Mechanisms and therapeutic implications of ferritinophagy in fibrotic diseases (Review)

SIYING SUN[1,2*], JIE YU[3,4*], XUEMEI LI[1,2,5-7] and HONGFEI LIAO[1,2,5-7]

[1]School of Optometry, Jiangxi Medical College, Nanchang University, Nanchang, Jiangxi 330006, P.R. China; [2]Department of Orbital Diseases and Ocular Oncology, Jiangxi Research Institute of Ophthalmology and Visual Science, Nanchang, Jiangxi 330006, P.R. China; [3]Department of Orthopedics Surgery, People's Hospital of Yichun City, Yichun, Jiangxi 336000, P.R. China; [4]Department of Orthopedics Surgery, Yichun Affiliated Hospital, Nanchang University, Yichun, Jiangxi 336000, P.R. China; [5]Department of Orbital Diseases and Ocular Oncology, Jiangxi Clinical Research Center for Ophthalmic Disease, Nanchang, Jiangxi 330006, P.R. China; [6]Jiangxi Provincial Key Laboratory for Ophthalmology, Nanchang, Jiangxi 330006, P.R. China; [7]Department of Orbital Diseases and Ocular Oncology, National Clinical Research Center for Ocular Diseases, Nanchang, Jiangxi 330006, P.R. China

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Abstract. Iron homeostasis depends on the coordinated regulation of iron uptake, storage, utilization and export to maintain cellular metabolism and redox balance. Ferritinophagy is an iron-specific form of autophagy mediated by the selective cargo receptor nuclear receptor coactivator 4. By delivering ferritin to the autophagy-lysosome system for degradation and releasing Fe^{2+}, ferritinophagy regulates the intracellular labile iron pool and influences reactive oxygen species generation, lipid peroxidation and the ferroptosis threshold. Fibrosis is an aberrant repair response driven by chronic injury and is characterized by persistent inflammation, fibroblast activation and excessive extracellular matrix deposition. Increasing evidence has indicated that iron deposition and iron metabolic reprogramming are common features across a number of fibrotic disorders. Oxidative stress resulting from disrupted iron homeostasis can interact with the TGF-β signaling network to promote tissue remodeling. As an upstream regulatory mechanism, ferritinophagy may connect abnormal iron metabolism, oxidative stress, ferroptosis and profibrotic signaling through modulation of bioavailable iron, with bidirectional effects depending on cell type and disease stage. The present review summarizes the molecular basis and regulatory networks of ferritinophagy, whilst integrating recent advances regarding its role in fibrosis across different tissues or organs. It further discusses the potential balancing role of ferritinophagy in parenchymal cell injury and effector cell fate regulation, highlighting antifibrotic strategies targeting upstream metabolic regulation based on modulation of the ferroptosis threshold.

Correspondence to: Dr Xuemei Li or Professor Hongfei Liao, School of Optometry, Jiangxi Medical College, Nanchang University, 463 Bayi Avenue, Donghu, Nanchang, Jiangxi 330006, P.R. China
E-mail: 360014230132@email.ncu.edu.cn
E-mail: liaohongfei@ncu.edu.cn

*Contributed equally

Abbreviations: ACSL4, acyl-CoA synthetase long-chain family member 4; AMPK, AMP-activated protein kinase; ATG, autophagy-related protein; CAF, cancer-associated fibroblast; c-Jun, Jun proto-oncogene; DAMP, damage-associated molecular pattern; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; ESCRT, endosomal sorting complex required for transport; FTH1, ferritin heavy chain 1; FTL, ferritin light chain; GATE16, Golgi-associated ATPase enhancer of 16 kDa; GPX4, glutathione peroxidase 4; HERC2, HECT and RLD domain containing E3 ubiquitin protein ligase 2; HIF, hypoxia-inducible factor; HREs, hypoxia response elements; HSCs, hepatic stellate cells; IRE, iron-responsive element; IRP, iron regulatory protein; JAK, Janus kinase; KAT2A, lysine acetyltransferase 2A; Keap1, Kelch-like ECH-associated protein 1; LIP, labile iron pool; NCOA4, nuclear receptor coactivator 4; NOX, NADPH oxidase; NRF2, nuclear factor erythroid 2-related factor 2; Rab7, Ras-related protein Rab-7a; ROS, reactive oxygen species; STING, stimulator of interferon genes; TFEB, transcription factor EB; TfR1, transferrin receptor 1; VAMP, vesicle-associated membrane protein; α-SMA, α-smooth muscle actin

Key words: autophagy, ferritins, fibrosis, oxidative stress, iron metabolism disorders, therapeutics

Contents

1. Introduction
2. Molecular mechanisms of ferritinophagy
3. Role of ferritinophagy in fibrosis
4. Role of ferritinophagy in organ-specific fibrotic diseases
5. Discussion
6. Conclusion

1. Introduction

Iron homeostasis is key in maintaining cellular metabolism, redox balance and diverse physiological functions, relying on

the coordinated regulation of iron uptake, storage, utilization and export. As a major intracellular iron-storage complex, ferritin serves a central role in buffering iron toxicity while maintaining iron availability (1,2). In recent years, ferritinophagy, a selective form of autophagy that has attracted increasing attention, has been closely associated with ferritin degradation and has been shown to serve an important role in regulating cellular iron homeostasis under the mediation of nuclear receptor coactivator 4 (NCOA4) (3,4). Acting as a specific cargo receptor, NCOA4 recognizes and binds ferritin at the early stage of autophagy and mediates its delivery to the autophagy-lysosome pathway for degradation. This process promotes the conversion of stored iron into bioavailable iron; however, under conditions of dysregulated iron control, it may also exacerbate iron overload and trigger cellular dysfunction (5-7). Previous evidence has suggested that NCOA4 is a central receptor involved in ferritinophagy and also exhibits a key regulatory function in lysosome-mediated transport, degradation and recycling of ferritin-derived iron (8,9). NCOA4 was initially identified in association with the RET-fusion gene and its biological function is currently considered to encompass broader regulation of cellular stability (10). NCOA4-mediated ferritin degradation releases Fe^{2+} into the intracellular labile iron pool (LIP), which, upon Fenton chemistry, drives reactive oxygen species (ROS) production and triggers ferroptosis (11,12). As awareness of ferroptosis, as an example of regulated cell death that involves iron-dependent lipid peroxidation, has increased, iron homeostasis is expected to be increasingly regarded as the upper-limit regulator of the ferroptosis threshold and NCOA4-mediated ferritinophagy serves a notable role in this regulation.

Fibrosis is a pathological condition characterized by excessive accumulation of extracellular matrix (ECM) components (13-15). Previous research regarding fibrosis has repeatedly demonstrated an association between ferroptosis and iron metabolism disorder, with the degree of ferroptosis usually being positively associated with fibrotic progression (11,14,16). Iron-derived ROS activate TGF-β/Smad signaling and drive fibroblast-to-myofibroblast conversion (17-20). However, the upstream regulatory mechanisms governing iron availability in fibrosis remain incompletely understood. Ferritinophagy, by controlling ferritin degradation and iron mobilization, may serve as such an upstream checkpoint.; however, direct evidence is still fragmented and ferritinophagy may exert distinct effects depending on cell type and disease stage, thus underscoring the need for systematic investigation (21,22).

Therefore, within this context, it is of marked importance to systematically examine the role of ferritinophagy in fibrotic diseases from the perspective of upstream iron homeostasis regulation. The majority of existing studies have focused primarily on ferroptosis or oxidative stress, whereas the roles of ferritinophagy in fibrosis across different organs, as well as its interactions with ferroptosis and classical profibrotic signaling networks, remain insufficiently summarized or mechanistically integrated (13,14,21). However, despite increasing recognition of ferritinophagy as a key regulator of cellular iron metabolism (4,10), its precise role in fibrotic diseases remains incompletely understood. It is still unclear whether ferritinophagy represents a universal driver of fibrotic progression or rather functions as a context-dependent adaptive response influenced by cell type, tissue microenvironment and disease stage. Furthermore, current evidence is primarily derived from *in vitro* models and experimental animal studies, while the causal association between ferritinophagy activation and fibrosis development, as well as its relative contribution compared with other iron-regulatory pathways, requires further clarification (13,14,21). Therefore, the present review aimed to not only summarize the molecular mechanisms by which ferritinophagy regulates iron homeostasis, ferroptosis and fibrotic remodeling, but to also critically evaluate its functional roles across different fibrotic diseases. By integrating current evidence and identifying unresolved controversies, the present study sought to provide a conceptual framework for understanding ferritinophagy as a metabolic checkpoint in fibrosis and to offer new perspectives for developing anti-fibrotic strategies (Fig. 1).

2. Molecular mechanisms of ferritinophagy

NCOA4-mediated selective recognition of ferritin and initiation of ferritinophagy. Ferritin represents a key intracellular form of iron storage and serves a central role in maintaining iron homeostasis by reversibly storing and releasing iron ions to regulate intracellular iron levels (23,24). Structurally, ferritin forms a hollow spherical complex composed of 24 subunits, including ferritin heavy chain (FTH1) and ferritin light chain (FTL). FTH1 possesses ferroxidase activity that catalyzes the conversion of Fe^{2+} into the more stable Fe^{3+} form, whereas FTL promotes iron core formation and maintains the structural stability of the ferritin complex (25,26). The coordinated actions of FTH1 and FTL enable ferritin to safely store large quantities of iron while allowing dynamic iron release when required by the cell, thereby maintaining intracellular iron homeostasis while preventing free iron toxicity.

Previous research has shown that the function of the lysosomal system is important for ferritin degradation and iron excretion (27,28). In 2014, Mancias *et al* (29) first proposed the concept of ferritinophagy. The authors found that NCOA4 was the main receptor for ferritin phagocytosis during ferritin engulfment and that ferritin was delivered to autolysosomes after being recognized by NCOA4 to fuse with lysosomes to decompose ferritin and release iron ions. NCOA4 exists as two isoforms, NCOA4α (70 kDa) and NCOA4β (287 amino acids), both of which share an N-terminal coiled-coil domain and a portion of the C-terminal region. Notably, the C-terminal domain of NCOA4α contains binding sites for FTH1 and the E3 ubiquitin ligase HECT and RLD domain containing E3 ubiquitin protein ligase 2 (HERC2) (6,29-31). NCOA4 binds to FTH1 through its C-terminal domain and promotes the directed transport of ferritin complexes into lysosomes for degradation (32,33). Previous studies regarding structural biology have shown that selective recognition of NCOA4 for binding to FTH1 is based on the presence of 16 highly conserved residues in the FTH1 surface, including K180, R183 and D186. Each ferritin molecule can bind ≤24 NCOA4 molecules (29-31); thus, due to its numerous binding capabilities, ferritin can be more easily recognized and degraded in the autophagy pathway. In particular, the NCOA4-FTH1 interaction is dynamically modulated by intracellular iron content: In an iron-deficient environment, their affinity rises and ferritin

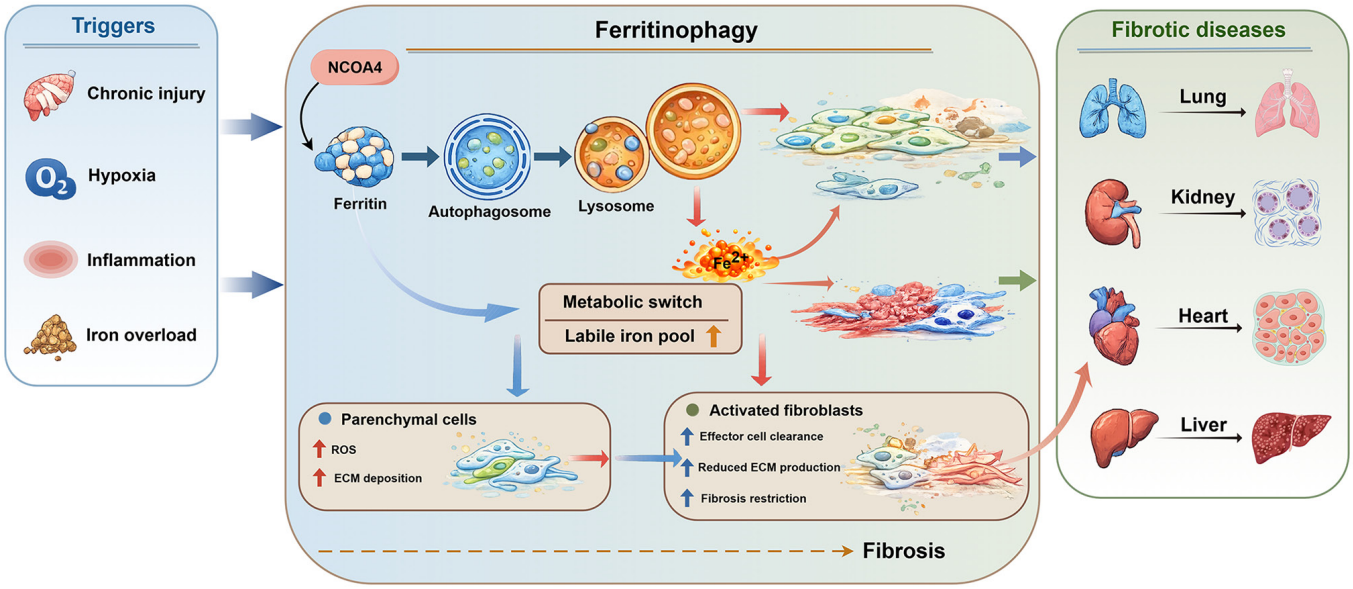


Figure 1. Ferritinophagy links iron metabolism to ferroptosis and fibrotic remodeling by coupling labile iron release to oxidative stress and TGF-β signaling. Its context-dependent effects highlight a dual role in promoting tissue injury or eliminating profibrotic cells. Figure created using Figdraw (version 1.0; www.figdraw.com). NCOA4, nuclear receptor coactivator 4; ROS, reactive oxygen species; ECM, extracellular matrix.

degrades to liberate iron ions, whereas, under iron-replete conditions, their binding weakens and the ferritin degradation rate decreases to reduce free iron accumulation. NCOA4 exhibits a direct interaction with Golgi-associated ATPase enhancer of 16 kDa (GATE16)/LC3 family members through two short linear domains at its C-terminus to anchor ferritin particles onto the autophagosome membrane (34). These two motifs exhibit a weak binding affinity for GATE16; however, acting together, they can achieve a higher degree of binding that allows NCOA4 to accurately distinguish between the inactive soluble state of LC3/GABA type A receptor-associated protein and the active conjugate at the membrane-bound ferritin complex, thus ensuring the precise delivery of the ferritin complex (35).

When NCOA4 expression is reduced, intracellular iron release becomes restricted, leading cells to increase iron uptake and sensing through the upregulation of transferrin receptor 1 (TfR1) and iron regulatory protein 1 (IRP1), reflecting a compensatory response to insufficient iron supply (36,37). Ferritinophagy is not constitutively active but is precisely regulated by intracellular iron levels, forming a dynamic negative feedback loop. Under iron-replete conditions, the E3 ubiquitin ligase HERC2 recognizes and binds NCOA4, mediating its K48-linked ubiquitination and subsequent degradation through the proteasomal pathway, thereby inhibiting ferritin degradation and limiting excessive iron release. In 2025, Liu *et al* (38) elucidated the underlying molecular mechanism of this regulatory process, revealing that NCOA4 senses intracellular iron levels by binding a [2Fe-2S] iron-sulfur cluster through its hybrid-binding domain (38). NCOA4 bound to the iron-sulfur cluster efficiently binds the cysteine-, proline- and histidine-rich domain and IRP2-binding domain of HERC2 through a bivalent mode, whereas NCOA4, lacking the cluster, binds HERC2 only weakly through a monovalent interaction. Consequently, under iron-deficient conditions, NCOA4 stability increases, promoting ferritin degradation and iron release, while, under iron-replete conditions, NCOA4 is efficiently degraded by HERC2, thereby inhibiting ferritinophagy to prevent iron overload (29,33). Meanwhile, the classical IRP1/IRP2-iron-responsive element (IRE) regulatory system also contributes to maintaining iron homeostasis, primarily by regulating ferritin synthesis. Under iron-deficient conditions, IRP1 binds to IREs and inhibits ferritin translation; by contrast, when intracellular iron levels increase, IRP2 is degraded through F-box and leucine-rich repeat protein 5-mediated pathways, thereby relieving the inhibition of ferritin translation (39-41) (Fig. 2). Collectively, NCOA4 specifically recognizes FTH1 through its C-terminal domain to achieve selective capture of ferritin, binds GATE16/LC3 through short linear motifs to complete targeted delivery of ferritin to the autophagic-lysosomal system and senses iron levels through its [2Fe-2S] cluster to form a negative feedback loop mediated by HERC2. The coordinated action of these mechanisms establishes NCOA4 as a central regulatory molecule in ferritinophagy. However, the recognition of ferritin by NCOA4 represents only the initiation phase of ferritinophagy and subsequent degradation still depends on the collaborative action of the autophagic execution machinery.

Molecular execution of ferritinophagy: Autophagosome formation and lysosomal degradation pathway. Following NCOA4-mediated cargo recognition, ferritin is routed through the canonical autophagy-lysosome pathway for degradation. The execution of ferritinophagy shares the core autophagic machinery with bulk autophagy, encompassing initiation, isolation membrane expansion, autophagosome closure and lysosomal fusion (Fig. 3). Autophagy initiation is governed by cellular energy status: Under nutrient-rich conditions, mTOR suppresses autophagy, whereas under energy stress, AMP-activated protein kinase (AMPK) activates the UNC-51-like kinase 1/2 (ULK1/2)-autophagy-related protein (ATG)-13-FAK family kinase-interacting protein

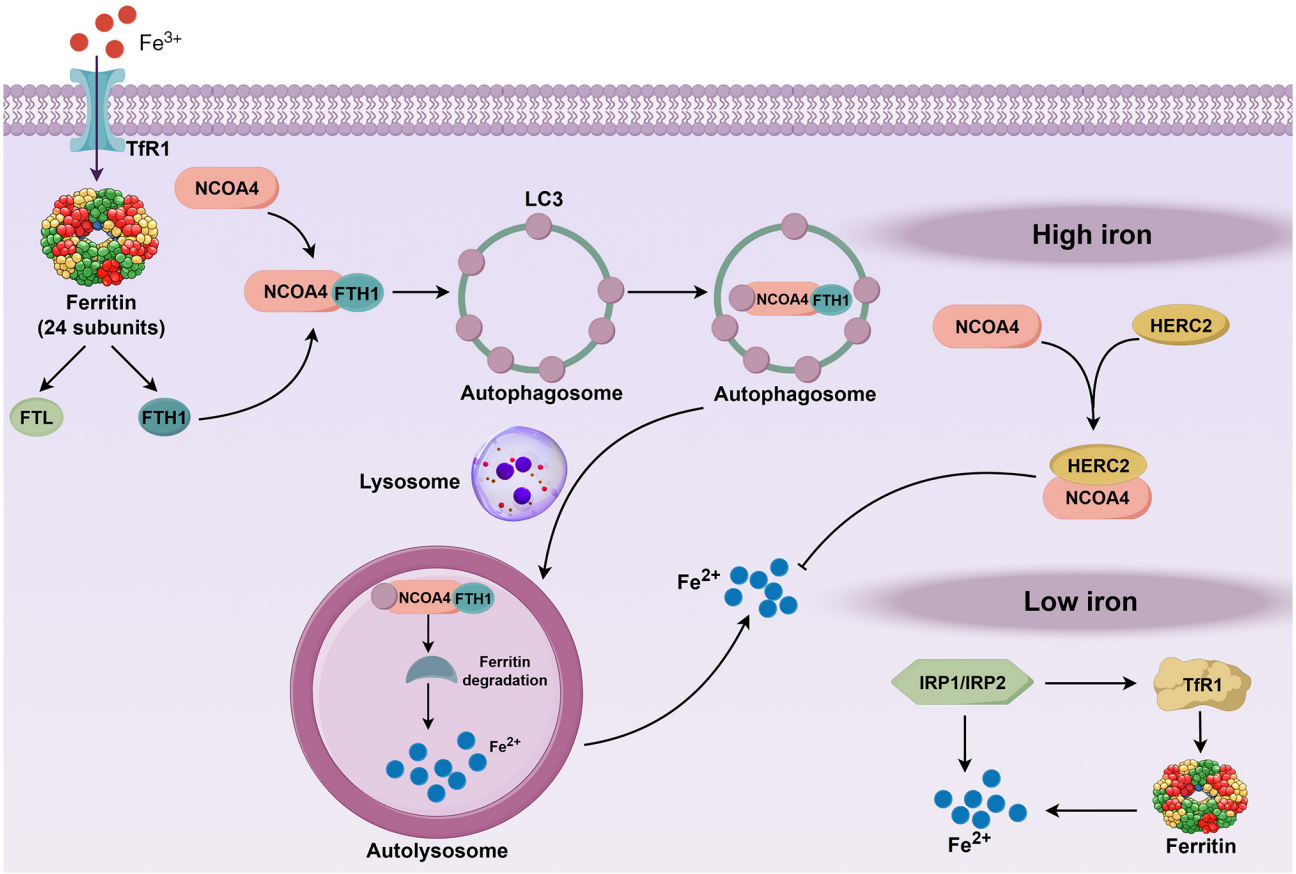


Figure 2. NCOA4-mediated ferritinophagy and its iron-dependent regulatory mechanisms. Schematic diagram summarizing the central role of ferritinophagy in iron storage, mobilization and recycling. NCOA4 acts as a selective autophagy receptor that recognizes ferritin and delivers it to autophagosomes, which subsequently fuse with lysosomes to complete degradation and release Fe^{2+} into the labile iron pool. This process is dynamically regulated by cellular iron status: Under iron-replete conditions, HERC2 promotes NCOA4 degradation, thereby suppressing ferritinophagy, whereas, under iron-deficient conditions, NCOA4 stability increases, while IRP1/IRP2 regulate the expression of TfR1 and ferritin to maintain iron homeostasis. Figure created using Figdraw (version 1.0; www.figdraw.com). NCOA4, nuclear receptor coactivator 4; IRP, iron regulatory protein; HERC2, HECT and RLD domain containing E3 ubiquitin protein ligase 2; TfR1, transferrin receptor 1; IRP, iron regulatory protein; FTH1, ferritin heavy chain 1; FTL, ferritin light chain.

of 200 kDa complex, which subsequently recruits the PI3K complex to generate phosphatidylinositol-3-phosphate, nucleating the isolation membrane and mediating lipid delivery to the autophagosomal membrane (42-47). Subsequently, the ATG5-ATG12-ATG16L complex facilitates LC3 lipidation to LC3-II, which anchors onto the autophagosomal membrane to drive its expansion and closure (48-53). ATG9 and ATG2 further contribute to membrane lipid transfer and expansion, thereby supporting autophagosome expansion and closure and ensuring the efficient engulfment of the NCOA4-ferritin complex for subsequent lysosomal degradation (54-57).

Once the NCOA4-ferritin complex has been loaded into the autophagosome, this matures and subsequently fuses with lysosomes to form autolysosomes. The autophagy adaptor protein p62/SQSTM1 participates in regulating NCOA4 and facilitates the localization of the complex to autophagosomes (58). The endosomal sorting complex required for transport (ESCRT) machinery subsequently mediates the closure of the autophagosomal membrane (59-61). In parallel, syntaxin 17 and synaptosomal-associated protein 29 interact with the lysosomal membrane proteins, vesicle-associated membrane protein 7/8 (VAMP7/8), to form the soluble N-ethylmaleimide-sensitive factor attachment protein receptor complex, thereby promoting fusion between autophagosomes and lysosomes (62-64). Ras-related protein Rab-7a (Rab7) further facilitates autophagosome maturation and lysosomal trafficking by recruiting effector proteins, such as WD repeat domain 91 and Rab-interacting lysosomal protein (65,66). Following the fusion of autophagosomes with lysosomes, the acidic lysosomal environment promotes ferritin degradation and iron release, thereby completing the execution stage of ferritinophagy (Fig. 3).

Regulatory network of ferritinophagy. Ferritinophilic degradation of ferroptosis regulation is regulated at the level of a set of fundamental elements to maintain iron balance in various states. Nuclear factor erythroid 2-related factor 2 (NRF2) is an antioxidant-response regulator promoting cells to defend against oxidative damage through the regulation of ferritinophagy. Previous research has indicated that NRF2 may enhance cell antioxidant-defense mechanisms through activation and stabilization of NCOA4, thus inducing ferritin degradation (67). Under conditions of oxidative stress or toxicity exposure, cells can dissociate NRF2 from Kelch-like ECH-associated protein 1 (Keap1), move into the nucleus and activate the expression of numerous antioxidant-associated genes, such as heme oxygenase-1, NAD(P)H quinone dehydrogenase 1 and glutamate-cysteine ligase modifier

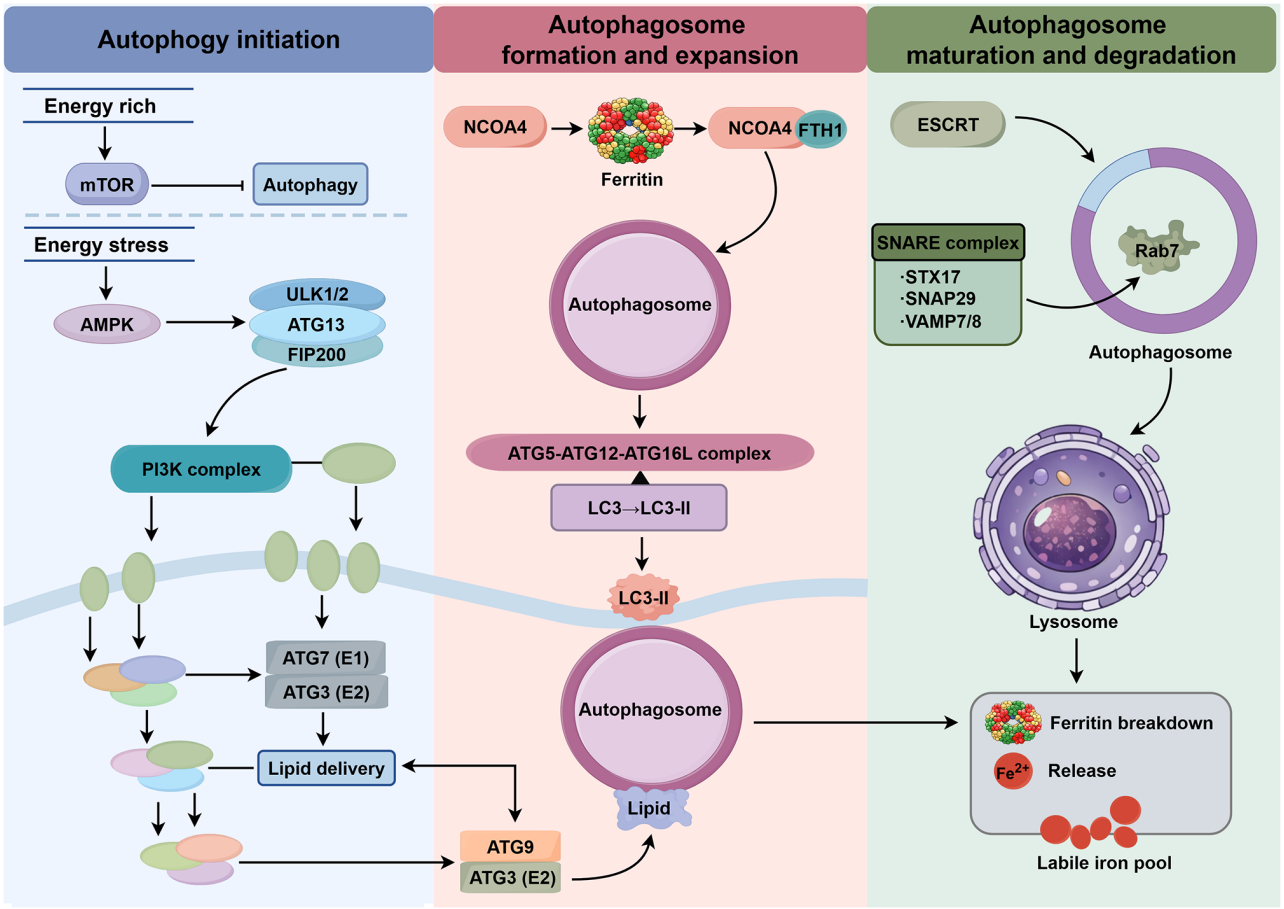


Figure 3. Molecular execution of ferritinophagy: Autophagy initiation, autophagosome formation and degradation. Ferritinophagy proceeds through the canonical autophagy pathway. Under nutrient-rich conditions, activation of mechanistic target of rapamycin suppresses autophagy. Under energy stress, AMPK activates the ULK1 complex to initiate autophagy, followed by activation of the PI3K and the LC3, which mediates the formation of an isolation membrane and the expansion of the autophagosome. NCOA4 loads ferritin into autophagosomes and mature autophagosomes subsequently fuse with lysosomes through the participation of Rab7 and SNAP receptor complexes. Ferritin is then degraded and Fe^{2+} is released, thereby completing intracellular iron turnover. Figure created using Figdraw (version 1.0; www.figdraw.com). AMPK, AMP-activated protein kinase; ULK1, UNC-51-like kinase 1; NCOA4, nuclear receptor coactivator 4; Rab7, Ras-related protein Rab-7a; SNAP, N-ethylmaleimide-sensitive factor attachment protein; ATG, autophagy-related protein; FTH1, ferritin heavy chain 1; FIP200, FAK family kinase-interacting protein of 200 kDa; ESCRT, endosomal sorting complex required for transport; STX, syntaxin 17; VAMP, vesicle-associated membrane protein.

subunit (68-71). This transcriptional activation not only improves the antioxidant capacity of cells, but also inhibits the stability of NCOA4, inhibits ferritin degradation and releases fewer free iron ions, thus reducing the risk of iron overload and ferroptosis and stabilizing cellular redox state and iron homeostasis. Anandhan *et al* (72) found that NRF2 regulates ferritinophagy through HERC2 and VAMP8, with HERC2 participating in NCOA4 degradation and VAMP8 involved in autophagosome-lysosome fusion (72).

Complementary to the action of NRF2, hypoxia-inducible factor 1 (HIF-1) also serves a central role in ferritinophagy, particularly under hypoxic conditions. Previous studies have shown that, under hypoxia, HIF-1 influences ferritinophagy by regulating NCOA4 expression: Enhanced stability of HIF-1 increases NCOA4 mRNA levels, promoting ferritin degradation and iron release (10,73). Furthermore, HIF-1α and HIF-2α bind to hypoxia response elements (HREs) in the NCOA4 promoter, further enhancing NCOA4 transcription, leading to markedly increased ferritinophagy and iron release (74). Through this mechanism, HIF-1 promotes ferritin degradation and iron release under hypoxic conditions to support cellular energy metabolism and other physiological processes, such as erythropoiesis, mitochondrial respiration and DNA synthesis (75). In addition to influencing the levels of NCOA4, HIF-1 can affect iron uptake or storage in cells through modulation of cell-level changes in intracellular iron balance. Hypoxia-stimulated expression of HIF-1 causes ferritin degradation in order to release more iron ions for cellular utilization as an energy source. HIF-1 and NRF2 may interact to regulate iron use inside cells under low-oxygen environments to keep the homeostasis of the cell.

In addition to NRF2 and HIF-1, it has been reported that the JNK/Jun proto-oncogene (c-Jun) signalling pathway directly modulates NCOA4 transcription. JNK, one of the members of the MAPK family, is activated upon various stimulatory factors, including oxidative stress, inflammatory cytokines and iron overload. Activated JNK phosphorylates c-Jun at Ser63 and Ser73 to promote its nuclear transfer. Therefore, it enhances the transcriptional activity of c-Jun. Nuclear-localized activated c-Jun specifically binds to activator protein-1-binding sites in the NCOA4 promoter region and activates transcription by increasing the expression of

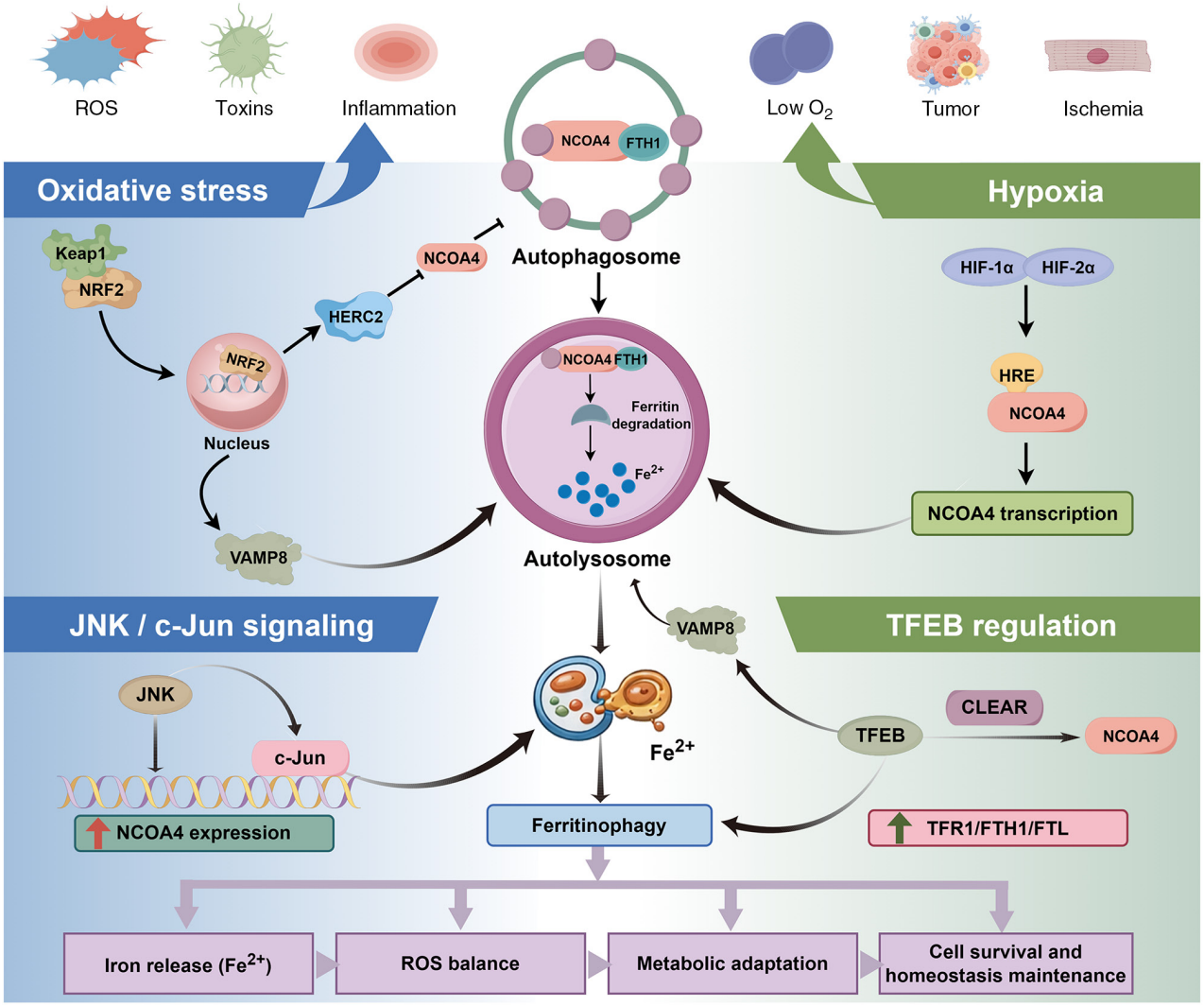


Figure 4. Regulatory network of ferritinophagy under oxidative stress, hypoxia and stress-responsive signaling pathways. Under oxidative stress, NRF2 dissociates from Keap1 and translocates into the nucleus, where it attenuates ferritinophagy by reducing NCOA4 stability through HERC2-mediated degradation and by regulating autophagosome-lysosome fusion through VAMP8. By contrast, hypoxia stabilizes HIF-1α and HIF-2α, which bind to hypoxia response elements in the NCOA4 promoter, thereby enhancing NCOA4 transcription and promoting ferritin degradation and iron release. The JNK/c-Jun signaling pathway further induces NCOA4 expression through activator protein-1-dependent transcriptional activation. In addition, TFEB, a master regulator of the autophagy-lysosome system, promotes ferritinophagy by transcriptionally activating NCOA4 and iron metabolism-associated genes (TfR1, FTH1 and FTL), while facilitating autophagosome-lysosome fusion through VAMP8. These coordinated regulatory mechanisms converge on NCOA4-mediated ferritin degradation within autolysosomes, leading to controlled Fe^{2+} release and maintenance of intracellular iron homeostasis. Figure created using Figdraw (version 1.0; www.figdraw.com). NRF2, nuclear factor erythroid 2-related factor 2; VAMP, vesicle-associated membrane protein; HIF, hypoxia-inducible factor; HRE, hypoxia response element; CLEAR, coordinated lysosomal expression and regulation; NCOA4, nuclear receptor coactivator 4; ROS, reactive oxygen species; HERC2, HECT and RLD domain containing E3 ubiquitin protein ligase 2; Keap1, Kelch-like ECH-associated protein 1; TFEB, transcription factor EB; TfR1, transferrin receptor 1; FTH1, ferritin heavy chain; FTL, ferritin light chain.

NCOA4, thus elevating ferritinophagy-associated proteins, such as LC3-II and p62/SQSTM1 (76). As shown by this regulatory axis in numerous disease types, including osteoarthritis, under light-induced retinal degeneration conditions, all-trans-retinal activates the JNK/c-Jun signalling pathway to promote NCOA4 expression and then triggers ferroptosis through ferritinophagy-mediated mechanisms (77). In osteoarthritic chondrocytes, the JNK inhibitor SP600125 can block c-Jun phosphorylation to reduce NCOA4 expression, which reduces the ferroptosis-induced degradation of the ECM (78,79).

Furthermore, the MiT/TFE family transcription factor transcription factor EB (TFEB) has also been shown to participate in ferritinophagy regulation. TFEB is a master transcriptional regulator of the autophagy-lysosome pathway and serves a key role in lysosomal biogenesis and autophagic flux regulation. TFEB participates in ferritinophagy regulation through multiple mechanisms: It directly binds to coordinated lysosomal expression and regulation elements in the NCOA4 promoter region to upregulate NCOA4 transcription. Simultaneously, TFEB transcriptionally activates iron metabolism-related genes such as TfR1, FTH1 and FTL, promoting autophagosome-lysosome fusion by regulating vesicle-associated membrane protein 8 (VAMP8) expression, thereby ensuring the smooth completion of the ferritinophagy process (80-82) (Fig. 4). Notably, TFEB exerts fine-tuned balancing regulation in iron metabolism: On the one hand, it promotes ferritin degradation through NCOA4 upregulation

to release iron ions, whereas, on the other hand, it enhances transferrin-mediated iron uptake by upregulating TfR1 and promoting lysosomal iron storage, while simultaneously increasing ferritin synthesis to safely store excess iron ions, collectively maintaining the intracellular LIP at a low level.

In summary, NRF2 and HIF-1 serve central roles through transcriptional regulation under oxidative stress and hypoxic conditions, whereas JNK/c-Jun and TFEB complement the transcriptional regulatory network of ferritinophagy with regard to stress signal response and autophagy-lysosomal regulation. These multi-layered regulatory mechanisms coordinate with one another to collectively maintain iron homeostasis under numerous physiological conditions and to ensure normal cellular metabolic activities.

3. Role of ferritinophagy in fibrosis

Molecular mechanisms of fibrosis

Tissue injury and aberrant repair responses. Fibrosis is a slowly progressive disease that ultimately leads to tissue degeneration and can have marked consequences in multiple organs, including the heart, lung, liver, kidney and skin (83). It is characterized by excessive accumulation of fibrous connective tissue within ECM regions of damaged tissues, with collagen (particularly type I and III collagen) being the key component of fibrotic scar tissue. As the disease progresses, tissues remain in a persistent state of abnormal repair, ultimately resulting in disruption of organ architecture and functional impairment (84). Tissue injury activates both the innate and adaptive immune systems and modulates the magnitude and direction of inflammatory responses (85). When injurious stimuli such as chronic inflammation, hypoxia, oxidative stress or metabolic abnormalities persist, the repair program shifts towards pathological fibrotic remodeling (14,86), during which inflammatory cells release profibrotic mediators and cytokines that interact with oxidative stress and other factors, initiating fibroblast activation and driving sustained fibrotic progression (87,88).

Fibroblast activation and myofibroblast formation. During the process of fibrosis, due to differentiation, myofibroblast cells exhibit increased secretion ability, contraction force and ECM production (86). Previous single-cell sequencing studies have shown that myofibroblasts display a markedly diverse gene-expression pattern and evolve dynamically in the context of fibrosis across numerous organ types (89,90). The differentiation trajectories of fibroblasts vary across organs: In pulmonary fibrosis, the differentiation paths of mesenchymal cells differ markedly between normal and fibrotic states (91), while in the liver, hepatic stellate cells (HSCs) serve as the principal pro-fibrotic cell type (92,93). Notably, myofibroblasts can arise from fibroblasts in other parts of the body. Immune cell contributions, epithelial-mesenchymal transition (EMT) and endothelial-mesenchymal transition-induced EMT, have also been found to increase the number of myofibroblasts and further cause their activation (94). In particular, although inhibiting the proliferation and activation of myofibroblasts is considered a core approach for antifibrosis treatment, myofibroblasts develop resistance to apoptosis during differentiation as they mature into fibroblasts, which limits the effects of programmed-cell-death pathways and may explain why strategies targeting a reduced number of myofibroblasts fail alone (95).

Canonical and non-canonical TGF-β signaling pathways. During sustained activation of myofibroblasts, numerous signaling pathways participate in the regulation of fibrotic responses, among which TGF-β signaling is widely regarded as the central molecular axis driving fibrosis progression. TGF-β promotes fibrotic responses through both canonical and non-canonical signaling pathways (96).

In the canonical Smad signaling pathway, TGF-β first binds to the TGF-β type II receptor (TGFBR2) on the cell membrane, inducing the recruitment and phosphorylation of the TGF-β type I receptor (TGFBR1). Activated TGFBR1 subsequently phosphorylates Smad2 and Smad3, which form a complex with Smad4 and translocate into the nucleus to initiate the transcription of pro-fibrotic target genes such as collagens and α-smooth muscle actin (α-SMA) (97,98). Smad7 functions as a key negative feedback regulator by competitively binding to TGFBR1 and recruiting ubiquitin ligases to promote TGFBR1 degradation, thereby terminating signal transduction (99-101).

In addition to the classical Smad axis, TGF-β can also activate a number of non-canonical signaling pathways that are independent of Smad protein phosphorylation and synergistically promote fibrotic responses through other signal transduction routes (102). Among these, the PI3K/Akt pathway promotes fibroblast survival and myofibroblast transformation (103,104), while the MAPK pathway regulates fibroblast proliferation and migration (105,106) and the Janus kinase (JAK)/STAT pathway enhances inflammatory cytokine release and myofibroblast differentiation (107,108) (Fig. 5). In summary, TGF-β directly initiates pro-fibrotic gene transcription through the canonical Smad pathway while synergistically enhancing fibroblast activation, proliferation and survival through non-canonical pathways such as PI3K/Akt, MAPK and JAK/STAT, thereby forming a multi-dimensional, positive-feedback pro-fibrotic signaling network.

Oxidative stress and the TGF-β positive feedback loop. Previous research has identified an oxidative stress-induced pathogenesis that leads to fibrotic conditions through certain mechanisms. ROS is not only the downstream effector of TGF-β to stimulate fibroblast proliferation, but latent forms of TGF-β are also activated and form an additive-positive-feedback cycle that promotes persistent growth of fibrotic tissues. TGF-β-induced oxidative stress primarily arises from the activation of the NADPH oxidase (Nox) family. Among these, NADPH oxidase 4 (Nox4) has been found to be key in initiating such processes (109,110). TGF-β1 stimulation can greatly enhance the level of Nox4 expression in fibroblasts. Furthermore, it also produces hydrogen peroxide by oxidizing this receptor through reversible oxidation of its cysteine residue to modulate pathways subsequently (111). Previous research has shown that TGF-β1 treatment can enhance the expression of Nox4 and α-SMA in primary human cardiac fibroblasts. On the other hand, after removing Nox4 from fibroblasts, a decrease in TGF-β1-triggered α-SMA production is observed, indicating that ROS serves as a mediator for this change (112).

ROS-TGF-β bidirectionally regulated the expression of target genes through a positive-feedback regulatory loop to sustain fibrotic damage: On the one hand, TGF-β can stimulate

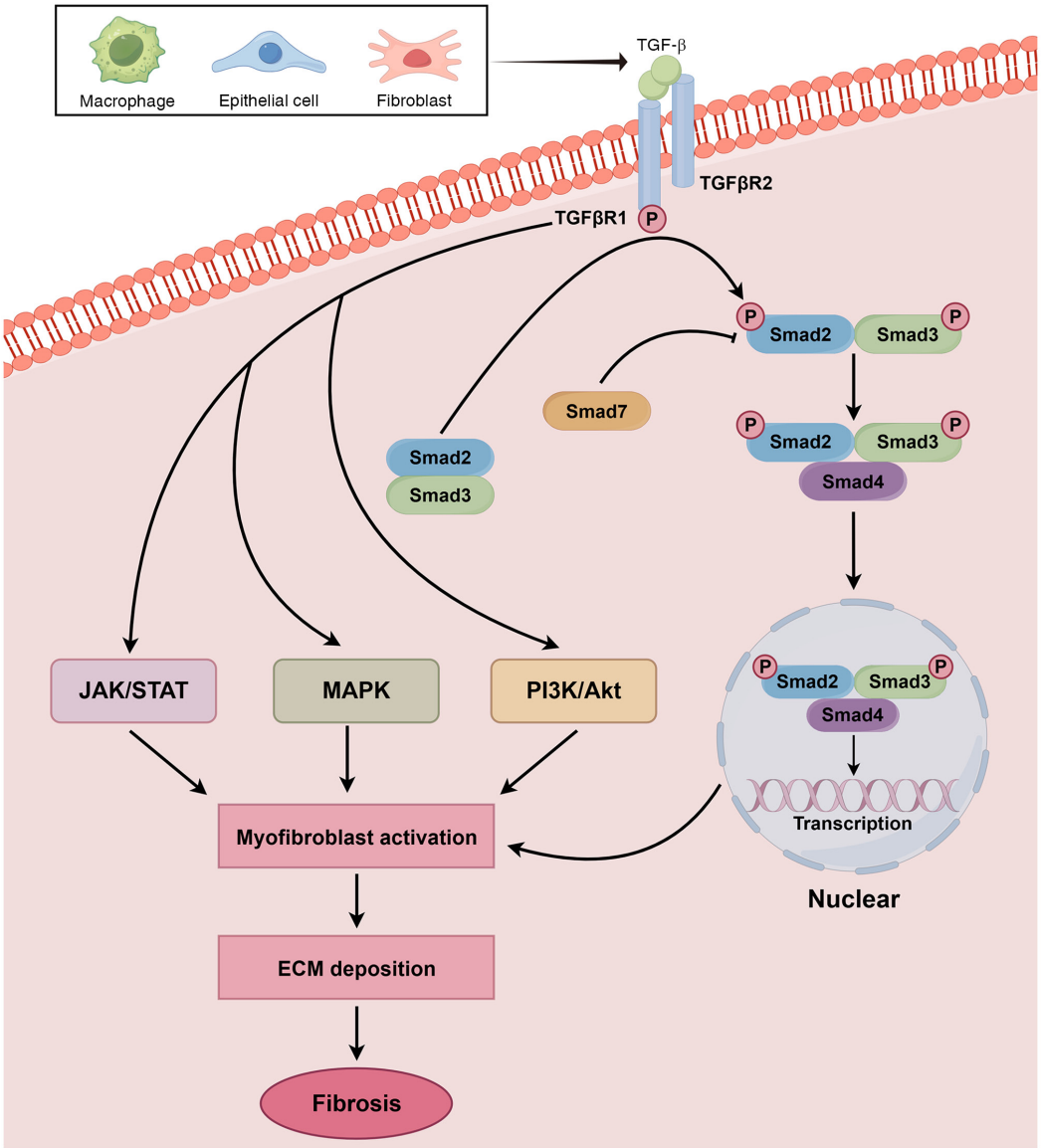


Figure 5. Central regulatory mechanisms of TGF-β signaling in fibrosis. Schematic summarizing the central regulatory role of the TGF-β signaling network in fibrotic processes. TGF-β can be secreted by multiple cell types, including macrophages, epithelial cells and fibroblasts and activates downstream signaling through binding to the TGF-βR2/TGF-βR1 receptor complex. In the canonical pathway, phosphorylation of Smad2/3 enables the formation of a complex with Smad4 that translocates into the nucleus to induce the transcription of profibrotic genes, whereas Smad7 functions as a negative regulator of this pathway. Meanwhile, TGF-β can also activate non-canonical signaling pathways such as PI3K/Akt, MAPK and JAK/STAT, which collectively promote fibroblast activation, myofibroblast differentiation and deposition of collagen and ECM, ultimately leading to fibrosis. Figure created using Figdraw (version 1.0; www.figdraw.com). JAK, Janus kinase; ECM, extracellular matrix.

the expression of ROS production through Nox4 and inhibit antioxidant defense systems to disrupt the balance of intracellular redox potential (113). On the other hand, ROS is also activated by several pathways to release latent TGF-β. ROS can directly oxidize the cysteine residues in the latency-associated peptide (LAP) of the latent TGF-β complex to form a conformational change and release free TGF-β. Alternatively, ROS activates MMPs and promotes TGF-β activity through a proteolytic pathway (114). In addition, ROS can activate non-canonically activated TGF-β signal transduction pathways through the activation of MAPK and PI3K/Akt to regulate the transcriptional activity of TGF-β1 (115). The positive feedback mechanism continuously strengthens the fibrotic signal in the local microenvironment and may become self-perpetuating even in the absence of continued stimulation.

Collectively, this ROS-TGF-β feedforward loop constitutes a self-reinforcing network that sustains fibrotic signaling and ECM deposition. Since ferritinophagy directly modulates Fe^{2+}-driven ROS generation through NCOA4-mediated ferritin degradation, this loop provides a direct molecular entry point for ferritinophagy into the fibrotic regulatory network. By tuning the LIP, ferritinophagy influences the intensity of this ROS-TGF-β loop, exerting bidirectional effects depending on cell type and disease stage, which will be systematically discussed in subsequent sections with organ-specific evidence.

Molecular mechanisms linking fibrosis and ferritinophagy. Existing evidence has suggested that dysregulated iron metabolism and iron deposition are common features within the fibrotic microenvironment across numerous organs. As a

key intracellular pathway responsible for mobilizing stored iron, ferritinophagy may expand the LIP and amplify oxidative stress, thereby coordinating inflammatory responses and profibrotic signaling networks to promote ECM deposition and tissue remodeling (116,117).

Iron dyshomeostasis and formation of a fibrotic microenvironment. Disruption of iron homeostasis in fibrotic tissues typically presents as increased iron accumulation, abnormal expression of iron transport-associated genes or proteins and elevated concentrations of free iron. Collectively, these changes lead to an increase in the volume of labile iron inside cells (116,118). In conditions of iron overloading, Fe^{2+} serves as a substrate in the Fenton reaction to generate ROS continuously through oxidation (119). Persistent oxidative stress is considered a key feature of the fibrotic microenvironment and can interact with inflammatory responses, causing activation of TGF-β/SMAD signaling and fibroblast activation, thus ultimately driving excessive ECM deposition (117,118).

With regard to pathological circuits, parenchymal cells are more susceptible to injury and death under conditions of disrupted iron metabolism and oxidative stress. Chronic injury and persistent inflammation provide long-term stimuli that promote fibrosis. Dampened by damaged parenchymal cells releasing damage-associated molecular patterns (DAMPs) that activate immune cells and promote the release of profibrotic mediators to accelerate fibrosis development. For example, in liver fibrosis, long-term hepatic injury causes the release of DAMPs and ROS by hepatocytes, which activates Kupffer cells, leading to increased production of profibrotic mediators such as TGF-β and platelet-derived growth factor and thus promotes the activation state of HSCs and excessive deposition of ECM (120,121). Therefore, iron dyshomeostasis can be considered one of its early components. It increases oxidative stress and induces a strong cellular stress response, triggering an inflammatory reaction and pro-fibrogenic signaling pathways to maintain a persistent amplification state and create conditions for iron-related autophagy processes within the system of fibrotic regulation network (122). Given these circumstances, whether cells can mobilize available iron stores to form a more stable LIP to alleviate prolonged oxidative damage needs to be evaluated. Ferritinophagy functions as one such execution mechanism (123).

NCOA4-mediated ferritinophagy regulates oxidative stress. The core mechanism of ferritinophagy involves NCOA4-mediated selective autophagic degradation of ferritin. NCOA4 binds to the FTH1 and delivers ferritin to autophagosomes, where it is subsequently degraded in lysosomes to release Fe^{2+} (124). Once released into the LIP, Fe^{2+} can generate hydroxyl radicals through the Fenton reaction and enhance lipid peroxidation, thereby demonstrating an association between ferritin turnover and oxidative damage at the molecular level (117,125).

In the context of stress associated with fibrosis, this process is particularly important given that ferritinophagy directly influences the size of the LIP. Expansion of the LIP increases the probability of iron-dependent ROS generation, transforming oxidative stress from a transient event into a more sustained state and thereby providing continuous driving forces for inflammatory responses and tissue remodeling. In addition, previous studies have indicated that ferritinophagy activity is dynamically regulated by cellular iron status and exhibits cross-regulation with mTOR signaling, core autophagy proteins and the NRF2 antioxidant axis (43,58,72). Notably, the role of autophagy itself in fibrosis remains controversial, with evidence supporting both pro-fibrotic (such as autophagy-driven epithelial injury in the kidney) and anti-fibrotic (such as autophagy-mediated hepatocyte protection) functions, largely depending on cell type and tissue context. These findings suggest that the influence of ferritinophagy on oxidative stress is not fixed but rather depends on the cellular iron load and stress regulatory status (72,126). This provides a framework for understanding how ferritinophagy-mediated ferroptosis may be either detrimental or protective.

Bidirectional regulation between ferritinophagy and TGF-β signaling. Within the fibrotic signaling network, activation of TGF-β signaling and the differentiation of fibroblasts into myofibroblasts represent one of the classical central axes. Existing studies have indicated that enhanced ferritinophagy promotes Fe^{2+} release and increases ROS levels. ROS subsequently activates TGF-β signaling pathways, thereby inducing fibroblast activation, collagen deposition and fibrotic progression, establishing a close connection between iron homeostasis dysregulation and classical profibrotic signaling networks (117,119,124).

Meanwhile, the NRF2-mediated antioxidant pathway serves a key balancing role within this regulatory network. The NRF2 antioxidant pathway counteracts this ROS-TGF-β loop by limiting labile iron expansion and attenuating TGF-β signaling activation (72,126,127). Consequently, NRF2 signaling activity is considered an important determinant of the functional direction of ferritinophagy, as its regulatory status determines whether ferritinophagy tends to amplify tissue injury or maintain redox homeostasis.

Conversely, chronic inflammation and persistent oxidative stress within the fibrotic microenvironment may also regulate autophagy and iron metabolic reprogramming. DAMPs released from injured cells enhance immune responses and stimulate TGF-β expression, accelerating ECM deposition and causing ferritinophagy to exert different effects at distinct stages of disease progression (117). During the early stage of injury, excessive ferritinophagy in parenchymal cells amplifies tissue injury and profibrotic transformation through ROS and TGF-β signaling. By contrast, during chronic stages, induction of iron-dependent cell death in activated fibroblast populations may reduce the number of pathological ECM-producing cells and thereby limit fibrotic progression (121,124). Collectively, the association between ferritinophagy and TGF-β signaling is not a simple linear pathway but rather a bidirectionally coupled regulatory module within the inflammatory and oxidative stress network that is modulated by the NRF2 antioxidant axis.

Ferritinophagy participates in cell fate determination. By modulating the LIP and redox status, ferritinophagy reshapes the cellular fate decision network and exerts bidirectional effects within the fibrotic microenvironment. In parenchymal cells (such as epithelial cells, renal tubular epithelial cells, cardiomyocytes and hepatocytes), enhanced ferritinophagy leads to elevated Fe^{2+} levels and ROS generation, predisposing cells to oxidative damage and cell death (123,128). Damaged or dying cells release DAMPs and pro-inflammatory factors,

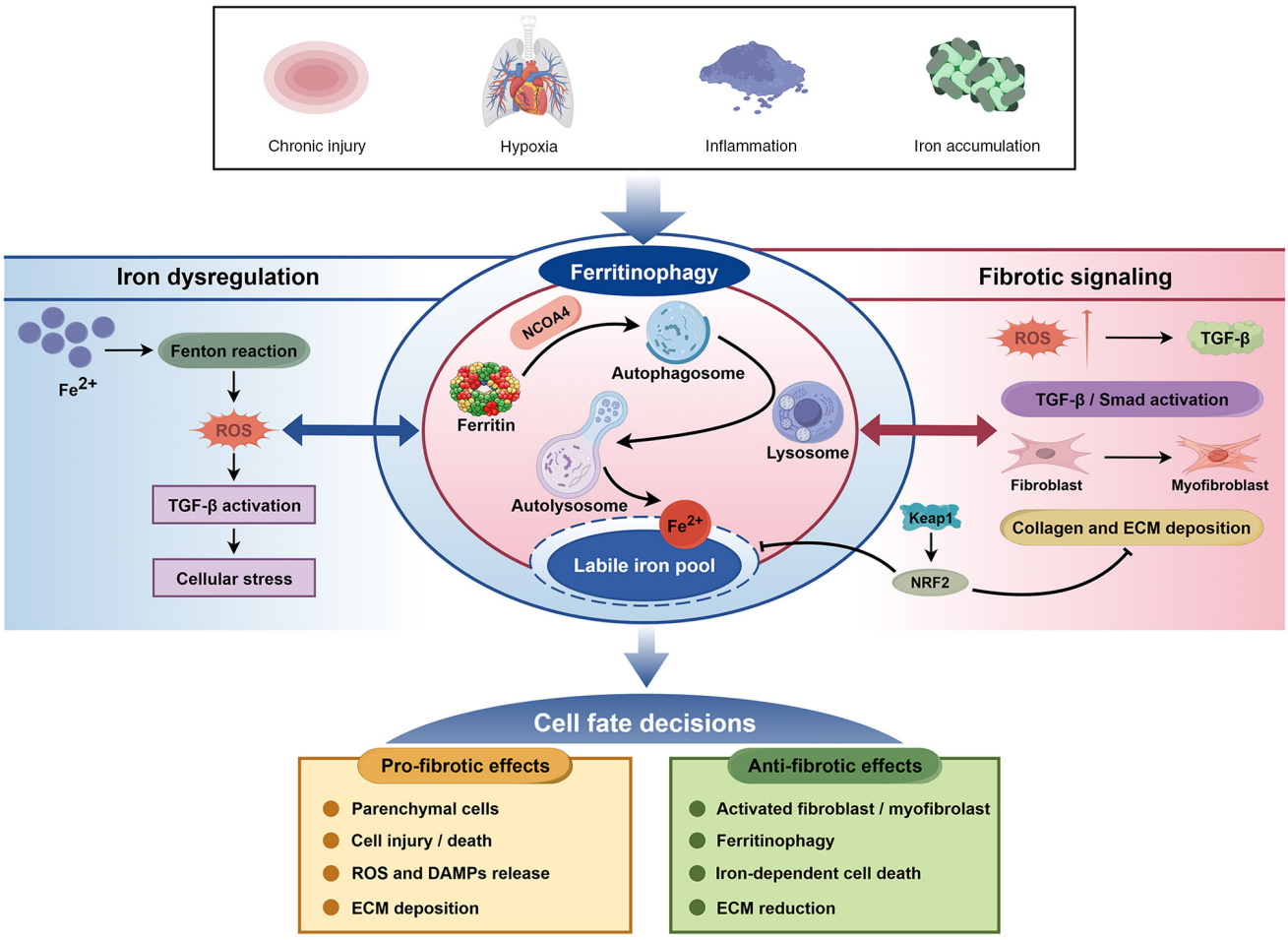


Figure 6. Integrated mechanism by which ferritinophagy participates in fibrotic progression. Chronic injury, hypoxia, inflammation and iron deposition collectively promote ferritinophagy activation, leading to the release of Fe^{2+}, enhanced ROS generation and activation of TGF-β signaling, thereby aggravating tissue injury and ECM deposition while interacting with the NRF2 antioxidant axis. In addition, ferritinophagy exhibits cell-type-and stage-dependent bidirectional regulatory effects during fibrosis. On the one hand, in parenchymal cells, it exacerbates oxidative injury, cell death, damage-associated molecular pattern release and ECM deposition, thereby promoting fibrotic progression. On the other hand, in activated fibroblasts and myofibroblasts, iron-dependent cell death may reduce pathological matrix-producing cells and thus exert potential antifibrotic effects. Figure created using Figdraw (version 1.0; www.figdraw.com). ECM, extracellular matrix; NCOA4, nuclear receptor coactivator 4; ROS, reactive oxygen species; NRF2, nuclear factor erythroid 2-related factor 2; Keap1, Kelch-like ECH-associated protein 1; DAMP, damage-associated molecular pattern.

such as interleukin (IL)-1β, IL-6 and tumor necrosis factor-α, which activate immune cells and amplify profibrotic signals, thereby promoting fibroblast activation and ECM deposition (117).

Conversely, in activated fibroblasts and myofibroblasts (which are the primary cellular sources of ECM), ferritinophagy-associated iron-dependent cell death may exert a potential antifibrotic effect by reducing the number of effector cells that continuously produce ECM (129,130). Emerging evidence has suggested that different cell types exhibit markedly distinct responses to alterations in iron homeostasis: Enhanced ferritinophagy tends to exacerbate injury and inflammation in parenchymal cells, whereas, in overactivated fibroblast populations, it may facilitate pathological cell clearance, thereby limiting the progression of fibrosis (127) (Fig. 6). Thus, the role of ferritinophagy in fibrosis is not unidirectional but exhibits clear cell type- and disease stage-dependent characteristics. Its overall impact on the fibrotic process depends on the target cell type, the stage of the disease and the dynamic balance between oxidative stress levels and antioxidant regulatory networks.

Current evidence, limitations and controversies in ferritinophagy-mediated fibrosis. Although increasing evidence (117,121,124) has indicated that ferritinophagy is closely associated with fibrotic progression, whether ferritinophagy represents a direct driver of fibrosis or a secondary response to tissue injury remains incompletely understood (131). The majority of previous studies have demonstrated alterations in NCOA4 expression, ferritin degradation, iron accumulation or ferroptosis-associated markers during fibrosis; however, the causal contribution of ferritinophagy itself requires further validation (132).

The biological outcomes of ferritinophagy are notably context dependent. In parenchymal cells, excessive ferritinophagy promotes iron release, oxidative stress and ferroptotic injury, thus accelerating fibrotic remodeling. In activated fibroblasts, however, sustained ferritinophagy may increase ferroptotic vulnerability and limit pathological ECM deposition (133). To reconcile these opposing effects, three-tiered framework can be proposed: i) Tier I: Stress sensing, wherein hypoxia, oxidative stress and inflammation converge on HIF-1α, NRF2 and TFEB to regulate NCOA4; ii) tier II:

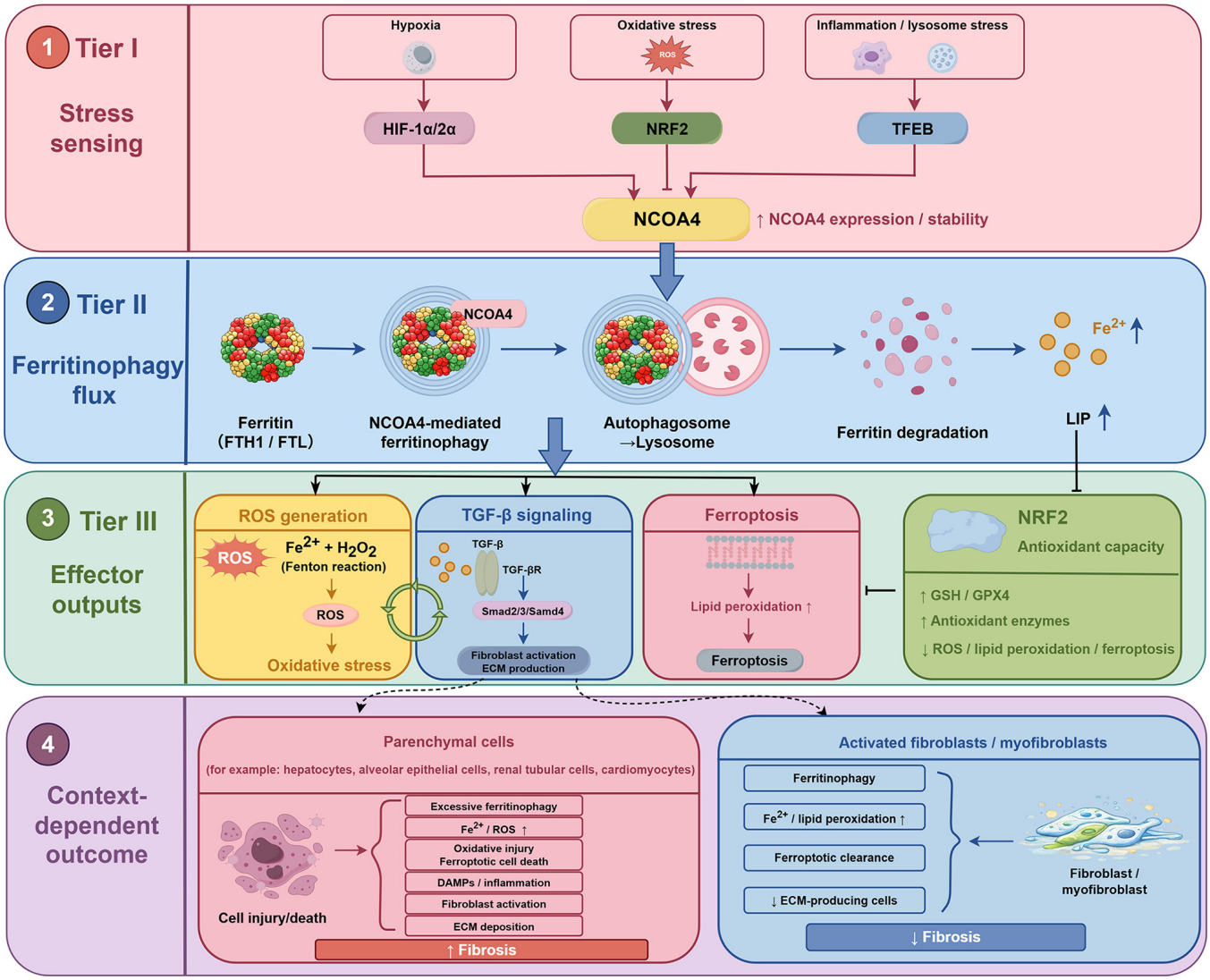


Figure 7. Integrated mechanistic framework linking ferritinophagy to ferroptosis and fibrotic remodeling. Tier I: Upstream stress signals (hypoxia, oxidative stress and inflammation) converge on HIF-1α, NRF2 and TFEB to regulate NCOA4 expression and stability. Tier II: NCOA4 mediates ferritin delivery to the autophagy-lysosome system, releasing Fe^{2+} into the LIP. Tier III: Increased iron availability drives ROS generation, TGF-β activation and ferroptosis, with the net outcome determined by cellular antioxidant capacity (including NRF2 and GSH/GPX4). Tier IV: Cell type- and disease stage-dependent effects determine the final fibrotic outcome. Arrows (↑ and ↓) indicate upregulation and downregulation, respectively. Figure created using Figdraw (version 1.0; www.figdraw.com). HIF, hypoxia-inducible factor; ROS, reactive oxygen species; NRF2, nuclear factor erythroid 2-related factor 2; TFEB, transcription factor EB; NCOA4, nuclear receptor coactivator 4; ferritin heavy chain; FTL, ferritin light chain; LIP, labile iron pool; ECM, extracellular matri; GSH, glutathione; GPX4, glutathione peroxidase 4; DAMP, damage-associated molecular pattern.

Ferritinophagy flux, releasing Fe^{2+} into the LIP; and iii) tier III: Effector outputs, driving ROS generation, TGF-β activation and ferroptosis, with net outcome determined by cellular antioxidant capacity (Fig. 7). Notably, nearly all current evidence derives from experimental models, whereas clinical data from human fibrosis remain scarce. Whether ferritinophagy operates similarly in human disease awaits investigation using patient-derived samples, spatial transcriptomics and cell-type-specific genetic approaches.

4. Role of ferritinophagy in organ-specific fibrotic diseases

Pulmonary fibrosis. In pulmonary fibrosis, particularly idiopathic pulmonary fibrosis, iron deposition and iron metabolic reprogramming are considered important contributors to sustained tissue injury (134,135). Based on current evidence, ferritinophagy is not just involved in maintaining iron homeostasis but may participate in pulmonary fibrotic remodeling by regulating intracellular iron availability. NCOA4-mediated ferritinophagy promotes ferritin degradation, releasing Fe^{2+}, expanding the LIP and enhancing lipid peroxidation, thereby rendering alveolar epithelial cells more susceptible to oxidative damage and iron-dependent cell death. Experimental inhibition of NCOA4 expression or ferritinophagy activity has been reported to reduce epithelial cell death and collagen deposition in fibrotic lung models, supporting a pathogenic role for excessive ferritinophagy-associated iron mobilization in pulmonary fibrosis (136,137). Epithelial injury further triggers inflammatory responses and amplifies TGF-β signaling, driving persistent fibroblast ECM deposition (123,135,138). Collectively, pulmonary fibrosis can be understood as a metabolic dysregulation state in which ferritinophagy represents an

important regulatory mechanism associating iron dyshomeostasis with inflammatory amplification and fibrotic remodeling. However, whether ferritinophagy acts as an initiating driver of pulmonary fibrosis or functions primarily as an amplifier of established injury responses remains to be fully elucidated. Therapeutically, recent studies are shifting from targeting terminal fibrotic responses toward modulating upstream metabolic events associated with ferritinophagy. Reducing labile iron levels or inhibiting lipid peroxidation alleviates pulmonary fibrosis in experimental models, suggesting that interventions targeting ferritinophagy-mediated iron release may have potential value (135,139). Importantly, ferritinophagy exhibits marked cell context dependence. In alveolar epithelial cells, its enhancement often promotes injury progression, whereas moderate induction of iron-dependent death in activated fibroblasts may limit pathological matrix accumulation (140). Therefore, the key to future antifibrotic strategies lies not in simply inhibiting or activating ferritinophagy, but in achieving cell-type and disease stage specific precision regulation. Based on this perspective, ferritinophagy is more likely to function as a regulatory node in antifibrotic therapy rather than as a single therapeutic target.

Renal fibrosis. Renal fibrosis typically arises during the progression of chronic kidney injury, with key pathological events including prolonged exposure of renal tubular epithelial cells to oxidative stress and inflammatory stimuli, leading to a profibrotic phenotype. Previous research has shown that chronic kidney injury is accompanied by notable iron metabolism dysregulation and intracellular iron overload, with elevated labile iron levels contributing to sustained tissue injury (141). Ferritinophagy, through NCOA4-mediated ferritin degradation and Fe^{2+} release, may continually expand the LIP, thereby enhancing lipid peroxidation, inflammatory responses, mitochondrial dysfunction and metabolic reprogramming (142,143). During this process, injured renal tubular epithelial cells become a persistent source of proinflammatory and profibrotic signals, driving the activation of interstitial fibroblasts and ECM deposition. However, whether ferritinophagy directly mediates renal fibrogenesis or represents a secondary response to chronic kidney injury remains to be clarified. Ferritinophagy may therefore represent a potential association between iron dysregulation and renal fibrotic progression (144,145).

Given the important function of labile iron in maintaining oxidative stress, recently, there have been numerous studies (142,143,145) regarding modulating renal fibrosis by intervening in iron metabolism. Regulating iron metabolism may alleviate tubular injury and interstitial fibrosis, although the specific contribution of ferritinophagy modulation remains incompletely understood (141). Current perspectives emphasize fine-tuning ferritinophagy activity rather than completely inhibiting it, aiming to maintain iron availability while preventing excessive oxidative damage (143,145,146). Further research is needed to study the functional transformation of ferritinophagy in different renal cells and stages of disease to provide a theoretical basis for stage-specific intervention.

Hepatic fibrosis. Hepatic fibrosis is an injury- driven chronic pathological process that features persistent inflammation, oxidative stress and the activation of HSCs and results in ECM accumulation. Dysregulated iron metabolism exists in numerous etiologies of liver fibrosis and the extent of hepatic iron deposition is closely associated with the severity of fibrosis (147-149). Ferritinophagy, through NCOA4-mediated selective ferritin degradation and Fe^{2+} release into the LIP, represents a key mechanism regulating hepatic labile iron levels. Enhanced ferritinophagy increases Fe^{2+} availability and promotes the Fenton reaction, which produces ROS and causes lipid peroxidation, further activating the TGF-β/Smad pathway to drive HSCs into the myofibroblast phenotype (150,151). Simultaneously, iron-dependent oxidative damage kills hepatocytes and releases inflammatory mediators that stimulate Kupffer cells, creating an ongoing pro-fibrotic microenvironment. However, whether this iron release oxidative stress inflammation amplification cascade is directly controlled by ferritinophagy remains unclear. Ferritinophagy may therefore represent a potential metabolic regulator linking iron dyshomeostasis and hepatic fibrosis progression, although direct causal evidence remains limited (152).

Ferritinophagy during hepatic fibrosis has a marked cell-type specificity. In hepatocytes, ferritinophagy-mediated increase of labile iron enhances oxidative injury and inflammation, which leads to fibrosis. In activated HSCs, elevated iron-dependent lipid peroxidation may cause cell death and decrease ECM production, indicating that ferritinophagy participates in both fibrotic progression and reversal. However, direct experimental evidence demonstrating cell-specific effects of ferritinophagy in hepatic fibrosis remains insufficient (149,153). Reflecting the bidirectionality of this regulation, existing research has begun to move away from broad-spectrum antioxidants towards specific iron balance and ferroptosis points. Reducing the iron load or inhibiting lipid peroxidation can mitigate hepatic fibrosis and linking autophagy regulation with antioxidant systems to regulate the stability of glutathione peroxidase 4 (GPX4) and ferroptosis sensitivity is regarded as a prospective treatment option (120). Consequently, ferritinophagy is more likely to be regarded as a key node controlling the reversibility of hepatic fibrosis, with future studies aiming to focusing on cell-type- and stage-specific interventions to balance parenchymal cell protection with removal of pathological HSCs.

Cardiac fibrosis. Cardiac fibrosis frequently occurs during tissue remodeling following myocardial infarction or other injuries, with the core pathology involving persistent inflammation and interstitial remodeling induced by cardiomyocyte death. Previous studies have demonstrated that myocardial injury is accompanied by enhanced iron-dependent lipid peroxidation, and intracellular Fe^{2+} accumulation combined with impaired GPX4 antioxidant defense promotes ferroptosis (154-156). Although these findings highlight the importance of iron-dependent oxidative damage in cardiac remodeling, direct evidence to demonstrate the association between NCOA4-mediated ferritinophagy and cardiac fibrosis remains limited. In this context, ferritinophagy may modulate cardiomyocyte susceptibility to oxidative stress by regulating ferritin degradation and labile iron availability. When ferritinophagy-mediated iron release exceeds cellular antioxidant capacity, lipid peroxidation is further amplified, promoting

ferroptotic cardiomyocyte death. Injured cardiomyocytes subsequently release inflammatory signals that paracrinally induce fibroblast activation, increasing α-SMA expression and collagen deposition, thereby driving cardiac structural remodeling (124). Downregulation of antioxidant enzymes such as glutathione S-transferase Mu 1 exacerbates lipid peroxidation and ferroptosis, whereas inhibition of iron-dependent oxidative damage notably alleviates myocardial fibrosis, indicating that ferritinophagy contributes to regulating cardiomyocyte death thresholds and serves as a key link between metabolic stress and cardiac remodeling (157).

Based on such mechanistic explorations, interventions targeting iron-dependent oxidative stress have been studied as possible anti-fibrotic strategies for the heart. The findings revealed that ferroptosis inhibitors lessen collagen accumulation and enhance cardiac function, implying that iron homeostasis regulation may exert therapeutic effects in the remodeling period (155). However, whether selective modulation of ferritinophagy can provide therapeutic benefits beyond general iron or ferroptosis regulation remains unclear. The role of ferritinophagy in the heart is to maintain the balance between life and death of cardiomyocytes, rather than merely influencing inflammation or preserving chronic injury. Therefore, in the future, research could further study the cross-talk mechanism of ferritinophagy and antioxidant systems, clarify its functional changes at different time points after injury and identify precise intervention measures to protect cardiomyocytes while restraining excessive interstitial remodeling.

Autoimmune diseases. Systemic scleroderma is an autoimmune disease where fibrosis normally happens above ongoing immune events, with the primary driver being the chronically maintained inflammatory microenvironment rather than acute parenchymal cell injury. Previous research has shown that there is widespread iron metabolism disorder, increased lipid peroxidation and antioxidant system damage and macrophages serve an important role in iron homeostasis reprogramming (158). The impact of ferritinophagy on macrophages exhibits notable inflammatory stage-dependent and subset-specific characteristics. During acute/early inflammation, macrophages polarize toward the M1 phenotype, which is accompanied by elevated LC3B expression, reduced FTH1 levels and enhanced NCOA4-LC3B colocalization, indicating ferritinophagy activation (159). Lysine acetyltransferase 2A (KAT2A) promotes M1 polarization and inflammatory cytokine release by activating cyclic GMP-AMP synthase (cGAS)-STING signaling through NCOA4-mediated ferritinophagy (160). In the chronic stage, M2 macrophages display increased susceptibility to ferroptosis, which is regulated by ferritinophagy through the NRF2/ERK pathway. Suppression of ferritinophagy alleviates M2 macrophage ferroptosis and attenuates liver injury (161). Thus, cGAS-STING signaling is primarily involved in the early/acute stage, whereas the NRF2/ERK pathway is involved in the chronic stage (161-163). Ferritinophagy, through the regulation of ferritin degradation and labile iron release, changes the content of free iron in immune cells, thus affecting its sensitivity to lipid peroxidation and iron-dependent cell death. The bleomycin-induced systemic sclerosis model has exhibited upregulation of acyl-CoA synthetase long-chain family member 4 (ACSL4), which promotes polyunsaturated lipid remodeling and enhances lipid peroxidation, accompanied by macrophage iron accumulation and ferroptosis increase, forming a metabolic loop to maintain inflammation and amplify fibrotic signals (158). Ferritinophagy-mediated iron release may influence fibrosis indirectly through the remodeling of immune cell metabolism, which promotes fibroblasts activation and collagen deposition.

Recent research has focused on immune-metabolites and not simply activated fibroblasts. ACSL4 inhibition decreases iron and lipid peroxidation and markedly improves tissue fibrosis, suggesting the possibility of targeting iron homeostasis networks in therapy. In autoimmune-associated fibrosis, ferritinophagy may work through influencing the inflammatory microenvironment without directly determining the extent of tissue damage (164). Future studies should aim to delineate the differential regulatory mechanisms of ferritinophagy in M1 vs. M2 macrophages, identify the functional switch points through which ferritinophagy transitions from promoting M1 polarization in early inflammation to modulating M2 ferroptosis in chronic stages and further explore novel anti-fibrotic strategies targeting NCOA4 or associated signaling cascades (such as cGAS-STING and NRF2/ERK) to achieve immunometabolic reprogramming.

Malignant tumors. In malignant tumors, fibrosis typically appears as tumor-associated stroma remodeling rather than classical organ scarring and the continuous activation of cancer-associated fibroblasts (CAFs) and abnormal ECM deposition are its basic characteristics. Previous studies have shown that iron metabolism disorder and increased lipid peroxidation exist in the tumor microenvironment, affecting both the survival of tumor cells and the function of stromal cells (17,165). Ferritinophagy, through the regulation of ferritin degradation and labile iron, may regulate iron homeostasis in the tumor microenvironment and affect cellular sensitivity to iron-dependent oxidative injury. Current evidence indicates that iron-dependent cell death may affect CAF activity and ECM deposition, indicating that the iron regulatory network is key in tumor stroma construction (166,167). However, whether ferritinophagy directly controls CAF activation or ECM remodeling remains largely unexplored. Therefore, ferritinophagy may be involved in shaping the tumor stroma by regulating the microenvironmental iron content rather than by directly causing damage to a specific cell type.

With the increasing understanding of tumor microenvironment metabolism, certain previous studies (17,165,166) have focused on the impact that modulation of iron homeostasis has on stroma remodeling and therapy. Regulating iron metabolism and lipid peroxidation would change fibroblast function and ECM structure, which suggests that ferritinophagy-associated pathway may be a new method to regulate tumor microenvironment (168). However, direct evidence regarding ferritinophagy in the tumor stroma is limited and the specific cell types and time evolution have not been thoroughly clarified. Future research combining spatial omics technology and microenvironment analysis is needed to systematically clarify the dynamic regulatory associations of ferritinophagy among tumor, immune and stromal cells and thus provide a basis for combinatorial strategies targeting microenvironment

Table I. Characteristics of ferritinophagy in fibrosis across different organs.

Disease type	Key cell types	Main stages of iron autophagy	Core molecular mechanisms	Major pathological effects	Potential treatment strategies	(Refs.)
Pulmonary fibrosis	Alveolar epithelial cells and activated fibroblasts	Damage trigger	NCOA4-mediated ferritin degradation → release of Fe^{2+} → lipid peroxidation → activation of TGF-β signaling	Epithelial damage, inflammation exacerbation	Inhibit lipid peroxides	(123,135-140)
Renal fibrosis	Renal tubular epithelial cells	Chronic maintenance	Iron autophagy releases Fe^{2+} → increased oxidative stress → mitochondrial dysfunction and metabolic reprogramming	Persistent inflammation, interstitial fibrosis	Regulating iron homeostasis	(141-146)
Liver fibrosis	Hepatocytes, Kupffer cells and hepatic stellate cells	Reversible control window	NCOA4-iron release → reactive oxygen species accumulation → TGF-β/SMAD activation → HSC activation or ferroptotic clearance	HSC activation or clearance, hepatocyte injury	Eliminating activated HSCs and precisely regulating ferroptosis	(147-153)
Cardiac fibrosis	Cardiomyocytes and cardiac fibroblasts	Reset trigger	Fe^{2+} accumulation and impaired GPX4 function + downregulation of GSTM1 → lipid peroxidation → ferroptosis of cardiomyocytes	Myocardial necrosis, remodeling	Inhibit ferroptosis and restore antioxidant defense	(154-157)
Autoimmune diseases	Macrophages and immune cells	Inflammation maintenance	ACSL4 ↑ → lipid remodeling/oxidation and iron accumulation → immune-driven fibrosis cycle	Sustained immune activation, secondary fibrosis	Targeted immune metabolic reprogramming	(158-161, 164)
Malignant tumor	Cancer-associated fibroblasts	Shaping the microenvironment	Altered iron turnover → changes in iron availability → iron-mediated cell death and activation of stromal cells	ECM refactoring	Targeted intervention in the tumor microenvironment through the regulation of iron metabolism	(17,166-168)

NCOA4, nuclear receptor coactivator 4; HSC, hepatic stellate cell; ECM, extracellular matrix; ACSL4, acyl CoA synthetase long chain family member 4; GSTM1, glutathione S-transferase Mu 1; GPX4, glutathione peroxidase 4.

remodeling in both cancer treatment and fibrosis suppression (Table I).

5. Discussion

Overall, current evidence suggests that, although ferritinophagy is important for maintaining iron homeostasis, it actually serves as a central metabolic node that regulates the balance between tissue damage and repair (117,169). NCOA4 mediates ferritin degradation, converting stored iron to labile iron, which changes redox balance and cell fate (4,32,170,171). Under conditions of chronic injury or sustained metabolic stress, increased labile iron promotes lipid peroxidation and maintains oxidative stress in an autoamplified network with inflammatory mediators and profibrotic signals such as TGF-β. This drives tissue repair progressively away from regenerative processes toward fibrotic remodeling. This way, ferritinophagy may serve as an upstream checkpoint that

influences whether fibrosis is initiated and which pathogenic program subsequently follows, rather than functioning merely as a downstream bystander. Importantly, ferritinophagy exhibits dual effects on fibrosis (154). This bidirectional effect is cell type- and disease stage-dependent. In parenchymal cells, including alveolar epithelial cells, renal tubular epithelial cells, hepatocytes and cardiomyocytes, enhanced ferritinophagy during the early injury phase increases labile iron and ROS, exacerbating oxidative damage and inflammation and promoting fibrotic initiation (36,142). By contrast, in activated effector cells, such as myofibroblasts, HSCs and CAFs, ferritinophagy during the chronic phase may induce iron-dependent cell death, reducing ECM-producing cells and potentially limiting fibrosis progression (149). Macrophages also exhibit stage-specific responses: ferritinophagy promotes M1 polarization during acute inflammation through the KAT2A-cGAS-STING axis, whereas it regulates M2 ferroptosis during chronic inflammation through the NRF2/ERK pathway. A closer examination of this 'dual-role' paradigm, however, reveals numerous key issues that warrant further elaboration. The mechanistic basis of this divergence lies in three interconnected variables: i) Baseline antioxidant buffering capacity; ii) lipid peroxidation susceptibility (such as ACSL4 expression) (172,173) and ferroportin-mediated iron efflux, all of which differ markedly across cell lineages; and iii) disease stages. Methodologically, the majority of previous evidence derives from broad-spectrum ferroptosis inhibitors or global NCOA4 ablation, which are approaches that cannot dissect cell-autonomous ferritinophagy effects from secondary inflammatory modulation. Macrophage NCOA4 deletion, for instance, may indirectly alter fibroblast behavior through cytokine changes (159). The therapeutic assumption that myofibroblast ferroptosis is uniformly beneficial is also tempered by the observation that ferroptotic debris can activate toll-like receptor 4 signaling, potentially offsetting the benefit of ECM clearance. Furthermore, nearly all data originate from acute animal models, leaving it uncertain whether ferritinophagy operates similarly in human fibrosis, which is a process spanning decades amid comorbidities and medications. In addition, ferritinophagy flux reporters have yet to be validated in human tissues (174-176). Collectively, these considerations suggest that the net effect of ferritinophagy should be viewed not as a binary switch but as a threshold-governed rheostat, whose direction depends on the integrated cellular stress response and redox equilibrium, a nuance that calls for quantitative, spatiotemporally resolved investigations in future studies.

Despite the aforementioned caveats, cross-organ evidence indicates that iron metabolic re-programming is nearly ubiquitous in fibrotic disease and, thus, ferritinophagy may provide a common metabolic basis for fibrosis (128). However, its biological outcomes are highly affected by the tissue-specific cell lineages and microenvironment context. This is particularly evident for NCOA4: In the kidney, NCOA4 drives tubulointerstitial fibrosis, whereas in the liver, NCOA4-mediated ferritinophagy promotes hepatic stellate cell senescence and alleviates fibrosis, while, in the heart and lung, NCOA4 upregulation exacerbates fibrotic remodeling. This indicates that ferroptosis induction through ferritinophagy can have opposite outcomes depending on the organ. In pulmonary, renal and cardiac fibrosis, ferritinophagy is mainly associated with parenchymal cell damage and inflammatory amplification. Hepatic fibrosis participates in hepatocyte damage and HSC fate decision-making, affecting the reversibility of fibrosis. Ferritinophagy mainly alters the immune metabolic state in autoimmune and tumor-associated fibrosis, thus influencing the formation of matrix, which shows that ferritinophagy is an adaptive expression of the common metabolic strategy among different tissue ecosystems. Besides organ-specific differences, disease stage also decides ferritinophagy function (177). Early in the injury, ferritinophagy enhancement increases oxidative stress and initiates fibrosis formation. During the chronic phase, if the majority of iron-dependent damage occurs on pathological effector cells, then ferritinophagy can decrease abnormal matrix accumulation and impact results.

The aforementioned hierarchical framework positions ferritinophagy as an attractive upstream checkpoint for antifibrotic intervention. However, clinical translation faces key challenges. Systemic toxicity is a primary concern, as global NCOA4 inhibition may impair erythropoiesis and mitochondrial function, necessitating cell-type-selective delivery strategies (178). The therapeutic window is also stage-dependent, since attenuating ferritinophagy may protect parenchymal cells in early injury, whereas activating it could eliminate pathological myofibroblasts in established fibrosis. Pharmacologically, although preclinical agents targeting the NCOA4-FTH1 interaction (such as compound 9a, a first-in-class inhibitor that directly binds $NCOA4^{383-522}$ to disrupt ferritin binding and reduce labile iron) or modulating ferritinophagy (such as curcumol, which exerts bidirectional effects depending on cell type or schisandrin B, an NCOA4-mediated ferritinophagy inducer that promotes activated HSC senescence) have shown efficacy, to the best of our knowledge, none of them have advanced to clinical trials for fibrosis (129,179). Beyond these, a proteolysis-targeting chimera-based NCOA4 degrader (V3) has recently been developed as a tool compound for ferritinophagy inhibition, while natural products such as morroniside and daphnetin have been identified as selective ferritinophagy activators that promote ferroptosis in activated HSCs to alleviate liver fibrosis in preclinical models (180-182). In addition, ferroptosis inhibitors have been shown to reduce collagen accumulation and improve cardiac function after myocardial infarction, indicating that inhibition of iron-dependent oxidative damage can also be therapeutically beneficial (183). Future efforts should aim to prioritize cell-type-selective nanocarriers, patient stratification based on iron overload status and combinatorial regimens that integrate ferritinophagy modulation with antioxidant or TGF-β-targeted therapies (184,185). Emerging tools such as spatial transcriptomics and ferritinophagy flux reporters will be key in defining the optimal intervention window.

Ferritophagy is important in connecting metabolic pathways, including iron metabolism, cellular stress response and tissue remodeling and its functionality relies on different cell types and disease states. The spatiotemporal regulation of this process may provide a novel understanding of the commonalities among multiple organ fibrosis and set forth a next-generation anti-fibrotic approach.

6. Conclusion

Ferritinophagy is a key way of controlling iron in cells and its association with iron dyshomeostasis, oxidative stress and

multiple organ fibrosis, as well as cell fate change. Ferritinophagy is known to participate in both initiating and developing fibrosis; it can also influence the reversibility of tissue remodeling through altering effector cell survival, which makes ferritinophagy have a dual effect, stage-specificity and cellular-type-dependent nature. Combining ferritinophagy with the classical profibrotic signaling pathway provides a metabolic perspective for the reinterpretation of fibrosis and lays the theoretical basis for precise regulation of iron homeostasis in future antifibrosis strategies.

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Availability of data and materials

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Authors' contributions

All authors contributed to the present review. SS, XL, JY and HL were responsible for study conceptualization. SS, XL and JY were responsible for original manuscript draft preparation. XL and HL were responsible for writing, reviewing and editing the manuscript. SS was responsible for visualization, including the design and preparation of the figures and schematic illustrations. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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