy that can influence macrophage polarization and

assist in the perpetuation of pro-inflammatory programs (96). Significantly, despite the generally comparable levels of LPO along with the expression of core ferroptosis regulators in M_1 and M_2 macrophages, M_1 cells typically exhibit high inducible nitric oxide synthase (iNOS) activity. The resulting NO· radicals can quench lipid-derived radicals and attenuate LPO-associated injury, whereas the relatively low or negligible iNOS expression in M_2 macrophages leaves them less protected and more susceptible to oxidative membrane damage (97). The inhibition of apolipoprotein C1 has been reported to perturb iron and lipid metabolic pathways, elevate ROS, engage ferroptotic signalling and drive the repolarization of macrophages from an M_2- to an M_1-like state. This reshapes the immune microenvironment in hepatocellular carcinoma and enhances the effectiveness of immunotherapy (98). Additionally, changes in TME homeostasis influence the behavior of macrophages. For instance, short-term acidosis (24-72 h) upregulates zinc finger AN1 domain-containing protein 5, which regulates SLC3A2 protein via ubiquitination, promoting the polarization of TAMs towards the M_1 phenotype. This enhances their phagocytic ability and ferroptosis-inducing effects on breast cancer cells (99). Accordingly, therapeutic strategies that target ferroptosis in M_2-like macrophages, thereby facilitating their repolarization towards an M_1 state, have the potential to enhance macrophage phagocytic capacity, mitigate immunosuppressive constraints within the TME and improve antitumor efficacy.

T regulatory cells (Tregs). Tregs are a $CD4^+$ T-cell subset with immunosuppressive properties, often referred to as the 'brakes' of the immune system. In the TME, Tregs are often excessively accumulated and hyperactive, inhibiting the activation and proliferation of effector T cells, weakening the body's antitumor immunity and creating an immunosuppressive state (100). The survival and function of Tregs depend on iron homeostasis, with FTH being a key regulator of iron homeostasis and a suppressor of ferroptosis in Tregs. FTH is involved in iron metabolism and influences the intracellular redox state, thereby maintaining the activity of ten-eleven translocation (TET) enzymes, which require iron ions as essential cofactors (101). The transcription factor forkhead box protein P3 (Foxp3) is a key regulator of Treg cell function, controlling the expression of specific genes that define their suppressive program. TET enzymes regulate the methylation and transcription of the Foxp3 gene, influencing Treg transcriptional activity and function, and ultimately affecting autoimmune and antitumor responses (102). Notably, Tregs from the TME exhibit higher basal levels of LPO, indicating that the antioxidant enzyme GPX4 is crucial for maintaining the lipid redox balance, preventing ferroptosis and preserving their suppressive activity (103). When GPX4 is specifically deleted in Tregs, LPO accumulates excessively, inducing ferroptosis, particularly when T-cell receptor and co-stimulatory signals are activated. These cells also release pro-inflammatory factors such as interleukin-1β, thus promoting type 17 T-helper cell-mediated inflammatory responses and disrupting immune tolerance (104). Therefore, selectively inducing ferroptosis in Tregs within the TME could specifically weaken their immunosuppressive function, thereby releasing cytotoxic T cells to target the tumor.

DCs. DCs are defined as designated antigen-presenting cells that interface innate and adaptive immunity (105). By capturing tumor-derived antigens and consequent presentation to T cells, DCs orchestrate T cell-mediated anti-tumor responses. Emerging evidence signifies that lipid metabolic rewiring during ferroptosis has the ability to compromise DC function. The LPO-derived aldehyde 4-HNE activates the endoplasmic reticulum stress sensor X-box binding protein 1, resulting in aberrant lipid accumulation and disruption of DC lipid homeostasis. Functionally, this DC impairment suppresses local T-cell responses in the TME (106). Peroxisome proliferator-activated receptor γ (PPARγ), a crucial nuclear receptor in lipid metabolism, can be activated by the GPX4 inhibitor RSL3 to induce ferroptosis in DCs. Specific knockdown of PPARγ using genetic methods effectively reverses the ferroptosis induced by RSL3, restoring DC maturation (107,108). Recent research has shown that programmed death ligand-1 (PD-L1) binds to SLC7A11 mRNA to prevent its degradation, thereby maintaining the ferroptosis resistance of DCs and mitigating the damage caused by ferroptosis inducers (109). Additionally, in inflammatory diseases, Sestrin2 protects DCs from ferroptosis triggered by lipopolysaccharide. However, its protective mechanisms in the tumor context still require further investigation (110). Notably, ferroptosis in tumor cells can also regulate DC function. Li *et al* (111) demonstrated that inducing ferroptosis in head and neck squamous cell carcinoma cells triggered an endogenous double-stranded DNA (dsDNA) cascade, which significantly promotes DCs infiltration and maturation, thereby enhancing the suppression of tumor growth. Therefore, ferroptosis can both weaken the antitumor activity of DCs and influence immune responses through the tumor cell-DCs interaction network. Understanding the molecular mechanisms involved and restoring DC functionality may provide new strategies to enhance tumor immunotherapy.

Natural killer (NK) cells. NK cells play a role in tumor immune surveillance by releasing cytolytic granules containing perforin and granzyme B, which can differentiate and eliminate target cells that are transformed, infected or under stress (112). NK cells in the TME undergo ferroptosis, characterized by morphological changes, increased expression of LPO and oxidative stress-related proteins, which impair NK cell function (113). Previous research has shown that NK cells activate an integrated stress response centered around activating transcription factor 3 (ATF3), which induces ferroptosis through NCOA4-mediated iron overload by inhibiting Nrf2, reducing NK cell survival and tumor-killing efficacy in the TME (114). Of note, tumor cells and their associated components play a crucial role in regulating NK cell ferroptosis. In gastric cancer, cancer-associated fibroblasts (CAFs) not only promote iron transfer into the TME, expanding the unstable iron pool within NK cells, but also promote NCOA4-mediated ferritinophagy via follostatin-like-protein 1 derived from CAFs, ultimately inducing ferroptosis (115). However, the microbiota in hepatocellular carcinoma (such as *B. parabrevis*) enhances lipolysis, generating higher levels of acetyl-CoA and increasing RAR-related orphan receptor C acetylation to upregulate NEDD4L expression, which promotes the ubiquitination of iron transporters and inhibits NK cell ferroptosis (116). Tumors often exhibit antigen heterogeneity and

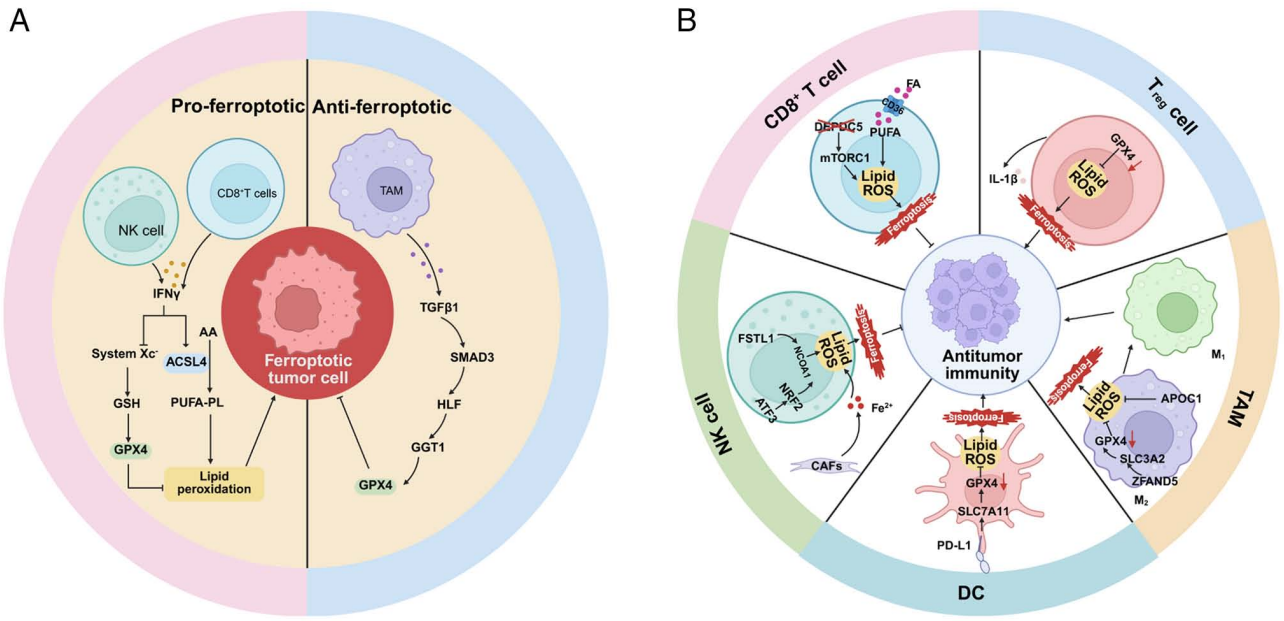

Figure 3. Ferroptosis-mediated crosstalk in the TME. (A) Ferroptosis of tumor-associated immune cells can either promote or suppress antitumor immunity. (B) Immune cells act on tumor cells by regulating ferroptosis in the TME. TME, tumor microenvironment; IFNγ, interferon γ; ACSL4, acyl-CoA synthetase long-chain family member 4; AA, arachidonic acid; GSH, glutathione; GPX4, glutathione peroxidase 4; PUFA-PLs, PUFA-containing phospholipids; NK cell, natural killer cell; TAMs, tumor-associated macrophages; DC, dendritic cell; Tregs, regulatory T cell; TGF-β, transforming growth factor β; SMAD3, SMAD family member 3; HLF, hepatic leukemia factor; GGT1, γ-glutamyltransferase 1; DEPDC5, DEP domain-containing protein 5; PUFA, polyunsaturated fatty acid; MTORC1, mechanistic target of rapamycin complex 1; FA, fatty acid; IL-1β, interleukin 1β; APOC1, apolipoprotein C1; SLC3A2, solute carrier family 3 member 2; ZFAND5, zinc finger AN1 domain-containing protein 5; PD-L1, programmed death ligand-1; SLC7A11, solute carrier family 7 members 11; CAF, cancer-associated fibroblast; Nrf2, nuclear factor E2-related factor 2; ATF3, activation transcription factor 3; FSTL1, follistatin-like protein 1.

immune evasion, enabling them to escape the cytotoxic effects of immune cells. Chimeric antigen receptor (CAR)-NK cell therapy has garnered increasing attention in recent years due to its ability to target both antigen-specific and non-specific cancer cells through CAR-dependent and independent pathways (117). The combination of this therapy with ferroptosis not only induces ferroptosis by releasing IFN-γ to downregulate the expression of system Xc^- subunits SLC7A11/SLC3A2, leading to GSH depletion in tumor cells, but also achieves targeted delivery of ferroptosis inducers via exosomes derived from CAR-NK cells, showing potential in eliminating malignant tumors (118,119). Therefore, protecting NK cells in the TME from ferroptosis and optimizing CAR-NK therapy can more effectively induce ferroptosis in tumor cells, providing an important approach for expanding clinical applications.

CAFs. CAFs, as an essential component of the TME, regulate tumor progression through multiple mechanisms. CAFs influence the remodelling of local immunity, thus facilitating immune evasion and diminishing antitumor surveillance (120). Recent research has positioned CAFs as key mediators of ferroptotic vulnerability within tumors. For illustrative purposes, consider the findings of Zhang *et al* (121), which revealed that CAF-derived lactate suppresses ferroptosis in triple-negative breast cancer cells, contributing to resistance to the anthracycline doxorubicin. By contrast, the ferroptotic status of malignant cells has been observed to have the capacity to reprogram the behaviour of CAFs. In cases of gastrointestinal tumors, the inhibition of ferroptosis subsequent to anoctamin 1 has been observed to be associated with increased transforming growth factor-β release. Such release has been hypothesized to drive CAF accumulation and activation, in turn limiting CD8+ T cell infiltration and weakening anti-tumor immunity, ultimately promoting resistance to immunotherapy (122). Exosome-mediated intercellular communication provides an additional tier of regulatory control: CAF-derived exosomes enriched in microRNA-432-5p repress CHAC1, decrease LPO in prostate cancer cells and reduce ferroptosis, thereby rendering resistance to docetaxel. Furthermore, engineering CAF-derived exosomes can enhance targeting efficiency, significantly promoting ferroptosis and improving chemotherapy efficacy (123,124). Therefore, a deeper exploration of the ferroptosis regulatory network between CAFs and tumor cells, and targeting this mechanism, may provide a new path for overcoming tumor resistance (Fig. 3 and Table I).

5. Ferroptosis inducers in CRC combination therapy

Patients with CRC face remarkable clinical challenges, including high mortality rates, widespread drug resistance and limited effective treatment options. There is a correlation between cancer-related genes and ferroptosis-associated pathways, making tumor cells (including CRC cells) more prone to ferroptosis compared to normal cells. Accordingly, integrating ferroptosis-inducing agents with established therapeutic modalities has the potential to offer a compelling strategy for significantly enhancing therapeutic efficacy in CRC.

Chemotherapy. Despite notable progress in CRC treatment, chemotherapy remains a key approach for treating patients with unresectable metastatic tumors. Oxaliplatin, a first-line chemotherapy drug for CRC, forms a

Table I. Roles and regulatory mechanisms of ferroptosis in the tumor microenvironment.

Cell type	Regulator/target	Regulatory mechanism	Effect on ferroptosis	(Refs.)
$CD8^+$T cells	IFN-γ↑	Downregulates system Xc^- and upregulates ACSL4 in the presence of AA	Promotes tumor cell ferroptosis	(84,85)
	CD36↑	Enhances fatty acid uptake	Promotes ferroptosis in $CD8^+$ T cells	(90)
	SCD	Downregulates SLC7A11	Promotes ferroptosis in $CD8^+$ T cells	(91)
	DEPDC5↓	Increases lipid ROS accumulation	Promotes ferroptosis in $CD8^+$ T cells	(92)
TAMs	TGF-β1↑	Increases GSH levels	Inhibits tumor cell ferroptosis	(94)
	iNOS↑	Attenuates LPO-induced cellular injury	Ferroptosis in M_2 macrophages	(97)
	APOC1↓	Increases lipid ROS accumulation	Facilitates M_2-to-M_1 repolarization through ferroptosis	(98)
	ZFAND5↑	Downregulates GSH	Promotes tumor cell ferroptosis	(99)
Tregs	FTH↑	Maintain iron homeostasis	Inhibits ferroptosis in Treg cells	(101,102)
	GPX4↓	Promotes lipid peroxide accumulation	Promotes ferroptosis in Treg cells	(104)
DCs	RSL3	Activates the PPARγ pathway	Promotes ferroptosis in DCs	(107,108)
	PD-L1	Protects SLC7A11 mRNA from degradation	Inhibits ferroptosis in DCs	(109)
NK cells	ATF3↑	Induces NCOA4-mediated iron overload	Promotes ferroptosis in NK cells	(114)
	FSTL1↑	Induces NCOA4-mediated ferritinophagy	Promotes ferroptosis in NK cells	(115)
	NEDD4L↑	Promotes ferroportin ubiquitination	Inhibits ferroptosis in NK cells	(116)
	IFN-γ↑	Downregulates system Xc^-	Promotes tumor cell ferroptosis	(118)

↑, increased/upregulated; ↓, decreased/downregulated; IFNs, interferons; AA, arachidonic acid; SCD, sickle cell disease; ROS, reactive oxygen species; TGF-β1, transforming growth factor-β1; iNOS, inducible nitric oxide synthase; NK, natural killer; APOC1, apolipoprotein C1; ZFAND5, zinc finger AN1 domain-containing protein 5; FTH, ferritin heavy chain 1; PPARγ, peroxisome proliferator-activated receptor γ; PD-L1, programmed death ligand-1; ATF3, activating transcription factor 3; NCOA4, nuclear receptor coactivator 4; FSTL1, follostatin-like-protein1; NEDD4L, developmentally downregulated 4-like protein; DCs, dendritic cells; Treg cells, T-regulatory cells; LPO, lipid peroxidation; SLC7A11, solute carrier family 7 member 11; CD36, cluster of differentiation 36; DEPDC5, DEP domain-containing protein 5; GPX4, glutathione peroxidase 4; RSL3, RAS-selective lethal 3.

1,2-diaminocyclohexane-platinum complex that inserts into dsDNA, inhibiting DNA repair enzyme activity and enhancing its cytotoxic effects (125). Although oxaliplatin-based chemotherapy regimens have improved response rates in patients with CRC, chemotherapy resistance remains an important challenge (126). Since the majority of tumor cells are iron-dependent and prone to ferroptosis induction, triggering ferroptosis can overcome resistance and is considered an effective anticancer strategy.

The transcription factor forkhead box A (FOXA) inhibits ferroptosis by activating the Nrf2/GPX4 pathway, thereby increasing oxaliplatin resistance in CRC cells. Conversely, the E3 ubiquitin ligase tripartite motif containing 36 (TRIM36) mediates FOXA2 degradation, acting as a key factor in restoring ferroptosis sensitivity and overcoming CRC resistance (127). Mitochondrial carrier homolog 2 (MTCH2) blocks its ubiquitin-proteasomal degradation pathway, stabilizing E2F4 protein, inhibiting TFRC transcription and reducing iron uptake, thereby blocking ferroptosis. Targeting MTCH2 and combining it with the ferroptosis inducer sorafenib effectively inhibits CRC cell proliferation and metastasis (128). In another study, E3 ubiquitin-protein ligase UBR5 maintains signaling pathway stability through Lys-11-linked polyubiquitination, inhibiting ferroptosis and mediating chemotherapy resistance in CRC. The combination of UBR5 inhibitors and ferroptosis inducers enhances the chemotherapy sensitivity to oxaliplatin (129). This suggests that dual or triple therapy combining oxaliplatin, ferroptosis inducers and targeted inhibitors holds great research potential, particularly for CRC and other drug-resistant tumors. SLC7A11 is a critical factor for Cys uptake, and its inhibition reduces GSH synthesis, triggering ferroptosis in cancer cells. Previous research indicates that the long non-coding RNA (lncRNA) HMG recruits the E3 ubiquitin ligase MDM2 to trigger p53 ubiquitination and proteasomal degradation, thus derepressing SLC7A11 expression and inducing resistance to ferroptosis and chemotherapy in CRC cells (130). In a previous study, Qiu *et al* (131) reported that p52-zinc finger estrogen receptor interaction clone 6 drives DAZAP1 transcription and, independently of p53, stabilizes SLC7A11 mRNA, ultimately reinforcing ferroptosis resistance in CRC cells. Therefore, investigating the regulatory mechanisms of SLC7A11 and developing targeted inhibitors to reverse SLC7A11-mediated ferroptosis resistance could effectively suppress CRC growth, metastasis and resistance.

In summary, ferroptosis has great potential for overcoming CRC chemotherapy resistance. Developing new inhibitors and combining them with ferroptosis inducers can better target and regulate ferroptosis-related genes, providing an effective strategy to improve CRC chemotherapy resistance.

Immunotherapy. Immunotherapy has emerged as a central therapeutic modality in CRC, acting principally by inducing coordinated innate and adaptive immune responses. However, the overall efficacy of this approach in CRC remains limited due to strong immune suppressive mechanisms in the TME, including impaired T cell infiltration, high genomic heterogeneity and low PD-L1 expression (132). Based on the aforementioned discussion regarding ferroptosis and immune regulation, inducing ferroptosis holds promise as a strategy to enhance CRC response to immunotherapy.

Immune checkpoint inhibitors (ICIs) have demonstrated antitumor potential. Because ferroptosis exerts immunomodulatory effects and can contribute to ICI-mediated antitumor activity, combining ICIs with ferroptosis inducers can synergistically suppress CRC growth *in vitro* and *in vivo* (133). Specifically, Icariin induces ferroptosis in CRC cells by triggering mitochondrial dysfunction. When combined with anti-PD-1 therapy, Icariin produces a dose-dependent antitumor effect (134). Conversely, overexpression of apolipoprotein L3 (APOL3) increases CRC cell susceptibility to ferroptosis and enhances CD8+ T-cell cytotoxicity by downregulating LDHA. In the setting of combined RSL3 and PD-1 blockade, APOL3 overexpression further amplifies this synergistic antitumor effect (135). Collectively, the synergy between inducing tumor-cell ferroptosis and reprogramming immune effector function may enhance the therapeutic efficacy of ICIs.

Monoclonal antibodies (mAbs) are widely used in oncology due to their target specificity and high affinity. Increasing evidence also highlights their potential to trigger ferroptosis and thereby reverse therapy resistance in tumor cells (136). A mAb targeting the extracellular domain of LGR4 reportedly blocked LGR4-Wnt signaling and downregulated SLC7A11, promoting ferroptosis and increasing the chemosensitivity of drug-resistant CRC cells (137).

Antibody-drug conjugates (ADCs) achieve targeted delivery to tumor cells by coupling mAbs to potent cytotoxic small-molecule payloads. By contrast, bispecific ADCs (BsADCs) recognize two tumor-associated targets, which can improve tumor binding and internalization relative to conventional single-target ADCs (138). Based on the overexpression of CDH17 and guanylate cyclase 2C in CRC, Zhang *et al* (139) designed a BsADC that recognizes both antigens and is conjugated to the ferroptosis inducer RSL3. This BsADC markedly increased binding to and internalization by CRC cells, enabling dual-targeted delivery and activation of ferroptosis. Its antitumor efficacy and safety were superior to those of the corresponding single-target ADCs.

Although CAR-T cell therapy is highly promising, its efficacy in solid tumors such as CRC remains inferior to that observed in hematological malignancies (140). Li *et al* (141) showed that combining CAR-T cells with ferroptosis inducers can trigger ferroptosis via LPO and the ACSL4 axis, thereby increasing CAR-T responsiveness and improving outcomes in non-small cell lung cancer. This combination strategy may be extendable to solid tumors, including CRC, in future studies.

On the other hand, while ferroptosis can enhance antitumor immunity, it may also exert detrimental effects on immune cells themselves. Within the TME, $CD8^+$ T cells are more susceptible to ferroptosis than CRC cells; therefore, preserving a stable antioxidant defense system is essential for maintaining their antitumor function. Combined treatment with an adenosine A2A receptor inhibitor and liproxstatin-1 could preserve GSH/GPX4 homeostasis in $CD8^+$ T cells, thereby inhibiting ferroptosis and enhancing the antitumor immune response (142). Therefore, the application of ferroptosis-based immunotherapy in CRC should carefully balance its dual effects by enhancing CRC cells' susceptibility to ferroptosis while minimizing adverse effects on immune cells.

Gut microbiota-based therapy. The gut microbiota comprises a multifaceted ecosystem within the intestinal lumen that influences the epithelial and immune compartments by means of microbe-derived metabolites, proteins and other macromolecules, thereby exerting a pivotal influence on CRC initiation and progression (143). Increasing evidence continues to implicate a potentially tractable therapeutic axis involving 'gut microbiota-ferroptosis'. A more comprehensive understanding of the mechanisms by which microbial signals influence ferroptotic vulnerability in CRC has the potential to reveal novel intervention opportunities.

For example, the probiotic *Lactobacillus plantarum* MM89 secretes γ-linolenic acid, which induces ferroptosis centered on mitochondrial damage and thereby suppresses CRC progression (144). By contrast, *Fusobacterium nucleatum*, an oncogenic bacterium enriched in patients with CRC, activates the E-cadherin/β-catenin/TCF4 axis, upregulates GPX4 and suppresses ferroptosis, thereby promoting oxaliplatin resistance in CRC cells (145). Collectively, a strategy that eliminates pathogenic bacteria using antimicrobials, while combining ferroptosis inducers with probiotics, may help reverse chemotherapy resistance, reduce recurrence and improve prognosis.

Beyond the microbiota itself, gut microbiota-derived metabolites can also shape CRC outcomes through ferroptosis (146). An anaerobic *Peptostreptococcus* species enriched in CRC produces the tryptophan metabolite trans-3-indoleacrylic acid, which specifically activates aryl hydrocarbon receptor and upregulates aldehyde dehydrogenase 1 family member A3 (ALDH1A3) transcription. ALDH1A3 promotes NADH production via retinaldehyde metabolism, thereby suppressing the antioxidant pathway mediated by the FSP1-CoQ10 system and inhibiting ferroptosis, which in turn accelerates CRC progression (147).

In addition, fecal microbiota transplantation (FMT), which can restore gut microbial metabolites involved in redox homeostasis, has the capacity to modulate ferroptosis (148). In mice, curcumin-conditioned FMT alters the abundance of microbes such as *Lactobacillus* and *Akkermansia*, reshapes host metabolism, and downregulates GPX4 and SLC7A11 to induce ferroptosis in CRC. It also enhances intratumoral infiltration of $CD8^+$ T cells, further suppressing CRC progression (149). Notably, dietary patterns can influence the availability of microbial enzymes and microbiota-derived metabolites, thereby modulating the development of CRC (150). Recent studies indicate that rational dietary interventions, such as creatine supplementation, increasing butyrate levels and adopting a low-arginine diet, can enhance CRC cell sensitivity to ferroptosis by modulating ferroptosis-related pathways, highlighting their potential as adjunct strategies for CRC management (151-153).

Therefore, a systematic investigation into how the gut microbiota and its metabolites regulate ferroptosis and intestinal homeostasis, in conjunction with healthy dietary habits and microbiome-informed precision interventions, may substantially improve therapeutic outcomes in patients with CRC.

Nanotherapy. Although ferroptosis inducers have attracted increasing interest in oncology, the majority of candidates remain limited by poor aqueous solubility and low *in vivo* bioavailability, which substantially hampers their potential as therapeutics. By contrast, nanotechnology can enhance the druggability of ferroptosis inducers by improving solubility, prolonging systemic circulation, facilitating efficient drug loading and reducing toxicity (154). Therefore, nanocarriers engineered to deliver ferroptosis inducers hold strong promise for the treatment of CRC.

Zhang *et al* (155) developed a biomimetic nanocarrier, RSV-NPs@RBCm, by encapsulating resveratrol (RSV) in poly(ε-caprolactone)-poly(ethylene glycol) nanoparticles and subsequently coating the RSV-loaded nanoparticles with a red blood cell membrane (RBCm). This engineered system markedly improved RSV solubility, while the RBCm coating conferred immune-evasive properties and prolonged systemic circulation. When co-administered with the iRGD peptide, the system further increased intratumoral accumulation and penetration, ultimately downregulating SLC7A11 and GPX4 to induce ferroptosis in CRC cells. However, because ferroptosis is governed by a coupled, multi-target and multi-pathway regulatory network, interventions that act on a single pathway often fail to achieve durable and clinically meaningful efficacy. Accordingly, integrating ferroptosis-based strategies with other therapeutic modalities on nanoplatforms may produce synergistic antitumor effects.

Phototherapy is a widely used synergistic approach, primarily including photodynamic therapy (PDT) and photothermal therapy (PTT). In PDT, photoactivated sensitizers generate ROS within tumors, disrupting redox homeostasis and amplifying LPO to promote ferroptosis (156). Luo *et al* (157) reported a ferroptosis-sensitizing nano-photosensitizer that releases chlorin e6 and Fe^{3+} in the acidic TME. This release initiates a ROS cascade that increases LPO. Co-delivery of evodiamine further inhibits GPX4, thereby intensifying ferroptosis and enhancing PDT sensitivity. By contrast, PTT uses photothermal agents to raise local temperature, disrupt cellular membranes and facilitate iron influx, which enhances the Fenton reaction and accelerates ferroptosis (158). For example, a photothermal nanoplatform assembled from camptothecin (CPT) and IR820 (L820/CPT-CPT NPs) triggers ferroptosis after cellular uptake. Cleavage of diselenide bonds continuously depletes intracellular GSH in CRC cells, leading to GPX4 inactivation. Meanwhile, linoleic acid and the IR820-mediated photothermal effect further elevate LPO, producing an amplified ferroptosis-driven antitumor response (159).

Ferroptosis also has immunostimulatory potential and can synergize with immunotherapy through a positive-feedback mechanism (160). Li *et al* (161) developed a photothermal metal-phenolic network platform. This ovalbumin-coated metal-phenolic network leverages the phenomenon of enhanced permeability and retention to achieve selective accumulation at tumor sites. Within this system, Fe^{3+}-gallic acid MPNs simultaneously produce a photothermal effect and drive an Fe^{3+}-mediated Fenton reaction, sustaining high ROS levels. In addition, buthionine sulfoximine suppresses GSH biosynthesis, weakening GPX4-dependent antioxidant defense and thereby amplifying ferroptosis. Subsequently, DAMPs released from ferroptotic cells stimulate antitumor immunity. Activated $CD8^+$ T cells secrete IFN-γ, which downregulates antioxidant components (including GPX4) in CRC cells. This 'closed-loop' positive-feedback circuit increases CRC sensitivity to ferroptosis.

Therefore, under a multimodal combination framework, nanocarriers should be engineered for co-loading of photo-/thermo-agents, ferroptosis modulators and immunoregulatory agents within a single platform, with on-demand release triggered by signals such as pH, ROS, light or heat. Notably, conventional systemic administration is often associated with off-target damage, limited targeting specificity and suboptimal delivery efficiency, whereas local administration can increase drug accumulation at the lesion site and reduce adverse effects caused by systemic exposure (162). For example, Ye *et al* (163) designed a liposome-loaded ROS-responsive hydrogel for intratumoral injection that undergoes network cleavage in response to elevated ROS in the TME, enabling localized release of the NAMPT inhibitor FK866 and the STAT3 inhibitor C188-9. FK866 depletes NAD^+, thereby inhibiting STAT3 activation and downregulating its downstream effector GPX4 to induce ferroptosis in CRC cells. Co-administration of C188-9 further strengthens ferroptosis and promotes immune activation (164-167) (Fig. 4 and Table II).

In summary, the use of rationally designed multifunctional nanocarriers that integrate biomimetic engineering, stimulus-responsive release and localized delivery while enabling deep synergy between ferroptosis and complementary therapies may support the development of ferroptosis-driven treatment paradigms and improve therapeutic outcomes in CRC.

6. Effects of ferroptosis inhibition on IBD-to-CRC transition

Chronic inflammation triggered by infectious agents, dysregulated immune function or unhealthy lifestyle behaviors is a major high-risk factor that promotes tumorigenesis. Although only a minority of CRC cases can be unequivocally attributed to chronic inflammatory conditions, intestinal inflammation can impair the epithelial barrier through oxidative stress. This dysfunction increases epithelial susceptibility to environmental mutagens and thereby elevates the risk of somatic mutations. Therefore, elucidating the mechanisms by which chronic inflammation contributes to CRC remains important (14,168). IBD, primarily encompassing Crohn's disease and ulcerative colitis, is an immune-mediated chronic intestinal disorder. Its hallmark features include epithelial barrier disruption, aberrant immune regulation and structural remodeling of the gut. Under persistent inflammatory pressure, IBD progression arises from multifactorial interactions, including genetic and epigenetic alterations, oxidative stress, immune dysregulation

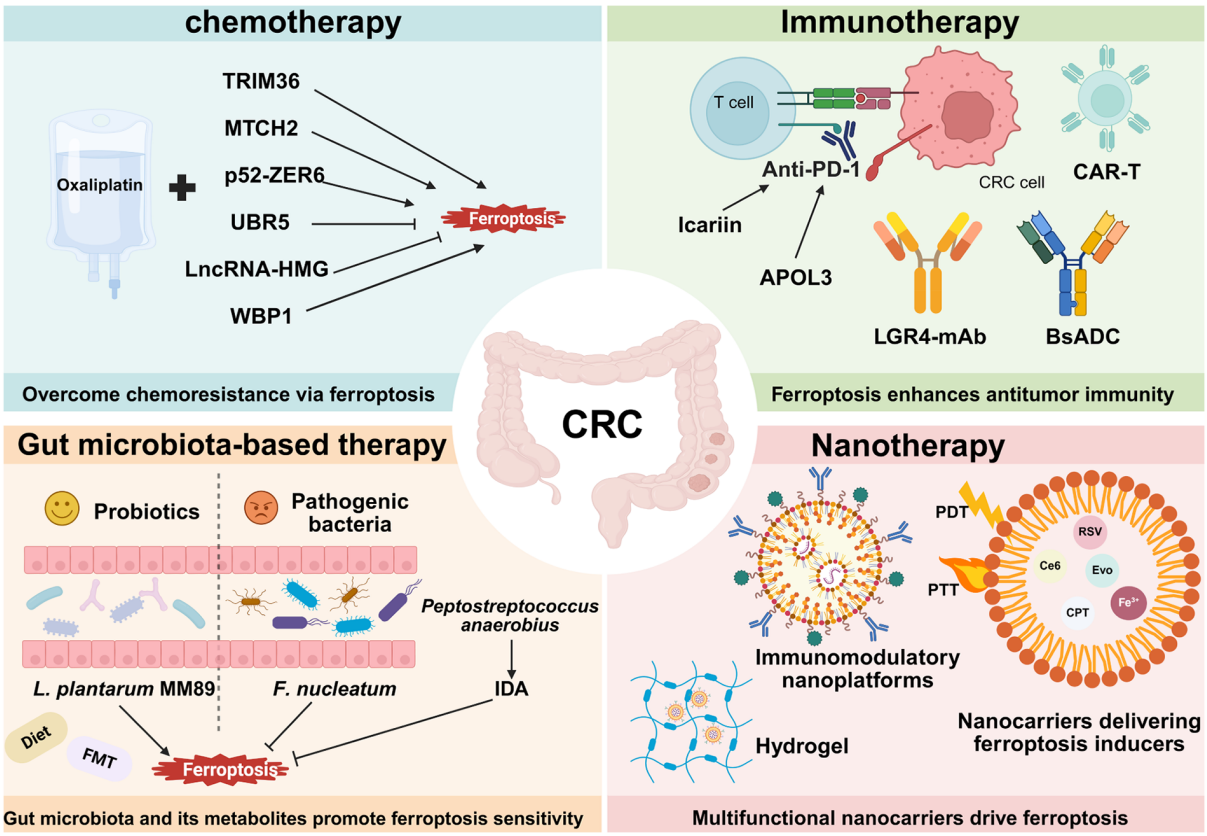

Figure 4. Integration of ferroptosis inducers with chemotherapy, immunotherapy, gut microbiota-based therapy and nanotherapy to suppress CRC progression, overcome therapeutic resistance and limit immune evasion. BsADCs, bispecific ADCs; FMT, fecal microbiota transplantation; CAR-T, chimeric antigen receptor T-cell; PDT, photodynamic therapy; PTT, photothermal therapy; CRC, colorectal cancer; TRIM36, tripartite motif containing 36; MTCH2, mitochondrial carrier homolog 2; ZER6, zinc-finger estrogen receptor interaction clone 6; UBR5, ubiquitin protein ligase E3 component N-recognition protein 5; lncRNAs, long non-coding RNAs; WBP1, WW domain-binding protein 1; APOL3, apolipoprotein L3; PD-1, programmed cell death protein 1; mAbs, monoclonal antibodies; IDA, trans-3-indoleacrylic acid; *L. plantarum* MM89, *Lactobacillus plantarum* MM89; *F. nucleatum*, *Fusobacterium nucleatum*; Ce6, chlorin e6; Evo, evodiamine; CPT, camptothecin; RSV, resveratrol.

and microbial dysbiosis. Together, these processes drive lesions along the 'inflammation-dysplasia-carcinoma' sequence, making CRC among the most severely affecting complications of IBD (169-171).

During the active inflammatory phase of IBD, inhibition of ferroptosis generally exerts a protective effect. The maintenance of intestinal mucosal barrier integrity is imperative for the preservation of gut homeostasis. Mucus and digestive secretions produced by IECs dilute toxins and inhibit or eliminate bacteria, thereby forming a critical line of defense. However, ferroptosis in IECs can compromise tissue repair, disrupt the mucosal barrier and weaken immune function, thereby increasing the risk of CRC (172,173). Previous evidence indicates that NEDD4 like E3 ubiquitin protein ligase (NEDD4L) regulates the stability of SLC3A2 via K63-linked ubiquitination, which enhances GPX4 activity and suppresses ferroptosis in IECs. Loss of NEDD4L exacerbates intestinal barrier injury and amplifies inflammatory responses. Consistently, ferroptosis inhibitors can alleviate NEDD4L-deficiency-driven colitis and its associated CRC progression (174).

This antiferroptotic effect also indirectly reduces the risk of inflammation-driven carcinogenesis. In immune regulation, pro-inflammatory M_1 macrophages play a pivotal role in maintaining intestinal homeostasis. During host defense against external insults, M_1 macrophages elicit a controlled pro-inflammatory response that facilitates pathogen clearance and preserves the intestinal microenvironmental balance. However, once the threat is resolved, this inflammatory program must be restrained to prevent excessive tissue damage and reduce the likelihood of progression from IBD to CRC (175,176). OTSSP167, an inhibitor of maternal embryonic leucine zipper kinase, not only ameliorates gut dysbiosis and suppresses ferroptosis in IECs, but also markedly reduces macrophage infiltration in murine colitis models. It promotes polarization toward an antitumor-associated M_1 phenotype and decreases the secretion of pro-inflammatory mediators, thereby exerting anti-inflammatory effects and suppressing the initiation and progression of colitis-associated CRC (177). In the early stages of inflammation-driven carcinogenesis, moderate inhibition of ferroptosis in specific cell populations may help interrupt the transition from IBD to CRC.

However, once tissues enter the inflammation-to-cancer transition or tumor cell selection stage, resistance to ferroptosis is no longer merely an adaptive stress response, but gradually becomes a critical event that promotes tumor survival and progression. To adapt to a microenvironment characterized by high ROS levels, hypoxia and persistent exposure to inflammatory cytokines, tumor cells often actively establish anti-ferroptotic programs, thereby sustaining survival, proliferation and malignant evolution. On the one hand, during

Table II. Ferroptosis-modulating therapeutic strategies in CRC.

Therapeutic method	Representative agent/target	CRC cell models	Main mechanism	(Refs.)
Chemotherapy	TRIM36	HCT116, LoVo, HT2, Caco-2, SW480, SW620	Promotes FOXA2 degradation, inhibits the NRF2 pathway	(127)
	MTCH2	RKO, SW620, HCT116, SW480	MTCH2 loss induces ferroptosis through the E2F4-TFRC axis	(128)
	UBR5	SW1116, HCT116, SW620	Maintains Smad3-SLC7A11 signaling	(129)
	LncRNA-HMG	LoVo, HCT116, SW480	Promotes p53 degradation and upregulates SLC7A11 and VKORC1L1	(130)
	p52-ZER6	HCT116, LoVo, HT29	Regulates DAZAP1 transcription to upregulate SLC7A11 expression	(131)
	Trifluridine/tipiracil	RKO, HT29, HCT116, DLD-1	Activates p53, suppresses SLC7A11 expression	(164)
	WBP1	HCT116, SW480	WBP1 inhibition impairs mitochondrial function	(165)
	SNX1	HCT116, SW480, SW948, SK-CO-1, Caco-2, LoVo, HT29	Modulates the EGFR downstream PPAR-ACSL1/4 axis	(166)
Immunotherapy	Icariin	HCT116, SW620, MC38, CT26	Induces mitochondrial dysfunction	(134)
	APOL3	RKO, HCT116, Caco-2	Promotes LDHA degradation, and enhances CD8+ T-cell function	(135)
	LGR4-mAb	HCT116, HT-29	Inhibits LGR4-Wnt signaling and downregulates SLC7A11	(137)
	CDH17-GUCY2C BsADC	COLO-205, HT-29, HCT116, T84, LS1034, LS-180, SW620, LoVo, COLO-201, RKO, SW1463, SW403	Dual targeting of CDH17 and GUCY2C enables RSL3 delivery to CRC cells	(139)
	CYP1B1	RKO, HCT116, HT29, MC38	CYP1B1 inhibition is reported to promote ACSL4 degradation	(167)
Gut microbiota-based therapy	*L. plantarum* MM89	DLD-1, HT-29	Secretion of γ-linolenic acid induces mitochondrial damage	(144)
	F. nucleatum	HCT116, HT-29	Upregulates GPX4	(145)
	IDA	HT29, MC38	Enhances FSP1-mediated antioxidant defense	(147)
	Curcumin	RKO, CT26	Curcumin-treated FMT downregulates GPX4 and SLC7A11 expression	(149)
	Arginine	HCT15, LoVo, SW620	Activates the AMPK-p53-p21 pathway	(151)
	Butyrate	HCT116, SW480, SW620, RKO	Inhibits xCT and reduces GSH synthesis	(152)
	Creatine	DLD-1, SW480, MC38	Induces FSP1 phosphorylation	(153)
Nanotherapy	RSV-NPs@RBCm	HT29, HCT116	Downregulates SLC7A11 and GPX4 expression	(155)
	FCE NPs	CT26	Triggers a Fe^{3+}-mediated Fenton reaction, Ce6-induced ROS generation, and Evo- mediated GPX4 inhibition	(157)
	L820/CPT-CPT NPs	DLD-1, HCT116, SW480, RKO	Combines GPX4 inactivation with linoleic acid oxidation	(159)
	BOFG	CT26	Impairs GPX4-mediated antioxidant defense; IFN-γ secreted by immune cells further downregulates GPX4	(161)

Table II. Continued.

Therapeutic method	Representative agent/target	CRC cell models	Main mechanism	(Refs.)
	Liposome-loaded hydrogel	MC38, CT26	Depletes NAD, activates the STAT3/GPX4 axis	(163)

TRIM36, tripartite motif containing 36; FOXA2, forkhead box transcription factor A2; MTCH2, mitochondrial carrier homolog 2; UBR5, ubiquitin protein ligase E3 component N-recognition protein 5; TFRC, transferrin receptor; lncRNAs, long non-coding RNAs; VKORC1L1, vitamin K epoxide reductase complex subunit 1 like 1; ZER6, zinc-finger estrogen receptor interaction clone 6; DAZAP1, deleted in azoospermia associated protein 1; WBP1, WW domain-binding protein 1; SNX1, Sorting nexin 1; EGFR epidermal growth factor receptor; APOL3, apolipoprotein L3; LDHA, lactate dehydrogenase A; BsADCs, bispecific ADCs; CYP1B1, cytochrome P450 1B1; IDA, trans-3-indoleacrylic acid; FSP1, ferroptosis suppressor protein 1; *L. plantarum* MM89, *Lactobacillus plantarum* MM89; *F. nucleatum*, *Fusobacterium nucleatum*; FMT, fecal microbiota transplantation; AMPK, adenosine monophosphate-activated protein kinase; NPs, nanoparticles; Ce6, chlorin e6; Evo, evodiamine; CPT, camptothecin; CRC, colorectal cancer; STAT3, signal transducer and activator of transcription 3; BOFG, constructed by coating BSO and ovalbumin with an Fe^{3+}/gallic acid coordination network; GPX4, glutathione peroxidase 4; E2F4, E2F transcription factor 4; SLC7A11, solute carrier family 7 members 11; PPAR, peroxisome proliferator-activated receptor; ACSL, acyl-CoA synthetase long-chain family member; GSH, glutathione; FSP1, ferroptosis suppressor protein; RSV, resveratrol; RSV-NPs@RBCm, RSV-loaded poly(ε-caprolactone)-poly(ethylene glycol) nanoparticles with erythrocyte membrane; FCE NPs, ferroptosis-boosted nanophotosensitizer; L820/CPT-CPT NPs, multifunctional chemo-photothermal nanoplatform based on camptothecin and IR820; NAD, nicotinamide adenine dinucleotide.

chronic inflammation-driven colorectal carcinogenesis, serine protease 22 (PRSS22) is progressively upregulated in IECs. Its overexpression attenuates ferroptosis by suppressing heme oxygenase 1-mediated iron release and ROS accumulation, thereby supporting the survival of CRC cells. In addition, PRSS22 can proteolytically cleave osteopontin, generating bioactive fragments that enhance the migratory and metastatic potential of CRC cells, and further accelerate tumor progression (178). On the other hand, at the CRC stage, the RNA-binding protein interleukin enhancer-binding factor 3 (ILF3) reduces CRC cells' sensitivity to ferroptosis by stabilizing SLC3A2 mRNA, thereby enhancing cystine uptake and GSH synthesis. Furthermore, TNF-α in the inflammatory microenvironment can further upregulate ILF3, reinforcing this anti-ferroptotic state and consequently promoting CRC progression (179). In premalignant and malignant cell stages, inhibition of ferroptosis essentially confers a survival advantage that supports continued tumor progression.

Therefore, across the continuous disease course from IBD to CRC, ferroptosis regulation does not exert a uniformly protective or pathogenic effect, but instead displays marked stage dependency and dual biological roles. During the early or active phase of intestinal inflammation, moderate inhibition of ferroptosis may help reduce epithelial cell injury, preserve mucosal barrier integrity and, to a certain extent, limit the persistent amplification of chronic inflammation, thereby exerting a protective effect against inflammation-associated tumorigenesis. However, once the disease progresses to the inflammation-to-cancer transition stage or an established TME has formed, sustained enhancement of anti-ferroptotic capacity may impair the elimination of abnormally proliferating cells and create favorable conditions for tumor cell survival and malignant progression. Accordingly, the therapeutic relevance of ferroptosis in the IBD-CRC axis should be defined as a stage-specific precision regulatory strategy rather than a simple approach of global activation or complete inhibition. Future studies should systematically elucidate the specific functions of distinct regulatory nodes of ferroptosis during the transition from IBD to CRC, with consideration of disease stage, key target cell populations and underlying molecular mechanisms, thereby providing a theoretical basis for precision therapy.

7. Clinical research progress targeting ferroptosis

Clinical trials. The translation of ferroptosis research from bench to bedside has progressed substantially and numerous clinical studies have explored the therapeutic potential of targeting ferroptosis-related pathways in CRC. In this context, therapeutic strategies targeting ferroptosis have attracted considerable attention from both researchers and clinicians, and an increasing number of ferroptosis modulators have entered clinical trials (180-191) (Table III). Accordingly, a variety of candidate drugs, technical approaches and therapeutic strategies targeting ferroptosis have been developed, and related clinical studies are gradually shifting from early empirical exploration toward mechanism-based design. In clinical practice, ferroptosis-targeted interventions are more likely to be used as combination therapies tailored to specific pathological contexts of CRC, with the potential to overcome apoptotic resistance in tumor cells, enhance the responsiveness of CRC to immunotherapy and chemotherapy, and suppress metastatic growth. Future research should improve the targeting specificity of these interventions for colorectal tissues and promote the integration of multi-mechanistic agents to enhance overall efficacy while reducing drug dosage and minimizing off-target effects as much as possible.

Potential ferroptosis biomarkers. The pathophysiological role of ferroptosis in CRC has attracted increasing attention and the associated molecular alterations provide an important basis for the development of highly sensitive biomarkers. To date, research on ferroptosis biomarkers has mainly focused on molecular events that reflect dysregulated iron metabolism,

Table III. Clinical trials targeting ferroptosis in colorectal cancer.

Drug	Target	Trial ID	Phase	(Refs.)
Sorafenib	SLC7A11	NCT07505472 NCT01715441 NCT01471353 NCT01383343	Marketed	(128,180-182)
Sulfasalazine	SLC7A11	NCT06134388	Marketed as an anti-inflammatory agent; phase I in cancer	(164)
Neratinib	Iron	NCT03919292	Marketed	(183)
Artesunate	Iron	NCT07095309	Marketed as an antimalarial drug, in oncology phase II trials	(184)
Cisplatin	GSH	NCT07433673 NCT06704724 NCT06621563 NCT04457284	Marketed	(185-188)
Gemcitabine	GPX4	NCT05733000	Marketed	(189)
Carbon nanoparticle-loaded iron	Iron metabolism	NCT06048367 NCT07433283	Phase I	(190,191)

GSH, glutathione; GPX4, glutathione peroxidase 4.

LPO accumulation and abnormalities in antioxidant systems. Because these changes often precede the appearance of canonical ferroptotic phenotypes, they may serve as pharmacodynamic biomarkers for assessing ferroptosis-inducing effects (192). For example, malondialdehyde, 4-HNE, ACSL4, TFR1 and GPX4 have been proposed as candidate biomarkers of ferroptosis susceptibility. However, most of these indicators are indirect measures, with limited ability to distinguish ferroptosis from nonspecific oxidative damage, and they are readily influenced by multiple factors, including pre-analytical sample stability, dietary factors and comorbidities (193). Although imaging approaches based on ROS-sensitive probes can provide a certain degree of spatial information, their application remains limited by insufficient probe specificity and poor tissue penetration (194). In addition to molecular and imaging biomarkers, ferroptosis-related lncRNAs are also considered promising biomarkers in CRC. Accumulating evidence indicates that these molecules are involved not only in the regulation of CRC cell proliferation, metastasis and drug resistance, but are also closely associated with patient prognosis, the risk of recurrence and metastasis, and treatment response (195). For instance, a prognostic model comprising 15 ferroptosis-related lncRNAs constructed by Ge *et al* (196) could independently predict survival outcomes in patients with CRC and potentially help evaluate treatment sensitivity. However, these biomarkers remain largely at an early stage of research, and their stability, consistency and reproducibility still require further validation. Notably, CRC exhibits substantial heterogeneity in genetic drivers, metabolic reprogramming and the TME, suggesting that ferroptosis-directed therapy will more likely depend on biomarker-guided precision patient stratification rather than uniform application.

A recent large-scale TME atlas constructed from single-cell CRC data further classified patients into six subtypes with distinct immune evasion mechanisms, indicating that CRC stratification should not be limited to a simple 'immune-hot' vs. 'immune-cold' classification (197). On this basis, multimodal machine-learning strategies integrating lipidomic features, oxidized phospholipid burden, pathological parameters and radiomic data may help identify those patients who are most likely to benefit from ferroptosis-related interventions, and will be critical for translating ferroptosis-targeted therapy into clinical practice in CRC.

8. Discussion

As an iron-dependent and non-reversible mode of cell death, ferroptosis has emerged as a promising target for CRC therapy. However, despite the exploration of various ferroptosis-centered therapeutic strategies, important challenges remain to be overcome before these strategies can be broadly translated into clinical applications.

The regulatory network governing ferroptosis is highly complex, involving multiple interconnected signaling pathways and metabolic axes. However, the key molecular events and hierarchical regulatory logic remain incompletely understood, particularly their association with other cell death programs such as autophagy, which remains controversial. Autophagy may suppress ferroptosis in certain contexts, while in others, autophagy-dependent ferroptosis can be initiated. Conversely, ferroptosis can also occur independently of autophagy. These context-dependent interactions require further mechanistic clarification (198). Current evidence indicates that, among the GPX4-independent ferroptosis defense pathways, the GCH1-BH4 axis is the most promising regulatory target for therapeutic translation in CRC. Inhibition of this pathway enhances erastin-induced ferroptosis by activating ferritinophagy and produces synergistic antitumor effects. By

contrast, the biological roles and therapeutic potential of other GPX4-independent pathways in CRC remain to be systematically evaluated (199). Notably, canonical ferroptosis inducers such as erastin and RSL3 primarily act by disrupting iron homeostasis and redox balance. However, their limited target selectivity can cause off-target toxicity, and high doses may induce additional injury in normal tissues, including the liver and kidney (200). Therefore, future studies should aim to increase the mechanistic understanding of ferroptosis-associated networks and exploit CRC-specific metabolic vulnerabilities, such as dysregulated iron metabolism and impaired redox homeostasis, to guide precision drug design. This approach may enable the development of novel ferroptosis modulators with higher selectivity and fewer off-target effects, maximizing antitumor efficacy while maintaining an acceptable safety profile.

Ferroptosis and antitumor immune responses exhibit a complex bidirectional association. Combining ferroptosis inducers with immunotherapy can improve efficacy in certain settings. Ferroptotic tumor cells have also been observed to remodel the TME towards immunosuppression, dampening T-cell function and thereby enabling immune escape. This highlights the necessity for strategies that selectively trigger ferroptosis in tumor cells while preserving immune effector cells from ferroptotic destruction. One strategy that has been suggested is the disturbance of inhibitory feedback circuits in the TME that propagate danger- or signal-induced secondary ferroptosis to immune cells in the subsequent sequence of tumor-cell ferroptosis. Another approach is to develop antigen-guided drug-delivery systems that release ferroptosis inducers specifically within tumor cells, thereby minimizing off-target toxicity to immune cells. Notably, post-translational modifications (PTMs) can markedly alter cellular sensitivity to ferroptosis by regulating the stability, activity and intermolecular interactions of key ferroptosis-related proteins (201). Combining PTM-based ferroptosis-targeting strategies with ICIs may both reprogram immune-cell function to strengthen antitumor immunity and offer a new combinatorial approach to overcome therapeutic resistance in CRC (202).

With the widespread adoption of single-cell sequencing, researchers can more precisely characterize how the gut microbiota and its metabolites regulate immune cell populations. Emerging evidence suggests that the gut microbiota may shape the antitumor immune microenvironment by selectively promoting or inhibiting ferroptosis (146,203). Although the gut microbiome plays essential roles in numerous physiological processes, its specific contribution to ferroptosis remains insufficiently and systematically investigated. This gap may stem from relatively small fecal sample sizes and the difficulty of definitively identifying specific microbial taxa or small-molecule metabolites that modulate ferroptosis. Consequently, current profiles of gut microbiota alterations in patients with cancer may be incomplete. Therefore, existing microbiome-related evidence for ferroptosis is largely indirect and remains limited. Further studies are needed to elucidate associations between key microbial taxa and ferroptosis-related genes.

Although nanocarrier delivery systems can improve drug bioavailability and pharmacokinetics, their clinical manufacturability and long-term safety require more rigorous evaluation. Overly complex nanosystems often compromise reproducibility and process scalability. By contrast, carriers with well-defined physicochemical properties and simpler architectures are more likely to achieve batch-to-batch consistency and meet the clinical trial quality control requirements. Certain nanodrug delivery systems are poorly biodegradable and may accumulate in organs such as the liver and kidneys, increasing metabolic burden and causing organ-specific toxicity (160). Furthermore, numerous current nano-assemblies are designed around biochemical and immunological profiles representative of the main population, which may limit their ability to address the tumor heterogeneity frequently encountered in clinical practice.

Notably, artificial intelligence (AI) and machine learning are increasingly used to screen novel compounds, optimize carrier architectures and enhance drug-loading efficiency. By modeling *in vivo* pathophysiological responses, these approaches also accelerate the development of nanotherapeutic systems with improved tumor targeting and microenvironmental adaptability (204). Therefore, AI-enabled nanomedicine strategies could be leveraged to optimize the delivery of ferroptosis inducers. Priorities include developing biodegradable, scalable and multi-stimuli-responsive delivery platforms, alongside strengthening systematic safety-evaluation frameworks to reduce systemic toxicity and off-target effects.

The inflammatory consequences of inducing ferroptosis and the associated potential pro-tumor risks should be rigorously evaluated. Ferroptosis has substantial cytotoxic potential against tumor cell populations that are refractory to conventional therapies. However, accompanying processes, including inflammatory responses, increased genomic instability, epigenetic remodeling and activation of cytokine signaling pathways, may under certain conditions facilitate tumor initiation or progression toward increased malignancy (205). The goal of anti-inflammatory therapy is to suppress pro-tumor inflammation while preserving or even enhancing antitumor immune responses. Given the systemic and multifactorial nature of inflammation, interventions that target multiple proteins implicated in inflammatory signaling and tumorigenesis may be more effective than approaches focused on a single gene, protein or pathway. Furthermore, the clinical efficacy of inflammation-targeted therapies remains inconsistent, partly due to the lack of validated biomarkers for treatment selection and to interpatient heterogeneity, including age and tumor molecular profiles (206). Therefore, integrating multi-omics data with AI-based modeling may enable the identification of disease-specific inflammatory phenotypes in patients with intestinal disorders. This framework could guide the selective inhibition of ferroptosis in IECs, thereby improving the balance between inflammation control and immune surveillance, and facilitating the implementation of personalized therapies.

The majority of previous studies rely on simplified cell lines and conventional animal models; however, neither of them fully captures the complex physiological and pathological features of CRC progression. Human three-dimensional *in vitro* models derived from stem-cell technologies such as organoids and organ-on-a-chip platforms can more accurately recapitulate human tissue architecture and microenvironmental dynamics. These systems provide a more translational

platform for screening personalized combination therapies. Future research should prioritize clinical trials to systematically evaluate the efficacy and safety of ferroptosis-targeted therapies and to accelerate their translation into clinical practice. Notably, the application of AI may further accelerate clinical translation (207,208). AI-driven models that evaluate patient-specific redox trajectories and ferroptosis sensitivity may help optimize therapeutic benefit and improve clinical outcomes.

In summary, current evidence supports ferroptosis as a promising therapeutic target in CRC. Its involvement is primarily linked to several key biological processes, including dysregulated iron metabolism, enhanced LPO and impaired antioxidant defense systems. Furthermore, the induction of ferroptosis shows considerable potential for increasing the sensitivity of CRC to chemotherapy, immunotherapy and emerging drug-delivery strategies. However, these advances remain far from clinical translation. First, the core regulatory network that determines ferroptosis sensitivity in CRC has not yet been fully defined, and differences in vulnerability across distinct biological contexts remain to be clarified. Second, ferroptosis-based interventions have a dual nature. A major challenge for optimizing combination immunotherapy is how to enhance tumor cell killing while preserving the functional integrity of immune cells, including $CD8^+$ T cells, NK cells and TAMs, to the greatest extent possible. Third, current evidence for interactions between the gut microbiota and ferroptosis is largely correlative, and their causal association and underlying molecular basis require further investigation. Finally, biomarkers for patient stratification, treatment-response prediction and dynamic monitoring, as well as delivery platforms with high targeting specificity and low toxicity, are not yet sufficiently mature. Therefore, future research should leverage single-cell omics, spatial multi-omics and AI-assisted analysis to focus on identifying responsive patient populations, determining the optimal timing for intervention and developing precise delivery strategies. Such efforts will help advance ferroptosis research from mechanistic exploration toward clinical application in CRC.

Acknowledgements

The figures were created with BioRender (biorender.com).

Funding

This study was supported by Hubei Provincial Natural Science Foundation (grant no. JCZRLH20260143).

Availability of data and materials

Not applicable.

Authors' contributions

MW and MZ conceived the study, constructed figures and edited the manuscript. MW performed the literature review and wrote the manuscript. MZ provided overall supervision. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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