Crosstalk between autophagy and ferroptosis in liver diseases (Review)

YANMING WEI[1], KUN ZHOU[2], YUERUI SU[1], ZHIHUA LUAN[3], PENGCHENG LI[1], YINXIA CHANG[1], BO HAN[4], HUIFANG LI[1], YUANBIAO QIAO[3,5] and JINHONG REN[1,5]

[1]College of Chinese Medicine and Food Engineering, Shanxi University of Chinese Medicine, Jinzhong, Shanxi 030619, P.R. China; [2]Department of Energy Chemistry and Materials Engineering, Shanxi Institute of Energy, Taiyuan, Shanxi 030600, P.R. China; [3]Experimental Management Center, Shanxi University of Chinese Medicine, Jinzhong, Shanxi 030619, P.R. China; [4]College of Basic Medicine, Shanxi University of Chinese Medicine, Jinzhong, Shanxi 030619, P.R. China; [5]Shanxi Key Laboratory of Innovative Drug for the Treatment of Serious Diseases Basing on The Chronic Inflammation, Shanxi University of Chinese Medicine, Jinzhong, Shanxi 030619, P.R. China

Received September 5, 2025; Accepted March 12, 2026

DOI: 10.3892/ijmm.2026.5813

Abstract. Ferroptosis is a novel form of regulated cell death triggered by iron-dependent accumulation in lipid peroxidation. Multiple intracellular catabolic processes and signaling pathways are implicated in ferroptosis regulation. One is autophagy, which delivers cytoplasmic materials to lysosomes for degradation and is critical for the preservation of cellular homeostasis. The discovered role of autophagy in driving ferroptosis have motivated further explorations of the functional interactions and signal pathways between ferroptosis and autophagy, particularly their crosstalk in the pathogenesis or treatment for various liver diseases, such as drug-induced liver injury, toxin-induced liver injury, liver fibrosis and hepatocellular carcinoma. The present review presented an in-depth overview of research on the crosstalk between autophagy and ferroptosis in diverse liver diseases, including the ones aforementioned. The diverse regulatory mechanisms involved in this process are also analyzed to open a new perspective on the interpretation of liver diseases manifestations and provide potential targets for drug discovery and effective intervene.

Correspondence to: Dr Yanming Wei or Dr Jinhong Ren, College of Chinese Medicine and Food Engineering, Shanxi University of Chinese Medicine, 121 Daxue Street, Jinzhong, Shanxi 030619, P.R. China
E-mail: weiyanming2005@aliyun.com
E-mail: jhren@sxtcm.edu.cn

Abbreviations: PUFA-PLs, phospholipid containing polyunsaturated fatty acid chains; CMA, chaperone-mediated autophagy; Hsc70c, heat shock cognate 71 KDa protein cytosolic; FTH1, ferritin heavy chain 1; LC3, microtubule-associated protein light chain 3; NCOA4, nuclear receptor coactivator 4; Rab7, Ras-related protein Rab7a; HSCs, hepatic stellate cells; FUNDC1, FUN14 domain-containing protein 1; ELAVL1, ELAV like RNA binding protein 1; MSC-ex, mesenchymal stem cells-derived exosomes; circFAM134B, circRNA of the family with sequence similarity 134, member B; PTBP1, polypyrimidine tract-binding protein 1; TSPO, mitochondrial translocator protein; BCAT2, branched-chain amino acid aminotransferase 2; WTAP, WT1 associated protein; USP24, ubiquitin-specific protease 24; ARNTL, brain and muscle ARNT-like protein 1; EChLESs, electrophilic sesquiterpenes isolated from *Eupatorium chinense* L.; TFEB, transcription factor EB; YAP1, Yes-associated protein 1

Key words: ferroptosis, autophagy, crosstalk, drug-induced liver injury, toxin-induced liver injury, liver fibrosis, hepatocellular carcinoma

Contents

1. Introduction

Liver diseases are hepatic pathological changes caused by numerous endogenous and exogenous pathogenic factors such as drugs, chemical agents, viral infection, chronic alcohol consumption and malnutrition. According to epidemiological statistics, liver diseases account for two million deaths worldwide annually and are gradually becoming a major challenge to public health (1). Comprehensively understanding the pathogenesis underlying liver diseases and precisely clarifying specific therapeutic targets may provide new diagnostic approaches and improve the prognosis. Ferroptosis is a unique form of regulated cell death which is morphologically, biochemically and genetically different from other regulated cell deaths,

such as apoptosis, necroptosis, autophagy and pyroptosis. This process is driven by iron-dependent phospholipid peroxidation, which relies on reactive oxygen species (ROS), metal iron and phospholipid containing polyunsaturated fatty acid chains (PUFA-PLs). The correlation of ferroptosis with the pathogenesis of various diseases involving almost every organ in the body has been identified recently (2). Particularly, the liver plays a central role in cell metabolism and is the primary iron storage organ, making it a preferential target of ferroptosis. Emerging evidence supports the implication of ferroptosis in the occurrence and progression of various liver diseases, including drug-induced liver injury, liver ischemia-reperfusion injury, alcohol-associated liver disease, non-alcoholic fatty liver disease (NAFLD) and hepatocellular carcinoma (HCC) (3).

Autophagy is a tightly orchestrated intracellular process in eukaryotic cells by which cytoplasmic materials are conveyed to the lysosomal compartment for degradation and recycling (4). To date, three major types of autophagy have been defined: Macroautophagy, microautophagy and chaperone-mediated autophagy (CMA). During macroautophagy, *de novo*-synthesized double membrane-bound vesicle (referred to as an autophagosome) engulfs cytosolic substrates and then fuses with lysosomes to form an autolysosome. In microautophagy, a portion of the cytoplasm is directly captured through invaginations or protrusions of the lysosomal membrane.

CMA involves the identification of KFERQ-like motifs present in the cytosolic proteins by heat shock cognate 71 kDa protein cytosolic (Hsc70c), a chaperone protein, followed by the direction to the lysosomal membrane receptor lysosomal-associated membrane protein 2A and the translocation of cargo proteins to the lysosomal lumen (5). Among these three forms, macroautophagy is the best characterized and is hereafter referred to as autophagy for simplicity. Autophagy occurs at a basal level for the constitutive turnover of cytosolic components to maintain normal cellular homeostasis. This sensitive and highly inducible process drives cell response to diverse stress conditions, such as nutrient deprivation, metabolic stress, oxidative stress, endoplasmic reticulum (ER)-stress and microbial infection (6). Thus, autophagy is primarily regarded as a cytoprotective mechanism, although prolonged constitutive defective or excessive autophagy can be deleterious. Accordingly, this process has implications for substantial human pathologies. Autophagy deregulation in either liver cells or non-parenchymal cells contributes to numerous liver diseases, including NAFLD, alcohol liver injury, drug-induced liver injury and HCC (7).

Although ferroptosis was originally identified as a type of autophagy-independent cell death, extensive evidence has uncovered the crosstalk between autophagy and ferroptosis. The present review outlined the research on the crosstalk between ferroptosis and autophagy under the pathogenesis or treatment of liver diseases, delineated the pivotal role of the crosstalk and analyzed the involved molecular regulators or signal pathways, hopefully providing new insights into liver diseases and effective strategies for their prevention or amelioration.

2. Overview of ferroptosis

Cells undergoing ferroptosis typically round up, detach and lose plasma membrane integrity. Alterations in mitochondrial morphology and cristae structure are the characteristic morphological features used as ferroptosis markers. Obvious mitochondrial shrinkage with condensed membrane densities, reduction or disappearance of mitochondrial cristae and rupture of the outer mitochondrial membrane are observed in response to ferroptosis activators (8). However, the size and structural integrity of the nucleus are retained, and nuclear condensation or chromatin margination is rarely observed during ferroptosis (9). A number of genes regulate the highly intricated ferroptotic process. For example, ferroptosis induction may depend on the *RAt Sarcoma virus* (*RAS*), which is the most common oncogene in cancers. Cancer cells harboring *RAS* mutations are highly sensitive to ferroptosis (10). Lung cancer cells transfected with short hairpin RNAs targeting *RAS* exhibited resistance to ferroptosis inducer erastin (11) and rhabdomyosarcoma cells overexpressing RAS were markedly less susceptible to ferroptosis, indicating the positive regulatory role of RAS in ferroptosis (12). By contrast, *heat shock protein beta-1* (*HspB1*) was a highly expressed following ferroptosis induction in cervical cancer cells, osteosarcoma cells and prostate cancer cells. It negatively regulates ferroptosis *in vitro* and *in vivo*: ferroptosis is promoted by silencing *HspB1* but inhibited by upregulating *HspB1* (13).

In biochemical aspects, one central event leading to ferroptosis is aberrant iron homeostasis (14). Iron is an indispensable element required by all living organisms, and the control of its levels is a dynamic process involving its uptake, storage, utilization and efflux. Serum ferric ion is bound by transferrin and subsequently imported into cells via transferrin receptor (TFR1)-mediated endocytosis. In the endosomes, ferric iron is reduced to ferrous iron and then released into a labile iron pool in the cytoplasm. Excess iron can be stored in ferritin, which is the primary iron storage protein complex composed of ferritin light chain (FTL) and ferritin heavy chain 1 (FTH1). Iron export requires the iron efflux pump ferroportin-1 (FPN1), which produces ferric iron from ferrous iron (15). Ferrous iron plays numerous important functions in the regulation of multiple biochemical processes. In addition to catalyzing ROS generation via the Fenton reaction, iron is incorporated into several ROS-generating enzymes and thus induces the other core event in ferroptosis, as shown by the accumulation of lipid peroxidation accompanied by depleted glutathione (GSH) and insufficient glutathione peroxidase 4 (GPX4) (16). GSH is a tripeptide synthesized from glutamate, cysteine and glycine and acts as a direct ROS scavenger and a powerful antioxidant that limits oxidative damage to cellular components. The rate-limiting precursor for GSH synthesis is cysteine, which is imported into cells by system Xc-, a cystine and glutamate antiporter in the plasma membrane comprising xCT (solute carrier family 7 member 11) and solute carrier family 3 member 2. GSH is a necessary cofactor of GPX4, an antioxidant enzyme that utilizes reduced GSH to convert toxic lipid peroxides to non-toxic phosphatidyl alcohols to confer resistance to lipid peroxidation and subsequently prevent ferroptosis (17). Therefore, an increase in labile iron pool and lipid peroxidation are considered typical presentations of ferroptosis and are used as markers of ferroptotic cell death (Fig. 1).

Intra- and intercellular signaling events, environmental stresses or small molecules can regulate ferroptosis by

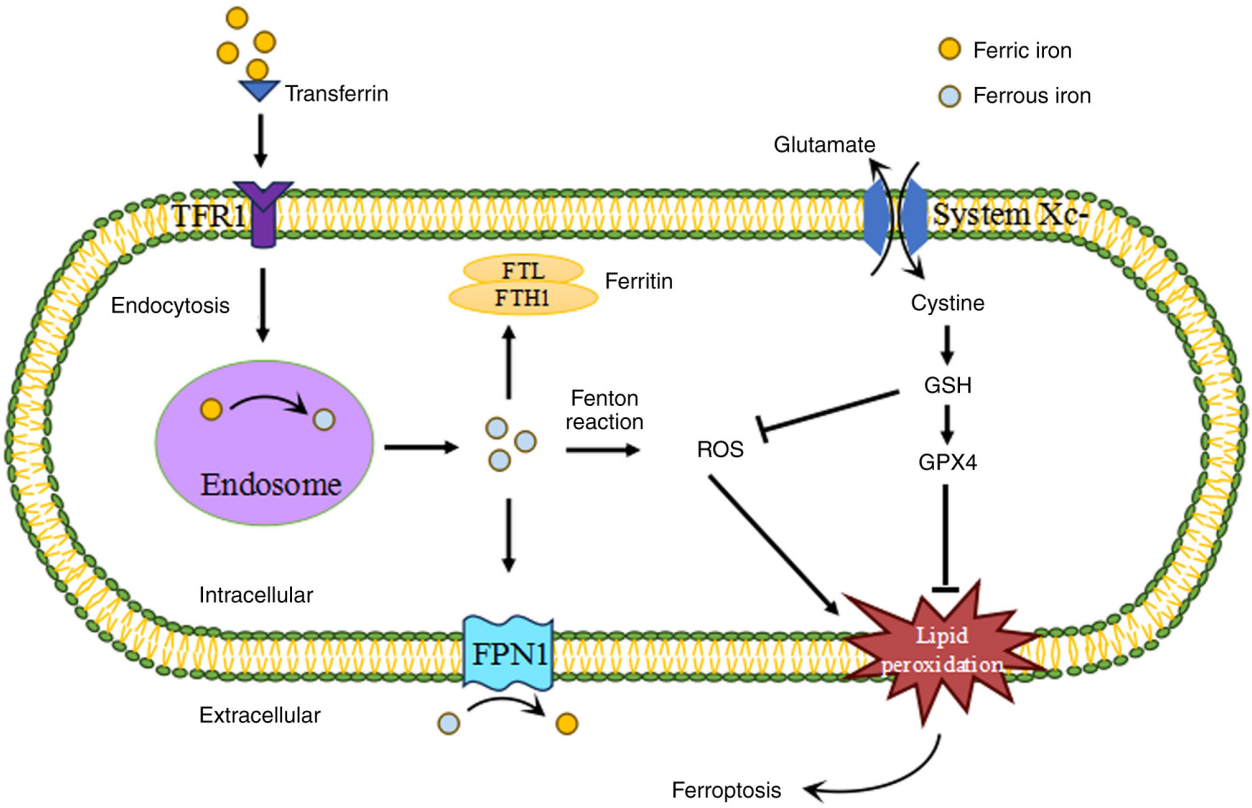

Figure 1. The process of ferroptosis. Cells acquires transferrin-bound ferric iron via TFR1-mediated endocytosis. Ferric iron is reduced to ferrous iron in the endosome and then released into the cytoplasm. Excess iron can be stored by ferritin, including FTL and FTH1. Iron export requires the iron efflux pump FPN1, which produces ferric iron from ferrous iron. System Xc- imports cysteine into cells with a 1:1 countertransport of glutamate and then induces the generation of GSH. GSH is a major ROS scavenger and a necessary cofactor of GPX4, an antioxidant enzyme that converts the toxic lipid peroxides to non-toxic phosphatidyl alcohols for preventing ferroptosis. Therefore, ferroptosis is characterized by the iron overload and lipid peroxidation. TFR1, transferrin receptor 1; FTL, ferritin light chain; FTH1, ferritin heavy chain 1; FPN1, ferroportin-1; GSH, glutathione; ROS, reactive oxygen species; GPX4, glutathione peroxidase 4.

directly or indirectly controlling iron accumulation and/or lipid peroxidation (18). For example, exogenous iron (such as ferric ammonium citrate and ferric citrate) supplementation, increased iron uptake (such as TFR1 overexpression), decreased iron storage (such as ferritin knockdown) and impaired iron efflux (such as FPN1 knockdown) contribute to iron overload and enhance the sensitivity to ferroptosis (19,20). By contrast, iron chelators such as deferoxamine or desferrioxamine mesylate block ferroptosis via the inhibition of iron overload (21). Blocking of system Xc^--mediated cystine import using excessive glutamate results in GSH depletion and consequent ROS accumulation, ultimately leading to a void in the antioxidant defenses and lipid peroxidation that triggers ferroptosis (22). Ferroptosis can also be triggered by downregulated GPX4 through genetic deletion, covalently inactivating GPX4 (such as RSL3 and ML162) and promoting GPX4 degradation (such as FIN56), whereas overexpressing GPX4 or pharmacologically blocking its degradation may enhance antioxidant capacity and display potent protective effects against ferroptosis (23). Lipid metabolism regulates ferroptosis by controlling the peroxidizable levels of PUFA-PLs, the most important lipids required for ferroptosis, and the associated processes of phospholipid peroxidation. The arachidonic acid-mediated depletion of PUFA-PLs severely counteracts ferroptosis in a number of cell lines, and a similar phenomenon is observed upon the pharmacological inhibition or genetic inactivation of the acyl-coenzyme A synthetase long chain, which is a requirement for the synthesis of PUFA-PLs. Furthermore, lipid antioxidants such as ferrostatin-1 (Fer-1) or liproxstatin-1 prevent ferroptosis by inhibiting lipid peroxidation and are commonly used as ferroptosis inhibitors (24).

3. Overview of autophagy

As an evolutionarily conserved degradation system, the complete autophagic process encompasses a series of consecutive steps. Upon induction, the nucleation of the initial autophagosomal vesicle (a very flat organelle similar to Golgi cisterna and designated as phagophore or isolation membrane) occurs at multiple sites throughout the cytoplasm. Subsequent to nucleation, the phagophore expands to sequester its cargos via the addition of membrane presumably derived from the ER, Golgi complex, plasma membrane and mitochondria. The edges of the phagophore bend and ultimately seal to generate a typically spherical, double-membraned autophagosome with a diameter of 300-900 nm, depending on the organisms and cargo types (6). The autophagosome then moves to lysosome, and its outer membrane fuses with the lysosome to form an autolysosome, where the inner membrane of the autophagosome and its contents are degraded by lysosomal hydrolases (5). Before fusing with the lysosome, the autophagosome is hypothesized to firstly fuse with early or late endosomes to become an amphisome and acquire the necessary machineries for its subsequent fusion with the lysosome (25). Finally, the

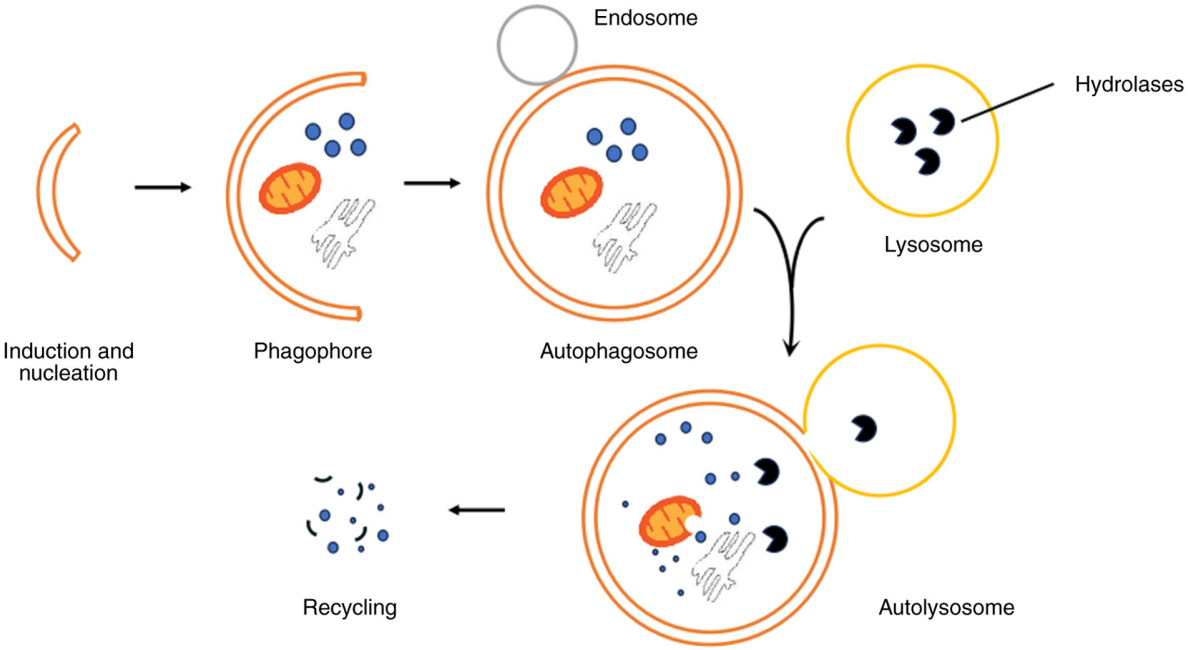

Figure 2. The process of autophagy. Upon induction, the *de novo*-synthesized double-membrane vesicle, autophagosome, sequesters and transports cargos to the lysosome, leading the degradation of their contents by resident hydrolases and the release of the breakdown products back into the cytosol for recycling.

breakdown parts are exported back into the cytoplasm by membrane permeases for reuse as building blocks of anabolic processes or as an energy supplement (Fig. 2).

A specific family of genes called *autophagy-related genes* (*Atgs*) constitutes the multistage molecular machinery of autophagy. Originally identified in yeast, >30 mammalian *Atg* orthologs have been found to play critical roles in autophagy. Among these Atg proteins, the essential subsets in autophagosome formation and maturation are referred to as the core molecular machinery and grouped into the following four categories based on their respective functions: The UNC51-like kinase 1 kinase complex; two ubiquitin-like conjugation systems; class III phosphatidylinositol 3-kinase (PI3KIII) complex; and two transmembrane proteins, Atg9 and vacuole membrane protein 1(VPM1) (26,27). The ULK1 kinase complex is composed of ULK1 and its regulatory subunit FIP200, Atg13 and Atg101 and carries out the initiation of autophagy. Under nutrient deprivation conditions, ULK1 is stimulated and Atg13, FIP200 and ULK1 itself are phosphorylated, resulting in the recruitment of other autophagy proteins for phagophore nucleation and assembly (28). Two ubiquitin-like [Atg12 and Atg8/microtubule-associated protein light chain 3 (LC3)] conjugation systems facilitate phagophore membrane elongation and expansion. The first conjugation event involves the covalent attachment of Atg12 to Atg5, which requires Atg7 and Atg10 acting as E1 and E2-like enzymes, respectively. Atg12-Atg5 then interacts noncovalently with Atg16 and oligomerizes to a large units called Atg16L complex, which functions as an E3-like enzyme in the second conjugation system to facilitate the conjugation of a single phosphatidylethanolamine (PE) to the carboxyl terminus of LC3. For this conjugation to occur, LC3 is initially cleaved by Atg4 protease. The proteolyzed LC3 (LC3I) is then processed by the same E1-like enzyme Atg7 and are further transferred to the E2-like enzyme Atg3. The Atg16 complex finally ligates LC3I to PE to form LC3II, a lipidated form attached to autophagosome. Of note, the distribution of cytosolic LC3 to autophagosomes and the amount of LC3II are commonly regarded as markers for autophagy (29). The PI3KIII complex, which comprises vacuolar protein sorting 34 (Vps34), Beclin1/Atg6 and Vps15, preforms membrane modification involving phosphatidylinositol phosphorylation to produce phosphatidylinositol 3-phosphate. This molecule then serves as a docking particle that promotes Atg protein complex formation at the nucleation site, membrane enclosing and the cytoplasmic components sequestration (26). The transmembrane protein Atg9 localizes to autophagy-related structures, namely, omegasomes, as well as the Golgi apparatus and endosomes. Atg9 shuttles among these organelles and potentially contributes to membrane transport to the forming autophagosome (30). VPM1 is an ER- and Golgi apparatus-associated membrane protein. By directly interacting with Beclin1, VPM1 may bring PI3KIII components to the phagophore and promote the autophagosome formation (31).

Autophagy regulation is extremely complicated and involves multiple stimulatory or inhibitory factors or signal pathways, such as PI3KI-protein kinase B (AKT)-mammalian target of rapamycin complex 1 (mTORC1), adenosine monophosphate-dependent protein kinase (AMPK)-mTORC1 pathway, B cell lymphoma 2 (Bcl2)-Beclin1 pathway and p53. mTOR is a conserved serine/threonine protein kinase and exists in two distinct complexes, mTORC1 and mTOR2, which are formed by binding with multiple companion proteins and defined by the presence of the companion proteins Raptor and Rictor, respectively. Particularly, mTORC1 integrates various upstream signaling pathways to block or induce autophagy. PI3KI can increase the membrane recruitment of phosphoinositide-dependent kinase 1, which phosphorylates and activates AKT. AKT further inhibits the downstream tuberous sclerosis complex (TSC) and activates mTORC1, leading to

autophagy suppression. By contrast, AMPK can phosphorylate and activate TSC and induce autophagy by inhibiting mTORC1 activity (32). Beclin1 is a mammalian autophagy protein identified as a novel Bcl2-interacting protein. Increased Beclin1 and Bcl2 interaction disturbs the PI3KIII complex formation, thus inhibiting autophagy. By contrast, the disruption of the Bcl2-Beclin1 complex upregulates autophagy (33). p53 may exert both pro- and anti-autophagy functions depending on its compartmental localization. Cytosolic p53 effectively represses autophagy, whereas nuclear p53 stimulates autophagy through the transcriptional repression of mTORC1 activity and the induction of damage-regulated autophagy modulator expression (34). Furthermore, epigenetic alterations, including DNA methylation, histone modification and non-coding RNAs expression, not only modify *Atgs* but also affect signaling genes, thus inhibiting or promoting of autophagy (35) (Fig. 3). Of note, these regulatory pathways may be interconnected and influence the dynamic autophagic process at different steps.

Autophagy can be a bulk, nonselective, degradative process, with random engulfment of cellular components. Under certain circumstances, autophagy occurs in a selective manner dependent on autophagy adaptor proteins, such as p62, neighbor of BRCA1, optineurin and nuclear dot protein 52 KDa. These proteins interact simultaneously with cargos and LC3 protein anchored in the autophagosomal double membrane for autophagosome targeting. Selective autophagy contributes to organelle quality control and homeostasis regulation by degrading specific soluble proteins (ferritinophagy), damaged and excess organelles (mitophagy, lipophagy, lysophagy, ER-phagy, ribophagy, perophagy and nucleophagy), aggregated proteins (aggrephagy) and invasive bacteria (xenophagy) (36).

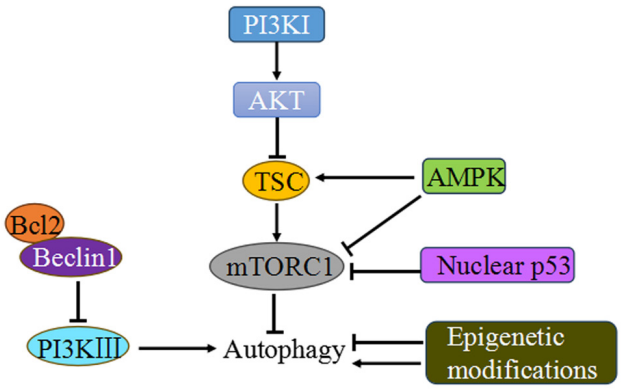

Figure 3. Major regulatory pathways of autophagy. Autophagy regulation involves multiple stimulatory or inhibitory factors or signal pathways, such as PI3KI-AKT-mTORC1, AMPK-mTORC1, Bcl2-Beclin1 pathways, p53 and epigenetic modulations. PI3KI, class I phosphatidylinositol 3-kinase; AKT, protein kinase B; TSC, tuberous sclerosis complex; mTORC1, mammalian target of rapamycin complex 1; AMPK, adenosine monophosphate-dependent protein kinase; Bcl2, B cell lymphoma 2; PI3KIII, class III phosphatidylinositol 3-kinase.

4. Crosstalk between autophagy and ferroptosis in diverse liver diseases

Multiple *Atg*s, such as *Atg5*, *Atg7* and *Beclin1*, have been identified as potential positive regulators of ferroptosis using RNAi screening methods. The genetic and pharmacological inhibition of autophagy greatly attenuates and delays ferroptosis, highlighting the vital involvement of autophagy in the regulation of ferroptotic cell death (37). Particularly, selective autophagy including nuclear receptor coactivator 4 (NCOA4)-mediated ferritinophagy, Ras-related protein Rab7a (Rab7)-mediated lipophagy, p62-mediated clockophagy and Hsp90-mediated CMA, degrades ferritin, lipid droplets, aryl hydrocarbon receptor nuclear translocator-like protein 1 and GPX4 to induce iron overload and/or lipid peroxidation, eventually promoting ferroptosis (Fig. 4). Conversely, ferroptosis induction activates autophagy by stimulating autophagosomes formation, whereas ferroptosis inhibition impairs autophagic degradation in a context-dependent manner (38). Thus, the signal pathways or essential molecules involved in these two processes may either be shared or be interconnected (39). The crosstalk between autophagy and ferroptosis has emerged as a vital factor in the occurrence, development and therapeutic application of various liver diseases. Studies have demonstrated that this crosstalk is an important mechanism underlying drug- or toxin-induced liver injury (40-55), and is also closely associated with liver fibrosis (23,56-65) and HCC (66-81). Moreover, it functions in the liver damage of metabolic syndrome (MS) (82), NAFLD (83), non-alcoholic steatohepatitis (NASH) (84), acute liver injury (ALI) (85-89), diabetic liver injury (90) and liver cell senescence (91). Further details supporting this crosstalk as a pivotal mediator in these liver diseases are listed in Table I).

Crosstalk between autophagy and ferroptosis in drug-induced liver injury. Drug-induced liver injury is one of the most challenging liver diseases in clinical practice. It considerably interrupts the drug therapy and increases treatment difficulty (92). Increasing evidence substantiates that the crosstalk between autophagy and ferroptosis participates in the pathogenesis of drug-induced liver injury. Rifampicin, a common chemotherapy agent for tuberculosis, not only promotes ferroptosis, manifested by increasing lipid peroxidation and intracellular iron content, but also markedly increases the expressions of LC3II and NCOA4 while decreasing the expressions of p62 and ferritin, thereby inducing NCOA4-mediated ferritinophagy (40). NCOA4 is a specific ferritinophagy receptor that recognize ferritin and binds to its hub subunit FTH1 and interacts with LC3, transporting ferritin to the autophagosome for lysosomal degradation and iron release (93). In cell or mouse models, blocking ferritinophagy via knockdown of *NCOA4* or *Atg5*, or with the treatment of 3-methyladenine (3-MA), reduces ferritin degradation and iron overload, partially alleviating ferroptosis and ultimately mitigating rifampicin-induced cytotoxicity, liver steatosis and tissue injury. Hsc70 is supposed to manipulate ferritinophagy by modulating the ferritin degradation and ferroptosis sensitivity of liver cells. Its expression decreases with the prolonged rifampicin treatment. Hsc70 inducer treatment substantially inhibits NCOA4-mediated ferritinophagy and ferroptosis, thereby alleviating the liver injury caused by rifampicin (40).

Liver injury is a common adverse reaction to methotrexate, a drug broadly employed for the treatment of rheumatoid arthritis and various tumors treatment (94). Research has highlighted the significant role of ferritinophagy-dependent

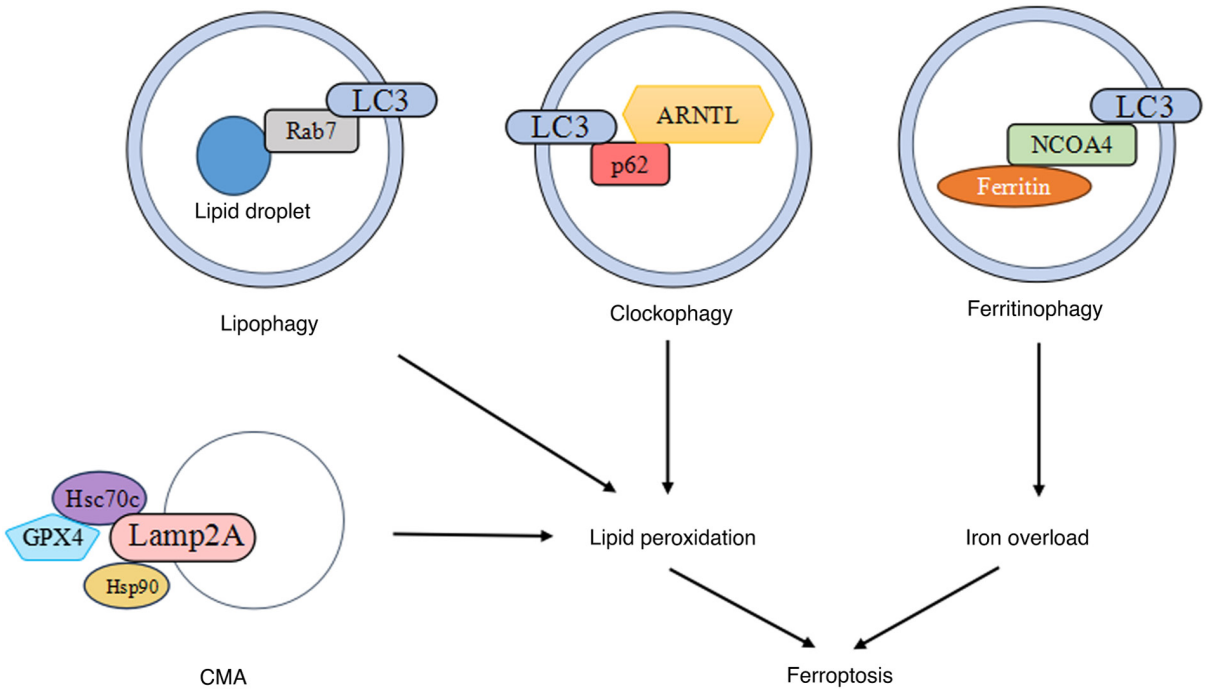

Figure 4. Selective autophagy promotes ferroptosis. Rab7-mediated lipophagy, p62-mediated clockophagy and Hsp90-mediated CMA promote lipid peroxidation in ferroptosis; NCOA4-mediated ferritinophagy promotes iron accumulation in ferroptosis. Rab7, Ras related protein Rab7a; LC3, microtubule-associated protein light chain 3; ARNTL, aryl hydrocarbon receptor nuclear translocator-like protein 1; Hsc70c, heat shock cognate 71 KDa protein cytosolic; Lamp2, lysosome-associated membrane protein 2; Hsp90, heat shock protein 90; GPX4, glutathione peroxidase 4; CMA, chaperone-mediated autophagy; NCOA4, nuclear receptor coactivator 4.

ferroptosis in methotrexate-induced hepatotoxicity. In liver cells, methotrexate treatment upregulates LC3II and NCOA4, reduces p62 and FTH1 and triggers ferroptosis. Additionally, NCOA4 knockdown clearly inhibits FTH1 degradation, suppresses ferroptosis, and mitigates methotrexate-induced cell death, indicating that NCOA4-mediated ferritinophagy induced by methotrexate facilitates ferroptosis. Mechanistically, the overexpression and cytoplasmic translocation of high-mobility group box 1 (HMGB1), a damage-associated molecular pattern molecule (95), is responsible for the regulation of methotrexate-induced ferritinophagy and ferroptosis. Depletion or pharmacological inhibition of HMGB1 substantially alleviates methotrexate-induced hepatotoxicity by diminishing ferritinophagy-mediated ferroptosis (41).

Ferritinophagy-dependent ferroptosis also contributes to the liver injury caused by toosendanin, which is a natural compound extracted from traditional Chinese medicine, *Melia toosendan* Sieb. et Zucc. with multiple bioactivities (96). Toosendanin treatment reduces liver cell viability in a concentration-dependent manner; causes mouse liver injury; increases ROS, lipid peroxidation and iron contents; and decreases GSH level and GPX4 expression, all of which are consistent with the process of ferroptosis. Moreover, the activation of protein kinase R-like endoplasmic reticulum kinase (PERK)-eukaryotic initiation factor 2 α subunit (eIF2a)-activation transcription factor 4 (ATF4) signaling pathway causes cellular iron overload and enhanced sensitivity to ferroptosis by upregulating the ATF3-mediated expression of NCOA4 and TFR1, which are related to the impaired iron storage caused by ferritinophagy induction and the increased iron uptake caused by the promotion of iron importation, respectively (42).

Triptolide is a natural compound isolated from *Tripterygium wilfordii* Hook. F. with severe liver injury (97). Previous reports have demonstrated triptolide-induced liver cells ferroptosis as a biological process highly dependent on lipophagy. Triptolide administration markedly elevates Rab7 and LC3II expressions, reduces p62 expression and augments the colocalization of LC3 and Rab7 proteins in human normal liver cells and mice livers, supporting the activation of Rab7-mediated lipophagy. Triptolide also increases the levels of malondialdehyde, iron and prostaglandin endoperoxide synthase 2, depletes GSH and GPX4, and causes significant mitochondria damage. Genetic or pharmacological depletion of lipophagy reverses ferroptosis and attenuates liver cell damage (43). Given the lipolytic effect of lipophagy on lipid droplets (98), the activation of Rab7-mediated lipophagy is hypothesized to promote the release of free fatty acids, which subsequently impair mitochondrial function and amplify oxidative stress. This cascade ultimately drives lipid peroxidation, ferroptosis and liver injury development.

Acetaminophen (paracetamol) overdose is responsible for the greatest proportion of drug-induced liver injury in Western countries (99). The reactive metabolite of acetaminophen induces GSH depletion and covalently binds to mitochondrial proteins, initiating mitochondrial damage and ROS overproduction and resulting in impaired antioxidant capacity and lipid peroxidation (100). ROS generation from damage mitochondria also trigger autophagy induction in mouse livers and in primary cultured liver cells following acetaminophen treatment (101). ROS-induced autophagy is a critical factor that controls intracellular iron concentration through ferritin degradation and TFR1 expression during ferroptosis (38). In

Table I. Crosstalk between autophagy and ferroptosis in diverse liver diseases.

Authors, year	Type of liver diseases	Autophagy/ ferroptosis modulators	Experimental models		Autophagy/ ferroptosis status	Related biological effects	(Refs.)
			In vitro	*In vivo*			
Zhou *et al*, 2022	Drug-induced liver injury	Rifampicin	HepG, AML12	C57BL/6 mice	Ferritinophagy↑; ferroptosis↑	NCOA4, LC3II, acidic vesicular organelles, FTH1-LC3 colocalization, iron content, MDA↑; p62, FTH1, HspA8↓	(40)
Wang *et al*, 2024		Methotrexate	HepG2, AML12	C57BL/6 mice	Ferritinophagy↑; ferroptosis↑	NCOA4, LC3II, autophagosomes, FTH1-LC3 colocalization, HMGB1, MDA↑; p62, FTH1, GSH, GPX4↓	(41)
Liang *et al*, 2023		Toosendanin	HepG2	Balb/c mice	Ferritinophagy↑; ferroptosis↑	NCOA4, TFR1, ferrous ion, ROS, lipid peroxidation, PERK, p-PERK, p-eIF2α, ATF4↑; FTH1, GPX4, FPN1↓	(42)
Liu *et al*, 2025		Triptolide	HL7702	C57BL/6J mice	Lipophagy↑; ferroptosis↑	Rab7, LC3II, LC3-Rab7 colocalization, iron content, mtROS, ROS, MDA, Ptgs2, FFAs↑; p62, GSH, GPX4, lipid droplets, MMP↓	(43)
Wu *et al*, 2024		Acetaminophen	Mouse primary hepatocytes	KM mice	Ferritinophagy↑; ferroptosis↑	LC3II, Iron content, MDA, Keap1↑; p62, FTH1, xCT, SLC3A2, GSH, Nrf2, HO-1↓	(44)
Cai *et al*, 2022		Acetaminophen	HL7702	C57BL/6 mice	Autophagy↓; ferroptosis↑	LC3II, p62, ROS, xCT↑; FTH1, Nrf2, HO-1, GPX4↓; mitochondrial shrinkage and cristae loss	(45)
Ren *et al*, 2025		Acetaminophen	AML12, HepG2	C57BL/6J mice	Autophagy↓; ferroptosis↑	Foxo1, iron content, MDA, ROS, Ptgs2, p62↑; LC3II, GSH, MMP, xCT, GPX4↓	(46)
Huang *et al*, 2023	Toxin-induced liver injury	Acrylamide	HepG2	C57BL/6J mice	Ferritinophagy↑; ferroptosis↑	NCOA4, LC3II, autophagy flux, iron content, ROS, lipid ROS, MDA↑; p62, FTH1, GSH, GPX4, MMP, Nrf2↓	(47)
Zhong, *et al* 2024		Copper sulfate		Broiler chicks	Ferritinophagy↑; ferroptosis↑	NCOA4, ACLS4, MDA, Keap1, TXNIP, lipid peroxidation↑; GPX4, GSH, xCT, FSP1, Nrf2, SOD1, TRX↓; mitochondrial shrinkage or cristae loss	(48)
He *et al*, 2022		Cadmium chloride	AML12	Balb/c mice	Ferritinophagy↑; ferroptosis↑	LC3II, iron content, ferrous ion, MDA, lipid peroxidation, Ptgs2, GRP78, p-PERK, p-elF2α, ATF4, CHOP↑; NCOA4, p62, FTH1, GSH, GPX4↓	(49)

Table I. Continued.

Authors, year	Type of liver diseases	Autophagy/ ferroptosis modulators	Experimental models		Autophagy/ ferroptosis status	Related biological effects	(Refs.)
			In vitro	*In vivo*			
Wei *et al*, 2022		Nickel chloride		ICR mice	Ferritinophagy↑; ferroptosis↑	Iron content, mtROS, MDA, Ptgs2↑; NCOA4, FTH1, GSH, GPX4, MMP, mitochondrial respiratory chain complexes↓	(50)
Yu *et al*, 2023		Sodium arsenite	LMH	HY-line white chickens	Ferritinophagy↑; ferroptosis↑	NCOA4, LC3II, Atg5, Atg7, autophagosomes, iron content, lipid ROS, MDA, Ptgs2, p-AMPK (Thr172), p-ULK1 (Ser555)↑; p62, FTH1, GPX4, xCT, MMP, p-mTOR (Ser2448) ↓; mitochondrial shrinkage and cristae loss	(51)
Xu *et al*, 2023		Sodium fluoride	BRL3A	SD rats	Autophagy↓; ferroptosis↑	LC3II, p62, ferrous ion, mtROS, MDA, ACSL4, TFR1, TOMM20↑; FTH1, autophagy flux, MMP, GSH, GPX4↓	(52)
Song *et al*, 2022		Ethanol- or acetaldehyde	HepG2, HL7702		Ferritinophagy↑; mitophagy↓; ferroptosis↑	NCOA4, ferritin-lysosome colocalization, iron content, ROS, MDA, TFR1↑; p62, GSH, FTH1, PINK1, Parkin↓	(53)
Song *et al*, 2024		Aflatoxin B1	HepG2	C57BL/6 J mice	Ferritinophagy↑; ferroptosis↑	GPX4, T-AOC, CAT↓ Ferritin, FTH11, FTL↓; Beclin1, LC3II, Atg5, p-mTOR, p-AKT, p-PI3K, p-ULK1↑	(54)
Jiang *et al*, 2024		Deoxynivalenol	AML12	C57BL/6 mice	Ferritinophagy↑; mitophagy↑; ferroptosis↑	Iron content, MDA, Ptgs2, ACSL4, NCOA4, PINK1, Parkin, LC3II, p-JNK, p-JUN↑; NCOA4-FTH1 interaction↑; mitochondria-lysosomes colocalization↑; xCT, GPX4, CAT, SOD, FTH, p62, PDCD4↓	(55)
Liang *et al*, 2023	Liver fibrosis	Silica nanoparticles	HL7702	F344 rats	Ferritinophagy↑; ferroptosis↑	NCOA4, LC3II, ferrous ion, MDA, Ptgs2↑; GPX4, FTH1↓, mitochondrial membrane rupture	(56)
Bi *et al*, 2024		CCl4	HepG2	Friend Virus B mice; liver tissues of patients with liver fibrosis	Mitophagy↑; ferroptosis↑	MDA, iron content, Pink1, Parkin, FUNDC1↑; FUNDC1-GPX4 interaction↑; GSH, MMP, xCT↓; mitochondrial shrinkage and cristae loss	(57)

Table I. Continued.

Authors, year	Type of liver diseases	Autophagy/ ferroptosis modulators	Experimental models		Autophagy/ ferroptosis status	Related biological effects	(Refs.)
			In vitro	*In vivo*			
Zhang *et al*, 2020		Sorafenib, erastin, or RSL3	HSC-LX2, HSC-T6, primary mouse HSCs primary, human HSCs	BDL-induced liver fibrosis model in C57BL/6 mice; human liver resection tissues with liver cirrhosis complicated with HCC	Ferritinophagy↑; ferroptosis↑	NCOA4, LC3II, LC3 puncta, Atg16L1, autophagy flux, autophagic vesicles, iron content, MDA, ACSL4, Ptgs2, xCT, SLC11A2, FBXW7, FBXW7-ZFP36 interaction↑; p62, FTH1, GSH, GPX4, ZFP36↓	(23)
Zhang *et al*, 2018		Erastin, buthionine sulfoximine, and sorafenib	HSC-LX2, HSC-T6, primary mouse HSCs, primary human HSCs	BDL-induced liver fibrosis model in C57BL/6 mice; human liver resection tissues with liver cirrhosis complicated with HCC	Ferritinophagy↑; ferroptosis↑	NCOA4, LC3II, Beclin1, autophagic vesicles, iron content, lipid ROS, ROS, MDA, GSH, ELAVL1, Ptgs2, ACSL4, xCT, SLC11A2↑; p62, FTH1↓	(58)
Shen *et al*, 2021		Erastin, sorafenib and RSL3	HSC-LX2, HSC-T6, primary mouse HSCs, primary human HSCs	CCl4-induced liver fibrosis model in ICR mice; human liver resection tissues with liver cirrhosis complicated with HCC	Ferritinophagy↑; ferroptosis↑	NCOA4, LC3II, LC3 puncta, Beclin1, autophagy flux, iron content, lipid ROS, MDA, Ptgs2, METTL4, m^6A RNA methylation↑; p62, FTH1, GSH, FTO↓	(59)
Tan *et al*, 2022		MSC-ex	HSC-LX2	CCl4 induced liver fibrosis model in BALB/c mice	Ferritinophagy↑; ferroptosis↑	LC3II, Beclin1, ferrous ion, ROS, lipid peroxidation↑; GSH, GPX4, MMP, xCT↓; mitochondrial shrinkage	(60)

Table I. Continued.

Authors, year	Type of liver diseases	Autophagy/ ferroptosis modulators	Experimental models		Autophagy/ ferroptosis status	Related biological effects	(Refs.)
			In vitro	*In vivo*			
Kong *et al*, 2019		Artesunate	HSC-LX2, primary mouse HSCs	CCl4 induced liver fibrosis model in ICR mice	Ferritinophagy↑; ferroptosis↑	LC3II, LC3 puncta, autophagic flux, autophagosomes ferrous ion, lipid ROS, MDA, lipid peroxidation, Ptgs2↑; NCOA4, FTH1, p62, GSH, GPX4↓; mitochondrial shrinkage	(61)
Zheng *et al*, 2022		Curcumol	HSC-T6		Ferritinophagy↑; ferroptosis↑	NCOA4, LC3II, Beclin1, autophagy flux, iron content, ROS, ACSL4, Ptgs2↑; p62, FTH1, MMP, GPX4, xCT↓; mitochondrial shrinkage and cristae loss	(62)
Zhang *et al*, 2021		Dihydroartemisinin	Primary rat HSCs	CCl4 induced liver fibrosis model in SD rats	Ferritinophagy↑; ferroptosis↑	NCOA4, LC3II, Atg5, iron content, lipid ROS, MDA, ACSL4, SLC11A2↑; GPX4, xCT, GSH↓; mitochondrial shrinkage and cristae loss	(63)
Li *et al*, 2025		Artemether	HSC-LX2	CCl4 induced liver fibrosis model in ICR mice	Ferritinophagy↑; ferroptosis↑	NCOA4, LC3II, MDA, ROS, iron content↑; FTH1, p62, GSH↓	(64)
Yi *et al*, 2021		Berberine	HSC-LX2, HSC-T6	Thioacetamide (TAA) and CCl4-induced liver fibrosis model in C57BL/6 mice	Autophagy↓; ferroptosis↑	p62, ferrous ion, ROS, MDA, 4-HNE, Ptgs2, FTH1 ubiquitination↑; LC3II, Atg5, Atg7, FTH1, GSH, GPX4, autophagosome, autophagic flux↓; mitochondrial shrinkage	(65)
Liu *et al*, 2020	HCC	Sorafenib	HepG2, Huh7		Ferritinophagy↑; ferroptosis↑	LC3II, autophagic flux, autophagosome, ferrous ion, MDA, cIARS, cIARS-ALKBH5 interaction, BCl2-Beclin1 interaction↑; NCOA4, p62, FTH1, GSH ↓	(66)
Bi *et al*, 2023		Lenvatinib; erastin	HepG2, Huh7		ER-phagy↑; ferroptosis↑	circFAM134B, LC3II, ferrous ion, MDA, ROS↑; FAM134B, REEP5, GSH, GPX4, xCT↓	(67)
Liu *et al*, 2022		Sorafenib	HepG2, Huh7		ER-phagy↑; ferroptosis↑	Autophagosomes engulfed ER fragments, swelled and deformed ER, ferrous ion, lipid ROS↑; FAM134B, Trap-α, REEP5, GPX4↓	(68)

Table I. Continued.

Authors, year	Type of liver diseases	Autophagy/ ferroptosis modulators	Experimental models		Autophagy/ ferroptosis status	Related biological effects	(Refs.)
			In vitro	*In vivo*			
Yang *et al*, 2023		Sorafenib	HepG2, Huh-7		Ferritinophagy↑; ferroptosis↑	NCOA4, ferrous ion, lipid ROS, MDA, PTBP1↑; GSH, FTH1↓	(69)
Hu *et al*, 2022; Han *et al*, 2021		PNO1	Hep3B, HLE	Xenografted human HCC from BALB/c nude mice	Autophagy↑; ferroptosis↓	LC3II, Beclin1, Atg5, Atg7, autophagic flux, p-Erk, xCT, GSH↑; p62, lipid ROS, MDA↓	(70,71)
Zhang *et al*, 2023		TSPO	HCCLM3, MHCC97H	Xenografted human HCC from BALB/c nude mice	Autophagy↓; ferroptosis↓	p62, GSH, GPX4, Nrf2, HO-1, NQO1, GCLC, GCLM, PPAR-γ↑; LC3II, autophagy flux, ferrous ion, ROS, lipid ROS, Keap1-Nrf2 interaction↓	(72)
Wang *et al*, 2021		Erastin, sorafenib, or sulfasalazine	HepG2	Xenografted human HCC from C57BL/6 mice	Ferritinophagy↑; ferroptosis↑	GFP-LC3 puncta, ferrous ions, MDA, p-AMPK(Thr172) ↑; NCOA4, GSH, system Xc-activity, BCAT2, SREBP1, SREBP1-BCAT2 interaction↓	(73)
Wu *et al*, 2023		IGF1	HCCLM3, Huh7	Xenografted human HCC from BALB/c nude mice	CMA↓; ferroptosis↓	GPX4, GSH, GPX4-CKB interaction, AKT-CKB interaction, p-CKB (Thr133), p-GPX4 (Ser104)↑; lipid ROS, GPX4-Hsc70c-Lamp2A interaction↓	(74)
Li *et al*, 2024		Erastin, sorafenib, RSL3	HepG2, Huh7	Xenografted human HCC from BALB/c nude mice	Ferritinophagy↑; ferroptosis↑	ROS, iron content, MDA, LC3II, Atg5, NCOA4, WTAP, YTHDC2↑; GSH FTH1, p62↓	(75)
Cao *et al*, 2024		USP24	HepG2, SMMC-7721, Huh7, HCCLM3	Xenografted human HCC from BALB/c nude mice	Ferritinophagy↑; ferroptosis↑	NCOA4, ULK1, Atg5, Beclin1, LC3II, autophagic vesicles, USP24-Beclin1 interaction, iron content, TFR1, MDA↑; Beclin1 polyubiquitination, p62, GPX4, FPN1, GSH↓	(76)
Jiang *et al*, 2025		USP2	Huh7, HepG2, SMMC-7721, and SNU-449	Xenografted human HCC from BALB/c nude mice	Clockophagy↓; ferroptosis↓	ARNTL, USP2-ARNTL interaction, GSH, HIF1α, xCT↑; ARNTL polyubiquitination, ROS, MDA↓	(77)

Table I. Continued.

Authors, year	Type of liver diseases	Autophagy/ ferroptosis modulators	Experimental models		Autophagy/ ferroptosis status	Related biological effects	(Refs.)
			In vitro	*In vivo*			
Xiu *et al*, 2022		Caryophyllene oxide	HCCLM3, HUH7	Xenografted human HCC from BALB/c nude mice	Ferritinophagy↑; ferroptosis↑	NCOA4, LC3II, LC3II-NCOA4 colocalization, lysosome, ferrous ions, ROS, lipid peroxidation, MDA↑; GPX4, Nrf2, HO-1, and NQO1, T-AOC, FTH1↓; mitochondrial shrinkage and cristae loss	(78)
Xiu *et al*, 2023		Esculetin	HUH7, HCCLM3	Xenografted human HCC from BALB/c nude mice	Ferritinophagy↑; ferroptosis↑	NCOA4, LC3II, autophagy flux, lysosome, ferrous ions, ROS, MDA, lipid peroxidation↑; p62, FTH1, GPX4, NFE2L2, HO-1, T-AOC, MMP↓; mitochondrial shrinkage and cristae loss	(79)
Zhu *et al*, 2023		EChLESs	SNU-387, HUH-7, Bel7402	Xenografted human HCC from BALB/c nude mice	Ferritinophagy↑; ferroptosis↑	NCOA4, LC3II, autophagosomes, ferrous ions, mtROS, lipid peroxidation, HIF-α↑; p62, FTH1, GSH, MMP, p-mTOR (Ser2448), mTOR↓; mitochondrial shrinkage	(80)
Li *et al*, 2021		Artesunate combined with sorafenib	HepG2, Huh7, SNU-182, SNU-449	Xenografted human HCC from BALB/c nude mice	Ferritinophagy↑; ferroptosis↑	Ferrous ions, ROS, mtROS, MDA, lipid peroxidation, cathepsin L, cathepsin B, lysosomal activity↑; FTH1, FTL, TFR1, GSH, MMP, ATP↓	(81)
Cui *et al*, 2023	MS liver injury	High-fat and high-fructose diet		SD rats	Ferritinophagy↓; ferroptosis↑	FTH1, TFR1, Iron content, MDA, lipid peroxidation↑; NCOA4, GPX4, SOD, xCT, FPN1, NCOA4-FTH1 colocalization and interaction↓	(82)
Liu *et al*, 2023	NAFLD	Saturated fatty acids	AML12	C57BL/6J	Autophagy↓; ferroptosis↑	p62, lipid droplets, MDA, lipid peroxidation, Keap1, Ptgs2, ACSL4, p-mTOR↑; LC3II, Atg7, autophagic flux, autophagosome, GSH, GPX4, Nrf2, xCT↓	(83)
Honma *et al*, 2023	NASH	Iron dextran		HFC diet fed SHRSP5/ Dmcr rats	Ferritinophagy, lipophagy↑; ferroptosis↑	NCOA4, Rab10, nuclear TFEB, DNM2, ULK1, UVRAG, Atg14, Lamp2, TRPML1, CLN3, iron content, 4-HNE, ALOX15, Ptgs2, calcineurin activity↑; GPX4↓; mitochondrial shrinkage	(84)

Table I. Continued.

Authors, year	Type of liver diseases	Autophagy/ ferroptosis modulators	Experimental models		Autophagy/ ferroptosis status	Related biological effects	(Refs.)
			In vitro	*In vivo*			
Li *et al*, 2023	Acute liver injury	Liensinine	RSL3-treated alternatively activated macrophages	LPS/D-GalN-induced liver injury model in C57BL/6 mice	Ferritinophagy↓; ferroptosis↓	LC3II, p62, autophagosomes↑; ferrous ions, ROS, lipid peroxidation, damaged mitochondria ↓; ferritin-Lamp1 colocalization, LC3-Lamp1 co localization↓	(85)
Zhang *et al*, 2025		Quercetin	Mouse primary hepatocytes	LPS/γ-D-glutamyl-meso-diaminopimelic acid-induced liver injury model in C57 mice	Ferritinophagy↓; ferroptosis↓	MDA, iron content, lipid ROS, ACSL4, ALOX15, NCOA4, LC3-NCOA4 colocalization, FTH1-Lamp1 colocalization, p-STAT3, IL-6↓; GPX4, GSH, xCT, SLC3A2, FTH1↑; mitochondrial shrinkage and cristae loss	(86)
Wang *et al*, 2022		YAP1	LPS-treated HL7702 cells	CLP-induced liver injury model in C57BL/6 mice	Ferritinophagy↓; ferroptosis↓	FTH1, xCT, GSH, GPX4↑; NCOA4, LC3II, ROS, lipid ROS, ferrous ions, MDA, ACSL4, SFXN1, LC3-ferritin co localization, ferritin-Lamp1 colocalization, NCOA4-FTH1 interaction, damaged mitochondria↓	(87)
Jia *et al*, 2022		SARS-CoV-2		SARS-CoV-2 patients' liver	Ferritinophagy↑; ferroptosis↑	NCOA4, LC3II, serum ferritin, iron content, ROS, lipid peroxidation↑; FTH1↓	(88)
Liu *et al*, 2023		Sulforaphane	H_2O_2 treated HL7702 or BRL cells	CCL4-induced liver injury model in SD rats	Autophagy↑; ferroptosis↓	LC3II, autophagic flux, Nrf2, xCT, GSH, GPX4, Beclin1-xCT interaction↑; p62, ferrous ion, ROS, lipid ROS, damaged mitochondria↓	(89)
Savic *et al*, 2024	Diabetic liver damage	Sulforaphane		Streptozotocin-induced diabetes model in C57BL/6 mice	Ferritinophagy↓; ferroptosis↓	GSH, GPX4, p-Nrf2, p-ACC, SOD, MnSOD, CAT, TrxR↑; FTH1, FPN1, FTH1-LC3 colocalization, iron content, 4-HNE, lipofuscin↓	(90)

Table I. Continued.

Authors, year	Type of liver diseases	Autophagy/ ferroptosis modulators	Experimental models		Autophagy/ ferroptosis status	Related biological effects	(Refs.)
			In vitro	*In vivo*			
Wang *et al*, 2024	Liver cell senescence	DMC	Etoposide treated HL77O2 cells	C57BL/ 6J mice	Ferritinophagy↑; ferroptosis↑	NCOA4, LC3II, FECH, iron content, MDA, LPCAT3, POR, ALOX5↑; p62, ferritin↓; mitochondrial shrinkage and cristae loss	(91)

↑, upregulation; ↓, downregulation; NCOA4, nuclear receptor coactivator 4; LC3II, microtubule-associated protein light chain 3 II; MDA, malondialdehyde; FTH1, ferritin heavy chain 1; HspA8, heat shock protein A8; HMGB1, high-mobility group box 1; GSH, glutathione; GPX4, glutathione peroxidase 4; TFR1, transferrin receptor 1; ROS, reactive oxygen species; PERK, protein kinase R-like endoplasmic reticulum kinase; eIF2α, eukaryotic initiation factor 2α subunit; ATF4, activation transcription factor 4; FPN1, ferroportin 1; Rab7, Ras related protein Rab7a; mtROS, mitochondrial reactive oxygen species; Ptgs2, prostaglandin endoperoxide synthase 2; FFAs, free fatty acids; MMP, mitochondrial membrane potential; Keap1, Kelch-like ECH-associated protein 1; xCT, solute carrier family 7 member 11; SLC3A2, solute carrier family 3 member 2; Nrf2, E2-related factor 2; HO-1, heme oxygenase-1; Foxo1, forehead box transcription factor class O 1; ACSL4, acyl-coenzyme A synthetase long-chain family member 4; TXNIP, thioredoxin-interacting/inhibiting protein; FSP1, ferroptosis suppressor protein 1; SOD1, superoxide dismutase 1; TRX, thioredoxin; GRP78, glucose-regulated protein 78; CHOP, C/EBP homologous protein; Atg, autophagy-related gene; AMPK, adenosine monophosphate-dependent protein kinase; ULK1, UNC51-like kinase 1; mTOR, mammalian target of rapamycin; TOMM20, translocase of outer mitochondrial membrane protein 20; PINK1, phosphatase and tensin homolog-induced kinase 1; T-AOC, total antioxidant capacity; PI3K, phosphatidylinositol 3-kinase; JNK, JNK, c-Jun N terminal kinase; PDCD4, programmed cell death protein 4; CCl4, carbon tetrachloride; FUNDC1, FUN14 domain-containing protein 1; HSC, hepatic stellate cell; BDL, bile duct ligation; HCC, hepatocellular carcinoma; Atg16L1, autophagy related 16 like 1; SLC11A2, solute carrier family 11 member 2; ZFP36, ZFP36 ring finger protein; FBXW7, F-box and WD repeat domain containing 7; ELAVL1, ELAV like RNA binding protein 1; m6A, N6-methyladenosine; METTL4, methyltransferase like 4; FTO, obesity-associated protein; MSC-ex, mesenchymal stem cells-derived exosomes; 4-HNE, 4-hydroxynonenal; cIARS, hsa_circ_0008367; ALKBH5, AlkB Homolog 5; Bcl2, B cell lymphoma 2; circFAM134B, hsa_circ_0128505; FAM134B, family with sequence similarity 134 member B; REEP5, receptor expression-enhancing protein 5; Trap-α, translocon-associated protein α; ER, endoplasmic reticulum; PTBP1, polypyrimidine tract-binding protein 1; PNO1, partner of NOB1; Erk, extracellular signal-regulated kinase; TSPO, mitochondrial translocator protein; NQO1, NAD(P)H quinone oxidoreductase 1; GCLC, glutamate-cysteine ligase; GCLM, glutamate-cysteine ligase modifier subunit; PPAR-γ, peroxisome proliferator-activated receptor γ; SREBP1, sterol response element binding protein 1; BCAT2, Branched-chain amino acid; IGF1, insulin-like growth factor 1; CKB, creatine kinase B; AKT, protein kinase B; Hsc70c, heat shock cognate 71 kDa protein cytosolic; Lamp2, lysosome-associated membrane protein 2; WTAP, WT1 associated protein; YTH domain-containing protein 2, USP24, ubiquitin-specific protease 24; ARNTL, brain and muscle ARNT-like protein 1; NFE2L2, nuclear factor erythroid 2 like 2; EChLESs, electrophilic sesquiterpenes isolated from *Eupatorium chinense* L.; HIF-α, hypoxia-inducible factor α; FTL, ferritin light chain; ATP, adenosine triphosphate; MS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; NASH, Non-alcoholic steatohepatitis; HFC, high-fat and high-cholesterol; SHRSP5/Dmcr, stroke-prone spontaneously hypertensive; TFEB, transcription factor EB; DNM2, dynamin 2; UVRAG, UV radiation resistance-associated gene; TRPML1, transient receptor potential cation channel, mucolipin subfamily, member 1; CLN3, lysosomal/endosomal transmembrane protein, battenin; ALOX15, arachidonate 15-lipoxygenase; LPS, lipopolysaccharide; D-GalN, D-galactosamine; YAP1, Yes-associated protein1; CLP, cecal ligation and puncture; SFXN1, siderofexin 1; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; H_2O_2, hydrogen peroxide; ACC, acetyl-CoA carboxylase; CAT, catalase; TrxR, thioredoxin reductase; DMC, 4,4'-dimethoxychalcone; FECH, ferrochelatase; LPCAT3, lysophosphatidylcholine acyltransferase 3; POR, NADPH-cytochrome P450 reductase; ALOX5, arachidonate 5-lipoxygenase.

acetaminophen-induced liver injury, excessive lipid peroxidation, GSH depletion, GPX4 suppression, increased LC3II expression, p62 degradation and autophagosomes accumulation were observed in hepatic cells, which are in accordance with the typical features of ferroptosis and autophagy, respectively. Ferroptosis is responsible for acetaminophen-induced liver injury, and ferroptosis inhibitor could eliminate these ferroptosis characteristics and alleviate acute hepatotoxicity. These studies collectively demonstrate the involvement of autophagy and ferroptosis in acetaminophen-induced liver injury and raise the possibility of a positive feedback loop between autophagy and ferroptosis in liver cells in response to acetaminophen (101,102). However, this relationship between autophagy and ferroptosis during acetaminophen-induced liver injury remains controversial. It has been reported that acetaminophen injection led to a significant release of intracellular iron and subsequent ROS accumulation by activating ferritinophagy on the one hand and inhibiting the endogenous nuclear factor E2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) antioxidant pathway on the other hand, which contributes to clear intracellular ROS. The combined effect of both factors culminates in liver cell ferroptosis and finally induces significant liver injury (44). In contrast to a cell death mechanism favoring ferroptosis, autophagy also plays a critical protective role against acetaminophen-induced hepatic cell death. Instead of exacerbating acetaminophen-induced liver injury, the pharmacological induction of autophagy exhibits a protective effect. The removal of damaged mitochondria by mitophagy and the consequent reduction in ROS production could mediate this protection (101). Another study demonstrated that acetaminophen administration decreased the expression levels of molecules related to the Nrf2/HO-1 antioxidant pathway and increased the ROS content, resulting in impaired antioxidant capacity and oxidative stress in mouse liver. Simultaneously, weakened autophagy activity and enhanced ferroptosis were observed (45). Furthermore, it has been confirmed that the forehead box transcription factor class O 1 (Foxo1) is a promoter for both the suppression of autophagy and the induction of ferroptosis triggered by acetaminophen. Notably, mice subjected to acetaminophen treatment exhibit elevated levels of Foxo1. However, hepatocyte-specific deletion of Foxo1 ameliorates liver injury by stimulating autophagy and inhibiting ferroptosis (46).

Taken together, drugs such as rifampicin, methotrexate, toosendanin, and triptolide induce liver damage through ferritinophagy- or lipophagy-dependent ferroptosis. Acetaminophen overdose also involves both autophagy and ferroptosis, but their relationship is a subject of debate, with autophagy exerting both protective and detrimental effects (Fig. 5).

Crosstalk between autophagy and ferroptosis in toxin-induced liver injury. The liver is the main organ in the body for the accumulation and detoxification of a number of toxins, making it highly susceptible to their adverse effects. The crosstalk between autophagy and ferroptosis is implicated in the molecular mechanisms of liver injury induced by various exogenous toxins. Acrylamide is a heat-induced toxic agent that widely exists in the environment, and liver injury is a prevalent reported toxic effect of this chemical (103). An RNA-sequencing and bioinformatics analysis for evaluating

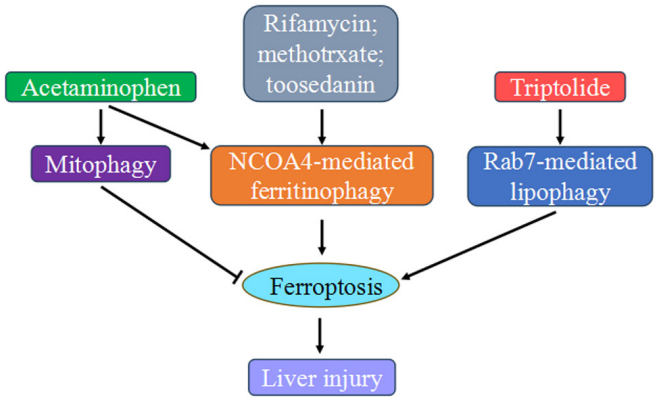

Figure 5. Crosstalk between autophagy and ferroptosis in drug-induced liver injury. NCOA4, nuclear receptor coactivator 4; Rab7, Ras related protein Rab7a.

and comparing the overall gene expression pattern of liver cells showed that exposure to acrylamide markedly activated oxidative stress signaling pathways and upregulated autophagy and ferroptosis pathways (47). Further experiments confirmed that acrylamide decreased mitochondrial membrane potential (MMP) and increased ROS production and Nrf2 levels, leading to GSH deactivation and GPX4 degradation and inevitably inducing oxidative stress and ferroptosis (47,104). Acrylamide also induced autophagy activation as indicated by LC3II elevation and p62 reduction (105). Moreover, ROS scavenger and autophagy inhibition consistently and markedly suppressed acrylamide-induced autophagy and ferroptosis. These results suggest that acrylamide-induced ferroptosis is dependent on oxidative stress-driven autophagy. Acrylamide treatment also increases the NCOA4 level and decreases the FTH1 level, indicating the activation of ferritinophagy. Notably, quercetin, a natural antioxidant flavonoid, possesses the ability to counter acrylamide-induced liver injury by targeting autophagy-dependent ferroptosis. Quercetin effectively reduces ROS accumulation to combat acrylamide-induced oxidative stress and autophagy and eventually inhibits ferroptosis. Additionally, quercetin specifically binds to NCOA4 protein to disrupt the NCOA4A-FTH1 interaction, impairs ferritinophagy, and consequently blocks ferroptosis by preventing FTH1 degradation and reducing the amount of bioavailable intracellular iron in acrylamide-exposed liver cells (47).

Cadmium, nickel and copper are common harmful heavy metals released by industrial manufacturing or naturally present in the environment. They greatly endanger liver health. Excessive intake leads to abnormal accumulation and homeostasis imbalance of these metals in the liver, damaging its histomorphology and interfering with its normal physiological functions (106). Autophagy and ferroptosis are pivotal underlying mechanisms involved in the liver injury induced by these metals and the crosstalk between these processes occur during the pathogenesis of this condition. In chicken liver, copper exposure inactivates the Nrf2/Kelch-like ECH-associated protein 1 (KEAP1) signaling pathway, reduces the expression of its downstream gene targets such as *xCT* and *GPX4*, disrupts the endogenous antioxidant GSH metabolism, promotes lipid peroxidation and induces the typical morphological characteristics in mitochondria associated with ferroptosis. Copper also markedly augments the mRNA and protein expression

levels of NCOA4. Therefore, NCOA4-mediated ferritinophagy plays a critical role in promoting copper induced ferroptosis in the liver (48). Similar patterns occur with nickel or cadmium exposure, which enhances ferritin degradation through NCOA4-mediated ferritinophagy and activates ferroptosis as indicated by the occurrence of iron accumulation, lipid peroxidation and impairment of the antioxidant system. The use of ferroptosis inhibitors or autophagy inhibitors markedly promotes ferroptosis resistance and reduces liver damage. These results demonstrate that ferritinophagy as a trigger of ferroptosis is closely involved in the cell death caused by nickel or cadmium exposure (49,50). Mechanistically, mitochondria damage, manifesting as mitochondrial ROS increase, MMP depolarization and interference with mitochondrial respiratory chain, is a significant factor for autophagy and ferroptosis induction under nickel exposure (50). Regarding the toxic effect of cadmium on the liver, the ER stress response is also activated through the PERK-eIF2α-ATF4-C/EBP homologous protein signaling pathway. ER stress activation not only initiates autophagy but also exacerbates ferroptosis, indicating that ER stress participates in the synergistic effect of ferritinophagy and ferroptosis (49).

Arsenic and fluoride are widely known as hazardous nonmetallic pollutants. Their contamination poses severe threats to livestock and humans and the liver is an important target organ of their toxicology (107). Chicken liver injury induced by long-term arsenic exposure is inseparable from ferritinophagy-mediated ferroptosis, and the mitochondria might play a crucial role in the process. Arsenic exposure induced mitochondrial dysfunction and led to enhanced ROS production, which triggered ferritinophagy via the AMPK/mTOR/ULK1 signaling pathway and markedly altered the expression levels of ferroptosis-related proteins in chicken livers (51). Mitochondrial damage, increased mitochondrial ROS generation and free iron-mediated ferroptosis are typically observed in cell and animal models of fluoride-induced liver injury (108). Increased LC3II expression and p62 accumulation are also noted, indicating the fusion of autophagosomes and lysosomes is inhibited and autophagic degradation is hindered (52). Such outcomes might be attributed to the excess iron, which exerts an inhibitory effect on the autophagic process (109). The autophagy activator rapamycin not only ameliorates fluoride-induced autophagic flux blockage by correcting autophagic degradation impairment but also inhibits fluoride-mediated ferroptosis by reducing the iron content and suppressing lipid peroxidation. Additionally, the ferroptosis inhibitor Fer-1 simultaneously ameliorates ferroptosis and alleviates the impaired autophagic degradation at the same time (52). Thus, a bidirectional regulation exists between autophagy and ferroptosis in fluoride-induced liver injury.

Dysregulated ferroptosis has been implicated in alcohol liver injury, as evidenced by iron disorder and the increased intracellular lipid peroxidation (53,110). The ferroptosis-promoting effect of ethanol and its highly active metabolite acetaldehyde is highly dependent on autophagy. On the one hand, ethanol or acetaldehyde promotes ferritin degradation and free iron release via NCOA4-mediated ferritinophagy, contributing to ferroptosis. On the other hand, PTEN-induced putative kinase 1 (PINK1)/Parkin-mediated mitophagy is arrested, leading to mitochondrial damage

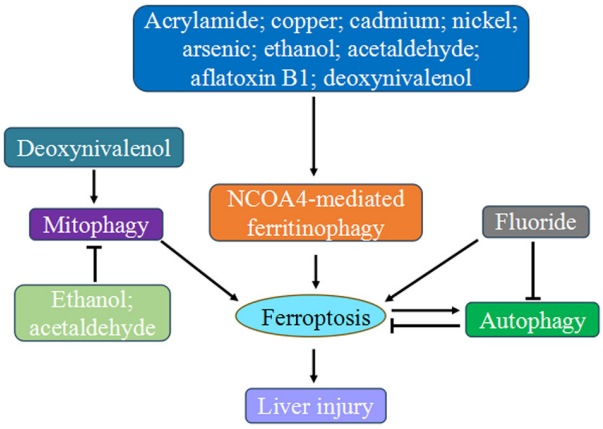

Figure 6. Crosstalk between autophagy and ferroptosis in toxin-induced liver injury. NCOA4, nuclear receptor coactivator 4.

without clearance in time and elevated ROS and further stimulating ferroptosis. Ferroptosis inhibitor Fer-1 reverses elevated ferritinophagy, implying that ferroptosis induces autophagy activation in a feedback manner (53). Silibinin is the major active constituent of milk thistle seed extract and has multiple targets. It simultaneously reverses NCOA4-mediated ferritinophagy, restores PINK1/Parkin-mediated mitophagy, modulates iron metabolism and limits lipid peroxidation, thereby exhibiting hepatoprotective properties in ethanol- or acetaldehyde-induced liver injury model (53).

Aflatoxin B1 and deoxynivalenol, two extensively prevalent mycotoxins, poses a considerable public health threat owing to its high propensity to contaminate agricultural products and induce liver damage upon consumption. One manner in which both of them inflicts liver damage is through ferritinophagy-mediated ferroptosis (54,55). At the molecular level, aflatoxin B1 disturbs iron balance by affecting ferritinophagy, a process that is reliant on the PI3K/AKT/mTOR/ULK1 pathway. The disruption leads to iron accumulation, which in turn intensifies lipid peroxidation and causes ferroptosis (54). The ability of deoxynivalenol to regulate ferritinophagy is achieved partly by accelerating the ubiquitination-mediated degradation of programmed cell death protein 4, thereby upregulating NCOA4 expression through the c-Jun N-terminal kinase-c-Jun axis. Moreover, deoxynivalenol has the capacity to induce excessive mitophagy, and the administration of a mitophagy activator further exacerbated the hepatic cell ferroptosis-promoting effect of deoxynivalenol, suggesting that mitophagy actually promotes ferroptosis, rather than exerting an inhibitory effect (55).

Overall, these findings provide substantial evidence of a crosstalk between autophagy and ferroptosis in the liver injury caused by various toxins, including acrylamide, heavy metal, nonmetallic pollutants, alcohol, and mycotoxins. Mainly through activating ferritinophagy, they disrupt iron homeostasis, leading oxidative stress and lipid peroxidation, which trigger ferroptosis (Fig. 6). Notably, substances like quercetin and silibinin show promise in mitigating liver damage by targeting these pathways.

Crosstalk between autophagy and ferroptosis in liver fibrosis. Liver fibrosis is a reversible pathophysiological condition

mainly characterized by the death of normal liver cells and the excess deposition of extracellular matrix. Activated hepatic stellate cells (HSCs) are the most important producers of extracellular matrix (111). The crosstalk between autophagy and ferroptosis happens during the induction or prevention of liver fibrosis. Silica nanoparticles (SiNPs) are composed of silicon dioxide and have a number of applications, including in biomedicine, food and chemical and textile industries. Animal experiments on respiratory exposure to SiNPs reveal that SiNPs accumulate primarily in the liver and induce liver toxicity, manifested as ferritinophagy-mediated ferroptosis and fibrosis (56,112). SiNPs administration causes mitochondrial vacuolation and mitochondrial membrane rupture, increases lipid peroxidation and iron accumulation and decreases GPX4 levels, suggesting that SiNPs lead to ferroptosis in liver cells. SiNPs exposure also evokes ferritinophagy, indicated by NCOA4 and LC3II upregulation and FTH1 downregulation. NCOA4 knockdown can alleviate SiNP-triggered ferroptosis in liver cells, indicating that NCOA4-mediated ferrinophagy is responsible for ferroptosis (56). Mitophagy is also reported to promote liver fibrosis through a ferroptosis-dependent manner. FUN14 domain-containing protein 1 (FUNDC1), a mitophagy receptor highly expressed in the liver tissues of patients suffering from liver fibrotic injury as well as carbon tetrachloride-challenged mice, has been identified as a culprit in eliciting liver cell ferroptosis. Through directly interacting with GPX4, FUNDC1 facilitates the recruitment of GPX4 into mitochondria, where it undergoes degradation by mitophagy, ultimately triggering ferroptosis (57). Parenchymal cell death further activates HSCs, resulting in the upregulated expression of liver fibrosis indicators, especially a-smooth muscle actin and collagen I and II (56).

Targeted scavenging of activated HSCs and the consequent blocking of the fibrogenic effect at the source have been proposed as an effective therapeutic approach to reverse liver fibrosis. Ferroptosis induction has been proven to be a new control measure for HSCs activation. RNA binding proteins ZFP36 ring finger protein (ZFP36) and ELAV like RNA binding protein 1(ELAVL1) plays a pivotal role in triggering HSCs ferroptosis to alleviate liver fibrosis caused by ferroptosis inducers such as sorafenib, erastin, and RSL3. The activation of ferritinophagy is necessary for both proteins to regulate ferroptosis in HSCs (23,58). Exposure to ferroptosis inducers apparently increases the expression level of E3 ubiquitin ligase F-box and WD repeat domain containing 7 (FBXW7) in HSCs. As shown by immunocoprecipitation assay and ubiquitination assay, FBXW7 directly binds to ZFP36 and decreases ZFP36 protein expression by ubiquitination-mediated proteasomal degradation. ZFP36 downregulation promotes ferritinophagy activation by stabilizing *Atg16L1* mRNA, which mediates ferroptosis by degrading FTH1 in a NCOA4-dependent manner (23). Contrary to the decrease in ZFP36, ELAVL1 expression increases markedly through the inhibition of the ubiquitin-proteasome pathway following ferroptosis inducers treatment. ELAVL1 abrogates *Beclin1* mRNA decay by binding to the AU-rich elements within the 3'-untranslated region (UTR), and in turn contributes to ferritinophagy activation and ferroptosis induction in HSCs (58). Additionally, the autophagy signaling pathway is involved in N6-methyladenosine (m^6A) modification-induced HSC ferroptosis. RNA sequencing shows that ferroptosis inducers markedly increases m^6A modification in *Beclin1* mRNA by upregulating methylase METTL4 and downregulating demethylase FTO. m^6A-binding protein YTHDF1 promotes *Beclin1* production by recognizing m^6A binding sites, thereby triggering ferritinophagy, and eventually leading to ferroptosis (59). Moreover, Beclin1 protein is enriched in mesenchymal stem cells-derived exosomes (MSC-ex), which are the membrane vesicles encapsulating MSCs-derived proteins, lipids, mRNAs and noncoding RNA (113). MSC-ex specifically targets HSCs activation and promotes HSCs ferroptosis by delivering Beclin1 proteins into HSCs, which improves autophagy marker LC3II expression and promotes iron release. Possibly MSC-ex induce ferroptosis through exosomal Beclin1-induced ferritinophagy, and Beclin1 can be a potential biofactor for alleviating liver fibrosis (60).

Natural active products from traditional Chinese medicines, such as artesunate, berberine, curcumol, dihydroartemisinin and artemether, have made marked advances in the prevention and treatment of liver fibrosis by inducing ferroptosis. Studies have highlighted the importance of autophagy as an emerging mechanism of these products in enhancing ferroptosis and proposed a potential novel therapeutic strategy for liver fibrosis. Artesunate, berberine, curcumol, dihydroartemisinin or artemether treatment clearly promote ferroptosis to eliminate activated HSCs, reduce the deposition of extracellular matrix, alleviate mouse liver fibrosis and restore mouse liver function. In terms of mechanism, artesunate, curcumol, dihydroartemisinin and artemether mediate FTH1 degradation by increasing NCOA4, leading to ferritinophagy activation, iron accumulation, lipid peroxidation elevation, antioxidant capacity loss and ferroptosis occurrence. By contrast, the interdiction of ferritinophagy completely abolishes the induced ferroptosis and diminishes the efficacy of these natural products against liver fibrosis (61-64). Regarding the anti-fibrosis effect of berberine, the autophagy impairment caused by berberine is incapable of eliminating the increased ROS production and contributes to oxidative stress via a feed-forward loop, which accelerates the ubiquitin-mediated degradation of ferritin and the release of iron. Iron accumulation further amplifies ROS generation through the Fenton reaction, and triggers ferroptosis through lipid peroxidation and GSH depletion in activated HSCs, thereby providing a brake on the fibrogenic response (65).

Thus, liver fibrosis involves liver parenchymal cell ferroptosis and HSCs activation. Ferritinophagy and mitophagy can promote this process. Targeting activated HSCs through ferroptosis induction offers a therapeutic approach. Natural products from traditional Chinese medicine have potential in preventing liver fibrosis by promoting ferroptosis, with autophagy playing a key role (Fig. 7).

Crosstalk between autophagy and ferroptosis in HCC. HCC is among the most widely occurring tumors with high incidence and mortality rates (66). Differentially expressed ferritinophagy-related genes are markedly associated with patient prognosis: individuals with high FTH1 and FTL expression levels exhibit considerably poorer survival rates than individuals with low expression levels (114). Hence, ferritinophagy possibly regulates HCC by influencing ferroptosis. Circular

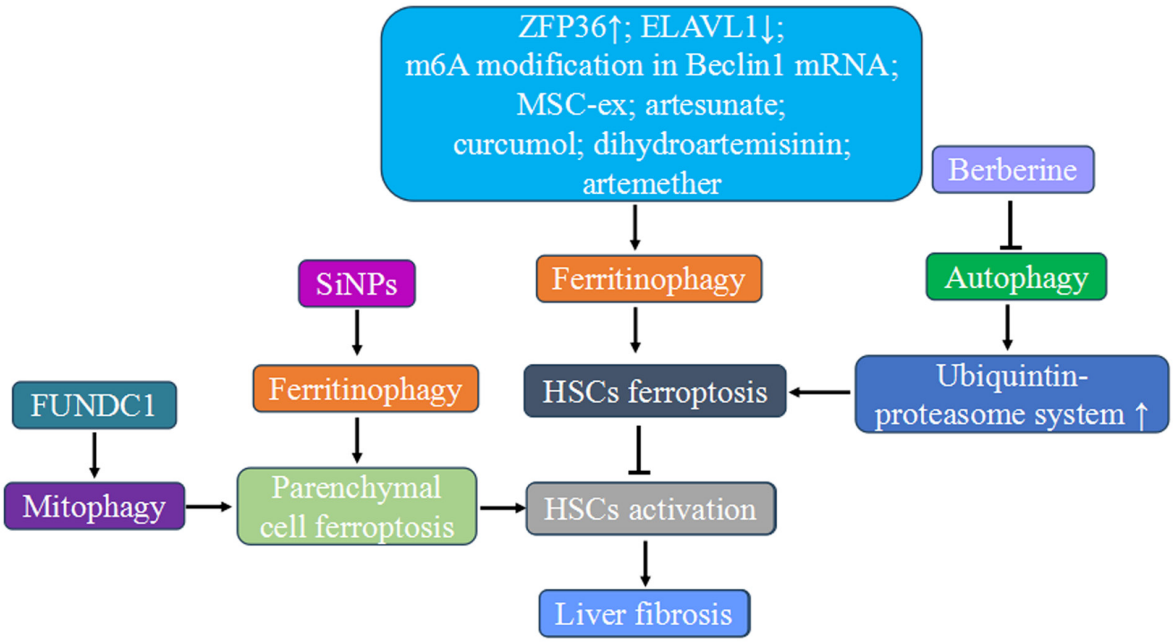

Figure 7. Crosstalk between autophagy and ferroptosis in liver fibrosis. ZFP36, ZFP36 ring finger protein; ELAVL1, ELAV like RNA binding protein 1; MSC-ex, mesenchymal stem cells-derived exosomes; SiNPs, Silica nanoparticles; FUNDC1, FUN14 domain-containing protein 1; HSCs, hepatic stellate cells.

RNAs (circRNAs) and RNA-binding proteins participates in the development and progression of HCC by regulating autophagy-mediated ferroptosis. CircRNAs, a group of endogenous non-coding RNAs with covalently closed-loop structures, originate from the back-splicing events of primary mRNAs. By binding with their corresponding microRNAs or proteins, circRNAs participate in the multifaceted biological regulation of cellular metabolism (115). A study has found that circIARS, a novel circRNA derived from the *IARS* gene, was the most highly expressed circRNA after ferroptosis inducer sorafenib treatment in HCC cells (66). circIARS increased the vulnerability to sorafenib and this effect partially depended on repressing the biological role of the RNA binding protein AlkB Homolog 5 (ALKBH5), a negative regulator of ferritinophagy in HCC cells. Mechanistic identification revealed that circIARS physically interacted with ALKBH5 and promoted phagophore nucleation and ferritinophagy induction by suppressing the dissociation of Bcl2-Beclin1 complex, resulting in the ferroptotic events by increasing iron-binding ferritin turnover and iron release (66). Another study demonstrated the regulatory effect of the circRNA of the family with sequence similarity 134, member B (circFAM134B) for ER-phagy-mediated ferroptosis in HCC cells treated with multi-targeted tyrosine kinase inhibitor lenvatinib. FAM134B is a receptor protein for selectively recognizing and degrading ER fragments and the expressions of both circFAM134B and FAM134B in HCC cells were effectively induced by lenvatinib. circFAM134B acted as a sponge that competitively bound to poly (A) binding protein cytoplasmic 4, thereby destabilizing *FAM134B* mRNA by facilitating nonsense-mediated mRNA decay and suppressing the process of FAM134B-mediated ER-phagy. Moreover, circFAM134B is a positive regulator of ferroptosis, and loss of circFAM134B markedly reversed the ferroptosis phenotype in HCC cells. Concurrently, the levels of FAM134B and its colocalization with LC3 markedly increased after si-circFAM134B transfection. These results suggest that targeting circFAM134B could markedly affect FAM134B-mediated ER-phagy, thereby improving the ferroptosis sensitivity of HCC cells to lenvatinib (67). FAM134B-mediated ER-phagy also plays an important role in the execution of sorafenib-induced ferroptosis in HCC cells. Sorafenib effectively induced the direct interaction between PABPC1 and *FAM134B* mRNA, promoting the translational activation of FAM134B and inducing ER-phagy. *FAM134B* knockdown not only blocked ER-phagy, but also improved the ferroptosis sensitivity of HCC cells (68). Distinct from other selective autophagy pathways that often promote ferroptosis by degrading the cellular components critical for redox homeostasis, ER-phagy inhibits ferroptosis by maintaining ER integrity and modulating stress signaling (116). Moreover, upregulated polypyrimidine tract-binding protein 1 (PTBP1), an RNA-binding proteins, was observed in sorafenib-treated HCC cells. PTBP1 physically interacted with the 5'UTR of the *NCOA4* mRNA sequence and promoted the activation of ferritinophagy by regulating *NCOA4* translation, causing the enhanced degradation of ferritin, accelerated accumulation of intracellular iron and impaired ferroptosis resistance of HCC cells (69). Partner of NOB1 (PNO1) is another RNA-binding protein that inhibits autophagy-mediated ferroptosis by GSH metabolic reprogramming in HCC cells. By promoting autophagy via the mitogen-activated protein kinases signaling pathway, PNO1 mainly affects the levels of intracellular glutamate, which activates system Xc- to import additional cysteine. This highly activated GSH biosynthesis inhibits lipid ROS generation and finally counteracts ferroptosis. Thus, PNO1 is a bona fide ferroptosis inhibitor. The combination of PNO1 inhibition with ferroptosis-inducing drugs markedly strengthens ferroptosis sensitivity (70,71).

Mitochondria damage has become a major factor in oxidative stress and tumorigenesis. Mitophagy prevents the

accumulation of dysfunctional mitochondria to ensure the quantity and quality of the mitochondrial population and maintain stable ROS levels, which lead to oxidative stress (117). Mitophagy and ferroptosis are associated with HCC prognosis. A mitophagy-related signature based on a consensus clustering analysis has identified several mitophagy-related genes closely related to the ferroptosis status and progression of HCC. This signature also exhibits a predictive effect on the prognosis of patients with HCC (118). Moreover, owing to its critical role in maintaining cellular function, targeting mitochondria can be a promising new strategy for HCC treatment. For example, mitochondrial translocator protein (TSPO), a conserved transmembrane protein primarily localized at the outer mitochondrial membrane, is highly expressed in HCC and is markedly associated with poor tumor differentiation, advanced stage, and poor prognosis. Thus, TSPO serves as a putative oncogene and represents a viable candidate for mitochondrial-directed therapeutic strategies in HCC treatment (119). Gain- and loss-of-function experiments present that TSPO upregulation inhibits ferroptosis in HCC cells through the Nrf2-mediated upregulation of antioxidant gene expression, thereby promoting HCC development. Additionally, autophagy inhibition is involved in the underlying mechanisms of TSPO action in HCC. TSPO directly interacts with the autophagy receptor p62, thus interfering with the autophagy degradation of p62. The excessively accumulated p62 competes with Nrf2 for binding to the E3 ubiquitin ligase KEAP1 and disrupts the KEAP1-Nrf2 association, thus preventing Nrf2 from proteasomal degradation and leading to Nrf2 stabilization. Ultimately, ferroptosis is inhibited through the Nrf2-mediated activation of antioxidant gene transcription (72).

Some metabolic enzymes controlling ferroptosis sensitivity in HCC cells involve the autophagy pathway. Branched-chain amino acid aminotransferase 2 (BCAT2) is a key aminotransferase enzyme acting upon sulfur amino acids for the synthesis of glutamate and positively regulates the function of system Xc^- (120). It serves as a specific ferroptosis inhibitor in HCC because the BCAT2-induced increase in intracellular glutamate levels boosts system Xc^- activity, enhances cystine uptake and increases GSH levels to protect HCC cells against ferroptosis (73). The ferritinophagy induction mediated by ferroptosis inducers (erastin, sorafenib and sulfasalazine) leads to rapid ROS accumulation because of the increased cellular iron levels. It also induces AMPK phosphorylation on threonine residue 172, which inhibits the nuclear translocation of sterol response element binding protein 1 and consequently suppresses the transcription of its direct target gene, BCAT2 and enhances the ferroptosis susceptibility of HCC cells (73). Similar to BCAT2, creatine kinase B (CKB) is a novel ferroptosis suppressor regulated by CMA. This metabolic enzyme catalyzes the reversible transfer of a phosphoryl group from ATP to creatine and is pivotal in maintaining cellular energy balance (121). The activation of insulin-like growth factor 1 receptor signaling, which frequently occurs in HCC, enhances the interaction between AKT and CKB. Subsequently, AKT-mediated CKB Thr133 phosphorylation reduces its binding to creatine, thereby gained the ability to interact with GPX4 and phosphorylated GPX4 at Ser104. This phosphorylation is adjacent to the CMA target motif in GPX4 and counteracts CMA-mediated GPX4 degradation, which is dependent on its binding to Hsc70, therefore greatly alleviating ferroptosis in HCC cells and exacerbating tumor growth (74).

In HCC, the crosstalk between autophagy and ferroptosis involves the coordination of the post-transcriptional and post-translational modulation. For example, m^6A modification in HCC cells was clearly stimulated by ferroptosis inducers and the elevated level of m6A writer, WT1 associated protein (WTAP), served as the primary cause of this observed increase. *Atg5* mRNA is recognized as a downstream target of WTAP-driven m6A modification, which is then recognized and bound by YTH domain-containing protein 2. This process increases Atg5 translation and expression, subsequently initiating ferritinophagy and resulting in ferroptosis activation in HCC (75). Moreover, other investigations have emphasized that the importance of ubiquitination regulation as a critical mechanism governing autophagy-dependent ferroptosis in HCC. Ubiquitin-specific protease 24 (USP24) downregulation and USP2 upregulation were detected in HCC tissues, showing significant correlation with altered autophagy-ferroptosis axis (76,77). USP24 maintains Beclin1 stability by inhibiting its polyubiquitination, which prevents its proteasomal degradation. This facilitates ferritin degradation via ferritinophagy and subsequently increase the sensitivity of HCC cells to ferroptosis (76). Conversely, USP2 functions as a negative regulator of clockophagy-induced ferroptosis. Mechanistically, USP2 interacts with brain and muscle ARNT-like protein 1 (ARNTL), which promotes its deubiquitination and weakens its interaction with p62. This process reduces the autophagic degradation of ARNTL and stabilizes this protein. Consequently, stabilized ARNTL directly activates transcription of hypoxia inducible factor 1α (HIF1α) and xCT, thereby reducing the susceptibility of HCC cells to ferroptosis (77).

The poor clinical efficacy, serious adverse reactions and side effects have greatly limited the drug therapy for treating HCC. Compounds found in plants open new avenues for anti-HCC medication development because of their unique chemical structures and potent efficacy. It has been revealed that these compounds may kill HCC cells *in vitro* and *in vivo* through triggering ferritinophagy-mediated ferroptosis (78,79). A number of plants, such as *Senecio salignus*, *Chenopodium ambrosioides* L., and *Cannabis sativa* L., contain caryophyllene oxide, a natural bicyclic sesquiterpene that possesses significant anti-HCC activities by promoting ferritinophagy and ferroptosis (122). Caryophyllene oxide markedly increases the expressions of NCOA4 and LC3II and the release of free iron by degrading ferritin, leading to a ferritinophagy-related phenomenon. When the HCC cells accumulate a substantial amount of ROS produced by the Fenton reaction, it causes oxidative stress and lipid peroxidation and induces ferroptosis and finally affects the growth and proliferation of HCC cells (78). A similar relation between the inhibitory effects of esculetin on HCC and ferritinophagy-mediated ferroptosis was validated. As a coumarin derivative extracted from lemon leaves, *Rehmannia glutinosa* (*Rehmannia glutinosa var.*), belladonna (*Belladonna baccifera* Lam.) and other plants (123), esculetin specifically targets NCOA4, FTH1 and LC3II to activate ferritinophagy. As a consequence of iron deposition, increased ROS generation results in oxidative stress and lipid peroxidation. Meanwhile, esculetin decreases GSH

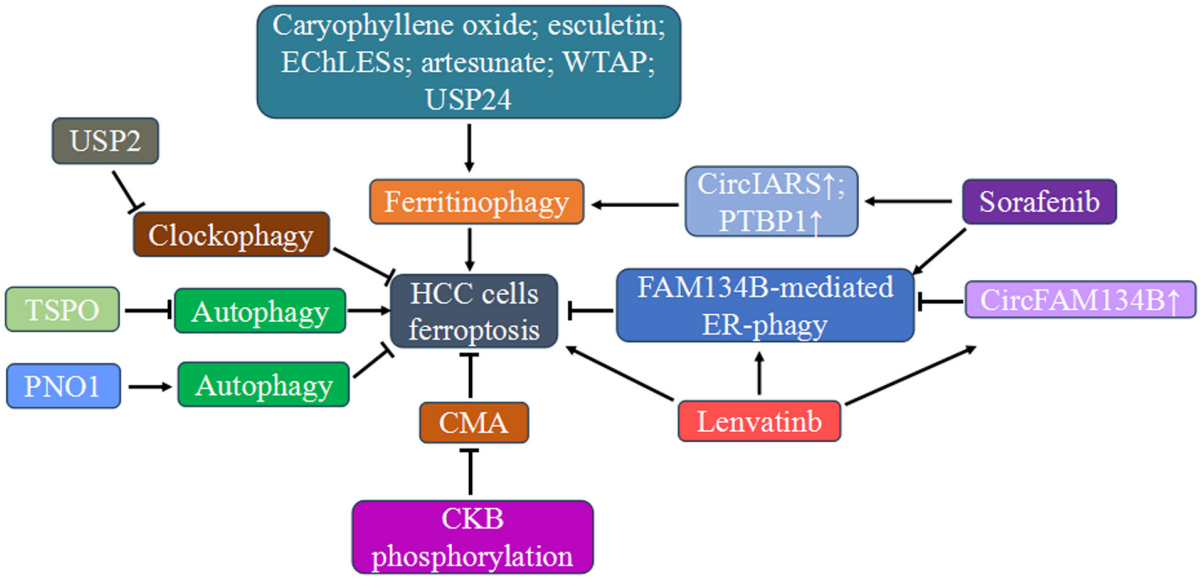

Figure 8. Crosstalk between autophagy and ferroptosis in HCC. HCC, hepatocellular carcinoma; USP24, ubiquitin-specific protease 24; WTAP, WT1 associated protein; PTBP1, polypyrimidine tract-binding protein 1; EChLESs, electrophilic sesquiterpenes isolated from *Eupatorium chinense* L.; TSPO, mitochondrial translocator protein; PNO1, partner of NOB1; CircFAM134B, circRNA of the family with sequence similarity 134, member B; CMA, chaperone-mediated autophagy; CKB, creatine kinase B.

contents by suppressing the Nrf2 signal pathway and inhibiting the expression of its target antioxidant proteins (GPX4 and HO-1). This activity further promotes ROS accumulation, thus triggering ferroptosis in HCC cells (79). Another study has demonstrated that the electrophilic sesquiterpenes isolated from *Eupatorium chinense* L. (EChLESs) suppressed HCC growth by enhancing ferritinophagy-mediated ferroptosis. Following exposure to EChLESs, ferroptosis was induced in HCC cells characterized by the crumpled and broken mitochondria, elevated mitochondrial reactive oxygen species (mtROS) levels, inactivated GSH-dependent antioxidant defense system, increased intracellular iron levels and the excessive lipid peroxidation. EChLESs elevated the mRNA expression levels of *NCOA4* by activating HIF1α and weakened the degradation of NCOA4 protein at transcriptional and post-transcriptional levels in HCC cells. *NCOA4* knockdown partly abolished ferroptosis and reversed the cell viability inhibition caused by EChLESs, indicating that NCOA4-mediated ferrinophagy constitutes an indispensable mechanism underlying EChLESs-elicited ferroptosis (80). Sorafenib, a potent ferroptosis inducer, is an effective first-line therapeutic drug for advanced HCC. Unfortunately, drug resistance markedly limits its efficacy (124). Artesunate is an ideal compound that could increase sorafenib sensitivity in HCC treatment. The synergistic effect of these agents involves enhancing ferroptosis by activating lysosome function and promoting ferritin degradation. Sorafenib directly acts on oxidative stress via the impairment of mitochondrial functions and the inhibition of GSH contents, whereas artesunate mainly activates lysosomes, as evidenced by the increased cathepsin L and cathepsin B levels and subsequent ferritin degradation. The convergence of oxidative stress triggered by sorafenib and ferritinophagy mediated by artesunate gives rise to uncontrolled lipid peroxidation, ultimately culminating in ferroptosis (81).

Therefore, these results demonstrate the crosstalk between autophagy and ferroptosis markedly influences HCC progression and prognosis. Various factors, including circRNAs, RNA-binding proteins, metabolic enzymes and post-transcriptional and post-translational modifications, regulate this crosstalk. Natural plant compounds enhance ferritinophagy-mediated ferroptosis for HCC treatment. Combining these compounds with existing drugs like sorafenib may overcome resistance and improve therapeutic efficacy (Fig. 8).

Crosstalk between autophagy and ferroptosis in other liver diseases. MS is a pathological condition defined by a cluster of metabolic disorders that increases the risk of cardiovascular diseases and diabetes. Iron overload holds a crucial position in the causation of liver damage in MS (125). In a liver injury rat model of MS induced by a high-fat and high-fructose diet, the protein expression levels of FTH1 and TFR1 were increased, whereas those of NCOA4 and FPN1 and the NCOA4-FTH1 interaction were decreased in the liver tissues compared with those in the control group. Moreover, the ferroptosis-related proteins GPX4 and xCT were markedly decreased, and oxidative stress was markedly induced in the liver of MS rats. Therefore, decreased NCOA4 expression and impaired binding of NCOA4 to FTH1 diminish the FTH1 degradation by downregulating ferritinophagy, and decreased FPN1 expression inhibits iron output and release to other tissues, both of which effectively increase liver iron overload and, in turn, trigger oxidative stress and ferroptosis (82). NAFLD is an abnormal liver condition associated with MS. In high-fat diet-induced NAFLD murine models, autophagosomes biogenesis was suppressed through both mTOR activation and Atg7 downregulation, resulting in decreased lipophagy that promoted lipid droplets accumulation and lipotoxicity, such as lipid peroxidation, a key determinant of ferroptosis (43). In addition to enhanced lipid peroxidation, the suppression of autophagosome formation, which alters the protein abundance or subcellular distribution of p62, stabilizes KEAP1 by disturbing the balance between the KEAP1-p62 and

KEAP1-Nrf2 interaction and enhances ferroptosis by counteracting the anti-ferroptotic functions of Nrf2 (83). NASH is a progressive subtype of NAFLD, and iron overload is often observed in patients with NASH (126). Iron overload is followed by oxidative stress and the increased uptake of intracellular calcium ions. The calcium ion-activated calcineurin mediates the dephosphorylation of cytosol transcription factor EB (TFEB) and promotes its subsequent migration into the nucleus. In nuclear, TFEB upregulates the mRNA expression of autophagy- and lysosome-related genes and simultaneously accelerates NCOA4-mediated ferritinophagy and lipophagy. These iron overload-mediated double effects on lipid and iron metabolic dysregulation acts together to aggravate NASH via ferroptosis (84).

ALI is an acute inflammatory liver disease induced by various factors and accompanied by severe impairment of liver function (127). Alternatively activated macrophages (AAMs) exert a beneficial hepatoprotection in ALI by producing anti-inflammatory factors, inhibiting the necroptosis-necroinflammation axis and slowing down liver inflammation progression. However, AAMs exhibit a high degree of sensitivity towards ferroptosis, and the quantity of AAMs is below the normal levels during ALI pathogenesis (128). Liensinine, a major pharmacologically active ingredient isolated from lotus seeds, possesses potential therapeutic effects against ALI. By inhibiting ferroptosis while increasing the number of AAMs, liensinine alleviated the lipopolysaccharide (LPS)/D-galactosamine-induced pathological liver injury and the liver inflammatory response in a mouse model. *In vitro* experiments revealed that liensinine could alleviate ferritinophagy and inhibit ferrous iron release and lipid peroxidation to boost AAMs resistance to ferroptosis, potentially by blocking the autophagosome-lysosome fusion and subsequently inhibiting the recruitment of ferritin into the lysosomes for degradation (85). Likewise, quercetin demonstrated a hepatoprotective effect against LPS and γ-D-glutamyl-meso-di aminopimelic acid-induced ALI by targeting the interplay between ferritinophagy and ferroptosis. Specifically, quercetin suppressed interleukin-6/signal transducer and activator of transcription 3-dependent ferritinophagy, thereby attenuating liver cell ferroptosis and liver damage (86). Another study reported the protective effect of Yes-associated protein 1 (YAP1) in sepsis-induced ALI by regulating the process of ferritinophagy-mediated ferroptosis (87). As a transcriptional coactivator controlled by the Hippo signaling pathway (129), YAP1 deficiency markedly exacerbated the oxidative damage, aggravated ferroptosis- and ferritinophagy-associated morphological features and inflammatory response in the septic liver tissue. Consistently, YAP1 overexpression restrained the ferrous iron synthesis by disrupting the association between NCOA4 and ferritin and preventing siderofexin 1-induced mitochondria iron accumulation, which consequently suppressed mtROS generation and lipid peroxidation. Eventually, the liver cells were protected from ferroptosis in this sepsis-induced ALI model (87). Ferritinophagy-mediated ferroptosis is also involved in the pathophysiological mechanism behind the liver injury caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Presumably, SARS-CoV-2 infection-induced cytokine storms, which are characterized by the exuberant release of inflammatory cytokines, stimulate liver cells to secrete ferritin and encourage hyperferritinemia. Elevated ferritin levels can initiate NCOA4-mediated ferritinophagy followed by the induction of ferroptosis. With the death of hepatic cells, more ferritin is further released. Therefore, the mutual stimulation of ferritin and liver cells destruction establishes a vicious loop that continuously aggravates liver injury (88). A further study demonstrated that Nrf2-dependent autophagy activation is essential for preventing ferroptosis in ALI under sulforaphane intervention. As a powerful Nrf2 agonist found in cruciferous vegetables (130), Nrf2 activation induced by sulforaphane treatment not only upregulates its downstream target genes, including *xCT*, *GPX4* and multiple *Atgs*, but also disrupts the formation of Beclin1-xCT complex by promoting autophagy. Consequently, the membrane localization of xCT and its cysteine transport function for GSH synthesis are enhanced, cooperatively generating anti-ferroptosis effects in carbon tetrachloride-induced rat ALI model and H_2O_2-induced liver cell injury model (89).

Diabetes is accompanied by the development of profound pathological alterations in the liver, and the loss of liver cells resulting from ferroptosis contributes to diabetic liver damage (131). Similar anti-ferroptotic potential and hepatoprotective effect via the activation of Nrf2 signaling pathways in the diabetic liver were observed following the treatment with of sulforaphane, and the occurrence of anti-ferroptotic phenotype within the diabetic liver was associated with attenuated ferritinophagy levels. Sulforaphane treatment of diabetic mice markedly restored Nrf2 expression, increased the levels of its downstream target proteins related to antioxidative defense, reversed the increase in iron accumulation by suppressing the colocalization of FTH1 and LC3 for degradation and by diminishing iron absorption from endosomes, and finally prevented iron-induced lipid peroxidation and ferroptosis (90).

Cellular senescence is a state of permanent, terminal cell cycle arrest resulting in the degeneration of cellular structure and function (132). With the concomitant impairment of ferrinophagy and ferroptosis, senescent cells alter cellular iron acquisition and storage. The selective elimination of senescent cells via ferroptosis improves physical function and ameliorates age-related pathologies (133). 4,4'-Dimethoxychalcone (DMC) is a natural flavonoid enriched in *Angelica keiskei koidzumi* and has the ability to induce the ferroptosis of senescent liver cells and alleviate senescence-associated phenotypes in old mouse liver (91). The clearance of senescent liver cells triggered by DMC is synergistically mediated by the activation of ferritinophagy and the inhibition of ferrochelatase (FECH), an essential enzyme for heme biosynthesis by inserting a ferrous ion into protoporphyrin IX (134). By binding to FECH, DMC inhibits the former's enzymatic activity, which likely contributes to free iron accumulation. Meanwhile, the autophagic degradation of ferritin after DMC treatment led to the accumulation of labile iron pool and finally caused ferroptosis in senescent liver cells (91).

In summary, the crosstalk between autophagy and ferroptosis emerges as a key event in diverse liver diseases, including those associated with MS, NAFLD, NASH, ALI, diabetic liver damage and liver cell senescence. Interventions at this pathway bring about significant opportunities for disease management, as evidenced by compounds like liensinine, quercetin, and sulforaphane.

5. Conclusion and future perspectives

A number of liver diseases have a tight connection with the occurrence of autophagy and ferroptosis (3,7). While recent reviews have expertly summarized the research advancements on the autophagy-ferroptosis crosstalk within specific conditions such as steatohepatitis and alcohol liver injury (135,136), the scope is inherently confined to single liver disease categories and may not capture the full spectrum of how this crosstalk operates across the heterogeneous landscape of liver pathologies. A comprehensive and systematic investigation into the functional interplay and signaling pathways linking ferroptosis and autophagy, particularly in relation to the progression or potential therapeutic strategies for diverse liver diseases, remains notably limited. To address this gap, the present review systematically categorized liver diseases into four major types, mainly including drug-induced liver injury, toxin-induced liver injury, liver fibrosis and HCC. This novel classification allows the present study to dissect the shared and distinct mechanisms of autophagy-ferroptosis crosstalk across different types of liver diseases, providing a comparative framework not covered in previous reviews. Moreover, prior reviews acknowledge the dual roles of autophagy in ferroptosis but lack a unified framework to explain these contradictions. The present review presented an interpretive framework to reconcile the contradictory roles of autophagy in ferroptosis, highlighting critical context-dependency (such as disease type, disease stage or cell type) as a key determinant.

Undoubtedly, the extensive research aforementioned has provided conclusive evidence that crosstalk between ferroptosis and autophagy frequently occurs in liver pathological conditions. Nevertheless, the intricate interplay between the mechanisms underlying ferroptosis and autophagy has led to conflicting conclusions in existing studies. In addition, the fact that some studies employ inappropriate experimental methods or models may exert an impact on the interpretation of experimental results. The present study critically analyzed the conflicting findings and evaluate methodological limitations in current researches, which has remained unaddressed in prior reviews.

Analysis of conflicting findings. Dependent upon the available observation, autophagy plays dual roles in the occurrence of ferroptosis (both promoting and inhibiting). Ferroptosis sensitivity is positively correlated with intracellular autophagy level in most cases. In drug-induced liver injury (40-42,44), toxin-induced liver injury (47-51,53-55), liver fibrosis (23,56,58-64) and HCC models (66,69,73,75,76,78-81), the activation of NCOA4-mediated ferritinophagy facilitated ferroptosis by enhancing ferritin decomposition. However, compromised ferritinophagy, iron accumulation and increased ferroptosis levels were observed in MS rat liver (82). Moreover, autophagosome biogenesis downregulation and ferroptosis promotion constitute the significant molecular mechanism underlying the development of NAFLD (83). Mitophagy also shows contradictory effects on ferroptosis (53,55,57). On the one hand, cells undergo mitophagy to remove damaged mitochondria, thereby protecting cells from oxidative stress and suppressing ferroptosis (53,101). On the other hand, mitophagy may amplify lipid peroxidation and ferroptosis by promoting GPX4 degradation (55,57). Such discrepancy suggests that the role of autophagy in ferroptosis is highly context-dependent. It may stem from variations in pathological stages with altered basal autophagy levels, which critically influence whether autophagy acts as a pro- or anti-ferroptotic mechanism. During the early stages of liver injury, autophagy likely plays a predominantly protective role by eliminating damaged organelles (such as mitochondria via mitophagy) and mitigating oxidative stress (such as GSH metabolic reprogramming via autophagy) (70,71), thereby suppressing ferroptosis. With the progression of liver diseases, cells are persistently stimulated by external factors (such as oxidative stress, pathogens) or internal factors (such as hormonal fluctuations or iron overload), the basal autophagy levels changes, thereby modifying the cell's susceptibility to ferroptosis. For example, prolonged autophagy (such as ferritinophagy or lipophagy) activation may shift toward intensifying ferroptosis by promoting iron overload and/or lipid peroxidation (43,53,58,76), contributing to liver disease progression. The regulation of autophagy-ferroptosis crosstalk may also involve compensatory mechanisms. Take the MS live injury model as an example: Simultaneous downregulation of ferritinophagy and upregulation of ferroptosis were observed. This phenomenon reflects that, under condition of iron overload, autophagy might undergo compensatory inhibition to limit further iron release and ferroptosis (82). Moreover, various liver cell types may display unique reactions to autophagy modulation. The diverse cellular pathways come into play when liver cells with various phenotypes are stimulated, giving rise to varying regulatory effects on ferroptosis. For example, liver cells possibly depend more on autophagy for ferritin breakdown and iron homeostasis, making them susceptible to ferroptosis upon autophagy activation. Conversely, stellate cells may employ autophagy for fibrotic purposes, with a weaker impact on ferroptosis (3).

In liver cells subjected to cadmium, nickel, erastin, sorafenib, or sulfasalazine to induce ferritinophagy, a decline in FTH1 expression was observed, accompanied by a parallel downward trend in NCOA4 levels instead of the anticipated increase (49,50,73). Given the NCOA4 abundance is dually modulated by autophagy and the ubiquitin-proteasome system, its downregulation might indicate a feedback mechanism involving ubiquitin-dependent proteasomal degradation, which is promoted by high iron levels and involves iron-dependent binding to the E3 ubiquitin ligase HERC2 (137). However, the detailed molecular events underlying NCOA4 regulation to determine its preferred interaction with HERC2 and mediate its proteasomal degradation remain undefined. Besides, a highly orchestrated network of transcription factor (such as ATF3 and TFEB) (43,84), epigenetic effectors (such as ELAVL1 and circIARS) (58,66) and signaling hubs (such as PI3K/AKT and AMPK) (51,54) dictate the regulation of NCOA4 expression and the following ferritinophagy. Whether the relevant pathways present in different liver diseases have a same role in NCOA4 regulation and whether they have the same regulatory role in the different pathological stages are concerns that deserve sustained attention.

Limitations of experimental methods and models. Current researches indeed exhibit some methodological limitations. Using pharmacologic modulators such as rapamycin,

chloroquine, 3-MA and bafilomycin A1 (52,61,81,105), they have largely explored the effect of autophagy on ferroptosis in certain experimental liver disease animal and cellular models. However, these pharmacological modulators have off-target effects (such as mTOR-independent roles for rapamycin), complicating data interpretation. In the future, specific genetic approaches to regulate the autophagy pathway should be combined to interpretate these data. Measuring autophagy and ferroptosis at one specific moment may fail to reflect the ongoing and evolving changes in these processes, thereby restricting the accuracy of result analysis. Dynamic time-course experiments are required to elucidate the mechanistic interplay between autophagy and ferroptosis at critical stages. Since transmission electron microscopy (TEM) is universally acknowledged as the gold-standard technique for the detection of autophagy and ferroptosis, the lack of ultrastructural validation via TEM in various studies remains a limitation (40-44,47,49,50,52,53,66,69,70-74,81,87,88,90). Incorporating this approach will be critical to strengthen evidence for the functional role of the autophagy-ferroptosis crosstalk in liver diseases.

A shared characteristic of these investigations is their emphasis on the regulatory activities of ferritinophagy on ferroptosis. By contrast, reports regarding other types of autophagy that modulate ferroptosis are comparatively limited. Notably, researchers appear to have neglected the reverse regulation of ferroptosis on autophagy. Except for the mutual regulation of autophagy and ferroptosis in fluoride-induced liver injury (52), this phenomenon has not been reported in the other previously discussed liver diseases. The fact that there are more studies on the role of autophagy in ferroptosis compared with the regulation of autophagy by ferroptosis may be related to the easier observation of the responses of ferroptosis when regulating autophagy, the clearer regulatory pathways of autophagy on ferroptosis, and the greater clinical application potential of regulating ferroptosis through autophagy. Thus, whether other forms of selective autophagy occur concurrently and play functional roles in ferroptosis modulation and whether ferroptosis reciprocally regulates autophagy to form a feedback loop remain to be further elucidated.

Future directions. The autophagy-ferroptosis axis has emerged as a promising target across diverse liver diseases. Indeed, modulating this axis can markedly alleviate drug- or toxin-induced hepatotoxicity (40,41,47), reverse the progression of liver fibrosis (61,64), effectively eliminate HCC cells (78,79), or counteract drug resistance in HCC cells (81), exhibiting a broad range of beneficial effects. However, to translate these mechanistic insights into clinical applications, addressing the following testable questions and methodological challenges is imperative.

First, the functional outcome of the autophagy-ferroptosis crosstalk is highly dependent on the specific pathological stage and the involved cell type, leading to a paradigm where context defines therapeutic strategy. In drug- or toxin-induced acute liver injury, early activation of autophagy may prevent liver cells from undergoing ferroptosis, thereby limiting the spread of injury. However, if the injury becomes chronic, persistent autophagic stress may ultimately drive ferroptosis and contribute to the progression from injury to fibrosis (40). In established liver fibrosis, while protecting hepatocytes from ferroptosis remains crucial, a parallel goal is to eliminate activated HSCs. In this context, selectively enhancing autophagy in HSCs can trigger ferroptosis and reverse fibrosis (61). By contrast, activating autophagy to induce ferroptosis in HCC cells could be an effective way to suppress tumor growth and overcome chemoresistance (78,81). Therefore, a universal solution is unlikely to be effective; instead, biomarker-guided, stage-specific interventions are required. For example, in liver fibrosis, inhibiting unrestrained autophagy-mediated ferroptosis in liver cells may be crucial in protecting against liver injury and fibrosis, while for stellate cells, promoting autophagy-mediated ferroptosis to eliminate activated HSCs might be the more important therapeutic approach. This raises a key question: How can we design delivery systems to selectively induce pro-ferroptotic autophagy in activated HSCs while ensuring that liver cells are shielded from such effects? Nanoparticle-based drug delivery systems that are decorated with ligands specific to liver cells or HSCs surface markers offer a promising strategy to achieve this selective modulation.

Second, the intricate integration of autophagy and ferroptosis processes poses significant challenges for developing targeted therapies. It is necessary to elucidate their regulatory pathways in specific contexts. For instance, what are the key molecular switches that determine whether autophagy inhibits or promotes ferroptosis? Additionally, is it possible for the dual effects of autophagy on ferroptosis to occur simultaneously and could the simultaneous modulation of autophagy and ferroptosis yield more favorable therapeutic outcomes on liver diseases compared to targeting either one alone? Moreover, the role of liver-resident cells such as Kupffer cells, endothelial cells and stellate cells in modulating the response of liver cells to autophagy and ferroptosis must be considered, since these cells may modulate disease progression through paracrine signaling or direct cell-cell interactions. To dissect these multi-layered interactions, advanced omics technologies are indispensable. Specifically, single-cell and spatial transcriptomics facilitates the identification of core responsive cell types mediating the autophagy-ferroptosis crosstalk and the signal transmission between adjacent cells by high-resolution mapping of cellular heterogeneity and spatial localization patterns in the liver microenvironment (138). For instance, Kupffer cells may modulate autophagy-ferroptosis crosstalk in neighboring liver cells through the secretion of cytokines such as interleukin-6 and tumor necrosis factor-a. These cytokines can either activate or inhibit autophagy in liver cells, thereby influencing ferroptosis sensitivity (85,86). In addition to Kupffer cells, liver sinusoidal endothelial cells also play a role in the regulatory network. They release extracellular vesicles containing key autophagy factors, which can be taken up by liver cells and thus affect the balance between autophagy and ferroptosis (139). Moreover, HSCs transmit paracrine stimuli, such as certain cytokines and non-coding RNAs, via exosomes. The levels of these stimuli and autophagy are concomitantly or reciprocally regulated, which in turn alters the ferroptosis status in liver cells (140). This integrative method also enables the discovery of context-dependent regulators governing this crosstalk or representative biomarkers linking autophagic and ferroptotic pathways, thereby providing a rational basis for developing precision medicine approaches targeting specific

liver pathologies, particular disease stages, and specific cells. Taking liver fibrosis as an instance, the interaction between activated HSCs and liver cells through autophagy-ferroptosis regulation can promote the deposition of extracellular matrix (56). Specific blockage of the paracrine signaling between HSCs and liver cells might restore the normal autophagy- ferroptosis balance in liver cells, thereby slowing down or reversing the progression of liver fibrosis.

Third, a wide range of compounds modulate autophagy and/or ferroptosis, either inducing or inhibiting these processes (141). Owing to the close interconnection between autophagy and ferroptosis in regulating cellular metabolism, their overlapping signaling pathways and regulatory mechanisms are primarily manifested in the regulation of iron metabolism, lipid peroxidation, the AMPK/mTOR pathway, as well as the interactions among key regulatory proteins (37-39). These existing compound libraries hold the potential to provide a wealth of candidates for the identification of specific modulators of autophagy-ferroptosis crosstalk. Additionally, they can bring considerable convenience for accelerating the screening speed and improving the screening efficiency. However, it must be pointed out that a number of these substances that modulate autophagy and/or ferroptosis lack sufficient specificity and whether other mechanisms are involved in their actions and the cytotoxicity in non-diseased tissues remains a concern (142). A critical issue for future interventions is how to optimize the selectivity and targeting specificity of autophagy and ferroptosis modulation to pathological tissues while minimizing undesired deleterious consequences on normal tissues. Moreover, several chemotherapy drugs (such as sorafenib and lenvatinib) exhibit dual regulatory effects on autophagy and ferroptosis in liver cells (58,76); however, their efficacy is compromised by adverse reactions and drug resistance. Hence, further screening for safe and effective therapeutic drugs with higher specificity is necessary. Multiple studies have demonstrated that bioactive phytochemicals isolated from traditional Chinese medicine exert potent regulatory effects on autophagy-ferroptosis crosstalk, thus presenting novel therapeutic options for liver diseases treatment (61-65,78-81,86). However, their multiple-targets and multiple-pathways mechanisms may contribute to the translational gap between the preclinical findings and actual clinical outcomes (43,97), highlighting the necessity for optimized translational research designs. Organoids and patient-derived xenografts are emerging as promising models that can more accurately mimic the cellular heterogeneity and spatial organization of human liver tissues (143). Advanced computational tools, such as artificial intelligence-based drug screening and bioinformatics tools, aid in finding novel therapeutic compounds targeting specific components of the autophagy-ferroptosis axis. They also predict the potential off-target effects and drug resistance mechanisms, facilitating the optimization of therapeutic regimens (144,145). Future work should integrate advanced models with complementary high-performance tools to overcome current limitations and unlock their therapeutic promise.

Last, beyond the currently recognized liver diseases, the crosstalk between autophagy and ferroptosis in understudied liver diseases (such as cholestatic liver injury and hepatic encephalopathy) has yet to be clarified. Future research should explore whether dysregulation of this axis contribute to diseases progression by dissecting specific regulatory mechanisms.

In conclusion, the crosstalk between autophagy and ferroptosis represents a crucial event in multiple liver diseases. Further advances in unveiling the detailed signals and mechanisms of these phenomena may offer a novel outlook for interpreting the symptoms of these liver diseases and hold significant implications for developing therapeutic strategies targeting the autophagy-ferroptosis crosstalk in the management of liver diseases.

Acknowledgements

Not applicable.

Funding

The present study was supported by the Fundamental Research Program of Shanxi Province (grants nos. 202103021224295 and 202303021222294), the Open Fund of Shanxi Key Laboratory of Innovative Drug for the Treatment of Serious Diseases Basing on the Chronic Inflammation, Shanxi University of Chinese Medicine (grant no. SXInFDL2024-009), the Research Project Supported by Shanxi Scholarship Council of China (grants nos. 2022-166 and 2024-134), and Funding for the Discipline Construction of Pharmacology and Toxicology of Traditional Chinese Medicine, Shanxi University of Chinese Medicine (grant no. 2025XK36).

Availability of data and materials

Not applicable.

Author's contributions

YW wrote and revised the manuscript. KZ, YS, ZL, PL, YC, BH, HL and YQ revised the manuscript for important intellectual content. JR conceived the present study. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Wang C, Ma C, Gong L, Guo Y, Fu K, Zhang Y, Zhou H and Li Y: Macrophage polarization and its role in liver disease. Front Immunol 12: 803037, 2021.
2. Wang X, Zhou Y, Min J and Wang F: Zooming in and out of ferroptosis in human disease. Front Med 17: 173-206, 2023.

3. Chen J, Li X, Ge C, Min J and Wang F: The multifaceted role of ferroptosis in liver disease. Cell Death Differ 29: 467-480, 2022.
4. Klionsky DJ, Petroni G, Amaravadi RK, Baehrecke EH, Ballabio A, Boya P, Bravo-San Pedro JM, Cadwell K, Cecconi F, Choi AMK, *et al*: Autophagy in major human diseases. EMBO J 40: e108863, 2021.
5. Parzych KR and Klionsky DJ: An overview of autophagy: morphology, mechanism, and regulation. Antioxid Redox Signal 20: 460-473, 2014.
6. Zhang C, Wang W, Du C, Li H, Zhou K, Luan Z, Chang Y, Liu S and Wei Y: Autophagy in the pharmacological activities of celastrol (Review). Exp Ther Med 25: 268, 2023.
7. Qian H, Chao X, Williams J, Fulte S, Li T, Yang L and Ding WX: Autophagy in liver diseases: A review. Mol Aspects Med 82: 100973, 2021.
8. Xie Y, Hou W, Song X, Yu Y, Huang J, Sun X, Kang R and Tang D: Ferroptosis: Process and function. Cell Death Differ 23: 369-379, 2016.
9. Dolma S, Lessnick SL, Hahn WC and Stockwell BR: Identification of genotype-selective antitumor agents using synthetic lethal chemical screening in engineered human tumor cells. Cancer Cell 3: 285-296, 2003.
10. Andreani C, Bartolacci C and Scaglioni PP: Ferroptosis: A specific vulnerability of RAS-driven cancers? Front Oncol 12: 923915, 2022.
11. Yagoda N, von Rechenberg M, Zaganjor E, Bauer AJ, Yang WS, Fridman DJ, Wolpaw AJ, Smukste I, Peltier JM, Boniface JJ, *et al*: RAS-RAF-MEK-dependent oxidative cell death involving voltage-dependent anion channels. Nature 447: 864-868, 2007.
12. Schott C, Graab U, Cuvelier N, Hahn H and Fulda S: Oncogenic RAS mutants confer resistance of RMS13 rhabdomyosarcoma cells to oxidative stress-induced ferroptotic cell death. Front Oncol 5: 131, 2015.
13. Sun X, Ou Z, Xie M, Kang R, Fan Y, Niu X, Wang H, Cao L and Tang D: HSPB1 as a novel regulator of ferroptotic cancer cell death. Oncogene 34: 5617-5625, 2015.
14. Rochette L, Dogon G, Rigal E, Zeller M, Cottin Y and Vergely C: Lipid peroxidation and iron metabolism: Two corner stones in the homeostasis control of ferroptosis. Int J Mol Sci 24: 449, 2022.
15. Chen X, Yu C, Kang R and Tang D: Iron metabolism in ferroptosis. Front Cell Dev Biol 8: 590226, 2020.
16. Yang WS and Stockwell BR: Ferroptosis: Death by lipid peroxidation. Trends Cell Biol 26: 165-176, 2016.
17. Chen X, Li J, Kang R, Klionsky DJ and Tang D: Ferroptosis: Machinery and regulation. Autophagy 17: 2054-2081, 2021.
18. Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, Patel DN, Bauer AJ, Cantley AM, Yang WS, *et al*: Ferroptosis: An iron-dependent form of nonapoptotic cell death. Cell 149: 1060-1072, 2012.
19. Liu J, Kuang F, Kroemer G, Klionsky DJ, Kang R and Tang D: Autophagy-dependent ferroptosis: machinery and regulation. Cell Chem Biol 27: 420-435, 2020.
20. Chen HJ, Sugiyama M, Shimokawa F, Murakami M, Hashimoto O, Matsui T and Funaba M: Response to iron overload in cultured hepatocytes. Sci Rep 10: 21184, 2020.
21. Yao X, Zhang Y, Hao J, Duan HQ, Zhao CX, Sun C, Li B, Fan BY, Wang X, Liu WX, *et al*: Deferoxamine promotes recovery of traumatic spinal cord injury by inhibiting ferroptosis. Neural Regen Res 14: 532-541, 2019.
22. Liu Y, Wang W, Li Y, Xiao Y, Cheng J and Jia J: The 5-lipoxygenase inhibitor zileuton confers neuroprotection against glutamate oxidative damage by inhibiting ferroptosis. Biol Pharm Bull 38: 1234-1239, 2015.
23. Zhang Z, Guo M, Li Y, Shen M, Kong D, Shao J, Ding H, Tan S, Chen A, Zhang F and Zheng S: RNA-binding protein ZFP36/TTP protects against ferroptosis by regulating autophagy signaling pathway in hepatic stellate cells. Autophagy 16: 1482-1505, 2020.
24. Liang D, Minikes AM and Jiang X: Ferroptosis at the intersection of lipid metabolism and cellular signaling. Mol Cell 82: 2215-2227, 2022.
25. Klionsky DJ and Codogno P: The mechanism and physiological function of macroautophagy. J Innate Immun 5: 427-433, 2013.
26. Ariosa AR and Klionsky DJ: Autophagy core machinery: Overcoming spatial barriers in neurons. J Mol Med (Berl) 94: 1217-1227, 2016.
27. Yang Z and Klionsky DJ: Mammalian autophagy: Core molecular machinery and signaling regulation. Curr Opin Cell Biol 22: 124-131, 2010.
28. Hosokawa N, Hara T, Kaizuka T, Kishi C, Takamura A, Miura Y, Iemura S, Natsume T, Takehana K, Yamada N, *et al*: Nutrient-dependent mTORC1 association with the ULK1-Atg13-FIP200 complex required for autophagy. Mol Biol Cell 20: 1981-1991, 2009.
29. Zhang S, Yazaki E, Sakamoto H, Yamamoto H and Mizushima N: Evolutionary diversification of the autophagy-related ubiquitin-like conjugation systems. Autophagy 18: 2969-2984, 2022.
30. Webber JL, Young AR and Tooze SA: Atg9 trafficking in mammalian cells. Autophagy 3: 54-56, 2007.
31. Ropolo A, Grasso D, Pardo R, Sacchetti ML, Archange C, Lo Re A, Seux M, Nowak J, Gonzalez CD, Iovanna JL and Vaccaro MI: The pancreatitis-induced vacuole membrane protein 1 triggers autophagy in mammalian cells. J Biol Chem 282: 37124-37133, 2007.
32. Deleyto-Seldas N and Efeyan A: The mTOR-autophagy axis and the control of metabolism. Front Cell Dev Biol 9: 655731, 2021.
33. Xu HD and Qin ZH: Beclin 1, Bcl-2 and autophagy. Adv Exp Med Biol 1206: 109-126, 2019.
34. White E: Autophagy and p53. Cold Spring Harb Perspect Med 6: a026120, 2016.
35. Hu LF: Epigenetic regulation of autophagy. Adv Exp Med Biol 1206: 221-236, 2019.
36. Vargas JNS, Hamasaki M, Kawabata T, Youle RJ and Yoshimori T: The mechanisms and roles of selective autophagy in mammals. Nat Rev Mol Cell Biol 24: 167-185, 2023.
37. Gao M, Monian P, Pan Q, Zhang W, Xiang J and Jiang X: Ferroptosis is an autophagic cell death process. Cell Res 26: 1021-1032, 2016.
38. Park E and Chung SW: ROS-mediated autophagy increases intracellular iron levels and ferroptosis by ferritin and transferrin receptor regulation. Cell Death Dis 10: 822, 2019.
39. Lv X, Tang W, Qin J, Wang W, Dong J and Wei Y: The crosslinks between ferroptosis and autophagy in asthma. Front Immunol 14: 1140791, 2023.
40. Zhou J, Tan Y, Hu L, Fu J, Li D, Chen J and Long Y: Inhibition of HSPA8 by rifampicin contributes to ferroptosis via enhancing autophagy. Liver Int 42: 2889-2899, 2022.
41. Wang C, Leng M, Ding C, Zhu X, Zhang Y, Sun C and Lou P: Ferritinophagy-mediated ferroptosis facilitates methotrexate-induced hepatotoxicity by high-mobility group box 1 (HMGB1). Liver Int 44: 691-705, 2024.
42. Liang Y, Chen S, Han S, Luo L, Shen F and Huang Z: Toosendanin induced hepatotoxicity via triggering PERK-eIF2α-ATF4 mediated ferroptosis. Toxicol Lett 377: 51-61, 2023.
43. Liu S, Su Y, Han B, Yin L, Li H, Wang Y, Zhou K, Li P and Wei Y: Activation of Rab7-mediated lipophagy is required for triptolide to induce ferroptosis in hepatic cells. Food Chem Toxicol 203: 115568, 2025.
44. Wu A, Li M, Chen Y, Zhang W, Li H, Chen J, Gu K and Wang X: Multienzyme active manganese oxide alleviates acute liver injury by mimicking redox regulatory system and inhibiting ferroptosis. Adv Healthc Mater 13: e2302556, 2024.
45. Cai X, Hua S, Deng J, Du Z, Zhang D, Liu Z, Khan NU, Zhou M and Chen Z: Astaxanthin activated the Nrf2/HO-1 pathway to enhance autophagy and inhibit ferroptosis, ameliorating acetaminophen-induced liver injury. ACS Appl Mater Interfaces 14: 42887-42903, 2022.
46. Ren J, Wang Z, Zhang Y, Pei H, Wen R, Zhang Z, Zhu S, Sun X, Yin B, Li S and Ma Y: Sesamin alleviates drug-induced hepatotoxicity via autophagy enhancement and ferroptosis inhibition. Redox Rep 30: 2588863, 2025.
47. Huang T, Zhang K, Wang J, He K, Zhou X and Nie S: Quercetin alleviates acrylamide-induced liver injury by inhibiting autophagy-dependent ferroptosis. J Agric Food Chem 71: 7427-7439, 2023.
48. Zhong G, Li Y, Ma F, Huo Y, Liao J, Han Q, Hu L and Tang Z: Copper exposure induced chicken hepatotoxicity: Involvement of ferroptosis mediated by lipid peroxidation, ferritinophagy, and inhibition of FSP1-CoQ10 and Nrf2/SLC7A11/GPX4 axis. Biol Trace Elem Res 202: 1711-1721, 2024.
49. He Z, Shen P, Feng L, Hao H, He Y, Fan G, Liu Z, Zhu K, Wang Y, Zhang N, *et al*: Cadmium induces liver dysfunction and ferroptosis through the endoplasmic stress-ferritinophagy axis. Ecotoxicol Environ Saf 245: 114123, 2022.
50. Wei L, Zuo Z, Yang Z, Yin H, Yang Y, Fang J, Cui H, Du Z, Ouyang P, Chen X, *et al*: Mitochondria damage and ferroptosis involved in Ni-induced hepatotoxicity in mice. Toxicology 466: 153068, 2022.

51. Yu L, Lv Z, Li S, Jiang H, Han B, Zheng X, Liu Y and Zhang Z: Chronic arsenic exposure induces ferroptosis via enhancing ferritinophagy in chicken livers. Sci Total Environ 890: 164172, 2023.
52. Xu W, Hu Z, Zhang J, Tang Y, Xing H, Xu P, Ma Y and Niu Q: Cross-talk between autophagy and ferroptosis contributes to the liver injury induced by fluoride via the mtROS-dependent pathway. Ecotoxicol Environ Saf 250: 114490, 2023.
53. Song XY, Liu PC, Liu WW, Zhou J, Hayashi T, Mizuno K, Hattori S, Fujisaki H and Ikejima T: Silibinin inhibits ethanol- or acetaldehyde-induced ferroptosis in liver cell lines. Toxicol In Vitro 82: 105388, 2022.
54. Song C, Wang Z, Cao J, Dong Y and Chen Y: Hesperetin alleviates aflatoxin B1 induced liver toxicity in mice: modulating lipid peroxidation and ferritin autophagy. Ecotoxicol Environ Saf 284: 116854, 2024.
55. Jiang J, Zhou X, Chen H, Wang X, Ruan Y, Liu X and Ma J: 18β-Glycyrrhetinic acid protects against deoxynivalenol-induced liver injury via modulating ferritinophagy and mitochondrial quality control. J Hazard Mater 471: 134319, 2024.
56. Liang Q, Ma Y, Wang F, Sun M, Lin L, Li T, Duan J and Sun Z: Ferritinophagy was involved in long-term SiNPs exposure induced ferroptosis and liver fibrosis. Nanotoxicology 17: 157-175, 2023.
57. Bi Y, Liu S, Qin X, Abudureyimu M, Wang L, Zou R, Ajoolabady A, Zhang W, Peng H, Ren J and Zhang Y: FUNDC1 interacts with GPx4 to govern hepatic ferroptosis and fibrotic injury through a mitophagy-dependent manner. J Adv Res 55: 45-60, 2024.
58. Zhang Z, Yao Z, Wang L, Ding H, Shao J, Chen A, Zhang F and Zheng S: Activation of ferritinophagy is required for the RNA-binding protein ELAVL1/HuR to regulate ferroptosis in hepatic stellate cells. Autophagy 14: 2083-2103, 2018.
59. Shen M, Li Y, Wang Y, Shao J, Zhang F, Yin G, Chen A, Zhang Z and Zheng S: N (6)-methyladenosine modification regulates ferroptosis through autophagy signaling pathway in hepatic stellate cells. Redox Biol 47: 102151, 2021.
60. Tan Y, Huang Y, Mei R, Mao F, Yang D, Liu J, Xu W, Qian H and Yan Y: HucMSC-derived exosomes delivered BECN1 induces ferroptosis of hepatic stellate cells via regulating the xCT/GPX4 axis. Cell Death Dis 13: 319, 2022.
61. Kong Z, Liu R and Cheng Y: Artesunate alleviates liver fibrosis by regulating ferroptosis signaling pathway. Biomed Pharmacother 109: 2043-2053, 2019.
62. Zheng Y, Zhao T, Wang J, Jiang R, Huang J, Li W and Wang J: Curcumol alleviates liver fibrosis through inducing autophagy and ferroptosis in hepatic stellate cells. FASEB J 36: e22665, 2022.
63. Zhang Z, Wang X, Wang Z, Zhang Z, Cao Y, Wei Z, Shao J, Chen A, Zhang F and Zheng S: Dihydroartemisinin alleviates hepatic fibrosis through inducing ferroptosis in hepatic stellate cells. Biofactors 47: 801-818, 2021.
64. Li M, Sun Y, Wei Y, Li Y, Shao JJ, Guo M, Zheng S and Zhang Z: Artemether relieves liver fibrosis by triggering ferroptosis in hepatic stellate cells via DHHC12-mediated S-palmitoylation of the BECN1 protein. Free Radic Biol Med 231: 120-135, 2025.
65. Yi J, Wu S, Tan S, Qin Y, Wang X, Jiang J, Liu H and Wu B: Berberine alleviates liver fibrosis through inducing ferrous redox to activate ROS-mediated hepatic stellate cells ferroptosis. Cell Death Discov 7: 374, 2021.
66. Liu Z, Wang Q, Wang X, Xu Z, Wei X and Li J: Circular RNA cIARS regulates ferroptosis in HCC cells through interacting with RNA binding protein ALKBH5. Cell Death Discov 6: 72, 2020.
67. Bi T, Lu Q, Pan X, Dong F, Hu Y, Xu Z, Xiu P, Liu Z and Li J: circFAM134B is a key factor regulating reticulophagy-mediated ferroptosis in hepatocellular carcinoma. Cell Cycle 22: 1900-1920, 2023.
68. Liu Z, Ma C, Wang Q, Yang H, Lu Z, Bi T, Xu Z, Li T, Zhang L, Zhang Y, *et al*: Targeting FAM134B-mediated reticulophagy activates sorafenib-induced ferroptosis in hepatocellular carcinoma. Biochem Biophys Res Commun 589: 247-253, 2022.
69. Yang H, Sun W, Bi T, Wang Q, Wang W, Xu Y, Liu Z and Li J: The PTBP1-NCOA4 axis promotes ferroptosis in liver cancer cells. Oncol Rep 49: 45, 2023.
70. Hu X, He Y, Han Z, Liu W, Liu D, Zhang X, Chen L, Qi L, Chen L, Luo Y, *et al*: PNO1 inhibits autophagy-mediated ferroptosis by GSH metabolic reprogramming in hepatocellular carcinoma. Cell Death Dis 13: 1010, 2022.
71. Han Z, Liu D, Chen L, He Y, Tian X, Qi L, Chen L, Luo Y, Chen Z, Hu X, *et al*: PNO1 regulates autophagy and apoptosis of hepatocellular carcinoma via the MAPK signaling pathway. Cell Death Dis 12: 552, 2021.
72. Zhang D, Man D, Lu J, Jiang Y, Ding B, Su R, Tong R, Chen J, Yang B, Zheng S, *et al*: Mitochondrial TSPO promotes hepatocellular carcinoma progression through ferroptosis inhibition and immune evasion. Adv Sci (Weinh) 10: e2206669, 2023.
73. Wang K, Zhang Z, Tsai HI, Liu Y, Gao J, Wang M, Song L, Cao X, Xu Z, Chen H, *et al*: Branched-chain amino acid aminotransferase 2 regulates ferroptotic cell death in cancer cells. Cell Death Differ 28: 1222-1236, 2021.
74. Wu K, Yan M, Liu T, Wang Z, Duan Y, Xia Y, Ji G, Shen Y, Wang L, Li L, *et al*: Creatine kinase B suppresses ferroptosis by phosphorylating GPX4 through a moonlighting function. Nat Cell Biol 25: 714-725, 2023.
75. Li Y, Guo M, Qiu Y, Li M, Wu Y, Shen M, Wang Y, Zhang F, Shao J, Xu X, *et al*: Autophagy activation is required for N6-methyladenosine modification to regulate ferroptosis in hepatocellular carcinoma. Redox Biol 69: 102971, 2024.
76. Cao J, Wu S, Zhao S, Wang L, Wu Y, Song L, Sun C, Liu Y, Liu Z, Zhu R, *et al*: USP24 promotes autophagy-dependent ferroptosis in hepatocellular carcinoma by reducing the K48-linked ubiquitination of Beclin1. Commun Biol 7: 1279, 2024.
77. Jiang H, Wang X, Zhu Z, Song C, Li D, Yun Y, Hui L, Bao L, O'Connor DP, Ma J and Xu G: DCAF7 recruits USP2 to facilitate hepatocellular carcinoma progression by suppressing clockophagy-induced ferroptosis. Cell Death Dis 16: 654, 2025.
78. Xiu Z, Zhu Y, Han J, Li Y, Yang X, Yang G, Song G, Li S, Li Y, Cheng C, *et al*: Caryophyllene oxide induces ferritinophagy by regulating the NCOA4/FTH1/LC3 pathway in hepatocellular carcinoma. Front Pharmacol 13: 930958, 2022.
79. Xiu Z, Li Y, Fang J, Han J, Li S, Li Y, Yang X, Song G, Li Y, Jin N, *et al*: Inhibitory effects of esculetin on liver cancer through triggering NCOA4 pathway-mediation ferritinophagy in vivo and in vitro. J Hepatocell Carcinoma 10: 611-629, 2023.
80. Zhu ZH, Xu XT, Shen CJ, Yuan JT, Lou SY, Ma XL, Chen X, Yang B and Zhao HJ: A novel sesquiterpene lactone fraction from Eupatorium chinense L. suppresses hepatocellular carcinoma growth by triggering ferritinophagy and mitochondrial damage. Phytomedicine 112: 154671, 2023.
81. Li ZJ, Dai HQ, Huang XW, Feng J, Deng JH, Wang ZX, Yang XM, Liu YJ, Wu Y, Chen PH, *et al*: Artesunate synergizes with sorafenib to induce ferroptosis in hepatocellular carcinoma. Acta Pharmacol Sin 42: 301-310, 2021.
82. Cui F, Mi H, Wang R, Du Y, Li F, Chang S, Su Y, Liu A and Shi M: The effect of chronic intermittent hypobaric hypoxia improving liver damage in metabolic syndrome rats through ferritinophagy. Pflugers Arch 475: 1251-1263, 2023.
83. Liu P, Anandhan A, Chen J, Shakya A, Dodson M, Ooi A, Chapman E, White E, Garcia JG and Zhang DD: Decreased autophagosome biogenesis, reduced NRF2, and enhanced ferroptotic cell death are underlying molecular mechanisms of non-alcoholic fatty liver disease. Redox Biol 59: 102570, 2023.
84. Honma K, Kirihara S, Nakayama H, Fukuoka T, Ohara T, Kitamori K, Sato I, Hirohata S, Fujii M, Yamamoto S, *et al*: Selective autophagy associated with iron overload aggravates non-alcoholic steatohepatitis via ferroptosis. Exp Biol Med (Maywood) 248: 1112-1123, 2023.
85. Li J, Huang Q, Lv M, Ma W, Sun J, Zhong X, Hu R, Ma M, Han Z, Zhang W, *et al*: Role of liensinine in sensitivity of activated macrophages to ferroptosis and in acute liver injury. Cell Death Discov 9: 189, 2023.
86. Zhang H, Shi H, Li X, Zhou S, Song X, Ma N, Meng M, Chang G and Shen X: Quercetin alleviates LPS/iE-DAP-induced liver injury by suppressing ferroptosis via regulating ferritinophagy and intracellular iron efflux. Redox Biol 81: 103557, 2025.
87. Wang J, Zhu Q, Li R, Zhang J, Ye X and Li X: YAP1 protects against septic liver injury via ferroptosis resistance. Cell Biosci 12: 163, 2022.
88. Jia FJ and Han J: Liver injury in COVID-19: Holds ferritinophagy-mediated ferroptosis accountable. World J Clin Cases 10: 13148-13156, 2022.
89. Liu J, Huang C, Liu J, Meng C, Gu Q, Du X, Yan M, Yu Y, Liu F and Xia C: Nrf2 and its dependent autophagy activation cooperatively counteract ferroptosis to alleviate acute liver injury. Pharmacol Res 187: 106563, 2023.
90. Savic N, Markelic M, Stancic A, Velickovic K, Grigorov I, Vucetic M, Martinovic V, Gudelj A and Otasevic V: Sulforaphane prevents diabetes-induced hepatic ferroptosis by activating Nrf2 signaling axis. Biofactors 50: 810-827, 2024.

91. Wang T, Yang C, Li Z, Li T, Zhang R, Zhao Y, Cheng T, Zong Z, Ma Y, Zhang D and Deng H: Flavonoid 4,4'-dimethoxychalcone selectively eliminates senescent cells via activating ferritinophagy. Redox Biol 69: 103017, 2024.
92. Björnsson HK and Björnsson ES: Drug-induced liver injury: Pathogenesis, epidemiology, clinical features, and practical management. Eur J Intern Med 97: 26-31, 2022.
93. Hou W, Xie Y, Song X, Sun X, Lotze MT, Zeh HJ III, Kang R and Tang D: Autophagy promotes ferroptosis by degradation of ferritin. Autophagy 12: 1425-1428, 2016.
94. Di Martino V, Verhoeven DW, Verhoeven F, Aubin F, Avouac J, Vuitton L, Lioté F, Thévenot T and Wendling D: Busting the myth of methotrexate chronic hepatotoxicity. Nat Rev Rheumatol 19: 96-110, 2023.
95. Ni YA, Chen H, Nie H, Zheng B and Gong Q: HMGB1: An overview of its roles in the pathogenesis of liver disease. J Leukoc Biol 110: 987-998, 2021.
96. Zhuo Y, Zhang Y, Li M, Wu H, Gong S, Hu X, Fu Y, Shen X, Sun B, Wu JL and Li N: Hepatotoxic evaluation of toosendanin via biomarker quantification and pathway mapping of large-scale chemical proteomics. Food Chem Toxicol 153: 112257, 2021.
97. Wei YM, Wang YH, Xue HQ, Luan ZH, Liu BW and Ren JH: Triptolide, a potential autophagy modulator. Chin J Integr Med 25: 233-240, 2019.
98. Bai Y, Meng L, Han L, Jia Y, Zhao Y, Gao H, Kang R, Wang X, Tang D and Dai E: Lipid storage and lipophagy regulates ferroptosis. Biochem Biophys Res Commun 508: 997-1003, 2019.
99. Jaeschke H and Ramachandran A: Acetaminophen hepatotoxicity: Paradigm for understanding mechanisms of drug-induced liver injury. Annu Rev Pathol 19: 453-478, 2024.
100. Lőrincz T, Jemnitz K, Kardon T, Mandl J and Szarka A: Ferroptosis is involved in acetaminophen induced cell death. Pathol Oncol Res 21: 1115-1121, 2015.
101. Ni HM, Bockus A, Boggess N, Jaeschke H and Ding WX: Activation of autophagy protects against acetaminophen-induced hepatotoxicity. Hepatology 55: 222-232, 2012.
102. Yamada N, Karasawa T, Kimura H, Watanabe S, Komada T, Kamata R, Sampilvanjil A, Ito J, Nakagawa K, Kuwata H, *et al*: Ferroptosis driven by radical oxidation of n-6 polyunsaturated fatty acids mediates acetaminophen-induced acute liver failure. Cell Death Dis 11: 144, 2020.
103. Zhang L, Yang L, Luo Y, Dong L and Chen F: Acrylamide-induced hepatotoxicity through oxidative stress: mechanisms and interventions. Antioxid Redox Signal 38: 1122-1137, 2023.
104. Tan X, Li L, Wang J, Zhao B, Pan J, Wang L, Liu X, Liu X and Liu Z: Resveratrol prevents acrylamide-induced mitochondrial dysfunction and inflammatory responses via targeting circadian regulator Bmal1 and Cry1 in hepatocytes. J Agric Food Chem 67: 8510-8519, 2019.
105. Erfan OS, Sonpol HMA and Abd El-Kader M: Protective effect of rapamycin against acrylamide-induced hepatotoxicity: The associations between autophagy, apoptosis, and necroptosis. Anat Rec (Hoboken) 304: 1984-1998, 2021.
106. Esfandiari M and Hakimzadeh MA: Assessment of environmental pollution of heavy metals deposited on the leaves of trees at Yazd bus terminals. Environ Sci Pollut Res Int 29: 32867-32881, 2022.
107. González-Alfonso WL, Petrosyan P, Del Razo LM, Sánchez-Peña LC, Tapia-Rodríguez M, Hernández-Muñoz R and Gonsebatt ME: Chronic exposure to arsenic and fluoride starting at gestation alters liver mitochondrial protein expression and induces early onset of liver fibrosis in male mouse offspring. Biol Trace Elem Res 203: 930-943, 2025.
108. Wang HW, Liu J, Wei SS, Zhao WP, Zhu SQ and Zhou BH: Mitochondrial respiratory chain damage and mitochondrial fusion disorder are involved in liver dysfunction of fluoride-induced mice. Chemosphere 241: 125099, 2020.
109. Jahng JWS, Alsaadi RM, Palanivel R, Song E, Hipolito VEB, Sung HK, Botelho RJ, Russell RC and Sweeney G: Iron overload inhibits late stage autophagic flux leading to insulin resistance. EMBO Rep 20: e47911, 2019.
110. Liu CY, Wang M, Yu HM, Han FX, Wu QS, Cai XJ, Kurihara H, Chen YX, Li YF and He RR: Ferroptosis is involved in alcohol-induced cell death in vivo and in vitro. Biosci Biotechnol Biochem 84: 1621-1628, 2020.
111. Horn P and Tacke F: Metabolic reprogramming in liver fibrosis. Cell Metab 36: 1439-1455, 2024.
112. Huang Y, Li P, Zhao R, Zhao L, Liu J, Peng S, Fu X, Wang X, Luo R, Wang R and Zhang Z: Silica nanoparticles: Biomedical applications and toxicity. Biomed Pharmacother 151: 113053, 2022.
113. Liu J, Yan Z, Yang F, Huang Y, Yu Y, Zhou L, Sun Z, Cui D and Yan Y: Exosomes derived from human umbilical cord mesenchymal stem cells accelerate cutaneous wound healing by enhancing angiogenesis through delivering angiopoietin-2. Stem Cell Rev Rep 17: 305-317, 2021.
114. Wang G, Li J, Zhu L, Zhou Z, Ma Z, Zhang H, Yang Y, Niu Q and Wang X: Identification of hepatocellular carcinoma-related subtypes and development of a prognostic model: A study based on ferritinophagy-related genes. Discov Oncol 14: 147, 2023.
115. Zhang Y, Luo J, Yang W and Ye WC: CircRNAs in colorectal cancer: Potential biomarkers and therapeutic targets. Cell Death Dis 14: 353, 2023.
116. Chen Y, Mi Y, Zhang X, Ma Q, Song Y, Zhang L, Wang D, Xing J, Hou B, Li H, *et al*: Dihydroartemisinin-induced unfolded protein response feedback attenuates ferroptosis via PERK/ATF4/HSPA5 pathway in glioma cells. J Exp Clin Cancer Res 38: 402, 2019.
117. Vara-Perez M, Felipe-Abrio B and Agostinis P: Mitophagy in cancer: A tale of adaptation. Cells 8: 493, 2019.
118. Liu C, Wu Z, Wang L, Yang Q, Huang J and Huang J: A Mitophagy-related gene signature for subtype identification and prognosis prediction of hepatocellular carcinoma. Int J Mol Sci 23: 12123, 2022.
119. Pan JH, Kang YQ, Li Q, Xing W, Chen YH, Yan Y, Luo DX, Qiu Y, Yuan YF, Zeng WA and Chen DT: TSPO is a novel biomarker for prognosis that regulates cell proliferation through influencing mitochondrial functions in HCC. Heliyon 9: e22590, 2023.
120. Fu F, Lai Q, Hu J, Zhang L, Zhu X, Kou J, Yu B and Li F: Ruscogenin alleviates myocardial ischemia-induced ferroptosis through the activation of BCAT1/BCAT2. Antioxidants (Basel) 11: 583, 2022.
121. Rahbani JF, Roesler A, Hussain MF, Samborska B, Dykstra CB, Tsai L, Jedrychowski MP, Vergnes L, Reue K, Spiegelman BM and Kazak L: Creatine kinase B controls futile creatine cycling in thermogenic fat. Nature 590: 480-485, 2021.
122. Fidyt K, Fiedorowicz A, Strządała L and Szumny A: β-caryophyllene and β-caryophyllene oxide-natural compounds of anticancer and analgesic properties. Cancer Med 5: 3007-3017, 2016.
123. Zhang L, Xie Q and Li X: Esculetin: A review of its pharmacology and pharmacokinetics. Phytother Res 36: 279-298, 2022.
124. Tang W, Chen Z, Zhang W, Cheng Y, Zhang B, Wu F, Wang Q, Wang S, Rong D, Reiter FP, *et al*: The mechanisms of sorafenib resistance in hepatocellular carcinoma: Theoretical basis and therapeutic aspects. Signal Transduct Target Ther 5: 87, 2020.
125. Kim JE, Kim JS, Jo MJ, Cho E, Ahn SY, Kwon YJ and Ko GJ: The roles and associated mechanisms of adipokines in development of metabolic syndrome. Molecules 27: 334, 2022.
126. Sheka AC, Adeyi O, Thompson J, Hameed B, Crawford PA and Ikramuddin S: Nonalcoholic steatohepatitis: A review. JAMA 323: 1175-1183, 2020.
127. Woolbright BL and Jaeschke H: Sterile inflammation in acute liver injury: Myth or mystery? Expert Rev Gastroenterol Hepatol 9: 1027-1029, 2015.
128. Starkey Lewis P, Campana L, Aleksieva N, Cartwright JA, Mackinnon A, O' Duibhir E, Kendall T, Vermeren M, Thomson A, Gadd V, *et al*: Alternatively activated macrophages promote resolution of necrosis following acute liver injury. J Hepatol 73: 349-360, 2020.
129. Szulzewsky F, Holland EC and Vasioukhin V: YAP1 and its fusion proteins in cancer initiation, progression and therapeutic resistance. Dev Biol 475: 205-221, 2021.
130. Otoo RA and Allen AR: Sulforaphane's multifaceted potential: From neuroprotection to anticancer action. Molecules 28: 6902, 2023.
131. Stancic A, Velickovic K, Markelic M, Grigorov I, Saksida T, Savic N, Vucetic M, Martinovic V, Ivanovic A and Otasevic V: Involvement of ferroptosis in diabetes-induced liver pathology. Int J Mol Sci 23: 9309, 2022.
132. Di Micco R, Krizhanovsky V, Baker D and d'Adda di Fagagna F: Cellular senescence in ageing: from mechanisms to therapeutic opportunities. Nat Rev Mol Cell Biol 22: 75-95, 2021.
133. Masaldan S, Clatworthy SAS, Gamell C, Meggyesy PM, Rigopoulos AT, Haupt S, Haupt Y, Denoyer D, Adlard PA, Bush AI and Cater MA: Iron accumulation in senescent cells is coupled with impaired ferritinophagy and inhibition of ferroptosis. Redox Biol 14: 100-115, 2018.
134. Sishtla K, Lambert-Cheatham N, Lee B, Han DH, Park J, Sardar Pasha SPB, Lee S, Kwon S, Muniyandi A, Park B, *et al*: Small-molecule inhibitors of ferrochelatase are antiangiogenic agents. Cell Chem Biol 29: 1010-1023. e14, 2022.

135. Zhao S, Guo Y and Yin X: Autophagy, ferroptosis, apoptosis and pyroptosis in metabolic dysfunction-associated steatotic liver disease. Front Biosci (Landmark Ed) 29: 30, 2024.
136. Wang Y, Zhou X, Chen H and Li Z: Molecular mechanisms of alcohol-associated liver disease-ferroptosis and autophagy crosstalk. Mol Biol Rep 52: 361, 2025.
137. Mancias JD, Pontano Vaites L, Nissim S, Biancur DE, Kim AJ, Wang X, Liu Y, Goessling W, Kimmelman AC and Harper JW: Ferritinophagy via NCOA4 is required for erythropoiesis and is regulated by iron dependent HERC2-mediated proteolysis. Elife 4: e10308, 2015.
138. Andrews TS, Nakib D, Perciani CT, Ma XZ, Liu L, Winter E, Camat D, Chung SW, Lumanto P, Manuel J, *et al*: Single-cell, single-nucleus, and spatial transcriptomics characterization of the immunological landscape in the healthy and PSC human liver. J Hepatol 80: 730-743, 2024.
139. Chen T, Zhang H, Shan W, Zhou J and You Y: Liver sinusoidal endothelial cells in hepatic fibrosis: Opportunities for future strategies. Biochem Biophys Res Commun 766: 151881, 2025.
140. Mastoridou EM, Goussia AC, Glantzounis GK, Kanavaros P and Charchanti AV: Autophagy and exosomes: Cross-regulated pathways playing major roles in hepatic stellate cells activation and liver fibrosis. Front Physiol 12: 801340, 2022.
141. Ahsan A, Liu M, Zheng Y, Yan W, Pan L, Li Y, Ma S, Zhang X, Cao M, Wu Z, *et al*: Natural compounds modulate the autophagy with potential implication of stroke. Acta Pharm Sin B 11: 1708-1720, 2021.
142. Wu Z, Zhu Y, Liu W, Balasubramanian B, Xu X, Yao J and Lei X: Ferroptosis in liver disease: Natural active compounds and therapeutic implication. Antioxidants (Basel) 13: 352, 2024.
143. Hou X, Du C, Lu L, Yuan S, Zhan M, You P and Du H: Opportunities and challenges of patient-derived models in cancer research: patient-derived xenografts, patient-derived organoid and patient-derived cells. World J Surg Oncol 20: 37, 2022.
144. Liu X, Zhang J, Wang X, Teng M, Wang G and Zhou X: Application of artificial intelligence large language models in drug target discovery. Front Pharmacol 16: 1597351, 2025.
145. Ren J and Wu M: Identification of novel therapeutic targets for MAFLD based on bioinformatics analysis combined with Mendelian randomization. Int J Mol Sci 26: 3166, 2025.