Journal of Translational Medicine

REVIEW Open Access

Crosstalk between ferroptosis and autophagy: broaden horizons of cancer therapy

Xingyu Liu[1], Halahati Tuerxun[1], Yixin Zhao[1], Yawen Li[1], Shuhui Wen[1], Xi Li[1] and Yuguang Zhao[1*]

Abstract
Ferroptosis and autophagy are two main forms of regulated cell death (RCD). Ferroptosis is a newly identified RCD driven by iron accumulation and lipid peroxidation. Autophagy is a self-degradation system through membrane rearrangement. Autophagy regulates the metabolic balance between synthesis, degradation and reutilization of cellular substances to maintain intracellular homeostasis. Numerous studies have demonstrated that both ferroptosis and autophagy play important roles in cancer pathogenesis and cancer therapy. We also found that there are intricate connections between ferroptosis and autophagy. In this article, we tried to clarify how different kinds of autophagy participate in the process of ferroptosis and sort out the common regulatory pathways between ferroptosis and autophagy in cancer. By exploring the complex crosstalk between ferroptosis and autophagy, we hope to broaden horizons of cancer therapy.

Keywords Ferroptosis, Autophagy, Cancer therapy, Crosstalk

Introduction

Since it was first observed by the ancient Greek "father of medicine" Hippocrates as early as 400 BC, scientists have never stopped exploring the mysteries of cancer. However, cancer was still a terror for human beings because of its intractability and high mortality rate. Cancer is a major public health problem worldwide and is contributing to a growing burden of disease. Lately, an increasing number of studies have explored approaches to hinder the occurrence and progression of cancer by targeted induction of different modes of cell death, such as apoptosis, necroptosis, autophagy, pyroptosis, ferroptosis, and so on.

Ferroptosis is a form of regulated cell death (RCD) driven by iron accumulation and lipid peroxidation [1]. In terms of morphology, biochemistry, and genetic composition, ferroptosis differs from other forms of cell death. Ferroptosis is characterized morphologically by smaller mitochondria, condensed mitochondrial membrane density, reduced or absent mitochondrial cristae, and ruptured outer mitochondrial membranes. Ferroptosis has been demonstrated to have a strong link to cancer [2]. By regulating ferroptosis, the progression of cancer can be influenced. We also see the great potential of ferroptosis to play a synergistic role in reversing drug resistance along with common cancer therapy [2, 3].

The process by which lysosomes break down harmful proteins, invasive microorganisms, and damaged organelles is known as autophagy. Multiple autophagy-related genes (ATGs) and intricate signaling networks control autophagy, which is crucial for controlling organism growth and preserving cellular homeostasis [4]. In general, we have found both autophagy and ferroptosis play key roles in varieties of diseases, and we also found that focusing on the crosstalk between ferroptosis and autophagy may provide some inspiration for exploring

*Correspondence:
Yuguang Zhao
zhaoyuguang@jlu.edu.cn
[1]Cancer Center, The First Hospital of Jilin University, Changchun 130021, China

the occurrence and development of neurodegenerative diseases, ischemia-reperfusion injury, cancer, and other diseases. In this article, we will have an overview of the mechanisms of ferroptosis and autophagy and their relationships with cancer. By summarizing the functions played by autophagy in ferroptosis and searching for the common regulatory pathways of ferroptosis and autophagy, we will try to figure out new breaches for the treatment of cancer.

Overview of ferroptosis and autophagy

Mechanisms of ferroptosis

Ferroptosis was first proposed by Dixon and his colleagues in 2012 and is a different form of regulated cell death (RCD). It was defined as iron-dependent lipid peroxidation [1]. Figure 1 Iron is an essential trace element in the organism with a variety of physiological functions including but not limited to oxygen transportation, catalysis, and electron transferring in the respiratory chain. Thus, iron is an indispensable factor in the redox system. Iron homeostasis is an important part of the regulation of ferroptosis and ferritin as the main form of storage iron, play a critical role in maintaining iron homeostasis. Ferritin is made up of two parts: ferritin heavy chain 1 (FTH1) and ferritin light chain (FTL). Trivalent iron (Fe3+) bound to transferrin (TF) constitutes the majority of systemic iron in circulation [5]. Next, iron-containing TF is recognized by the transferrin receptor (TFRC) on the cell membrane and is transported into the cell via endosomes, where six-transmembrane epithelial antigen of prostate 3(STEAP3), a ferrireductase, converts Fe^{3+} to ferrous iron (Fe^{2+}). Then, Fe^{2+} is released from the endosome to cytoplasm with the assistance of SLC11A2 (also known as DMT1). A portion of these Fe^{2+} is incorporated into ferritin, while the remainder free or weakly bound Fe^{2+} constitutes the so-called labile iron pool (LIP), which is redox-active [6]. Fe^{2+} catalyzes the Fenton reaction that converts hydrogen peroxide into the strongly oxidizing hydroxyl radical, which is the most reactive type of reactive oxygen species (ROS). ROS will then participate in the process of lipid peroxidation and it is another key molecule in ferroptosis. Lipid peroxidation

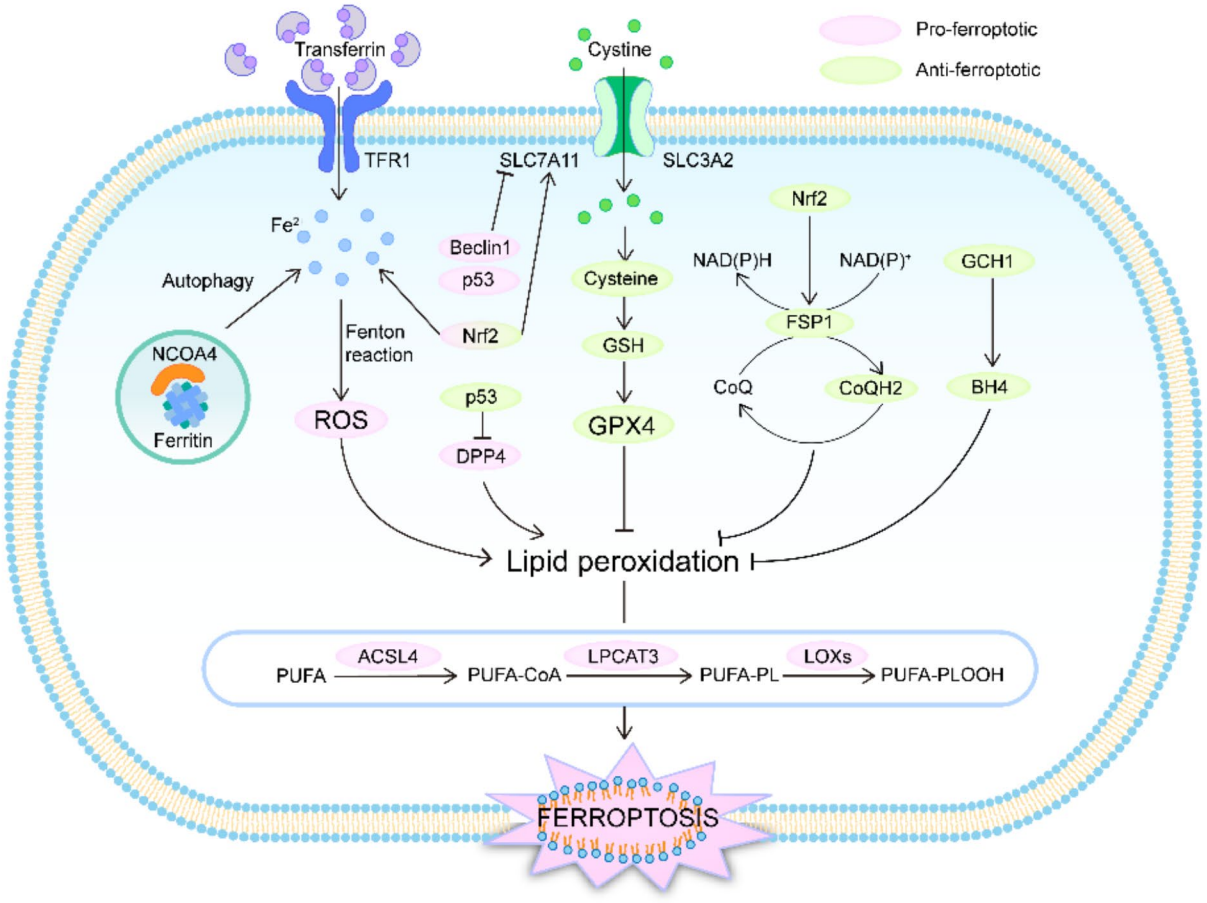

Fig. 1 Major mechanisms of ferroptosis. Ferroptosis is a form of regulated death induced by the accumulation of iron and lipid peroxides. Lipid peroxidation is the core process of ferroptosis. The figure shows the most important oxidant and anti-oxidant factors and mechanisms involved in ferroptosis

is central to the pathogenesis of ferroptosis, targeting primarily polyunsaturated fatty acids (PUFAs) in the cell membrane. Reactive oxygen species can initiate a chain reaction attacking the unstable double-bond structure of PUFAs, leading to the formation of lipid hydroperoxides (PLOOH) and propagating lipid peroxidation to adjacent PUFA-phospholipids, ultimately compromising cell membrane integrity. Long-chain acyl-coenzyme A synthetase family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3) are important promoters of ferroptosis. PUFAs react with coenzyme A via the catalytic action of ACSL4 to form acyl-coenzyme A. Subsequently, LPCAT3 facilitates the conversion of acyl-coenzyme a to membrane phosphatidylethanolamine through esterification to generate PUFA-PE. This increases the amount of PUFA in the membrane phospholipid structure and renders the membrane structure more susceptible to peroxidation. Additionally, certain lipoxygenases (LOXs) can directly oxidize PUFAs in biological membranes, mediating lipid peroxidation [7].

Correspondingly, several mechanisms exist to protect cells from excessive lipid peroxide accumulation and ferroptosis occurrence, among which the antioxidant mechanism with Glutathione peroxidase 4 (GPX4) as the centerpiece occupies a crucial position [8]. GPX4, as a selenoprotein, can utilize glutathione (GSH) as a substrate to reduce cellular PUFA phospholipid hydroperoxides (PUFA-PL-OOHs) to non-lethal PUFA phospholipid alcohols (PUFA-PL-OOHs) [9]. GSH, as a powerful antioxidant, is indispensable in the action of GPX4, and numerous studies have confirmed that depletion of GSH levels will increase cellular sensitivity to ferroptosis. Therefore, the cystine/glutamate antiporter (system x_c^-), which consists of two subunits including SLC7A11 and SLC3A2 and is responsible for the import of cysteine, the raw material for GSH synthesis, as well as the associated substrates and enzymes responsible for GSH synthesis, are equally important targets for ferroptosis [10].

Furthermore, studies in recent years have identified several other GPX4-independent anti-ferroptosis mechanisms. The gene product of the retinoid protein apoptosis-inducing factor mitochondria-associated 2 (AIFM2), now also known as ferroptosis inhibitory protein 1 (FSP1), can protect against ferroptosis induced by the absence of GPX4[9]. FSP1 reduces ubiquinone (CoQ10) to ubiquinol (CoQ-H2) by using the reductase type of the enzyme cofactor adenosine diphosphate (NADPH), and ubiquinol serves as a potent lipophilic free radical trapping antioxidant that can directly reduce lipid free radicals in membranes, thereby preventing uncontrollable lipid peroxidation reactions [11]. GTP cyclic hydrolase 1 (GCH1) prevents ferroptosis mediated by its metabolites, tetrahydrobiopterin (BH4) and dihydrobiopterin (BH2). GCH1 synthesizes dihydrobiopterin (BH2), which is then reduced to BH4 (tetrahydrobiopterin) by dihydrofolate reductase (DHFR). BH4, on the one hand, serves as a lipophilic radical trapping antioxidant preventing the lipid peroxidation process, on the other hand, BH4 also proves to be involved in the synthesis of ubiquinone [12].

Corresponding to the key molecules mentioned above in the ferroptosis mechanism, various ferroptosis inducers or drugs with ferroptosis-inducing function have been discovered. These ferroptosis inducers, with their diversity and complexity of mechanism of action, have played an important role in ferroptosis-related studies, and have provided important tools and targets for the research and treatment of related diseases. Erastin and its derivatives, glutamate, sorafenib, and sulfasalazine(SSZ) act by inhibiting the system x_c^-, and are considered type I ferroptosis inducers [13]. RSL3, FIN56, and ML162 induce ferroptosis by directly inhibiting the degradation of GPX4, and are type II ferroptosis inducers. Type III inducers reduce the production of CoQ10 to promote ferroptosis by reducing CoQ10 production, such as iFSP1 and statins, among which Fin56 also enhances sensitivity to ferroptosis by over-consuming CoQ10. Type IV ferroptosis inducers induce lipid peroxidation through iron or PUFA overload, including heme, artemisinin, artesunate, FINO2, etc.

Ferroptosis and cancer

As the research on ferroptosis keeps deepening, the relationship between ferroptosis and cancer has come to light. It is now evident that ferroptosis is implicated in both oncogenesis and the response to anticancer therapies. Many cancer-related genes, tumor suppressors, and signaling pathways also play essential roles in regulating ferroptosis, and their alteration in cancer cells can be used as biomarkers to predict the therapeutic effects. Targeting the resistance to ferroptosis in tumor cells, which often arises from specific mutations, could potentially be leveraged to induce ferroptosis, offering a novel therapeutic strategy to enhance synergistic antitumor effects or to overcome resistance to conventional treatments. For instance, the anti-oncogene *Tumor Protein P53* (*TP53*) has been shown to sensitize cells to ferroptosis by repressing the expression of SLC7A11 via transcriptional or post-translational mechanisms [14]. Tp53 can also bind to dipeptidyl-peptidase-4 (DPP4) and promote the accumulation of DPP4-TP53 complex in the nucleus, thereby blocking DPP4-dependent lipid peroxidation and inhibiting ferroptosis in colorectal cancer cells [15]. Ferroptosis was also identified as one of the key cell death responses triggered by multiple mainstream cancer therapies, including radiotherapy, immunotherapy, chemotherapy, and targeted therapy. Sorafenib, as the first-line treatment for advanced hepatocellular carcinoma, has been shown to induce ferroptosis by inhibiting

system x_c^- [16]. With the discovery of diverse novel ferroptosis-inducing agents, the advent of nanotechnology [17], and the reinforcing role of bioinformatics, the rational application of ferroptosis inducers shows promising potential for cancer treatment. Meanwhile, the unique metabolic characteristics of cancer cells, including their high metabolic demand, high ROS load, and the highly iron-dependent nature of tumor cells, particularly tumor stem cells, as well as their specific gene mutations, render certain types of cancer cells more susceptible to ferroptosis. This susceptibility allows ferroptosis to be targeted as a potential vulnerability in therapeutic strategies [18, 19]. In the early stages of ferroptosis in tumor cells, a significant release of damage-associated molecular patterns (DAMPs) occurs, stimulating the immune response, activating macrophage polarization, and promoting T-cell infiltration into tumor tissues [20–22]. On the other hand, various components within the tumor microenvironment (TME) influence the sensitivity of tumor cells to ferroptosis via different interactions [23]. The potential to regulate the sensitivity of tumor cells to ferroptosis by targeting specific TME components warrants exploration in future studies.

Mechanisms of autophagy

Autophagy is the process driven by autophagy-related (ATG) genes/proteins by which cells use lysosomes to degrade their proteins and damaged organelles. In essence, autophagy represents a dynamic process of membrane rearrangement regulated by autophagy-induced signaling pathways. Based on the different pathways by which the substrate enters the lysosome, autophagy is classified into three major types: macroautophagy, microautophagy, and chaperone-mediated autophagy. Figure 2 Macroautophagy, referred to as autophagy hereinafter, is one of the most dominant self-regulatory mechanisms under cellular stimulations and it is the earliest and most thoroughly studied type among the three mentioned [24]. During macroautophagy, the packaging of autophagic cargo relies on the formation of double-membrane vesicles known as autophagosomes, which facilitate membrane fusion [25]. Microautophagy involves the direct invagination of the lysosomal membrane to engulf cytoplasmic material [26, 27]. Chaperone-mediated autophagy relates to lysosome-associated membrane protein 2A (LAMP2A). Lysosomes, under the mediation of molecular chaperones such as heat shock protein 70 (Hsc70), specifically recognize intracellular soluble proteins containing a KFERQ-like pentapeptide motif. These proteins are eventually translocated into the

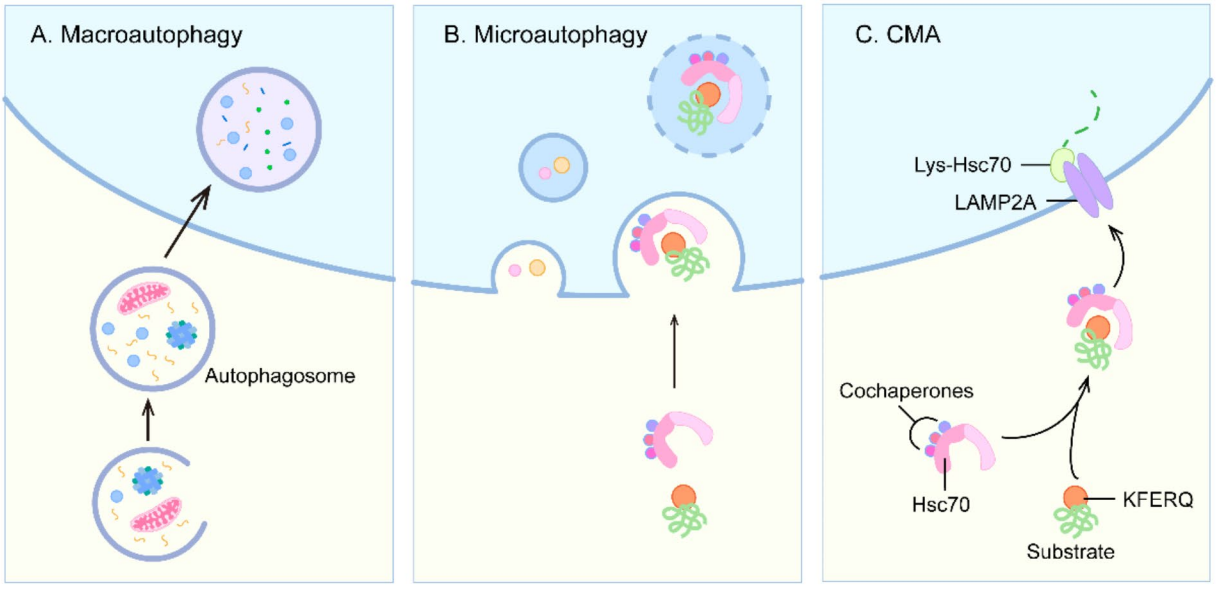

Fig. 2 Major mechanisms of autophagy. Based on the distinct pathways by which substrates are delivered to the lysosome, autophagy is classified into three principal forms: macroautophagy, microautophagy, and chaperone-mediated autophagy. Macroautophagy initially involves the formation of double-membrane autophagosomes, which subsequently fuse with the endoplasmic reticulum, endosomes, and lysosomes to form autolysosomes. Microautophagy entails the direct engulfment of small cytoplasmic fragments or proteins by lysosomes. Chaperone-mediated autophagy facilitates the direct translocation of cytosolic proteins across the lysosomal membrane, delivering them directly into the lysosomal lumen

lysosomes and ultimately degraded through binding to the LAMP2A on the lysosomal membrane [28].

Either the inactivation of the mammalian target of rapamycin (mTOR) complex1 (mTORC1) or the activation of 5-AMP-activated protein kinase (AMPK), both of which are traditional inducers of the autophagic response, initiates the basic process of autophagy [29, 30]. The unc-51-like autophagy-activating kinase 1 (ULK1) complex, comprising ULK1, FIP200, Atg13, and Atg101, is activated when cells are under stress or nutrient restriction through the inhibition of mTOR or the activation of AMPK. The activated ULK1 complex then activates Class III phosphatidylinositol 3- kinase complex I (PI3KC3C1), which consists of VPS34/PIK3C3 (catalytic subunit),

PIK3R4, Beclin1, Atg14, and NRBF2, and catalyzes the production of phosphatidylinositol 3- phosphate (PI3P). Then PI3P triggers the collection of autophagy related proteins including Atg3, Atg7, and Atg12-Atg5-Atg16 complex [31, 32]. Then, driven by a series of ubiquitin-like conjugation events, the LC3/GABARAP protein family conjugated to lipid phosphatidylethanolamine (PE) leading to the the formation of autophagosomes [33]. These autophagosomes transport their cargo to the lysosome, where fusion with the lysosome and degradation by lysosomal hydrolases occur.

Selective autophagy can be categorized by the different substrates, such as mitophagy, endoplasmic reticulum autophagy, pexophagy, lipophagy et al. Specific adaptors recognize the contents and localize them to Atg8/LC3 on the autophagosome membrane for selective autophagy [34]. Under physiological conditions, autophagy serves as a cellular protective mechanism and plays a central role in maintaining cellular homeostasis and preserving cell viability [35, 36].

Autophagy and cancer

Autophagy is an important protective mechanism in physiological conditions, while under pathological conditions, yet it assumes specialized roles within the microenvironment during pathological states. Autophagy exhibits bidirectional effects in tumor development depending on different tumor types and tumor stages. On the one hand, autophagy has a negative regulatory effect on tumorigenesis. Several studies have shown that tumor cells are under oxidative stress due to high levels of metabolism and rapid proliferation [37, 38]. ROS generated by excessive metabolism can induce DNA damage and promote tumorigenesis [39]. Autophagy, particularly through peroxisomal and mitochondrial autophagy, is instrumental in neutralizing ROS and safeguarding cells from oxidative stress. The inhibition of autophagy-related genes has been observed in the early stages of the development of several types of tumors. The absence of autophagy-related genes promotes the development of tumors, also demonstrating the suppressive role of autophagy in tumor development. Research has demonstrated that Beclin1 protein expression in human breast cancer tissues is notably lower than in normal mammary epithelial cells. And enforced expression of the *Beclin1* promotes autophagy in human breast carcinoma and thus suppresses tumor growth [40]. In *Atg7* knockdown mice models, the loss of hepatic autophagy drove early stages of hepatic tumor initiation [41]. The P62/Nrf2 pathway, which will be provided with a detailed introduction in another section, is considered to have tumor-promoting effect [42]. Keeping p62 at an appropriate level through autophagy is also a vital mechanism to prevent the development of tumors.

On the other hand, autophagy also plays a role in cancer progression. Rapidly growing cancer cells are under great material-energy demand [43]. Certain substances recycled from autophagy provide the material basis for the growth of cancer cells. For example, in $Braf^{V600E}$ induced lung cancer cells, the deletion of *Atg7*, a key gene for autophagy, reduces the level of cellular glutamine and thus inhibits the survival of tumor cells at later stages of tumorigenesis [44]. This suggests that such tumor cells depend on glutamine procured through autophagy to satisfy their physiological requirements for proliferation and synthesis.

Autophagy in ferroptosis

Ferritinophagy provides ingredients for autophagy-dependent ferroptosis

Ferritinophagy is a selective autophagy that degrades ferritin, which is the main form of intracellular iron. Ferritinophagy mediated by nuclear receptor coactivator 4 (NCOA4) is recognized as a major pathway for the activation of ferroptosis. The cytosolic autophagy receptor NCOA4 mediates the autophagic degradation of ferritin by binding to a critical surface arginine in FTH1. As a result, iron sequestered within ferritin is released into LIP, thereby promoting ferroptosis [45, 46]. In several cancer cell lines, including HT1080 and PANC1, the knockdown of NCOA4 prevents erastin-induced ferritin breakdown, iron buildup, and ferroptosis. Similar effects on iron-dependent ferroptosis were seen when ATG genes (such as ATG3, ATG5, ATG7, and ATG13) were inhibited [47]. As a feedback mechanism, NCOA4 can be targeted for degradation by the ubiquitin–proteaso pathway in response to high levels of intracellular iron [48]. The occurrence of ferroptosis also has a regulatory impact on autophagy. Iron deprivation has been shown to activate protective autophagy in a variety of cell lines treated with anticancer drugs, and this induction can be abrogated by replenishing iron with ferric ammonium

citrate (FAC), suggesting that ferroptosis may modulate autophagy incidence [49].

According to Huang et al., overexpression of SIRT6 increased the formation of ROS in vitro by depleting the histone H3 lysine 56 acetylation (H3K56ac) of the negative regulator of ROS. After accumulating ROS, ER stress (endoplasmic reticulum stress) was triggered, which in turn triggered autophagy [50]. They also confirmed SIRT6-driven sensitivity to ferroptosis via NCOA4-dependent autophagy [51].

Zhang et al. found that knocking down COPZ1 would induce ferritinophagy through the NCOA1/FTH1 axis thereby triggering ferroptosis. In glioma patients, the overexpression of COPZ1 was linked to an advanced tumor grade and a poorer prognosis [52].

Mitophagy generates ROS to promote ferroptosis

ROS is the most important ingredient in the process of ferroptosis, and mitochondria are the main intracellular site of ROS production. Excessive ROS production by mitochondria can inflict damage on mitochondrial membrane proteins, DNA, and phospholipids. Mitochondrial autophagy is a process that preserves the integrity and homeostasis of mitochondrial networks by selectively breaking down aged or damaged mitochondria. Mitophagy ensures the quality of intracellular mitochondria by selectively degrading damaged mitochondria to avoid inducing excessive oxidative stress. Studies have shown that a moderate induction of mitophagy within a specific temporal window can preserve mitochondrial number and function. However, chronic and excessive mitophagy can lead to mitochondrial depletion, impacting cellular homeostasis and energy metabolism, potentially culminating in cell death [53]. Excessive mitophagy leads to the removal of large numbers of mitochondria, resulting in the release of large amounts of iron, ROS, and lipid peroxidation from the mitochondria, which activates multiple ROS-induced cell death pathways, including ferroptosis [54, 55]. It has been discovered that by releasing iron from the multitude of iron-sulfur clusters that participate in oxidative phosphorylation, mitophagy can contribute to LIP expansion [56]. Rademaker, G. et al. discovered that myoferlin targeting with the pharmaceutical drug WJ460 caused mitophagy and ROS accumulation, leading to lipid peroxidation and cell death independent of apoptosis [57]. The current study clarified a novel mechanism by which the ROS/HO1/GPX4 axis mediates the protection against cisplatin-induced renal tubular epithelial cell ferroptosis for both BNIP3-mediated and PINK1-PARK2-mediated mitophagy [58]. It was verified by Basit, F. et al. that melanoma cells undergo ferroptosis as a result of mitophagy-dependent ROS accumulation brought on by inhibition of mitochondrial complex I [59].

Lipophagy promotes lipid peroxidation for ferroptosis

Lipophagy is another form of autophagy that regulates ferroptosis. The substrate for lipophagy is a unique neutral lipid storage organelle, lipid droplets (LDs). LDs are formed between the bilayer membranes of the endoplasmic reticulum as a result of the continuous deposition of neutral lipids. When the organisation suffers from nutrient deficiency, lipids stored in LDs are hydrolysed to fatty acids in the form of triglycerides to produce energy. At the same time, starvation also induces autophagy, in which LDs bind to autophagosomes and release free fatty acids, known as lipophagy [60]. Free fatty acids (FFAs) produced by lipophagy are essential ingredients of lipid peroxidation during ferroptosis. LDs are also found to be essential regulators of ferroptosis. Increasing evidence suggests that LDs act as potential ROS scavengers and antioxidants, and play an important role in assisting cancer cells in adapting to stress conditions, which makes it a potential target for overcoming drug resistance of cancers [61–63]. A large concentration of lipid droplets suppresses ferroptosis in hepatocytes, and it is adversely regulated by LDs [64] Recent research has established that LDs production during cell cycle arrest reduces ferroptosis by sequestering excess polyunsaturated fatty acids, providing a protective barrier against lipid peroxidation [65]. Nonetheless, lipophagy, which carries intracellular lipid droplets to lysosomes for destruction and triggers lipid peroxidation-mediated ferroptosis, can regulate the amounts of lipids in cells [66].

Other types of autophagy involved in ferroptosis

There are other types of autophagy involved in regulating ferroptosis. GPX4 is one of the most important antioxidants in the process of ferroptosis. Molecular chaperone-mediated autophagy (CMA) was found to participate in ferroptosis. Molecular chaperones recognize specific amino acid sequences in the substrate, bind to lysosome-associated membrane protein type 2 A (LAMP2A) and enter the lysosome, resulting in substrate destruction. Ferroptosis activation increases LAMP2A levels and produces CMA in an HSP90-dependent way, which then mediates GPX4 degradation and promotes ferroptosis [67]. Creatine kinase B (CKB) inhibited the binding of HSC70 to GPX4 by phosphorylating GPX4, therefore preventing the breakdown of GPX4 via CMA, attenuating ferroptosis and increasing tumor growth [68]. Similarly, it has been found that GPX4 promotes ferroptosis through copper-induced macroautophagy [69].

The peroxisome is a widespread organelle in eukaryotes encapsulated by a single phospholipid membrane that contains a variety of enzymes marked by catalase. These organelles exhibit remarkable plasticity, dynamically altering their internal enzyme composition, number, and morphology in response to environmental cues.

They play a pivotal role in preserving cellular metabolism and maintaining redox balance. Peroxisomes are effective in scavenging hydrogen peroxide and other toxic substances produced during cellular metabolism, and they are the main site of β-oxidation of fatty acids. Damaged peroxisomes are degraded via both macroautophagy and microautophagy, called pexophagy. Pexophagy is essential for the regulation of lipid metabolism and the maintenance of intracellular redox homeostasis [70]. Recent findings indicate that peroxisomes contribute to the susceptibility and resistance to ferroptosis by synthesizing polyunsaturated ether phospholipids (PUFA-ePL). Therefore, it is reasonable to hypothesize that targeting pexophagy might be a new direction for inducing ferroptosis [71]. Figure 3.

Common regulatory pathways in both ferroptosis and autophagy

Even though strong links exist between ferroptosis and autophagy, the relationship between them is more than a simple positive or negative correlation, different regulatory mechanisms emerge depending on the situation. Therefore, finding the common regulatory pathways in both ferroptosis and autophagy may be a potential entry point. In the following sections we summarize the important regulators or signaling pathways that have so far been confirmed in the regulatory mechanisms of both ferroptosis and autophagy. Table 1 Some of these common regulatory pathways have been experimentally demonstrated to act synergistically on the processes of ferroptosis and autophagy in certain cell lines. Some other signaling pathways may be shown to play a role in the processes of ferroptosis and autophagy individually, but their common role has not yet been reported. However, we believe these complex crosstalks may be a potential stock for future research. Targeting such signaling pathways to regulate ferroptosis and autophagy synergistically may be explored to leverage their anti-tumor or drug-resistance reversal effects to a greater extent.

P53

P53, the most thoroughly studied protein that suppresses cancers in humans, has two effects on autophagy. On the one hand, nuclear P53 promotes autophagy by binding to the promoter area of genes encoding PR autophagic regulators, such as Bcl-2 family members, AMPK, DAPK-1, and TSC2 [72]. Furthermore, P53 activation increases autophagy by suppressing mTOR activity [73]. P53 inhibits autophagy in the cytoplasm using mechanisms that have yet to be described [74]. Depending on the type of cancer and the intracellular metabolic conditions, P53 has a double-sided ferroptosis regulatory mechanism [75]. Recent studies have revealed that nuclear P53 also induces ferroptosis by suppressing the expression of

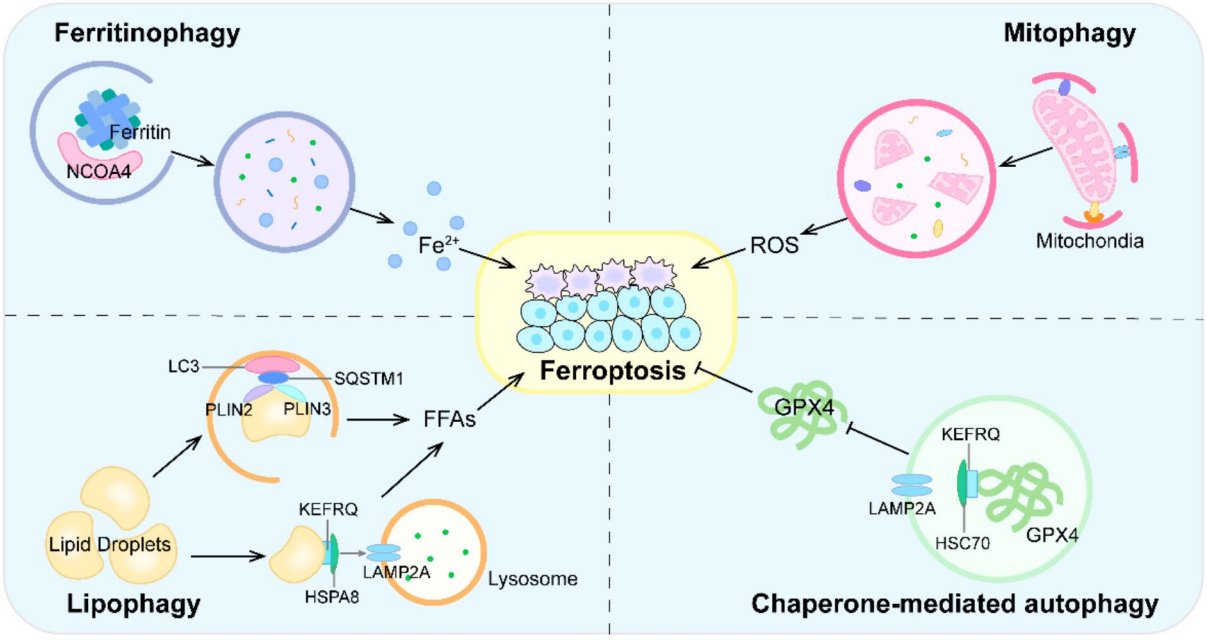

Fig. 3 Different forms of selective autophagy participate in the execution of ferroptosis. The figure shows selective autophagy involved in ferroptosis, categorized mainly based on different substrates. Ferritinophagy, mitophagy, lipophagy and chaperone-mediated GPX4 autophagy act promoting roles in ferroptosis

Table 1 Common regulators and their effects on ferroptosis and autophagy

Common regulators	Effect on ferroptosis	References	Effect on autophagy	References
P53	Promoting: **a**.P53 promotes ferroptosis by suppressing the expression of *SLC7A11*. **b**.P53 induces the expression of SAT1, which promotes the function of ALOX15 to promote ferroptosis. **c**.P53 increases GLS2 expression and promotes glutamine metabolism regulates GSH synthesis and inhibits ferroptosis.	[76–78]	Promoting: **a**.Nuclear P53 binds to the promoter area of genes encoding PR autophagic regulators. **b**.P53 activation increases autophagy by suppressing mTOR activity	[72, 73]
	Suppressing: P53 binds to DPP4 to suppress ferroptosis.	[15]	Suppressing: Cytoplasmic p53 inhibits autophagy through undefined mechanisms	[74]
Nrf2	Suppressing: Nrf2 upregulates genes like xCT, GCLC, and GCLM to prevent cells from ferroptosis.	[79, 81, 82]	Promoting: Nrf2 up-regulates transcription of autophagy-associated genes.	[42, 80, 83]
Beclin1	Promoting: Beclin 1 binds to SLC7A11 and promotes ferroptosis.	[87, 88]	Promoting: Beclin1 is a key protein in the initiation of autophagy	[40]
mTOR	Promoting/ Suppressing: MTOR modulates the expression and activity of proteins involved in iron metabolism, lipid metabolism, and GPX4.	[92]	Suppressing: Activated mTOR can inhibit autophagy.	[30, 103]
STAT3	Suppressing: STAT3 promotes the expression of GPX4, SLC7A11, and FTH1 and serves as a negative regulator of ferroptosis.	[88, 94]	Promoting/ Suppressing: Nuclear STAT3 regulates the transcription of multiple autophagy-related genes, including those in the BCL2 family, to fine-tune autophagy. Differentially localized STAT3 regulates autophagy in distinct ways.	[95]
AMPK	Promoting/ Suppressing: AMPK regulate ferroptosis through the modulation of p53, mTOR signaling pathways, and autophagy associated with ferroptosis.	[111–113]	Promoting: **a**.AMPK directly phosphorylates autophagy-associated proteins in the mTORC1, ULK1, and PIK3C3/VPS34 complexes. **b**.AMPK regulates the expression of autophagy-associated genes downstream of transcription factors (e.g., FOXO3, TFEB, and BRD4). **c**.AMPK can induce upregulation of mitophagy.	[90, 102, 104, 109, 110]
ATF4	Suppressing: **a**.ATF4 bound GPX4 and protected against GPX4 protein degradation. **b**.ATF4 upregulates the expression of SLC7A11 and prevents cells from ferroptosis.	[117, 118]	Promoting: ATF4 upregulates autophagy-related genes and promotes autophagy.	[115]

SLC7A11, the gene encoding system x_c^-, which, in a transcription-dependent manner, reduces cystine absorption and makes cells more susceptible to ferroptosis [76]. P53 induces the expression of spermidine/spermine N1-acetyltransferase 1(SAT1), and activation of SAT1 promotes the expression of arachidonate 15-lipoxygenase (ALOX15), thereby promoting the process of lipid peroxidation and thus ferroptosis [77]. Phosphate-activated mitochondrial glutaminase (GLS2) is another P53 target gene that regulates GSH synthesis and inhibits ferroptosis by promoting glutamine metabolism and reducing intracellular ROS level [78]. On the contrary, P53 binds to dipeptidyl peptidase 4 (DPP4), a regulator of lipid metabolism and ferroptosis, to suppress ferroptosis through a transcription-independent mechanism [15].

Nrf2

Nuclear factor-erythroid 2-related factor 2 (Nrf2) is an essential transcription factor cellular in regulating cellular redox balance. Under homeostatic conditions, Nrf2 binds predominantly to Kelch-like ECH-associated protein 1 (KEAP1), prevents its activation, and is constantly degraded by the proteasome by ubiquitination, keeping Nrf2 at a basally low level. Upon cellular exposure to oxidative stress induced by electrophilic compounds or reactive oxygen species (ROS), Nrf2 dissociates from KEAP1, becomes activated, and translocates to the nucleus where it binds to the antioxidant response element (ARE). This binding event initiates the transcription of proteins and enzymes critical for cellular defense mechanisms. In ferroptosis, Nrf2 acts as a protector to prevent cells from ferroptosis [79]. Nrf2 can positively promote the synthesis of GSH and ferritin by upregulating relative genes like xCT, GCLC, and GCLM [80, 81]. Nrf2 can also

upregulate the expression of FTH1 and FTL and thus, protecting cells against ferroptosis by conditioning iron homeostasis [82].

As for autophagy, on the one hand, regulation of autophagy by Nrf2 is mediated by p62/SQSTM1, which binds ubiquitin and LC3 and is a selective substrate for autophagy [43]. P62 competitively binds to keap1 to form a complex that chelates Keap1 into the autophagosome, which prevents Keap1-mediated degradation of Nrf2, leading to activation of the Nrf2 pathway. Nrf2 up-regulates transcription of autophagy-associated genes, such as *Atg5*, *p62*, and others. When autophagy is dysfunctional, it causes intracellular p62 accumulation, leading to the activation of the Nrf2 pathway and thus compensating for the lack of autophagy [83, 84]. On the other hand, Nrf2-related axis can also antagonize autophagy. For example, Astaxanthin was found to enhance autophagy by activation of the Nrf2/HO-1 pathway [85]. El-Horany et al. found that empagliflozin has a promoting effect on autophagy via modulating the Nrf2/HO-1 signaling pathway and then protecting against BLM-induced pulmonary fibrosis in rats [86].

Beclin1

As we have mentioned before, beclin1 is a key protein in the initiation of autophagy. Recent studies revealed its critical role in ferroptosis. It is found that beclin 1 binds to SLC7A11 during ferroptosis and blocks the activity of system x_c^-. Levels of the Beclin1- SLC7A11 complex determine the sensitivity and resistance of cancer cells to ferroptosis [87]. MCL1 assumes an insulating role. Sorafenib downregulates MCL1, increases the level of available Beclin 1, and results in more binding between Beclin 1 and SLC7A11, which inhibits system x_c^-, leading to the accumulation of lipid ROS, and triggers ferroptosis in hepatocellular carcinoma cells [88]. Ubiquitin-specific protease 11 (USP11) may be another significant factor in the functioning of beclin1. USP11 is discovered to stabilize beclin 1, increase the breakdown of autophagic ferritin, and eventually lead to iron-dependent ferroptosis [89]. Given that the role of beclin1 in autophagy and ferroptosis involves the most critical parts of each of the two mechanisms, we believe that beclin1 may be a promising target for research. Targeting beclin1 may be a potential breakthrough in cancer therapy.

mTOR

MTOR is a key regulatory molecule in the process of autophagy. Activated mTOR can inhibit autophagy, while negative regulation of mTOR promotes it. When mTOR activity is elevated, it suppresses the initiation and progression of autophagy. MTORC1, in particular, inhibits the formation of autophagosomes by phosphorylating proteins such as ULK1 and ATG13, thereby suppressing autophagy [90]. Additionally, mTORC1 acts as a nutrient sensor that is activated in response to abundant nutrient conditions and sufficient growth factors, which in turn inhibits autophagy.

The occurrence of ferroptosis is also influenced by the mTOR signaling pathway. MTORC1 regulates ferroptosis by modulating the expression and activity of proteins involved in iron metabolism, lipid metabolism, and GPX4 [16, 91, 92]. The activity of mTORC1 is also related to the sensitivity to ferroptosis inducers. Some studies have shown that the inhibition of mTORC1 can increase the sensitivity of cancer cells to ferroptosis-inducing agents [93].

STAT3

A crucial oncogene, STAT3 is a signal transducer and activator of transcription 3 that performs both transcriptional activation and signal transduction. Angiogenesis, metastasis, immunosuppression, and cell proliferation are all significantly impacted by STAT3 hyperactivation, which is a key factor in the development of most human malignancies. Understanding the role of STAT3 signaling in the regulation of ferroptosis and autophagy may provide insight into cancer therapy. STAT3 plays important roles in the pathway of the regulation of both ferroptosis and autophagy, which makes it a potential target molecule. Ouyang, S. et al. demonstrated that as one of the promoters of the FNR-associated genes (GPX4, SLC7A11, and FTH1), STAT3 binds to consensus DNA response elements and controls their expression, serving as a major negative regulator of ferroptosis in gastric cancer [94]. Furthermore, recent results suggest that autophagy is impacted differently by the subcellular localization patterns of STAT3. For instance, nuclear STAT3 regulates the transcription of multiple autophagy-related genes, including those in the BCL2 family, to fine-tune autophagy [40, 95]. Furthermore, the translocation of STAT3 into the mitochondria prevents oxidative stress-induced autophagy and may effectively protect mitochondria against mitophagy-induced degradation [96–98].

AMPK

The Adenosine monophosphate (AMP) activated protein kinase (AMPK) signaling pathway is a key player in regulating cellular energy homeostasis. The AMPK signaling pathway has been identified as a potential target for cancer therapy, and it plays a complex and multidimensional role in the metabolism and growth of tumor cells, as well as in the immune regulation of the tumor microenvironment [99–101]. Upon activation, AMPK can phosphorylate key proteins of multiple signaling pathways mentioned above to exert regulatory effects. The AMPK signaling pathway plays a crucial role in autophagy. First, AMPK acts as a sensor of cellular energy status and is

activated by detecting an increase in cytoplasmic AMP because of energy withdrawal to initiate the autophagy process [102]. AMPK promotes autophagy directly by phosphorylating autophagy-associated proteins in the mTORC1, ULK1, and PIK3C3/VPS34 complexes [90, 103, 104] or indirectly by regulating the expression of autophagy-associated genes downstream of transcription factors (e.g., FOXO3, TFEB, and BRD4) [105–107]. AMPK also induces fragmentation of damaged mitochondria in the network and promotes translocation of the autophagy machinery to damaged mitochondria, thereby upregulating mitophagy [108–110].In the previous sections, we have discussed the specific pathways through which p53 regulates ferroptosis. AMPK, on the other hand, activates p53 through phosphorylation, thereby acting as an upstream molecule in the signaling cascade to modulate ferroptosis [111]. The regulation of ferroptosis by AMPK is achieved through the modulation of p53, mTOR signaling pathways, and autophagy associated with ferroptosis. Several studies have confirmed the negative correlation between AMPK and mTOR [92]. It was found that AMPK could be activated and thus inhibit mTORC1 when cells were at lower energy levels. The activation of the AMPK signaling pathway could induce ferroptosis by down-regulating SLC7A11 expression through inhibition of mTOR/p70S6k signaling pathway in colorectal cancer [112].

Melanoma-associated antigen A6 (MAGEA6) with oncogenic activity is highly expressed in triple-negative breast cancer (TNBC) cell lines and tumor tissues and is involved in the acquisition of drug resistance. Silencing MAGEA6 was found to enhance the chemosensitivity of TNBC to doxorubicin (DOX) in vitro and in vivo. Mechanistically, MAGEA6 depletion sensitizes TNBC to DOX by regulating autophagy, and knockdown of MAGEA6 decreases the ubiquitination of AMPKα1, which increases the levels of AMPKα1 and p-AMPKα, activates AMPK signaling, and raises the level of LC3II/I, which in turn promotes autophagy in TNBC. In addition, silencing of MAGEA6 resulted in ferroptosis mediated through the MAGEA6/AMPK/SLC7A11 pathway [113].

Other

There are also other signal pathways in the intersection of ferroptosis and autophagy. We have found more genes and signaling molecules play an important role not only in ferroptosis but also in autophagy. *Activating transcription factor 4 (ATF4)* is a pivotal gene in the regulation of endoplasmic reticulum stress [114]. It is involved in the transcription of genes for the antioxidative response, autophagy, and amino acid biosynthesis and translocation. Liu et al. found that *ATF4* was expressed significantly in ovarian cancer tissues and associated with poor prognosis [115]. Anisomycin can downregulate the expression of AT*F4* to inhibit autophagy signal transduction and glutathione metabolism pathways, leading to the inhibition of ovarian cancer stem cell activity [116]. Activating ATF4 can induce the heatshock 70-kDa protein 5 (HSPA5), which would bound GPX4 and protected against GPX4 protein degradation and subsequent lipid peroxidation in human pancreatic ductal adenocarcinoma cells [117]. ATF can also upregulate the expression of SLC7A11 and reverse the susceptibility to ferroptosis, thereby suppressing hepatocarcinogenesis [118].

Through the autophagic breakdown of intracellular material, Paraoxonase 1 (PON1) increased the amount of Glu. This, in turn, activated system x_c^-, which transferred Cys into intracellular space. Furthermore, by affecting TP53-SLC7A11, PON1 causes cells to become resistant to ferroptosis [119]. Since these regulatory elements perform distinct roles depending on cell types and environments, finding their co-moderating role toward both ferroptosis and autophagy may be rare to discover. However, these overlapping parts are still potential research targets. With the discovery of these media, we can see greater potential to find a breakthrough in cancer therapy with the help of ferroptosis as well as autophagy.

The crosstalk between ferroptosis and autophagy in cancer treatment

Triggering ferroptosis via regulating autophagy

Given the involvement of various autophagy types in ferroptosis, modulating autophagy to regulate ferroptosis may be an approach for cancer treatment. While existing studies have primarily focused on the role of autophagy-dependent ferroptosis in tumor progression, the specific types of autophagy involved remain unclear. Further studies to identify new target molecules and a clearer regulatory relationship between autophagy and ferroptosis in pathological pathways may provide new insights into cancer progression and therapeutic prospects.

Annexin A10 (ANXA10, A10) belongs to the calcium-dependent phospholipid-binding protein family. *BRAF* mutant colorectal cancer (CRC) cells overexpressed ANXA10, which was linked to a poor prognosis. By blocking autophagy-mediated TFRC degradation, ANXA10 knockdown causes cellular ferroptosis and inhibits the growth of CRC [120]. Ginsenoside Rh4 inhibited CRC cell proliferation by activating autophagy to induce ferroptosis [121]. Polyphyllin VII (PPVII), a pennogenin isolated from the rhizomes of Paris polyphylla, was detected to suppress the growth of gastric cancer by inducing autophagy-mediated ferroptosis [122]. Sulfasalazine (SASP), which has been approved for the clinical treatment of chronic inflammatory diseases such as ulcerative colitis, has been found to have anti-cancer activity as well. SASP promotes ferroptosis in triple-negative breast cancer cells by inhibiting system

x_c^-, and autophagy is a necessary segment in this process. Tamoxifen could play as an effective autophagy regulator in SASP-induced ferroptosis [123].

Arachidonate 5-lipoxygenase (ALOX5) is downregulated in melanoma, and this downregulation is an independent prognostic factor that positively correlates with patient prognosis. ALOX5 overexpression may stimulate the AMPK/mTOR pathway and suppress GPX4 expression, which would encourage autophagy-dependent ferroptosis in melanoma [124].

Regulation of ferroptosis through autophagy may also provide a possible breakthrough in overcoming drug resistance. Treatment with lysosomal inhibitors reduces the burst of ROS associated with ferroptosis and partially blocks intracellular iron transport by reducing autophagic degradation of ferritin. Temozolomide (TMZ), used for the treatment of glioblastoma, appears to induce autophagy and partially inhibit cancer cell proliferation. Combination with an autophagy inhibitor was able to sensitize glioma cells to TMZ in advanced stages of tumor growth [125]. 4-octyl itaconate was found to induce ferroptosis by targeting NCOA4-mediated ferritin autophagy thereby killing multi-drug resistance human retinoblastoma cells [126]. Bhatt, V. et al. found that the combination of the autophagy inhibitor hydroxychloroquine (HCQ) and the MEK inhibitor trametinib has synergistic antiproliferative activity against $Kras^{G12D/+;}Lkb1^{-/-}$ (KL) lung cancer cells. KL lung cancer cells can become more susceptible to the MEK drug Trametinib by targeting autophagy through HCQ-induced lysosomal function inhibition. HCQ in combination with Trametinib impairs glucose-mediated metabolism, leading to mitochondrial dysfunction, resulting in destructive oxidative stress that triggers ferroptosis [127]. This provides a potential therapeutic strategy for resistant KL tumors.

Nanotechnology, a powerful catalyst in modern medicine, has shown its potential in regulating ferroptosis. Ultrasmall iron oxide nanoparticles (USIONPs) have shown their regulatory capacity to ferroptosis. In glioblastoma cells, USIONPs can upregulate autophagy via Beclin1/ATG5-related pathways and consequently trigger ferroptosis .

It has been shown that Anomanolide C (AC), a naturally occurring withanolide extracted from Tubocapsicum anomalum, inhibits the development and spread of triple-negative breast cancer via ubiquitinating GPX4 and promoting autophagy-dependent ferroptosis [128].

Upregulation of the tumor suppressor protein Par-4 promotes ferroptosis via NCOA4-mediated ferritinophagy. In a mouse xenograft model, Par-4 knockdown effectively blocked ferroptosis-mediated tumor suppression, suggesting the potential use of Par-4 for cancer therapy [129].

Targeting lipophagy to regulate ferroptosis is also a promising idea. Heme-binding protein progesterone receptor membrane component 1 (PGRMC1) is highly expressed in a variety of resistant cancer cell types. Available studies suggest that PGRMC1 promotes autophagy by directly binding to LC3, a key component of the autophagy machinery, and participates in lipophagy by increasing tubulin tyrosination and interaction with mitochondria. You, J. H.et al. found that PGRMC1 promotes ferroptosis in paclitaxel-tolerant persister cancer cells by xCT inhibition via lipophagy and tubulin detyrosination [130]. One primary steroidal saponin that comes from Anemarrhena asphodeloides Bge is called Timosaponin AIII (TA-III), and it may have anticancer properties. Research has indicated that TA-III stimulates ferroptosis by inducing lipophagy in CRC cells through the Rab7 gene [131].

Novel inducers for synergistic cancer therapy

Some new inducers can synergistically regulate both ferroptosis and autophagy in cancer. A new compound 2,3,5,40-T etrahydroxystilbene (TG1) has shown its anti-cancer ability in colorectal cancer. TG1 treatment increased the level of autophagy in cells, its cytotoxicity can be abrogated by ferroptosis inhibitor, suggesting that ferroptosis played a crucial role in TG1-induced cytotoxicity [132]. In CRC cell lines with intrinsic cetuximab resistance, 3-Bromopyruvate (3-BP), also referred to as hexokinase II inhibitor II, has synergistically caused an antiproliferative impact by activating autophagy-dependent ferroptosis [133]. Compound 10p, a novel urea derivative synthesized by the researchers, also showed potent antitumor activity against HT-29 cells. Compounds10p combines the induction of both ferroptosis and autophagy, making it a potential candidate for the treatment of CRC [134]. In prostate cancer cells, 6-gingerol inhibits cell survival, migration, and invasion by activating protective autophagy, autophagic cell death, and ferroptosis-mediated cell death [135].

It was found that Ailanthone (AIL), a monomer extracted from the traditional Chinese medicine Ailanthus, could perform antitumor effects in non-small cell lung cancer Lewis cells by inducing autophagy and ferroptosis [136].

Nanomedicine also shows its potential in cancer treatment by synergistic inducing ferroptosis and autophagy. A novel carrier-free nano-drug called nanoparticle ferritin-bound erastin and rapamycin (NFER) showed an improved control of tumor recurrence in the tumor resection model. The application of nanotechnology combined the effection of ferroptosis inducer and autophagy inducer. Ferroptosis was further strengthened by the rapamycin-induced

autophagy process in NFER [137]. And also in the nanomedicine field, Zhang et al. created an incredibly tiny polyvinylpyrrolidone (PVP)–Fe–Cu–Ni–S (PVP-NP) nano-agent which can synergistically trigger ferroptosis and autophagy in photothermal cancer therapy [138].

Conclusion and perspective

Altogether, as two major forms of regulated cell death, both ferroptosis and autophagy play crucial roles in cancer development. Ferroptosis and autophagy, as two separate forms of cell death, develop a looping relationship through oxidative stress. The accumulation of ROS, stemming from redox imbalances, serves as a trigger for both ferroptosis and autophagy. Autophagy, on the one hand, can degrade damaged organelles and peroxidation products and act as an essential protective mechanism to maintain redox balance. On the other hand, autophagy also generates ROS, which may induce oxidative stress. Important molecules involved in ferroptosis, including ferritin, lipids and lipid peroxides, can be substrates for autophagy, these with these natural mediators establishing an inextricable link between the two processes.

On the other hand, ferroptosis and autophagy share common upstream regulatory pathways. These key genes or signalling molecules can simultaneously regulate the processes of ferroptosis and autophagy. It opens up new sights for cancer treatment by exploring the relationship between ferroptosis and autophagy in specific situations. Targeting the synergistic or antagonistic relationship between ferroptosis and autophagy in different tumor types and tumor stages may provide breakthroughs in the treatment of tumors.

Acknowledgements
Not applicable.

Author contributions
ZY has made substantial contributions to the conception of the work. LX was responsible for the original manuscript and figure and was a major contributor to the manuscript. TH substantively revised it. ZY reviewed and proofread the manuscript. LY polished the manuscript. All authors read and approved the final manuscript. WS revised it. LX revised it.

Funding
Not applicable.

Data availability
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 4 October 2024 / Accepted: 24 December 2024
Published online: 06 January 2025

References

1. Dixon SJ, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. Cell. 2012;149:1060–72. https://doi.org/10.1016/j.cell.2012.03.042.
2. Chen X, Kang R, Kroemer G, Tang D. Broadening horizons: the role of ferroptosis in cancer. Nat Rev Clin Oncol. 2021;18:280–96. https://doi.org/10.1038/s41571-020-00462-0.
3. Lei G, Zhuang L, Gan B. The roles of ferroptosis in cancer: tumor suppression, tumor microenvironment, and therapeutic interventions. Cancer Cell. 2024;42:513–34. https://doi.org/10.1016/j.ccell.2024.03.011.
4. Boya P, Reggiori F, Codogno P. Emerging regulation and functions of autophagy. Nat Cell Biol. 2013;15:713–20. https://doi.org/10.1038/ncb2788.
5. Gammella E, Buratti P, Cairo G, Recalcati S. The transferrin receptor: the cellular iron gate. Metallomics: Integr Biometal Sci. 2017;9:1367–75. https://doi.org/10.1039/c7mt00143f.
6. Lv H, Shang P. The significance, trafficking and determination of labile iron in cytosol, mitochondria and lysosomes. Metallomics: Integr Biometal Sci. 2018;10:899–916. https://doi.org/10.1039/c8mt00048d.
7. Winterbourn CC. Toxicity of iron and hydrogen peroxide: the Fenton reaction. Toxicol Lett. 1995;82–83:969–74. https://doi.org/10.1016/0378-4274(95)03532-x.
8. Forcina GC, Dixon SJ. GPX4 at the crossroads of lipid homeostasis and Ferroptosis. Proteomics. 2019;19(e1800311). https://doi.org/10.1002/pmic.201800311.
9. Yang WS et al., Regulation of ferroptotic cancer cell death by GPX4. Cell 2014;156:317–331. https://doi.org/10.1016/j.cell.2013.12.010.
10. Parker JL et al., Molecular basis for redox control by the human cystine/glutamate antiporter system xc. Nature communications 2021;12:7147. https://doi.org/10.1038/s41467-021-27414-1.
11. Doll S, et al. FSP1 is a glutathione-independent ferroptosis suppressor. Nature. 2019;575:693–8. https://doi.org/10.1038/s41586-019-1707-0.
12. Kraft VAN et al., GTP Cyclohydrolase 1/Tetrahydrobiopterin Counteract Ferroptosis through Lipid Remodeling. ACS Cent Sci 2020;6:41–53. https://doi.org/10.1021/acscentsci.9b01063.
13. Hasegawa M et al., Functional interactions of the cystine/glutamate antiporter, CD44v and MUC1-C oncoprotein in triple-negative breast cancer cells. Oncotarget 2016;7:11756–11769. https://doi.org/10.18632/oncotarget.7598.
14. Jiang L, et al. Ferroptosis as a p53-mediated activity during tumour suppression. Nature. 2015;520:57–62. https://doi.org/10.1038/nature14344.
15. Xie Y, et al. The tumor suppressor p53 limits ferroptosis by blocking DPP4 activity. Cell Rep. 2017;20:1692–704. https://doi.org/10.1016/j.celrep.2017.07.055.
16. Dixon SJ, et al. Pharmacological inhibition of cystine-glutamate exchange induces endoplasmic reticulum stress and ferroptosis. Elife. 2014;3:e02523. https://doi.org/10.7554/eLife.02523.
17. Li Q et al., Glycyrrhetinic acid nanoparticles combined with ferrotherapy for improved cancer immunotherapy. Acta biomaterialia 2022;144:109–120. https://doi.org/10.1016/j.actbio.2022.03.030.
18. Glorieux C, Liu S, Trachootham D, Huang P. Targeting ROS in cancer: rationale and strategies. Nat Rev Drug Discov. 2024;23:583–606. https://doi.org/10.1038/s41573-024-00979-4.
19. Cosialls E, et al. Ferroptosis: Cancer Stem cells rely on Iron until to die for it. Cells. 2021;10:103390cells10112981.
20. Dai E, et al. Autophagy-dependent ferroptosis drives tumor-associated macrophage polarization via release and uptake of oncogenic KRAS protein. Autophagy. 2020;16:2069–83. https://doi.org/10.1080/15548627.2020.1714209.
21. Xu H, Ye D, Ren M, Zhang H, Bi F. Ferroptosis in the tumor microenvironment: perspectives for immunotherapy. Trends Mol Med 2021;27:856–867. https://doi.org/10.1016/j.molmed.2021.06.014.
22. Wiernicki B, et al. Cancer cells dying from ferroptosis impede dendritic cell-mediated anti-tumor immunity. Nat Commun. 2022;13(3676). https://doi.org/10.1038/s41467-022-31218-2.

23. Ma X, et al. CD36-mediated ferroptosis dampens intratumoral CD8(+) T cell effector function and impairs their antitumor ability. Cell Metab. 2021;33:1001–12. https://doi.org/10.1016/j.cmet.2021.02.015. e1005.
24. Feng Y, He D, Yao Z, Klionsky DJ. The machinery of macroautophagy. Cell Res. 2014;24:24–41. https://doi.org/10.1038/cr.2013.168.
25. Mizushima N, Levine B, Cuervo AM, Klionsky DJ. Autophagy fights disease through cellular self-digestion. Nature. 2008;451:1069–75. https://doi.org/10.1038/nature06639.
26. Mijaljica D, Prescott M, Devenish RJ. Microautophagy in mammalian cells: revisiting a 40-year-old conundrum. Autophagy 2011;7:673–682. https://doi.org/10.4161/auto.7.7.14733.
27. Shpilka T, Elazar Z. Shedding light on mammalian microautophagy. Dev Cell. 2011;20:1–2. https://doi.org/10.1016/j.devcel.2010.12.010.
28. Kaushik S, Cuervo AM. Chaperone-mediated autophagy: a unique way to enter the lysosome world. Trends Cell Biol. 2012;22:407–17. https://doi.org/10.1016/j.tcb.2012.05.006.
29. Egan DF, et al. Phosphorylation of ULK1 (hATG1) by AMP-activated protein kinase connects energy sensing to mitophagy. Sci (New York N Y). 2011;331:456–61. https://doi.org/10.1126/science.1196371.
30. Rangwala R et al., Combined MTOR and autophagy inhibition: phase I trial of hydroxychloroquine and temsirolimus in patients with advanced solid tumors and melanoma. Autophagy 2014;10:1391–1402. https://doi.org/10.4161/auto.29119.
31. Walczak M, Martens S. Dissecting the role of the Atg12-Atg5-Atg16 complex during autophagosome formation. Autophagy. 2013;9:424–5. https://doi.org/10.4161/auto.22931.
32. Nishimura T, Tooze SA. Emerging roles of ATG proteins and membrane lipids in autophagosome formation. Cell Discovery. 2020;6(32). https://doi.org/10.1038/s41421-020-0161-3.
33. Mizushima N, et al. A protein conjugation system essential for autophagy. Nature. 1998;395:395–8. https://doi.org/10.1038/26506.
34. Kabeya Y et al., LC3, a mammalian homologue of yeast Apg8p, is localized in autophagosome membranes after processing. Embo j 2000;19:5720–5728. https://doi.org/10.1093/emboj/19.21.5720.
35. Xie Z, Klionsky DJ. Autophagosome formation: core machinery and adaptations. Nat Cell Biol. 2007;9:1102–9. https://doi.org/10.1038/ncb1007-1102.
36. Kim KH, Lee MS. Autophagy–a key player in cellular and body metabolism. Nat Rev Endocrinol. 2014;10:322–37. https://doi.org/10.1038/nrendo.2014.35.
37. Bergers G, Fendt SM. The metabolism of cancer cells during metastasis. Nat Rev Cancer. 2021;21:162–80. https://doi.org/10.1038/s41568-020-00320-2.
38. Warburg O. On the origin of cancer cells. Sci (New York N Y). 1956;123:309–14. https://doi.org/10.1126/science.123.3191.309.
39. Abdi S, Ali A. Role of ROS modified human DNA in the pathogenesis and etiology of cancer. Cancer Lett. 1999;142:1–9. https://doi.org/10.1016/s0304-3835(99)00112-3.
40. Liang XH et al., Induction of autophagy and inhibition of tumorigenesis by beclin 1. Nature 1999;402:672–676. https://doi.org/10.1038/45257.
41. Barthet V et al. J A Autophagy suppresses the formation of hepatocyte-derived cancer-initiating ductular progenitor cells in the liver. Sci Adv 7. 2021. https://doi.org/10.1126/sciadv.abf9141.
42. Komatsu M, et al. The selective autophagy substrate p62 activates the stress responsive transcription factor Nrf2 through inactivation of Keap1. Nat Cell Biol. 2010;12:213–23. https://doi.org/10.1038/ncb2021.
43. Bjørkøy G, et al. p62/SQSTM1 forms protein aggregates degraded by autophagy and has a protective effect on huntingtin-induced cell death. J Cell Biol. 2005;171:603–14. https://doi.org/10.1083/jcb.200507002.
44. Strohecker AM et al., Autophagy sustains mitochondrial glutamine metabolism and growth of BrafV600E-driven lung tumors. Cancer discovery 2013;3:1272–1285. https://doi.org/10.1158/2159-8290.Cd-13-0397.
45. Mancias JD, Wang X, Gygi SP, Harper JW, Kimmelman AC. Quantitative proteomics identifies NCOA4 as the cargo receptor mediating ferritinophagy. Nature 2014;509:105–109. https://doi.org/10.1038/nature13148.
46. Hou W et al., Autophagy promotes ferroptosis by degradation of ferritin. Autophagy 2016;12:1425–1428. https://doi.org/10.1080/15548627.2016.1187366
47. Xie Y et al., Ferroptosis: process and function. Cell death and differentiation 2016;23:369–379. https://doi.org/10.1038/cdd.2015.158.
48. Mancias JD et al. Ferritinophagy via NCOA4 is required for erythropoiesis and is regulated by iron dependent HERC2-mediated proteolysis. Elife. 2015;4. https://doi.org/10.7554/eLife.10308.
49. Bauckman KA, Haller E, Flores I, Nanjundan M. Iron modulates cell survival in a Ras- and MAPK-dependent manner in ovarian cells. Cell death & disease 2013;4:e592. https://doi.org/10.1038/cddis.2013.87.
50. Yang Z et al., The SIRT6-Autophagy-Warburg Effect Axis in Papillary Thyroid Cancer. Frontiers in oncology 2020;10:1265. https://doi.org/10.3389/fonc.2020.01265.
51. Yang Z, et al. SIRT6 drives sensitivity to ferroptosis in anaplastic thyroid cancer through NCOA4-dependent autophagy. Am J cancer Res. 2023;13:464–74.
52. Zhang Y et al., Loss of COPZ1 induces NCOA4 mediated autophagy and ferroptosis in glioblastoma cell lines. Oncogene 2021;40:1425–1439. https://doi.org/10.1038/s41388-020-01622-3.
53. Lee S et al., Autophagy mediates an amplification loop during ferroptosis. Cell death & disease 2023;14:464. https://doi.org/10.1038/s41419-023-05978-8.
54. Kuang F, Liu J, Tang D, Kang R. Oxidative Damage and Antioxidant Defense in Ferroptosis. Frontiers in cell and developmental biology 2020;8:586578. https://doi.org/10.3389/fcell.2020.586578.
55. Li S et al. The Role of Mitophagy in Regulating Cell Death. Oxidative medicine and cellular longevity 2021;6617256. https://doi.org/10.1155/2021/6617256.
56. Allen GF, Toth R, James J, Ganley IG. Loss of iron triggers PINK1/Parkin-independent mitophagy. EMBO reports 2013;14:1127–1135. https://doi.org/10.1038/embor.2013.168.
57. Rademaker G et al., Myoferlin targeting triggers mitophagy and primes ferroptosis in pancreatic cancer cells. Redox biology 2022;53:102324. https://doi.org/10.1016/j.redox.2022.102324
58. Lin Q et al., Mitophagy alleviates cisplatin-induced renal tubular epithelial cell ferroptosis through ROS/HO-1/GPX4 axis. International journal of biological sciences 2023;19:1192–1210. https://doi.org/10.7150/ijbs.80775.
59. Basit F et al., Mitochondrial complex I inhibition triggers a mitophagy-dependent ROS increase leading to necroptosis and ferroptosis in melanoma cells. Cell death & disease 2017;8:e2716. https://doi.org/10.1038/cddis.2017.133.
60. Zhang S et al., The regulation, function, and role of lipophagy, a form of selective autophagy, in metabolic disorders. Cell death & disease 2022;13:132. https://doi.org/10.1038/s41419-022-04593-3
61. Sun Y, Xue Z, Huang T, Che X, Wu G. Lipid metabolism in ferroptosis and ferroptosis-based cancer therapy. Frontiers in oncology 2022;12:941618. https://doi.org/10.3389/fonc.2022.941618.
62. Bailey AP et al., Antioxidant Role for Lipid Droplets in a Stem Cell Niche of Drosophila. Cell 2015;163:340–353. https://doi.org/10.1016/j.cell.2015.09.020.
63. Koizume S, Miyagi Y, Lipid Droplets. A Key Cellular Organelle Associated with Cancer Cell Survival under Normoxia and Hypoxia. International journal of molecular sciences 2016;17. https://doi.org/10.3390/ijms17091430.
64. Schott MB et al., Lipid droplet size directs lipolysis and lipophagy catabolism in hepatocytes. J Cell Biol 2019;218:3320–3335. https://doi.org/10.1083/jcb.201803153
65. Lee H et al., Cell cycle arrest induces lipid droplet formation and confers ferroptosis resistance. Nature communications 2024;15:79. https://doi.org/10.1038/s41467-023-44412-7.
66. Bai Y et al., Lipid storage and lipophagy regulates ferroptosis. Biochemical and biophysical research communications 2019;508:997–1003. https://doi.org/10.1016/j.bbrc.2018.12.039
67. Wu Z et al., Chaperone-mediated autophagy is involved in the execution of ferroptosis. Proceedings of the National Academy of Sciences of the United States of America 2019;116:2996–3005. https://doi.org/10.1073/pnas.1819728116
68. Wu K et al., Creatine kinase B suppresses ferroptosis by phosphorylating GPX4 through a moonlighting function. Nat Cell Biol 2023;25:714–725 (2023). https://doi.org/10.1038/s41556-023-01133-9
69. Xue Q et al., Copper-dependent autophagic degradation of GPX4 drives ferroptosis. Autophagy 2023;19:1982–1996. https://doi.org/10.1080/15548627.2023.2165323.
70. Li J, Wang W. Mechanisms and Functions of Pexophagy in Mammalian Cells. Cells 2021;10. https://doi.org/10.3390/cells10051094.
71. Zou Y et al., Plasticity of ether lipids promotes ferroptosis susceptibility and evasion. Nature 2020;585:603–608 (2020). https://doi.org/10.1038/s41586-020-2732-8.
72. Maiuri MC et al., Autophagy regulation by p53. Current opinion in cell biology 2010;22:181–185 (2010). 10.1016/j.ceb.2009.12.001.
73. Feng Z, Zhang H, Levine AJ, Jin S. The coordinate regulation of the p53 and mTOR pathways in cells. Proceedings of the National Academy of Sciences of the United States of America 2005;102:8204–8209 (2005). https://doi.org/10.1073/pnas.0502857102.

74. Tasdemir E et al., Regulation of autophagy by cytoplasmic p53. Nat Cell Biol 2008;10:676–687. https://doi.org/10.1038/ncb1730.
75. Ji H et al., A double-edged sword in tumor ferroptosis. Pharmacological research 2022;177:106013. https://doi.org/10.1016/j.phrs.2021.106013.
76. Gnanapradeepan K et al., The p53 Tumor Suppressor in the Control of Metabolism and Ferroptosis. Frontiers in endocrinology 2018;9:124. https://doi.org/10.3389/fendo.2018.00124.
77. Ou Y, Wang SJ, Li D, Chu B, Gu W. Activation of SAT1 engages polyamine metabolism with p53-mediated ferroptotic responses. Proceedings of the National Academy of Sciences of the United States of America 2016;113:E6806-e6812. https://doi.org/10.1073/pnas.1607152113.
78. Suzuki S et al., Phosphate-activated glutaminase (GLS2), a p53-inducible regulator of glutamine metabolism and reactive oxygen species. Proceedings of the National Academy of Sciences of the United States of America 2010;107:7461–7466. https://doi.org/10.1073/pnas.1002459107.
79. Kobayashi A et al., Oxidative and electrophilic stresses activate Nrf2 through inhibition of ubiquitination activity of Keap1. Molecular and cellular biology 2006;26:221–229. https://doi.org/10.1128/mcb.26.1.221-229.2006.
80. Ishii T et al., Transcription factor Nrf2 coordinately regulates a group of oxidative stress-inducible genes in macrophages. The Journal of biological chemistry 2000;275:16023–16029. https://doi.org/10.1074/jbc.275.21.16023
81. Chang LC et al., Heme oxygenase-1 mediates BAY 11-7085 induced ferroptosis. Cancer Lett 2018;416:124–137. https://doi.org/10.1016/j.canlet.2017.12.025.
82. Fan Z et al., Nrf2-Keap1 pathway promotes cell proliferation and diminishes ferroptosis. Oncogenesis 2017;6:e371. https://doi.org/10.1038/oncsis.2017.65.
83. Jiang T et al., p62 links autophagy and Nrf2 signaling. Free Radic Biol Med 2015;88:199–204. https://doi.org/10.1016/j.freeradbiomed.2015.06.014
84. Bjørkøy G, Lamark T, Johansen T. p62/SQSTM1: a missing link between protein aggregates and the autophagy machinery. Autophagy 2006;2:138–139. https://doi.org/10.4161/auto.2.2.2405.
85. Cai X et al., Astaxanthin Activated the Nrf2/HO-1 Pathway to Enhance Autophagy and Inhibit Ferroptosis, Ameliorating Acetaminophen-Induced Liver Injury. ACS applied materials & interfaces 2022;14:42887–42903. https://doi.org/10.1021/acsami.2c10506.
86. El-Horany HE et al. Empagliflozin Ameliorates Bleomycin-Induced Pulmonary Fibrosis in Rats by Modulating Sesn2/AMPK/Nrf2 Signaling and Targeting Ferroptosis and Autophagy. International journal of molecular sciences 2023;24. https://doi.org/10.3390/ijms24119481.
87. Kang R, Zhu S, Zeh HJ, Klionsky DJ, Tang D. BECN1 is a new driver of ferroptosis. Autophagy 2018;14:2173–2175. https://doi.org/10.1080/15548627.2018.1513758.
88. Huang CY, Chen LJ, Chen G, Chao TI, Wang CY. SHP-1/STAT3-Signaling-Axis-Regulated Coupling between BECN1 and SLC7A11 Contributes to Sorafenib-Induced Ferroptosis in Hepatocellular Carcinoma. International journal of molecular sciences 2022;23. https://doi.org/10.3390/ijms231911092.
89. Rong Y et al., USP11 regulates autophagy-dependent ferroptosis after spinal cord ischemia-reperfusion injury by deubiquitinating Beclin 1. Cell death and differentiation 2022;29:1164–1175. https://doi.org/10.1038/s41418-021-00907-8.
90. Kim J et al., Differential regulation of distinct Vps34 complexes by AMPK in nutrient stress and autophagy. Cell 152, 290–303 (2013). https://doi.org/10.1016/j.cell.2012.12.016.
91. Doll S et al., ACSL4 dictates ferroptosis sensitivity by shaping cellular lipid composition. Nat Chem Biol 2017;13:91–98. https://doi.org/10.1038/nchembio.2239.
92. Liu Y, Wang Y, Liu J, Kang R, Tang D. Interplay between MTOR and GPX4 signaling modulates autophagy-dependent ferroptotic cancer cell death. Cancer Gene Ther. 2021;28:55–63. https://doi.org/10.1038/s41417-020-0182-y.
93. Chen P et al., Combinative treatment of β-elemene and cetuximab is sensitive to KRAS mutant colorectal cancer cells by inducing ferroptosis and inhibiting epithelial-mesenchymal transformation. Theranostics 2020;10:5107–5119. https://doi.org/10.7150/thno.44705.
94. Ouyang S et al., Inhibition of STAT3-ferroptosis negative regulatory axis suppresses tumor growth and alleviates chemoresistance in gastric cancer. Redox biology 2022;52:102317. https://doi.org/10.1016/j.redox.2022.102317.
95. Feng Y et al., Metformin promotes autophagy and apoptosis in esophageal squamous cell carcinoma by downregulating Stat3 signaling. Cell death & disease 2014;5:e1088. https://doi.org/10.1038/cddis.2014.59.
96. Wegrzyn J et al., Function of mitochondrial Stat3 in cellular respiration. Science (New York, N.Y.) 2009;323:793–797. https://doi.org/10.1126/science.1164551.
97. Szczepanek K, Chen Q, Larner AC, Lesnefsky EJ. Cytoprotection by the modulation of mitochondrial electron transport chain: the emerging role of mitochondrial STAT3. Mitochondrion 2012;12:180–189 (2012). https://doi.org/10.1016/j.mito.2011.08.011.
98. Elschami M, Scherr M, Philippens B, Gerardy-Schahn R. Reduction of STAT3 expression induces mitochondrial dysfunction and autophagy in cardiac HL-1 cells. Eur J Cell Biol 2013;92:21–29. https://doi.org/10.1016/j.ejcb.2012.09.002.
99. Hsu CC, Peng D, Cai Z, Lin HK. AMPK signaling and its targeting in cancer progression and treatment. Semin Cancer Biol 2022;85:52–68. https://doi.org/10.1016/j.semcancer.2021.04.006.
100. Xiao J et al., 25-Hydroxycholesterol regulates lysosome AMP kinase activation and metabolic reprogramming to educate immunosuppressive macrophages. Immunity 2024;57:1087–1104.e1087. https://doi.org/10.1016/j.immuni.2024.03.021.
101. Keerthana CK et al., The role of AMPK in cancer metabolism and its impact on the immunomodulation of the tumor microenvironment. Front Immunol 2023;14:1114582. https://doi.org/10.3389/fimmu.2023.1114582.
102. Park JM, Lee DH, Kim DH. Redefining the role of AMPK in autophagy and the energy stress response. Nature communications 2023;14:2994. https://doi.org/10.1038/s41467-023-38401-z.
103. Kim J, Kundu M, Viollet B, Guan KL. AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. Nat Cell Biol 2011;13:132–141. https://doi.org/10.1038/ncb2152.
104. Kim J, Guan KL. AMPK connects energy stress to PIK3C3/VPS34 regulation. Autophagy 2013;9:1110–1111. https://doi.org/10.4161/auto.24877.
105. Bowman CJ, Ayer DE, Dynlacht BD. Foxk proteins repress the initiation of starvation-induced atrophy and autophagy programs. Nat Cell Biol 2014;16:1202–1214. https://doi.org/10.1038/ncb3062.
106. Li Y, Chen Y. AMPK and Autophagy. Adv Exp Med Biol 2019;1206:85–108. https://doi.org/10.1007/978-981-15-0602-4_4.
107. Sakamaki JI et al., Bromodomain Protein BRD4 Is a Transcriptional Repressor of Autophagy and Lysosomal Function. Mol Cell 2017;66:517–532.e519. https://doi.org/10.1016/j.molcel.2017.04.027.
108. Poole LP, Macleod KF. Mitophagy in tumorigenesis and metastasis. Cell Mol Life Sci 2021;78:3817–3851. https://doi.org/10.1007/s00018-021-03774-1.
109. Drake JC et al. Mitochondria-localized AMPK responds to local energetics and contributes to exercise and energetic stress-induced mitophagy. Proceedings of the National Academy of Sciences of the United States of America 2021;118. https://doi.org/10.1073/pnas.2025932118.
110. Herzig S, Shaw RJ. AMPK: guardian of metabolism and mitochondrial homeostasis. Nat Rev Mol Cell Biol 2018;19:121–135. https://doi.org/10.1038/nrm.2017.95.
111. Jones RG et al., AMP-activated protein kinase induces a p53-dependent metabolic checkpoint. Mol Cell 2005;18:283–293. https://doi.org/10.1016/j.molcel.2005.03.027.
112. Zhang L et al. IMCA Induces Ferroptosis Mediated by SLC7A11 through the AMPK/mTOR Pathway in Colorectal Cancer. Oxidative medicine and cellular longevity 2020;1675613. https://doi.org/10.1155/2020/1675613.
113. Zhu H, Jiang CW, Zhang WL, Yang ZY, Sun G. Targeting oncogenic MAGEA6 sensitizes triple negative breast cancer to doxorubicin through its autophagy and ferroptosis by stabling AMPKα1. Cell Death Discov 2024;10:430. https://doi.org/10.1038/s41420-024-02196-9.
114. Outinen PA, et al. Homocysteine-induced endoplasmic reticulum stress and growth arrest leads to specific changes in gene expression in human vascular endothelial cells. Blood. 1999;94:959–67.
115. B'Chir W et al., The eIF2α/ATF4 pathway is essential for stress-induced autophagy gene expression. Nucleic Acids Res 2013;41:7683–7699. https://doi.org/10.1093/nar/gkt563.
116. Xiong Y, Liu T, Chen J. Anisomycin has the potential to induce human ovarian cancer stem cell ferroptosis by influencing glutathione metabolism and autophagy signal transduction pathways. Journal of Cancer 2023;14:1202–1215. https://doi.org/10.7150/jca.83355.
117. Zhu S et al., HSPA5 Regulates Ferroptotic Cell Death in Cancer Cells. Cancer Res 2017;77:2064–2077. https://doi.org/10.1158/0008-5472.Can-16-1979.
118. He F et al., ATF4 suppresses hepatocarcinogenesis by inducing SLC7A11 (xCT) to block stress-related ferroptosis. J Hepatol 2023;79:362–377. https://doi.org/10.1016/j.jhep.2023.03.016.
119. Hu X et al., PNO1 inhibits autophagy-mediated ferroptosis by GSH metabolic reprogramming in hepatocellular carcinoma. Cell death & disease 2022;13:1010. https://doi.org/10.1038/s41419-022-05448-7

120. Wang X et al., Knockdown of ANXA10 induces ferroptosis by inhibiting autophagy-mediated TFRC degradation in colorectal cancer. Cell death & disease 2023;14:588. https://doi.org/10.1038/s41419-023-06114-2.
121. Wu Y et al. Ginsenoside Rh4 Inhibits Colorectal Cancer Cell Proliferation by Inducing Ferroptosis via Autophagy Activation. Evidence-based complementary and alternative medicine: eCAM 2022;6177553. https://doi.org/10.1155/2022/6177553.
122. Xiang Y et al., Polyphyllin VII induces autophagy-dependent ferroptosis in human gastric cancer through targeting T-lymphokine-activated killer cell-originated protein kinase. Phytotherapy research: PTR 2023. https://doi.org/10.1002/ptr.7986.
123. Takatani-Nakase T, Ikushima C, Sakitani M, Nakase I. Regulatory network of ferroptosis and autophagy by targeting oxidative stress defense using sulfasalazine in triple-negative breast cancer. Life Sci 2024;339:122411. https://doi.org/10.1016/j.lfs.2023.122411.
124. Wang M et al., ALOX5 promotes autophagy-dependent ferroptosis by activating the AMPK/mTOR pathway in melanoma. Biochemical pharmacology 2023;212:115554. https://doi.org/10.1016/j.bcp.2023.115554.
125. Buccarelli M et al., Inhibition of autophagy increases susceptibility of glioblastoma stem cells to temozolomide by igniting ferroptosis. Cell death & disease 2018;9:841. https://doi.org/10.1038/s41419-018-0864-7.
126. Liu K et al., Induction of autophagy-dependent ferroptosis to eliminate drug-tolerant human retinoblastoma cells. Cell death & disease 2022;13:521. https://doi.org/10.1038/s41419-022-04974-8.
127. Bhatt V et al., Inhibition of autophagy and MEK promotes ferroptosis in Lkb1-deficient Kras-driven lung tumors. Cell death & disease 2023;14:61. https://doi.org/10.1038/s41419-023-05592-8.
128. Chen YM et al., Anomanolide C suppresses tumor progression and metastasis by ubiquitinating GPX4-driven autophagy-dependent ferroptosis in triple negative breast cancer. International journal of biological sciences 2023;19:2531–2550. https://doi.org/10.7150/ijbs.82120
129. Subburayan K et al., Tumor suppressor Par-4 activates autophagy-dependent ferroptosis. Commun Biol 2024;7:732. https://doi.org/10.1038/s42003-024-06430-z.
130. You JH, Lee J, Roh JL. PGRMC1-dependent lipophagy promotes ferroptosis in paclitaxel-tolerant persister cancer cells. Journal of experimental & clinical cancer research: CR 2021;40:350. https://doi.org/10.1186/s13046-021-02168-2.
131. Shen C et al., Timosaponin AIII induces lipid peroxidation and ferroptosis by enhancing Rab7-mediated lipophagy in colorectal cancer cells. Phytomedicine: international journal of phytotherapy and phytopharmacology 2024;122:155079. https://doi.org/10.1016/j.phymed.2023.155079.
132. Tsai KY et al. 2,3,5,4′-Tetrahydroxystilbene (TG1), a Novel Compound Derived from 2,3,5,4′-Tetrahydroxystilbene-2-O-β-D-glucoside (THSG), Inhibits Colorectal Cancer Progression by Inducing Ferroptosis, Apoptosis, and Autophagy. Biomedicines. 2023;11. https://doi.org/10.3390/biomedicines11071798.
133. Mu M et al., 3-Bromopyruvate overcomes cetuximab resistance in human colorectal cancer cells by inducing autophagy-dependent ferroptosis. Cancer Gene Ther 2023;30:1414–1425. https://doi.org/10.1038/s41417-023-00648-5.
134. Liang T et al., Discovery of novel urea derivatives as ferroptosis and autophagy inducer for human colon cancer treatment. Eur J Med Chem 2024;268:116277. https://doi.org/10.1016/j.ejmech.2024.116277.
135. Liu CM et al., 6-Gingerol suppresses cell viability, migration and invasion via inhibiting EMT, and inducing autophagy and ferroptosis in LPS-stimulated and LPS-unstimulated prostate cancer cells. Oncology letters 2022;23:187. https://doi.org/10.3892/ol.2022.13307.
136. Yang H et al., Ailanthone induces autophagy and ferroptosis in non–small cell lung cancer Lewis cells. Mol Clin Oncol 2024;20:25. https://doi.org/10.3892/mco.2024.2723.
137. Li Y et al., Nanoparticle ferritin-bound erastin and rapamycin: a nanodrug combining autophagy and ferroptosis for anticancer therapy. Biomaterials science 2019;7:3779–3787. https://doi.org/10.1039/c9bm00653b.
138. Zhang R et al., An ultrasmall PVP-Fe-Cu-Ni-S nano-agent for synergistic cancer therapy through triggering ferroptosis and autophagy. Nanoscale 2023;15:12598–12611. https://doi.org/10.1039/d3nr02708b.

Publisher's note