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Contents

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EDITORIAL

REVIEW

MINIREVIEWS

World Journal of Gastrointestinal Oncology

Monthly Volume 16 Number 6 June 15, 2024

Contents

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Monthly Volume 16 Number 6 June 15, 2024

Contents

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Contents

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REVIEW

Research progress of ferroptosis regulating lipid peroxidation and metabolism in occurrence and development of primary liver cancer

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Abstract

As a highly aggressive tumor, the pathophysiological mechanism of primary liver cancer has attracted much attention. In recent years, factors such as ferroptosis regulation, lipid peroxidation and metabolic abnormalities have emerged in the study of liver cancer, providing a new perspective for understanding the development of liver cancer. Ferroptosis regulation, lipid peroxidation and metabolic abnormalities play important roles in the occurrence and development of liver cancer. The regulation of ferroptosis is involved in apoptosis and necrosis, affecting cell survival and death. Lipid peroxidation promotes oxidative damage and promotes the invasion of liver cancer cells. Metabolic abnormalities, especially the disorders of glucose and lipid metabolism, directly affect the proliferation and growth of liver cancer cells. Studies of ferroptosis regulation and lipid peroxidation may help to discover new therapeutic targets and improve therapeutic outcomes. The understanding of metabolic abnormalities can provide new ideas for the prevention of liver cancer, and reduce the risk of disease by adjusting the metabolic process. This review focuses on the key roles of ferroptosis regulation, lipid peroxidation and metabolic abnormalities in this process.

Key Words: Ferroptosis; Lipid peroxidation; Primary liver cancer; Lipid metabolism; Review

Core Tip: As a highly aggressive tumor, the pathophysiological mechanism of primary liver cancer has attracted much attention. In recent years, factors such as ferroptosis regulation, lipid peroxidation and metabolic abnormalities have emerged in the study of liver cancer, providing a new perspective for understanding the development of liver cancer. Ferroptosis regulation, lipid peroxidation and metabolic abnormalities play important roles in the occurrence and development of liver cancer. The regulation of ferroptosis is involved in apoptosis and necrosis, affecting cell survival and death. Lipid peroxidation promotes oxidative damage and promotes the invasion of liver cancer cells.

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INTRODUCTION

Liver cancer is a kind of malignant tumor which threatens human health seriously[1]. Its highly invasive and high incidence has become a global public health problem[2-4]. According to the World Health Organization, liver cancer is the fourth leading cause of cancer death worldwide, killing hundreds of thousands of people each year. In China, the prevalence and death rate of liver cancer are also high, ranking first among all types of cancer[5]. Because the early symptoms of liver cancer are not obvious and are often ignored, most patients are already in the advanced stage when diagnosed, and the treatment effect is not good. Therefore, in-depth study of the pathogenesis of liver cancer and search for new therapeutic targets and prevention strategies are crucial to reduce the incidence of liver cancer and improve the survival rate of patients[6-8]. The pathogenesis of liver cancer is extremely complex, involving the combined effects of many factors, including viral infection, alcohol abuse, fatty liver, genetic factors, *etc*[9]. In recent years, studies have shown that ferroptosis regulation and abnormal lipid metabolism play an important role in the occurrence and development of liver cancer, which has attracted wide attention[10-12].

Ferroptosis regulation is a cellular response to iron homeostasis, involving the accumulation and regulation of iron ions in the cell. Excessive iron accumulation can cause oxidative stress, damage cell structure and function, and eventually lead to cell death. Recent studies[13-15] have shown that ferroptosis regulation is closely related to the occurrence and development of liver cancer. Ferroptosis regulation may play a key role in the proliferation and invasion of liver cancer cells by regulating cell survival and death processes[16]. Therefore, in-depth study of the mechanism of ferroptosis regulation in liver cancer is expected to provide new targets and strategies for the treatment of liver cancer. On the other hand, abnormal lipid metabolism is also closely related to liver cancer. The liver is an important organ of lipid metabolism in the body, and abnormal lipid metabolism may lead to fatty liver, thus increasing the risk of liver cancer[17-19]. In addition, the oxygen free radicals produced by lipid peroxidation can lead to oxidative damage of cell membrane and further promote the invasion and metastasis of liver cancer cells. Therefore, the study of the relationship between abnormal lipid metabolism and liver cancer is helpful to reveal the pathogenesis of liver cancer and provide new ideas for the prevention and treatment of liver cancer[20]. Research progress at home and abroad shows that ferroptosis regulation and abnormal lipid metabolism have attracted wide attention in the field of liver cancer[21-23]. Internationally, many research groups are exploring the specific mechanisms of ferroptosis regulation and lipid metabolism in liver cancer, searching for relevant signaling pathways, and developing corresponding drug targets[24-26]. Domestic research has also achieved a series of important results in this field, which provides strong support for the research of liver cancer [27-30].

The purpose of this study was to investigate the relationship between ferroptosis regulation and abnormal lipid metabolism and liver cancer, reveal its mechanism of action, and provide a new theoretical basis for the treatment and prevention of liver cancer. Through in-depth study of these factors, it is expected to provide more effective strategies for the early diagnosis, treatment and prevention of liver cancer, and ultimately improve the quality of life and prognosis of patients.

THE MECHANISM OF FERROPTOSIS

Definition and mechanism of ferroptosis

Ferroptosis is an iron-dependent regulatory mode of cell death caused by the accumulation of lipid peroxidation products and reactive oxygen species (ROS)[31]. Ferroptosis is different from other cell death modes (apoptosis, necrosis, *etc.*) in terms of morphology, biochemical characteristics and regulatory mechanisms (Table 1). The cell membrane did not break and typical apoptotic bodies appeared in the cell during apoptosis. Cell necrosis was characterized by cell swelling, nucleus concentration, fragmentation, dissolution, chromatin staining, flocculation, and organelle expansion or fragmentation. In ferroptosis, there were no typical cell apoptosis and necrosis, and the main manifestations were cell membrane rupture and vesiculation, mitochondrial atrophy, increased membrane density, decreased ridge, and lack of chromatin agglutination in the nucleus[32-35]. Biochemical characteristics and regulatory mechanisms. The apoptosis process mainly depends on cysteinyl aspartate specific proteinase (Caspase) containing cysteine[36]. During apoptosis,

Table 1 Comparison of three types of cell death

Cellular change	Apoptosis	Necrosis	Ferroptosis
Origin	Physiological or pathological signal stimulation	Pathological changes or severe injury	Accumulation of iron-dependent lipid peroxides
Cell morphology	Cell shrinkage	Increased cell volume	Cell shrinkage
Cell membrane morphology	Integrity	Loss of membrane integrity	Breakage and bubble
Chromatin morphology	Nuclear chromatin condensation	No agglutination but flocculation	No agglutination
Organelle morphology	No significant change	Swelling and breakage	Increased mitochondrial membrane density
Apoptotic body	Existence	Inexistence	Inexistence
Change in DNA	Regular degradation and DNA ladder	Irregular degradation and DNA smear	No significant change
Inflammatory response	Existence	Inexistence	Inexistence
Molecular mechanism	Dependence of Caspase	Dependence of RIPK3	Dependence of ROS and Fe

ROS: Reactive oxygen species; RIPK3: Receptor interacting protein kinase 3.

cytoplasmic Ca^{2+} and pH levels increase, and the activation of endonuclease leads to the fragmentation of nuclear DNA. Membrane phosphatidylserine ectropion, mitochondrial membrane potential decreased, permeability increased[37]. Cell necrosis induced locally severe inflammatory responses associated with a variety of signaling pathways, such as receptor interacting protein kinase 3. When iron died, Fe^{2+} aggregated, lipid peroxidation level increased significantly, ROS increased, cysteine uptake decreased, glutathione (GSH) was depleted, and arachidonic acid and other mediators were released. The essence of ferroptosis is the disturbance of Fe^{2+} accumulation and cell REDOX metabolism, that is, the decrease of cell antioxidant capacity, the accumulation of ROS and lipid peroxidation products in the cell, which can't be reduced, and then induce cell death[38-40]. There was no crossover with the mechanism of apoptosis and necrosis, and the small molecules that inhibited apoptosis and necrosis had no inhibitory effect on ferroptosis.

The mechanism of ferroptosis

More and more studies have proved that iron metabolism disorder and ROS accumulation are important initiating factors of ferroptosis under different pathophysiological conditions.

Iron metabolism disorder

The ROS accumulated during cell metabolism were mainly superoxide radical anion (O^{2-}) and hydrogen peroxide (H_2O_2). Under the action of free Fe^{2+}, it is converted into hydroxyl free radical (HO-), which further oxidizes macromolecules, especially lipid molecules such as polyunsaturated fatty acids (PUFAs), PUFAs, and generates lipid peroxides[41-43]. These reactions involving iron and generating hydroxyl or alkoxy radicals ($RO^{\cdot}$) are known as Fenton reactions. Once a large amount of lipid peroxidation products in cells are accumulated and can not be removed in time, it will cause oxidative damage to DNA, proteins and cell membranes, and eventually lead to cell ferroptosis[44]. It has also been shown that exogenous Fe^{2+} intake can aggravate ferroptosis induced by ferroptosis inducer erastin, while other bivalent metal ions do not aggravate the effect. Iron responsive element binding protein 2 (IREB2); [IREB2; Also known as iron regulatory protein 2 (IRP2)], mainly through the IRE-Responsive element-IRP system to regulate iron metabolism related genes after transcription[45]. It is an important protein that mediates erastin and causes ferroptosis in human fibrosarcoma cells HT-1080 and Calu-1[46-48]. In addition, another study found that phosphorylase kinase catalytic subunit γ2 (PHKG2) can positively regulate ferroptosis by regulating the content of free Fe^{2+}, while inhibiting PHKG2 expression can play a role in iron chelation[49]. However, the mechanism of PHKG2 regulating iron metabolism is still unclear and needs further study.

ROS accumulation

Under normal circumstances, lipoxygenase (LOXs) can catalyze the double oxygenation of membrane lipid PUFAs to produce fatty acid peroxides, which are then transformed into fatty acid alcohols under the guidance of glutathione peroxidase 4 (GPX4)[50]. However, when GPX4 is inactivated, the above process is blocked, and a large number of ROS in the cell can react with the membrane lipid PUFAs on Fenton, resulting in cell membrane damage and triggering ferroptosis. Therefore, the large accumulation of lipid ROS is one of the important factors driving ferroptosis. It has been found that inhibiting 5-LOX can inhibit the occurrence of ferroptosis and reduce the oxidative damage of the nervous system induced by glutamate[51-53]. Other studies have found that cells can take cystine from extracellular to produce cysteine through the cystine/glutamate antiporter system and then synthesize GSH. GPX4 can exert phospholipid peroxidase activity in the presence of GSH to catalyze the reduction of lipid peroxides[54]. Therefore, small molecule inhibition of system Xc- can lead to GSH depletion and indirectly inactivate GPX4, thereby increasing ROS levels and ultimately leading to accumulation of lipid peroxidation products and triggering ferroptosis. In addition, it has been

suggested that overexpression of GPX4 can significantly inhibit the occurrence of ferroptosis in cells. In addition, voltage-dependent anion channels (VDACs) located in the outer membrane of the mitochondria, which are transmembrane channels that transport ions and metabolites between the cytoplasm and mitochondria, also play an important regulatory role in ferroptosis[55]. It has been found that erastin can be used as an antagonist of VDACs tubulin to remove the inhibition of VDACs by tubulin, thereby promoting the release of a large amount of oxides, leading to ROS dependent mitochondrial dysfunction, biological energy failure and ferroptosis. VDAC2/3 knockdown decreased the incidence of Erastin-induced ferroptosis[56]. During erastin induced ferroptosis in melanoma cells, upregulation and activation of E3-ligase Nedd4 can promote ubiquitination degradation of VDAC2/3, thereby inhibiting ferroptosis. It is found that Nedd4-VDAC2/3 is an important negative feedback signaling pathway in erastin induced ferroptosis (Figure 1).

Inducers and inhibitors of ferroptosis

Since iron metabolism and lipid peroxidation are central links in ferroptosis, molecules that affect iron metabolism and lipid peroxidation to cause ROS accumulation can be considered as inducers or inhibitors of ferroptosis[57]. Studies[58-60] have shown that inducers of ferroptosis include system Xc- inhibitors that indirectly inhibit GPX4, such as erastin, sulfasalazine, sorafenib and L-glutamate, And rats arcomaviral oncogene selective lethal protein 3 (RSL3), Molecular Libraries 162, altretamine and FIN56, which directly inhibit GPX4. A recent study indicated that ferroptosis suppressor protein 1 (FSP1) is a key component of the ubiquinone (CoQ10) antioxidant system, and therefore small molecule inhibitors of FSP1 can also induce ferroptosis by inhibiting lipid peroxidation[61]. Common ferroptosis inhibitors include ROS inhibition (Fer-1), deferriamine inhibition of Fenton reaction, β-mercaptoethanol activation of system Xc-, and cypirox, an intracellular iron chelating agent[62-64]. In addition, other studies have found that acyl-CoA synthetase long chain family members 4 (ACSL4), lysophosphatidylcholine acyltransferase 3 and LOXs participate in fatty acid metabolism and catalyze PUFAs to double oxygenation during ferroptosis. It also plays an important role in ferroptosis induced by GPX4 inactivation.

MECHANISM OF FERROPTOSIS IN PRIMARY LIVER CANCER

Studies have shown that erastin, an ferroptosis inducer, can significantly inhibit the expression of GA-binding protein transcription factor subunit 1 (GABPB1) protein in hepatocellular carcinoma (HCC) cells, thus inhibiting the expression of peroxidase gene, resulting in continuous accumulation of intracellular ROS and malondialdehyde (MDA), leading to cell death[65]. Therefore, GABPB1 may be a key molecule mediating Erastin-induced ferroptosis in HCC cells. In addition, the expression of long-chain acyl-CoA synthetase 3 (ACSL3) and ACSL4 was found to be significantly upregulated in liver cancer cells, and ACSL4 may play A role in Erastin-induced ferroptosis through 5-hydroxyeicosatetraenoic acid mediated lipid toxicity. Sorafenib is currently the only anti-cancer drug that can treat liver cancer by inducing ferroptosis, but its resistance will greatly affect its therapeutic effect. Other studies have shown that inhibition of metallothionein 1G (MT1G) and oxidative stress-related protein sigma 1 receptor (S1R) can improve the resistance of HCC cells to sorafenib by inducing ferroptosis. It has also been reported that sorafenib can enhance the sensitivity of HCC cells to ferroptosis by down-regulating the expression of retinoblastoma (Rb) protein, thus enhancing its anticancer effect. A recent study demonstrated that ceruloplasmin (CP) inhibits ferroptosis by regulating iron homeostasis in HCC cells, and inhibition of CP significantly increases intracellular accumulation of Fe^{2+} and ROS, thereby promoting erastin and RSL^{3-} induced ferroptosis in HCC cells[66]. Therefore, the combination of drugs in patients with liver cancer may solve part of the problem of drug resistance, thereby improving its clinical effectiveness. At the same time, nanoparticle drugs also provide a new direction for in-situ induction of ferroptosis in liver cancer cells. Literature reports have shown that manganese-silica nanoparticles can induce ferroptosis in tumor cells by rapidly depleting intracellular GSH. Nanoparticles reconstituted from low-density lipoprotein-docosahexaenoic acid (L-DHA) can increase lipid peroxidation level, decrease GSH level and inhibit GPX4 function in liver cancer cells, thus inducing ferroptosis to kill liver cancer cells and inhibit the growth of in-situ liver tumors in rats[67-69]. Therefore, inducing ferroptosis of liver cancer cells may be a new direction for specific treatment of liver cancer in the future.

Ferroptosis in hepatocellular cancer cells is divided into two categories, one related to iron metabolism and the other related to lipid metabolism. Pioglitazone can reduce Erastin induced lipid peroxidation and ferroptosis in liver cancer cells by stabilizing iron-sulfur domains and inhibiting iron absorption by mitochondria. Desferriamine can affect the iron metabolism of HCC cells, inhibit the oxidative stress induced by sorafenib, and counteract the cytotoxic effect of sorafenib on HCC cells. In addition, in the process of sorafenib induced cell death, haloperidol can significantly increase the content of Fe^{2+} and GSH in the cells, as well as the level of ROS, and enhance the toxic effect of sorafenib on liver cancer cells. In addition to iron metabolism, lipid metabolism also plays an important role in ferroptosis in HCC[70]. In rat HCC models and mouse HCC cell lines, low-density lipoprotein docosahexaenoic acid induced ferroptosis of HCC cells by directly degrading GPX4, consuming GSH and promoting lipid peroxidation. As a negative regulator, MT1 down-regulation can increase GSH consumption and lipid peroxide production, accelerate sorafenib induced cancer cell death, and enhance the anticancer activity of sorafenib in subcutaneous transplanted tumor models[71]. Similar negative regulators of ferroptosis include Rb protein, nuclear factor erythrocyte 2-associated factor 2, p53, and inhibiting their expression can increase the efficacy of sorafenib and reduce the drug resistance of HCC cells. These molecules may be potential therapeutic targets for overcoming sorafenib resistance in human hepatocellular cancer cells.

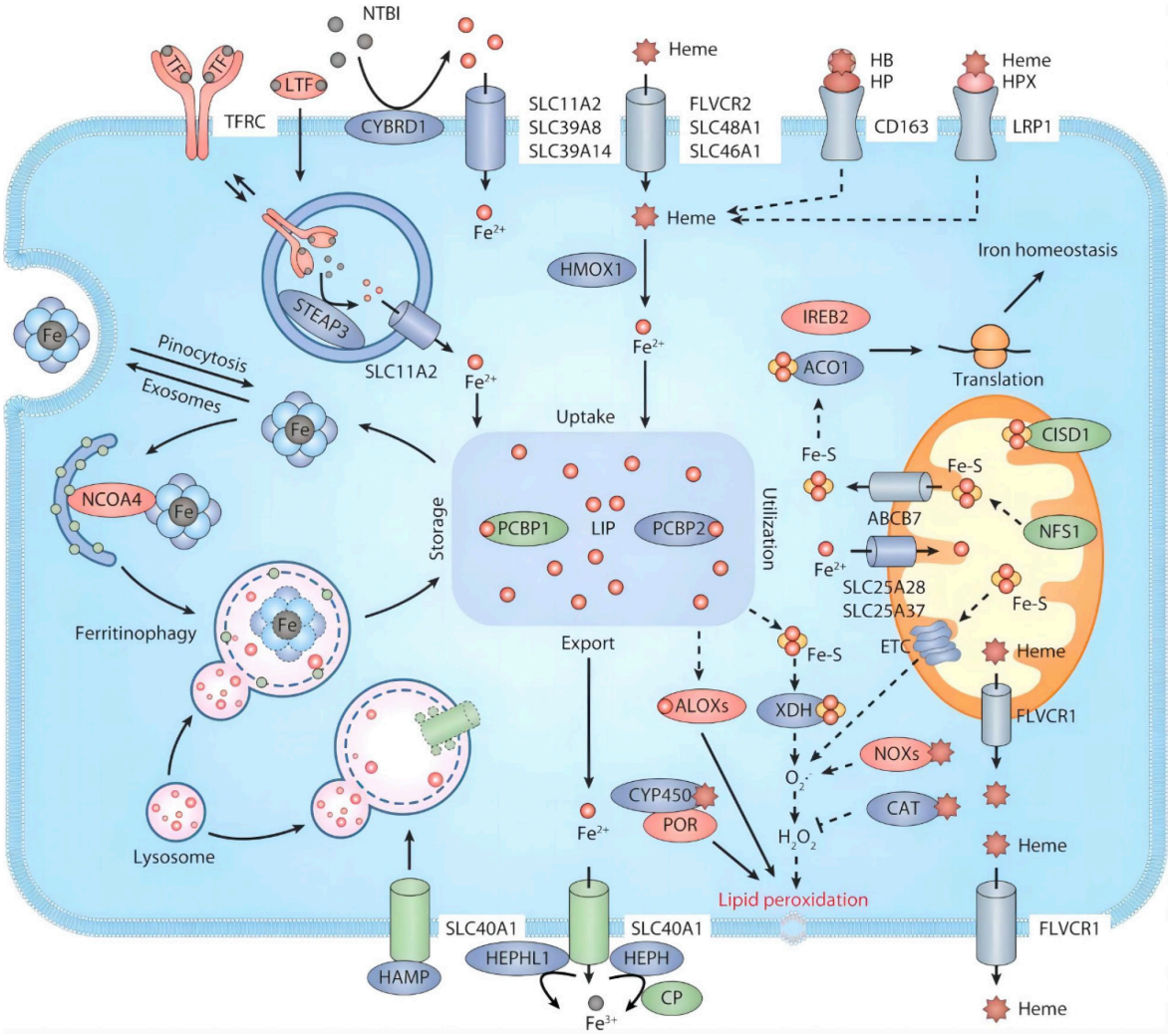

Figure 1 Iron metabolism and ferroptosis. Created with BioRender.com. TF: Tissue Factor; LTF: Lactoferrin; TFRC: Transferrin receptor; HB: Hemoglobin; HP: Haptoglobin; HPX: Hemopexin; LRP: Lipoprotein receptor protein; HAMP: Human hepcidin; CP: Ceruloplasmin; CAT: Catalase; ETC: Extracellular tissue; PCBP: Poly(rC)-Binding Protein; POR: P450 Oxidoreductase; NOXs: NADPH Oxidases; XDH: Xanthine dehydrogenase; ALOXs: Arachidonate lipoxygenases; LIP: Lymphocyte inhibitor peptide.

REGULATORY FACTORS INVOLVED IN FERROPTOSIS OF LIVER CANCER

Several regulators of ferroptosis have recently been identified in cancer cells. For example, GPX4, a unique member of selenium-dependent GSH peroxidase in mammals, plays a key role in inhibiting the production of lipid ROS during ferroptosis. Heat shock protein beta-1, a member of the chaperone molecule, regulates the dynamics of actin filaments and reduces iron absorption, thus promoting ferroptosis[72]. p53 was found to be a positive regulator of ferroptosis by inhibiting the expression of SLC7A11. It is known that the occurrence and development of liver cancer is regulated by a variety of cellular components and intracellular signaling pathways, but the detailed signal transduction pathways and key transcriptional regulatory factors related to ferroptosis in liver cancer are still under investigation[73]. Ferroptosis has shown great promise in the treatment of cancer, especially liver cancer.

Activation of the P62-Keap1-Nucleotide erythroid 2 phase related nucleotide 2 pathway inhibits ferroptosis in HCC cells

Nucleotide erythroid 2 phase related nucleotide 2 (NRF2) is a key regulator of antioxidant reaction. Under unstressed conditions, low levels of NRF2 are maintained primarily by proteasomal degradation mediated by Kelch-like ECH associated egg White 1 (Keap1)[74]. Affected by the type and stage of cancer, NRF2 plays a dual role in the prevention or treatment of cancer. For example, NRF2 prevents the development of carcinogenic processes mediated by chemical carcinogens or oncogenes; however, if the cancer has been transformed, NRF2 will accelerate the progression of cancer. Overexpression of NRF2 inhibits apoptosis and promotes chemical resistance in several cancers. The p62-Keap1-NRF2 pathway has been shown to play a central role in protecting liver cancer cells from ferroptosis by upregulating several fundamental factors involved in iron and ROS metabolism [quinoneoxydegenase 1 (NQO1), heme oxygenase 1 (HO1), and ferritin heavy chain 1 (FTH1)]. When exposed to compounds that induce ferroptosis, such as erastin, Sorafenib, and butylthiionine sulfoxide, p62 expression prevents NRF2 degradation and enhances subsequent NRF2 nuclear accumu-

lation. In addition, nuclear NRF2 interacts with the transcriptional coactivator small v-maf to activate the transcription of NQO1, HO1 and FTH1[75-77]. Because knockdowns of NQO1, HO1, and FTH1 inhibit the growth of liver cancer cells after ferroptosis, these NRF2 target groups are negative regulators of ferroptosis. Because Knockdowns of p62, NQO1, HO1 and FTH1 in HCC cells promoted erastin and sorafenib induced ferroptosis. Meanwhile, gene or drug inhibition of NRF2 expression/activity in HCC cells enhanced the anticancer activity of erastin and Sorafenib *in vitro* and xenograft tumor models. All these confirm that NRF2 status is one of the key factors in determining the response of liver cancer cells to ferroptosis targeted therapy[78]. The functional characteristics of P62-Keap1-NRF2 pathway in ferroptosis may provide a new idea for the treatment of liver cancer (Figure 2).

Protective effect of S1R on ferroptosis in HCC cells

S1R is a non-opioid receptor protein. In addition to the central nervous system, S1R is also found in liver, pancreas, and cancer cells. Recent studies have reported that S1R may inhibit ROS production in many organs by activating antioxidant response elements and reducing oxidized GSH and glutamate. Previous studies have shown that S1R regulates ROS by regulating the NRF2-Keap1 pathway and the cysteine/glutamate reverse exchange Xc-system, both of which are critical for ferroptosis. Studies[79-81] have confirmed that inhibiting S1R can regulate GPX4, iron metabolism and ROS accumulation, and can significantly block the increase of FTH1 and TFR1 induced by erastin and Sorafenib, suggesting that S1R negatively regulates iron metabolism to prevent ROS accumulation. Inhibition of S1R was found to enhance the anticancer effect of sorafenib on HCC cells *in vitro* and *in vivo*. In addition to causing the accumulation of ROS, iron overload in the liver is also a carcinogenic factor that regulates the immune system[82]. Therefore, iron may also play a dual role in liver cancer development and cancer cell death.

MicroRNA-214-3p targets ATF4 in liver cancer cells to enhance erastin induced ferroptosis

Micrornas are 18 to 24 nucleotides long and endogenous non-coding RNA molecules that regulate gene expression by destabilizing messenger RNA (mRNA) and/or inhibiting translation[83]. MiR-214 targets multiple genes, including Cateninβ1, hepatocarcino-derived growth factor, and Twist, to play an antitumor role in human liver cancer. ATF4 is an important factor in endoplasmic reticulum stress and has been shown to be a negative regulator of ferroptosis. Therefore, the deletion of ATF4 may make cancer cells vulnerable to ferroptosis. miR-214-3p is the upstream regulator of ATF4[84]. The effect of miR-214 on ferroptosis was investigated in two liver cancer cell lines. *In vitro*, they treated HepG2 and Hep3B cells with erastin (Ferroptosis inducer) to stably overexpress miR-214, and found that miR-214 enhanced Erastin-induced lipid oxidation of hepatoma cells, promoted the occurrence of ferroptosis and inhibited the expression of ATF4. *In vivo*, they administered erastin to nude mice with Hep3B xenografted tumors and found that miR-214 reduced tumor growth and reduced ATF4 expression in Erastin-treated nude mice[85]. They confirmed that the role of miR-214 in promoting ferroptosis in liver cancer cells is at least attributable to its inhibitory effect on ATF4.

Long-chain non-coding RNAs-GABPB1-AS1 and GABPB1 regulate oxidative stress during erastin induced ferroptosis in HepG2 cells

Few studies have investigated the use of long-chain non-coding RNAs (lncRNAs) in cell oxygenation response segments, especially in siderosis. The dependence of iron on ferroptosis suggests that peroxidase inactivation may be an important event in ferroptosis. Peroxidase prevents hydrogen peroxide from producing hydroxyl radicals in the presence of iron ions, thereby preventing ROS accumulation[86]. NRF2 is known to have three subunits (α, β and γ), and GABPB1 is the active subunit of NRF2. GABPB1 forms a tetramer complex with the alpha subunit and stimulates transcription of various genes, including the antioxidant gene peroxisase-5 (PRDX5). LncRNA GABPB1-AS1 is the antisense RNA of GABPB1 mRNA. Research[24] proved that erastin regulates lncRNAGABPB1-AS1, and the latter down-regulates GABPB1 protein level by blocking GABPB1 translation, leading to downregulation of PRDX5 gene, and ultimately inhibits the antioxidant capacity of cells. ROS and MDA accumulation and HepG2 cell death were induced[87]. The study also found that high expression levels of GABPB1 were associated with poor prognosis in HCC patients, while high levels of GABPB1-AS1 in liver cancer patients were associated with improved overall survival. These findings reveal that GABPB1-AS1 may be a key molecule in erastin induced ferroptosis of HCC cells, and enrich the understanding of lncRNA regulation of oxidative stress.

FERROPTOSIS IS INVOLVED IN THE TREATMENT OF LIVER CANCER

In patients with advanced liver cancer, neither surgical nor non-surgical treatment has achieved satisfactory results. Of several targeted agents, only sorafenib and regorafenib have been shown to successfully extend survival in HCC patients [88]. Sorafenib, a multikinase inhibitor, is the first systemic therapy to improve HCC survival, and oral sorafenib has become the standard treatment approved by the United States Food and Drug Administration for patients with unresectable HCC. It can inhibit the proliferation and angiogenesis of tumor cells and promote the apoptosis of various tumor cells[89]. More recently, it has been suggested that Sorafenib may block the Xc transport system, thereby inhibiting the synthesis of GSH, by a mechanism similar to erastin. Subsequently, other research teams have also shown that sorafenib can induce ferroptosis in cancer cells (Figure 3).

Ferroptosis of HCC cells was induced by endogenous pathway

Sorafenib induces ferroptosis in HCC cells: The mechanism of sorafenib's toxic action on HCC cells has been prelim-

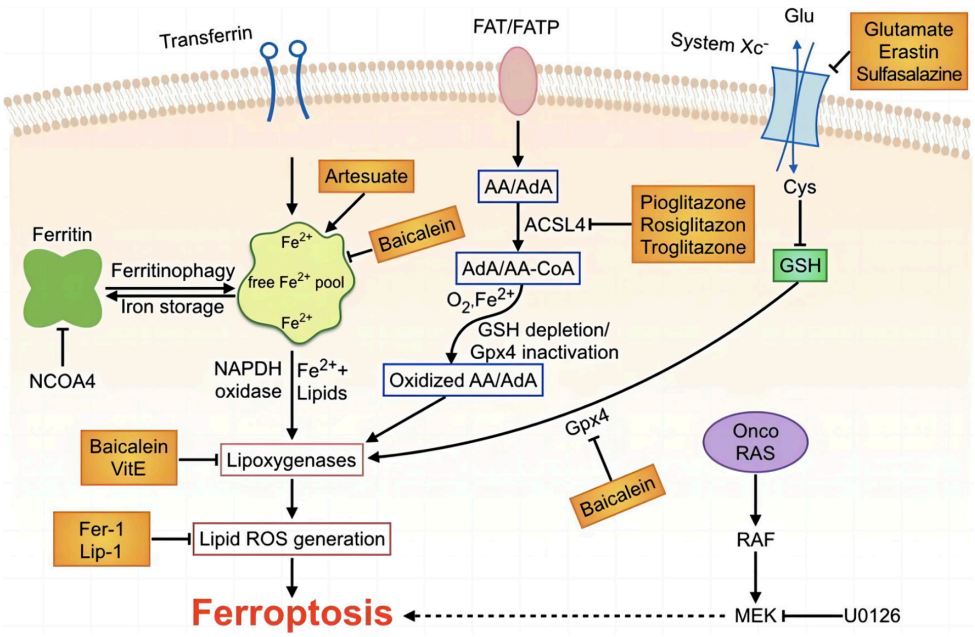

Figure 2 Anti-liver cancer therapy by targeting ferroptosis. Created with BioRender.com. FAT: Fatty acid translocase; FATP: Fatty acid transport protein; AA: Amino acid; RAS: Rats arcomaviral oncogene; NAPDH: Nicotinamide adenine dinucleotide phosphate hydrogen; ROS: Reactive oxygen species; RAF: Rapidly accelerated fibrosarcoma; GSH: Glutathione.

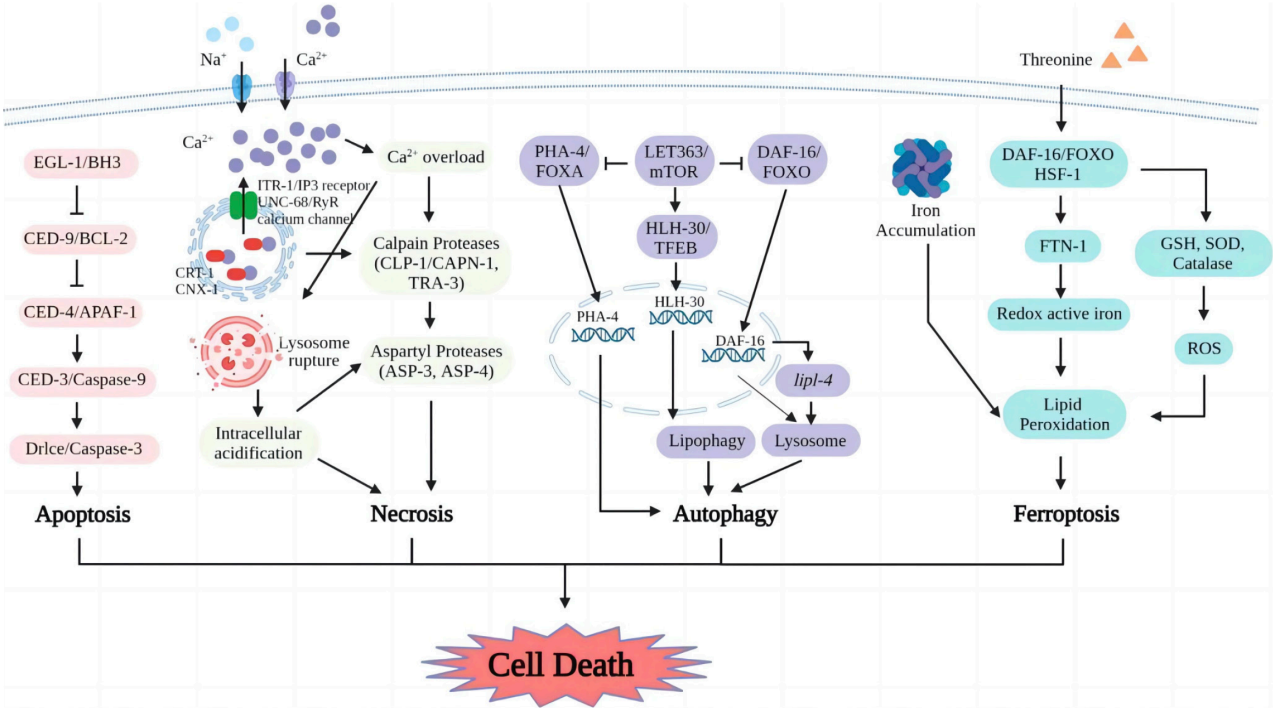

Figure 3 The mechanisms of cell death including apoptosis, necrosis, autophagy and ferroptosisin in hepatocellular carcinoma. Created with BioRender.com. GED: Gas electron detector; BCL: B-Cell lymphoma; APAF: Apoptotic protease-activating factor; CNX: Calnexin; CLP: Caudal-like protein; CAPN: Calpain; TRA: Tumor-related antigen; ASP: Asparaginase; HLH: Hemophagocytic lymphohistiocytosis; TFEB: Transcription factor EB; GSH: Glutathione; SOD: Superoxide dismutase; FTN: Ferritin; HSF: Heat shock factor; ROS: Reactive oxygen species.

inarily understood. It was initially reported that sorafenib could induce apoptosis of HCC cells. However, it was later found that sorafenib alone applied to HCC cells did not induce major mitochondrial events associated with apoptosis, such as cytoplasmic release of cytochrome C or activation of caspase. In addition, solafenib only binds to the chemical compound ABT-737 to become an effective decay inducer. The toxic effect of solafenib on HCC cells could be blocked by the potent chemical chelating agent of iron, desferramine (DFX). Therefore, sorafenib as a single agent should be used on HCC cellulae to induce cellulae death that is different from dying[90]. At the same time, the protection conferred by DFX depends on its ability to depleze iron deposits in HCC cells. The results suggest that solafenib can induce some form of

cell death in HCC cells, which is closely related to ferroptosis. In summary, inducing ferroptosis may be a feasible strategy to enhance the efficacy of solafenib in liver cancer.

Rb protein regulates ferroptosis caused by sorafenib in HCC cells: Rb protein regulates transcription of several genes in eukaryotes, and Rb protein is known for its regulatory role in cell proliferation and key role in G1/S checkpoint, mainly its ability to regulate the activity of E2F family transcription factors[91]. The loss of Rb protein function is known to be an important event in the pathogenesis of HCC, and whether Rb protein status is a regulatory factor for the response of HCC cells to sorafenib is still under study. Importantly, the study showed that the status of the Rb protein is a parameter that regulates the susceptibility of cancer cells to ferroptosis. HCC cells with low Rb expression were exposed to sorafenib, and the number of cell death increased by 2-3 times. Xenograft tumors grown in sorafenib treated BALB/c nude mice inoculated with low RB-expressing HCC cells showed complete tumor regression in 50% of the treated animals, compared with stable tumors in mice inoculated with control cells[92]. This suggests that the negative Rb protein status of HCC promotes ferroptosis after exposure to sorafenib. This finding highlights the role of Rb protein in response to sorafenib and regulation of ferroptosis in HCC cells.

Phosphoric acid modulating signals are involved in sorafenib treatment of ferroptosis induced by HCC cells: How Sorafenib is involved in inducing ferroptosis of liver cancer cells has been the direction of exploration by scholars[93]. Raf-Mek-Erk signaling pathway is not an important target for sorafenib to induce ferroptosis in HCC cells. Sorafenib has a unique mode of action to induce ferroptosis. Since sorafenib has been proposed to have extranuclear activity to suppress the XC-system compared to other similar excitase suppressors, a better understanding of the phosphorylation changes that sorafenib regulates the activity of the XC-system will help explain how kinase inhibitors such as sorafenib induce ferroptosis[94]. The early effects of sorafenib treatment on SKHep1 cells: Extensive regulatory effects on protein phosphorylation were observed within 30 min of drug treatment, and the effects were more intense after 60 min of treatment. The study included quantitative coverage of 6170 unique phosphate sites, using label free quantification phosphate proteomics to detect phosphorylation over time. This includes phosphoric acid sites at potential binding sites for Xc- and also phosphoric acid sites on proteins known to be associated with ferroptosis[95]. According to their findings, many sites on iron homeostasis and other proteins involved in ferroptosis were significantly regulated after sorafenib treatment. All these suggest that phosphorylation regulation signals may be involved in the induction of ferroptosis.

Ferroptosis of HCC cells is induced by exogenous pathway

Double GSH-depleted sorafenib loaded with manganese-silicon nanomaterials induced ferroptosis in HCC cells: GSH has antioxidant and detoxification capabilities, and its levels are closely related to tumor progression and chemotherapy resistance, while GSH levels are elevated in HCC cells[96]. Therefore, the researchers believe that the GSH depletion strategy will be one of the logical approaches to the treatment of HCC. A novel one-pot reaction for the synthesis of manganous-doped mesoporous silica nanoparticles (MMSNs), which can induce ferroptosis in tumor cells through intracellular GSH depletion caused by MMSNs degradation. MMSN's manganese oxidation bond breaks at high GSH concentrations, rapidly depleting GSH in the environment. The cleavage of 1 molecule -Mn-O- will consume 2 molecules of GSH. Thus, the efficiency of GSH consumption caused by degradation of MMSN is sufficient to deplete intracellular GSH[97]. At the same time, the degradation of MMSNs will lead to the release of supported sorafenib, thus blocking the Xc- transport system. After incubation with MMSns@SO (MMSNS-supported sorafenib), the GSH content in HCC cells is rapidly reduced and the synthesis of GSH is inhibited. Importantly, MMSNs@SO was much less toxic to normal hepatocytes than to HCC cells. They aim to exert excellent ferroptosis promoting effect by constructing MMSNs@SO to bidirectional depletion of intracellular GSH. The results show that this double-consuming GSH nanomaterials have great potential to induce ferroptosis in HCC cells and will contribute to the development of highly effective ferroptosis inducers for HCC. However, the cell can be adapted to the invariant microenvironment[98]. When GSH is consumed, the synthesis of GSH will be accelerated and continuous ferroptosis will be inhibited. Therefore, how to inhibit the synthesis of GSH in liver cancer cells is another key point to induce ferroptosis in tumor therapy.

Low density lipoprotein docosahexaenoic acid nanoparticles induction: An epidemiological study reported that a diet rich in polyunsaturated omega-3 fatty acids (omega-3PUFA) reduced the risk of HCC in patients with hepatitis. To this end, the researchers designed a LDL-DHA reconstructed with natural omega-3PUFA docosahexaenoic acid. LDL-DHA induces liver cancer cell death through ferroptosis pathway, which is a novel molecular mechanism of its anticancer activity. LDL-DHA nanoparticles were cytotoxic to both rat hepatoma and human HCC cell lines. After treatment with LDL-DHA, both rat and human HCC cells experienced significant lipid peroxidation, GSH depletion, and lipid antioxidant GPX4 inactivation prior to cell death. The death of HCC cells after treatment is not related to apoptosis, necrosis or autophagy pathway, which is consistent with the iron-dependent cell death mechanism. GPX4 is also the central regulator of LDL-DHA induced tumor cell death. They further investigated the effects of LDL-DHA on mice carrying transplanted human liver cancer tumors[99]. Long-term intratumoral injection of LDL-DHA can seriously inhibit the growth of HCC xenografts. Consistent with findings from *in vitro* studies, LDL-DHA treated HCC tumors experienced iron-dependent cell death characterized by elevated tissue lipid hydroperoxide levels and inhibition of GPX4 expression. LDL-DHA induced ferroptosis can achieve a potent antitumor effect because long-term tumor growth inhibition is well maintained after treatment is discontinued. These findings provide new insights into the molecular mechanisms by which LDL-DHA controls tumor cytotoxicity (Figure 4).

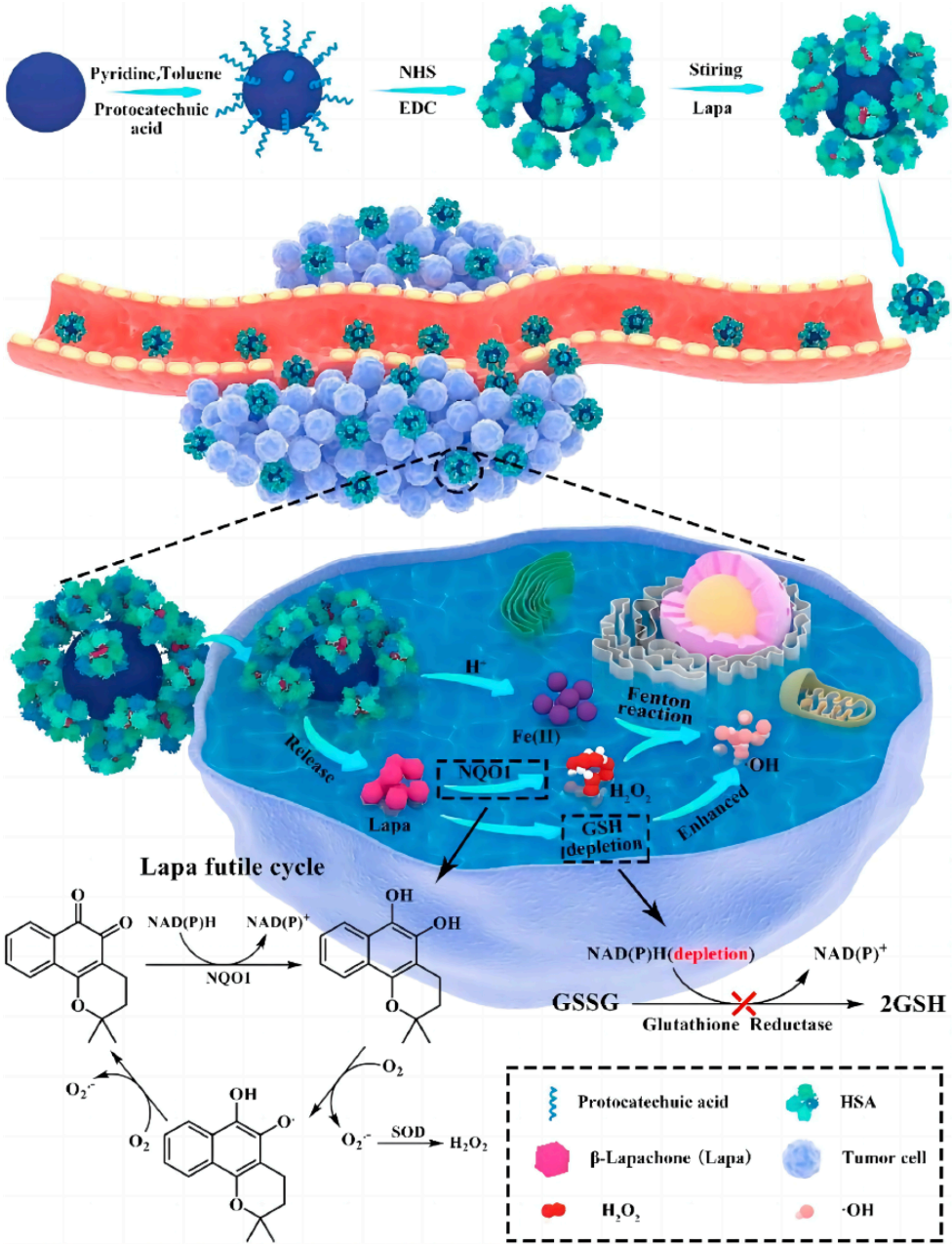

Figure 4 Preparation process of iron-dead biomaterials. Created with BioRender.com. NHS: N-Hydroxysuccinimide; EDC: Ethyl-dimethylaminopropyl carbodiimide; SOD: Superoxide dismutase; GSSG: Glutathione disulfide; GSH: Glutathione; HSA: Human serum albumin.

THE SIGNIFICANCE OF LIPID PEROXIDATION AND ABNORMAL METABOLISM IN HCC

The basic process of lipid peroxidation

Lipid peroxidation is a complex biochemical process that usually occurs in the unsaturated fatty acids of cell membranes. At the core of this process is the free radical mediated oxidation reaction, which results in the destruction of cell structure and function, which in turn affects cell survival and death[100].

In the initial stage of lipid peroxidation, free radicals (such as hydroxyl radicals) attack unsaturated fatty acids, triggering the removal of hydrogen atoms and the formation of fatty acid radicals. This radical further interacts with oxygen to form the lipoxylate radical. These lipid-greedy radicals can react with neighboring lipid-greedy molecules, triggering a chain reaction that leads to the oxidation of large amounts of lipid-greedy. With the progress of the reaction, a variety of oxidation products are formed, such as hydrogen peroxide, aldehydes and ketones[101-103]. These products not only damage the integrity of the cell membrane, but also can further affect the signaling pathway within the cell, leading to cell dysfunction. In particular, certain oxidation products such as 4-hydroxynonenal and MDA are highly reactive and can cross-link with proteins, nucleic acids, and other molecules within cells, leading to cell damage and death. In liver cancer, the increase of lipid peroxidation is considered to be one of the key factors promoting tumorigenesis and development. Excessive lipid peroxidation not only directly destroys the membrane structure of hepatocytes, but also interferes with intracellular signaling and metabolic processes through the oxidation products produced[104]. In

addition, lipid peroxidation is closely related to drug resistance, proliferation and metastasis of HCC cells. Therefore, a deeper understanding of the role of lipid peroxidation in liver cancer is of great significance for the development of new therapeutic strategies.

The role of lipid metabolism in liver cancer

Lipid metabolism plays an important role in the occurrence and development of liver cancer. Normally, lipid metabolism maintains the integrity of cell membranes, energy reserves, and the synthesis of signaling molecules[105]. However, when lipid metabolism is abnormal, it may promote the occurrence and progression of liver cancer.

Abnormal lipid metabolism in liver cancer cells usually manifests as increased lipid synthesis and accumulation[106]. These changes are mainly due to the higher demand for energy and structural components of tumor cells to meet their rapid proliferation and growth needs. Increased lipid synthesis not only provides tumor cells with essential membrane components, but also energy and bioactive molecules such as lipobutyric acid and cholesterol. In addition, abnormal lipid metabolism is closely related to signal transduction disorders in HCC cells. Intermediate products produced by lipid metabolism, such as lipobutyrate and cholesterol, can activate or inhibit certain signaling pathways, affecting cell growth, proliferation and apoptosis[107-109]. For example, certain lipobutyric acids can act as second messengers, involved in regulating calcium ion levels within cells and activating specific protein kinases. The abnormality of lipid metabolism is also related to the regulation of tumor microenvironment. By changing lipid metabolism, liver cancer cells can affect the surrounding microenvironment, such as regulating the function of immune cells by secreting certain lipids molecules, thereby promoting tumor growth and metastasis (Figure 5).

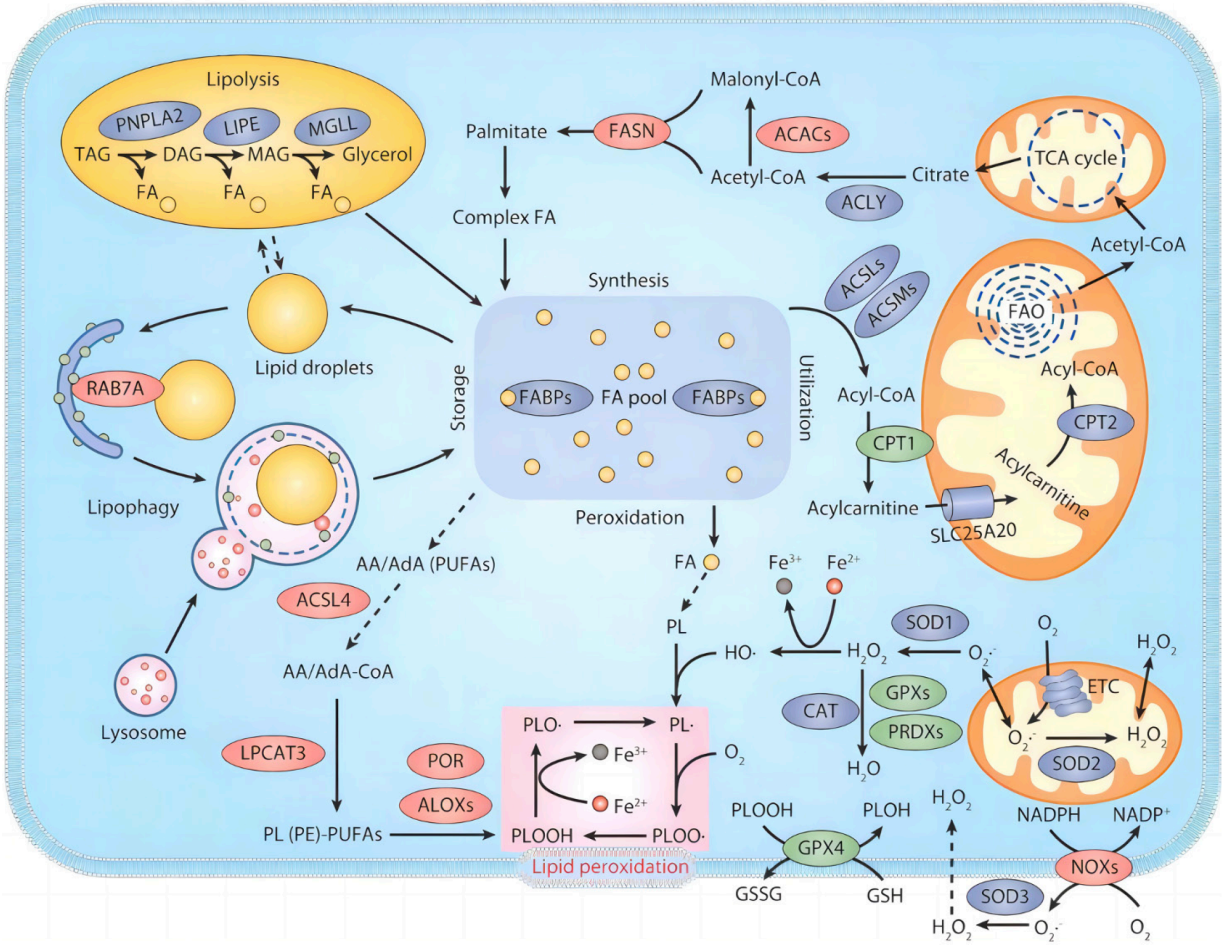

Figure 5 Both lipid catabolism and anabolic changes affect lipid peroxidation during ferroptosis. Created with BioRender.com. FASN: Fatty acid synthase; FABP: Fatty acid-binding protein; PUFA: Polyunsaturated fatty acids; LIPE: Lipase E; MGLL: Monoglyceride lipase; ACAC: Acetyl-CoA carboxylase.

In summary, abnormal lipid metabolism in liver cancer not only affects the biological behavior of tumor cells, but also further promotes the development of liver cancer by affecting the tumor microenvironment[110]. Therefore, a thorough understanding of the role and mechanism of lipid metabolism in liver cancer is of great significance for the discovery of new therapeutic targets and strategies.

CONCLUSION

Iron-dependent lipid peroxidation is a marker of ferroptosis, but the molecules that play a key regulatory role in the process of ferroptosis and the general signaling pathway have not been clarified. Iron acts as a catalyst to convert peroxides to free radicals to induce ferroptosis, but the mechanism of action is unclear, and it is uncertain whether other metabolic processes or other forms of regulatory cell death are involved in the regulation of ferroptosis. At the same time, as one of the important cell death modes to regulate body homeostasis, ferroptosis is also involved in the occurrence and development of a variety of liver diseases. If ferroptosis occurs in normal liver cells, it will lead to the disorder of cell REDOX metabolism and lead to the corresponding pathophysiological changes. However, increasing the sensitivity of liver cancer cells to ferroptosis can improve the therapeutic effect by reducing the drug resistance of tumor cells. At present, the existing literature reports on the role of ferroptosis in liver cancer are mostly indirect studies, and it is difficult to find the direct target of action, and it is difficult to achieve therapeutic effect by only using antioxidants to inhibit lipid peroxidation. Therefore, understanding its specific mechanism of action and causality is essential to analyze the role of ferroptosis in liver-related diseases. In recent years, the research on ferroptosis as the direction of disease treatment has developed rapidly, which may provide a certain reference for the future clinical treatment direction and strategy.

FOOTNOTES

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