

Review

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Structural and functional modulation of iron accumulation on α -synuclein protein in Parkinson's disease: a mini review

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How to cite this article: Xiang M, Zhang J, Wang C, Wu X, Cao S, Song D, Dou H, Feng C, Li W. Structural and functional modulation of iron accumulation on α -synuclein protein in Parkinson's disease: a mini review. *Ageing Neur Dis.* 2025;5:11. <https://dx.doi.org/10.20517/and.2024.37>

Received: 1 Dec 2024 **First Decision:** 7 Apr 2025 **Revised:** 29 Apr 2025 **Accepted:** 9 May 2025 **Published:** 27 May 2025

Academic Editor: Weidong Le **Copy Editor:** Pei-Yun Wang **Production Editor:** Pei-Yun Wang

Abstract

α -Synuclein (α -syn) aggregation represents a key pathological hallmark of Parkinson's disease (PD), with its aggregation and propagation closely associated with disease progression. While the precise mechanisms underlying α -syn amyloidogenesis remain unclear, iron deposition, another prominent pathological feature in PD, has been shown to promote α -syn aggregation through undefined pathways. Conversely, α -syn aggregates may influence iron-dependent cell death pathways. In this mini-review, we synthesize recent evidence on the direct structural interactions between iron and α -syn, the iron-mediated regulation of α -syn protein turnover, and the potential mechanisms by which α -syn promotes iron-dependent cell death. By elucidating these bidirectional interactions between proteinopathy and redox imbalance, we aim to provide mechanistic insights for developing pathology-targeted therapeutic strategies in PD.

Keywords: α -Synuclein (α -syn), iron accumulation, ferroptosis, Parkinson's disease (PD)



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INTRODUCTION

α -Synuclein (α -syn) aggregation is the pathological hallmark of Parkinson's disease (PD) and related disorders, including Lewy body dementia (DLB), multiple system atrophy (MSA), and Alzheimer's disease (AD) - collectively termed synucleinopathies^[1,2]. The protein sequence of α -syn contains 140 amino acids encoded by the *SNCA* gene, though its physiological roles remain incompletely understood. It regulates synaptic neurotransmitter release and consists of three domains: (1) an N-terminal lipid-binding amphipathic region; (2) a central amyloidogenic domain (residues 61-95, also called the non-amyloid- β component core); and (3) a C-terminal acidic domain that maintains the protein's intrinsically disordered structure. This unfolded conformation, combined with pathogenic *SNCA* mutations, may promote α -syn aggregation^[3]. Monomeric α -syn accumulates in neurons and glia, inducing cellular dysfunctions such as mitochondrial deficiency^[4], leading to cell death eventually. The exact mechanisms of α -syn aggregation formation are not yet clear, forming obstacles in studying effective pathology targeting therapy for synucleinopathies.

As early as 1988, iron was found accumulating in PD patients nigra and multiple brain regions, with an increased iron deposition level of 176% compared to control subjects^[5]. Quantitative susceptibility mapping analyses confirmed the significant deposition of iron in PD patients' substantia nigra (SN) pars compacta, accentuating the close link between iron deposition and PD progress^[6]. Moreover, iron was spotted in the core of Lewy bodies (LBs) in the residual neurons of postmortem brain tissue from PD patients^[7]. Pigmented staining of iron was found under electron microscopy in PD patient brain, co-existing with α -syn aggregation in both the SN and globus pallidus^[8]. Addition of iron elements triggered α -syn aggregation *in vitro*^[9,10]. Taken together, these findings strongly suggest the mechanistic link between iron accumulation and α -syn aggregation in PD. Revealing the pathomechanistic process of iron affecting pathology formation may be a niche for developing therapeutic interventions for PD.

In this mini-review, we systematically examine the potential association between iron deposition and α -syn aggregation through two primary mechanisms: (1) direct structural modifications and (2) indirect regulation via post-transcriptional, post-translational, and proteolytic processes. Furthermore, we explore the potential interplay between α -syn pathology and iron accumulation in the progression of dopaminergic neuron ferroptosis. Our analysis seeks to establish connections between PD pathogenesis and cellular redox imbalance. By synthesizing current evidence on iron-mediated promotion of α -syn aggregation and its molecular mechanisms, this review aims to provide a conceptual framework for future therapeutic development targeting both metal chelation and pathological protein aggregation in PD.

DIRECT STRUCTURAL LINKS BETWEEN IRON AND α -SYN CONFORMATION

Iron deposition has been shown to promote α -syn aggregation both *in vitro* and *in vivo*, although the exact structural basis and underlying mechanisms remain unknown. Recent studies have revealed structural links between iron and α -syn molecules. Both ferrous (Fe^{2+}) and ferric (Fe^{3+}) irons exhibit binding affinity for α -syn, suggesting a structural link between iron and α -syn protein conformation^[11]. A native nano-electrospray ionization ion mobility-mass spectrometry study showed specific effects of iron on electrostatic charge patterns and the complex structural space of α -syn aggregates^[12]. Additionally, cryo-electron microscopy findings support the direct binding of Fe^{3+} to α -syn, which accelerates α -syn fibrilization at low concentrations^[13]. All these suggest that iron can promote α -syn amyloidogenesis via direct structural binding.

Recent reports have revealed that iron ($\text{Fe}^{2+}/\text{Fe}^{3+}$) can bind to α -syn through multiple mechanisms, leading to conformational changes in the protein^[10,14]. Traditionally, Fe^{2+} was believed to bind primarily to specific sites of α -syn C terminus, with Asp121 residue as the main anchoring site. Similar binding behavior has been observed with other divalent metals, such as copper^[15,16]. However, the binding affinity of divalent iron was once shown to be only moderate. The Fe^{2+} - α -syn intermediate complex can be electrochemically oxidized to the α -syn- Fe^{3+} complex, resulting in more stable and persistent binding^[11]. At a single-particle level, Fe^{3+} has been shown to improve both the rate and size of oligomer formation, with formed large oligomers resistant to sodium dodecyl sulfate treatment, suggesting a rather stable intermediate formation between Fe^{3+} and α -syn compared to Fe^{2+} ^[17]. However, under hypoxic conditions, Fe^{2+} can bind to the N-terminus of α -syn and induce the formation of oligomeric structures that do not convert into β -sheet fibrils. When aerobic conditions are restored, these transient α -syn- Fe^{2+} complexes disappear^[18]. Notably, the amyloidogenic effect of Fe^{3+} on α -syn has been observed only at low molar ratios; at high concentrations, Fe^{3+} inhibits fibril formation^[12,13]. A Cryo-EM study revealed atomic-level interactions between α -syn and Fe^{3+} at His50 and Glu57, which together form a negatively charged pocket on the fibril surface^[13].

IRON DEPOSITION MODULATES THE PROTEIN TURNOVER OF α -SYN

Although iron directly influences α -syn aggregation through structural interactions, iron deposition can also indirectly modulate both α -syn protein levels and fibrillization through three key mechanisms: (1) altering α -syn biogenesis; (2) modifying post-translational processing of α -syn; and (3) impairing α -syn clearance.

Iron deposition promotes α -syn synthesis

Iron homeostasis in humans is regulated by the interaction between iron-regulatory proteins (IRPs) and iron-responsive elements (IREs)^[19]. When IRPs bind to IREs, they regulate the translation of ferritin mRNA^[20]. IREs are non-coding sequences in the untranslated regions of transcripts (UTRs) of mRNAs. These elements typically contain long RNA motifs, within which a CAGUGN sequence forms a stem-loop structure. The IRE motifs help control intracellular iron levels by regulating the mRNAs of ferritin, transferrin receptor (TFR), and divalent metal transporter-1 (DMT1)^[21,22]. The IRP-IRE regulatory system operates at the post-transcriptional level and is sensitive to cellular iron availability. Under conditions of iron deficiency, IRP-IRE coordinates an adaptation response to increase cellular iron uptake while reducing iron storage by stabilizing TFR mRNA - thus increasing transferrin expression - and blocking ferritin mRNA translation. The resulting upregulation of transferrin enhances iron uptake, while reduced ferritin levels limit iron storage and sequestration^[21].

The IRP-IRE pathway contributes to PD pathogenesis through multiple mechanisms. Experimental knockdown of IRPs has been shown to significantly reduce dopamine levels in mouse brains due to pathological cytoplasmic iron accumulation and subsequent redox toxicity^[23]. Correspondingly, IRP-deficient mice exhibit dopaminergic neuron dysfunction and motor deficits^[23,24]. Notably, recent studies have identified RNA stem-loop structures containing GAGUGN motifs in the 5'-untranslated region (5'-UTR) of α -syn mRNA, suggesting potential iron-mediated regulation of α -syn expression^[25,26]. Biochemical studies demonstrate that IRPs bind to these IRE motifs in α -syn mRNA, thereby inhibiting its translation. However, under conditions of iron overload, excess iron sequesters available IRPs, attenuating this inhibitory IRP-IRE interaction and consequently promoting α -syn protein accumulation and aggregation^[27]. Importantly, artificial IRE inhibitors have been shown to effectively substitute for IRP function and prevent excessive α -syn synthesis^[28]. The unique UTR sequences in human α -syn mRNA provide a molecular basis for iron accumulation to potentially stimulate α -syn production^[29]. The elevated iron deposition observed in both PD patients and animal models may therefore exacerbate α -syn pathology by enhancing its biosynthesis at the post-transcriptional level.

Post-translational modifications of α -syn and its interaction with iron

After its biosynthesis, α -syn undergoes multiple paths of post-translational modifications (PTMs). Some of these PTMs are closely related to the aggregation potency of α -syn, such as phosphorylation and ubiquitination^[3]. In postmortem brains of PD patients, increased levels of phosphorylated α -syn in different brain regions have been observed, implying the close relation between PTMs and pathology formation. Among different kinds of α -syn PTMs, phosphorylation is found in 90% of the α -syn in disease conditions, making it the major PTM associated with pathology development^[30]. There are currently no direct relations reported between iron deposition and the extents and types of α -syn PTMs. However, iron may promote the α -syn phosphorylation by regulating cellular oxidative stress. Overloaded iron was shown to increase the level of phosphorylated α -syn in cultured SH-SY5Y cells and PD rodent models, accompanied by Polo-like kinase 2 (PLK2) and Casein kinase 2 (CK2) accumulation^[31]. Increased levels of both PLK2 and CK2 could promote protein phosphorylation^[32-35]. The inhibition of both CK2 and PLK2 could reverse the upregulation of α -syn phosphorylation but not α -syn accumulation induced by iron deposition, reinforcing the direct pro-synthetic effect of iron on α -syn^[31]. The phosphorylation residues of α -syn mainly locate at the C-terminal, adjacent to iron-binding sites. It was shown that phosphorylation at Ser129 and Tyr125 residues increases the binding affinity of Fe^{2+} to α -syn, suggesting a pathogenic association between α -syn phosphorylation and iron modulation of α -syn aggregation^[36]. Tyr125 phosphorylation loci were reported to selectively bind to trivalent iron, inducing α -syn dimerization through metal ion cross-linking^[37]. PTMs, especially phosphorylation of α -syn, affect its iron-binding affinity, which may in turn influence the expression level of α -syn protein and the conformation of α -syn aggregates, forming a viscous cycle for α -syn amyloidogenesis.

Iron dysregulation impairs α -syn clearance

The clearance of intracellular α -syn relies mainly on the selective autophagy and proteasome degradation^[38]. The autophagy-lysosome pathway (ALP), including macroautophagy and chaperone-mediated autophagy (CMA), plays a major role in α -syn protein turnover^[39,40]. Early studies have documented the clearance of oligomeric α -syn by lysosomes^[41]. ALP inhibition by Bafilomycin increased the excretion of α -syn extracellularly, inducing an exacerbated microenvironment facilitating cell death^[42]. The ubiquitin-proteasome system (UPS) targets mainly small, damaged or misfolded proteins. Ubiquitinated α -syn stays in the soluble pool of protein, standing in queue for proteasome degradation, alleviating the aggregate burden of cells^[39,43,44]. Iron was reported to significantly inhibit autophagosome formation and induce α -syn aggregation by increasing reactive oxygen species (ROS) production *in vitro*, which can be attenuated by Rapamycin treatment^[45]. Iron overload in cells impairs autophagy flux and ferroptosis by inhibiting activating transcription factor 4 (ATF4), while insufficient cellular iron initiates endoplasmic reticulum (ER) stress and leads to apoptosis. Dyshomeostasis of iron metabolism regulates cell death pathways by inducing insufficient ALP function^[46]. Dysfunction in the ALP pathway could further inhibit the ferritin degradation by lysosomes, inducing ferritinophagy and more severe iron dyshomeostasis^[47]. Moreover, it has been reported that Fe^{3+} could directly permeabilize the lysosome membrane, potentially leading to ALP dysfunction and CMA deficiencies^[48]. Regarding the UPS system, ligand-binding iron complex was shown to inhibit 20S proteasome^[49]. A high concentration of trivalent iron inhibits the 26S proteasome, causing dose-dependent accumulation of polyubiquitinated proteins in multiple myeloma cells^[50]. Proteasome inhibition was proven able to rescue cyclin-dependent kinase deficiency caused by excessive iron chelation, reinforcing the interaction between iron deposition and UPS function^[51].

IRON AND α -SYN IN THE PROCESS OF FERROPTOSIS

Ferroptosis is a distinct form of iron-dependent regulated cell death characterized by iron accumulation and lipid peroxidation, differing mechanistically from classical apoptosis^[52]. Under physiological conditions, intracellular iron homeostasis is tightly regulated by the IRP-IRE system, which controls cytoplasmic iron

concentrations^[53]. Iron undergoes a dynamic cycle of internalization, utilization, storage, and excretion, cycling between its divalent (Fe^{2+}) and trivalent (Fe^{3+}) states^[54]. Following cellular uptake via transferrin-mediated endocytosis, iron is initially present as Fe^{3+} and sequestered within endosomal and nuclear vesicles, where it is subsequently reduced to Fe^{2+} ^[55-57]. The DMT1 then transports divalent iron to the plasma to form the labile iron pool^[57]. The functional iron for cell activities originates from the labile iron pool^[58]. However, excess cytosolic Fe^{2+} can catalyze the generation of ROS via Fenton chemistry^[59,60]. The resulting oxidative stress, marked by ROS overproduction, triggers detrimental downstream effects, including membrane lipid peroxidation - a defining feature of ferroptosis^[61].

Ferroptosis, while strongly associated with iron deposition, is simultaneously regulated through interconnected lipid and amino acid metabolic pathways. A critical biochemical aspect of ferroptosis involves the lipid peroxidation cascade, for which polyunsaturated fatty acids (PUFAs) serve as essential molecular substrates^[62,63]. These PUFAs form stable complexes with membrane phospholipids, creating the structural foundation for the peroxidation process that represents a defining feature of ferroptotic cell death. The peroxidation reactions can be initiated through two distinct mechanisms: (1) non-enzymatic catalysis via free Fe^{2+} through Fenton chemistry; or (2) enzymatic oxidation mediated by lipoxygenases and related oxidoreductases^[63]. Pathological dysregulation at any point in these complex biochemical pathways may result in the uncontrolled generation of lipid peroxides and ROS, thereby establishing the necessary conditions for ferroptosis to proceed.

The cellular defense against ferroptosis is principally mediated by glutathione peroxidase 4 (GPX4), which functions as the central inhibitory regulator of this cell death pathway. During oxidative stress conditions characterized by Fenton reaction activity, GPX4 catalyzes the critical conversion of toxic lipid hydroperoxides (L-OOH) into their non-toxic alcohol derivatives (L-OH), thereby interrupting the chain reaction of lipid peroxidation^[64-66]. This protective enzymatic activity absolutely requires reduced glutathione (GSH) as an essential cofactor - a tripeptide composed of glutamate, cysteine, and glycine residues^[67]. Consequently, any impairment or deficiency in GSH biosynthesis inevitably leads to compromised GPX4 activity and consequently heightened cellular susceptibility to ferroptosis.

Under the pathological conditions observed in PD, the accumulation of α -syn aggregates exerts profound effects on iron-dependent cell death processes by simultaneously disrupting three fundamental regulatory axes of ferroptosis: (1) iron homeostasis; (2) lipid metabolism; and (3) GSH synthesis [Figure 1]. Multiple studies have demonstrated that α -syn overexpression leads to significant upregulation of free Fe^{2+} concentrations in the cytoplasmic compartment, achieved primarily through increased expression of DMT1^[68,69]. This iron overload subsequently amplifies Fenton reaction kinetics and dramatically elevates downstream ROS production. Furthermore, α -syn has been shown to directly induce cellular oxidative stress through its inhibitory effects on mitochondrial oxidative phosphorylation complexes, thereby creating an additional source of ROS generation independent of iron metabolism^[70].

In patient-derived neural progenitor cells, SNCA triplication caused increased vulnerability of cells toward ferroptosis, accompanied by excessive lipid peroxidation. Decreasing α -syn expression level significantly lowered the severity of ferroptosis by reducing ether-linked phospholipids^[71]. Aggregated α -syn interacts directly with PUFAs and other membrane phospholipids, potentiating lipid peroxidation and sequential ferroptosis. The membrane-aggregate interaction is critical for the initiation of ferroptosis, impacting both the conformation of α -syn aggregates and the extent of lipid peroxidation. Excessive amount of glutamate and dopamine in human induced pluripotent stem cell (iPSC)-derived neurons drives more α -syn aggregates to the membrane, which facilitates lipid peroxidation and cell death^[72,73]. Enhanced intracellular

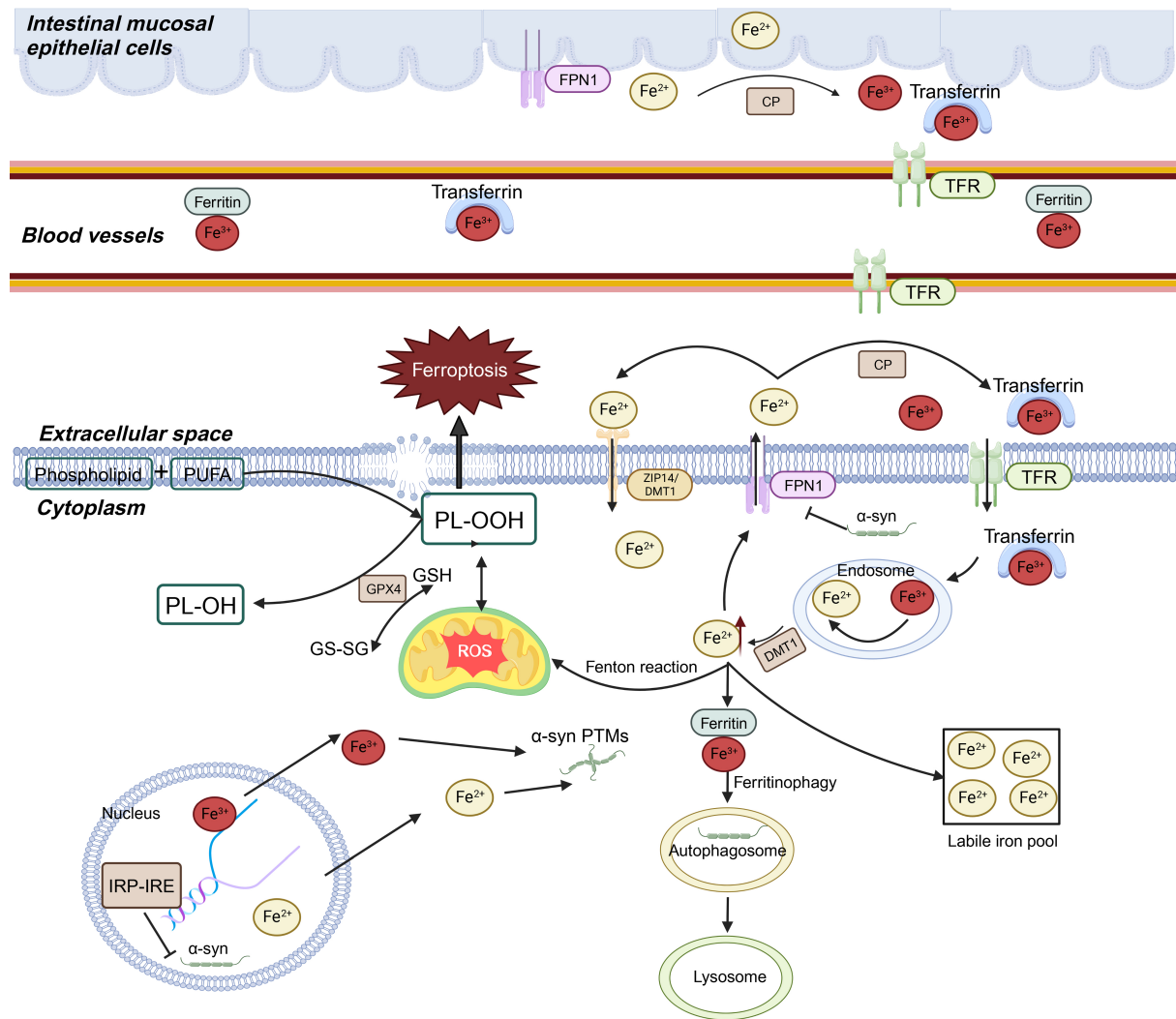


Figure 1. Iron metabolism pathways in physiological and α -syn-associated pathological conditions. FPN1: Ferroportin 1; TFR: transferrin receptor; PL-OOH: phospholipid hydroperoxide; PL-OH: phospholipid alcohols; PUFA: polyunsaturated fatty acid; GSH: glutathione; GPX4: glutathione peroxidase 4; GS-SG: glutathione disulfide; ROS: reactive oxygen species; DMT1: divalent metal transporter 1; IRP-IRE: iron regulatory protein-iron responsive element.

level of α -syn aggregation inhibits GPX4 function by disrupting the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway^[74]. In summary, in PD and related disorders, overloaded α -syn aggregates can promote ferroptosis, possibly by inducing iron accumulation, interacting with membrane lipids, and interrupting GPX4 function^[75].

This diagram depicts iron metabolism under physiological conditions, beginning with the absorption of dietary iron in its ferrous form (Fe^{2+}) by specialized intestinal mucosal epithelial cells (enterocytes) through apical membrane transporters. Following absorption, the Fe^{2+} is transported across the basolateral membrane into the bloodstream via ferroportin-mediated export. Within the circulation, the ferrous ions undergo oxidation to their ferric state (Fe^{3+}) through the enzymatic action of the multi-copper oxidase ceruloplasmin, which is essential for proper iron loading onto transferrin. The newly formed Fe^{3+} ions then partition into two distinct pools: a significant portion becomes incorporated into the iron-storage protein ferritin within cells throughout the body, while the remainder binds tightly to the plasma iron transport

protein transferrin, forming the transferrin-iron complex that circulates in the blood. The transferrin-bound iron gains entry into cells through the highly regulated TFR-mediated endocytosis, wherein the transferrin-receptor complex undergoes internalization within clathrin-coated pits. Additionally, a fraction of circulating iron exists as non-transferrin-bound iron (NTBI), which must first be reduced from Fe^{3+} back to Fe^{2+} by cell surface reductases before it can be transported across the plasma membrane through the combined action of the DMT1 and Zrt- and Irt-like Protein 14 (ZIP14) metal ion transporters. Cellular iron homeostasis is maintained through the regulated export of excess ferrous iron by the only known mammalian iron exporter, ferroportin 1 (FPN1), which works in concert with ceruloplasmin to facilitate iron release from tissues. Once inside cells through transferrin-mediated uptake, iron remains temporarily sequestered within endosomal compartments and nuclear vesicles, where the Fe^{3+} is reduced to Fe^{2+} by endosomal reductases before being transported into the cytosol through DMT1 present on endosomal membranes. This cytosolic iron can participate in the Fenton reaction, generating ROS through the reduction of hydrogen peroxide. Unincorporated iron ions may bind to cytosolic ferritin for safe storage or undergo ferritinophagy, the selective autophagic degradation of ferritin that releases iron back into the labile iron pool. Pathologically, α -syn disrupts these carefully balanced processes through multiple mechanisms: it promotes excessive iron transfer to the plasma by upregulating DMT1 expression; directly interacts with PUFAs and membrane phospholipids, making them more susceptible to peroxidation; interferes with normal iron metabolism by dysregulating the IRP-IRE system; and impairs mitochondrial function and autophagy pathways, collectively leading to dangerous iron accumulation and elevated ROS production that culminates in the iron-dependent programmed cell death pathway known as ferroptosis.

CONCLUSION AND FUTURE PERSPECTIVES

In this mini-review, we have systematically examined the multifaceted relationship between cellular iron deposition and α -syn pathology, encompassing its direct effects on α -syn structure, synthesis, proteolytic processing, and aggregation. Furthermore, we have analyzed how α -syn aggregation influences ferroptosis progression through its interactions with both iron and lipid metabolic pathways. Current evidence clearly demonstrates that iron directly binds to α -syn, significantly altering its amyloidogenic properties. Indirectly, iron modulates α -syn proteostasis through oxidative stress mechanisms and by affecting its transcriptional and translational regulation. Conversely, α -syn actively participates in iron homeostasis and promotes iron-dependent cell death pathways. Recent advances in PD pathogenesis research, particularly regarding iron accumulation and protein aggregation, have highlighted promising therapeutic opportunities for modulating α -syn pathology through targeted intervention of cellular redox processes.

Iron chelation targeting α -syn pathology

Elucidating the mechanisms by which iron potentiates α -syn pathology provides critical insights for developing iron chelation therapies in PD. Substantial evidence demonstrates pathological iron accumulation in both PD patient brains and preclinical models. Iron chelators function by forming stable complexes with iron ions, thereby mitigating iron's toxic effects on both α -syn aggregation and dopaminergic neuronal death^[76]. Clinical trials employing the iron chelator deferiprone (DFP) have shown its effectiveness in reducing cerebral iron load in PD patients^[77-79]. However, preclinical studies indicate that while DFP improves motor function in animal models, it does not significantly reduce α -syn aggregation^[80]. Other chelators, including deferoxamine (DFO), have demonstrated neuroprotective effects by decreasing iron deposition and enhancing cellular resistance to oxidative stress^[81]. Both DFO and deferasirox (DFX) have been shown to reduce pathological iron accumulation and attenuate lipid peroxidation in patients^[82]. Additionally, the iron chelator clioquinol has been reported to inhibit oxidative stress and ferroptosis in MPTP-induced PD mouse models^[83]. Emerging therapeutic candidates include next-generation iron chelators such as hydroxypyridinones and metal-protein attenuating compounds (MPACs). For instance, 8-hydroxyquinoline-2-carboxaldehyde isonicotinoyl hydrazone (INHHQ), a metal-binding compound, has

shown partial inhibition of α -syn oligomerization in cell culture models^[84]. Another novel MPAC, 1-methyl-1H-imidazole-2-carboxaldehyde isonicotinoyl hydrazone (X1INH), exhibits selective metal affinity for copper and has been demonstrated to reduce the size and compactness of α -syn aggregates in synucleinopathy models^[85,86].

Challenges facing iron chelation therapy

Despite its therapeutic potential, iron chelation therapy for PD faces several significant challenges. First, iron serves as an essential element for normal neuronal function, particularly in oligodendrocyte-mediated myelin synthesis. Over-chelation of biologically active iron may consequently lead to adverse effects, including impaired oligodendrocyte development and demyelination^[86,87]. As previously discussed, iron deficiency can also disrupt neuronal autophagy processes, potentially triggering apoptotic pathways^[86]. Furthermore, iron chelators exhibit considerable immunomodulatory effects that warrant careful consideration. These include hematological changes such as increased hemoglobin, platelet, and white blood cell counts, as well as induction of immunogenic stress responses characterized by interferon (IFN) production and natural killer (NK) cell activation^[88,89]. These immunological alterations must be evaluated in the context of neuroinflammation observed during iron chelation treatment^[79].

DECLARATIONS

Authors' contributions

Conceived this review article: Li W

Wrote the manuscript: Xiang M, Zhang J

Revised the manuscript: Xiang M, Zhang J, Wang C, Wu X, Cao S

Screened and gathered literature: Xiang M, Song D, Dou H, Feng C

Designed and completed pictures: Li W, Xiang M, Zhang J

Supervised the manuscript writing: Li W

Contributed to the manuscript discussion and editing: Xiang M, Zhang J, Wang C, Wu X, Cao S, Song D, Dou H, Feng C, Li W

Availability of data and materials

Not applicable.

Financial support and sponsorship

Research performed in this article was supported by the National Natural Science Foundation of China (82361138574, 81430025, 31800898, 82371273 and U1801681), the Sino-German Center Call for Bilateral Collaborative Proposals between China and Germany in COVID-19 related Research (C-0054), the Swedish Research Council (2019-01551, 2023-02216), ParkinsonFonden, the Strategic Research Area Multipark (Multidisciplinary research in Parkinson's disease at Lund University), Svenska Sällskapet för Medicinsk Forskning (SSMF, P18-0194), and the Scientific Research Fund of Liaoning Provincial Education Department (LJKMZ20221207).

Conflicts of interest

Li W is an Editorial Board member of the journal *Ageing and Neurodegenerative Diseases*. Li W is also a Guest Editor for the Special Issue *Iron in Ageing and Neurodegenerative Diseases*. Li W was not involved in any steps of editorial processing, notably including reviewer selection, manuscript handling, or decision making. The other authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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