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Ferroptosis Plays a Pivotal Role in Activating and Modulating Specific Intracellular Signaling Pathways Integrated into the Therapeutic Management of Colorectal Cancer

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ABSTRACT

It is expected that the amount of recently diagnosed colon cancer cases will increase to around 3.2 million yearly until 2040. Although early diagnostic procedures and management approaches have been improved, colorectal cancer (CRC) treatment remains challenging. There is an urgent need to discover new therapeutic agents to enhance therapeutic strategies. Ferroptosis is distinguished as a mode of regulated cell death considered by iron-dependent lipid peroxidation. Contemporary investigations suggest that induction of ferroptosis in CRC can effectively target neoplastic cells that are resistant to alternative forms of cell death. This review has summarized recent scientific work on the implications of ferroptosis in CRC treatment and highlights its underlying molecular and biological mechanisms. While investigating its therapeutic potential, it shows the importance of diverse modulators of ferroptosis, including the 7-membered solute carrier family 11 or xCT (SLC7A11), reactive oxygen species (ROS), glutathione (GSH), and iron in the context of CRC. Recent research has identified specific pathways and compounds that can induce ferroptosis in CRC, such as apatinib and elesclimol, which are involved in pivotal signaling cascades. Attenuation of proteins such as splicing factor, arginine/serine 9 (SFRS9), and Tp53-induced glycolysis and apoptosis regulator (TIGAR) may increase the sensitivity of CRC cells to ferroptosis, thus suggesting promising therapeutic avenues. Compounds including IMCA and β-elemene have shown efficacy in inducing ferroptosis while minimizing toxicity to normal tissues, thereby demonstrating their potential as therapeutic agents for CRC. Participating ferroptosis stimulator drugs with current treatment regimens, such as cetuximab and aspirin, may offer better treatment outcomes for CRC patients, especially those presenting resistance to conventional therapies.

Keywords: Colorectal cancer, epidemiology, screening tests, treatment approaches

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Introduction

Colorectal cancer (CRC) affects the colon and rectum and is the second leading cause of cancer death and the third most diagnosed cancer worldwide, representing a major public health challenge. In 2020, CRC accounted for about 9.4% of all cancer deaths, with prominence of its impact on mortality. The incidence of CRC has increased and projections suggest that it could more than double by 2035, especially in less industrialized regions. By 2040, new cases are projected to reach 3.2 million and deaths to reach 1.6 million annually, representing an alarming 73% increase in mortality (1, 2).

In 2012, Dixon introduced the term ferroptosis, describing it as a form of non-apoptotic, iron-dependent cell death characterized by the accumulation of lipid reactive oxygen species (ROS). Ferroptosis is distinct from necrosis, apoptosis, and autophagy in terms of cell morphology and function. Morphologically, it is characterized by reduced mitochondrial volume, increased bilayer membrane density, and reduced or absent mitochondrial cristae, while maintaining cell membrane integrity, normal nuclear size, and nonaggregated chromatin. Biochemically, ferroptosis is associated with decreased intracellular glutathione (GSH) levels and decreased glutathione peroxidase 4 (GPX4) activity. This deficiency disrupts lipid peroxide metabolism, while Fe 2+ accelerates lipid oxidation via a Fenton-like mechanism, generating reactive oxygen species (ROS) that induce ferroptosis. Various genes linked to iron homeostasis and lipid peroxidation pathways have been identified, but their regulatory mechanisms need further investigation. Despite noteworthy developments in oncology treatments, tumor resistance remains a major challenge. Preclinical and clinical studies have been dedicated on drug resistance and revealing the link between ferroptosis and treatment resistance in cancer. A distinct mesenchymal cell phenotype in carcinomas is associated with increased resistance to therapies. The research of Viswanathan *et al*. showed that this highly resistant mesenchymal phenotype relies on a GPX4-mediated lipid-peroxidase pathway that resists ferroptosis. Furthermore, several studies suggest that modulation of ferroptosis may increase the efficacy of CRC therapies and potentially reverse resistance. The purpose of this review is to investigate the mechanisms of ferroptosis and its therapeutic implications to overcome resistance to conventional treatments, including chemotherapy, targeted therapy, and immunotherapy. We will also evaluate the prospects and challenges of using ferroptosis regulation to tackle cancer therapy resistance, we hope that our findings will help as an appreciated reference for future research.

Literature Search and Selection of Articles

An extensive review of the current literature on recent advancements in therapeutic agents for CRC has been undertaken. The inclusion criteria encompassed articles written in English, available in full-text, comprehensive, and directly pertinent to the subject under investigation. An extensive search was conducted in the PubMed and Scopus databases in December 2023, utilizing keywords related to drugs, therapeutic agents, colorectal cancer/CRC, ferroptosis, and novel therapeutic methods. Initially, 125 articles were identified based on their titles, abstracts, and publication dates. After eliminating duplicate entries, 42 distinct articles were retained. These articles were thoroughly analyzed, and a subset of 5 articles relevant to the research question was selected. Subsequently, in March 2024, a supplementary search was conducted using Google Scholar, PubMed, and Scopus, identifying and including 3 additional articles directly related to the topic of interest (Figure 1).

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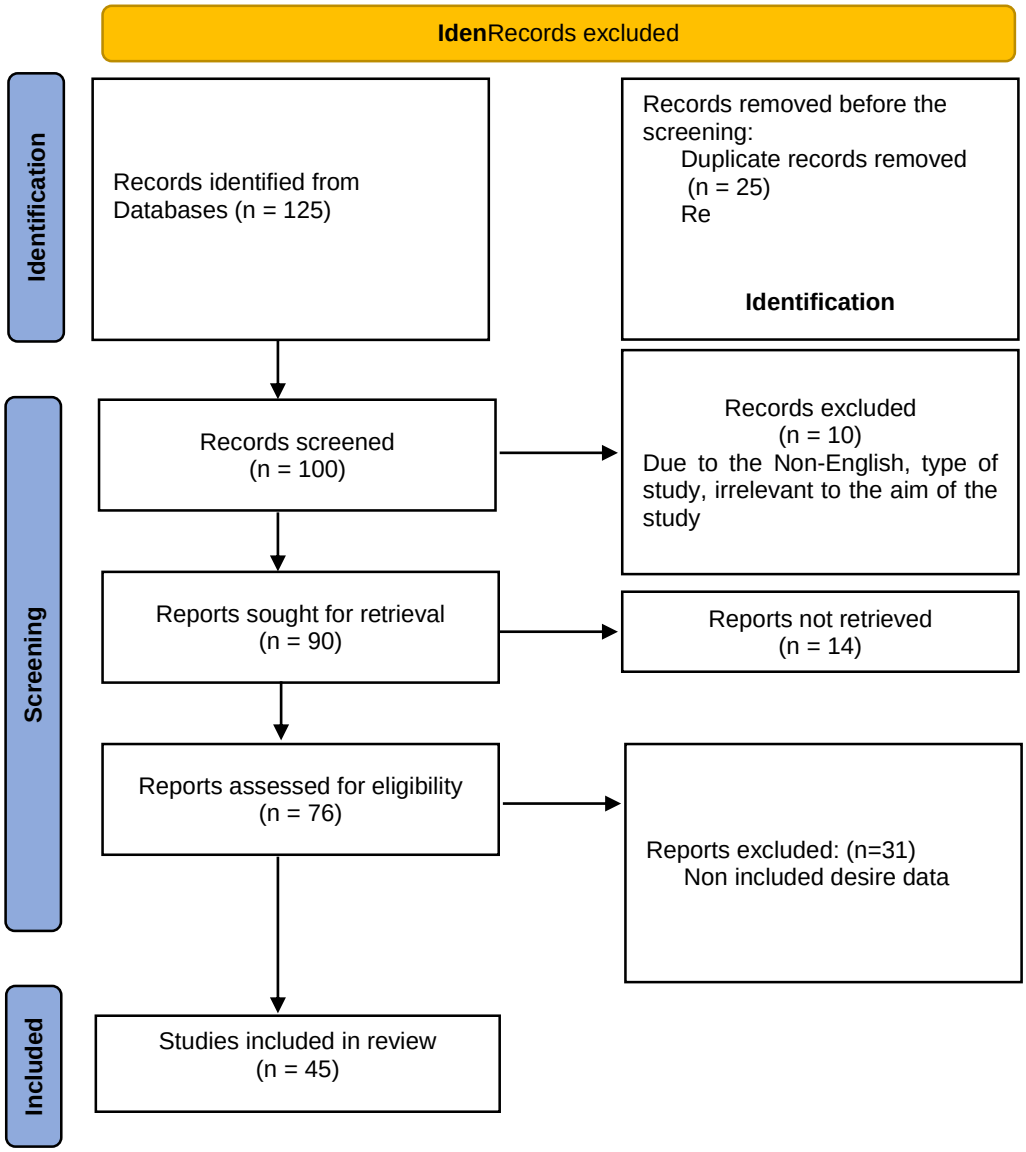


Fig. 1. Flow diagram of the steps for including studies in the review study

CRC molecular pathways

Research has recognized several regulatory genes involved in this process, including KRAS, BRAF, and p53. Clinical studies indicate that mutations in these genes are directly linked to the development of colorectal cancer, with findings showing that 47.5%, 31.8%, and 23% of CRC patients exhibit mutations in p53, KRAS, and BRAF, respectively (3). The findings from this research have improved our knowledge of the pathophysiological mechanisms underlying colorectal cancer (CRC) and have contributed important information for the creation of targeted therapeutic strategies (4). Nevertheless, the utility of these mutation-based studies in predicting patient survival and treatment responses remains limited. The regulation of colorectal cancer-associated tumor microenvironment (TME) by chronic inflammation occurs through various pathways, including the production of cytokines and pro-inflammatory mediators, as well as the

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regulation of angiogenesis and tissue remodeling (5). The role of macrophages is essential in maintaining the stability of the gastrointestinal microenvironment, with M1 macrophage infiltration being a prominent indicator of inflammatory diseases that can predispose individuals to colorectal cancer (CRC). Upon activation, both M1 and M2 macrophages can produce reactive oxygen species (ROS), and the elevated levels of ROS can result in substantial DNA damage, which in turn heightens the risk of tumorigenesis (6, 7).

In addition, the progression of colorectal cancer can be shaped by several other factors. Lipid metabolism, especially the metabolism of fatty acids, is essential for the physiological roles of colorectal cancer cells. Adipocytes originating from the adipose tissue of colorectal cancer patients can release large amounts of fatty acids, which are easily absorbed by the cancer cells. Under conditions of nutrient scarcity, these fatty acids can facilitate the growth and survival of colorectal cancer cells by activating AMPK, which promotes autophagy and boosts mitochondrial fatty acid β-oxidation (8, 9).

Long-chain fatty acids have been recently shown to cause tumorigenesis. Specifically, linoleic acid stimulated the receptor for advanced glycation end products in rats through azoxymethane activation, which leads to the formation of aberrant crypt foci and accelerates the growth of colorectal cancer tumors. Elaidic acid, a trans-fatty acid, has been found to enhance the growth, survival, and invasion of colorectal cancer cell lines, causing stem cell features and promoting epithelial-mesenchymal transition (EMT), where epithelial cells lose their environments that otherwise maintain their epithelial phenotype while they develop a mesenchymal phenotype associated with the initiation of a tumor, its invasion and metastasis, and resistance to treatment (9-11).

Ferroptosis

Ferroptosis is a unique and newly emerged form of cell death that is dependent on iron and differs from more classical modes of cell demise such as apoptosis, a programmed and peak cellular death with specialized signaling pathways, and necrosis, which is usually caused by acute cellular injury (12). Thus, the combination of these three major metabolic pathways, which are indispensably regulated by thiol compounds, lipid molecules and iron ions, is a typical and unique character in ferroptosis, and finally leads to the synthesis of lipid peroxides under iron regulation, resulting in irreversible cell death (13). There are two main antioxidant defenses that inhibit initiation and progression of ferroptosis: firstly, glutathione peroxidase 4 (GPx4), an enzyme involved in the reduction of lipid peroxides in a manner dependent on glutathione; secondly, the recently characterized ferroptosis suppressor protein, which catalyzes the regeneration of ubiquinone, or coenzyme Q10, functioning as a trap for putatively harmful lipid peroxyl radicals. Additionally, certain pharmacological inhibitors, especially ferrostatin-1, are also radical-trapping antioxidants that prevent the development of ferroptosis (14, 15). The ferroptosis pathway is mentioned in Figure 2.

Practically all ferroptogenic substances can be organized into four categories. The first class is mainly represented by erastin, the first recognized inducer of ferroptosis, whose core action is to specifically consume glutathione (GSH) by Xc- directly blocking cystine/glutamate antiporter system (14, 15). In addition, erastin targets the voltage-dependent anion channels (VDACs) and induces mitochondrial dysfunction manifesting himself in respiration breakdown and energy production. Recent research results have indicated that erastin-activated ferroptosis is also characterized by a rise in lysosomal-associated

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membrane protein 2a levels, which stimulates the process of chaperone-mediated autophagy and enhances the degradation of GPX4 underpinning the integrity of cellular antioxidant defense (13, 16, 17).



Fig. 2. The molecules involved in the ferroptosis pathway influence cell death and can be targeted for the treatment of colorectal cancer through ferroptosis.

The second group includes RSL3 and DPI7-commonly known as direct inhibitors of GPX4 enzymatic activity-and the consequent inducer of ferroptotic cell death. The third group has FIN56, inducing ferroptosis through dual mechanisms, namely co-enzyme Q10, degradation of GPX4, and binding to squalene synthase, hence sufficiently depleting endogenous coenzyme Q10, which in turn raises the sensitivity of cells to ferroptosis induced by FIN56. FINO2-which belongs to the fourth group-is an organic peroxide with some similarities in biochemical properties to artemisinin, inducing ferroptosis through a combination of mechanisms, including the direct oxidation of labile iron and GPX4 inactivation (18). As investigative research into the mechanistic underpinnings of ferroptosis continues to progress, a variety of specific inhibitors has been identified, including ferrostatin-1 (Fer-1), liproxstatin-1, and vitamin E, as well as various iron chelators, which collectively function to inhibit ferroptosis by effectively preventing the formation of lipid peroxides that are critical to the ferroptosis process (13, 19).

Significant progress has been made in oncological treatments; however, tumor resistance continues to pose a substantial obstacle. Extensive preclinical and clinical research has been dedicated to addressing drug resistance. Recent findings have established a link between ferroptosis and resistance to cancer therapies. The presence of a high mesenchymal cell state in carcinomas has long been associated with resistance to various treatment approaches. Research by Viswanathan et al. revealed that the therapy-resistant high-mesenchymal cell state is reliant on the GPX4-regulated lipid-peroxidase pathway, which offers protection against ferroptosis (20). Furthermore, a multitude of studies suggests that modulating ferroptosis may enhance the effectiveness of cancer treatments and potentially reverse resistance to therapy. In this review,

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we thoroughly examine the mechanisms underlying ferroptosis and its therapeutic potential in counteracting resistance to standard treatments, including chemotherapy, targeted therapy, and immunotherapy. We also explore the opportunities and challenges associated with utilizing ferroptosis regulation as a strategy to overcome cancer therapy resistance, with the hope that our findings will serve as a valuable resource for future research (21).

Ferroptosis and cancer

Ferroptosis is a distinct and highly specialized mechanism of cell death, chiefly characterized by a serious dependence on iron and redox state imbalance; it thus stands apart from the traditionally understood processes of apoptosis and necrosis, which are all fundamentally dissimilar at the biochemical level. The identification and subsequent understanding of ferroptosis, especially revealed through the investigations of the small molecule erastin in RAS-driven cancers, signify its possible importance in tumor suppression and general cancer therapies (22). Recent empirical studies have found increased evidence that ferroptosis intersects with anti-cancer therapy resistance, suggesting that with a full understanding of the mechanisms by which this type of cell death occurs, new perspectives on developing novel and efficacious guidelines for managing various malignancies might be opened. Ferroptosis is initiated by three major, non-exclusive pathways: the GPX4-dependent pathway, the iron metabolism pathway, and the lipid metabolism and peroxisome-proliferator-activated receptor gamma (PPAR-gamma)-signaling pathway, all of which adjust the redox balances, the lipoperoxides, and lipid peroxidation processes for cellular ferroptosis to occur (19, 22, 23).

The enzyme known as GPX4 holds an indispensable role in the biochemical process of reducing phospholipid hydroperoxides, and any form of inactivation or reduction in the expression levels of this enzyme can lead to a consequential accumulation of lipid peroxides, which ultimately precipitates cellular demise through the ferroptotic pathway that has been extensively characterized in the scientific literature. The availability and accessibility of the amino acid cysteine, which is significantly facilitated by the xCT transport system, are of critical importance for the biosynthesis of glutathione (GSH), and any depletion of this essential amino acid can indirectly obstruct the functional activity of GPX4, thereby exacerbating the ferroptotic process in cells that are particularly vulnerable to such metabolic disturbances (15). Through genetic investigations and extensive experimental studies, it has been convincingly established that the deliberate inhibition of GPX4 can effectively initiate the ferroptotic cell death pathway specifically in tumor cells, thereby illuminating its pivotal role and significance within the broader framework of cancer biology and potential therapeutic interventions aimed at treating malignancies. The mechanism by which iron is absorbed within cellular structures is predominantly facilitated by the protein transferrin and its corresponding receptor, while the process of autophagy is intricately involved in the degradation of ferritin to promote the ferroptotic process in various cell types (13).SLC7A11 plays a crucial role in metabolic reprogramming in both normal and cancerous cells, influencing nutrient dependency, particularly in glucose and glutamine metabolism, as well as maintaining intracellular redox balance (Figure 3).

Thus, augmented LIP causes an increase in the generation of reactive oxygen species, resulting in lipid peroxidation and eventually ferroptosis, especially on certain cancerous cells, which are readily getting killed by oxidative stress. Effectively, interference with iron metabolism has already shown in practice to sensitize

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cancer cells to ferroptosis, capable of conferring an excellent therapeutic potential in cancer formulations. Ferroptosis is a type of programmed cell death that is provoked during polyunsaturated fatty acid peroxidation into membrane phospholipids: the formation of distinct bioactive pathways that eventually lead to cell death. Various classes of enzymes-as well as non-enzymatic processes-are involved in the complex phenomena of lipid peroxidation. However, specific enzymes such as lipoxygenase and acyl-CoA synthetase long-chain family member 4 appear the most important in establishing the sensitivity of cells to ferroptosis (23, 24).

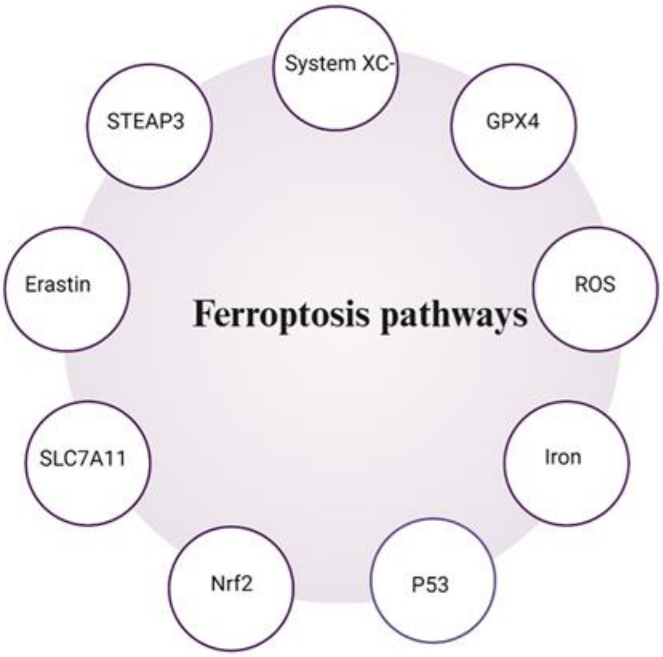


Fig. 3. The SCL7A11 and GPX4 pathways of ferroptosis and apoptosis and different risk factors that can affect this pathway.

Genetic and pharmacological modulation of lipid metabolism can enhance ferroptosis, providing potential therapeutic avenues. The mechanisms of ferroptosis can be leveraged to reverse chemotherapy resistance through the GPX4-regulated, iron metabolism, and lipid metabolism pathways. Targeting these pathways may enhance the efficacy of existing chemotherapeutic agents by inducing ferroptosis in resistant cancer cells. Various studies have identified strategies to induce ferroptosis and overcome drug resistance by targeting GPX4 and related pathways. Inhibitors of the xCT system and compounds that disrupt GSH synthesis have shown promise in reversing resistance to treatments like temozolomide and cisplatin (25, 26).

Modulating iron homeostasis through proteins like LCN2 and DMT1 can enhance ferroptosis in cancer cells, providing a strategy to overcome drug resistance. Increasing intracellular iron levels has been linked to sensitizing cancer cells to ferroptosis, suggesting a therapeutic target in resistant tumors (23). Ferroptosis induction has been explored as a means to overcome resistance to targeted therapies, with promising results in preclinical models. Combining ferroptosis inducers with targeted therapies may enhance treatment efficacy in resistant cancer types. The xCT system and its role in GSH synthesis are critical in mediating ferroptosis resistance, particularly in BRCA-proficient ovarian cancer. Combining ferroptosis inducers with existing therapies may provide a novel approach to enhance treatment responses in resistant cancers (27, 28). The

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upregulation of metallothionein-1G (MT-1G) can limit ferroptosis and contribute to resistance in hepatocellular carcinoma, indicating a potential target for therapy. In lung cancer, acquired resistance to EGFR-TKIs can be overcome by inducing ferroptosis, highlighting the therapeutic potential of this approach. Studies indicate that inducing ferroptosis can reduce GPX4 levels and GSH in drug-resistant cells, suggesting a new strategy for overcoming resistance (22, 23).

Ferroptosis is an encouraging and novel goal to quell both intrinsic and acquired resistance in cancer therapies. Areas meriting exploration are precise types of cancers like colorectal cancer to benefit from inducers of ferroptosis and the development of biomarkers of their clinical application. Moreover, indications about the use of inducers of ferroptosis in the treatment of different diseases merit a cautious approach to developing these drugs so as not to elicit any collateral effects on normal human physiology.

Colorectal cancer targeting by ferroptosis

Colorectal cancer (CRC) is one of the major malignant tumors affecting the digestive tract. Over the past couple of decades, multiple chemotherapeutics, such as oxaliplatin and fluorouracil, have been used for the treatment of CRC, but mortality rates are still alarmingly high. There has been considerable research in the last few years surrounding ferroptosis within oncology and several scientific findings have revealed the link between CRC and ferroptosis.

Research shows that Apatinib targets the ELOVL6-ACSL4 signaling pathway to cause ferroptosis in CRC. Another study also unraveled that LPCAT3 is significantly downregulated and correlated with an increased risk of poor prognosis, which implied that certain ferroptosis pathways may serve as potential molecular targets for CRC treatment. Furthermore, elesclimol, a copper chelator, has been shown tentatively to exert anticancer activity, with copper chelation likely being inhibition of CRC by ferroptosis (29, 30).

SFRS9 functions as a ferroptosis inhibitor by promoting the expression of the GPX4 protein. In contrast, decreasing SFRS9 levels may represent a viable strategy for colorectal cancer treatment. The TP53-induced glycolysis and apoptosis regulator (TIGAR) is a gene activated by p53 that contributes to metabolic regulation and protects cells from apoptosis (14). TIGAR has been indicated as a putative contributor to the possible resistance of CRC against ferroptosis as mediated by the ROS/AMPK/SCD1 signaling pathway. Of interest, the silencing of TIGAR appears to significantly increase lipid peroxidation products that confer heightened sensitivity of CRC cells to Erastin triggered ferroptosis. More interestingly, TIGAR inhibition also results in the downregulation of SCD1 synthesis that is redox-regulated and manipulated by the work of AMPK. In addition, some researchers suggest that system xc- may be a good target for promoting ferroptosis in hopes of inducing an anti-cancer action. In several screening efforts, a benzopyran derivative, 2-imino-6-methoxy-2H-chromene-3-carbothioamide (IMCA) was identified as selective towards reducing viability in colorectal cancer cells while sparing original toxicity in other organs. Subsequent studies confirmed that IMCA significantly induces ferroptosis when tested in colorectal cancer cells. Mechanistically, IMCA downregulated SLC7A11 expression to decrease the contents of cysteine and glutathione, initiating ROS accumulation and ferroptosis (14, 31).

In multiple screening studies, a benzopyran derivative named 2-imino-6-methoxy-2H-chromene-3-carbothioamide (IMCA) has demonstrated a significant reduction in the viability of colorectal cancer cells, while showing minimal toxicity to other organs. Further investigations revealed that IMCA effectively

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induced ferroptosis in CRC cells (32). The mechanism behind this effect involved the downregulation of SLC7A11 expression, which resulted in decreased levels of cysteine and glutathione, leading to an increase in reactive oxygen species and the initiation of ferroptosis. Additionally, the overexpression of SLC7A11 was found to significantly counteract the ferroptosis triggered by IMCA. Furthermore, IMCA was shown to affect the AMPK/mTOR/p70S6k signaling pathway, which is linked to SLC7A11 function and ferroptosis. Collectively, these findings provide experimental support for the activity and mechanisms of ferroptosis induced by IMCA, indicating its potential as a promising therapeutic agent for colorectal cancer (32-34).

The knockdown of GCH1 unexpectedly does not enhance ferroptosis induced by RSL3 in colorectal cancer. Additionally, the use of an autophagy inhibitor can reverse the resistance observed in GCH1-knockdown cells to erastin. Furthermore, cetuximab, a monoclonal antibody that targets the epidermal growth factor receptor (EGFR), has been shown to promote RSL3-induced ferroptosis by inhibiting the Nrf2/HO-1 signaling pathway in KRAS mutant CRC cells, a finding recently has been validated in a nude mouse model (35, 36).

The study indicates that cetuximab amplifies the cytotoxic effects of RSL3 on KRAS mutant CRC cells and enhances RSL3-induced ferroptosis through the activation of p38 MAPK while inhibiting the Nrf2/HO-1 pathway. It has also been demonstrated that cetuximab reduces carbohydrate metabolism by decreasing glucose uptake and glycolysis, rather than merely increasing reactive oxygen species accumulation gradually (35, 36). Additionally, vitamin C can induce ferroptosis by disrupting iron homeostasis. The combination of VitC and cetuximab facilitates a lethal metabolic cell death characterized by ATP depletion and oxidative stress, which diminishes the acquired resistance to anti-EGFR antibodies. Given that high doses of VitC are considered safe for cancer patients, this presents a promising strategy for CRC patients who develop resistance to anti-EGFR therapies. Recent research has identified a natural compound, β-elemene, as a novel inducer of ferroptosis that enhances the sensitivity of KRAS mutant CRC cells when used in conjunction with cetuximab by promoting ferroptosis and inhibiting epithelial-mesenchymal transition (EMT) (37).

Lipocalin 2, a siderophore protein involved in the regulation of iron homeostasis, is found to be upregulated across various tumor types. Its overexpression can diminish ferroptosis by lowering intracellular iron concentrations and enhancing the expression of GPX4 and xCT, which contributes to resistance against 5-Fluorouracil (5-FU) in colon cancer cells, both in laboratory settings and in animal models. Consequently, Lipocalin 2 presents a promising therapeutic target, and its associated monoclonal antibody could serve as a potential treatment option for colon cancer patients who are unresponsive to chemotherapy. Furthermore, miRNA-15a-3p has been shown to promote ferroptosis by directly targeting GPX4 in colorectal cancer. Colorectal cancer stem cells are widely recognized as the primary source of colorectal cancer progression (38, 39).

Research has shown that dichloroacetate (DCA) can diminish the stemness of CRC cells in a dose-dependent manner, evidenced by a decrease in stemness marker expression, reduced tumor spheroid formation, and impaired cell migration capabilities. Additionally, DCA can chelate iron within lysosomes, promoting ferroptosis and further decreasing the stemness of CRC cells (40, 41). Erastin has been identified as an inhibitor of SLC7A11, exhibiting significantly enhanced cytotoxic effects on cancer stem cells (CSCs) in both in vitro and in vivo studies, and it can help mitigate chemoresistance in these cells. This research

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suggests that CSCs exhibit heightened sensitivity to ferroptosis, positioning it as a potential strategy to combat CRC progression and chemoresistance. Furthermore, another study indicates that the regulation of GPX4 by SRSF9 plays a crucial role in CRC tumorigenesis and the resistance to Erastin-induced ferroptosis, potentially offering new avenues to increase Erastin sensitivity in CRC cells (42, 43).

Another newly identified ferroptosis inducer, talaroconvolutin A (TalaA), exhibits a dose- and time-dependent cytotoxic effect on CRC cells. However, TalaA does not induce apoptosis but effectively triggers ferroptosis, demonstrating superior efficacy in inhibiting colorectal cancer cells compared to Erastin, a well-known ferroptosis inducer, positioning it as a promising candidate for CRC treatment (44).

Aspirin is a commonly utilized non-steroidal anti-inflammatory drug that has shown potential therapeutic benefits in cancers with oncogenic PIK3CA mutations, which encode the p110α subunit of phosphoinositide 3-kinase (PI3K). In our research, we discovered that aspirin increased the sensitivity of cancer cells with activated PIK3CA to ferroptosis. The underlying mechanism revealed that aspirin inhibited the AKT/mTOR signaling pathway, reduced the expression of sterol regulatory element-binding protein 1 (SREBP-1), and diminished the lipogenesis of monounsaturated fatty acids mediated by stearoyl-CoA desaturase-1 (SCD1), thereby facilitating RSL3-induced ferroptosis in colorectal cancer cells. Furthermore, the genetic deletion of SREBP-1 or SCD1 made cancer cells more susceptible to ferroptosis. These findings indicate that aspirin amplifies the cytotoxic effects of RSL3 in cancers with PIK3CA mutations, suggesting that the combination of aspirin and ferroptosis inducers may offer promising therapeutic strategies in cancer treatment. Numerous medications have demonstrated efficacy in triggering ferroptosis in colorectal cancer (CRC) cells. Among these, RRx-001, a derivative of dinitroazetidine, is notable for its ability to activate the Nrf2 pathway through the release of reactive oxygen species (ROS), which subsequently induces ferroptosis in CRC cells. Moreover, mollugin has been investigated for its capacity to suppress cell proliferation and promote ferroptosis in CRC. Additionally, the combination of cetuximab with RSL3 has been shown to enhance ferroptosis specifically in KRAS-mutant CRC cells, offering a potential approach to address drug resistance. Cetuximab has been demonstrated to effectively suppress Nrf2/HO-1 signaling via the activation of p38 MAPK in KRAS-mutant colorectal cancer cell lines, which in turn enhances RSL3-induced ferroptosis. This finding opens new avenues for investigating the use of cetuximab in the management of KRAS-mutant colorectal cancer (45).

As much as recent updates have been made in diagnosis and treatment, prognosis for CRC is grim and calls for the need for new drug regimens that target treatment outcomes. Ferroptosis as a regulated form of cell death characterized by iron-dependent lipid peroxidation is considered a possible strategy to target CRC cells, especially the ones resistant to conventional therapies. Some critical regulators of ferroptosis in CRC involve SLC7A11, reactive oxygen species (ROS), glutathione (GSH), and iron, and understanding these key regulators can lead to the discovery of targeted therapies. Ferroptosis inducers may further open new avenues for developing refreshed conventional strategies for colorectal cancer.

So practical implications of the research on ferroptosis in colorectal cancer include

Development of Novel Therapeutics

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The findings highlight the potential of ferroptosis as a therapeutic target in CRC. By understanding the mechanisms that trigger ferroptosis, researchers can develop new drugs that specifically induce this form of cell death in cancer cells, potentially leading to more effective treatments for CRC patients.

Targeting Drug Resistance

The research indicates that ferroptosis can effectively target cancer cells that are resistant to traditional therapies. This suggests that incorporating ferroptosis-inducing agents into treatment regimens could improve outcomes for patients with advanced or resistant CRC.

Personalized Medicine Approaches

The identification of key regulators of ferroptosis, such as SLC7A11 and GPX4, allows for the possibility of personalized medicine. By assessing the expression levels of these regulators in patients, clinicians could tailor treatments that enhance ferroptosis in individual tumors, potentially improving therapeutic efficacy.

Combination Therapies

The study suggests that combining existing therapies, such as aspirin, with ferroptosis inducers could enhance treatment responses. This approach could be particularly beneficial for patients with specific genetic mutations, such as PIK3CA, making it a promising avenue for future clinical trials.

Addressing Chemoresistance

The research emphasizes the role of compounds like dichloroacetate (DCA) in reducing the stemness of CRC cells and promoting ferroptosis. This could lead to strategies that not only target the primary tumor but also address the cancer stem cells that contribute to recurrence and metastasis.

Future Research Directions

The paper outlines the need for further exploration of ferroptosis-related genes and their mechanisms. This could lead to the discovery of additional therapeutic targets and strategies to overcome obstacles in CRC treatment, ultimately improving patient outcomes.

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