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Review

Crosstalk between Endoplasmic Reticulum Stress and Ferroptosis in Liver Diseases

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Abstract

The endoplasmic reticulum (ER) played an important role in the folding, assembly and post-translational modification of proteins. ER homeostasis could be disrupted by the accumulation of misfolded proteins, elevated reactive oxygen species (ROS) levels, and abnormal Ca^{2+} signaling, which was referred to ER stress (ERS). Ferroptosis was a unique programmed cell death model mediated by iron-dependent phospholipid peroxidation and multiple signaling pathways. The changes of mitochondrial structure, the damage of glutathione peroxidase 4 (GPX4) and excess accumulation of iron were the main characteristics of ferroptosis. ROS produced by ferroptosis can interfere with the activity of protein-folding enzymes, leading to the accumulation of large amounts of unfolded proteins, thus causing ERS. On the contrary, the increase of ERS level could promote ferroptosis by the accumulation of iron ion and lipid peroxide, the up-regulation of ferroptosis related genes. At present, the studies on the relationship between ferroptosis and ERS were one-sided and lack of in-depth studies on the interaction mechanism. This review aimed to explore the molecular mechanism of cross-talk between ferroptosis and ERS, and provide new strategies and targets for the treatment of liver diseases.

Keywords: endoplasmic reticulum stress; ferroptosis; crosstalk; liver disease

1. Introduction

The endoplasmic reticulum (ER) is a complex membrane system that serves as an essential site for the synthesis, folding, and posttranslational modification of secreted and membrane proteins [1]. Imbalance in ER caused by certain physiological or pathological factors leads to the accumulation of a large number of unfolded or misfolded proteins in cells, resulting in ER stress [2]. To restore ER homeostasis and reduce the amount of faulty or unfolded proteins in the reticulum, the unfolded protein response (UPR) is activated [3]. The UPR is regulated by three proteins, including activating transcription factor 6 (ATF6), protein kinase R-like ER kinase (PERK) and inositol requiring enzyme 1 (IRE1) [4]. These three ER transmembrane proteins reversibly bind to the endoplasmic reticulum partner binding immunoglobulin protein (BiP)/heat shock protein family A member 5 (HSPA5)/glucose-regulated protein 78 (GRP78) to inhibit activity under normal physiological conditions; however, HSPA5 dissociates from this protein when the UPR occurs. These three proteins are activated and initiate a response, thus regulating transcription and translation, activating protein degradation pathways and reducing the accumulation of faulty proteins in the ER to restore ER homeostasis [5]. More intense endoplasmic reticulum stress (ERS) occurs when the three sensors of the UPR are insufficient to restore unfolded proteins in the ER to a normal state [6].

As a new mode of death, ferroptosis differs from other programmed types of death, such as apoptosis, necrosis and autophagy, and its occurrence depends on the accumulation of iron in cells. Its biochemical, morphological and genetic characteristics are significantly different from those of other types of programmed cell death [7,8]. Morphology is mainly manifested by mitochondrial agglutination or swelling, increased membrane density, a reduced or disappeared ridge and outer membrane rupture [9]. When glutathione (GSH) is exhausted in the cell, the activity of GPX4 is reduced, the GPX4 catalytic reduction reaction cannot metabolize lipid peroxides and a large amount of reactive oxygen species (ROS) are generated to induce ferroptosis [10]. Intracellular iron accumulation, lipid peroxidation and an abnormal antioxidant System Xc- are the key factors involved in ferroptosis. Ferroptosis is induced by ROS, which are produced by various sources, such as iron metabolism, the mitochondrial electron transport chain and the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) protein family.

An increasing number of studies have shown that ferroptosis and ERS are mutually regulated and that ferroptosis and ERS are involved in the occurrence of various liver diseases. In this review, the authors summarize the mecha-

nisms by which ERS interacts with ferroptosis and the roles of these mechanisms in common liver diseases.

2. Mechanism of ERS

2.1 PERK Pathway

PERK is a kinase of phosphorylated eukaryotic initiation factor 2α (eIF2α) and nuclear factor erythroid 2-related factor (Nrf2). When ERS occurs, PERKs separate from HSPA5s and are activated. Activated PERK phosphorylates eIF2α and Nrf2. The activation of eIF2α can cause most protein translation to decrease, and the protein load in the endoplasmic reticulum is also reduced [1]. The expression of activating transcription factor 4 (ATF4) is upregulated when the level of phosphorylated eIF2α reaches a certain level [11]. ATF4 is a major regulator of the stress response and regulates the expression of genes involved in amino acid metabolism and redox and protein homeostasis at the transcriptional level. ATF4 enhances mitochondrial respiration and promotes oxidative metabolism by activating the comprehensive stress-promoting respiratory supercomplex [12]. The activation of Nrf2 can promote the expression of heme oxygenase-1 (HO-1), ATF3 activating transcription factor 3 (ATF3) and solute carrier family 7 member 11 (SLC7A11), which are other target groups, as well as upregulate ROS and induce ERS [13].

2.2 The IRE1 Pathway

IRE1α is a type I transmembrane protein that recognizes unfolded proteins and misfolded proteins in the ER via its N-terminal peptide-binding domain. IRE1α and GRP78 bind to the downstream X-box-binding protein 1 (XBP1) mRNA transcript after it is bound to a misfolded protein. Spliced X-box binding protein 1 (XBP1s) is a transcription factor responsible for regulating the transcription of genes associated with the ER quality control and ERAD pathways. In addition, regulated IRE1α-dependent decay (RIDD), which degrades or translates mRNA, reduces the protein load in the ER and restores ER homeostasis [14–16].

2.3 The ATF6 Pathway

ATF6 is a type II transmembrane protein with two subtypes known as ATF6α and ATF6β. ATF6α is separated from GRP78 and disrupted by the site-1protease (S1P) and site-2 protease (S2P) when ERS occurs. The amino-terminal cytoplasmic fragment (ATF6f) is released and translocated to the nucleus to participate in the expression of proteins, thereby increasing the folding ability of the ER and restoring ER homeostasis [17,18]. XBP1 is a target molecule regulated by ATF6. ATF6 can also upregulate the transcription of XBP1 mRNA, increase the level of XBP1s and activate ERS [19,20].

3. Mechanism of Ferroptosis

3.1 Iron Accumulation

Iron is an important trace metal in the body and is involved in biosynthesis, oxygen transport and the respiratory chain. Cellular iron production is mediated by transferrin (Tf) and transferrin receptor 1 (TfR1). Intracellular iron can be transported outside of the cell by the ferroportin (FPN) [21]. Iron overload is an important cause of ferroptosis. When a large amount of Fe^{2+} accumulates in the cell, it induces the Fenton reaction, results in the production of a large number of ROS, hydroxyl groups and free radicals and activates iron-containing enzymes. Many known organic compounds, such as carboxylic acids, alcohols and esters, can be peroxidized by the Fenton reaction and produce corresponding peroxide products, which ultimately lead to ferroptosis [22–24].

The iron uptake pathway mediated by Tf and TfR1 is involved in ferroptosis. The inhibition of the expression of TfR1 can effectively reduce the ferroptosis induced by erastin. The addition of fe-containing Tf or ferric ammonium citrate to the cell medium resulted in an increase in the Fe^{2+} concentration and induced ferroptosis [25,26]. Nedd4-like E3 ubiquitin protein ligase (NEDD4L) can increase the degradation of lactotransferrin (LTF), inhibit intracellular iron accumulation and reduce ferroptosis [27]. The initial signal of ferroptosis has not yet been determined; however, ferroptosis must be involved, and the degree of iron accumulation in the cell directly determines the course of ferroptosis.

3.2 Lipid Peroxidation

The initiation and execution of ferroptosis are regulated by lipids. Polyunsaturated fatty acids (PUFAs) are essential substrates for fat metabolism and are catalyzed by coenzyme A (CoA) and 4acyl-CoA synthetase long-chain family member 4 (Acsl4) to produce polyunsaturated fatty acid membrane phospholipids (PUFA-PLs) [28]. PUFA-Pls is catalyzed by lipoxygenase (LOX) or cytochrome P450 oxidoreductase (POR) to produce lipid peroxides (LPOs) [8]. LPO can activate protein kinase βII (PKCβII) to promote ACSL4 activation and oxidize additional PUFAs to produce additional LPO [29]. LPO can produce lipids to freely form lipid ROS through lipid oxidation reactions [30]. Furthermore, malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) levels are biomarkers of ferroptosis [31].

3.3 Antioxidant System Xc- Abnormalities

The oxidation and antioxidant reactions in the cell are in balance under physiological conditions. When the redox balance system is disrupted, this scenario causes the accumulation of free radicals and triggers ferroptosis. System Xc- is a glutamate/cystine reverse transporter. Cystine, glutamate and glycine are catalyzed by glutamate cysteine ligase (GCL) and glutathione synthase (GS) to become glu-

tathione (GSH). GSH is an important intracellular antioxidant that can alleviate oxidative stress by scavenging free radicals in the body [32]. Additionally, GPX4 is a ferroptosis inhibitor that uses GSH as a coenzyme, which can reduce LPO to nontoxic lipid alcohols and reduce ROS and free radical accumulation [33]. Ferroptosis can be induced by reduced activity or insufficient levels of GPX4 [34].

4. The Interaction between Ferroptosis and ERS

4.1 Ferroptosis-Inducing ERS

Ferroptosis and ERS play important roles in cell death. In recent years, studies have shown that ferroptosis can be accompanied by ERS, which may be closely related to ROS produced during ferroptosis. ROS can interfere with the activity of protein folding enzymes, thus resulting in ER protein peroxidation, dysfunction of ER molecular chaperones and the accumulation of unfolded proteins in the ER. Eventually, ERS is induced. Additionally, ROS binds to the inositol receptor 1,4,5-triphosphate (IP3R) in the ER, resulting in high intracellular Ca^{2+} accumulation and ultimately ERS [35,36]. Furthermore, organic extracts of fine particulate matter (PM2.5) can produce a large amount of ROS by binding to the aromatic hydrocarbon receptor (AHR) and significantly increase the expression level of CHOP. CHOP can simultaneously activate the three receptors of ERS, PERK, IRE1, and ATF6, thereby inducing strong ERS [37]. Iron is also involved in the occurrence of ERS, and iron activates the PERK-eIF2α-ATF4-CHOP pathway, thereby inducing p53 to upregulate the expression of apoptosis regulator (PUMA). Ferroptosis inducers that induce ferroptosis in cells also activate ERS. Ferroptosis inducers can inhibit cystine-glutamate exchange in cells, increase the expression of ERS-related protein ChaC glutathione-specific gamma-glutamylcyclotransferase 1 (CHAC1), and activate ERS. CHAC1 is involved in the ATF4-CHOP pathway in ERS [38]. Artesunate can be used as an inducer of ferroptosis for the treatment of Burkitt lymphoma (BL), but artesunate not only induces ferroptosis in BL cells but also induces a strong UPR. Activation of the ATF4-CHOP-CHAC1 pathway induces an ERS response, while CHAC1 reduces GSH levels, decreases cell tolerance to ROS and lipid peroxidation, and increases ferroptosis. Ferrostatin-1 (Fer-1) and desferriamine not only inhibit ferroptosis but also inhibit ERS [39]. Ferroptosis inducers can also induce an increase in PUMA expression upregulated by p53 through the ATF4-CHOP-CHAC1 pathway, thereby causing ERS [38]. In a model of cadmium-induced hepatocyte damage, cadmium induced ferroptosis in hepatocytes and activated the PERK-eIF2α-ATF4-CHOP pathway to induce ERS, and the iron chelating agent deferriamine effectively inhibited ferroptosis and ERS [40]. Activation of the PERK-eIF2α-ATF4-CHOP-CHAC1 pathway may be an important factor in the activation of ERS by ferroptosis inducers. The pathways by which ferroptosis induces ERS are shown in Fig. 1.

4.2 ERS Induces Ferroptosis

Ferroptosis is regulated by ERS, and under certain conditions, ERS can promote ferroptosis. The PERK-eIF2α-ATF4-CHOP pathway is not only involved in ferroptosis-induced ERS but also involved in ferroptosis induced by ERS. Xu *et al.* [41] reported that the levels of iron ions and phospholipids in the intestinal epithelial cells of the ulcerative colitis (UC) group were significantly greater than those in the control group, and the observed mitochondrial atrophy was consistent with the morphological characteristics of ferroptosis. These findings suggested that ferroptosis may be closely related to UC. However, the activation of PERK-eIF2α-ATF4-CHOP pathway was also observed during this process. Combining PERK inhibitors with RSL3 (a ferroptosis inducer) did not inhibit PERK-eIF2α-ATF4-CHOP and ERS activation but also reduced ferroptosis in cells. ERS was also found to activate the PERK/eIF2α signalling pathway and induce mitochondrial dysfunction to regulate ROS production and promote ferroptosis in cells induced by whole-smoke condensates [42]. Peroxisome proliferator-activated receptor γ (PPARγ) is involved in the regulation of lipid metabolism and blood glucose. PPARγ is also involved in ferroptosis induced by ERS. When ERS occurs, the PERK signalling pathway is activated, the expression of PPARγ is inhibited, the level of PPARγ decreases, and the level of lipid peroxide increases, promoting ferroptosis [43,44]. Additionally, PERK can upregulate p53 to inhibit the transcription of SLC7A11, decreasing the activity of System Xc- and promoting ferroptosis [45]. In exploring novel therapeutic strategies for lung cancer, Fu *et al.* [46] also reported that biomineralized liposomes (LDMs) containing dihydroartemisinin (DHA) and pH-responsive calcium phosphate (CaP) can drive and enhance ferroptosis by inducing ERS. Mechanistically, CaP causes a sharp increase in the intracellular Ca^{2+} concentration, triggering intense ERS, followed by mitochondrial dysfunction, ROS accumulation, and ferroptosis. This is followed by a surge of Ca^{2+} entering the cell through iron pathways on the cell membrane, driving the "Ca^{2+} burst-ER stress-ferroptosis" cycle. Further experiments revealed that the process by which ERS promotes ferroptosis is also the process by which ROS and LPO accumulation trigger cell swelling and cell membrane destruction. Nrf2 is also involved in ERS-induced ferroptosis. Nrf2 is an upstream element involved in the PERK-Nrf2-HO-1 cascade in ERS. Activated Nrf2 activates target genes, including *HO-1*, and increases HO-1 expression. HO-1 metabolizes heme to Fe^{2+} and induces ferroptosis by regulating the increase in unstable iron content and ROS production in the iron pool [13,47]. ATF3 is an ERS-induced transcription factor that can regulate the transcription of target genes according to the cellular environment [48]. When activated,

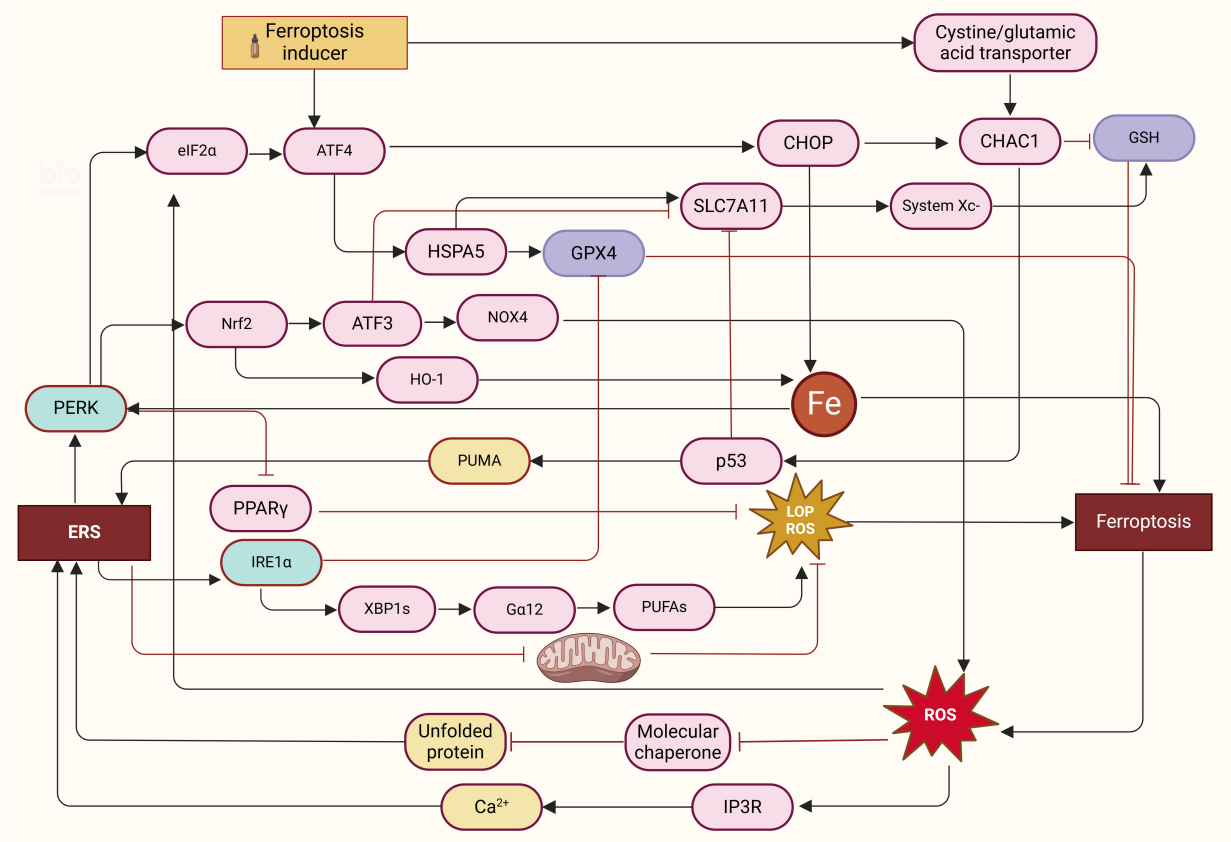

Fig. 1. The mutual regulatory mechanism between ERS and endoplasmic death. (1) Ferroptosis induces ERS: Ferroptosis can inhibit the chaperone function of molecules by releasing a large number of ROS, resulting in the accumulation of a large number of unfolded proteins, and binding with IP3R releases a large amount of Ca^{2+} accumulation, resulting in ERS. Excess iron activation via the PERK-eIF2α-ATF4-CHOP pathway induced increased expression of PUMA. Ferroptosis inducers can inhibit cystine-glutamate exchange in cells and increase the expression of CHAC1. (2) Ferroptosis induced by ERS: ERS induces mitochondrial dysfunction and activates PERK-eIF2α-ATF4-CHOP, PERK-Nrf2-HO-1, PERK-PPARγ, PERK-P53-SLC7A11-System Xc-, PERK-Nrf2-ATF3-SLC7A11/NOX4, and IRE1α-XBP1s-Gα12-PUFAs to induce ferroptosis. (3) ERS negatively regulates ferroptosis: ERS increases the levels of System Xc- and GSH and the activities of System Xc- and GPX4 in cells and reduces the production of lipoperoxide by activating the PERK-ATF4-HSPA5/SLC7A11 pathway. ERS, endoplasmic reticulum stress; ROS, reactive oxygen species; IP3R, inositol receptor 1,4,5-triphosphate; PUMA, p53 to upregulate the expression of apoptosis; GSH, glutathione; GPX4, glutathione peroxidase 4; LOP, lipid oxidation product.

Nrf2 can bind to the ATF3 promoter and upregulate the expression of ATF3 through ROS, inhibiting the expression of SLC7A11 and resulting in reduced activity of System Xc-, a lack of intracellular GSH, the promotion of lipid peroxidation, and the induction of intracellular ferroptosis [49]. ATF3 can also upregulate the expression of NADPH oxidase 4 (NOX4), activate NADPH oxidase, promote the production of superoxide and ROS, and promote iron-mediated cell death [50]. Therefore, ATF3 plays an important role in the regulation of ferroptosis by ERS. IRE1α is also involved in the regulation of ferroptosis. On the one hand, IRE1α can inhibit GPX4 expression and promote ferroptosis; on the other hand, IRE1α can promote the transcription of XBP1s and activate Gα12 to promote iron peroxide-mediated death in PUFAs [51,52]. The pathways by which ferroptosis is induced by ERS are shown in Fig. 1.

4.3 ERS Inhibits Ferroptosis

ERS and ferroptosis coparticipate in cell death. Under certain conditions, ERS can inhibit ferroptosis and participate in cancer cell resistance. In cancer cell ferroptosis induced by ferroptosis inducers, the ERS response is simultaneously activated, and the PERK-eIF2α-ATF4 pathway inhibits ferroptosis by upregulating the expression of HSPA5, System Xc-, and other molecules [53]. When pancreatic ductal adenocarcinoma (PDAC) cells were treated with a certain dose of erastin, the transcriptional translation level of the ER chaperone HSPA5 was significantly greater than that in the control group. The PERK and eIF2α-ATF4 pathways were also activated in these cells, the expression of ATF4 and the molecule CHOP was upregulated, and the expression of the ATF4 target gene HSPA5 was also upreg-

ulated. Erastin-induced lipid peroxidation can be significantly enhanced by inhibiting HSPA5 expression via RNA interference (RNAi) or knocking out the *ATF4* gene, leading to ferroptosis. The above results indicate that HSPA5 can inhibit ferroptosis in PDAC cells, which might be related to the inhibition of GPX4 degradation by HSPA5 to improve the intracellular antioxidant capacity [54]. As an anticancer drug, dihydroartemisinin can induce ferroptosis in glioma cells, and the activation of PERK-ATF4-HSPA5 pathway was also found when studying the related mechanism; additionally, upregulated HSPA5 increased the activity of GPX4 and reduced the production of lipoperoxide [53]. ATF4 is highly expressed in injured cardiomyocytes induced by Sorafenib (SOR), and ATF4 can enhance the expression of SLC7A11, the active regulatory subunit of System Xc-, through transcriptional regulation, increase the activity of System Xc-, inhibit ferroptosis, and promote the survival of cardiomyocytes [55]. Harding *et al*. [56] reported that wild-type mouse fibroblasts were prone to amino acid depletion when the *ATF4* gene was knocked out. In the absence of exogenous amino acid supplementation, peroxides rapidly accumulate in cells, resulting in cell death. Ferroptosis inducers such as artesunate and dihydroartemisinin can induce ferroptosis in cells and negatively regulate ferroptosis, and ERS is activated. The expression of HSPA5 and SLC7A11 increased under the regulation of ATF4, which increased the levels of System Xc- and GSH and the activities of System Xc- and GPX4 in cells and reduced the occurrence of ferroptosis [53]. This finding suggested that the expression level of ATF4 may be closely related to the sensitivity of cells to oxidative stress and that ATF4 may be another important molecule involved in the regulation of ferroptosis by ERS. The pathways by which ERS inhibits ferroptosis are shown in Fig. 1.

5. The Role of ERS and Ferroptosis Cross-Talk in Common Liver Diseases

5.1 Non-Alcoholic Fatty Liver Disease (NAFLD)

The disease progression of non-alcoholic fatty liver disease (NAFLD) encompasses a range of diseases from simple steatosis to non-alcoholic hepatitis (NASH), which can progress to cirrhosis and hepatocellular carcinoma (HCC), a metabolic syndrome of liver damage with an unknown pathogenesis. However, ferroptosis and ERS are closely related to the occurrence of NAFLD. IRE1α/XBP1 plays an important role in lipid regulation in hepatocytes. IRE1α/XBP1 can directly upregulate the regulation of sterol regulatory element-binding protein-1c (SREBP-1c), which is involved in fatty acid synthesis. When IRE1α/XBP1 is continuously activated, it leads to the accumulation of triglycerides and cholesterol in the liver, resulting in NAFLD [57]. GRP78 is an ER molecular chaperone, and the expression of ATF6, an ERS receptor, is significantly increased in the cells of mice fed a high-fat diet. Aerobic exercise can reduce the expression levels of GRP78 and ATF6 and reduce ERS, thus improving the symptoms related to NAFLD [58]. PERK is also activated in ERS through the PERK-eIF2α-ATF4 pathway to increase the intracellular CHOP level, activate the CHOP pathway, and induce cell apoptosis; at the same time, CHOP can induce PPARγ expression and promote lipid accumulation in NAFLD [59]. In NAFLD cells, the increased expression level of lysophosphatidylcholine acyltransferase (LPCAT) increases the content of intracellular amino acids, which are one of the substrates of PUFAs. The increase in the content of amino acids can significantly increase the level of lipid peroxidation and induce ferroptosis. Although GPX4 can inhibit ferroptosis, the overexpression of GPX4 in liver cells can activate enolase3 (ENO3) and increase the content of intracellular lipids to induce ferroptosis [60]. Ferroptosis and ERS participate in the occurrence of NAFLD and can regulate each other. Sodium arsenite (NaAsO2) is a carcinogen that can cause immune inflammation, fibrosis, and even cancer in liver cells. Ferroptosis in a NaASO2-induced NAFLD rat model involved ERS. After NaAsO2 treatment, the iron content significantly increased, MDA, ACSL4, and 5-hydroxy eicosatetraenoic acid (5HETE) expression increased, GSH expression decreased, and linear membrane rupture and ridge reduction were observed in rat hepatocytes. When liver cells were pretreated with Fer-1 or ACSL4 inhibitors, GPX4 levels were significantly restored, mitochondrial structure and morphology were significantly improved, and ferroptosis was inhibited. In rat hepatocytes treated with NaAsO2, the expression of IRE1α, one of the receptors of ERS, was upregulated, which activated ERS, and IRE1α promoted NAFLD and ferroptosis in hepatocytes by upregulating 5-HETE, ACSL4, and MDA and inhibiting GPX4 expression [51]. The ferroptosis and ERS pathways in NAFLD are shown in Fig. 2A.

5.2 Hepatocellular Carcinoma (HCC)

HCC is a malignant tumor that occurs in hepatocytes or intrahepatic bile duct epithelial cells and has a poor prognosis, and it is urgent to explore the pathogenesis of HCC [61]. Recent studies have shown that HCC can develop from NAFLD and viral hepatitis B [62,63]. The team of Wu [64] reported that ERS was activated in hepatitis B virus (HBV)-induced HCC cells. HBV significantly increased the expression of ERS-related proteins BiP and ATF4, and the secretion of fibroblast growth factor 19 (FGF19) increased under the regulation of ATF4, which activated Janus kinase 2 (JAK2)/activator of transcription 3 (STAT3) pathway and leaded to epithelial-mesenchymal transition (EMT) in HCC cells. EMT is closely related to the occurrence of HCC, and when EMT is inhibited, it can inhibit the formation of hepatic vessels [65,66]. IRE1α is also involved in the development of HCC. IRE1α is overexpressed in HCC cells, and a large amount of IRE1α accumulates in cells to stimulate RNase activity and catalyze the formation of XBP1s. XBP1s increased IL-6 expression

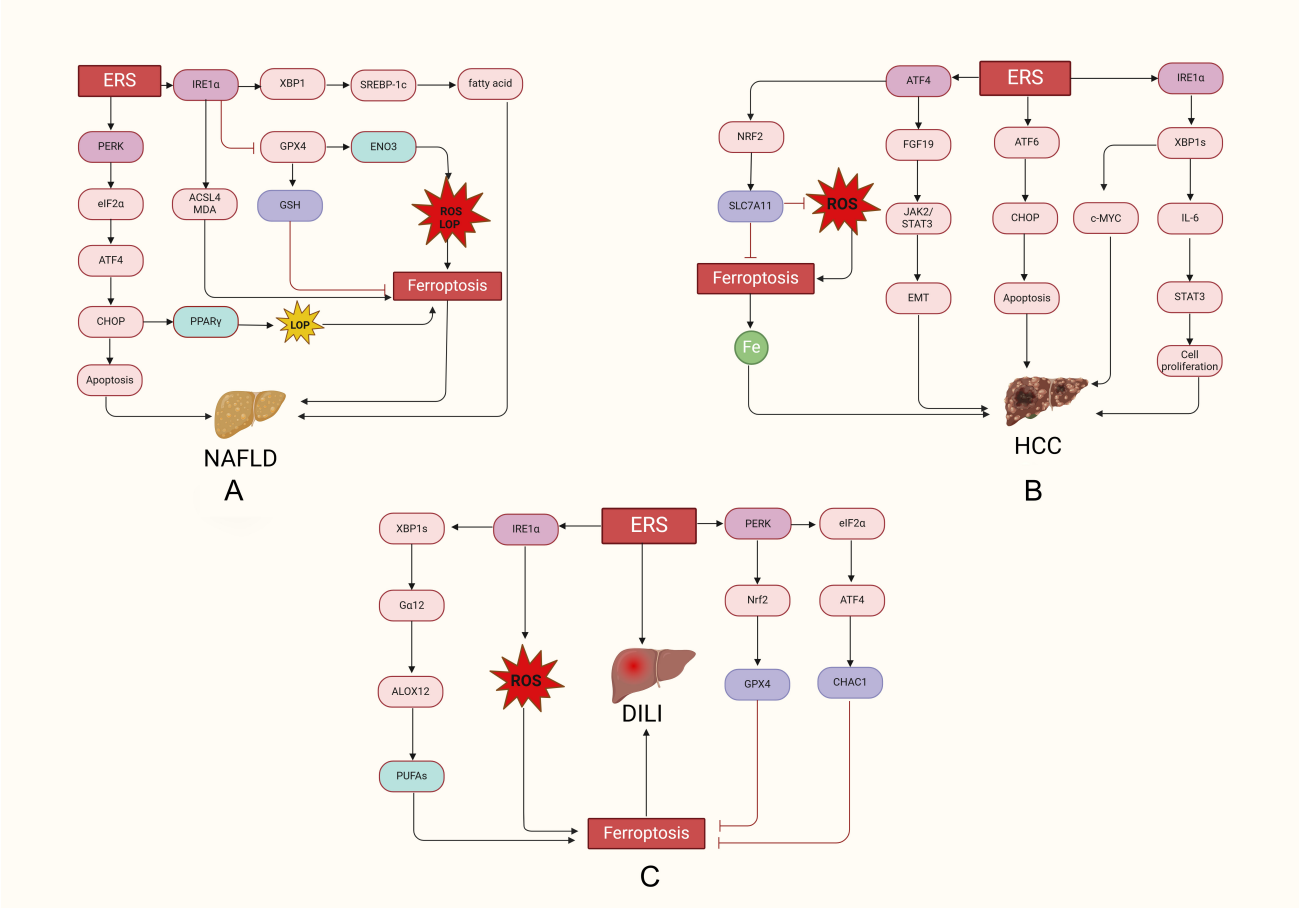

Fig. 2. Ferroptosis and the regulation of ERS in liver disease. (A) In NAFLD, ERS increased the expression of IRE1α, PERK, ACSL4 and GRP78 related proteins, and IRE1α promoted ferroptosis in hepatocytes by upregulating 5-HETE, ACSL4 and MDA and inhibiting GPX4 expression. (B) In HCC, ERS promotes the growth and proliferation of cancer cells through the ATF4-FGF19-JAK2/STAT3-EMT, IRE1α-XBP1s-IL-6-STAT3, and IRE1α-XBP1s-c-MYC pathways and inhibits ferroptosis through the PERK-ATF4-Nrf2-SLC7A11 pathway. (C) In DILI, ERS induces ferroptosis in hepatocytes by activating IRE1α-XBP1-Gα12-ALOX12-PUFAs and PERK eIF2α-ATF4-CHAC1, but ERS inhibits ferroptosis in hepatocytes via PERK Nrf2-GPX4. NAFLD, non-alcoholic fatty liver disease; DILI, Drug-induced liver injury; HCC, hepatocellular carcinoma; PERK, protein kinase R-like ER kinase; ACSL4, 4acyl-CoA synthetase long-chain family member 4; GRP78, glucose-regulated protein 78; MDA, malondialdehyde.

through signal transduction, induced STAT3 activation, and promoted the proliferation of HCC cells. Treatment of HCC with toluene can significantly improve the value-added effect of IL-6-STAT3 on HCC [67]. c-MYC is closely related to the occurrence of cancer and has a strong carcinogenic effect, participating in the drug resistance of cancer cells. Knockout of *IRE1*α can inhibit the IRE1α-XBP1s-C-MYC pathway, which can significantly improve the resistance of HCC to sorafenib [60–69]. In addition, ATF6 and its target gene (*CHOP* apoptosis gene) are involved in the development of HCC [70]. ATF6/CHOP is significantly activated in hepatocytes treated with cytochrome P450 2E1 (CYP2E1), which inhibits the apoptotic pathway of hepatocytes and promotes the occurrence and development of HCC [71]. Moreover, single nucleotide polymorphisms (SNPs) in ATF6α significantly increase the risk of HCC [72]. Studies have shown that long-term iron overload in cells can cause cell damage, which eventually manifests as HCC [73]. Excessive accumulation of iron in HCC can promote the proliferation of cancer cells and promote the growth of tumors [74]. Moreover, studies have shown that the expression of GPX4, a regulator of ferroptosis, is significantly increased in HCC, which may be related to the reduction in oxidative stress in cancer cells caused by GPX4 [75]. Both ERS and ferroptosis regulators are involved in the development of HCC, and inducing ferroptosis in HCC is a promising therapeutic strategy. Thus, there is mutual regulation between ERS and ferroptosis, and the same is true in HCC. ATF4 is a transcription factor activated by ERS, and ATF4 and Nrf2 can coupregulate the expression of SLC7A11 in HCC, reduce oxidative stress, and inhibit ferroptosis [76]. The ferroptosis and ERS pathways in HCC are shown in Fig. 2B.

5.3 Drug-Induced Liver Injury (DILI)

Drug-induced liver injury (DILI) refers to liver damage caused by the drug itself or its metabolites, as well as due to the supersensitivity or tolerance of special constitutions to the drug during the use of the drugs, which can lead to liver failure. Moreover, liver injury caused by acetaminophen (APAP) is more common [77]. APAP is catalyzed by cytochrome P450 2E1 (CYP2E1) to produce N-acetyl-p-benzoquinoneimine (NAPQI), which is a highly toxic product. An excessive concentration of APAP *in vivo* increases GSH consumption and NAPQ and ROS levels, and this process leads to ferroptosis and ERS, ultimately leading to hepatocyte death [78,79]. ERS is involved in drug-induced liver damage, and Galpha12 (Gα12) is associated with cell activity. Apap-induced acute liver damage in patients with significantly increased Gα12 expression, downregulated GPX4 expression, lipid peroxide accumulation and typical ferroptosis may also be observed. An increase in ERS was positively correlated with the expression of Gα12 and trans-activated Gα12 through the IRE1α-XBP1 pathway. Moreover, Gα12 can promote the peroxidation of PUFAs and induce ferroptosis in hepatocytes by inducing arachidonate 12-lipoxygenase (ALOX12) [52]. These results indicate that ERS can promote ferroptosis in hepatocytes by increasing the expression of Gα12 and that Gα12 is expected to be a new target for the treatment of DILI. Xu and his team [80] reported the protective effect of ERS in mouse hepatocytes with APAP-induced acute liver injury, which promoted ferroptosis in hepatocytes through the activation of PERK-eIF2α-ATF4-CHAC1. The morphology of mitochondria is a characteristic feature of ferroptosis, and a large amount of ROS, iron and lipid peroxides can accumulate in a liver injury model induced by carbon tetrachloride (CCl_4). Similarly, the expression levels of SLC7A11 and GPX4 were significantly lower in these cells than in control cells. However, bicyclol can improve ferroptosis by directly increasing the activity of other enzymes. This effect can also be achieved by activating another branch of PERK known as the Nrf2-GPX4 axis [81]. In addition, CCl_4 can lead to decreased transcription levels of antioxidant enzymes, including GSH and superoxide dismutase (SOD), as well as increased ROS levels and activation of the ERS-related protein IRE1-α. The production of excessive ROS further promotes the occurrence of ERS. *P. umbrosa* can significantly improve ferroptosis in hepatocytes and ERS [82]. The ferroptosis and ERS pathways involved in DILI are shown in Fig. 2C.

6. The Application of ERS and Ferroptosis in the Treatment of Liver Disease

Compared with that in normal cells, the metabolism of iron in cancer cells is significantly increased, and the demand for iron is also increased, so cancer cells have a higher susceptibility to ferroptosis. Sorafenib is a systemic therapy for the treatment of advanced HCC, and the development of drug resistance is the main reason for its limited use. Metallothionein (MT)-1G is an Nrf2-dependent protein that can reduce the levels of GSH and lipid peroxidation in HCC, inhibiting ferroptosis in cells. The upregulation of MT-1G expression is related to the resistance of hepatocellular carcinoma cells to sorafenib [83]. Additionally, ERS participates in sorafenib resistance by upregulating pyruvate kinase subtype M2 (PKM2) through the microRNA-188-5p (miR-188-5p)/heterogeneous nuclear ribonucleoprotein A2B1 (hnRNPA2B1) pathway [84]. These findings demonstrate that both ferroptosis and ER are involved in sorafenib resistance. The Nrf2, as the junction of ferroptosis and ER stress, may effectively improve sorafenib resistance and enhance its anticancer efficacy. Currently, there is a lack of effective drugs for NAFLD treatment, but acacetin can effectively improve NAFLD by leveraging the crosstalk between ERS and ferroptosis. Acacetin can reduce the expression of MDA, GSH, ATF6, and CHOP in high-fat diet-fed mice, inhibiting ferroptosis and ERS. Acacetin can directly inhibit ferroptosis and indirectly inhibit the expression of ACSL4, a promoter of ferroptosis, by inhibiting the ATF4-CHOP axis in ERS. Therefore, acacetin has a strong ability to inhibit lipid accumulation in liver cells and is expected to become a candidate drug for the treatment of NAFLD in the future [85]. ERS and ferroptosis promote each other and participate in the occurrence and development of drug-induced liver injury. Salidroside inhibited the cationic transport regulator CHAC1 and the PERK-eIF2α-ATF4 pathways in mouse models, reducing GSH degradation and the intracellular iron content, inhibiting ferroptosis, and preventing APAP-related liver damage caused by ERS. Increased transcription of the PERK activators CCT020312 and ATF4 can reduce the inhibitory effect of salidroside on CHAC1. Additionally, the activation of AMP-activated protein kinase (AMPK)/sirtuin-1 (SIRT1) signal transduction plays an important role in the inhibition of ferroptosis and ERS by salidroside, and when SIRT1 is inhibited, the protective effect of salidroside on ferroptosis and ERS can be weakened [80]. In fact, many studies have shown that daglizin and irisin can inhibit ferroptosis and ERS by activating SIRT1, reducing ROS and MDA production, reducing the intracellular iron content, and inhibiting the PERK-eIF2α-ATF4 axis [86,87]. These findings suggest that the activation of SIRT1 may be a valuable target for evaluating DILI treatment.

7. Summarize

According to recent studies, ferroptosis can induce ERS by activating the PERK-eIF2α-ATF4-CHOP pathway and upregulating PUMA and ROS, while ERS can negatively regulate ferroptosis by activating the PERK-ATF4-HSPA5/System Xc-, PERK-Nrf2-GPX4, and other pathways. However, ERS can also induce ferroptosis through PERK-eIF2α-ATF4-CHOP, PERK-Nrf2-HO-1, and other pathways. Additionally, cross-talk between ferroptosis and

ERS also plays an important role in diseases. In NAFLD, HCC and DILI, ferroptosis characteristics are observed, such as increased ROS and lipid peroxides, as well as iron accumulation, while in NAFLD, ERS manifests as increased expression of IRE1α, PERK, and GRP78. In HCC, the expression of ERS-related proteins such as IRE1α, XBP1s, ATF6, and CHOP was upregulated, and ferroptosis was inhibited by PERK-ATF4-Nrf2-SLC7A11. In DILI, the activation of the IRE1α-XBP1-Gα12-ALOX12 pathway promotes ferroptosis, but ERS inhibits ferroptosis through the PERK-Nrf2-GPX4 pathway. Understanding the circumstances under which the ability of ERS to induce ferroptosis is greater than that of ERS to negatively regulate ferroptosis may lead to the identification of new therapeutic targets for overcoming cell drug resistance. Moreover, the targeting of ferroptosis plays an important role in preventing diseases mediated by ROS, lipid peroxidation and inflammatory infiltration. The involvement of the ERS also provides additional options and directions for the treatment of related diseases. The combination of ERS and ferroptosis inhibitors may achieve improved efficacy. However, the mechanism of crosstalk related to ERS and ferroptosis has still not been studied in detail, and the crosstalk between ERS and ferroptosis has not yet undergone clinical translation. A further elucidation of the crosstalk mechanism between ERS and ferroptosis for clinical application will be beneficial for the treatment of related diseases.

Author Contributions

MH, YW, WL and XW conceived and designed the study. MH, YW, and XW drafted the manuscript. MH and YW revised the paper. WL edited the article. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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