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Unveiling the Hidden Power of Ferroptosis: A Promising Strategy for Treating Colorectal Cancer

Yalong Li[1], Jian Cheng[2], Chunling Li[2], Juan Miao[2], Jie Yang[2], Luyi Zhang[3], Chuyi Yang[1], Heng Zhang[2]

[1]The Third Clinical College of Yunnan University of Traditional Chinese Medicine, Kunming, China; [2]Department of Proctology, Kunming Hospital of Traditional Chinese Medicine, Kunming, China; [3]The First Clinical College of Guizhou University of Traditional Chinese Medicine, Guiyang, China

Correspondence to: Heng Zhang, ZH296114872@163.com
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ABSTRACT

With the emphasis on human health, colorectal cancer (CRC) has become the focus of public discussion. There are no effective treatments for CRC in clinical practice, and CRC patients tend to develop problems such as cancer recurrence in their prognosis. Therefore, new targets and strategies are urgently needed to treat CRC in clinical practice. Ferroptosis is a mode of cell death composed of iron ion accumulation and lipid peroxidation. It has been found that ferroptosis plays an important role in CRC. CRC cells often inhibit ferroptosis for survival, and therapeutic strategies aim to promote it. However, the specific molecular mechanism of ferroptosis in CRC has not been clearly investigated. In this manuscript, we present the molecular mechanisms of ferroptosis, the role of ferroptosis in CRC, and the possibility that targeting ferroptosis can diagnose and treat CRC early, providing new perspectives and directions for clinical treatment of CRC.

1. INTRODUCTION

Colorectal cancer (CRC) is a common and deadly disease compared to other types of cancer. According to 2022 data, nearly 1,500,000 people around the world will receive a new diagnosis, and approximately 900,000 individuals will lose their lives every year [1, 2]. Consequently, it ranks third globally in terms of its occurrence and second regarding cancer-related death rates [3]. CRC has multifaceted origins, including poor lifestyle and dietary habits, disorders in intestinal flora, and abnormal immune response mechanisms [4-6]. These factors can function as unilateral or multifaceted triggers and may coexist. While several therapies, *i.e.*, drug therapy, surgical resection, immunotherapy and radiotherapy, have demonstrated their efficacy in treating CRC, they may have specific drawbacks [7-10]. These include the emergence of drug

resistance, local toxic side effects of radiotherapy, and the associated risks related to surgery [11]. Consequently, it is imperative to devise novel targets and approaches to tackle CRC.

Ferroptosis is a form of non-apoptotic cell death that results from the accumulation of iron ions and lipid peroxidation. It was first proposed by Brent Stockwell's team in 2012 [12]. Ferroptosis is characterised by increased levels of Fe^{2+} within cells, oxidative stress of polyunsaturated fatty acid phospholipids, and the accumulation of lipid peroxides [13, 14]. Many studies have demonstrated a potential link between ferroptosis and different types of cancer. Modulating ferroptosis may offer a new method for treating CRC.

This manuscript investigates the pathogenesis of CRC and ferroptosis, analyses the signalling pathways involved in ferroptosis and the metabolic mechanisms implicated in ferroptosis in CRC. In addition, the paper examines the mechanisms that impede ferroptosis and suggests possibilities for diagnosing and treating CRC by means of ferroptosis.

2. THE PATHOGENESIS OF CRC

There are three main mechanisms of CRC carcinogenesis: 1) Accumulation of genetic and epigenetic alterations in CRC stem cell genome; 2) Microenvironmental abnormalities such as inflammation and dysbiosis; 3) Lipid metabolism [15, 16]. Conventional adenomas and serrated tumours are currently the two dominant precancerous lesions, accounting for 70% to 90% and 10% to 20% of colorectal cancers, respectively. The conventional adenoma-carcinoma pathway occurs after a genomic event triggered by adenomatous polyposis coli mutation, followed by P53 loss of function or KRAS activation, whereas the serrated tumour pathway is characterised by a CpG island methylation phenotype. Microsatellite stable and unstable oncogenic pathways associated with KRAS and BRAF mutations and epigenetic alterations pass through benign tubular adenomas or polyps and further oncogenes colorectal epithelial cells [16]. Numerous studies in the literature suggest that microenvironmental abnormalities also play a role in CRC pathogenesis [17-20]. In the inflammatory microenvironment, immune cells are involved in activating mesenchymal stromal cells that determine the extent of cancer progression [18]. Inflammation regulates the tumour microenvironment through the production of cytokines and pro-inflammatory mediators that affect, among other things, blood circulation and tissue cell remodelling. Macrophages are the most abundant immune cells in the human body, and two subgroups that produce different functions through macrophage polarisation are the M1 phenotype and the M2 phenotype. M1 is involved in the pro-inflammatory response by producing pro-inflammatory cytokines (IL-1β, TNF-α, IFN-γ, etc.). It can also help to improve the tumor microenvironment by activating the nicotinamide adenine phosphate dinucleotide (NADPH) oxidase system and producing reactive oxygen species (ROS). M2 activates STAT6 and STAT3 to drive polarisation by cytokines (IL-4, IL-13, IL-10, etc.), mediates ROS-induced tissue damage, and has anti-inflammatory and anti-tumor activities [21-23]. In addition, inflammation affects the production of reactive nitrogen species (RNS), the high expression state of nitricoxide synthase produces excess -NO, which can alter the homeostasis of normal intestinal epithelial cells, ROS/RNS levels are involved in tumour cell proliferation, survival and metastasis by inducing DNA mutations, creating genomic instability, silencing tumour suppressor genes or acting as a signalling molecule [24-27]. Patients with inflammatory bowel disease are therefore more likely to develop CRC [28].

Furthermore, intestinal flora dysfunction is a causative agent of CRC by following mechanisms: 1) Flora with its infiltrating metabolites (including secondary bile acids, H2S and NOCs) promotes inflammation, which influences initiation, promotion and progression of carcinogenesis. 2) Pathogens by cellular adhesion to intestinal epithelial cells (IECs) of intestinal epithelial cells with production of mycotoxic factors and genotoxins to promote carcinogenesis. 3) The causative organisms, through the cellular adhesion to the IECs of intestinal epithelial cells with the production of mycotoxic factors and genotoxins to promote carcinogenesis. 4) Biofilms formed by microorganisms influence carcinogenesis progression through IL-6 and STAT3. Cancer cells carry out cancer cell value-adding, survival, and invasion by utilising the energy produced by lipid metabolism and biofilm components and signalling molecules. For example, carnitine palmitoyltransferase 1a during the metabolism of long-chain fatty acids promotes the expansion and value-

added of stem cells, thereby increasing intestinal tumour formation [29, 30].

3. THE CONCEPT OF FERROPTOSIS

Ferroptosis is a novel programmed cell death, distinct from apoptosis, necrosis, pyrodeath and autophagy, that consists of iron accumulation and lipid peroxidation [12, 31, 32]. It was initially proposed by Scott J Dixon in 2012. Iron, an element involved in cellular metabolism, also plays a crucial role in tumor cell progression and characteristics, including activity, invasion, and metastasis [31]. Iron is a double-edged sword in tumour metabolism. The iron addiction of tumor cells determines that the iron demand is more than that of healthy cells, which leads to cell death due to ferroptosis, mainly depending on the accumulation of iron ions, the metabolism of lipid peroxides and the regulation of related enzymes [33]. The distinguishing features of erroptosis are: 1) Dark mitochondrial colour; 2) Mitochondrial outer membrane crumpled or ruptured, mitochondrial crest reduced or absent, and mitochondria smaller; 3) Nuclei are normal; 4) Cell membranes are broken [34-37]. In addition, ferroptosis susceptibility is associated with many human diseases, such as periventricular leukomalacia, pulmonary fibrosis, alcohol-induced liver injury, etc. [38-41]. Therefore, understanding the mechanism of ferroptosis holds significant importance for studying diverse human diseases.

4. MECHANISM OF FERROPTOSIS INDUCTION

4.1. Iron Metabolism

Approximately 65% of the body's iron is found in the form of haemoglobin iron, with 25% stored in ferritin and ferrous haemoflavin, and only about 0.1% bound to transferrin (Tf). Metabolic processes such as absorption, storage, excretion and recycling are responsible for regulating iron levels in the body [42, 43]. Iron cations (Fe^{3+}) are absorbed from food by intestinal epithelial cells, mainly in the duodenum and upper part of the jejunum [44]. Duodenal epithelial cytochrome b reductase 1 (DCYTB) converts Fe^{3+} to ferrous iron (Fe^{2+}) in the presence of the reducing agent vitamin C or gastric acid [45, 46], and then transports it into the intestinal epithelial cells via the divalent metal transporter 1 (DMT1) [47]. Some of the iron is stored as ferritin, so supplementation with Fe and vitamin C, as well as overexpression of DMT1, can promote iron uptake and sensitivity to iron-induced cell death [48]. The remaining reduced Fe^{2+} enters the plasma via endocytosis by binding to the iron transporter (FPN) in intestinal epithelial cells. Hepcidin—the dominant regulator of systemic iron homeostasis—binds to FPN to modulate cellular iron export, thereby influencing iron availability for ferroptosis in tumor cells. Subsequently, exported iron is oxidised by ceruloplasmin to Fe^{3+} and binds to transferrin (Tf) [49]. Transferrin enters cells after passing through the transferrin receptor 1 (TFR1) on the cell surface [50] and is reduced by prostate transmembrane epithelial antigen 3 (STEAP3) to Fe^{2+}, which is then stored as ferritin. Some free Fe^{2+} is also stored in the labile iron pool (LIP) [51]. Degradation or autophagy of ferritin in response to other regulators such as autophagy-associated protein (Atg) and Nuclear receptor coactivator 4 can result in release of Fe^{2+} from ferritin into the LIP [52]. Excess labile iron is cytotoxic and can lead to lipid peroxidation and the generation of large amounts of ROS via the Fenton reaction or auxiliary lipid oxidases (LOXs) [53-55]. Therefore, depleting iron stores and increasing ferritin autophagy to increase unstable iron levels may promote iron-induced cell death [56].

4.2. Lipid Peroxidation

Lipid peroxidation is a crucial process in ferroptosis, yet the mechanism of the oxidative system involved remains elusive and controversial. What is clear, however, is that polyunsaturated fatty acids (PUFAs) play a central role in ferroptosis by undergoing peroxidation. This leads to the accumulation of oxidized phospholipids on cell and organelle membranes, resulting in the formation of lipid peroxides and ultimately, ferroptosis [57, 58]. Specifically, arachidonic acid (AA) and adrenoic acid (AdA) are dienophiles that are susceptible to oxidation by lipoxygenase (LOX), generating AA-PE-OOH or AdA-PE-OOH [59, 60]. These oxidized lipids disrupt membrane integrity [61], leading to ferroptosis. LOX-12 and LOX-15 also contribute

to oxidative stress and depletion of glutathione (GSH), further increasing lipid peroxides. Acyl coenzyme A synthase long-chain family member 4 (ACSL4) and lysophosphatidylcholine transferase (LPCAT3) are enzymes that mediate the biosynthesis, remodelling [62], and transmembrane properties of PUFAs, promoting their oxidation to phosphatidylethanolamine (PE) [63]. Additionally, the oxidative degradation of PUFAs generates two secondary lipid peroxides, 4-hydroxy-2-nonenal (4-HNE) and malondialdehyde (MDA), which are highly expressed during the onset of ferroptosis and serve as markers of this process. Interestingly, 4-HNE and MDA can activate the autophagic lysosomal pathway and promote ferritin degradation, further promoting ferroptosis [64, 65].

4.3. The Metabolic Pathways of Amino Acids

The metabolic pathways of amino acids involved in ferroptosis are centered around the molecules glutathione (GSH), glutathione peroxidase 4(GPX4), and system Xc^- [2]. GPX4, an enzyme, plays a crucial role in the cellular antioxidant defense system by catalytically neutralizing lipid peroxides, converting them into non-toxic alcohols [66]. GSH, a non-protein molecule, influences the activity of GPX4 by serving as a recyclable substrate for the enzyme's thiol group. Inactivation of GPX4 can occur in the presence of the inhibitor Ras-selective Lethal 3 (RSL3) or by binding to cisplatin, leading to the accumulation of ROS and ultimately promoting ferroptosis [67]. Furthermore, resbufogenin has been found to inhibit oxidative stress and promote the eradication of colorectal cancer cells [68].

System Xc^- is a heterodimer composed of SLC7A11 and SLC3A2, also known as the cysteine/glutamate transport system [66]. Its primary function is to regulate the levels of intracellular cysteine, which is essential for GSH synthesis. Inhibiting system Xc^- reduces GSH production, thereby diminishing the activity of GPX4 and leading to ROS accumulation, ultimately driving ferroptosis in CRC cells [61, 69-72]. Additionally, the expression of SLC7A11 can be downregulated by the tumor suppressor protein P53 [73]. Erastin, in conjunction with SLC7A5 and the SLC7A5/SLC3A2 complex, also downregulates the expression of SLC3A2 and SLC7A11, thereby influencing the occurrence of ferroptosis [12, 74, 75].

The thioredoxin reductase (TXN) system, alongside system Xc^- GPX4-GSH, plays a critical role in antioxidant defence [76, 77]. Comprised of TXN, thioredoxin reductase (TrxR), and nicotinamide adenine dinucleotide phosphate (NADPH), this system facilitates the reduction of oxidative GSH to its active form in response to NADPH [78], thereby supporting the removal of cytotoxic GSH by GPX4 [79, 80]. This process helps to combat toxic peroxides, maintain the intracellular reduced state, and prevent DNA and lipid peroxidation. In addition, TXN acts as an antioxidant by facilitating the reduction of oxidised proteins through cysteine-thiol-disulfide bond exchange [81, 82]. Consequently, inhibition of TXN, TrxR and NADPH can lead to inhibited glutathione uptake, reduced GPX4 levels, increased levels of peroxides and oxidised proteins, and ultimately to iron-mediated cell death.

4.4. The Mitochondrial Activity

Ferroptosis also involves mitochondrial activity [83, 84]. Mitochondria are important sites for ferroptosis as they undergo oxidative exergy via the electron transfer chain (ETC) and the tricarboxylic acid (TCA) cycle, generating ROS [83, 85]. Glutamine is a protein that provides energy for the TCA cycle by metabolically degrading glutamine and generating ROS. Carbonyl cyanide m-chlorophenyl hydrazine renders the inner mitochondrial membrane permeable to H+, leading to membrane potential destabilisation on both sides of the inner mitochondrial membrane, and then, via the Pink1-Parkin pathway, which is specific for membrane potential destabilisation, the mitochondria undergo further membrane potential (MMP) hyperpolarisation, which generates ROS. MMP hyperpolarisation, leading to mitochondrial autophagy and mitochondrial deletion. Cysteine deprivation (CC) leads to mitochondrial membrane potential hyperpolarisation and accumulation of lipid peroxides. Mitochondrial TCA cycle, MMP hyperpolarisation and ETC have all been shown to be involved in CC starvation-induced ferroptosis [84]. However, mitochondrial function is not essential for GPX4 inhibition-induced ferroptosis. This means that when mitochondrial activity is disrupted, as is the case with w inhibitors, low levels of GPX4 can still trigger ferroptosis.

In addition, mitochondria-associated stress releases mtDNA from the mitochondria into the cytoplasm, which activates a variety of immune responses and induces ferroptosis [86]. mtDNA is required for a large amount of Fe^{2+}, and iron ions in the mitochondria are mainly used for synthesis of haemoglobin and the Fe-S family, or are stored in mitochondrial ferritin [37, 87]. Haem can directly induce ferroptosis under the regulation of mitochondrial haem oxygenase 1 and cytoplasmic haem oxygenase. Ferroptosis can also be directly induced when mitochondria are destroyed and ferritin is degraded [86, 88] (**Figure 1** and **Figure 2**).

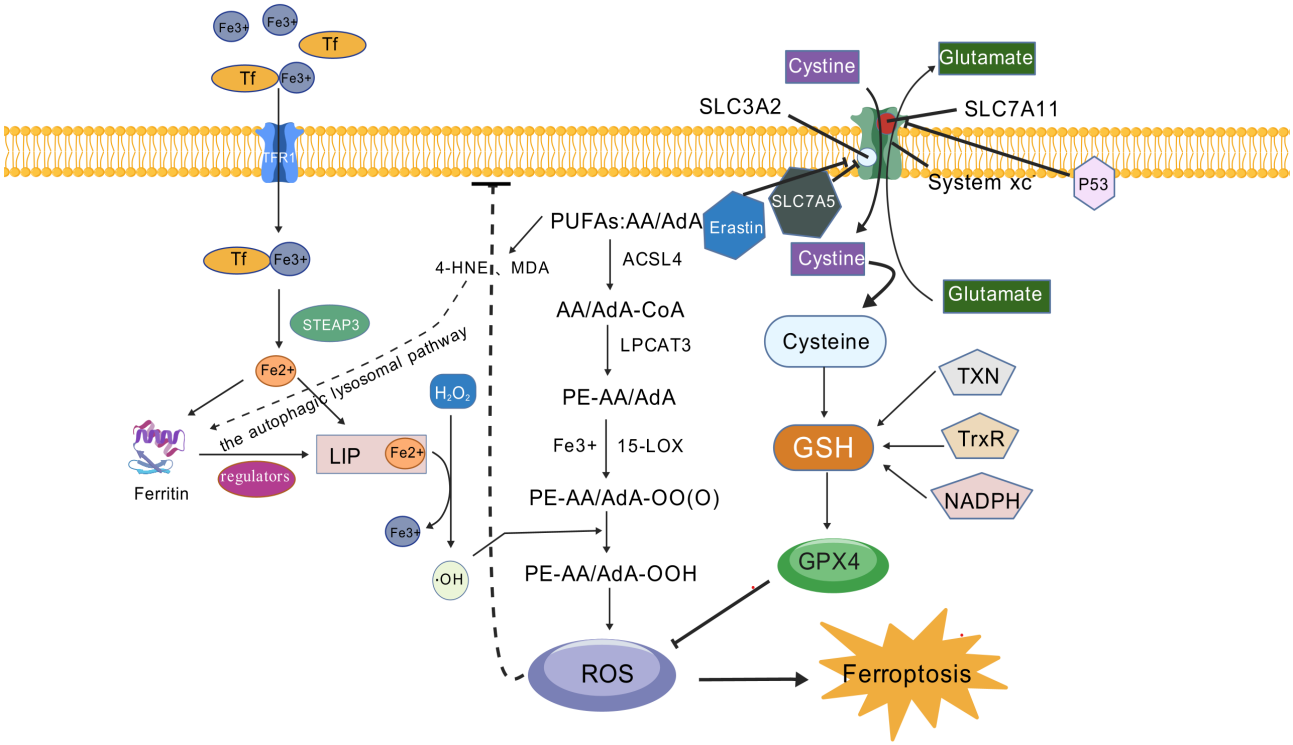

Figure 1. Schematic diagram of the main inducing mechanism of ferroptosis. Autophagic ferritin degradation liberates Fe^{2+}, which activates LOXs (e.g., 15-LOX) to catalyze PUFA (e.g., AA, AdA) peroxidation. PUFAs are esterified into PE via the ACSL4/LPCAT3 axis, forming peroxidation-susceptible PE-PUFA substrates (e.g., PE-AA/AdA). LOX-mediated peroxidation of PE-PUFA generates lipid hydroperoxides (PE-AA/AdA-OOH) and hydroxyl radicals (•OH), key ferroptosis executioners. GPX4 utilizes GSH to detoxify lipid peroxides. Consequently, GSH depletion or direct GPX4 inhibition precipitates lethal peroxide accumulation. GSH regeneration depends on NADPH (pentose phosphate pathway-derived reducing equivalents), critically influencing ferroptotic susceptibility. The tumor suppressor protein p53 can regulate ferroptosis by modulating the expression of SLC7A11 and other genes involved in iron and lipid metabolism.TF: transferrin; TFR1: transferrin receptor 1; STEAP3: prostate transmembrane epithelial antigen 3; LIP: labile iron pool; PUFAs: poly unsaturated fatty acids; AA: arachidonic acid; AdA: adrenaline; ACSL4: acyl-CoA synthetase long-chain family member 4; LPCAT3: lysophosphatidylcholine acyltransferase 3; 15-LOX: 15-lipoxygenase; MDA: malondialdehyde; 4-HNE: 4-hydroxy-2-nonenal; System Xc^-: cystine/glutamate transporter; SLC7A5: Solute Carrier Family 7 Member 5; GSH: glutathione; GPX4: glutathione peroxidase 4; NADPH: nicotinamide adenine phosphate dinucleotide; ROS: reactive oxygen species; TXN: thioredoxin reductase; TrxR: thioredoxin reductase.

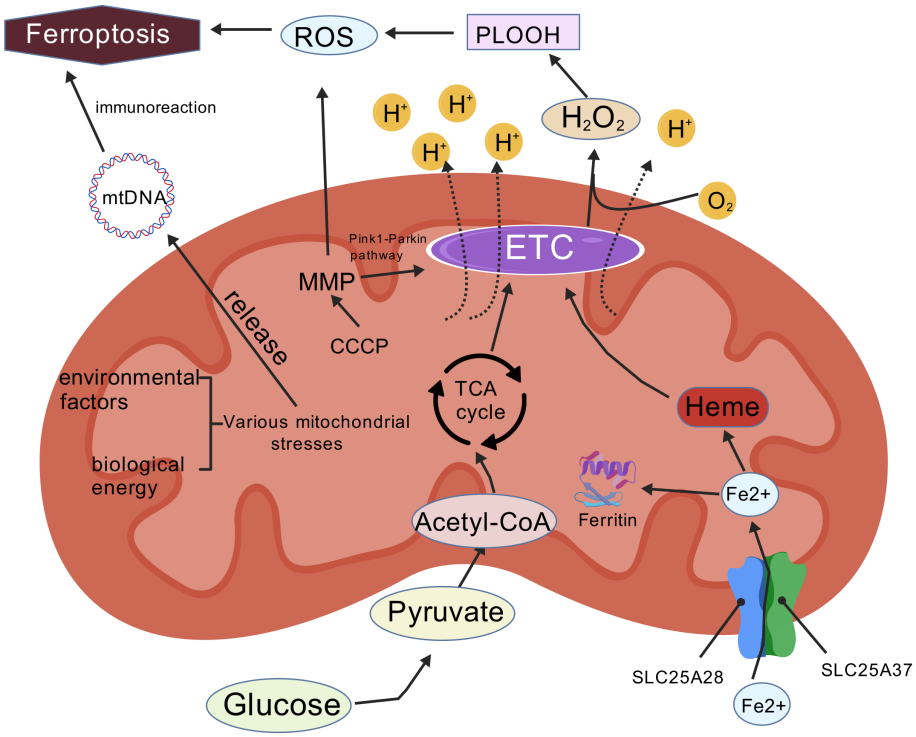

Figure 2. The role of mitochondria in promoting ferroptosis. ETC can promote PUFAperoxidation and thereby ferroptosis. The released mtDNA can promote the ferroptosis pathway through an immune response. CCCP dissipates the mitochondrial proton gradient, depolarizing the inner mitochondrial membrane. This activates the Pink1-Parkin pathway. Subsequently, compensatory hyperpolarization of the mitochondrial membrane potential occurs, leading to excessive ROS generation. ETC: electron transfer chain; TCA cycle: tricarboxylic acid cycle; CCCP: carbonyl cyanide m-chlorophenyl hydrazine; MMP: membrane potential. We confirm that all figures in this article are original and were created by the BioGDP [89].

4.5. The Other Metabolic Pathways

Selenium primarily regulates ferroptosis by influencing selenoprotein levels. Selenocysteine is crucial for maintaining GPX4 activity, so a deficiency in selenium leads to reduced GPX4 activity and increased sensitivity to ferroptosis [90, 91]. Coenzyme Q10 (CoQ10), also known as ubiquinone, is a fat-soluble vitamin analog produced in the inner mitochondrial membrane through the mevalonate pathway [92]. It has an antioxidant effect and protects cells from ferroptosis [93, 94]. Its inhibitors, such as statin drugs, reduce levels of free radical scavenging and trigger ferroptosis. Sugar metabolism, including glycolysis, the pentose phosphate pathway, and the TCA pathway, plays a crucial role in the generation of ferroptosis-related compounds like NADPH, GSH, and ROS, which indirectly contribute to ferroptosis. Research indicates that glucose deprivation leads to an increase in the AMP/ATP ratio, activation of the LKB1-AMPK pathway, inhibition of PUFA synthesis, and suppression of ferroptosis. Consequently, AMP inhibitors or glucose supplementation can be utilized to promote ferroptosis [95, 96].

Nevertheless, it has also been demonstrated that glucose deficiency, activation of the system Xc^- system, high expression of SLC7A11, elevated NADP+/NADPH ratio, extensive NADPH consumption, cystine accumulation, and decreased GSH levels collectively drive ferroptosis [97].

5. SIGNALING PATHWAYS INVOLVED IN IRON SAG

5.1. E-Cadherin-NF2-Hippo-YAP/TAZ Pathway

Hippo is a protein kinase, and yes-associated protein (YAP) is a transcription factor. When iron ion accumulation reaches a certain level, oxidative stress activates the Hippo pathway, which includes the oncogene NF2 and kinases [98, 99]. These kinases phosphorylate YAP, reducing its transcriptional activity level [98]. At the same time, Hippo inhibits the G1/S transition point in the cell cycle, thereby inhibiting cell proliferation and differentiation. Additionally, the Hippo-YAP pathway promotes the G2/M transition to promote apoptosis [100].

Numerous studies have demonstrated that intestinal epithelial cells are more vulnerable to ferroptosis in a low-density environment. The mechanism is mediated by E-cadherin-mediated cell-to-cell contact, activation of the Hippo-YAP pathway via the NF2/Merlin tumor suppressor protein, and inhibition of Hippo with increased levels of YAP activity. YAP targets and regulates ACSL4 and TFRC (transferrin), which increases susceptibility to ferroptosis [61, 101]. TAZ, an analogue of YAP, is also involved in ferroptosis in a density-regulated manner, as per the research [102].

5.2. AMPK-Related Pathways

The AMP-activated protein kinase (AMPK) is a heterotrimeric complex that regulates ATP levels via serine/threonine kinase activity. AMPK is involved in several pathways that induce ferroptosis, including AMPK-mTOR-SLC7A11, AMPK-BECN1-SLC7A11, and TIGAR-AMPK-SCD1 [103-105]. SLC7A11 is a key regulator of autophagy, while mTOR is a serine/threonine kinase involved in cell proliferation. Glucose starvation activates AMPK, which promotes phosphorylation of BECN1 at the S90 and S93 sites, leading to increased binding of BEC7A11 to SLC7A11 and decreased SLC7A11 binding. AMPK also downregulates SLC7A11 activity, inhibits system Xc^-, and decreases cystine transport and GSH levels, ultimately leading to ROS accumulation and the onset of ferroptosis [104, 106].

High levels of ROS can lead to TIGAR overexpression, which increases antioxidant capacity by reducing the NADP+/NADPH ratio and increasing GSH [105, 107]. However, a TIGAR inhibitor can inhibit stearoyl-CoA desaturase 1 (SCD1), which induces ROS and promotes ferroptosis [105, 108].

5.3. Nrf2-Related Signaling Pathway

The nuclear factor erythrocyte 2-associated factor 2 (Nrf2) pathway is a major intracellular antioxidant stress pathway that plays an important role in oxidative stress response, cytoprotection and anti-inflammation in cells. It helps cells to resist and repair free radicals and other harmful substances [109-111]. Nrf2-related pathways are mainly AKT-GSK3β-Nrf2-ARE, MKLP2-APK5/PP1β-GSK3β-Nrf2, KEAP1-Nrf2.

Both protein kinase B (AKT) and glycogen synthase kinase 3 β (GSK3β) are serine/threonine kinases. They are involved in cell proliferation, signalling, etc. A certain level of ROS phosphorylates AKT at the Ser9 site and downregulates GSK3β, promoting the nuclear translocation of Nrf2 and AKT [112, 113]. Nrf2 reduces ferroptosis by regulating the expression of genes related to iron metabolism and activating the expression of antioxidant enzymes in the cell [114]. The mitotic kinesin-like protein 2 (MKlp2) is a kinesin involved in mitosis [115]. AMPK-related protein kinase 5 (ARK5) is a kinase that has the ability to enable p53 binding activity and regulates the activity of protein phosphatase 1β (PP1β) [116, 117]. While PP1β induces GSK3β activation and decreases nuclear Nrf2 levels, thereby promoting ferroptosis, the presence of ROS upregulates MKLP2, increases GPX4 and GSH levels, and decreases ferroptosis [118, 119]. At the same time, MKLP2 activates ARK5 or ARK5 inhibits PP1β activity, thereby decreasing GSK3β activity, increasing nuclear translocation of Nrf2 and inhibiting ferroptosis [120]. Therefore, ARK5 inhibitors such as WZ4003 and HTH-01-015 can be used to reduce Nrf2 levels in the nucleus and drive ferroptosis [121, 122]. In addition, Kelch-like ECH-associated protein 1 (KEAP1) binds to Nrf2, mediates its ubiquitination and degradation [123], and inhibits its nuclear translocation activity [124]. when ROS accumulate, they can be released from Nrf2 bound to KEAP1 by an oxidative reaction to increase antioxidant capacity [124, 125].

In addition, research has shown that the absence of Nrf2 leads to the downregulation of vesicle-associated membrane protein 8, causing ferritin autophagy and the accumulation of nuclear receptor coactivator 4/apoferritin autophagosomes, which regulate ferritin synthesis and degradation, increasing LIP and thereby increasing susceptibility to ferroptosis [126].

5.4. SAPK/JNK signaling pathway

The stress-activated protein kinase/c-Jun N-terminal kinase pathway (SAPK/JNK) plays a crucial role in regulating cell growth, apoptosis, and inflammatory response [127, 128]. It primarily influences ferroptosis through several pathways. In an iron-deficient or hypoxic environment, activation of the SAPK/JNK pathway can enhance transferrin synthesis and iron ion uptake, leading to elevated intracellular iron levels. Simultaneously, the SAPK/JNK pathway can suppress ferroportin expression, limiting the efflux of intracellular iron and further contributing to iron accumulation, thus promoting ferroptosis [129, 130]. Furthermore, activation of the SAPK/JNK pathway can stimulate the release of inflammatory factors, such as NF-κB, a transcription factor involved in regulating inflammation and apoptosis. SAPK/JNK activation inhibits NF-κB activity, reducing its anti-apoptotic effects and weakening its protective role against oxidative stress and apoptosis [131, 132]. The mitogen-activated protein kinase (MAPK) signaling pathway is also involved in regulating cell growth, differentiation, and apoptosis [133]. SAPK/JNK activation can influence the activity of the MAPK pathway, impacting cell survival and death. Additionally, when activated, the SAPK/JNK pathway can trigger the P53-YAP1 pathway, decrease GPX4 levels, promote ROS accumulation, and increase susceptibility to ferroptosis [134-136].

5.5. STAT3 Signaling Pathway

Signal transduction and transcription activator 3 (STAT3) can be activated by phosphorylation of extracellular signaling molecules and then enter the nucleus, bind to DNA, regulate the transcription of ferroptosis-related genes (e.g., GPX4, superoxide dismutase, etc.) and affect the production of ROS, thereby inhibiting ferroptosis [137]. In addition, STAT3 can regulate the membrane expression of a variety of mitochondrial and cell membrane-related genes, thereby affecting mitochondrial function and cell membrane integrity, thereby affecting cell survival and death. STAT3 is highly expressed in various tumor cells [138, 139]. Therefore, STAT3 inhibitors (e.g., isoproterenol, thiostreptozotocin, etc.) can be used to induce ferroptosis. It is worth noting that thiostreptozotocin promotes ferroptosis by downregulating GPX4 mRNA and GPX levels mainly by decreasing intracellular STAT3 and p-STAT3 expression rather than affecting SLC7A11 protein expression [140].

5.6. Other Signalling Pathways Ferroptosis

In addition to the main mechanism of ferroptosis mentioned above, other pathways can also regulate ferroptosis. Voltage-dependent anion channels (VDAC) are a transmembrane pathway found in the cell membrane and mitochondria. It can interfere with the expression of VDAC, affecting the transport of -related substances and mitochondrial function, leading to the accumulation of oxidant substances [141]. Fatty acid elongase 6 is an endoplasmic reticulum enzyme that inhibits GPX4 and GSH expression and ferritin heavy chain 1 (FTH1) activity by interacting with ACSL4, leading to ROS accumulation [142, 143]. In addition, circular RNA inhibits ferroptosis by inhibiting miR-874-3p and regulating gene expression of related transmembrane proteins such as glycerophosphodiester phosphodiesterase 2 [144].

6. MECHANISM OF INHIBITING FERROPTOSIS

6.1. Transsulfur Pathway

Cysteine plays a crucial role in the synthesis of GSH. Apart from being produced through the exchange of cystine and glutamate, it can also be obtained via the transsulfur pathway (TSP). Cysteine-b-synthase and

cysteine gamma-lyase synthesize cysteine from the intermediate homocysteine and cysteine thioether in the presence of the sulfur donor methionine [145]. Consequently, when system Xc^- is inhibited, the diversion pathway can counteract ferroptosis resulting from system Xc^- inhibition [146]. Furthermore, research indicates that knocking out cysteine-TRNA synthetase can enhance GSH synthesis by inducing the sulfur transfer pathway, thereby inhibiting ferroptosis [147].

6.2. Mevalonate Pathway

The mevalonate (MVA) pathway is a metabolic pathway for synthesizing isoprenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate from acetyl coenzyme A. IPP can impact the production of selenocysteine tRNA, which in turn incorporates selenocysteine into GPX4, thereby affecting its activity [148]. As a result, the MVA pathway can stimulate GPX4 synthesis and impede ferroptosis by increasing IPP levels. Squalene, CoQ10, and cholesterol generated by the MVA pathway are also implicated in ferroptosis. Squalene, an isoprenoid compound with multiple unsaturated hydrocarbons, binds various free radicals, boosts the expression of SLC7A11 and GPX4, and exerts an antioxidant effect, reducing susceptibility to ferroptosis [149, 150]. However, depletion of CoQ10 leads to squalene synthase SQS triggering ferroptosis in response to the agonist FIN56 [76, 151]. Cholesterol is inherently sensitive to oxidants such as hydroxyl radicals, and exogenous hydroperoxycholesterol contributes to ferroptosis in a dose-dependent manner. Specifically, 7-dehydrocholesterol, a cholesterol precursor, exhibits significantly greater oxidizing activity than cholesterol and arachidonic acid. However, there is no direct evidence that it promotes ferroptosis [151-153].

GCH1/ BH4 represents a lipid antioxidant pathway that operates independently of GPX4. Guanosine triphosphate cyclohydrolase (GCH1) has the ability to limit the production of tetrahydrobiopterin (BH4), which possesses lipophilic antioxidant properties [76, 154]. Moreover, GCH1 can facilitate the restructuring of the lipid membrane environment, leading to an increase in the presence of CoQ10. Furthermore, BH4 can facilitate the conversion of phenylalanine to tyrosine, thereby promoting the synthesis of CoQ10 [155]. The combined depletion of GPX4 and the inducer of ferroptosis, PUFAPL, works synergistically to decrease the susceptibility of cancer cells to ferroptosis.

6.3. Related Mediated Enzymes

Some enzymes also play a critical role in regulating ferroptosis, including GPX4, FSP1, DHODH, iNOS, IL4i1, and others. GPX4, which was mentioned earlier, will be further elaborated on, while the following four will be the main focus.

Ferroptosis Suppressor Protein 1 (FSP1) is a glutathione-independent NADPH-ubiquinone reductase that inhibits ferroptosis by aggregating on cell membranes through myristoylation and catalyzing ubiquitin ketone to produce the antioxidant dihydroubiquinone (CoQH2). Dihydroorotate dehydrogenase (DHODH), located in the inner mitochondrial membrane, catalyzes the pyrimidine nucleotide pathway to produce CoQH2, thereby increasing antioxidant capacity [156]. Nitric oxide synthase (iNOS) can reduce lipid peroxidation and inhibit ferroptosis by producing nitric oxide [157]. Interleukin-4 inducible protein 1 (IL4i1) is a metabolic enzyme found in high levels in tumor cells, and In3Py is its metabolite. IL4i1/In3Py regulates ferroptosis by scavenging free radicals and regulating ferroptosis-related suppressor genes [158].

6.4. Other Mechanisms

In the presence of FSP1, vitamin K is converted to vitamin K hydroquinone, VKH_2, a powerful lipophilic antioxidant that can neutralize lipid peroxides in the cell membrane. Vitamin K epoxide reductase complex subunit 1 contributes to the generation of VKH_2 [159]. Additionally, FSP1 also reduces CoQ10 to hydroquinone, further suppressing ferroptosis. Membrane-bound O-acyltransferase domain-containing 2 (MBOAT2), a ferroptosis inhibitor, operates independently of GPX4 or FSP1 [160]. When activated by sex hormone signaling transcription, specifically estrogen receptor and androgen receptor, MBOAT1 and MBOAT2 facilitate the restructuring of cytophospholipid composition to impede ferroptosis in cancer cells. Lipocalin-2 is a protein that carries iron and is highly expressed in the tumor microenvironment. By disrupting iron

balance, it stimulates the expression of GPX4 and xCT to prevent ferroptosis [161]. B7H3 is a transmembrane protein belonging to the B7 immunostimulatory and co-inhibitory family. Research indicates that B7H3 can activate the AKT pathway and decrease sterol regulatory element binding protein 2-mediated cholesterol metabolism, thus inhibiting RSL3-mediated ferroptosis [162].

7. THE ROLE OF FERROPTOSIS IN DIAGNOSIS AND TREATMENT OF COLORECTAL CANCER

Ferroptosis has been suggested as a novel approach for treating CRC. While most cancers are typically treated with radiotherapy, ferroptosis may provide a new avenue for such treatment. The impact of radiation on SLC7A11 activity and GSH levels leads to the accumulation of lipid peroxides and the initiation of ferroptosis. Radiosensitisers can be utilized to enhance CRC susceptibility to ferroptosis. For instance, RRx-001, an anti-cancer agent containing a dinitroazocyclobutane derivative, stimulates ROS release from CRC, activating Nrf2 and driving ferroptosis [1]. Iron levels play a role in CRC progression and can be supplemented through intravenous or oral iron supplementation, with the former being preferred due to fewer gastrointestinal reactions [120, 163]. Additionally, drugs like dichloroacetic acid and ferric ammonium citrate can elevate iron levels, all of which are crucial in CRC treatment [164]. Biological nanomedicines have emerged as a promising approach for combating CRC, offering advantages such as improved drug diffusion efficiency, ROS release, targeted therapy, and reduced drug resistance [165, 166]. Various studies have demonstrated that targeting ferroptosis, including mechanisms involving epidermal growth factor receptor, PI3K, ACSL4, and Nrf2, promotes ferroptosis by activating different pathways to induce gene mutation [167-169], ROS accumulation, and reduction in GSH and GPX4 levels. Ultimately, the generation of excess ROS stands as a critical factor in the treatment of CRC through ferroptosis.

Rectal digital examination is widely used clinically and is one of the simplest ways to diagnose CRC; 80% of rectal cancers can be detected, but a negative digital examination does not completely rule out rectal cancer. Other tests such as colonoscopy, CT, MRI, ultrasound and faecal occult blood tests are therefore essential. Early diagnosis of CRC cells can also be achieved by testing the energy metabolism of CRC cells and the effectiveness of drugs after the use of CRC drugs. Numerous studies have shown that serum ferritin and transferrin levels are effective indicators for the diagnosis of CRC [170]. Low ferritin levels indicate a higher survival rate. Recent research has demonstrated that elevated expression of ferroptosis-suppressor genes GPX4, FTH1, and FTL, correlates with reduced 5-year overall survival in male CRC patients harboring KRAS mutations [171]. Furthermore, ferroptosis-associated genes RBMS1, NOX4, FABP4, CYB5R1, CPEB1, and ATM, exhibit significant associations with immune cell infiltration and adverse clinical outcomes [172]. In light of these reports, Ferroptosis-related genes may aid in the diagnosis of CRC, leading to a number of prognostic models based on the association between CRC differentiation-related genes and ferroptosis.

8. CONCLUSION

CRC has emerged as one of the most prevalent malignancies impacting human life and health. Ferroptosis, a novel mechanism governing cell death, has introduced fresh perspectives and advancements in the diagnosis and treatment of CRC. With the surge in research interest, several molecules and associated pathways have been identified as potential targets for CRC treatment, paving the way for the exploration of new drug therapies. Nonetheless, our review highlights several pivotal unanswered questions: 1) What are the mechanisms and regulators governing the binding of free polyunsaturated fatty acids to phospholipids? 2) Where within the cell does ferroptosis take place? 3) What other pathways contribute to ferroptosis? 4) Are there specific mechanisms or targets in CRC that render it susceptible to ferroptosis? 5) In cases where CRC coexists with other tumors, how does ferroptosis differ from other forms of cell death? 6) What are the downstream signals associated with ferroptosis? 7) How is ferroptosis linked to inflammation and immunity? 8) What metabolic connections exist between Kras mutations and ferroptosis? Addressing these inquiries could enhance our comprehension of ferroptosis physiology. Ultimately, harnessing the unique vulnerability of CRC cells to ferroptosis represents a transformative therapeutic opportunity; realizing its full clinical potential will likely depend on rationally designed combination strategies that simultaneously target

complementary resistance pathways and leverage ferroptosis as a cornerstone of precision oncology for colorectal cancer.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest regarding the publication of this paper.

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