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REVIEW

Interaction mechanisms between autophagy and ferroptosis: Potential role in colorectal cancer

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Abstract

Colorectal cancer (CRC) is a common malignancy that has the second highest incidence and mortality rate. Although there are many personalized treatment options for CRC, the therapeutic effects are ultimately limited by drug resistance. Studies have aimed to block the initiation and progression of CRC by inducing cell death to overcome this obstacle. Substantial evidence has indicated that both autophagy and ferroptosis play important regulatory roles in CRC. Autophagy, a lysosome-dependent process by which cellular proteins and organelles are degraded, is the basic mechanism for maintaining cell homeostasis. The duality and complexity of autophagy in cancer therapy is a hot topic of discussion. Ferroptosis, a regulated cell death pathway, is associated with iron accumulation-induced lipid peroxidation. The activation of ferroptosis can suppress CRC proliferation, invasion and drug resistance. Furthermore, recent studies have suggested an interaction between autophagy and ferroptosis. Autophagy can selectively degrade certain cellular contents to provide raw materials for ferroptosis, ultimately achieving antitumor and anti-drug resistance. Therefore, exploring the interaction between autophagy and ferroptosis could reveal novel ideas for the treatment of CRC. In this review, we describe the mechanisms of autophagy and ferroptosis, focusing on their roles in CRC and the crosstalk between them.

Key Words: Ferroptosis; Autophagy; Cell death; Colorectal cancer; Iron; Lipid peroxidation

Core Tip: Ferroptosis is a mode of cell death centered on iron accumulation and lipid peroxidation that plays a crucial role in colorectal cancer (CRC). Recently, an increasing number of studies have found that autophagy and ferroptosis have a cross-talk relationship in CRC. Enhancing the antitumor effect through autophagy-dependent ferroptosis will become a hot topic in medical biology. This review describes the mechanisms of autophagy and ferroptosis and their interactions in CRC with a goal of providing new strategies for the treatment of CRC.

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INTRODUCTION

Colorectal cancer (CRC) is the second most common cause of cancer-related death in both men and women. According to global cancer statistics, 52580 people in the United States will die from CRC in 2022[1]. At present, surgery is still the basis of CRC radical therapy. For unresectable metastatic CRC, systemic therapy, including cytotoxic chemotherapy, biologic therapy, immunotherapy, and their combinations, is the mainstay[2]. However, drug resistance in CRC significantly reduces the effectiveness of systemic treatment. Recently, an increasing number of studies have investigated methods to hinder the occurrence and development of CRC by targeted induction of different modes of cell death, such as apoptosis, necroptosis, pyroptosis, and ferroptosis[3].

Autophagy is a lysosome-dependent process for the degradation of proteins and organelles that involves the interaction of multiple protein complexes encoded by highly conserved autophagy-related (ATG) genes. Autophagy plays a central role in the maintenance of cellular homeostasis and is closely associated with human health and various diseases[4]. Current studies have shown that autophagy has a dual role in cancer, promotion or inhibition depending on the type of tumor cells, genetic background, stage of tumor progression and tumor microenvironment[5]. Nevertheless, the complex regulatory mechanisms still need further exploration. Thus, targeted autophagy has great potential in cancer therapy.

Ferroptosis is a mode of regulated cell death (RCD) centered on iron accumulation and lipid peroxidation. Originally in 2012, Dixon *et al*[6] discovered that erastin-induced death in RAS-mutant cancer cells could be prevented by iron chelators and antioxidants, and this iron-dependent mode of cell death was named ferroptosis. Unlike autophagy and other RCDs, such as necroptosis, the process of ferroptosis is lipid peroxidation-mediated plasma membrane damage catalyzed by iron accumulation. Morphologically, it is represented by obvious shrinkage of the mitochondria with increased membrane density, fewer or no mitochondrial cristae, and outer mitochondrial membrane rupture[7]. Because of its unique pathophysiological features, ferroptosis plays an important regulatory role in many diseases[8]. With the in-depth exploration of ferroptosis, relevant studies have indicated significant crosstalk between autophagy and ferroptosis [9-11]. The discovery of autophagy-dependent ferroptosis opens up new insights into cell death and holds great promise in the treatment of disease.

In this review, we summarized the mechanisms of autophagy and ferroptosis, as well as their roles in CRC. Next, we focused on the interaction between autophagy and ferroptosis in the context of CRC, aiming to provide new targets for clinical treatment.

AUTOPHAGY AND CRC

Mechanisms of autophagy

Depending on how cargo is delivered to lysosomes, autophagy can be classified as the following three types: Macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA). Macroautophagy transports a bulk of cytoplasm or specific cargoes to lysosomes for degradation by forming autophagosomes with a double-membrane structure[12]. Microautophagy sequesters cell cytosolic components for lysosomal degradation through lysosomal membrane invagination[13,14]. CMA occurs only in mammalian cells and involves the crucial steps of chaperone-mediated identification and targeting of specific proteins to lysosomes[15]. Among the three different forms of autophagy, macroautophagy is the major regulatory mechanism that responds to environmental and physiological cues, so it is commonly referred to as 'autophagy'[16].

Autophagy is a dynamic process regulated by ATG proteins and can be divided into the following five distinct stages: Initiation, nucleation, elongation of the autophagosome membrane and autophagosome maturation, fusion of autophagosomes with lysosomes, and degradation of the vesicular contents[17]. The Unc-51-like kinase-1 (ULK1) complex, which includes the ULK1/FAK family–interacting protein of 200 kD (FIP200)/ATG13, is responsible for integrating nutrient and energy signals and controls the autophagy switch[18,19]. Upon receiving a starvation signal, the ULK1 complex becomes activated and phosphorylates beclin1 (BECN1) at Ser 14, progressing to the second stage of autophagy[20]. The class III phosphatidylinositol 3-kinase (PtdIns3K) complex is composed of VPS34 (phosphatidylinositol 3-kinase), VPS15 (the

adaptor of VPS34), BECN1 and ATG14 to generate phosphatidylinositol 3-phosphate (PI3P), which facilitates the nucleation of autophagosomal membranes[20,21]. Following nucleation, elongation of the autophagosomal membrane involves two ubiquitin-like (Ubl) conjugation systems: ATG12-ATG5-ATG16L and LC3-phosphatidylethanolamine (PE) [22]. The C-terminus of microtubule-associated protein one light chain 3 (LC3), a mammalian ortholog of yeast Atg8, is cleaved by ATG4 to form LC3-I[23,24]. LC3-I is conjugated to PE to generate LC3-II in the presence of ATG3, ATG7, and the ATG12-ATG5-ATG16L complex[24-26]. The autophagosomal membrane is continuously elongated, eventually forming an autophagosome with closed bilayer membrane structures. Subsequently, mature autophagosomes fuse with lysosomes to form autolysosomes, which decompose the contents of vesicles.

The role of autophagy in CRC

Whether autophagy is enhanced or inhibited is a topic of discussion in cancer treatment. The mechanisms of autophagy in cancer are complex and diverse, involving numerous genes, proteins, and pathways. On the one hand, autophagy prevents cancer by removing intracellular damaged organelles or toxic substances, which helps maintain the integrity of cells and genes[27,28]. On the other hand, autophagy can provide energy and rich nutrients for tumor cells to promote their proliferation and progression[28,29]. In this way, the impact of autophagy in different stages of CRC and the mechanisms of tumor initiation and progression vary[30]. Enhancing or inhibiting autophagy may result in different effects at different stages of CRC. We now briefly introduce the roles of autophagy and several key autophagy regulatory proteins in CRC (Table 1).

The mammalian target of rapamycin (mTOR) is a serine/threonine kinase that primarily regulates cell growth and proliferation and plays an anabolic role[31]. mTOR is recognized as the upstream negative regulator of the autophagy initiation stage. Under nutrient-rich conditions, high mTOR activity prevents ULK1 activation by phosphorylating ULK1 Ser 757, thereby inhibiting autophagy[32]. As early as 2012, aspirin was found to induce autophagy by reducing mTOR signaling in CRC cells through inhibition of the mTOR effector S6K1[33]. Moreover, oxiconazole (OXI) can downregulate the expression of the peroxiredoxin-2 (PRDX2) protein, extinguish mTOR, and initiate autophagy[34]. Moreover, OXI can block the fusion of autophagosomes with lysosomes, resulting in the extreme accumulation of autophagosomes and subsequent inhibition of CRC cell growth[34]. In addition, there are numerous compounds that target the mTOR pathway to regulate autophagy in CRC, all with promising antitumor effects[35,36]. Thus, mTOR may serve as an effective target for the treatment of CRC.

BECN1 is a core protein in autophagy nucleation. In one study, BECN1 expression was higher in CRC tissues than in normal colorectal tissues[37]. Patients with lower BECN1 expression had longer overall survival than those with high BECN1 expression[37]. ABHD5, an activator of cellular lipolysis, binds to BECN1, preventing its cleavage and consequently increasing autophagic flux, thus suppressing CRC tumorigenesis[38]. These pieces of evidence support the idea that BECN1 can inhibit the occurrence of CRC. However, more recent studies tend to focus on the tumor-promoting effect and chemical resistance of BECN1 in CRC[39,40]. For example, sex-determining region Y-box2 (SOX2) transcriptionally induces BECN1 expression, thus activating autophagy to increase CRC chemoresistance[41]. In another study, firre intergenic repeating RNA element (FIRRE) combines with the polypyridine binding protein to form an RNA protein complex, which interacts with the 3' end of BECN1 mRNA to enhance autophagy activity and promote the development of CRC[42]. Studies addressing the relationship between BECN1 and CRC have not yet yielded a broadly uniform result, possibly due to the different pathways of BECN1-mediated autophagy that are involved in different stages of CRC; this complexity could be a challenge *vs* an opportunity in CRC therapy.

Sequestosome 1 (SQSTM1/p62) is both a cargo receptor for autophagy and a substrate for selective autophagy. P62 has been identified as having multiple domains, including the Phox1 and Bem1p (PB1) domain, zinc finger (ZZ), tumor necrosis factor receptor-associated factor 6 (TRAF6) binding domain, LC3-interacting region (LIR), KEAP1-interacting region (KIR) and ubiquitin-associated (UBA) domain[43]. While p62 attaches to the autophagosome by binding with LC3 *via* the LIR, its other domains bind the corresponding proteins, and eventually, they are degraded together in the autolysosome[44,45]. Therefore, the accumulation of p62 represents a decrease in autophagic flux. One group has shown that the expression of p62 is associated with the prognosis of CRC[46,47]. Increased autophagy leads to decreased p62 expression, which enables GATA4 to evade autophagic degradation, enhance NF-κB function, and drive the antioxidant reaction to support CRC survival[48]. Toll-like receptor (TLR) signaling acts as an immunomodulator that regulates inflammatory responses and plays a critical role in colitis-associated CRC[49]. TLR4 mediates the formation of the TRAF6-BECN1 complex, which activates autophagy, facilitating the migration and invasion of cancer cells[50]. P62 negatively regulates TLR4-induced autophagy activation and inhibits cancer cell progression[50]; thus, p62 may become a therapeutic target for CRC.

FERROPTOSIS AND CRC

Mechanisms of ferroptosis

Ferroptosis is a form of cell death caused by iron-dependent lipid peroxidation. In general, the regulatory mechanism of ferroptosis can be divided into three main pathways: iron metabolism, lipid metabolism, and the antioxidant system. The three pathways are inseparable, and an imbalance in any one of the pathways drives ferroptosis. The mechanisms of ferroptosis and its effect on CRC are summarized in Figure 1 and Table 2.

Iron metabolism: Iron is an essential trace element in physiological metabolism, and an imbalance in iron homeostasis might lead to many pathological processes[51]. Iron mainly exists in the form of ferric ions (Fe^{3+}) outside the cell, which are transported by transferrin (Tf). Iron-laden Tf binds to the transferrin receptor (TfR1) on the cell membrane to

Table 1 The role of autophagy in colorectal cancer

Intervention	Target	Effects and mechanism	Ref.
Aspirin	mTOR↓, AMPK↑	Inhibits mTOR signal transduction and activates AMPK to induce autophagy of CRC	[33]
TBK1	mTORC1↓	TBK1 initiates mTORC1 inhibition and induces autophagy to promote CRC progression	[139]
ABHD5	BECN1↑	ABHD5 prevents CASP3 from cleaving BECN1 and enhances autophagy flux to inhibit CRC	[38]
SOX_2	BECN1↑	SOX2-β-catenin/Beclin1/autophagy signaling axis promotes chemoresistance of CRC	[41]
FIRRE	Stabilize BECN1	Stabilizes BECN1 and promotes autophagy in a PTBP1 mediated manner to stimulate the development of CRC	[42]
IL-6	BECN1↑	IL-6/BECN1 pathway activates autophagy and promotes chemotherapy resistance of CRC	[39]
Pelareorep	BECN1↑	Upregulates BECN1 expression and induces autophagy to enhance CRC proliferation	[140]
Fusobacterium nucleatum	BECN1↑, CARD3↑	Upregulates CARD3 expression and activates autophagy signal to promote CRC metastasis	[141]
DCZ5248	p62↑	Induces lysosomal acidification and weakens lysosomal cathepsin activity to inhibit autophagy	[142]
Claudin 1	p62↓	Reduces the level of p62 and stimulates autophagy to promote CRC progression	[143]
DBTTS	p62↑	Induces accumulation of p62 protein and inhibits autophagy to induce CRC cell death	[47]

mTOR: The mammalian target of rapamycin; AMPK: Adenosine monophosphate-activated protein kinase; TBK1: TANK-binding kinase 1; mTORC1: mTOR complex 1; ABHD5: Abhydrolase domain containing 5; BECN1: Beclin1; CASP3: Caspase 3; SOX2: Sex-determining region Y-box2; FIRRE: Firre intergenic repeating RNA element; PTBP1: Polypyrimidine tract-binding protein; CARD3: Caspase activation and recruitment domain 3; DCZ5248: A heat shock protein 90 inhibitor; p62: Sequestosome 1; DBTTS: Diallyl tetrasulfide and its derivative, dibenzyl tetrasulfide; CRC: Colorectal cancer.

transport iron into the cell[52]. Intracellular Fe^{3+} is reduced to ferrous ions (Fe^{2+}) by six-transmembrane epithelial antigen of prostate 3 (STEAP3), forming the labile iron pool (LIP), which is involved in various metabolic reactions[53]. In ferroptosis, the role of iron can be summarized into two crucial types as follows: (1) Iron that catalyzes the nonenzymatic lipid autoxidation chain *via* the Fenton reaction; and (2) iron acting as an enzyme cofactor in enzymatic reactions of lipid peroxidation (see Figure 1). Fe^{2+} in LIP reacts with hydrogen peroxide (H_2O_2) to generate hydroxyl radicals (HO•), Fe^{3+}, and hydroxide ions, in a process known as the Fenton reaction[54]. HO• is a highly oxidative species that reacts with phospholipids to generate the phospholipid radical (PL•), initiating a lipid autoxidation chain reaction[55,56]. Ferrostatin-1 (fer-1), a ferroptosis inhibitor, can form a complex with Fe^{2+} to reduce LIP and scavenge alkoxy radicals produced by the lipid autoxidation chain, thereby inhibiting lipid peroxidation[57].

Lipid peroxidation: In addition to the iron-dependent Fenton reaction, another pathway of lipid peroxide production is the enzymatic reaction dominated by lipoxygenases (LOXs)[55]. Polyunsaturated fatty acids (PUFAs) are highly prone to peroxidation because of their bis-allylic carbons, and PUFAs play a central role in ferroptosis[58,59]. Polyunsaturated-fatty-acid-containing phospholipids (PUFA-PLs) are oxidized to phospholipid hydroperoxides (PLOOH) under the catalysis of LOXs[60]. The constant accumulation of lipid peroxides can destabilize membranes (membrane thinning and increased curvature), leading to pore formation, micellization, and ultimately cell death[61]. Furthermore, oxidative lipidomic analysis revealed that after cells were treated with ferroptosis inducers, the major oxidized phospholipid was PE[62]. Intracellular free PUFAs, especially arachidonic acid (AA) and adrenic acid (AdA), can be esterified to PE under the action of acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3), providing fuel for ferroptosis[58,63]. First, ACSL4 catalyzes the combination of coenzyme A (CoA) and PUFA to form a PUFA-CoA intermediate[64]. Next, LPCAT3 incorporates PUFA-CoA into membrane phospholipids[65]. The ACSL4 inhibitor rosiglitazone or LPCAT3 inhibitors can prevent ferroptosis[66,67]. Thus, ACSL4 and LPCAT3 are also important parts of the enzymatic reaction in ferroptosis.

Antioxidant defense systems: After the discovery of ferroptosis, researchers found the following common mediator for 12 ferroptosis-inducing small molecule compounds: glutathione peroxidase 4 (GPX4)[68]. GPX4 can reduce intracellular PLOOH to harmless phosphatidyl alcohol (PLOH), preventing the accumulation of lipid peroxides. This reaction requires the consumption of two molecules of glutathione (GSH) each time[69]. GSH, an important reducing substance in the body, is composed of three amino acids (glutamate, cysteine and glycine)[70]. Upon cellular oxidative stress, system Xc−, a cystine-glutamate antiporter, transports cystine into cells to provide raw materials for GSH synthesis[71]. At present, system Xc−-GSH-GPX4 is recognized as the most critical pathway by which the body resists ferroptosis. Ferroptosis inducers such as erastin inhibit system Xc− to prevent cystine uptake, resulting in the inability to synthesize GSH. GSH

Table 2 The role of ferroptosis in colorectal cancer

Intervention	Target	Effects and mechanism	Ref.
SRSF9	GPX4↓	Inhibition of SRSF9 increases erastin-induced iron death by downregulation of GPX4 level	[74]
IMCA	SLC7A11↓	IMCA induces SLC7A11 mediated ferroptosis through AMPK/mTOR pathway	[77]
TalaA	ROS↑, SLC7A11↓	TalaA induces ferroptosis to kill CRC cells	[144]
Lipocalin 2	GPX4↑, system Xc−↑	Overexpression of Lipocalin 2 inhibits ferroptosis and promotes CRC progression	[75]
TIGAR	GSH↓, ROS↑	TIGAR induces ferroptosis resistance in CRC by ROS/AMPK/SCD1 signaling pathway	[145]
HIF-2α	Iron↑	HIF-2α activation potentiates oxidative cell death in CRCs by increasing cellular iron	[79]
TP53	Lipid peroxidation, ACSL4↑	Restricts ferroptosis by blocking DPP4 activity in a transcription independent manner TP53	[91]
Tagitinin C	NRF2/HO-1↑, lipid peroxidation	Tagitin C activates NRF2/HO-1 pathway to induce ferroptosis	[82]
Cetuximab	NRF2↓, ROS↑	Cetuximab inhibits Nrf2/HO-1 pathway to promote ferroptosis in CRC	[85]
Beta-elemene	GSH↓, GPX4↓	Combined treatment with beta-elemene and cetuximab induces ferroptosis in CRC	[96]
Vitamin C	Iron↑, ROS↑	Vitamin C limits CRC resistance to EGFR-targeted therapies	[97]
FeOOH NSs	H_2S↓	FeOOH NSs eliminate endogenous H_2S to induce ferroptosis	[99]

SRSF9: Serine and arginine rich splicing factor 9; GPX4: Glutathione peroxidase 4; IMCA: The benzopyran derivative 2-imino-6-methoxy-2H-chromene-3-carbothioamide; SLC7A11: Solute carrier family 7 member 11; TalaA: Talaroconvolutin A; ROS: Reactive oxygen species; TIGAR: TP53-induced glycolysis and apoptosis regulator; GSH: Glutathione; SCD1: Stearoyl-coenzyme A desaturase-1; HIF-2α: Hypoxia-inducible factor 2α; TP53: Tumor suppressor p53; ACSL4: Acyl-CoA synthetase long-chain family member 4; NRF2: Nuclear factor erythroid 2-related factor 2; HO-1: Haem oxygenase 1; DPP4: Dipeptidyl-peptidase-4; FeOOH NSs: Iron oxide-hydroxide nanospindles; CRC: Colorectal cancer.

depletion inactivates the GPX4 enzyme, eventually triggering ferroptosis[56,68]. Another inducer, RSL3, binds directly to GPX4 to inactivate it[68]. Recently, new research has identified a GSH-independent pathway to inhibit ferroptosis. Ferroptosis suppressor protein 1 (FSP1) expression positively correlates with ferroptosis resistance[72]. Its main mode of action is that the reduced form of ubiquinone (also known as CoQ10) consumes lipid peroxyl radicals, while FSP1 uses NAD(P)H to catalyze the regeneration of ubiquinone[73].

The role of ferroptosis in CRC

Targeting the three pathways of ferroptosis described above can effectively impact CRC. Currently, there are more studies targeting system Xc−-GSH-GPX4 (versus the other two pathways) to regulate ferroptosis in CRC. Serine- and arginine-rich splicing factor 9 (SFRS9) is considered to be a carcinogen of cervical and bladder cancer. However, one group revealed that the expression of SFRS9 mRNA and protein was significantly higher in CRC tissues than in adjacent tissues. SFRS9 can bind to GPX4 mRNA and upregulate the expression of GPX4. Knockdown of SFRS9 inhibits CRC progression by triggering GPX4 reduction-mediated ferroptosis[74]. Lipocalin 2 has also been reported to inhibit ferroptosis by stimulating the expression of GPX4 and system Xc−[75]. Moreover, researchers isolated and purified petunidin 3-O-[rhamnopyranosyl-(trans-p-coumaroyl)]-5-O-(β-D-glucopyranoside) (Pt3R5G) from Lycium ruthenicum Murray, which inhibits RKO cell proliferation by downregulating solute carrier family 7 member 11 (SLC7A11), a subunit of system Xc−, which reduces ferroptosis[76]. In HCT116 cells, the benzopyran derivative 2-imino-6-methoxy-2H-chromene-3-carbothioamide (IMCA) downregulated SLC7A11 expression and decreased the content of cysteine and glutathione, leading to ROS accumulation and ferroptosis[77]. Therefore, inducing ferroptosis by inhibiting the system Xc−-GSH-GPX4 pathway may be an effective way to treat CRC. In addition, alterations in intracellular iron levels affect the growth of CRC cells. HIF-2α is a critical transcriptional regulator of cellular iron levels[78]. Activation of HIF-2α can lead to an increase in cellular iron and ROS levels; when this process is coupled with lipid-ROS induction by ferroptosis inducers, CRC cell death occurs[79].

In addition to the canonical system Xc−-GSH-GPX4 pathway, the nuclear factor erythroid 2-related factor 2/heme oxygenase 1 (NRF2/HO-1) axis also plays a major role in ferroptosis. NRF2 is the master transcription factor responsible for endogenous antioxidative stress, and many of its downstream target genes are also involved in the regulation of iron metabolism, particularly HO-1[80]. HO-1 catalyzes the cleavage of heme to produce Fe^{2+}, which increases the LIP and thus promotes ferroptosis[80,81]. For example, the natural product tagitinin C (TC), a novel inducer of ferroptosis, can

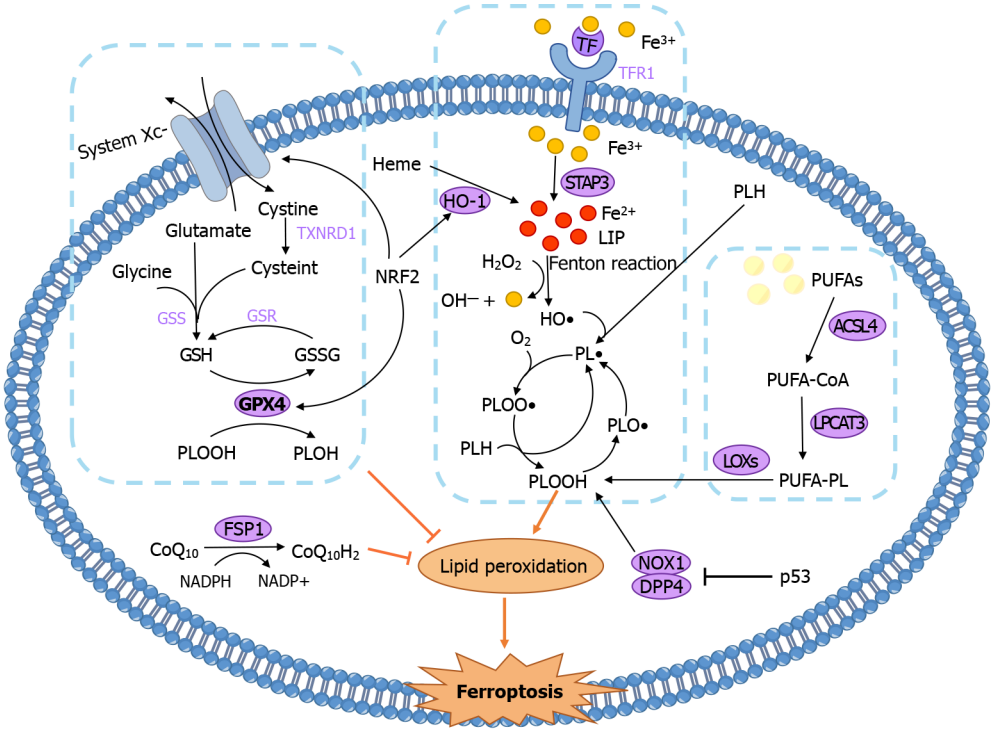

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Figure 1 Mechanisms of ferroptosis (created by Figdraw). TXNRD1: Thioredoxin reductase 1; GSS: Glutathione synthetase; GSH: Glutathione; GSSG: Oxidized glutathione; GSR: Glutathione-disulfide reductase; GPX4: Glutathione peroxidase 4; PLOOH: Phospholipid hydroperoxides; PLOH: Phosphatidyl alcohol; Fe^{3+}: Ferric ion; Fe^{2+}: Ferrous ion; TF: Transferrin; TfR1: Transferrin receptor 1; STEAP3: Six-transmembrane epithelial antigen of prostate 3; LIP: labile iron pool; H_2O_2: Hydrogen peroxide; HO•: Hydroxyl radicals; PL•: Phospholipid radical; PLH: Phospholipid; PLO•: Phospholipid alkoxyl radical; PLOO•: Phospholipid peroxyl radical; PUFAs: Polyunsaturated fatty acids; PUFA-PL: Polyunsaturated-fatty-acid-containing phospholipid; ACSL4: Acyl-CoA synthetase long-chain family member 4; LPCAT3: Lysophosphatidylcholine acyltransferase 3; LOXs: Lipoxygenases; NRF2: Nuclear factor erythroid 2-related factor 2; HO-1: Haem oxygenase 1; FSP1: Ferroptosis suppressor protein 1; CoQ_{10}: Ubiquinone; $CoQ_{10}H_2$: The reduced form of ubiquinone; p53: Tumor protein p53; DPP4: Dipeptidyl-peptidase-4; NOX1: A member of the NADPH oxidase protein family.

inhibit the growth of erastin-insensitive HCT116 cell lines[82]. Mechanistically, tagitinin C first induces oxidative stress, which activates the NRF2/HO-1 pathway and leads to the accumulation of iron, thus driving ferroptosis. Additionally, NRF2 is involved in the regulation of lipid metabolism. Another transcriptional target of NRF2 is GPX4, which allows NRF2 to exert anti-ferroptosis effects[83,84]. One group reported that cetuximab enhanced RSL3-induced lipid ROS accumulation by inhibiting the expression of NRF2 and HO-1 and ultimately promoted ferroptosis in KRAS-mutant CRC cells[85]. There is also research showing that lysionotin (Lys, a flavonoid) promotes the degradation of Nrf2, which leads to decreased expression of GPX4 and system Xc− and subsequently promotes ferroptosis[86]. Given the two different results of the above studies, further evidence is needed to clarify the relationship between NRF2, ferroptosis, and CRC. The balance between the driving effect and the suppressive effect is the key to treatment.

P53 is one of the most widely studied tumor suppressor genes, and it is mutated in almost all human cancers[87]. P53 is involved in a wide range of regulatory processes, including DNA repair, senescence, apoptosis, cell metabolism, ROS production, and ferroptosis[88]. P53 has a dual role in the regulation of ferroptosis[89]. The most classical pathway that promotes iron-mediated death involves p53-mediated repression of the transcription of the SLC7A11 gene, which decreases the expression of SLC7A11, affects the generation of GSH, and induces ferroptosis[90]. However, p53 has an antiferroptotic effect in CRC cells. Mechanistically, p53 binds with dipeptidyl peptidase 4 (DPP4) to block the formation of the DPP4-NOXI complex, leading to a decrease in DPP4-dependent lipid peroxidation, which suppresses ferroptosis [91]. In addition, TP53 target genes, such as cytochrome c oxidase 2 (SCO2), glutaminase 2 (GLS2), and spermidine/spermine N1 acetyltransferase 1 (SAT1), are also involved in the regulation of ferroptosis, but they have not been thoroughly studied in CRC[92,93].

Antitumor therapy based on ferroptosis in CRC

Cisplatin is one of the most widely used anticancer drugs in the clinic, and its most prominent mechanism of action is DNA damage and ultimately apoptosis. However, the chemotherapeutic efficacy of cisplatin has been greatly limited, as the attenuation of DNA damage-mediated apoptotic signaling leads to drug resistance[94]. However, recently, it was found that cisplatin could promote ferroptosis *via* GSH depletion and GPX inactivation in CRC and had a synergistic effect with erastin[95]. In addition, β-elemene, a compound isolated from the Chinese herb Curcumae Rhizoma, combined with cetuximab can induce ferroptosis in KRAS-mutant CRC cells by increasing cellular iron accumulation and lipid peroxidation, which inhibits CRC growth and metastasis[96]. Another study showed that combinatorial treatment with pharmacological doses of vitamin C and cetuximab can trigger ferroptosis, which ultimately prevents the emergence of

acquired resistance to anti-EGFR targeted therapy[97]. In addition to the drugs mentioned above, some novel compounds that inhibit CRC by inducing ferroptosis have also emerged with the rapid development of nanotechnology. For example, zinc oxide-coated virus-like silica nanoparticles (VZnO) can induce ferroptosis by scavenging H_2S and depleting GSH to inhibit CRC growth[98]. Additionally, iron oxide hydroxide nanospindles (FeOOH NSS) had similar effects and hold promise as therapeutic agents for CRC[99]. In summary, ferroptosis regulation has great potential for addressing the current problem of anticancer drug resistance and may provide a new strategy for the treatment of CRC.

THE INTERACTION BETWEEN AUTOPHAGY AND FERROPTOSIS

Autophagy and ferroptosis are two mechanistically distinct forms of cell death. Recent studies have revealed that autophagy inhibitors can prevent erastin-induced ferroptosis in cells and noted that ferroptosis is a form of autophagic cell death[9]. Although the interaction between autophagy and ferroptosis is not yet clear, several studies have noted the role of selective autophagy or certain autophagy factors in ferroptosis. For example, ferritinophagy, lipophagy, clockophagy, CMA and so on promote ferroptosis by inducing iron accumulation or lipid peroxidation[10,11,100]. Here, we summarize selective autophagy and possible regulatory pathways driving ferroptosis in the context of CRC (Figure 2).

Nuclear receptor coactivator 4-mediated ferritinophagy

Under normal physiological conditions, the LIP in cells maintains a dynamic balance, and excess Fe^{2+} is stored by ferritin [53]. Ferritin, composed of ferritin heavy chain 1 (FTH1) and ferritin light chain (FTL), protects against harmful oxidative stress under the condition of free iron overload. When cells are iron deficient, iron is released through an autophagy-related mechanism, known as "ferritinophagy"[101]. Nuclear receptor coactivator 4 (NCOA4), as a selective cargo receptor for ferritinophagy, transports ferritin for lysosomal degradation by binding to FTH1[102,103]. Ferritinophagy enhances cellular susceptibility to ferroptosis by controlling the size of the LIP[104,105]. New research has identified a novel ferroptosis inhibitor, 9a, that acts by disrupting the NCOA4-FTH1 interaction to reduce the amount of intracellular Fe^{2+}[106].

Immunohistochemistry of specimens from patients with colon adenocarcinoma showed that the expression of the NCOA4 protein in tumor tissues was lower than that in peritumoral neighboring tissues. Moreover, the NCOA4 expression level was highly correlated with overall survival, and patients with low protein expression had a worse prognosis[107]. One study showed that in CRC cells, inhibition of the GTP cyclohydrolase-1/tetrahydrobiopterin (GCH1/BH4) pathway resulted in increased levels of NCOA4 protein, decreased levels of FTH1, and the accumulation of free iron. This phenomenon can be reversed with the use of autophagy inhibitors. Altogether, inhibition of the GCH1/BH4 pathway promoted erastin-induced ferroptosis by activating ferritinophagy[108]. In contrast, another study showed that the knockdown of NCOA4 disrupted ferritinophagy and had no significant effect on erastin-induced ferroptosis in HCT116 cells[109]. We should consider whether there is another mechanism by which erastin-induced ferroptosis in CRC cells copes with iron reduction caused by decreased ferritinophagy. Therefore, we need more evidence to validate the role of ferritinophagy in CRC. Studies on ferritinophagy, which involves two major mechanisms, autophagy and ferroptosis, will provide new insights into the treatment of CRC.

BECN1-mediated system Xc− inhibition

BECN1 is a key factor in autophagy initiation, and its role in CRC is complex, as it can promote or inhibit autophagy. Thus far, in a variety of cancers, such as hepatocellular carcinoma, lung cancer, head and neck cancer, and others, there is substantial evidence that BECN1 regulates autophagy-dependent ferroptosis[110,111]. In several studies, BECN1 merely plays the classical role of activating autophagy, promoting the degradation of autophagic ferritin, which in turn leads to ferroptosis. For example, ELAV-like RNA binding protein 1 can bind to the 3'-untranslated region of BECN1, allow intracellular iron accumulation, and eventually lead to ferroptosis[112]. However, one study found that in CRC, BECN1 plays a direct role in regulating ferroptosis[113]. The transporter system Xc− in the anti-ferroptosis system is another agonist of this pathway. System Xc− consists of the following two core components: SLC7A11 and solute carrier family 3 member 2 (SLC3A2)[114]. BECN1 can block the activity of system Xc− by directly binding to SLC7A11, thereby promoting ferroptosis[113]. Adenosine monophosphate-activated protein kinase (AMPK) is upstream of this pathway, and its phosphorylation of BECN1 at Ser90/93/96 could promote the formation of a complex of BECN1 with system Xc− [113]. Taken together, these results indicate that BECN1 could be a regulatory target for ferroptosis, and its detailed regulatory pathways require further investigation.

P62-KEAP1-NRF2 pathway

NRF2 acts as an important defense factor against oxidative stress, and its negative regulator is Kelch-like ECH-associated protein 1 (KEAP1)[115]. Under normal physiological conditions, NRF2 binds to KEAP1, which is constantly ubiquitinated and degraded by the proteasome so that it has no function. When the organism undergoes oxidative stress, the site of KEAP1 binding to NRF2 changes so that NRF2 can translocate to the nucleus and activate the transcription of the antioxidant response element[116,117]. P62 is a selective cargo receptor for autophagy, and its regulation of NRF2-KEAP1 was revealed as early as 2010[118]. Upon autophagy deficiency and p62 accumulation, p62 competes with KEAP1 for the binding site of NRF2, exempting NRF2 from degradation and enabling the transcriptional activation of its target genes [119,120]. Recently, with the uncovering of new mechanistic insights into the regulation of ferroptosis by NRF2, a growing number of studies have demonstrated the role of the p62-KEAP1-NRF2 pathway in the regulation of ferroptosis [121,122]. A study showed that CRC cells could be treated with RH4 (the primary pharmacologically active component of

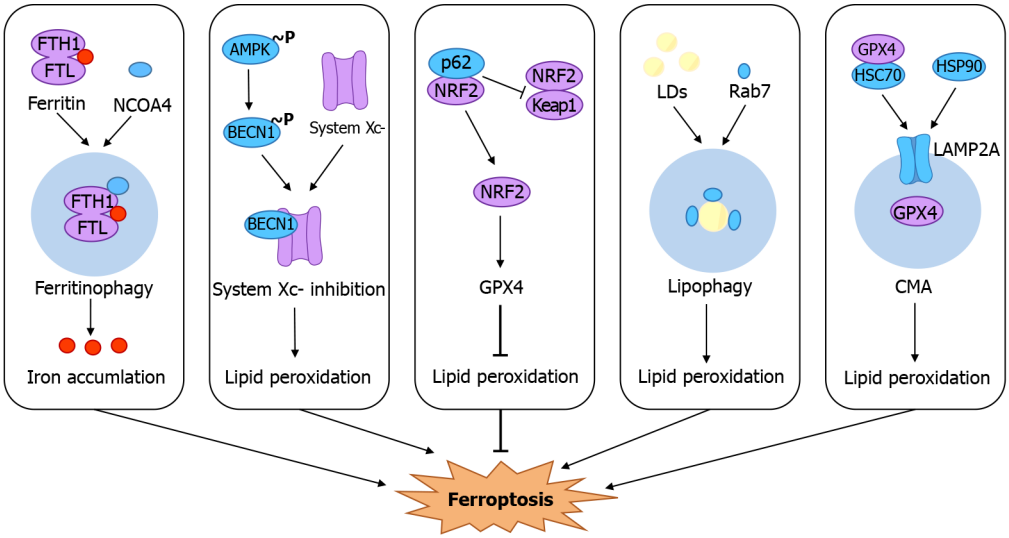

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Figure 2 The interaction mechanisms between autophagy and ferroptosis in colorectal cancer (created by Figdraw). Fe^{2+}: Ferrous ions; FTH1: Ferritin heavy chain 1; FTL: Ferritin light chain; NCOA4: Nuclear receptor coactivator 4; AMPK: Adenosine monophosphate-activated protein kinase; BECN1: Beclin1; p62: sequestosome 1; NRF2: Nuclear factor erythroid 2-related factor 2; KEAP1: Kelch-like ECH-associated protein 1; GPX4: Glutathione Peroxidase 4; LDs: Lipid droplets; Rab7: The small GTPase; HSC70: Heat shock cognate 71 kDa protein; HSP90: Heat shock protein 90; LAMP2A: Lysosome-associated membrane protein type 2A; CMA: Chaperone-mediated autophagy.

ginseng) and found an increase in Beclin1, LC3B, and NRF2 and a decrease in p62, which could ultimately induce ferroptosis. Treatment with the autophagy inhibitor 3-MA could reverse RH4-induced ferroptosis[123]. In another study, silencing NRF2 decreased the expression of p62, which improved the antitumor effects of tributyltin (IV) ferulate (TBT-F)[124]. These results establish a basis for the crosstalk between autophagy and ferroptosis and suggest that the p62-KEAP1-NRF2 pathway influences ferroptosis, which may be an important topic for future research.

Other potential pathways

In addition to the above, there are other potential mechanisms by which autophagy regulates ferroptosis in CRC. Lipophagy is a process in which intracellular lipid droplets (LDs) are targeted for transport into lysosomes for breakdown. LD is a dynamic organelle that stores neutral fatty acids and is involved in maintaining energy and redox homeostasis[125]. In hepatocytes, the small GTPase Rab7 recruits autophagosomes and lysosomes to the surface of LDs, resulting in lipophagy[126]. Tumor protein D52 (TPD52) or knockdown of Rab7 increased lipid storage, reduced lipid peroxidation, and suppressed RSL3-induced ferroptosis[127]. The results show that lipophagy is closely related to lipid peroxidation in ferroptosis. In addition, the accumulation of LDs contributes to chemoresistance in CRC[128]. Therefore, driving lipophagy, which leads to an increase in the occurrence of lipid peroxidation and promotes ferroptosis, may emerge as a novel treatment strategy for CRC. Most importantly, we must find the specific receptor of lipophagy in CRC.

CMA, unlike macroautophagy and microautophagy, is a type of selective autophagy that degrades only a specific subset of soluble proteins[129]. Heat shock cognate 71 kDa protein (HSC70) detects cytoplasmic proteins containing a KFERQ-like motif and then docks with lysosomes *via* lysosome-associated membrane protein type 2A (LAMP2A) to send the target proteins to lysosomes for degradation[130]. One research team found that GPX4 contains pentapeptide sequences (124 NVKFD 128, 169 LIDKN 173, and 187 QVIEK 191) consistent with a KFERQ-like motif, which is one of the substrates of CMA[131]. Heat shock protein 90 (HSP90) increases the levels of LAMP2A, mediating the degradation of GPX4 and leading to ferroptosis[131]. Antimony (sb) can upregulate the expression of HSP90, HSC70, and LAMP2A, which increases the rate of formation of the chaperone-GPX4 complex to mediate ferroptosis *via* CMA[132]. In addition, ACSL4 can also be recognized by HSC70 as a substrate for CMA-mediated ferroptosis[133]. In HCT116 cells, the lack of sorting nexin 10 (SNX10) promotes the proliferation of cancer cells by enhancing the degradation of the CMA substrate p21Cip1/WAF1[134]. The above studies laid the foundation for CMA-mediated ferroptosis of CRC cells. Future studies should focus on finding ferroptosis-related proteins containing a KFERQ-like motif and identifying the targets that drive CMA to degrade ferroptosis-related proteins.

Furthermore, hippocalcin-like 1 (HPCAL1), a neuronal calcium sensor, was identified as an important negative regulator of lipid synthesis and mTOR signaling activation, thereby blunting lipid metabolism to suppress tumorigenesis in the liver[135]. A recent study showed that HPCAL1 selectively degrades cadherin 2 and promotes lipid peroxidation to induce ferroptosis[136]. This phenomenon has been confirmed in a variety of cancer cells, including pancreatic cancer, non-small cell lung cancer, and bladder cancer cells, but this trend needs to be explored further in CRC.

CONCLUSION

In recent years, ferroptosis has consistently been under the spotlight in medical research. Ferroptosis can be used as a new treatment to clear cancer cells. For example, sorafenib itself is a ferroptosis inducer and ferroptosis inducers combined with chemotherapy drugs can overcome drug resistance; in addition, nanoparticulate anticancer drug delivery systems based on ferroptosis have emerged[137,138]. Although many studies are still in the experimental stage, these results have revealed the great potential of ferroptosis in cancer treatment. Furthermore, with a deeper understanding of the mechanisms of ferroptosis, an increasing number of studies have demonstrated crosstalk between ferroptosis and other types of RCD. Thus, autophagy-dependent ferroptosis takes the stage. Clarification of the crosstalk between autophagy and ferroptosis would not only provide a comprehensive understanding of the mechanisms of cell death but could also provide new insights for cancer treatment. Although much progress has been made, research on autophagy-dependent ferroptosis in CRC is still at an early stage. In this review, we summarized the mechanisms of autophagy and ferroptosis and their roles in CRC and focused on the possible pathways of crosstalk between them. While ferritinophagy, the BECN1–system Xc− pathway, and the p62-KEAP1-NRF2 pathway play a significant role in ferroptosis, the roles of lipophagy, CMA, or other regulators have not been validated in CRC. The mechanisms involved in the two different types of cell death are complex but also build a broader platform for subsequent research. Defining targets that regulate autophagy-dependent ferroptosis might lead to the discovery of novel therapeutic strategies for CRC.

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