Breaking the cycle of fibrosis: Ferroptosis as a therapeutic target (Review)

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Abstract. Fibrosis, characterized by abnormal deposition of extracellular matrix, is a chronic disease that progressively remodels tissues, leading to organ failure, earning it the moniker the 'silent killer' of organ function. Recently, ferroptosis, a novel form of regulated cell death, has garnered attention in research; its molecular mechanisms, including the lipid peroxidation cascade, dysregulation of glutathione metabolism and imbalance in iron ion homeostasis, have been closely linked to the progression of fibrosis. The present review systematically elaborates on the process of fibrosis, the main mechanisms of ferroptosis and the role of ferroptosis in fibrosis. The review also discusses intervention strategies targeting the key signaling nodes of ferroptosis during the inflammatory initiation and cell proliferation stages. In addition, it also elaborates on innovative therapeutic strategies based on regulating the ferroptosis pathway, including engineered exosome-mediated gene delivery systems and iron chelators encapsulated by multifunctional nanoparticles. Through a summary of current evidence, the present review provides a mechanistic rationale and new perspectives for the development of precision anti-fibrotic therapies targeting ferroptosis.

Contents

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Abbreviations: ACSL4, acyl-CoA synthetase long chain family member 4; ALOX12, arachidonate 12-lipoxygenase; CoQ10, coenzyme Q10; CoQH2, ubiquinol; DAMP, damage-associated molecular pattern; DMT1, divalent metal transporter 1; ECM, extracellular matrix; FSP1, ferroptosis suppressor protein 1; FPN, ferroportin; GPX4, glutathione peroxidase 4; GSH, glutathione; HIF-1α, hypoxia-inducible factor 1α; HSCs, hepatic stellate cells; LOOH, lipid hydroperoxide; NCOA4, nuclear receptor coactivator 4; Nrf2, nuclear factor erythroid 2-related factor 2; p53, tumor protein p53; PUFA, polyunsaturated fatty acids; SLC7A11, solute carrier family 7 member 11

Key words: ferroptosis, fibrosis, lipid peroxidation, GPX4, inflammation, proliferation

1. Introduction

Fibrosis is a core pathological process in the progression of a number of chronic diseases to end-stage organ failure, characterized by abnormal deposition of extracellular matrix (ECM), reduction of parenchymal cells and destruction of tissue structure. Fibrosis affects key organs such as the liver, lungs and kidneys, posing a serious threat to human health (1,2). Globally, ~25% of deaths are directly attributed to fibrotic disorders. China is facing a particularly heavy burden of hepatic fibrosis, with 20-40% of its 70 million chronic hepatitis B virus (HBV) carriers projected to develop liver fibrosis (3,4). Additionally, idiopathic pulmonary fibrosis in the Asia-Pacific region exhibits an incidence rate of 0.35-1.30 per 10,000 individuals, with a median survival period of merely 3-5 years post-diagnosis (5). At the molecular level, fibrosis fundamentally represents a pathological scarring process arising from dysregulated tissue repair; its core components include a persistent chronic inflammatory microenvironment, fibroblast activation and proliferation, and organ-specific remodeling (6-9). Based on this three-stage pathological evolution, the design of specific intervention strategies for key molecular events at each stage is expected to achieve precise inhibition of the fibrotic process and restoration of tissue function.

In recent years, with the discovery of novel cell death pathways such as ferroptosis, pyroptosis and autophagy, researchers' understanding of the pathogenesis of fibrosis has broken through the traditional binary cognitive framework of apoptosis and necrosis (10-12). Ferroptosis distinguishes the classical apoptotic pathway by its unique iron-dependent lipid peroxidation cascade. Under pathological conditions, intracellular iron overload triggers the Fenton reaction, resulting in a burst of reactive oxygen species (ROS). This oxidative stress not only triggers structural disintegration of the mitochondrial cristae and depolarization of the membrane potential, but also forms a positive feedback loop through the accumulation of lipid peroxidation products, ultimately leading to irreversible damage to the cell membrane (13,14). At the level of molecular mechanisms, ferroptosis is dominated by a core regulatory network involving glutathione peroxidase 4 (GPX4) inactivation, aberrant activation of lipoxygenases (LOXs) and iron dyshomeostasis (15,16).

Fibrosis progression initiates from an inflammatory microenvironment triggered by parenchymal cell death (6,17,18). Subsequently, macrophages and other immune cells secrete pro-fibrotic factors that activate resident effector cells (for example, fibroblasts and stellate cells). Following activation, these cells undergo proliferation and a phenotypic transition into α-smooth muscle actin (α-SMA)-positive myofibroblasts (18,19). Ultimately, excessive secretion of ECM leads to tissue stiffening and organ dysfunction (19). Through modulation of the ferroptosis pathway, the targeted protection of parenchymal cells or the elimination of activated effector cells has become a core strategy for anti-fibrotic therapy. Additionally, macrophage-targeted intervention represents a viable therapeutic alternative.

2. Mechanisms of fibrosis

Fibrosis is a pathological remodeling process that occurs following tissue injury. This process advances through three distinct phases: Inflammation, proliferation and remodeling (20). The molecular mechanisms involve multiple signaling pathways, including TGF-β/Smad, Wnt/β-catenin and yes-associated protein (YAP)/TAZ signaling axes. These pathways have a cascading amplification effect and self-reinforcing regulatory properties (21-24).

Inflammation. The pathological process of fibrosis is initiated by the death of parenchymal cells, which is triggered by mechanical, chemical or pathogenic injury. The subsequent release of damage-associated molecular patterns (DAMPs) activates the local innate immune response, which in turn leads to the activation of NOD-like receptor family pyrin domain containing 3 inflammatory vesicles via the Toll-like receptor 4 (TLR4)/NF-κB signaling axis (25-29). This process involves dual immune recruitment. On one hand, the monocyte-macrophage system polarizes into pro-inflammatory M1 phenotypes (secreting TNF-α, IL-1β and IL-6) and pro-fibrotic M2 phenotypes (secreting TGF-β) (7,30). On the other hand, neutrophils infiltrate the injured area through the CXCL8/CXCR2 chemotaxis pathway (28). Pro-inflammatory cytokines (for example, TNF-α and IL-1β) released by these immune cells, interact with ROS generated by NADPH oxidase to create an oxidative stress microenvironment, thereby sustaining a persistent inflammatory state (31) (Fig. 1).

Proliferation. The hallmark of the proliferative phase is the activation and differentiation of fibroblasts into α-SMA-positive myofibroblasts, stimulated by growth factors such as TGF-β and platelet-derived growth factor (18,32-34). These cells not only exhibit abnormal proliferation and migration characteristics but also overproduce ECM components, including type I and III collagen, and fibronectin (9,35). Concurrently, the upregulation of matrix metalloproteinase inhibitors suppresses matrix metalloproteinase (MMP) activity, resulting in an imbalance in ECM metabolism (9,35,36). At this stage, the TGF-β/Smad signaling pathway fulfills a central regulatory role (37,38). In addition, mechanical stress further sustains myofibroblast activation via the integrin-YAP/TAZ axis, ultimately leading to the formation of early fibrotic lesions characterized by disorganized tissue architecture (39,40) (Fig. 1).

Remodeling. The remodeling phase is characterized by tissue stiffening and destruction of organ structures due to excessive ECM deposition. Disruption of the tissue structure leads to upregulation of hypoxia-inducible factor-1α (HIF-1α), which in turn promotes an increase in pro-fibrotic factors such as connective tissue growth factor and vascular endothelial growth factor. In addition, the mechanical stress generated by the stiffening of the ECM continuously activates myofibroblasts through a positive feedback loop (41-43). Meanwhile, ECM degradation products act as DAMPs that reactivate the TLR/NF-κB signaling pathway, establishing a cycle of 'inflammation-fibrosis-reinflammation' (44,45). This stage is accompanied by abnormal angiogenesis and the replacement of functional parenchymal cells, ultimately leading to irreversible organ dysfunction (46) (Fig. 1).

3. Main mechanisms of ferroptosis

Within cells, ROS refer to a general category of highly reactive oxygen-containing molecules, mainly consisting of superoxide anion, hydroxyl radical, hydrogen peroxide, singlet oxygen and lipid hydroperoxide (LOOH). The accumulation of ROS is the primary driver of the ferroptosis process (47-50). ROS generation is mainly caused by the dysregulation of iron metabolism and lipid peroxidation cascades, with mitochondrial structural disruption as a secondary contributing factor (51-53).

Oxidation system: Source of ROS. Under chronic injury conditions, the upregulation of transferrin receptor 1 (TFR1) facilitates the endocytosis of extracellular ferric iron, which is subsequently reduced to ferrous iron (Fe^{2+}) by six-transmembrane epithelial antigen of the prostate 3 (54-56). Simultaneously, the autophagy pathway mediated by nuclear receptor coactivator 4 (NCOA4) accelerates the degradation of ferritin, thereby releasing free Fe^{2+} into the cytoplasm (57-59). Subsequently, Fe^{2+} undergoes the Fenton reaction with hydrogen peroxide to release highly reactive hydroxyl radicals. These radicals attack polyunsaturated fatty acids (PUFAs), thereby triggering lipid peroxidation (60,61) (Fig. 2A).

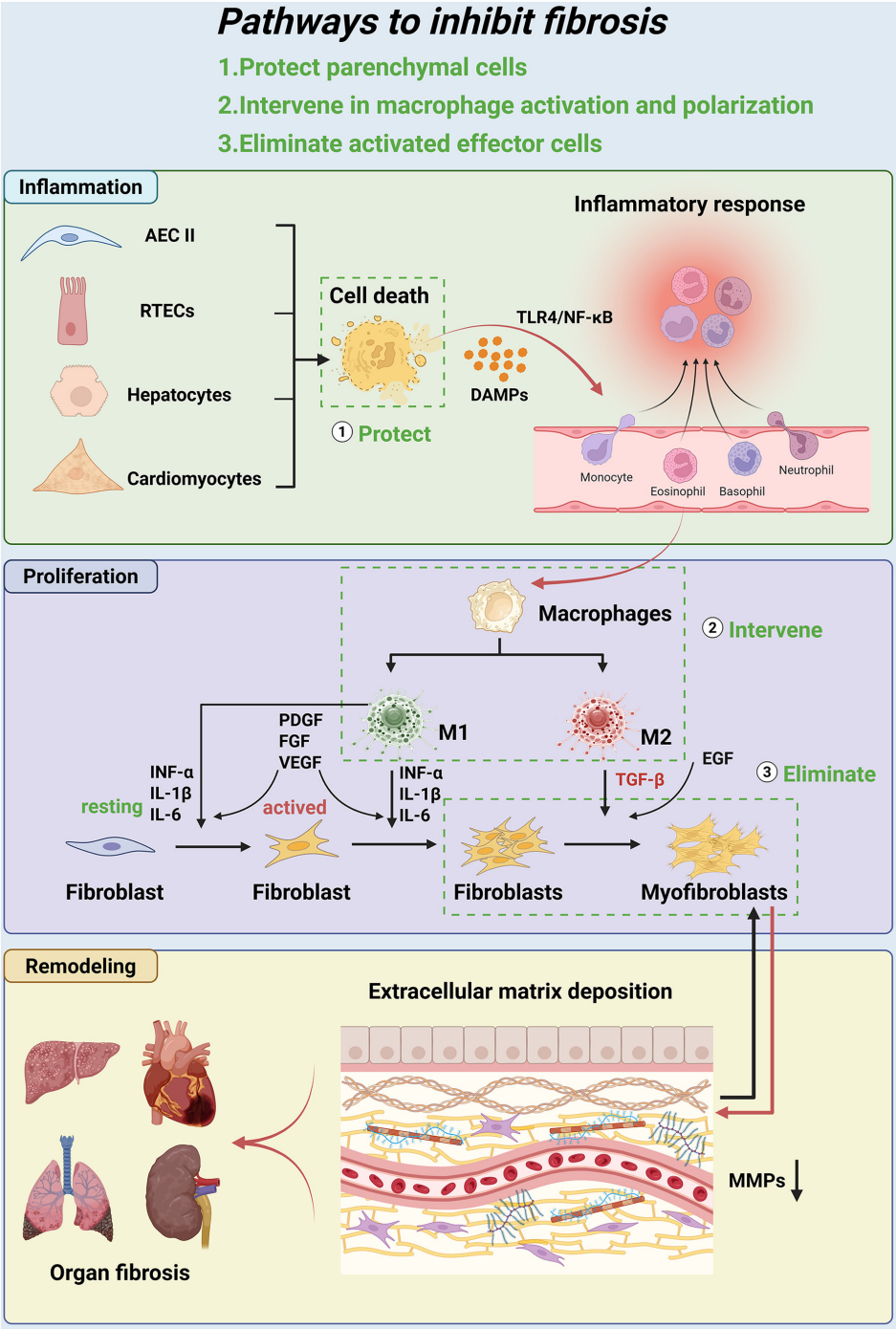

Figure 1. Three stages of fibrosis: Inflammation, proliferation and remodeling. At first, DAMPs released by cell death recruit immune cells through the TLR4/NF-κB pathway. Next, macrophages polarize into M1 and M2 types, which secrete proinflammatory factors to activate and proliferate quiescent fibroblasts, and TGF-β to convert activated fibroblasts into myofibroblasts. Myofibroblasts then synthesize and deposit ECM components in large numbers. The efficiency of ECM degradation decreases due to a marked decrease in the activity of MMPs. As a result, the consequent metabolic imbalance of ECM ultimately leads to irreversible remodeling of tissue structure. Based on this, fibrosis can be inhibited by protecting parenchymal cells, intervening in macrophage activation and polarization, and eliminating activated effector cells. DAMPs, damage-associated molecular patterns; TLR4, toll-like receptor 4; ECM, extracellular matrix; MMP, matrix metalloproteinase; AEC II, alveolar epithelial type II cell; IL, interleukin.

Acyl-CoA synthetase long chain family member 4 (ACSL4) catalyzes the enzymatic reaction that links PUFAs, such as arachidonic acid and linolenic acid, to CoA, producing acyl-CoA variants such as arachidonoyl-CoA and adrenoyl-CoA (62-65). These acyl-CoAs are subsequently esterified into phospholipids by lysophosphatidylcholine acyltransferase 3 (66,67). These phospholipids, enriched with PUFAs, are highly susceptible to peroxidation. A large number of hydroxyl radicals generated via the Fenton reaction attack PUFAs in phospholipids, generating lipid radicals. These radicals react with oxygen to form lipid peroxyl radicals, which further propagate the chain reaction by abstracting hydrogen from adjacent lipid molecules, generating LOOH (62,66,68). Accumulation of lipid peroxides leads to decreased cell membrane fluidity and increased permeability, ultimately triggering leakage of cell contents and cell death (Fig. 2B).

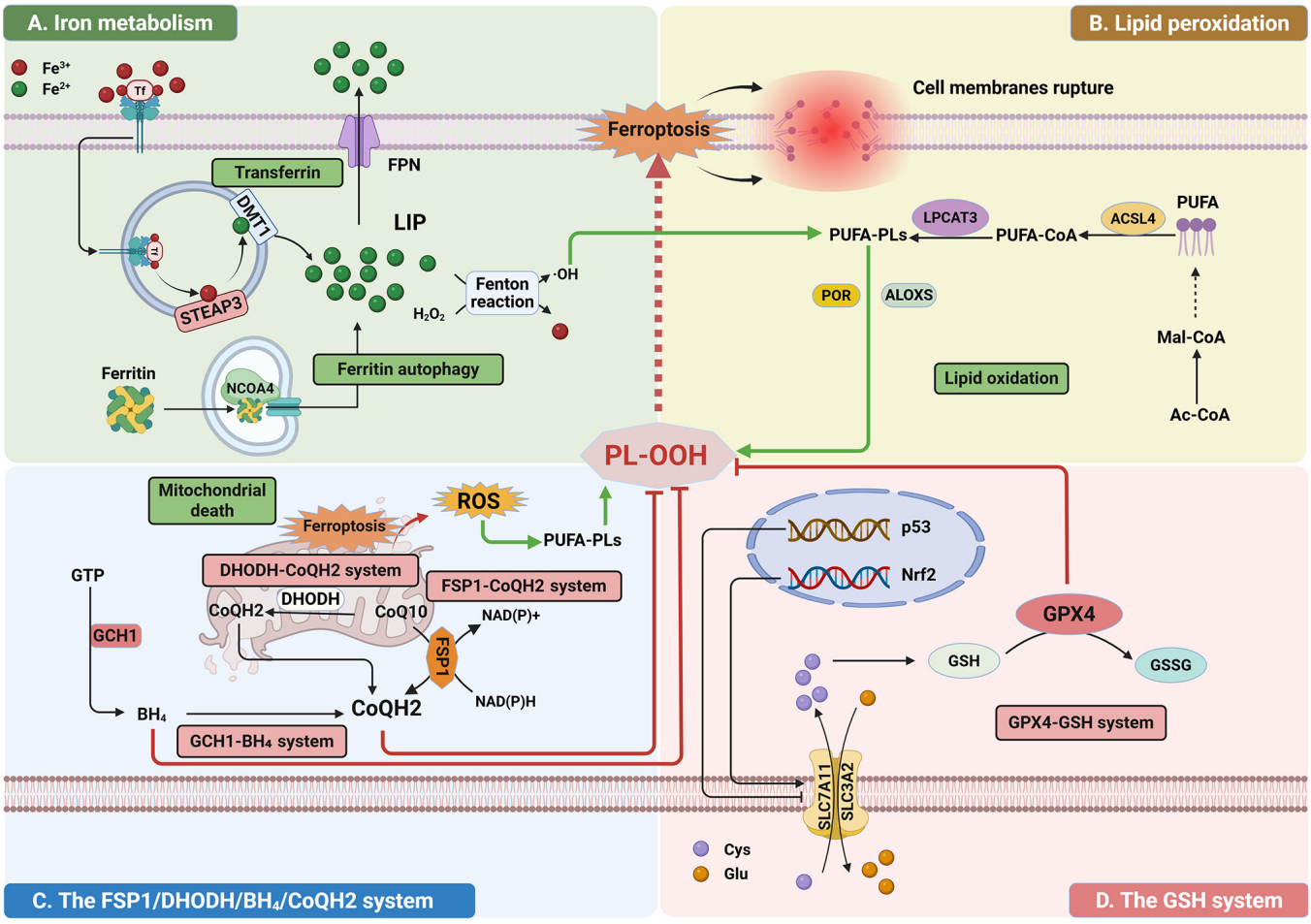

Figure 2. Main mechanisms of ferroptosis. (A) During chronic injury, TFR1 and ferritin autophagy lead to intracellular free Fe^{2+} accumulation, which catalyzes the generation of highly reactive -OH from H_2O_2 via the Fenton reaction. (B) Highly reactive OH radicals attack ACSL4/LPCAT3-mediated generation of PUFA phospholipids (such as PE-AA), triggering the lipid peroxidation chain reaction, and damaging the cell membrane and mitochondrial function. (C) At the same time, mitochondrial membrane damage leads to electron transport chain dysfunction and ROS burst, further amplifying oxidative stress. In the mitochondria, FSP1 scavenges free radicals by reducing CoQ10 to generate antioxidant-type CoQH2. DHODH catalyzes the synthesis of CoQH2 in the mitochondria to neutralize ROS and maintain energy metabolism. The GCH1-BH4 system inhibits ferroptosis by regulating phospholipid remodeling. (D) The core GPX4-GSH system relies on SLC7A11-mediated cystine uptake and GSH synthesis, which is utilized by GPX4 to reduce LOOH to non-toxic products, and its activity is positively regulated by Nrf2 and negatively regulated by p53. In the auxiliary system, FSP1 scavenges free radicals by reducing CoQ10 to generate antioxidant-type CoQH2. DHODH catalyzes the synthesis of CoQH2 in the mitochondria to neutralize ROS and maintain energy metabolism. The GCH1-BH4 system inhibits ferroptosis by regulating phospholipid remodeling. -OH, hydroxyl radicals; H_2O_2, hydrogen peroxide; TFR1, transferrin receptor 1; ACSL4, acyl-CoA synthetase long-chain family member 4; LPCAT3, lysophosphatidylcholine acyltransferase 3; PUFA, polyunsaturated fatty acid; PE, phosphatidylethanolamine; AA, arachidonic acid; ROS, reactive oxygen species; GPX4, glutathione peroxidase 4; GSH, glutathione; SLC7A11, solute carrier family 7 member 11; Nrf2, nuclear factor erythroid 2-related factor 2; p53, tumor protein p53; FSP1, ferroptosis suppressor protein 1; CoQ10, coenzyme Q10; CoQH2, ubiquinol; DHODH, dihydroorotate dehydrogenase; GCH1, GTP cyclohydrolase 1; BH4, tetrahydrobiopterin; LOOH, lipid hydroperoxide.

Furthermore, studies have shown that ferroptosis can also occur within the mitochondria (69-71). Mitochondria serve as a critical hub for intracellular iron metabolism, participating in the synthesis of heme, iron-sulfur clusters (Fe-S), and iron storage. Mitochondrial membranes are rich in PUFAs, making them highly susceptible to attack by hydroxyl radicals, which in turn triggers mitochondrial rupture and the release of ROS (72). Ruptured mitochondria release a substantial amount of iron ions, which subsequently catalyze the generation of hydroxyl radicals via the Fenton reaction (73). These newly generated hydroxyl radicals, together with ROS, further assault the mitochondrial membrane, thereby establishing a self-amplifying vicious cycle (65,74,75) (Fig. 2C).

Antioxidant system: Eliminate outbreak of ROS. Cells contain multiple antioxidant systems capable of eliminating ROS and lipid peroxides, thereby inhibiting the onset of ferroptosis. These systems are primarily divided into four pathways, with the GPX4-glutathione (GSH) system playing a leading role in eliminating cytotoxic LOOH. Furthermore, the ferroptosis suppressor protein 1 (FSP1)-ubiquinol (CoQH2) system, the dihydroorotate dehydrogenase (DHODH)-CoQH2 system and the GTP cyclase hydrolase 1 (GCH1)-biosynthesis of tetrahydrobiopterin (BH4) system have been shown to inhibit ferroptosis by eliminating ROS within the cell (14,15,54,76).

The GPX4-GSH system serves as the central antioxidant system, dynamically regulating lipid peroxidation via GPX4 and its associated metabolic network (77,78). GPX4 utilizes reduced GSH as an electron donor to reduce cytotoxic LOOH into non-toxic lipid alcohols, thereby halting lipid peroxidation chain reactions and preserving membrane integrity (79,80). The biosynthesis of GSH begins with the

uptake of cystine, which is mediated by the solute carrier family 7 member 11 (SLC7A11)-dependent cystine/glutamate antiporter. Intracellular cystine is reduced to cysteine, which is then combined with glutamate by glutamate-cysteine ligase to form γ-glutamylcysteine, and finally converted to GSH via glutathione synthetase (81-83). This metabolic pathway provides essential reducing equivalents for GPX4 activity. In terms of transcription factors, nuclear factor erythroid 2-related factor 2 (Nrf2) enhances antioxidant capacity by binding to antioxidant response elements to upregulate GPX4 and SLC7A11 expression (84-86). Conversely, tumor protein p53 (p53) promotes ferroptosis by suppressing SLC7A11 transcription and depleting GSH (87-89) (Fig. 2D).

The FSP1-CoQH2 pathway, as a GPX4-independent pathway, also plays a crucial role in the antioxidant process. FSP1, an NADH-dependent oxidoreductase, reduces coenzyme Q10 (CoQ10) to CoQH2, which directly neutralizes lipid peroxidation radicals and terminates chain reactions (90-92). FSP1 expression is positively regulated by Nrf2 and negatively regulated by p53 (93-95) (Fig. 2C).

The DHODH-CoQH2 system safeguards mitochondrial redox homeostasis by coupling pyrimidine biosynthesis with electron transport. DHODH is an enzyme localized to the inner mitochondrial membrane; it catalyzes the oxidation of dihydro-lactate to lactate, transferring electrons to CoQ10 in the process and generating CoQH2 (96,97). Under conditions of elevated ROS, this system enhances CoQH2 production to eliminate the burst of ROS and preserve mitochondrial function (98,99) (Fig. 2C).

The GCH1-BH4 axis is another intracellular ferroptosis defense pathway that operates independently of GPX4. GCH1 is the rate-limiting enzyme in the biosynthesis of BH4; it catalyzes the conversion of GTP to dihydropterin triphosphate, thereby initiating the *de novo* synthesis of BH4 (100,101). BH4 blocks lipid peroxidation chain reactions by directly scavenging lipid radicals, while also promoting the reduction of CoQ10 to CoQH2, thereby enhancing membrane antioxidant capacity and synergistically inhibiting the onset of ferroptosis (102-104) (Fig. 2C).

Since ROS burst is a central driver of ferroptosis, the following sections will systematically discuss strategies for regulating intracellular ferroptosis at three levels: Modulating iron metabolism pathways, modulating lipid peroxidation pathways and enhancing antioxidant systems.

4. Role of ferroptosis in fibrosis and strategies for intervening in fibrosis via ferroptosis

Role of ferroptosis in fibrosis. Ferroptosis, a distinct form of cell death, is present throughout the entire pathological process of organ fibrosis and primarily affects parenchymal cells, macrophages and effector cells (105,106). In the early stages of tissue injury, an imbalance in redox homeostasis and disrupted iron metabolism within parenchymal cells are the primary triggers of ferroptosis. As lipid peroxidation occurs, the cell membranes of damaged cells rupture and release DAMPs, which in turn activate the immune response and amplify the inflammatory cascade (106,107). Concurrently, ferroptosis in the inflammatory microenvironment drives polarization of macrophages (108). M1 macrophages secrete pro-inflammatory factors such as TNF-α and IL-1β, further exacerbating the inflammatory response (108). M2 macrophages, on the other hand, secrete TGF-β, which induces fibroblast proliferation, activation and myofibroblast differentiation, ultimately promoting fibrosis (109,110). The following sections will provide a detailed explanation of the specific mechanisms underlying cellular ferroptosis during the fibrotic process.

The fibrotic microenvironment can also exert positive feedback regulation on ferroptosis, a process that occurs primarily during the remodeling phase of fibrosis. During the remodeling phase, excessive deposition of the ECM can cause tissue stiffening and structural damage to organs, leading to tissue hypoxia and subsequent upregulation of HIF-1α (41). Under hypoxic conditions, lactate accumulation upregulates GPX4 expression, endowing activated fibroblasts with ferroptosis resistance and thereby maintaining their profibrotic phenotype. Conversely, reducing lactate levels restores the sensitivity of the cells to ferroptosis and alleviates fibrosis (111). Previous studies have shown that during hypoxia caused by acute ischemia or injury, HIF-1α plays a tissue-protective role by reducing tissue damage and mediating a moderate inflammatory response to prevent abnormal repair (112-114). However, in the context of long-term chronic hypoxia caused by fibrosis, HIF-1α acts as a promoter of fibrosis (106,115). For example, under conditions of chronic hypoxia in the liver and kidneys, HIF-1α promotes iron release by upregulating heme oxygenase-1 (HO-1). This is accompanied by downregulation of GPX4 and SLC7A11, which exacerbates ferroptosis in parenchymal cells, thereby accelerating organ fibrosis (116-118).

Liver fibrosis and ferroptosis. Liver fibrosis is a condition in which the liver undergoes abnormal repair and progresses toward sclerosis due to persistent stimulation from various forms of chronic liver injury. The core pathological mechanism involves hepatocyte death and the activation and transdifferentiation of hepatic stellate cells (HSCs). Recent research on ferroptosis has primarily focused on the two types of cells (119,120). Under pathological conditions, iron overload, accumulation of lipid peroxides and depletion of GSH occur in the liver, ultimately triggering ferroptosis in hepatocytes (121,122). For example, in alcohol-related liver disease, TFR1 expression in hepatocytes is markedly upregulated, leading to intracellular iron overload. Furthermore, microRNA (miRNA/miR)-214 can exacerbate the accumulation of lipid oxidation products by upregulating the expression of ACSL4 (123). In metabolic fatty liver disease, elevated levels of TFR1 and reduced levels of ferroportin (FPN) jointly lead to a significant expansion of the labile iron pool (124). At the same time, impaired function of the GPX4-GSH system further exacerbates ferroptosis (125).

Subsequently, liver cells undergoing ferroptosis release DAMPs, which activate Kupffer cells and induce their polarization toward the M1 and M2 phenotypes, leading to the secretion of cytokines such as TGF-β1 and IL-6 (108). These factors further drive the activation of quiescent HSCs into myofibroblasts, which secrete large amounts of ECM, ultimately leading to the development of liver fibrosis (105). In viral hepatitis, miR-222 generated by hepatocytes infected with HBV can inhibit ferroptosis in HSCs by suppressing the expression of the TFR1 in HSCs, thereby promoting their

activation (126). In the context of metabolic fatty liver disease, the accumulation of cholesterol within HSCs not only activates the HSCs but also confers resistance to ferroptosis by maintaining high levels of GPX4 expression (127).

Pulmonary fibrosis and ferroptosis. Pulmonary fibrosis is often triggered by environmental dust, infections, medications, autoimmune diseases or radiation (128,129). When alveolar epithelial cells are damaged, they release DAMPs, which trigger a series of immune and inflammatory responses (130). This process further drives the transdifferentiation of fibroblasts into myofibroblasts, induces epithelial-mesenchymal transition (EMT) in alveolar epithelial cells, and promotes massive deposition of ECM, ultimately disrupting the alveolar-capillary membrane structure and forming honeycomb-like scars (131).

The specific pathological processes driven by ferroptosis in pulmonary fibrosis are similar to those in liver fibrosis. Among these, alveolar epithelial type II cells (AEC II) play a key role in ferroptosis. In models of exposure to bleomycin, silica or PM2.5, AEC II can undergo ferroptosis, which is characterized by iron accumulation, decreased GPX4 expression and mitochondrial dysfunction (132,133). Furthermore, ficolin B carried by alveolar macrophage exosomes can promote ferroptosis in AEC II by activating the cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) signaling pathway, thereby exacerbating pulmonary fibrosis (134).

Renal fibrosis and ferroptosis. Renal fibrosis is a common pathological change observed in various chronic kidney diseases as they progress to end stage; it essentially represents an abnormal repair process that occurs following repeated damage to the kidneys (135,136). This process begins in damaged renal tubular cells, triggering a vicious cycle of inflammation and oxidative stress, which leads to the abnormal activation of the key factor TGF-β. This process subsequently drives fibroblast activation and EMT, ultimately leading to ECM deposition and scar formation, gradually replacing normal nephrons (8,21,137,138).

Ferroptosis of renal tubular epithelial cells is one of the core mechanisms underlying renal fibrosis. Under pathological conditions such as diabetic nephropathy and a high-fat diet, renal tubular epithelial cells undergo ferroptosis, characterized by downregulation of GPX4 and upregulation of ACSL4, which induces lipid peroxidation (139-141). Among these, the diamine acetyltransferase 1 (SAT1)/Nrf2 axis is a key pathway regulating ferroptosis in renal tubular epithelial cells, and SAT1 silencing can alleviate fibrosis (142). Furthermore, sigma-1 receptor (S1R) promotes ferroptosis in renal tubular epithelial cells and leads to renal fibrosis by inhibiting Nrf2 (143).

Cardiac fibrosis and ferroptosis. Cardiac fibrosis can be caused by factors such as hypertension, myocardial infarction and diabetes. Under the influence of mechanical stress, ischemia, inflammation and angiotensin II, damaged cardiac muscle cells release cytokines that activate fibroblasts and promote their transformation into myofibroblasts (144,145). Myofibroblasts excessively synthesize ECM while its degradation is suppressed, leading to aberrant collagen deposition and increased interstitial stiffness, ultimately impairing cardiac diastolic and systolic functions (146,147).

Ferroptosis plays a key regulatory role in cardiac fibrosis and occurs primarily within cardiomyocytes. At the level of iron metabolism, TFR1-mediated iron uptake and NCOA4-mediated ferritin autophagy constitute the sources of iron accumulation (148,149). In lipid metabolism, ACSL4 and arachidonate 15-LOX (ALOX15) act at the substrate end of synthesizing PUFA-containing phospholipids and the initiation end of lipid peroxidation, respectively, thereby determining cellular sensitivity to ferroptosis (150,151). Regarding glutathione metabolism, GPX4 and SLC7A11 are key factors in inhibiting ferroptosis, and their downregulation exacerbates oxidative damage (152). Furthermore, the acetylation of p53 and the ubiquitination of Nrf2 suppress the expression levels of GPX4 and SLC7A11 (153,154).

Strategies for intervening in fibrosis via the ferroptosis mechanism. Targeting ferroptosis to mitigate fibrosis has become a prominent research focus, with intervention strategies primarily focused on three key areas. Firstly, during the inflammatory stage, the death of parenchymal cells releases DAMPs, which trigger an inflammatory response and drive the fibrotic process (25,26). Inhibiting ferroptosis in these cells by modulating the oxidative or antioxidant systems can halt inflammation at its source, thereby impeding fibrosis progression (106,155).

Secondly, targeting macrophages is also a key focus of current research. Upon receiving inflammatory signals from upstream, macrophages can polarize into two phenotypes: Pro-inflammatory (M1) and pro-fibrotic (M2). These two polarization pathways are key drivers of the fibrotic process (156). Therefore, macrophages can be targeted in two ways to effectively inhibit the fibrotic process. On the one hand, inhibiting ferroptosis in macrophages can prevent their phenotypic transition. On the other hand, inducing ferroptosis can eliminate already polarized macrophages.

Additionally, inducing ferroptosis in activated effector cells, such as HSCs and fibroblasts, is a promising strategy (157). However, this strategy is currently primarily applied to liver fibrosis, with relatively limited research on fibrosis in other organs. The present review further elaborates on anti-fibrotic interventions centered on these three core strategies (Fig. 3).

5. Inflammatory phase: Protection of parenchymal cells

Inhibition of the oxidative system

Regulation of iron metabolism. i) Transfer iron pathway. Research indicates that the core strategy for regulating iron metabolism lies in modulating intracellular iron homeostasis through the transferrin pathway, thereby maintaining a dynamic balance of iron ions and ultimately inhibiting ferroptosis in parenchymal cells (106,158). In pulmonary fibrosis, upregulated TFR1 and divalent metal transporter 1 (DMT1) is a critical factor that drives ferroptosis in alveolar epithelial cells (132,159,160). The iron chelator deferoxamine markedly alleviates fibrosis by reducing intracellular iron accumulation via the downregulation of TFR1/DMT1 expression (159) (Fig. 4A-1). FPN functions to export intracellular iron into the extracellular space; its downregulation consequently results in hepatocellular iron accumulation (103). Rifaximin alleviates iron overload-induced ferroptosis in hepatocytes by restoring FPN function, ultimately ameliorating liver fibrosis (161,162). Iron regulatory protein 2 (IRP2) binds to iron-responsive elements in the mRNAs of TFR1 and FPN,

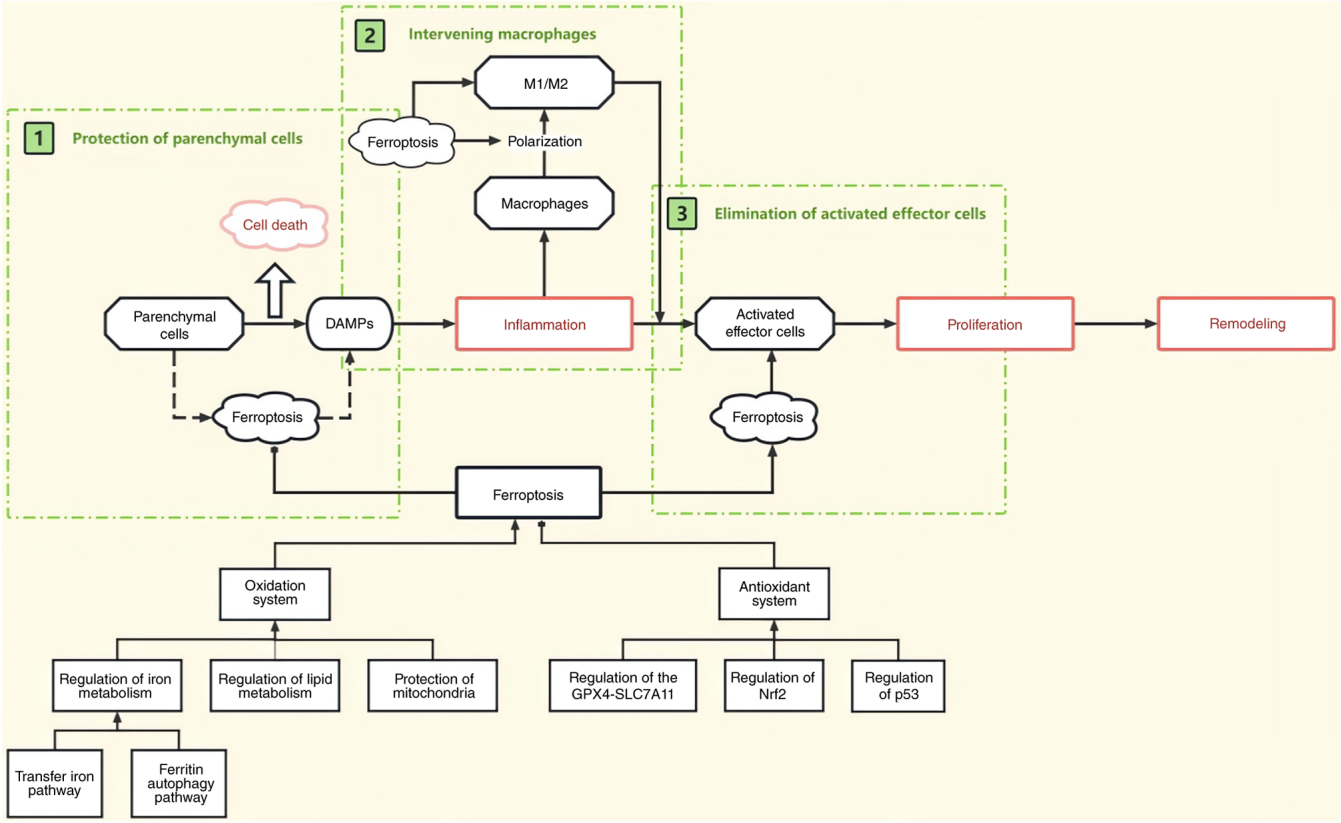

Figure 3. According to the three stages of fibrosis, fibrosis can be alleviated by inhibiting ferroptosis of parenchymal cells, intervening macrophages and promoting ferroptosis of activated effector cells. DAMP, damage-associated molecular pattern; GPX4, glutathione peroxidase 4; SLC7A11, solute carrier family 7 member 11; Nrf2, nuclear factor erythroid 2-related factor 2; p53, tumor protein p53.

thereby upregulating TFR1 protein expression and repressing FPN protein expression. These two proteins work together to promote the uptake of iron ions by cells (163). Therefore, inhibiting IRP2 can correct the imbalance of iron transport, thus alleviating fibrosis (164) (Fig. 4A-1).

ii) Ferritin autophagy pathway. Previous studies have shown that inhibiting ferritin autophagy can also prevent ferroptosis in parenchymal cells. Intracellular ferritin can bind to NCOA4, thereby triggering ferritin autophagy and releasing large amounts of iron ions (165-167). Therefore, upregulation of NCOA4 often leads to ferroptosis in parenchymal cells, thereby exacerbating fibrosis (59,168). For instance, the transcription factor Yin Yang 1 markedly upregulates NCOA4 expression, thereby inducing ferritin autophagy, which ultimately drives myocardial fibrosis and remodeling (169). Similarly, silica nanoparticle-induced hepatic fibrosis is driven by ferritin autophagy, and silencing the NCOA4 can suppress ferritin degradation and reverse the fibrotic phenotype (170). Therefore, targeting NCOA4 has become a strategic approach to restore iron homeostasis. Drugs such as dihydroquercetin and fraxetin can inhibit NCOA4 expression, thereby blocking the ferroptosis pathway and ultimately suppressing pulmonary fibrosis (171,172) (Fig. 4A).

Regulation of lipid metabolism. ACSL4 is a central hub in lipid metabolism. Upregulation of ACSL4 exacerbates the pathological accumulation of lipid peroxides, thereby triggering ferroptosis. In pulmonary fibrosis models, ACSL4 expression is markedly upregulated, exacerbating lipid peroxidation and thereby inducing alveolar epithelial cell death (173,174). In liver fibrosis, activation of the gp78-ACSL4 axis exacerbates ferroptosis in hepatocytes, and specific inhibitors targeting this axis have demonstrated therapeutic potential (175). In renal fibrosis, calcium oxalate crystals induce ferroptosis in renal tubular epithelial cells by activating the YAP-ACSL4 pathway, thereby accelerating interstitial fibrosis. Accordingly, silencing YAP or inhibiting ACSL4 can alleviate the progression of fibrosis (176,177). Currently, intervention strategies for ACSL4 include small-molecule inhibitors (such as rosiglitazone), epigenetic modulators (such as DNA methylation inhibitors), flavonoid derivatives (such as fisetin) and gene silencing technologies (for example, small interfering RNA), which provide a new direction in the treatment of fibrotic diseases (177-179) (Fig. 4A).

Protection of mitochondria. Mitochondria maintain cellular iron homeostasis through iron-sulfur cluster biosynthesis and heme metabolism. Previous reports have indicated that the mitochondrial membrane is susceptible to attack by hydroxyl radicals, which triggers mitochondrial rupture and leads to the leakage of large amounts of ROS from the mitochondria (69,180). Doxorubicin can bind to Fe^{2+} to form a complex, which inhibits GPX4 activity, leading to the massive accumulation of lipid peroxides within mitochondria. This subsequently triggers mitochondrial-dependent ferroptosis in cardiomyocytes, ultimately exacerbating myocardial fibrosis and cardiac dysfunction (150,181). FUN14 domain-containing protein 1 (FUNDC1) is a mitophagy receptor primarily

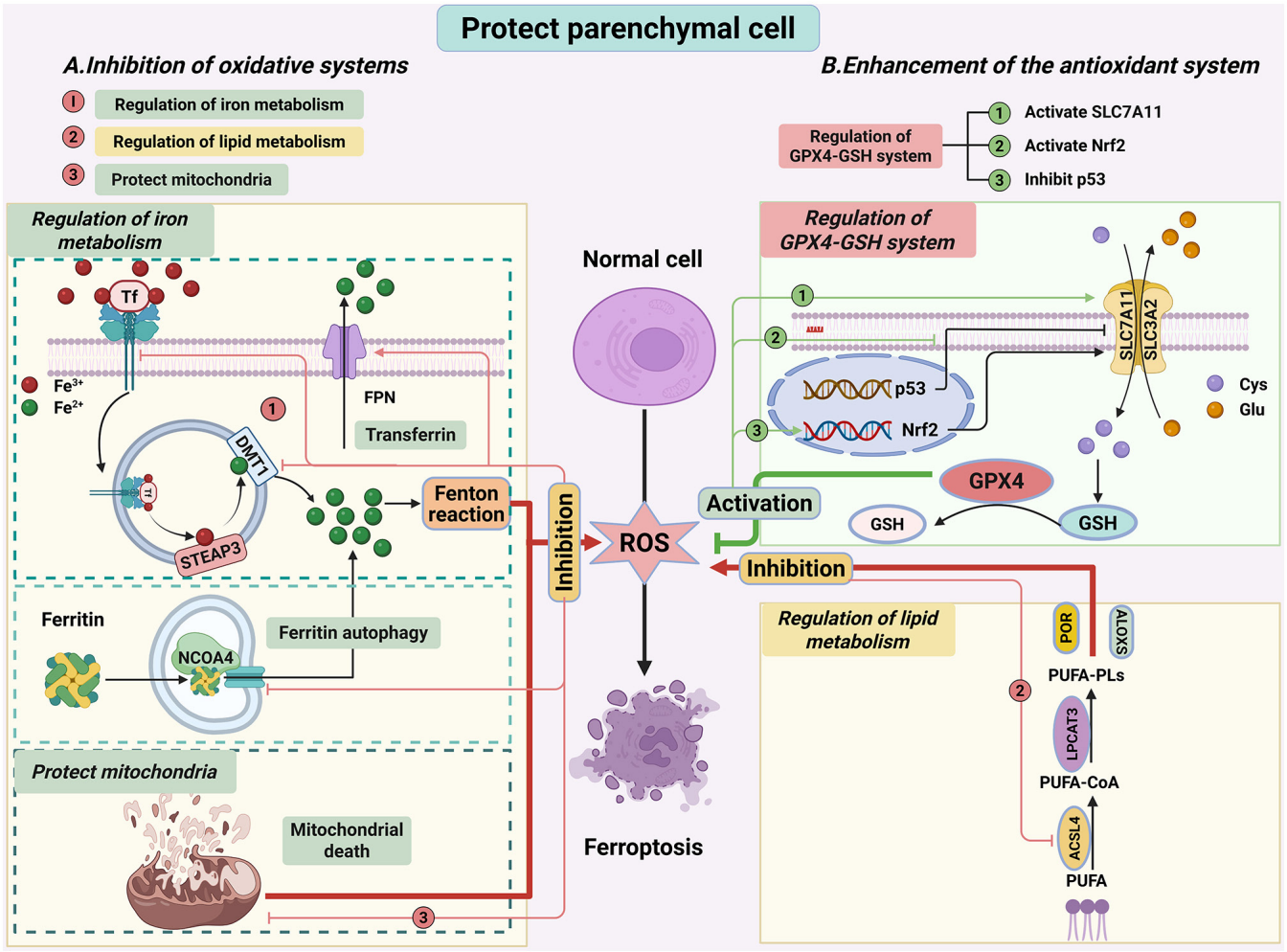

Figure 4. Core strategies for protecting parenchymal cells from ferroptosis primarily rely on two pathways: Inhibiting oxidative damage and activating antioxidant systems. (A) To mitigate oxidative damage, intracellular iron accumulation can be effectively reduced by inhibiting iron uptake mediated by TFR1 and DMT1, as well as ferritin autophagy mediated by NCOA4. Additionally, upregulating FPN expression to promote iron ion efflux can further reduce intracellular iron levels. At the same time, alleviating mitochondrial damage and inhibiting ACSL4-mediated lipid metabolism also help reduce oxidative stress. (B) In terms of activating the antioxidant system, SLC7A11 expression can be upregulated either directly or indirectly through approaches such as activating Nrf2 or inhibiting p53. TFR1, transferrin receptor 1; DMT1, divalent metal transporter 1; NCOA4, nuclear receptor coactivator 4; FPN, ferroportin; ACSL4, acyl-CoA synthetase long-chain family member 4; SLC7A11, solute carrier family 7 member 11; Nrf2, nuclear factor erythroid 2-related factor 2; p53, tumor protein p53; ALOXs, arachidonate lipoxygenases; POR, cytochrome P450 reductase.

located on the outer mitochondrial membrane, which mediates the entry of GPX4 into mitochondria. During mitophagy, GPX4 is degraded, thereby triggering cellular ferroptosis and ultimately leading to organ fibrosis. Knockout of FUNDC1 markedly alleviates this process (150,182). These findings suggest that modulating mitochondrial ferroptosis holds potential value in the treatment of fibrosis. For example, forsythiaside-A and melatonin enhance GPX4 function by activating the Nrf2 pathway, thereby alleviating mitochondrial ferroptosis (183,184). Additionally, the botanical extract WGX50 and salidroside can alleviate cardiac fibrosis by restoring the activity of mitochondrial GPX4 (185,186). The hydrogen sulfide donor AP39 inhibits mitochondrial ferroptosis via the PTEN-induced kinase 1/parkin pathway, thereby alleviating myocardial fibrosis (187) (Fig. 4A).

Enhancement of the antioxidant system

Regulation of the GPX4-SLC7A11 antioxidant axis. The GPX4-SLC7A11 system serves as the primary antioxidant barrier; its inactivation leads to substantial accumulation of lipid peroxides and accelerates fibrosis progression (188-191). Therefore, modulating the GPX4-SLC7A11 axis has become an important strategy for combating fibrosis. For instance, elabela peptide inhibits ferroptosis in cardiomyocytes by upregulating SLC7A11 expression through antagonism of the IL-6/STAT3 signaling pathway, thereby effectively suppressing myocardial fibrosis (192). The plant alkaloid tuberostemonine enhances the activity of the SLC7A11/SLC3A2 heterotetramer, thereby markedly increasing GPX4 activity in alveolar epithelial cells and inhibiting ferroptosis (193). Furthermore, *Salvia miltiorrhiza* injection promotes the deacetylation of SLC7A11 by activating sirtuin 1 (Sirt1), thereby enhancing the stability of the SLC7A11 protein, protecting renal tubular epithelial cells from ferroptosis and inhibiting renal interstitial fibrosis (194). Luteolin can also reverse carbon tetrachloride-induced liver fibrosis by modulating the GPX4-SLC7A11 axis (195) (Fig. 4B).

Regulation of Nrf2. Nrf2 is a key regulator of the oxidative stress defense system; it activates downstream antioxidant

systems (such as GPX4), thereby effectively scavenging lipid peroxides and maintaining redox homeostasis (196-198). In a renal fibrosis model induced by high glucose and high fat, the S1R protein in renal tubular epithelial cells was shown to bind to Nrf2 and promote its phosphorylation, thereby inhibiting GPX4 and subsequently exacerbating ferroptosis (143). Similar phenomena are also observed in liver fibrosis and pulmonary fibrosis. In these conditions, Nrf2 is suppressed, the expression of ferroptosis markers is markedly elevated, and fibrosis is aggravated accordingly (198,199) (Fig. 4B).

Drug development targeting the Nrf2 signaling network has evolved into three major categories: Herbal extracts, clinical drugs and small-molecule proteins. Herbal extracts (for example, fucoxanthin, ginkgolide B, cinnamaldehyde and triptolide) or traditional Chinese formulations (such as Taohongsiwu decoction and LuQi formula) alleviate organ fibrosis by modulating pathways (for example, Nrf2/GPX4, AKT/mTOR/Nrf2 and Nrf2/HO-1) to inhibit ferroptosis in parenchymal cells (200-204). Among clinical drugs, empagliflozin mitigates pulmonary fibrosis through the sestrin 2 (Sesn2)/AMPK/Nrf2 signaling (205). Meanwhile, melatonin concurrently suppresses mitophagy and ferroptosis via the AKT/mTOR/Nrf2 pathway to improve hepatic and renal fibrosis (183,206). Additionally, small-molecule proteins interact with Nrf2. Sirt7 ameliorates hypertensive renal fibrosis via the KLF15/Nrf2 axis (207). Sesn2 reduces ferroptosis through the Nrf2/activating transcription factor 4 (ATF4) pathway to alleviate idiopathic pulmonary fibrosis (208).

Regulation of p53. Studies have shown that p53 negatively regulates the GPX4-SLC7A11 system. In addition, p53 can activate ALOX12, thereby exacerbating lipid peroxidation. Therefore, targeting p53 can inhibit ferroptosis in parenchymal cells, thereby offering a potential therapeutic approach for fibrosis (209,210). For instance, SIRT1 deacetylates p53 to restore the antioxidant defense system, thereby markedly ameliorating the fibrotic phenotype (211). By contrast, SIRT3 knockout upregulates the acetylation level of p53 in cardiac fibrosis, which further induces ferroptosis in cardiomyocytes (212,213) (Fig. 4B-3).

6. Inflammatory phase: Intervening macrophages

Pathological role of macrophage ferroptosis in fibrosis. Studies have revealed that macrophage ferroptosis plays a vital role in the progression of fibrosis. For instance, the expression of ferroptosis-related genes in macrophages is markedly upregulated in both pulmonary fibrosis and systemic sclerosis models (214,215). Moreover, Fei *et al* (216) performed single-cell RNA sequencing analysis on hypertrophic ligamentum flavum tissues and identified a population of enriched secreted phosphoprotein 1-positive macrophages. These cells are not only involved in the fibrotic process but also exhibit highly activated metabolic pathways associated with ferroptosis.

Molecular mechanisms of ferroptosis-driven macrophage phenotypic polarization. Ferroptosis drives macrophage polarization into pro-inflammatory (M1) and pro-fibrotic (M2) phenotypes by modulating classical signaling pathways (156,217). Specifically, the formation of the pro-inflammatory M1 phenotype depends on the activation of the cGAS-STING pathway, which exacerbates chronic inflammatory microenvironments through the sustained secretion of inflammatory factors, such as IL-6 and TNF-α (218,219). By contrast, the pro-fibrotic M2 phenotype is synergistically driven by the coordinated activation of the Wnt/β-catenin and JAK-STAT pathways, which subsequently activate fibroblasts via the TGF-β/Smad signaling axis to induce pathological ECM deposition (220,221).

Targeted therapeutic strategies based on the modulation of ferroptosis. Interventions targeting macrophage ferroptosis can be implemented through two approaches: Suppressing phenotypic polarization and eliminating polarized cells. In terms of inhibiting polarization, targeted blockade of the ATF3-CD36 pathway can activate the Nrf2/GPX4 signaling axis, thereby suppressing macrophage ferroptosis (222,223). Additionally, inhibition of calpain downregulates ACSL4 expression, thereby reducing macrophage susceptibility to ferroptosis (179,215). In polarized cell elimination, current research focuses on pro-inflammatory M1 macrophages. For example, upregulating ACSL4 or inhibiting SLC7A11 expression can specifically increase intracellular lipid peroxidation levels, thereby inducing ferroptosis in M1 macrophages (179,224). Drugs represented by glyceraldehyde 3-O-mono-β-D-glucuronide can selectively eliminate inflammatory macrophages by activating the interferon regulatory factor 1/SLC7A11 signaling pathway, which provides new insights into reversing the progression of fibrosis (224).

7. Proliferation phase: Elimination of activated effector cells

Methods of eliminating special effector cells. During the progression of fibrosis, the inflammatory microenvironment activates tissue-resident effector cells, such as fibroblasts and HSCs, leading to their abnormal proliferation and differentiation into myofibroblasts. Targeting the elimination of activated effector cells has emerged as a pivotal strategy in anti-fibrotic therapy. Currently, this strategy is mainly applied to hepatic fibrosis; it induces ferroptosis of activated HSCs via multiple pathways to alleviate fibrosis (157,225-227).

Enhancement of the antioxidant system

Reinforcement of iron overload. i) Transfer pathway. Studies have demonstrated that modulating transferrin-related pathways to induce ferroptosis in HSCs and fibroblasts represents an effective strategy for alleviating fibrosis. YAP modulates the iron metabolic network by coordinately regulating iron uptake, storage and efflux. Mechanism analysis reveals that YAP promotes iron influx through the activation of TFR1 and DMT1, while suppressing the expression of FPN. This dysregulation leads to the abnormal accumulation of the iron ions in activated HSCs (228-230). Therefore, upregulation of YAP expression can trigger ferroptosis in HSCs, thereby alleviating fibrosis.

Furthermore, several drugs have been proven to inhibit fibrosis via this strategy. Artemether suppresses the ubiquitination of IRP2, thereby upregulating the expression of TFR/DMT1 and inhibiting FPN, and ultimately inducing

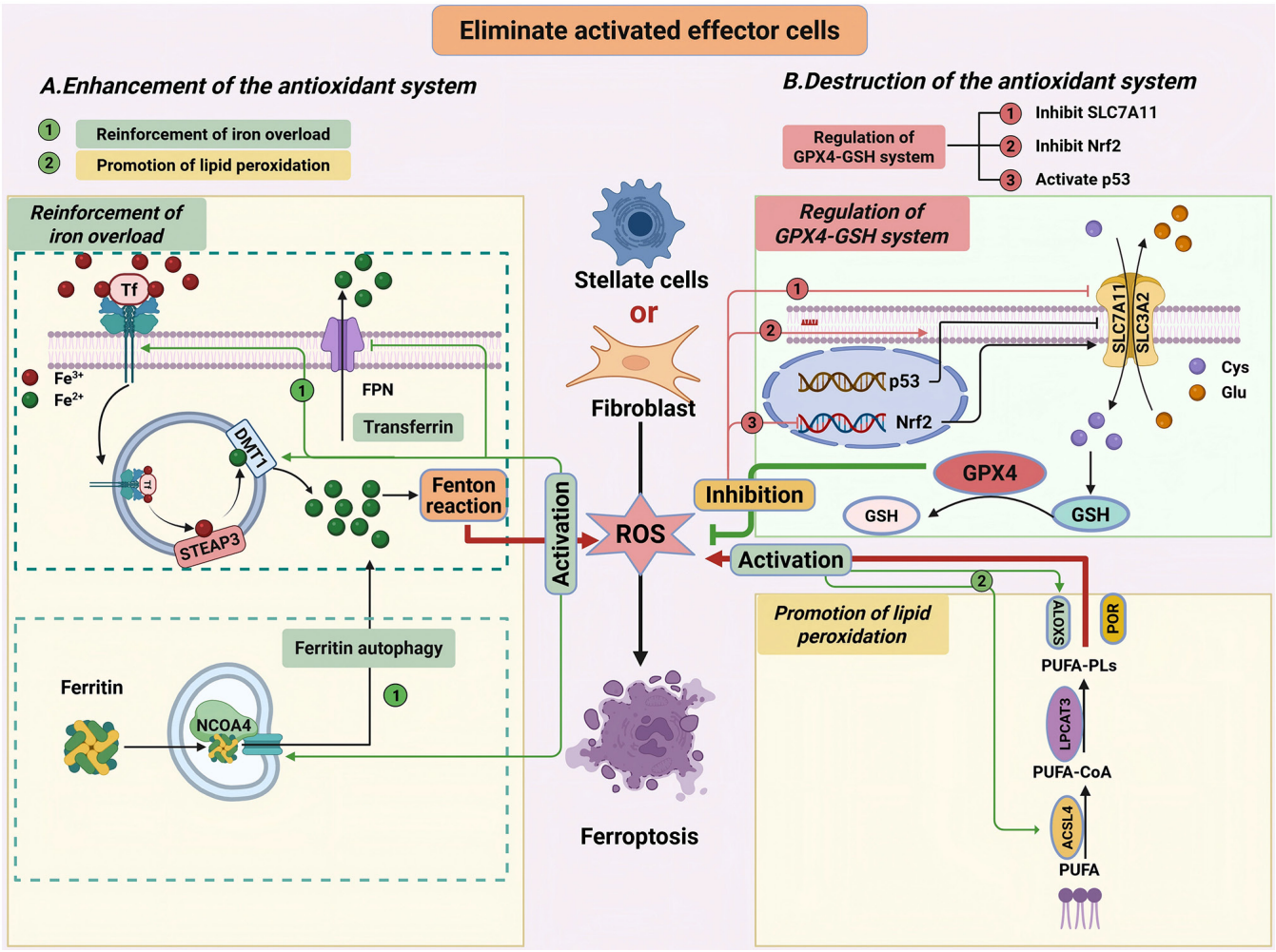

Figure 5. Elimination of activated effector cells (for example, fibroblasts and stellate cells) is mainly achieved by inhibiting the oxidative system and activating the antioxidant system. (A) The oxidative system aspect can be inhibited by activation of transferrin pathway (such as TF and DMT1), ferritin autophagy, mitochondrial damage, ALOXs and ACSL4, and inhibition of FPN. (B) In addition to this, the antioxidant system can be inhibited by inhibition of SLC7A11 and Nrf2, as well as activation of p53. TFR1, transferrin receptor 1; DMT1, divalent metal transporter 1; NCOA4, nuclear receptor coactivator 4; FPN, ferroportin; ACSL4, acyl-CoA synthetase long-chain family member 4; SLC7A11, solute carrier family 7 member 11; Nrf2, nuclear factor erythroid 2-related factor 2; p53, tumor protein p53; ALOXs, arachidonate lipoxygenases; POR, cytochrome p450 reductase.

ferroptosis in HSCs (164). Liquiritigenin upregulates the expression of TFR/DMT1, thereby activating ferroptosis in HSCs (227). Ellagic acid inhibits the transport function of FPN, leading to iron overload and ROS accumulation, and ultimately triggering ferroptosis in HSCs (231) (Fig. 5A-1).

ii) Ferritin autophagy. In addition, disrupting intracellular iron homeostasis via NCOA4-mediated ferritin autophagy also serves as a strategy for targeted elimination of effector cells (59,165,232). NCOA4 specifically recognizes and binds to the ferritin heavy chain (FTH1), forming an NCOA4-FTH1 complex, which subsequently mediates the transport of ferritin to lysosomes. Upon degradation of this complex within lysosomes, a large amount of iron ions is released. Natural compounds such as curcumin, artemisinin derivatives, taurine, naringin and berberine can accelerate the degradation of the NCOA4-FTH1 complex, releasing iron ions, which in turn induce ferroptosis in HSCs, thereby exerting an anti-fibrotic effect (233-241). In addition, the RNA-binding proteins embryonic lethal and zinc finger protein 36 (ZFP36) have been identified as regulators of the ferritin autophagy signaling pathway in HSCs, and their dysfunction is closely associated with the progression of fibrosis. These findings offer new insights for the development of targeted therapies (242,243) (Fig. 5A).

Promotion of lipid peroxidation. The enhancement of lipid metabolic pathways can also induce ferroptosis in activated effector cells (106,244). A recent study has shown that YTH N6-methyladenosine RNA-binding protein F2 can upregulate ACSL4 expression, enhance lipid oxidation pathways and thereby induce ferroptosis in activated HSCs (245). Ginsenoside Rg3 can restore ACSL4 expression by promoting its demethylation, thereby inducing ferroptosis in HSCs (246). ALOX15 directly activates the ferroptosis process by catalyzing the oxidation of PUFAs to form lipid peroxides (247,248). Dihydrotanshinone I promotes the demethylation of ALOX15 by downregulating the expression of DNA methyltransferase 1, thereby inducing ferroptosis in HSCs (249) (Fig. 5A).

Destruction of the antioxidant system. In addition to enhancing oxidative pathways, inhibiting the antioxidant system is

another potential therapeutic strategy (227,250). Studies have shown that various plant extracts can induce ferroptosis in activated HSCs by regulating the GPX4-SLC7A11 system. Ginkgolic acid and fig extract can downregulate GPX4 expression, thereby inducing ferroptosis in HSCs and ultimately improving liver fibrosis (251,252). Ginsenoside Rb1 and ginsenoside Rh2 inhibit SLC7A11, disrupting the cysteine-glutamate reverse transport system and thereby inducing ferroptosis in HSCs (253,254). Furthermore, simvastatin selectively downregulates GPX4 expression in HSCs, achieving anti-fibrotic effects while avoiding hepatotoxicity, demonstrating significant translational medical value (255).

At the transcriptional level, HIF-1α can upregulate the expression of SLC7A11. Sorafenib alleviates liver fibrosis by inhibiting the HIF-1α/SLC7A11 pathway, thereby triggering ferrocytosis in HSCs (225). Conversely, the tumor suppressor protein p53 promotes ferroptosis by inhibiting SLC7A11 transcription, thereby reducing the biosynthesis of GSH (256). For example, vogonolide and artemisinin can activate p53, disrupt the antioxidant system and consequently induce ferroptosis in HSCs (257,258) (Fig. 5B).

8. Novel therapeutic model based on ferroptosis

Exosome engineering. Exosome therapy, a novel therapeutic strategy based on extracellular vesicles (exosomes), regulates intercellular communication by delivering bioactive molecules (for example, proteins, miRNAs and mRNAs) and demonstrates potential in treating diverse diseases (259,260). As critical mediators of cell-cell communication, exosomes play a role in fibrotic processes by modulating ferroptosis signaling pathways. In pulmonary fibrosis, ficolin B secreted by alveolar macrophages can promote ferroptosis in pulmonary epithelial cells via the cGAS-STING signaling pathway, thereby exacerbating the progression of pulmonary fibrosis (134). Following HBV infection, miR-222 in exosomes secreted by hepatocytes can suppress ferroptosis in HSCs by inhibiting TFR1 expression (126). Additionally, exosomes derived from renal tubular epithelial cells can activate ATF3, which both inhibits the Nrf2/GPX4 signaling pathway and promotes M2 macrophage polarization, thereby synergistically driving renal fibrosis (261).

Exosome-engineered therapies have opened up a new dimension in fibrosis treatment through a two-way precision regulation strategy of promoting effector cell death and protecting parenchymal cells. In targeting effector cell ferroptosis, mesenchymal stem cell-derived exosomes (MSC-Exos) exhibit specific therapeutic advantages. For instance, human umbilical cord MSC-Exos (hucMSC-Exos) selectively induce HSC ferroptosis by delivering the Beclin 1 (BECN1) protein to suppress GPX4 expression (262). The miR-499a-5p carried by hucMSC-Exos interacts with the transcription factor ETS proto-oncogene 1 to downregulate SLC7A11 expression, thereby disrupting GSH synthesis and facilitating the precise elimination of HSCs (263,264). Similarly, bone marrow MSC-Exos utilize miR-144-3p to silence SLC7A11, thereby effectively inhibiting HSC activation (265).

In parenchymal cytoprotective strategies, engineered exosomes exhibit multifunctional regulatory properties. Spike receptor-binding domain (S-RBD)-modified MSC-Exos inhibit ferroptosis of alveolar epithelial cells by delivering miR-486-5p, while inhibiting SMAD2 signaling and activating the Akt pathway to achieve dual 'antifibrotic and anti-inflammatory' effects (266). Menstrual blood-derived SC-Exos deliver miR-let-7 to suppress Sp3 transcription factor expression and reduce recruitment to histone deacetylase 2, thereby alleviating the inhibition of Nrf2 and ultimately suppressing alveolar epithelial cell ferroptosis (267).

Nano drug delivery system. Nanodelivery platforms are drug delivery systems engineered using nanotechnology to enhance drug targeting, stability and therapeutic efficacy (268,269). Nanoparticles, owing to their unique targeting capabilities and controllable drug delivery properties, have emerged as cutting-edge strategies for modulating ferroptosis to alleviate fibrosis.

As innovative carriers for regulating ferroptosis, nanoparticles can protect parenchymal cells or eliminate effector cells through targeted drug delivery, thereby intervening precisely in fibrosis. In parenchymal cell protection, silica nanoparticles loaded with allicin are able to inhibit ferroptosis in cardiac microvascular endothelial cells, significantly improving myocardial fibrosis (270). Selenium-doped silica nanoparticles mitigate myocardial ischemia-reperfusion injury by synergistically alleviating ferroptosis and mitochondrial dysfunction (271).

In the elimination of effector cells, naringenin-loaded nanoparticles selectively remove HSCs by activating autophagy-dependent ferroptosis pathways (272). Carbon nitride-based hybrid nanoparticles induce HSC ferroptosis via downregulation of the HIF-1α/SLC7A11 signaling axis (273). Beyond that, taurine-conjugated lipid nanoparticles and fluorinated peptide-lipid hybrid nanoparticles enhance HSC ferroptosis sensitivity through multi-dimensional regulation (274,275).

While nanoparticles show promise in ferroptosis-targeted therapy, their design requires optimization to improve targeting specificity and reduce off-target toxicity. Future development of multifunctional platforms (for example, stimuli-responsive release and multi-target modulation) may offer more efficient solutions for fibrosis treatment.

9. Conclusions and perspectives

Fibrosis, a core pathological process that drives chronic diseases toward organ failure, is characterized by the abnormal deposition of ECM and involves three interconnected phases: Inflammation, proliferation and remodeling. Recent studies have shown that ferroptosis plays a key role in the fibrotic process. The present review systematically summarizes the process of fibrosis, the major mechanisms of ferroptosis and its role in fibrosis, and discusses therapeutic strategies and novel treatment modalities that target ferroptosis for the intervention of fibrosis.

Current therapeutic approaches primarily focus on two strategies: Protecting parenchymal cells during the inflammatory phase and eliminating activated effector cells during the proliferative phase. Both strategies target three core regulatory nodes: Iron metabolism pathways, lipid peroxidation pathways and antioxidant systems. Additionally, interventions targeting

macrophage represent a currently prominent strategy. Inhibiting macrophage polarization or eliminating polarized macrophages via the mechanism of ferroptosis can also alleviate fibrosis.

Novel ferroptosis-modulating therapies are evolving in multi-dimensional directions. In the field of delivery system innovation, engineered exosomes offer unique advantages. MSC-Exos achieve precise regulation of HSCs ferroptosis by delivering functional RNAs (such as miR-499a-5p and miR-144-3p) and proteins (such as BECN1). S-RBD-modified exosomes exert dual regulatory effects in pulmonary fibrosis by suppressing SMAD2/Akt signaling via miR-486-5p. Concurrently, nanodelivery platforms are advancing precision medicine. For instance, selenium-doped silica nanoparticles inhibit myocardial ferroptosis by restoring mitochondrial function, while naringenin-loaded nanoparticles eliminate activated HSCs via autophagy-dependent ferroptosis pathways. These innovations are steering ferroptosis-targeted therapies toward greater specificity and efficacy.

Despite the promise of ferroptosis modulation in fibrosis treatment, clinical translation faces challenges. First, off-target effects of existing delivery systems risk damaging healthy parenchymal cells, necessitating improved targeting through surface ligand modifications or organ-specific promoters. Second, dense ECM barriers impede drug penetration, driving the development of MMP-responsive nanocarriers or ultrasound microbubble-mediated delivery systems. Future research should prioritize intelligent nanoplatforms, gene-editing technologies and the integration of single-cell sequencing with spatial transcriptomics to map organ-specific regulatory networks. By bridging foundational discoveries with clinical precision medicine, these efforts may unlock transformative therapies for fibrosis.

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XF was primarily responsible for the writing, review and revision of the article. JZ participated in the literature review and provided revisions for this review. QM and CS provided guidance throughout the preparation of this manuscript and made revisions to the text. All authors have read and approved the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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