Ferritin in ferroptosis: Implications for neurodegenerative diseases (Review)

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Abstract. Neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis, are characterized by progressive loss of neurons. Although the precise pathogenesis of such diseases is complex and multifactorial, several molecular pathways have been implicated, including the aggregation of misfolded proteins, mitochondrial dysfunction, oxidative stress, neuroinflammation and disrupted iron homeostasis. Emerging evidence has underscored the pivotal role of ferroptosis, an iron-dependent, non-apoptotic form of cell death, in neurodegenerative disease progression. Ferritin, characterized by a 24-subunit hollow sphere structure composed of heavy and light chains, plays a key role in the network regulating cerebral iron homeostasis. In response to cellular iron overload, ferritin expression is upregulated to sequester labile iron and mitigate Fenton reaction-mediated toxicity, thus exerting a cytoprotective function. Paradoxically, ferritin can be degraded via ferritinophagy, a selective autophagic process that releases toxic ferrous iron and directly triggers ferroptosis. This review systematically reviews the role of ferritin within the iron homeostasis network to elucidate the connection between the dysregulation of iron metabolism and the pathological mechanisms of neurodegenerative diseases. The study focused on the potential role of ferritin as a biomarker for early diagnosis, therapeutic strategies targeting ferritin pathways to restore iron homeostasis and the clinical translational value of magnetic resonance imaging-based non-invasive quantification of cerebral iron deposition. It is crucial to elucidate the multidimensional roles of ferritin in neurodegeneration to provide a theoretical foundation for precision diagnostic and therapeutic approaches.

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Abbreviations: ApoE, apolipoprotein E; Aβ, β-amyloid; ACP, aceruloplasminemia; ACSL4, acyl-CoA synthetase long-chain family member 4; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; ARE, antioxidant response element; BACH1, BTB and CNC homolog 1; BPAN, β-propeller protein-associated neurodegeneration; CSF, cerebrospinal fluid; CNS, central nervous system; DMT1, divalent metal transporter 1; FA, Friedreich ataxia; FPN, ferroportin; FTH, ferritin heavy chain; FTL, ferritin light chain; GSH, glutathione; GPX4, glutathione peroxidase 4; HO-1, heme oxygenase-1; Iba1, ionized calcium-binding adapter molecule 1; IGFBP-2, insulin-like growth factor binding protein-2; IRP, iron regulatory protein; IRE, iron-responsive element; Keap1, Kelch-like ECH-associated protein 1; LOX, lipoxygenase; LC3, light chain 3; MS, multiple sclerosis; MSA, multiple system atrophy; MT, melatonin; MRI, magnetic resonance imaging; NBIA, neurodegeneration with brain iron accumulation; NFT, neurofibrillary tangle; Nrf2, nuclear factor erythroid 2-related factor 2; NCOA4, nuclear receptor coactivator 4; OS, oxidative stress; PM, particulate matter; PBMC, peripheral blood mononuclear cell; PI3K, phosphatidylinositol 3-kinase; p-tau, phosphorylated tau; PSP, progressive supranuclear palsy; PSEN, presenilin; PUFA, polyunsaturated fatty acid; PL, phospholipid; PPARδ, peroxisome proliferator-activated receptor δ; PCBP, poly(rC)-RNA-binding protein; PD, Parkinson's disease; QSM, quantitative susceptibility mapping; RLS, restless legs syndrome; ROS, reactive oxygen species; SWI, susceptibility weighted imaging; STEAP3, six-transmembrane epithelial antigen of prostate 3; T2D, type 2 diabetes; TfR, transferrin receptor; TFEB, transcription factor EB; TDP-43, TAR DNA-binding protein 43

Key words: ferritin, ferritinophagy, ferroptosis, Alzheimer's disease, Parkinson's disease

1. Introduction

Iron is an essential element of life and plays a central role in biological processes (1). Iron is required for the proper functioning of numerous enzymes. However, free ferrous iron (Fe^{2+}) exerts toxicity despite its biological importance. Dysregulation of intracellular iron homeostasis, a critical etiological factor in neurodegenerative diseases, triggers destructive effects via Fenton reaction-derived reactive oxygen species (ROS), ultimately leading to ferroptosis (2,3). Ferroptosis causes the oxidative destruction of the cell membrane through three key mechanisms: Dysregulation of the antioxidant system, disruption of iron metabolism and accelerated lipid peroxidation. To prevent detrimental effects, cellular systems tightly regulate iron levels through coordinated mechanisms, including the hepcidin-ferroportin (FPN) axis, the divalent metal transporter 1 (DMT1)-transferrin (Tf) system, and the ferritin-nuclear receptor coactivator 4 (NCOA4) pathway (1,2).

Ferritin is a highly conserved iron-containing storage protein ubiquitously distributed in living organisms. Its unique three-dimensional structure composed of a protein shell and an inorganic mineral core enables it to oxidize and store iron. The protein shell forms a hollow cavity assembled from two functionally distinct subunits: The ferritin heavy chain (FTH) with ferroxidase activity and the ferritin light chain (FTL), which facilitates iron mineralization. The mineral core sequesters up to 4,000 ferric iron (Fe^{3+}) ions. Ferritin, the primary iron storage protein in biological systems, stores iron predominantly in the iron oxyhydroxide form, potentially incorporating phosphorus-containing components (4). However, the precise mineral structure of this core remains unclear. The iron sequestration mechanism relies on the ferroxidase activity of FTH and the specialized chemical microenvironment within the cavity, which collectively promotes iron ion recruitment and mineralization. Importantly, excess free iron that is not properly incorporated into the ferritin core may induce oxidative stress (OS) by catalyzing ROS generation, leading to cellular damage (5). Ferritinophagy, a selective autophagy process mediated by NCOA4, plays a pivotal role in the regulation of systemic iron homeostasis. Under conditions of iron overload, ferritinophagy is activated, leading to the release of stored Fe^{2+} from ferritin. This increase in the labile iron pool can exacerbate ROS production via the Fenton reaction and, when coupled with insufficient antioxidant capacity, may trigger ferroptosis. The interconnected pathway between ferritinophagy and ferroptosis has been implicated in the pathogenesis of diverse human diseases, including metabolic disorders, neurodegenerative diseases, malignancies and infectious conditions. In this context, as iron overload and OS represent common pathological hallmarks across multiple disease entities, Jin *et al* (6) postulated that ferritinophagy may exhibit a broader disease relevance through its dual regulatory effects on iron homeostasis and ROS dynamics, which directly intersect with ferroptotic pathways.

Neurodegenerative diseases are characterized by progressive neuronal dysfunction and death due to hallmark pathologies, such as abnormal protein aggregation, synaptic loss and region-specific neurodegeneration. Major disorders include Alzheimer's disease (AD), which affects ~54.6 million patients in China alone (representing ~3.9% of its population), and is marked by deposits of β-amyloid (Aβ) plaques and tau tangles (7). The prevalence of AD increases with age, with an estimated incidence of 35% in adults aged 85 years and above (8). Furthermore, typical representative disorders comprise Parkinson's disease (PD), characterized by the aggregation of α-synuclein (α-Syn) leading to the loss of dopaminergic neurons - with projections indicating the global number of individuals living with PD will reach 25.2 million by 2050, more than double the 2021 figure - and amyotrophic lateral sclerosis (ALS), characterized by the degeneration of motor neurons (9). The etiology of neurodegenerative diseases involves multifactorial interactions such as genetic mutations, OS, mitochondrial dysfunction and neuroinflammation. Despite advances in the understanding of the molecular mechanisms, therapies that effectively halt disease progression remain unavailable. Current research focuses on early biomarker discovery, pathogenic protein clearance strategies and neuroprotective interventions, and breakthroughs are urgently needed to address the growing global burden on aging populations.

This review provides a comprehensive overview of the relationship between brain iron homeostasis and neurodegenerative diseases. Specifically, the review aimed to analyze the key molecular pathways of ferroptosis, elucidate the pathological consequences of ferritin dysregulation, discuss the diagnostic and translational potential of ferritin as a biomarker and evaluate the application of magnetic resonance imaging (MRI) for dynamic brain iron monitoring.

2. The role of ferritin in modulating cerebral iron homeostasis

Ferritin, a critical intracellular iron storage protein, plays a pivotal role in maintaining cellular iron homeostasis through its multi-subunit cavity structure, which mediates Fe^{2+} oxidation and iron core deposition. However, it plays two opposing roles: It protects cells from oxidative damage by sequestering iron, yet it can promote ferroptosis when ferritinophagy releases Fe^{2+} for the Fenton reaction. Once iron enters the brain parenchyma, it is distributed among neurons, astrocytes, microglia and oligodendrocytes, each of which has distinct iron requirements and regulatory mechanisms. In neuropathy, neuroinflammation frequently coexists with ferroptosis. This process involves the activation of primary immunocompetent cells such as microglia and astrocytes. Combined treatment with iron agents and lipopolysaccharides significantly increases the branch/process length of microglia and enhances astrocyte immunoreactivity in the hippocampal and cortical regions (10). The release of common inflammatory mediators during neuroinflammation is closely linked to the regulation of cellular iron metabolism. Microglia, which are the resident immune cells of the central nervous system (CNS), play a central role in neuroinflammation. Conventionally, iron

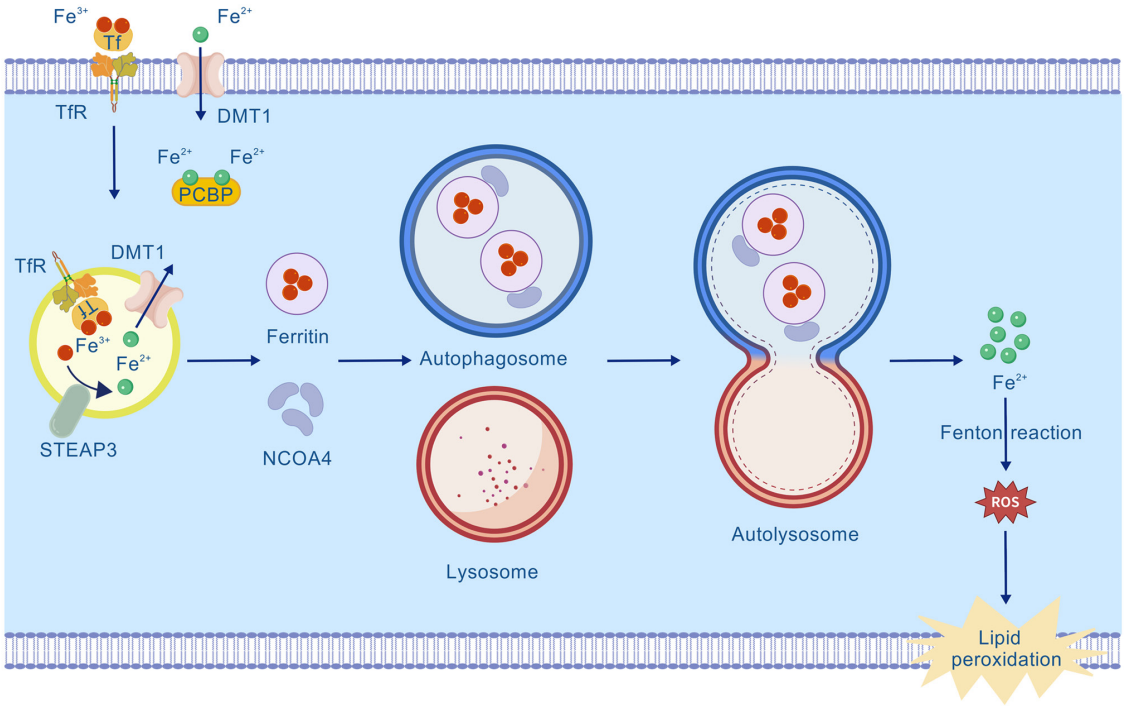

Figure 1. Iron uptake and ferritinophagy pathway. Cellular iron is acquired via TfR-mediated endocytosis or through the DMT1 transporter. Cytosolic Fe^{2+} is chaperoned by proteins such as PCBP and is subsequently stored in ferritin. NCOA4-mediated ferritinophagy targets ferritin to autolysosomes for degradation, thereby releasing Fe^{2+}. Overactivation of this process results in cellular iron overload, which subsequently generates excessive ROS via the Fenton reaction and induces lipid peroxidation. DMT1, divalent metal transporter 1; NCOA4, nuclear receptor coactivator 4; PCBP, poly(rC)-binding protein; ROS, reactive oxygen species; STEAP3, six-transmembrane epithelial antigen of the prostate 3; Tf, transferrin; TfR, transferrin receptor.

accumulation in microglia has been recognized to trigger pro-inflammatory activation. Iron overload markedly upregulates the expression of cofilin, a key protein regulating actin dynamics in microglia, suggesting that cofilin is involved in the iron overload-induced pro-inflammatory phenotypic transformation of these cells (11). Astrocytes, a key glial cell type, are the central regulators of iron homeostasis in the brain. In the hippocampal CA1 region, FTH1 and FTL1 mRNAs exhibit preferential localization to distal astrocytic compartments, such as the fine perisynaptic processes that ensheathe synapses, with FTH1 mRNA abundance significantly exceeding that of FTL1 (12). Aged mice demonstrate an ~1.8-fold increase in the FTH1/FTL1 ratio and redistribution of FTH1 mRNA towards these peripheral astrocytic processes (12). This shift toward a higher proportion of FTH1, which possesses ferroxidase activity, is likely a compensatory response to elevated OS in the aging brain, enhancing the capacity to sequester iron in a less reactive form. The functions of oligodendrocytes extend beyond synthesizing myelin sheaths to enable saltatory nerve conduction. One study proposed that oligodendrocytes participate in iron detoxification by secreting FTH1, a critical component of the neuronal antioxidant defense system (13).

Precise regulation of brain iron homeostasis is crucial for neuronal survival, with ferritin occupying a central position in this network as the primary intracellular iron storage protein. Cellular iron metabolism begins with the binding of Tf-bound Fe^{3+} to the Tf receptor 1 (TfR1), which is followed by endocytosis (Fig. 1) (14,15). Within the endosome, Fe^{3+} is reduced to Fe^{2+} by the six-transmembrane epithelial antigen prostate 3 and then transported into the cytosol via DMT1. Cytosolic Fe^{2+} is chaperoned by proteins such as poly(rC)-RNA-binding protein (PCBP) and delivered to ferritin for storage in a biocompatible form, thereby effectively preventing the neurotoxicity of labile iron (Fig. 1) (16). Dynamic ferritin expression is key to cellular iron-buffering systems. This process is precisely controlled by the iron regulatory protein (IRP)/iron-responsive element (IRE) system (Fig. 2). IRPs bind to IREs located in the 5' or 3' untranslated regions of iron-related mRNAs, thereby regulating the expression of iron uptake (TfR1) and storage (FTH1/FTL) proteins. Under iron-deficient conditions, IRPs bind to IREs with high affinity, repressing ferritin mRNA translation and stabilizing TfR1 mRNA. Conversely, when iron is sufficient, IRP binding is reduced, promoting ferritin synthesis and facilitating endonucleolytic degradation of TfR1 mRNA (17). This IRP/IRE-mediated regulation operates on a relatively rapid timescale, enabling cells to swiftly adapt to fluctuations in iron availability. This rapid response is particularly crucial in acute brain iron challenges, such as hemorrhage, where it serves as an immediate defense against iron toxicity. Conversely, in chronic conditions like neurodegenerative diseases, persistent iron overload may overwhelm or dysregulate this adaptive system, contributing to long-term iron accumulation and neuronal vulnerability. This core regulatory network is further integrated with upstream stress-signaling pathways. For example, the transcription factor EB, a master regulator of the autophagy-lysosome system, confers dual protection against ferroptosis. It upregulates TfR1 and promotes its lysosomal membrane localization to facilitate clearance of the labile iron pool, and cooperatively enhances the synthesis of FTL and FTH via a TfR1-dependent pathway, thereby reinforcing safe iron storage (18). Similarly, activation of peroxisome proliferator-activated receptor δ modulates the

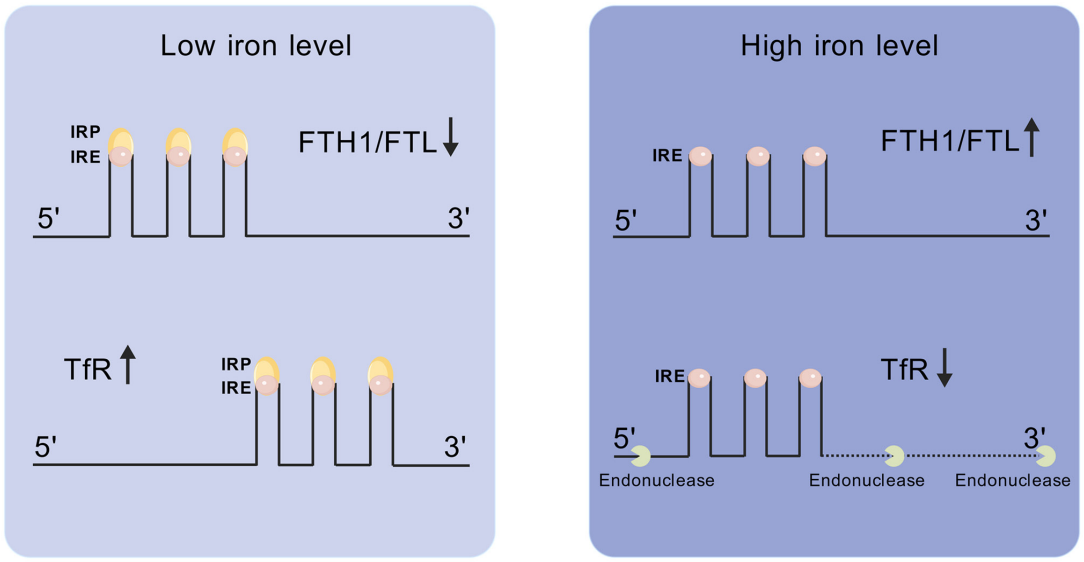

Figure 2. IRP/IRE system. The IRP/IRE system regulates cellular iron homeostasis post-transcriptionally. Low iron: High-affinity IRP-IRE binding inhibits FTH1/FTL translation and stabilizes TfR1 mRNA. High Iron: Reduced IRP binding derepresses ferritin synthesis and allows TfR1 mRNA degradation. FTH1, ferritin heavy chain 1; FTL, ferritin light chain; IRP, iron regulatory protein; IRE, iron-responsive element; TfR, transferrin receptor.

expression of DMT1, FPN1 and ferritin by regulating IRP1, ultimately restoring iron homeostasis and preventing neurotoxicity (19). Collectively, these findings reveal that ferritin is a key effector molecule involved in multiple neuroprotective pathways. Supporting this notion, a study using AD models demonstrated that TfR1 knockdown restored iron homeostasis and ameliorated mitochondrial dysfunction, a process possibly involving ferritin, suggesting that TfR1 is a potential target for mitigating iron overload in AD by modulating this network (20). Finally, cellular iron balance relies on efflux. FPN1, the sole known cellular iron exporter, mediates iron efflux during iron overload. This process is negatively regulated by hepcidin through its interaction with FPN1 (Fig. 3), working in concert with the storage function of ferritin to maintain precise intracellular iron homeostasis.

Ferritinophagy is a form of selective autophagy in which the receptor NCOA4 binds to FTH1, delivering ferritin to the autophagosome for degradation and the consequent release of redox-active Fe^{2+}. In essence, this NCOA4-mediated process degrades the cytosolic iron storage complex via autophagosomes to release bound iron into the labile iron pool. Excessive ferritinophagy activation disrupts iron metabolism, induces cerebral iron accumulation and triggers neuronal ferroptosis (Fig. 1) (21). This molecular mechanism has recently been implicated in the pathogenesis of multiple neurodegenerative diseases, and has emerged as a critical area of therapeutic target research (6). It is crucial to note that while ferritinophagy can be involved in basal iron recycling, its excessive activation - which is pathogenic and leads to ferroptosis - is primarily triggered by cellular iron overload and various stress signals, not merely by iron starvation. In NCOA4-deficient HT22 cells, alterations in the molecular markers associated with functional iron deficiency have been identified (22). Concurrently, differential gene expression linked to key neuronal processes, including development, mitochondrial function, apoptosis and neurodegenerative diseases, have been observed (22). These *in vitro* data suggested that NCOA4-mediated ferritinophagy may serve as a potential molecular target for the prevention of neurodegenerative disorders. Currently, the development of small-molecule inhibitors that block the NCOA4-FTH1 interaction has emerged as a novel therapeutic strategy for multiple diseases. However, a lack of structural information has forced drug discovery to rely on phenotypic screening rather than rational drug design, with the reported lead compounds primarily targeting NCOA4 (23). Through structural analyses, Hoelzgen *et al* (24) delineated critical features on the FTH1 surface essential for the formation of the NCOA4·FTH1 complex, providing precise targets for designing inhibitors of this complex. ADP-ribosylation-like factor 6 interacting protein 5 (JWA) is an all-trans retinoic acid-responsive gene that plays a multifaceted role in cellular homeostasis. JWA protein is critical for the survival of dopaminergic neurons in PD (25). However, whether JWA regulates ferroptosis in dopaminergic neurons remains unclear. Furthermore, JWA blocks ferritinophagy by occupying the FTH1-binding site of NCOA4, establishing JWA as a novel ferroptosis regulator that specifically inhibits NCOA4-mediated ferritinophagy (26).

3. Mechanisms of ferroptosis

Ferroptosis is triggered by the disruption of the intricate intracellular redox balance. Its core mechanisms revolve around three interconnected axes: i) The failure of the cystine/glutamate antiporter system Xc^-/glutathione (GSH)/GSH peroxidase (GPX)4 antioxidant axis, which eliminates the primary defense against lipid peroxides; ii) the presence of iron-driven lipid peroxidation, which supplies the lethal substrates; and iii) the Kelch-like ECH-associated protein 1 (Keap1)/nuclear factor erythroid 2-related factor 2 (Nrf2)/antioxidant response element (ARE) signaling pathway as a central regulatory hub. Critically, ferroptosis execution requires the simultaneous convergence of the first two axes: A compromised antioxidant capacity must coincide with active, iron-facilitated lipid peroxidation.

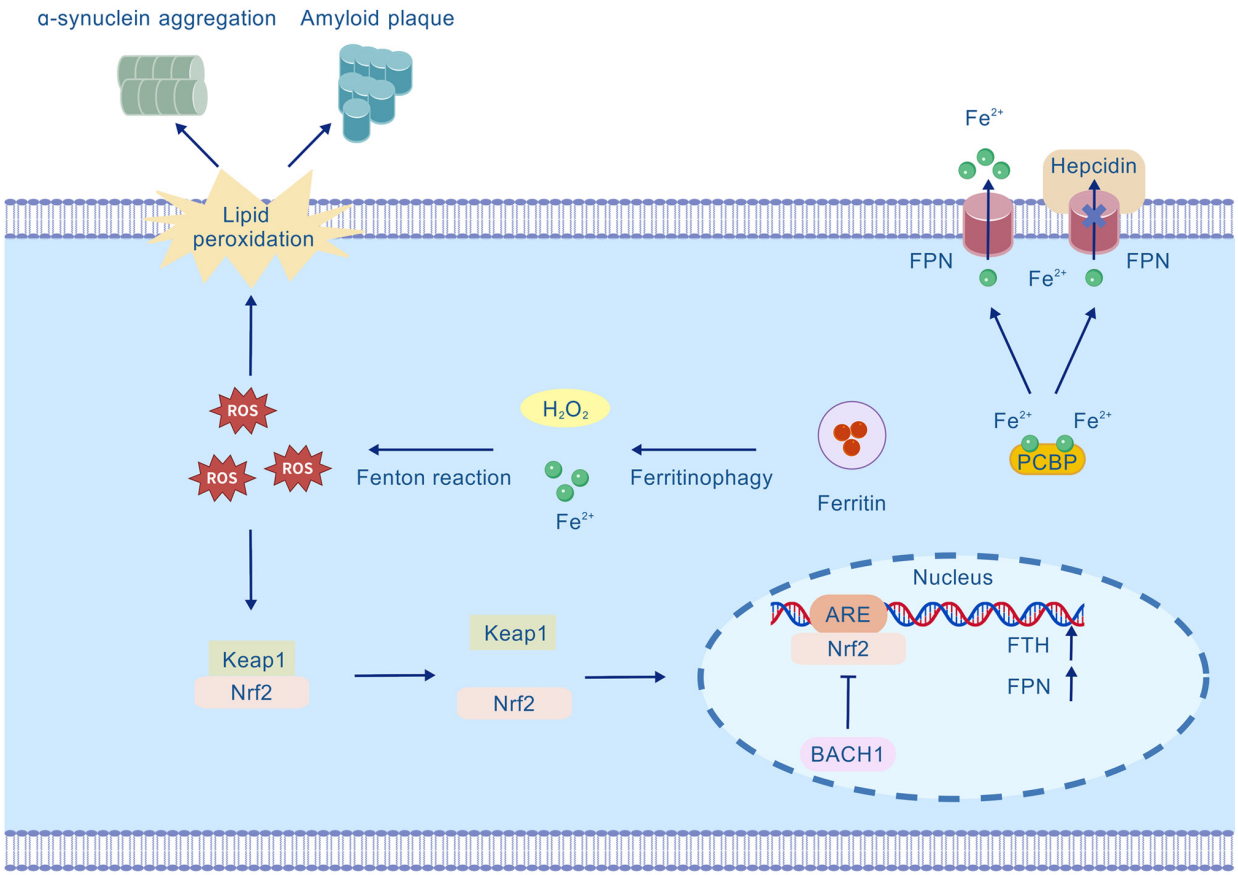

Figure 3. The Keap1/Nrf2/ARE axis in cellular iron homeostasis. FPN mediates cellular iron efflux, a process negatively regulated by hepcidin. Cytosolic oxidative stress such as ROS generated from the Fenton reaction between Fe^{2+} and H_2O_2 triggers the dissociation of Keap1 from Nrf2, thus enabling Nrf2 nuclear translocation. Nuclear Nrf2 binds to ARE and initiates the transcription of cytoprotective genes FTH and FPN. BACH1 antagonizes Nrf2 by competing for ARE binding. Fenton reaction-derived ROS also stimulates lipid peroxidation, contributing to neurodegenerative pathologies such as amyloid plaques and α-synuclein aggregates. ARE, antioxidant response element; BACH1, BTB and CNC homology 1; FPN, ferroportin; Keap1, Kelch-like ECH-associated protein 1; Nrf2, nuclear factor erythroid 2-related factor 2; PCBP, poly(rC)-binding protein; ROS, reactive oxygen species.

Xc^--GSH-GPX4 axis. The Xc^-/GSH/GPX4 axis constitutes the primary intracellular antioxidant defense mechanism against ferroptosis. This axis comprises the cystine/glutamate antiporter system Xc^-, GSH and GPX4, which function sequentially to maintain phospholipid redox homeostasis (Fig. 4). System Xc^- serves as the initial step of this defense axis. It is a heterodimeric transport complex composed of heavy chain solute carrier family 3 member 2 (SLC3A2; 4F2hc) and light chain SLC7A11 (xCT) (27). It exchanges intracellular glutamate with extracellular cystine in a 1:1 ratio. Upon cellular uptake, cystine is reduced to cysteine, which is a precursor for GSH synthesis. The selenoenzyme GPX4 utilizes GSH as a substrate to reduce toxic lipid hydroperoxides into nontoxic lipid alcohols, thereby playing a critical role in defending against ferroptosis (28). Impairment of any component of this protective axis markedly increases cellular susceptibility to ferroptosis. For instance, erastin inhibits system Xc^- activity, thereby blocking cystine uptake, depleting GSH and inducing ferroptosis (29). Conversely, the RAS-selective lethal compound 3 directly inhibits GPX4 activity, leading to uncontrolled lipid peroxide accumulation, membrane damage and ferroptosis (30).

Lipid peroxidation. Oxidation of polyunsaturated fatty acids (PUFAs) containing bis-allylic hydrogen atoms, such as arachidonic acid and adrenic acid, is a hallmark of ferroptosis (Fig. 4). First, PUFAs must be activated and esterified into membrane phospholipids. This process is initiated by acyl-CoA synthetase long-chain family member 4 (ACSL4), which converts free PUFAs into their acyl-CoA esters (PUFA-CoAs), a prerequisite for their incorporation into membrane lipids (31). As the primary enzyme that loads PUFAs into phospholipids, ACSL4 determines the cellular abundance of PUFA-containing membrane lipids, thereby establishing the membrane's intrinsic sensitivity to lipid peroxidation and ferroptosis. Lysophosphatidylcholine acyltransferase 3 catalyzes the remodeling of PUFA-CoAs into membrane phospholipids, generating PUFA-containing phospholipids (PUFA-PLs) (32). Membrane-integrated PUFA-PLs serve as direct substrates for lipid peroxidation. Lipoxygenases (LOXs), particularly 15-LOX, are highly selective for PUFA-PLs, including arachidonoyl phospholipids, and oxidize them to phospholipid hydroperoxides (PL-OOH). By contrast, large quantities of ferrous iron released from ferritin via ferritinophagy can efficiently promote the oxidation of PUFA-PLs to PL-OOH by generating high levels of ROS through the Fenton reaction. GPX4 is the key enzyme that prevents ferroptosis by catalyzing the reduction of PL-OOH to their corresponding non-toxic PL-OH, using GSH as a cofactor. Once formed, if not promptly reduced by GPX4, PL-OOH reacts with adjacent

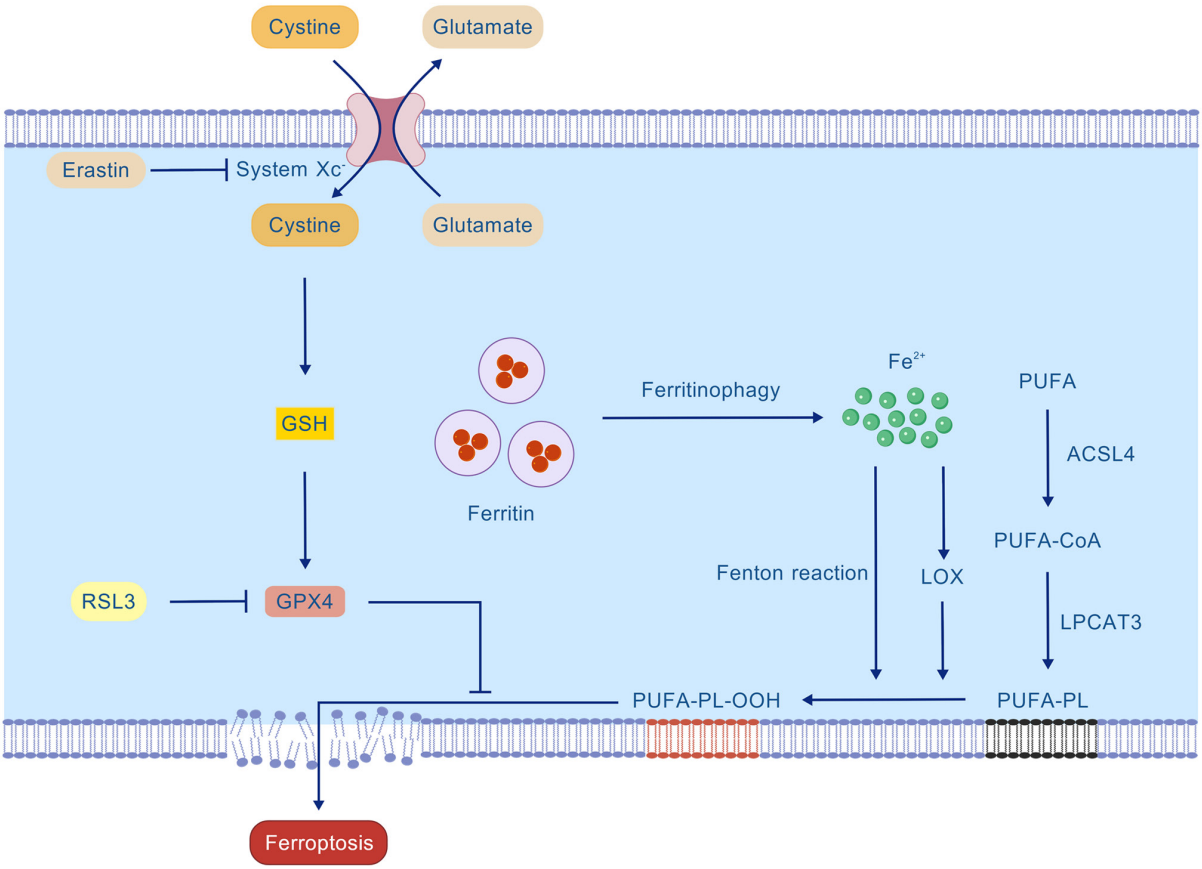

Figure 4. Lipid peroxidation and the Xc^-/GSH/GPX axis. The oxidation of membrane-integrated PUFA-PLs is an example of ferroptosis. Lipid peroxidation is promoted by LOXs or Fe^{2+} through the Fenton reaction. The selenoenzyme GPX4 serves as a central defense node by reducing phospholipid hydroperoxides using GSH. GSH synthesis depends on cystine uptake through the system Xc^- transporter. Pharmacological induction of ferroptosis can be achieved by exposure to erastin (system Xc^- inhibitor) or RSL3 (GPX4 inhibitor). ACSL4, acyl-CoA synthetase long-chain family member 4; GSH, glutathione; GPX4, glutathione peroxidase 4; LOX, lipoxygenase; LPCAT3, lysophosphatidylcholine acyltransferase 3; PUFA, polyunsaturated fatty acid; PL, phospholipid; PL-OOH, phospholipid hydroperoxide; RSL3, RAS-selective lethal 3.

PUFA-PLs, initiating a self-amplifying positive feedback cycle of lipid peroxidation. This uncontrolled chain reaction ultimately leads to irreversible disruption of membrane integrity and cell death (30).

The Keap1/Nrf2/ARE axis. Nrf2 is a key transcription factor regulating the cellular OS response, and many of its downstream target genes are directly involved in the regulation of ferroptosis (Fig. 3). These genes encompass proteins related to iron metabolism (such as FTH1 and FPN) and core antioxidant components (including GPX4, SLC7A11 and the GSH synthesis pathway). Under homeostatic conditions, the Neh2 domain of Nrf2 interacts with Keap1 via its ETGE and DLG motifs, leading to constitutive ubiquitination and degradation of Nrf2 and negative regulation of this pathway (33). When the cell encounters OS, such as that triggered by the Fenton reaction between cytosolic free Fe^{2+} and H_2O_2, which generates highly reactive hydroxyl radicals (·OH), Keap1 dissociates from Nrf2, allowing stable Nrf2 to accumulate and translocate into the nucleus. Inside the nucleus, Nrf2 binds to the ARE and recruits transcriptional coactivators such as cAMP response element-binding protein-binding protein/p300. Specifically, the Neh4 and Neh5 domains of Nrf2 interact with the TAZ1 and TAZ2 domains of CBP/p300, acting as a scaffold to facilitate chromatin remodeling and assembly of the transcription machinery (34). This interaction robustly initiates the transcription of its target genes. By upregulating FTH (enhancing iron storage) and FPN (promoting iron efflux), Nrf2 effectively reduces the intracellular labile iron pool. These two responses are not contradictory but form a balanced, coordinated strategy to mitigate iron toxicity. Simultaneously, Nrf2 directly enhances the cellular antioxidant capacity by positively regulating GPX4, thereby synergistically suppressing neuronal ferroptosis. The activity of this pathway is finely regulated by BTB and CNC homology 1 (BACH1). BACH1 competes with Nrf2 to bind ARE sequences, thereby repressing the transcription of Nrf2 target genes (35). In OS, BACH1 is inactivated, which relieves its transcriptional repression and consequently promotes an Nrf2-driven antioxidant response.

4. Pathophysiological contributions of ferritin dysregulation in neurodegenerative disorders

Neurodegenerative diseases are closely linked to dysregulation of ferritin-mediated iron homeostasis. Studies have indicated that these disorders are characterized by cerebral iron dyshomeostasis, with excessive iron deposition in specific regions. Iron overload exacerbates OS and lipid peroxidation via Fenton reactions, thereby driving neuronal damage. Ferritin, a critical iron storage protein, may exhibit compensatory upregulation

early in the disease to sequester labile iron. However, persistent overload or impaired degradation ultimately promotes pathological iron release. Such dysregulation facilitates toxic protein aggregation (e.g., Aβ, α-Syn) and activates cell death pathways like ferroptosis.

AD. AD neuropathology is characterized by extracellular Aβ plaques and intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau. Aβ plaques arise from aggregation of Aβ1-40/42 peptides derived from Aβ protein precursor cleavage, whereas NFTs result from the accumulation of phosphorylated tau (p-tau). Dysregulated iron metabolism in AD brains leads to pathological iron deposition in regions such as the hippocampus and cortex. Excess iron induces OS via Fenton reactions, promoting Aβ aggregation and tau hyperphosphorylation. Lactylation of the tau protein at the K677 site was found to confer neuroprotection in an AD mouse model. This modification acts by suppressing p38 mitogen-activated protein kinase-mediated ferritinophagy, thereby reducing iron release and mitigating ferroptosis and neuroinflammation (36). It should be noted that this protective effect has so far been demonstrated only in a mouse model. Thus, validation in human post-mortem brain tissues and other experimental systems is essential to confirm its pathophysiological relevance in patients with AD. These findings indicate that tau lactylation is a promising therapeutic target. Aβ is generated via β-secretase and γ-secretase cleavage of amyloid precursor protein. Mutations in presenilin (*PSEN*), which are linked to familial AD, impair γ-secretase activity. *PSEN* mutations exacerbate oxidative damage by blocking γ-secretase-mediated upregulation of FTH/FTL under iron challenge, implicating γ-secretase in IRP-IRE-regulated iron metabolism (37).

Iron is essential for myelination, synaptic plasticity, oxidative metabolism and neurotransmitter synthesis in the CNS (38). Iron overload contributes to ferroptosis, OS and neuroinflammation, disrupting the CNS microenvironment. During this process, hepcidin, which is primarily secreted by hepatocytes, maintains systemic iron homeostasis by suppressing the iron export function of FPN, the only known iron exporter. This regulatory process is corroborated in the context of AD. Analysis of the cingulate cortex from Braak stage III-VI patients with AD by Chaudhary *et al* (39) demonstrated that upregulated hepcidin transcription leads to decreased FPN expression, resulting in increased ferritin levels and elevated total brain iron content. It is generally thought that the upregulation of hepcidin is triggered by IL-6 released from activated glial cells or peripherally derived IL-6 transport - that is, inflammation induces hepcidin upregulation (40). However, it has not been ruled out that hepcidin upregulation may represent a physiological feedback response to early, localized iron overload.

Ferritin co-localizes with Aβ plaques in AD brains (41). In healthy brains, FTH is predominantly found in the oligodendrocytes and astrocytes (41). In AD mouse hippocampi, FTH1 mRNA accumulates in astrocytic somata, whereas FTL1 mRNA redistributes to thickened astrocytic processes near Aβ deposits, suggesting spatial regulation of iron homeostasis under physiological and pathophysiological conditions (12).

Activated microglia located near neuritic plaques exhibit robust ferritin expression (42). Neuritic plaques comprise neurons, microglia and Aβ, though their pathogenesis is incompletely understood. Microglial ferritin (iron sequestration) and Aβ (iron chelation) may synergistically promote plaque formation (43). FTL^{+} ionized calcium-binding adapter molecule 1^{+} microglia, a major Aβ-plaque-infiltrating subset, are elevated in patients with AD (44). Microglial activation coincides with ferritin upregulation, suggesting that iron storage modulates neuroinflammatory microenvironments in AD (45). Although AD involves concurrent iron accumulation and neuroinflammation, it remains unclear whether microglial iron retention and ferritin expression result from elevated iron levels, inflammatory activation or both. A study using human induced pluripotent stem cell-derived microglia revealed that microglial ferritin is regulated by iron rather than by inflammation; iron-laden microglia suppress pro-inflammatory responses but induce OS (46).

Apolipoprotein E (ApoE) is a major genetic risk factor for AD, and its role in the disease process may be closely linked to intracellular iron metabolism and tau pathology. Mice with the ApoE4 genotype exhibit significantly diminished ferritin expression in the CA1 and hippocampal regions and reduced FPN levels in the hippocampus (47). The decrease in ferritin levels may compromise the intracellular iron-binding capacity, whereas reduction in FPN restricts cellular iron export. Collectively, these alterations contribute to neuronal iron overload, which, in turn, drives the toxic accumulation of hyperphosphorylated tau. ApoE can activate the PI3K/AKT signaling pathway and inhibit the autophagic degradation of ferritin, a process known as ferritinophagy (48). This process reduces iron-dependent lipid peroxidation and maintains cellular iron homeostasis. By contrast, p-tau, a major component of NFTs, is significantly elevated in the cerebrospinal fluid (CSF) of patients with AD. Increased ferritin levels in the CSF of these patients are correlated with p-tau181, and this association is significantly mediated by CSF ApoE levels (49). These findings suggest that ApoE may indirectly influence tau phosphorylation and aggregation by regulating iron metabolism pathways. However, the precise molecular mechanisms underlying the interactions between ApoE, ferritin and tau hyperphosphorylation require further investigation.

PD. PD is characterized by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta, and iron dysregulation plays a central role in this process. Pathological iron deposition and α-Syn aggregation form a vicious cycle in the brain of patients with PD and drives neuronal damage. Furthermore, toxic interactions between iron and α-Syn can induce cellular senescence, a process that may precede overt neuronal loss (50). At the molecular level, this interaction triggers ferroptosis, an iron-dependent form of regulated cell death. For instance, microRNA (miR)-335 exacerbates ferroptosis by suppressing FTH1 expression, thereby increasing intracellular Fe^{2+} levels (51). However, the precise extent of FTH1 reduction by miR-335 remains to be quantified. By contrast, the neuroprotective hormone melatonin (MT) counteracts α-Syn-induced ferroptosis through MT1 receptor-mediated activation of the Sirtuin 1/Nrf2/heme oxygenase-1/GPX4 signaling axis (52).

Iron dysregulation exhibits cell-type-specific manifestations. In microglia, iron accumulation is closely correlated with neuroinflammation, as evidenced by the positive association

between microgliosis and iron load in the postmortem PD substantia nigra (53). Pathogenic mutations in leucine-rich repeat kinase 2, such as G2019S, disrupt iron handling by impairing the function of its substrate Ras-associated binding protein 8a, leading to significantly reduced FTH1 transcription in oligodendrocytes, astrocytes and microglia (54,55). These abnormalities are associated with, and may potentially contribute to, the formation of Lewy bodies, where both iron and ferritin are co-deposited (41). However, a direct causal link remains to be established.

The spatiotemporal dynamics of iron distribution are critical in the pathology of PD. The newly developed immunomicroprobe particle-induced X-ray emission technique, which enables the quantification of iron in specific structures such as Lewy bodies at a micron-level resolution, is a powerful tool for elucidating the fine spatiotemporal characteristics of iron metabolism (56). Clinically, CSF profiles from patients with PD experiencing excessive daytime sleepiness reveal a distinct pattern of elevated iron, reduced ferritin and increased IL-1β, suggesting that iron overload may promote excessive daytime sleepiness via microglial activation and neuroinflammation (57).

It is important to note that iron-related mechanisms in PD are context dependent. Although restless leg syndrome (RLS) in the general population is often associated with iron deficiency in the brain, a meta-analysis found no association between PD-RLS and systemic iron parameters, indicating that PD-RLS may involve a pathophysiology distinct from that of the classical iron deficiency hypothesis (58).

ALS. ALS, the most common motor neuron disease, is characterized by the progressive degeneration of the upper and lower motor neurons, leading to muscle atrophy, functional impairment and death. Most patients with ALS share the pathological hallmark of the abnormal cytoplasmic aggregation of TAR DNA-binding protein 43 (TDP-43) in motor neurons. As resident immune cells in the brain, microglia exhibit unclear responses to TDP-43 in ALS. Phosphorylated TDP-43 pathology was found to drive the microglial transition from a phagocytically active state, marked by early-stage neuroprotective phagocytic activity via elevated CD68 expression, to a dysfunctional state characterized by late-phase L-ferritin accumulation, thus offering novel insights into ALS pathogenesis (59). Significant spatial and functional associations between microglial activation and abnormal ferritin accumulation underscore their critical roles in ALS progression (60). Given that iron dysmetabolism also occurs during ALS progression, iron is likely to play a pivotal role in ALS pathology. Decreased activity of the AKT signaling pathway may be involved in the dysregulation of iron metabolism in ALS. Specifically, ALS downregulates AKT protein expression and upregulates iron import and storage-related proteins (TfR1, PCBP, FTL and FTH), whereas suppressing the expression of the iron exporter FPN1 may ultimately lead to increased iron accumulation in the skeletal muscle (61). Human spinal cord gene co-expression network analysis identified two key modules enriched for ALS genetic risk: SC.M4 (regulating RNA processing and epigenetics) and SC.M2 (enriched for oligodendrocyte-specific intracellular transport and autophagy-related genes) (62). Within the SC.M2 module, NCOA4 emerged as a computationally inferred hub gene based on co-expression and genome-wide association study data. This position identifies NCOA4 as a statistical risk association for ALS (58), implicating iron dysmetabolism and autophagic imbalance as potential contributors to neurodegeneration.

Aceruloplasminemia (ACP). ACP is a rare autosomal recessive disorder caused by mutations in the ceruloplasmin gene that lead to reduced ferroxidase activity. Patients with ACP typically exhibit a triad of clinical manifestations, including neurological symptoms (cognitive decline, neuropsychiatric abnormalities and movement disorders), retinal degeneration and diabetes mellitus (63). In ACP, Fe^{3+} can be transported to plasma Tf and delivered to other cells. The impaired ferroxidase function of ceruloplasmin in ACP disrupts the conversion of Fe^{2+} to Fe^{3+}, thereby inhibiting iron release from the storage sites and reducing systemic iron bioavailability. To meet the iron demands for neurotransmitter synthesis, neurons excessively uptake non-Tf-bound iron, a highly toxic, free iron species that exacerbates neuronal death. FTH, which possesses intrinsic ferroxidase activity, is upregulated in ceruloplasmin-knockout mouse models. This mouse-specific finding suggests a potential compensatory role in maintaining iron homeostasis following ceruloplasmin deficiency (64). Whether FTH is similarly upregulated in patients with ACP remains to be confirmed. Iron-related neurodegeneration in ACP is primarily linked to the abnormal accumulation of magnetic Fe^{3+} within ferritin/hemosiderin cores, predominantly in the form of ferrihydrite-iron, which serves as the principal driver of iron-sensitive MRI contrast (65). Given the rarity of this condition, case reports and individual case analyses remain important resources for investigating its clinical features, genetic mechanisms and therapeutic strategies (63,66).

Other neurodegenerative diseases. Friedreich ataxia (FA) is a rare inherited neurodegenerative disorder caused by mutations in the frataxin gene, leading to reduced frataxin protein levels. The most common mutation is a homozygous GAA trinucleotide repeat expansion in the first intron of the frataxin gene. Frataxin is a mitochondrial protein that is essential for mitochondrial function, and its deficiency results in mitochondrial dysfunction, iron accumulation and OS. The degeneration of large sensory neurons in the dorsal root ganglia is an early event in FA; however, the mechanism underlying their heightened vulnerability to frataxin deficiency remains unclear. Reduced ferritin levels (particularly FTH1) are critical for frataxin deficiency-induced ferroptosis, which exacerbates free iron toxicity and oxidative damage to drive neuronal death (67). Targeting ferritin expression or function, such as by enhancing FTH1 activity, may represent a potential therapeutic strategy for FA. In patients with FA, pathological damage to the dentate nucleus is characterized by the progressive atrophy of large neurons. Abnormal iron and ferritin accumulation in white matter oligodendrocytes may represent secondary pathological changes following neuronal atrophy (68). Patients with FA exhibit systemic iron storage depletion and intracellular alterations resembling iron starvation responses, indicating that iron dysregulation in FA reflects an intercompartmental iron redistribution imbalance rather than an absolute overload (69).

Hereditary ferritinopathy, a subtype of neurodegeneration with brain iron accumulation (NBIA), is primarily caused by frameshift mutations in the FTL gene. Its pathology involves the age-dependent amplification of cerebral iron/ferritin deposition. The core mechanism may not involve iron-mediated OS but rather aggregation of mutant FTL, ubiquitination and proteostasis imbalance, triggering cell death, a pathway shared with multiple neurodegenerative diseases (70).

TDP-43 pathological inclusions are hallmark features of limbic-predominant age-related TDP-43 encephalopathy neuropathological changes. Phosphorylated TDP-43 inclusions localized on the surface or interior of small blood vessels are termed Lin bodies. Shahidehpour *et al* (71) observed frequent co-localization of Lin bodies with ferritin, suggesting that post-hemorrhagic erythrophagocytosis elevates intracellular iron and iron storage proteins, including ferritin.

Progressive supranuclear palsy (PSP), a rare neurodegenerative disease, is characterized by the abnormal aggregation of 4-repeat tau and pathological tau structures (e.g., NFT, globular tangles). In patients with PSP, mitochondrial ferritin accumulates abnormally within substantia nigra neurons. Light chain 3 (LC3), an autophagosome marker, reflects the mitophagy status. The colocalization of LC3 with mitochondrial ferritin in the substantia nigra neurons of patients with PSP supports a model wherein the accumulation of mitochondrial ferritin initially exerts protective effects by chelating iron and reducing ROS levels (72). However, under sustained stress, this protective mechanism fails, leading to accumulated mitochondrial damage, enhanced mitophagy (marked by LC3 accumulation) and cell death (72).

Multiple sclerosis (MS) is a CNS autoimmune disease characterized by inflammatory demyelination and secondary neurodegeneration. Oligodendrocytes in the CNS produce myelin sheaths to wrap axons, enabling rapid saltatory conduction of nerve impulses and maintaining axonal structural integrity. A study using experimental autoimmune encephalomyelitis mice revealed that ferritinophagy controls the generation of lipid ROS via the Fenton reaction, inducing oligodendrocyte death and demyelination at the peak stage of the disease (73).

Multiple system atrophy (MSA), a rare neurodegenerative synucleinopathy, features α-Syn-positive cytoplasmic inclusions in oligodendrocytes, central to neurodegeneration. In an aged proteolipid protein-α-Syn mouse model, which overexpresses α-Syn in oligodendrocytes, iron accumulation and disrupted iron-ferritin interactions were observed in the substantia nigra, putamen and cerebellum (74). Iron elevation in MSA mice may involve ceruloplasmin dysfunction; therefore, targeting iron metabolism represents a potential therapeutic strategy (74).

Wilson's disease, also known as hepatolenticular degeneration, is a rare autosomal recessive disorder caused by ATPase copper transporting β mutations (13q14) that impair copper transport and cause copper accumulation in the liver, brain and kidneys. Of note, patients with Wilson's disease exhibit both copper and iron dysregulation. Elevated ferritin levels in Wilson's disease, which are partially reversible with copper chelation therapy, suggest that iron metabolism disturbances are linked to inflammation and copper toxicity, which require multidimensional interventions (75).

Other diseases. Ferroptosis, an iron-dependent, lipid peroxidation-driven form of cell death, has pathological significance extending beyond single diseases and is emerging as a core mechanism in diverse tissue injuries and chronic disorders. Understanding ferroptosis mechanisms in other diseases will facilitate the precise elucidation of its specificity in neurodegenerative pathologies.

With the global surge in the prevalence of type 2 diabetes (T2D), the associated cognitive dysfunction has become a research focus in neurometabolism, owing to its substantial impact on the quality of life of patients and as a public health burden. Elevated TfR levels alongside decreased ferritin, GPX4 and SLC7A11 levels in the hippocampal neurons of T2D model mice confirm that hippocampal neuronal ferroptosis activation is a crucial mechanism for cognitive impairment (76).

Iron accumulation and ROS synergistically induce neuronal dysfunction, which may constitute a critical mechanism of epileptogenesis. A previous study revealed that, compared with postmortem controls, ferritin expression in epileptic brains exhibited a significant relocation from microglia and oligodendrocytes to astrocytes (77). This finding suggests that strategies to reduce astrocytic iron uptake (thereby attenuating pro-inflammatory responses) may represent a novel therapeutic strategy for treating epilepsy (77).

Comparative analysis of ferritin dysregulation across neurodegenerative diseases. Neurodegenerative diseases share common pathways in iron dyshomeostasis, yet exhibit distinct, disease-specific manifestations. The common core lies in pathological iron accumulation within specific brain regions, which, through mechanisms such as OS and ferritinophagy, ultimately converges on ferroptosis, a shared cell death pathway. However, key features differ markedly among diseases: Regarding interacting pathological proteins, disrupted iron metabolism forms a vicious cycle with disease-specific protein aggregates: Aβ/tau in AD, α-Syn in PD and TDP-43 in ALS. In terms of predominantly affected cell types, ferritin responses in microglia are particularly prominent in AD and ALS, whereas oligodendrocyte dysfunction plays a more critical role in demyelinating disorders such as MS. In summary, ferritin-mediated iron dysregulation represents a shared pathological nexus in neurodegeneration, yet it is modulated by disease-specific molecular and cellular contexts. This understanding holds significant implications for developing broad-spectrum neuroprotective strategies and precision therapies targeted to specific diseases.

5. Ferritin as a biomarker for the diagnosis of neurodegenerative diseases

Early diagnosis and monitoring of neurodegenerative disorders, such as AD, PD and ALS, pose major challenges in clinical neuroscience. Dysregulated brain iron metabolism plays a pivotal role in neurodegenerative pathologies by mediating pathological processes, such as OS, protein misfolding and aggregation, and neuronal degeneration. As the core protein for intracellular iron storage, fluctuations in ferritin levels not only reflect the dynamic equilibrium of brain iron homeostasis but also highlight its double-edged sword nature; while buffering iron toxicity, ferritin may simultaneously

signal iron overload. This dual characteristic suggests that ferritin may be a promising multidimensional biomarker. Its disease-specific expression patterns in the CSF, peripheral blood and neuroimaging in heterogeneous conditions, such as AD, PD and ALS, offer new perspectives to overcome the spatiotemporal limitations of traditional biomarkers.

AD. AD is an irreversible neurodegenerative disorder characterized by chronic progressive dementia. Most patients with AD are diagnosed at advanced stages, and no effective therapies currently exist to halt or reverse its progression. Notably, AD has a prolonged preclinical phase before symptom onset; however, current diagnosis primarily relies on clinical observation, which underscores the urgent need for the early identification of specific biomarkers to enable precise diagnosis and intervention. AD is associated with chronic inflammation, OS, mitochondrial dysfunction and neurotoxicity. Studies have suggested that disrupted iron homeostasis may be another potential pathogenic factor in AD. Cerebral iron deposition exacerbates oxidative damage through the Fenton reaction, directly contributing to AD pathological processes. Iron homeostasis-associated proteins (e.g., ferritin, Tf), which are responsible for iron storage and transport, may reflect early-stage metabolic disturbances in AD through changes in their expression levels. Consequently, iron and iron-related proteins have emerged as potential biomarker candidates. However, its role in AD remains elusive.

CSF ferritin, a biomarker implicated in iron metabolism regulation and inflammatory responses, shows significant potential for the early detection of AD. CSF ferritin levels are significantly elevated during the preclinical stages of AD and correlate with complement activation and other inflammatory markers, suggesting its role as a key bridging molecule that links neuroinflammation and neurodegeneration (78,79). A recent systematic review and meta-analysis, encompassing 25 studies and 3,469 participants, confirmed that CSF ferritin levels are significantly elevated in patients with AD compared to controls (pooled standardized mean difference=0.44, 95% CI: 0.02-0.86) (80). This population-level evidence strengthens the case for ferritin as a quantifiable biomarker linked to AD pathology.

Regarding classic AD pathology, ferritin shows a particularly strong association with tau pathology. A positive correlation between CSF ferritin and p-tau levels was revealed and it was mediated by ApoE (49). Furthermore, regardless of the cerebral Aβ deposition status, CSF ferritin levels are consistently elevated in subjects with high total tau and correlate with other neuronal injury markers such as fatty acid-binding protein 3, collectively pointing to a tau-driven neurodegenerative pathway (38,81). However, CSF ferritin levels are not significantly associated with cerebral amyloid pathology (38). Taken together, these findings position CSF ferritin primarily as a marker related to tau pathology and consequent neurodegeneration, rather than a general marker of AD. This characteristic supports its utility in differential diagnosis. For instance, in cerebral amyloid angiopathy, which also features Aβ deposition, CSF ferritin correlates negatively with both Aβ-40 and Aβ-42 levels, a pattern distinct from that observed in AD, potentially aiding in distinguishing these frequently co-occurring disorders (82). It should be noted, however, that these findings are based on limited data and small sample sizes, necessitating further validation.

Serum ferritin levels in peripheral blood are also clinically relevant. Serum ferritin levels positively correlate with AD severity, and its combination with homocysteine and C-reactive protein significantly improves the diagnostic efficacy for AD with mild cognitive impairment (83). However, a longitudinal analysis of multiorgan blood parameters reported a negative correlation between plasma ferritin levels and AD severity, suggesting that its dynamic changes may be more complex and potentially useful as a marker of disease progression (84). Beyond AD-specific pathology, systemic factors such as chronic heart failure have been found to influence phosphorylated tau, possibly through the modulation of serum ferritin levels, revealing a potential interaction between systemic circulation and CNS pathology (85).

Finally, individual differences, including genotype and long-term dietary habits, significantly modulated the expression of AD biomarkers in the hippocampus (47). This adds a layer of complexity to the clinical application of ferritin and other biomarkers, emphasizing the necessity for a comprehensive perspective in future research and clinical interpretation that situates biomarkers within an individual's overall physiological and pathological contexts.

PD. Iron is essential for ROS generation, which induces OS and subsequent damage to neurons in the substantia nigra of patients with PD. Various techniques have been developed to assess iron and related biomarker concentrations. Biochemical analyses, histopathological studies and neuroimaging have demonstrated that iron deposition in patients with PD is primarily localized to the substantia nigra. However, investigations on iron levels across diverse biological fluids from patients with PD have yielded conflicting results regarding both the direction of change (increase, decrease or no difference) and their correlation with clinical features (86-88).

Emerging evidence suggests that ferritin levels are associated with disease progression and specific clinical manifestations of PD. In the CSF, a longitudinal study revealed a significant increase in total iron and a decrease in ferritin levels over time, indicating its potential as a dynamic marker of disease progression (87). Furthermore, elevated CSF ferritin levels negatively correlate with Mini-Mental State Examination scores in patients with PD dementia, supporting the detrimental role of cerebral iron accumulation in cognitive function (89). Furthermore, altered serum ferritin levels have been observed in patients with PD compared with healthy controls (90). Serum ferritin levels have also been positively correlated with the volumes of key brain structures, including the caudate nucleus and putamen, suggesting that serum ferritin levels may serve as a biomarker reflecting disease burden or the extent of neurodegeneration in PD (88). However, it is important to note that peripheral ferritin levels may not directly correlate with brain iron content as measured by specialized MRI techniques, and thus, their interpretation requires caution. Combining it with neuroimaging features could enhance this assessment.

The establishment of ferritin as a reliable biomarker faces significant challenges. First, study findings have been inconsistent. Some reports have found no significant differences in

serum ferritin or Tf levels between patients and controls (91). A systematic meta-analysis further highlighted that although neuroimaging techniques consistently show increased iron concentrations in the substantia nigra, serum and CSF iron-related parameters lack consistent changes (92). Second, ferritin lacks specificity, as plasma levels have been proven ineffective in predicting PD risk in individuals carrying pathogenic mutations in the gene encoding the enzyme β-glucocerebrosidase (93). More importantly, the correlation between peripheral iron indices and iron accumulation in the brain remains elusive. No significant association between subcortical iron and blood iron markers has been reported, suggesting that cerebral iron accumulation in neurodegeneration may be independent of systemic iron status and potentially regulated by local inflammatory processes (94).

Altogether, the value of ferritin as a biomarker is primarily related to disease progression and certain clinical symptoms. However, its specificity, sensitivity and complex relationship with the peripheral iron status are major obstacles. A Mendelian randomization study offered a new perspective, revealing a genetic causal link between lower serum iron levels (but not ferritin, total iron-binding capacity or Tf saturation) and increased PD risk (95). This Mendelian randomization study specifically links genetically lowered serum iron to PD risk. The absence of a link for ferritin in this analysis likely means that the genetic variants used are not strong drivers of ferritin levels; however, ferritin is not biologically unimportant in PD. This underscores the need to precisely define the roles of different iron metabolism parameters in future studies. Overall, ferritin is more likely to serve as a component of a multimodal biomarker panel than as a standalone diagnostic tool.

ALS. Emerging evidence highlights the critical role of ferritin as a biomarker of neurodegenerative disorders. Although dysregulated iron metabolism in PD is closely linked to nigral neurodegeneration and cognitive decline, similar iron homeostasis imbalances, marked by elevated serum ferritin levels, have been implicated in the pathophysiology of ALS, reflecting the shared yet distinct mechanisms of OS and neuroinflammation. A large-scale, multicenter, longitudinal, multimodal body fluid biomarker cohort study systematically evaluated the utility of multiple candidate biomarkers for ALS stratification and potential therapeutic evaluation, and demonstrated significantly elevated serum ferritin levels in patients with ALS (96). A systematic review and meta-analysis confirmed elevated serum ferritin levels in patients with ALS, and serum ferritin levels negatively correlated with survival (hazard ratio=1.38; 95% CI, 1.02-1.88; P=0.039) (97). These findings provide new evidence for the involvement of energy metabolism dysregulation, OS-mediated iron homeostasis imbalance and immune dysregulation in ALS pathophysiology.

Positioning and future directions of ferritin as a biomarker. Although ferritin levels in CSF and blood are altered (increased or decreased) in AD, PD and ALS, its use as an independent diagnostic biomarker with high sensitivity and specificity faces significant challenges. Most existing studies report associations but lack large-scale validation with unified, well-defined diagnostic cutoff values. Furthermore, the majority of research uses clinical diagnosis rather than more precise gold standards, such as amyloid-β positron emission tomography (Aβ-PET), tau-PET or neuropathology, as the reference, which introduces bias when evaluating diagnostic performance. Thus, the core clinical value of ferritin may not lie in replacing established core diagnostic markers, but rather in serving a complementary role. The most promising direction lies in combining ferritin with neurofilament light chain, neuroimaging measures and other inflammatory indicators to construct multimodal diagnostic models.

6. Therapeutic potential of ferritin in neurodegenerative diseases

Pathological progression of neurodegenerative diseases is closely linked to disrupted iron homeostasis in the brain. Ferritin, a key intracellular iron storage protein, mitigates OS by chelating free Fe^{3+}, thereby effectively reducing iron-mediated Fenton reactions and suppressing ROS generation. Studies have identified numerous compounds that target iron homeostasis for the treatment of neurodegenerative diseases (Table I) (98-109). For instance, ebselen, a synthetic organoselenium compound, reduces iron deposition by downregulating ferritin light chain expression, thereby suppressing oxidative stress and reversing cellular senescence (102). Donepezil, an acetylcholinesterase inhibitor used in Alzheimer's disease, has been shown to stabilize ferritin structure through high-affinity binding, suggesting a potential role in modulating cerebral iron metabolism beyond its cholinergic effects (103). However, none of these compounds have yet progressed to clinical trials. Therefore, it is important to note that their journey toward clinical application faces several recognized hurdles, which are critical areas for future research. Future efforts should focus on addressing these pharmacokinetic and safety challenges to advance the most viable candidates into the clinical development pipeline.

Promising preclinical data notwithstanding, several key challenges have hindered the clinical translation of ferroptosis inhibitors (e.g., ferrostatin-1) for neurodegenerative diseases (110). Key challenges include poor blood-brain barrier penetration, uncertain long-term safety given the physiological roles of iron and lipid metabolism and the coexistence of other cell death mechanisms (e.g., apoptosis), which may reduce the benefit of inhibiting ferroptosis alone. Advances in brain delivery, safety profiling and combination strategies are needed to move these agents toward clinical trials.

Furthermore, the unique hollow nanocage structure of ferritin makes it a promising nanocarrier for the targeted delivery of neuroprotective agents (111). Ferritin nanocages overcome the limitations of traditional delivery systems, owing to their superior biocompatibility, highly efficient hydrophobic molecule-loading capacity and targeted delivery properties. However, efficient crossing of the blood-brain barrier remains a significant challenge for these ~12-nm structures, with most work to date conducted *in vitro* or in peripheral cells (e.g., retina, peripheral blood mononuclear cells) rather than in the human brain *in vivo* (112,113). Ferritin nanocages enable the precise detection of pathological biomarkers, such as tau protein, and targeted drug delivery, providing innovative tools for non-invasive diagnosis and disease modulation. In one study, humanized ferritin nanocages were used to

Table I. Compounds targeting iron homeostasis for the treatment of neurodegenerative diseases and their mechanisms of action.

Name	Disease	Mechanism	Model	(Refs.)
Moschus	AD	Activates the Keap1/Nrf2 pathway to upregulate FTH1 expression, maintaining neuronal iron balance and inhibiting ferroptosis.	HT22 cells	(98)
SSF	AD	Significantly upregulates ferritin expression and reduces cerebral free iron levels, thereby inhibiting oxidative stress and ameliorating synaptic dysfunction and neuroplasticity damage.	Rats	(99)
Quercetin	AD	Specifically binds to key functional sites of human ferritin, stabilizing its conformation to regulate iron ion homeostasis.	In silico	(100)
Naringenin	AD	Specifically binds to key functional sites of human ferritin, stabilizing its conformation to regulate iron ion homeostasis.	In silico	(100)
Bryostatin 1	AD	Inhibits pathological iron accumulation through stable binding to ferritin.	In silico	(101)
Ebselen	AD	Reduces iron deposition by downregulating the FTL and reverses senescent cellular phenotypes.	SH-SY5Y cells	(102)
Donepezil	AD	Stabilizes the ferritin structure through high-affinity binding, potentially modulating cerebral iron metabolism.	In silico	(103)
EGCG	PD	Reduces iron influx by inhibiting the expression of the iron transporter Malvolio and promotes upregulation of the iron storage protein ferritin, thereby decreasing free iron levels and restoring cerebral iron homeostasis.	Drosophila	(104)
Morroniside	PD	Significantly reduced free iron levels by activating the nuclear factor Nrf2/ARE pathway and upregulating the expression of FTH1 and FPN.	Mice	(105)
Ginsenoside Rg1	PD	Regulates the expression of FTH and FTL in oligodendrocytes, restores cerebral iron metabolism homeostasis and suppresses lipid peroxidation, thereby enhancing dopaminergic neuron survival.	Mice	(106)
α-Lipoic acid	PD	Activates the SIRT1/Nrf2 signaling pathway, subsequently promoting the expression of FTH1 and GPX4, leading to significant improvement of motor dysfunction.	PC12 cells and mice	(107)
Ganoderic acid A	PD	Significantly alleviates dopaminergic neuron ferroptosis and motor impairments by specifically inhibiting the NCOA4-mediated ferritinophagy pathway.	Mice	(108)
Clozapine	PD	Its metabolite, clozapine-N-oxide, effectively blocks dopaminergic neuron ferroptosis by inhibiting ferritinophagy, thereby reducing intracellular iron release and lipid peroxidation.	SH-SY5Y cells and mice	(109)

SSF, flavonoids from stems and leaves of *Scutellaria baicalensis* Georgi; EGCG, epigallocatechin-3-gallate; AD, Alzheimer's disease; PD, Parkinson's disease; Keap1, Kelch-like ECH-associated protein 1; Nrf2, nuclear factor erythroid 2-related factor 2; FTH, ferritin heavy chain; FTL, ferritin light chain; ARE, antioxidant response element; FPN, ferroportin; SIRT1, sirtuin 1; GPX4, glutathione peroxidase 4; NCOA4, nuclear coactivator 4.

efficiently deliver the hydrophobic BODIPY fluorescent probe BT1, thus resolving the challenges of probe solubility and targeted delivery. This achieved high-sensitivity and low-toxicity detection of pathological tau proteins in live human retinal cells, establishing a novel nanotechnology platform for early non-invasive AD diagnosis (112). Peripheral blood mononuclear cells (PBMCs) from patients with AD exhibit neuron-like pathological features (e.g., mitochondrial dysfunction, OS) and serve as critical models for exploring neuroinflammation and apoptosis mechanisms. In addition, as a convenient *in vitro* platform, PBMCs are widely used to screen the therapeutic effects of drug candidates, offering vital insights for the development of AD treatment strategies. Researchers have developed H-subunit ferritin nanocages loaded with bisdemethoxycurcumin, which significantly improves water solubility, stability and blood-brain barrier penetration capability. This nanocarrier demonstrated targeted modulation of inflammation-related gene expression

in PBMCs from patients with AD, reversing the imbalance between pro-inflammatory and anti-inflammatory genes, thereby providing a novel delivery strategy for neuroinflammatory intervention (113). Another study developed a sequence-targeted nanodelivery system based on recombinant human H-ferritin, which significantly enhanced lycopene enrichment in neurons through receptor-mediated blood-brain barrier penetration and mitochondrial targeting, activating pro-survival mitophagy and clearing pathological α-Syn aggregates. This study demonstrated the unique advantages of ferritin nanocarriers for neurodegenerative disease treatment, including intrinsic biocompatibility, non-invasive delivery capability and multi-mechanism coordination, providing an innovative paradigm for next-generation brain-targeted nanotherapeutics (114).

7. MRI-based evaluation of brain iron homeostasis in neurodegenerative disorders

Dysregulated cerebral iron homeostasis is a pathological hallmark of neurodegenerative diseases. Exploiting the paramagnetic properties of iron, MRI is the only effective modality for *in vivo* assessment of brain iron deposition (65). Although conventional MRI techniques are sensitive to changes in total iron concentration, they lack the chemical specificity needed to distinguish between different iron pools, such as toxic redox-active iron and protective iron safely stored within proteins like ferritin (115). Recent advancements in novel MRI methodologies have shifted the paradigm from measuring iron deposition towards assessing the more biologically relevant iron homeostasis.

Emerging evidence indicates that the analysis of r_1-r_2^* relaxometry enables non-invasive evaluation of brain iron homeostasis *in vivo*. This technique successfully delineated the characteristic paramagnetic profiles of ferritin, Tf and free Fe^{2+}, revealing the spatial heterogeneity in the iron mobilization capacity across brain regions and its dynamic changes during aging (116). These findings suggest that novel biomarkers can be used for early diagnosis. The physical basis for this advancement lies in pathological alterations in the ferritin mineral core. Under physiological conditions, the ferritin core is predominantly composed of superparamagnetic ferrihydrite, whereas under pathological conditions, it is enriched with strongly magnetic magnetite. A comparative study evaluating relaxivity differences between native ferritin and magnetoferritin under a 7T magnetic field validated the ability of MRI to distinguish mineralogical features. This provides a potential tool for the non-invasive diagnosis of ferritin-related iron accumulation and pathogenic magnetization processes, as observed in neurodegenerative diseases (115). Complementarily, off-resonance saturation (ORS) MRI has achieved the specific quantification of ferritin-bound iron in postmortem human brain tissue. The distribution of this iron was highly co-localized with pathological iron deposits, further confirming that the magnetic properties of ferritin as superparamagnetic nanoparticles can be precisely captured (117).

In patients with PD, quantitative susceptibility mapping (QSM) and susceptibility weighted imaging (SWI) offer complementary functions; QSM provides an accurate three-dimensional quantification of the iron concentration in the substantia nigra, whereas SWI delivers a high-contrast visualization of lesions. Together, these studies reveal the core features of abnormally elevated iron concentrations in the substantia nigra pars compacta of patients with PD (92). Notably, iron overload in PD is initiated in the nigrosome-1 region, with most the iron bound to ferritin. Although neuromelanin has a lower total iron load, it is a major contributor to the R_2^* relaxation signal, indicating differential contributions of various iron pools to the MRI signal (118). However, it remains elusive whether this regional iron accumulation directly contributes to neuronal death or represents a compensatory mechanism. Furthermore, the strong correlation between QSM magnetic susceptibility and transcranial sonography (TCS) measures of substantia nigra echogenicity suggests that iron accumulation is the underlying mechanism of nigral hyperechogenicity. The combined application of QSM and TCS may provide a multimodal clinical assessment framework for PD (119,120).

In summary, novel MRI techniques such as r_1-r_2^* relaxometry, QSM, SWI and ORS are progressively deciphering the mechanisms of disrupted cerebral iron metabolism by revealing chemically specific changes in ferritin levels. These non-invasive imaging biomarkers hold significant promise as key players in the early diagnosis, subtype classification and therapeutic monitoring of neurodegenerative diseases.

8. Conclusions and future perspectives

Emerging evidence indicates that various environmental stressors, particularly airborne pollutants, such as formaldehyde and fine particulate matter (PM), can exert neurotoxic effects by dysregulating ferritinophagy, a selective form of autophagy for ferritin degradation. This dysregulation subsequently disrupts cellular iron homeostasis, implicating ferritinophagy as a critical mechanistic link in pollutant-induced neurotoxicity. Formaldehyde is neurotoxic and can trigger neurodegenerative diseases (121). Formaldehyde induced hippocampal neuronal cell damage by promoting ferritinophagy, while hydrogen sulfide (H_2S) exerted protective effects against formaldehyde-induced neurotoxicity in HT22 cells (a murine hippocampal neuronal cell line) (121,122). Furthermore, H_2S antagonizes formaldehyde neurotoxicity by upregulating growth differentiation factor 11, which suppresses ferritinophagy and ferroptosis (122). PM2.5 refers to particulate matter with an aerodynamic diameter ≤2.5 micrometers. Accumulating evidence indicates that chronic PM2.5 exposure induces neuroinflammation and neurodegeneration. In mouse neuroblastoma N2a cells, PM2.5 exposure disrupts autophagic flux by impairing lysosomal function. Autophagic dysfunction hinders the intracellular degradation of ferroptosis-related proteins, such as GPX4 and ferritin, thereby inhibiting ferroptosis (123). Conversely, a study in human neuroblastoma SH-SY5Y cells demonstrated that PM2.5 induces autophagy-dependent ferroptosis via endoplasmic reticulum stress, which is potentially linked to NCOA4-mediated ferritinophagy-driven iron accumulation (124). These findings reveal opposite effects of PM2.5 on autophagy and ferroptosis across different neuronal cell lines (inhibition vs. induction), underscoring the cell-type-specific nature of the response to this environmental stressor. Based on the shared mechanism by which formaldehyde and PM2.5 disrupt ferritinophagy to

exert neurotoxic effects, future research on neurodegenerative diseases in human populations must systematically integrate long-term individual environmental exposure data. Employing molecular epidemiological approaches to validate the environmental exposure-disrupted iron metabolism-disease onset pathway in human populations will provide crucial scientific evidence for the precise prevention and early identification of these diseases.

Emerging evidence suggests that both intrinsic physiological states and extrinsic environmental factors are critical modulators of iron homeostasis in the brain and influence the pathophysiology of neurodegenerative diseases. For instance, in a *Drosophila* phosphatase and tensin homolog induced kinase 1 knockdown model, mating behavior was found to alleviate OS via a dual mechanism: Suppression of iron import and upregulation of ferritin (125). Dietary iron intake is another potent regulator, with complex outcomes. Although an iron-restricted diet in adult rats triggers systemic metabolic adaptations that maintained brain iron levels (126), a high-iron diet in aged mice directly promotes the accumulation of AD-related pathological proteins (e.g., phosphorylated tau and Aβ1-42) in the hippocampus and cortex (127). These compelling findings highlight a significant and often-overlooked source of experimental variability. Therefore, future studies utilizing animal models of neurodegenerative diseases must systematically incorporate and report key parameters, such as mating status and dietary composition, as standard practice. Acknowledging and controlling these variables are essential for enhancing the reproducibility, interpretability and translational value of preclinical research.

β-propeller protein-associated neurodegeneration (BPAN), a recently identified subtype of NBIA, is the only X-linked dominant subtype caused by mutations in the WD repeat domain 45 (*WDR45*)/*WIPI4* gene (128). *WDR45* knockout in SH-SY5Y neuroblastoma cells does not alter NCOA4 levels, suggesting that *WDR45* deficiency impairs amphisome-lysosome fusion or lysosomal function, rather than autophagosome formation (129). However, Tsukida *et al* (130) observed significantly reduced NCOA4 expression in patient-derived cells harboring *WDR45* variants, leading to ferritinophagy dysfunction and subsequent dysregulation of iron metabolism. The temporal discrepancy between these studies warrants attention: NCOA4 downregulation observed by Tsukida *et al* (130) may represent a secondary effect of chronic lysosomal dysfunction, whereas acute *WDR45* knockout in SH-SY5Y models may not yet reach the threshold for triggering NCOA4 degradation. Further studies are required to elucidate how *WDR45* variants affect ferritinophagy inpatients exhibiting BPAN.

Insulin-like growth factor binding protein-2 (IGFBP-2) is a regulatory factor in diabetes that primarily modulates insulin metabolism via the IGF signaling pathway. miRNAs promote neuroinflammation and neuronal damage in AD by regulating IGFBP-2 overexpression and neuronal ferritin deposition, thereby disrupting the balance of the Nrf2/SLC7A11/GPX4 pathway and exacerbating OS and ferroptosis (131). These findings reveal a potential mechanistic link between diabetes and AD; IGFBP-2, a key regulatory factor in diabetes, may also drive AD neurodegeneration by mediating ferroptosis. This suggests that diabetes-related insulin resistance and metabolic disturbances may exacerbate cerebral OS and iron dyshomeostasis through shared molecules, such as IGFBP-2, thereby increasing the risk of AD. Elucidating this connection is important for understanding the comorbid mechanisms of these two diseases.

Although this review synthesizes substantial evidence linking dysregulated ferritin dynamics to neurodegenerative pathology, the findings primarily reflect correlational observations. A key knowledge gap remains regarding the direction of causality: It remains to be determined whether alterations in ferritin dynamics, such as aberrant expression or ferritinophagy, act as primary drivers of neuronal loss or represent secondary consequences of upstream pathological processes, including mitochondrial dysfunction and neuroinflammation. Future studies should prioritize research designs and analytical methods that strengthen causal inference. For example, Mendelian randomization analysis, which uses genetic variants as instrumental variables for iron homeostasis traits like serum ferritin and iron levels, can help estimate the potential causal effects of these traits on neurodegenerative disease risk while minimizing confounding from environmental factors (132). In addition to Mendelian randomization, future research should adopt longitudinal study designs to establish the temporality of ferritin dysregulation, determining whether these changes precede the onset of clinical symptoms. Investigating the dose-response relationship between brain iron accumulation and the rate of cognitive or motor decline will further support a causal link. In addition, evaluating these associations against established causal frameworks, such as the Bradford Hill criteria, can provide a structured approach to weigh the totality of evidence - from the strength and consistency of the observed associations across different studies to the biological plausibility and experimental evidence derived from *in vitro* and *in vivo* models of ferroptosis inhibition (133).

Iron dyshomeostasis participates profoundly in the pathological progression of neurodegenerative diseases, including PD, AD and ALS. As a core iron-storage protein, ferritin plays a critical role in the regulation of dynamic iron homeostasis in the brain. However, significant knowledge gaps persist regarding the transmembrane transport mechanisms between neurons and glial cells, as well as their functional transformation within disease microenvironments. Ferritinophagy, a central pathway for ferritin-mediated iron release, requires the systematic elucidation of its molecular regulatory networks and spatiotemporally specific activation patterns in neurodegenerative pathologies. Ferroptosis, an iron-dependent, lipid peroxidation-driven form of cell death, is increasingly implicated in neurodegenerative diseases. Of particular interest, advances in understanding ferroptosis regulatory pathways in other diseases, such as T2D and epilepsy, have provided novel perspectives on the molecular interplay between cerebral iron dysregulation and neuronal degeneration. From a clinical translation standpoint, ferritin has potential as a biomarker for early diagnosis of neurodegenerative diseases, although its sensitivity and specificity require further validation through multicenter large-scale cohort studies. In therapeutic development, ferritin-targeted interventions, such as modulating its synthesis/degradation balance or blocking pathological iron release, have shown preliminary efficacy in delaying disease progression by restoring cerebral iron homeostasis. Nonetheless, overcoming technical challenges, including

blood-brain-barrier delivery efficiency and cell-specific targeting, remains crucial. Future studies should integrate multiomics technologies, organoid models and live imaging approaches to systematically unravel the spatiotemporal regulatory dynamics of ferritin networks in neurodegeneration, thereby advancing the application of precision diagnostics and therapeutic strategies.

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Availability of data and materials

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Authors' contributions

WC, HT and RW wrote the manuscript. XC created the figures and table. YJ supervised the review, revised the manuscript, obtained financial support, conceptualized the review and performed the literature search. All the authors have read and approved the final version of this manuscript. Data authentication is not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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