Ferroptosis in Parkinson’s disease: glia–neuron crosstalk

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Parkinson’s disease (PD) is characterized by dopaminergic (DA) neuron loss and the formation of cytoplasmic protein inclusions. Although the exact pathogenesis of PD is unknown, iron dyshomeostasis has been proposed as a potential contributing factor. Emerging evidence suggests that glial cell activation plays a pivotal role in ferroptosis and subsequent neurodegeneration. We review the association between iron deposition, glial activation, and neuronal death, and discuss whether and how ferroptosis affects α-synuclein aggregation and DA neuron loss. We examine the possible roles of different types of glia in mediating ferroptosis in neurons. Lastly, we review current PD clinical trials targeting iron homeostasis. Although clinical trials are already evaluating ferroptosis modulation in PD, much remains unknown about metal ion metabolism and regulation in PD pathogenesis.

Glia activation and iron accumulation in the pathogenesis of PD

PD is one of the most common neurodegenerative diseases. Two major pathological hallmarks of PD are the progressive loss of DA neurons in the substantia nigra pars compacta (SNpc) and the formation of Lewy bodies and Lewy neurites. Misfolded and aggregated α-synuclein (α-syn; see Glossary) is the primary protein component of Lewy pathology [1].

To date, relatively little is known of PD pathogenesis, although potential disease mechanisms include immune activation, mitochondrial dysfunction, lipid dyshomeostasis, and metal ion imbalance [1]. Notably, glia activation is evident during the onset and progression of PD [2]. Activated glia may act as ‘double-edged swords’ because they can exert neuroprotective effects by releasing neurotrophic factors and phagocytosis, while mediating neuronal damage by releasing proinflammatory cytokines [3]. Brain imaging and pathological studies have shown correlations between iron deposition in the SNpc of PD patient brains and DA neuronal loss [4,5], indicating that imbalance of iron homeostasis may be a factor closely associated with neuronal death in PD. This type of iron-dependent cell death is termed ferroptosis [6]. Excessive iron accumulation in cultured DA cells can trigger ferroptosis [7]. Ferroptosis was also reported in SH-SYSY (human neuroblastoma) cells exposed to the DA neurotoxins, 1-methyl-4-phenylpyridinium (MPP+) and 6-hydroxydopamine (6-OHDA) [8,9]. Similar phenomena were observed in MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-induced PD mouse models [10]. Furthermore, ferroptosis inhibitors can rescue the DA neuron death in PD [10].

Both glial cell activation and iron dyshomeostasis are crucial events in PD pathogenesis. They can reciprocally influence each other and act as ‘partners in crime’ in boosting DA neuron degeneration [11,12]. Activated glia promote iron dyshomeostasis, which aggravates microglial activation [13]. These findings suggest that the association between iron deposition-induced ferroptosis, glia activation, and neurodegeneration could potentially underlie the pathogenesis of PD. To address the regulatory mechanisms of ferroptosis in neurons, especially the role of glia, we focus on the involvement of different glial cells in ferroptosis in PD. We first address the major

Highlights

- Iron uptake, storage, efflux, and utilization are essential for maintaining iron homeostasis. Abnormal expression of proteins involved in these processes related to iron homeostasis may cause iron overload and induce subsequent ferroptosis, which is associated with the pathogenesis of neurodegenerative disease.
- Crosstalk between glia and neurons underlies the ferroptotic alterations in DA neurons and forms a vicious circle in promoting PD pathogenesis.
- Possible mechanisms of iron transfer between glia and neurons include exosomes and tunneling nanotubes. They may determine the efficacy of ferroptosis inhibitors and provide a clue for exploring novel therapeutic interventions for PD.
- Joint medications with ferroptosis inhibitors and anti-inflammatory medicines may provide a potential strategy for the treatment of PD and related neurodegenerative diseases.

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phenomena of iron metabolism and the process and regulation of ferroptosis, with a particular focus on their impact on PD pathologies. We also discuss how different glia may regulate iron homeostasis and oxidative stress to modulate the process of DA neuron ferroptosis. Lastly, we review recent and ongoing clinical trials that leverage ferroptosis modulation for the treatment of PD.

Evidence of ferroptosis in PD pathology
The process and regulation of ferroptosis
Ferroptosis is an iron-dependent form of regulated cell death that is initiated by abnormal iron metabolism and severe lipid peroxidation, leading to oxidative stress and cell death [6]. Unlike apoptosis and other forms of cell death, ferroptosis-induced cytolological changes include cell volume shrinkage and the disappearance of mitochondria cristae, increased mitochondrial membrane density, and outer mitochondrial membrane rupture [6,14]. However, the nuclei of ferroptotic cells maintain their structural integrity, and there is no cytoplasmic or organelle swelling, plasma membrane rupture, or formation of apoptotic bodies [6].

Ferroptosis is probably regulated by multiple pathways, including iron metabolism, oxidative stress, and cytotoxic amino acid metabolism (Figure 1). In addition, susceptibility to ferroptosis may also be affected by other pathways such as ferroptosis suppressor protein 1 (FSP1)–coenzyme Q10 (CoQ10) [15]. Although the exact mechanisms of neuronal ferroptosis remain obscure, the participation of non-neuronal cell types such as glia is essential in mediating iron toxicity to neurons. Several studies have demonstrated the crucial effects of glia on regulating ferroptosis in DA neurons. For example, it is known that heme oxygenase 1 (HO-1), an inducible enzyme, catabolizes the heme group into carbon monoxide and biliverdin, which in turn converts to bilirubin and labile iron. In a model of aging in wild-type mice, HO-1 was upregulated accompanied by increased microglial activation, iron deposition, and ferroptosis. By contrast, cell-specific knockout of the Hmox1 gene in mice and treatment with iron chelator deferoxamine (DFX) showed preventive effects against ferroptosis [11].

Ferroptosis is a prominent pathway of neuron degeneration in PD
Although ferroptosis was first reported in cancer cells [6], it was also found to be involved in DA neuron death in PD [10]. Several mutations in ferroptosis genes have been linked to PD (Table 1), including DJ-1, autosomal recessive PD gene, that encodes a negative modulator of ferroptosis [16]. Moreover, the characteristics of ferroptosis induction are highly consistent with the pathological changes observed in PD patients, including increased iron content [4,5], lipid peroxidation [17–19], and defects in the antioxidant system such as decreased levels of cysteine/glutamate antiporter (xCT) [20], glutathione (GSH) [21], DJ-1 (that maintains cysteine and GSH biosynthesis) [16], and CoQ10 [22]. Furthermore, ferroptosis was observed in different PD cellular and animal models such as SH-SY5Y cells treated with MPP+ and 6-OHDA, and MPTP-lesioned mice [8–10]. Furthermore, inhibition of ferroptosis by using ferrostatin-1 (Fer-1) can alleviate locomotor behavioral deficits and rescue tyrosine hydroxylase (TH) neuronal loss in MPTP-induced PD mice [23]. A very recent study with combined MRI imaging, quantitative susceptibility mapping (QSM), and regional gene profiling in a cohort of PD (96) patients and 35 control subjects showed significantly increased cortical iron deposition in PD compared to the control subjects. Gene expression profiling has also demonstrated that genes related to heavy metal detoxification and synaptic function are predominantly and differentially expressed in astrocytes and glutamatergic neurons in PD patients [24], suggesting regional and selective vulnerabilities in relation to iron accumulation in PD. Although this evidence suggests a prominent role for iron homeostasis and ferroptosis in mediating neuron death in PD, how these contribute to each other and lead to neurodegeneration largely remains unknown. Further studies, particularly on the biological processes involved in iron deposition and associated cell death, are urgently needed.

Glossary
Activated microglia: microglia activated in response to a variety of neurological diseases, including PD. Once activated, microglia alter morphologically from ramified to amoeboid-like shapes. Activated microglia release cytokines, immune signaling molecules, and reactive oxygen species (ROS), and can have both protective and detrimental effects on neurons.
Brain-derived neurotrophic factor (BDNF): a neurotrophic factor widely expressed in the CNS. It functions as a neurotransmitter modulator to regulate neuronal plasticity. Abnormal expression of BDNF is involved in several neurodegenerative diseases.
Glutathione peroxidase 4 (GPX4): an antioxidant peroxidase that protects neurons by preventing membrane lipid peroxidation and suppressing ferroptosis.
Heme oxygenase 1 (HO-1): the rate-limiting enzyme in heme catabolism that degrades heme to carbon monoxide, free iron, and biliverdin. These metabolites have antioxidative and anti-inflammatory properties which sustain cellular homeostasis.
Lipid peroxidation: a process in which oxidants such as free radicals attack lipids containing carbon–carbon double bonds, especially polyunsaturated fatty acids (PUFAs). Lipid peroxidation has been linked with the pathogenesis of several neurodegenerative diseases.

1-Methyl-4-phenylpyridinium (MPP+ iodide): MPP+ is a metabolite of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) that is structurally similar to dopamine. MPP+ and MPTP inhibit the mitochondrial complex I activity, reduce ATP synthesis and rescue tyrosine hydroxylase (TH) neuronal loss in MPTP-induced PD mice [23]. A very recent study with combined MRI imaging, quantitative susceptibility mapping (QSM), and regional gene profiling in a cohort of PD (96) patients and 35 control subjects showed significantly increased cortical iron deposition in PD compared to the control subjects. Gene expression profiling has also demonstrated that genes related to heavy metal detoxification and synaptic function are predominantly and differentially expressed in astrocytes and glutamatergic neurons in PD patients [24], suggesting regional and selective vulnerabilities in relation to iron accumulation in PD. Although this evidence suggests a prominent role for iron homeostasis and ferroptosis in mediating neuron death in PD, how these contribute to each other and lead to neurodegeneration largely remains unknown. Further studies, particularly on the biological processes involved in iron deposition and associated cell death, are urgently needed.
Association of α-syn aggregation and ferroptosis

α-Syn aggregation in neurons and glia is a key pathological feature of PD. Different forms of aggregated α-syn can be spread from one cell to another from the peripheral tissues to the brain or within the brain [25–27]. Postmortem analyses from PD patient brains showed the coexistence of iron and α-syn in Lewy bodies in midbrain [28]. Iron accumulates in the substantial nigra of the midbrain and colocalizes with α-syn [29,30], suggesting an interaction between iron deposition and α-syn pathology. α-Syn is a metal-binding protein with affinity for ferric and ferrous iron, and iron binding to α-syn promotes α-syn aggregation by inducing conformational changes [31]. Iron also takes part in post-transcriptional regulation [32] and post-translational modifications, and iron binding to α-syn increases α-syn aggregation [33]. α-Syn mRNA contains an iron response element (IRE) within its 5′-untranslated region (UTR) [34]. In SH-SYSY and N2A (mouse neuroblastoma) cells, the addition of iron ions can accelerate α-syn spreading between cells and promote α-syn aggregation. The α-syn aggregates formed can be cytotoxic, leading to increased reactive oxygen species (ROS) production and cell death [35]. Iron depletion in HEK293 cells leads to reduced α-syn translation [32]. In an adenovirus-associated virus (AAV) α-syn-overexpression rat model, chronic intranasal administration of an iron chelator deferoxamine (DFO) was found to reduce iron levels and alleviate motor defects in the midbrain and colocalizes with α-syn [36]. Intranasal DFO can also improve memory in healthy wild-type mice [37]. The data indicate that iron may play a role in α-syn aggregation and contribute to cell death.

Conversely, α-Syn can also modulate iron homeostasis. Overexpression of α-syn in rat primary midbrain neurons results in iron overload [38], and the ferroductase activity of α-syn can increase intracellular ferrous iron content in SH-SYSY cells [39]. A recent study found that ferroptosis inhibitors could prevent the interaction between α-syn aggregates and cell membranes in induced pluripotent stem cell (iPSC)-derived neurons with triplication of the SNCA gene, and led to reduced accumulation of iron-dependent free radicals and further prevented neuronal death [40].

Evidence obtained from cellular and animal models and PD patients suggests a close association between iron accumulation and α-syn protein turnover, including expression, accumulation, aggregation, and degradation. However, this potentially vicious circle is the causal relationship between the two remains unclear. Although the human and in vivo data are still insufficient, considering that α-syn is the primary component for PD protein pathology, normal iron metabolism may be a key element in regulating the pathological progression of PD, and targeting iron homeostasis may have therapeutic potential.

Gli activation mediates DA neuronal death by regulating ferroptotic processes

Glia activation is involved in the onset and progression of PD through various pathways (Figure 2). Large numbers of activated microglia were found around the degenerated DA neurons in SN in PD patient brains [41]. Reactive astrocytes were also detected in autopsies of PD patient brains, accompanied by the formation of α-syn inclusions in neurons [42]. Activated glia can induce neuronal death in vitro by releasing proinflammatory factors, nitric oxide (NO), ROS, and glutamate [3,43]. PD-associated gene leucine-rich repeat kinase 2 (LRRK2) is highly expressed in oligodendrocytes, especially in the precursor cells (OPCs) [44,45]. Different types of glia may contribute to PD pathogenesis via different pathways such as demyelination and cytokine release. Upon activation, they may also induce neuronal ferroptosis by disrupting iron homeostasis, altering amino acid metabolism, and increasing oxidative stress.

Glia activation regulates ferroptosis of neurons by disrupting iron homeostasis

Microglia

Studies have shown that microglia play a role in regulating iron homeostasis in neuronal networks. First, iron can accumulate in activated microglia, resulting in increased iron deposition in the

production, and promote ROS overproduction, leading to DA neuron death.

Paraquat: a prototypic toxin known to exert neurotoxic effects by consuming the intracellular reducing agent NADPH and leading to overproduction of ROS. PQ decreases DA neurotransmitter level and induces PD-like behavioral phenotypes in rodents and non-human primates.

Reactive astrocytes: astrocytes undergoing morphological, molecular, and functional remodeling in response to acute injury, infection, and chronic neurological disease.

α-Synuclein (α-syn): a protein enriched in presynaptic nerve terminals. Encoded by the SNCA gene, the physiological function of α-syn is to regulate synaptic activity, including synaptic vesicle trafficking and neurotransmitter release. As the main pathological protein of PD, α-syn can aggregate into cytoplasmic inclusions named Lewy Bodies. Pathological aggregation and propagation of α-syn in the central nervous system and peripheral tissues play essential roles in PD pathogenesis.

Tunneling nanotubes (TNTs): F-actin-based and membrane-enclosed structures which play pivotal roles in intercellular communication between cells. TNTs can not only mediate cellular cargo transfer but also disseminate therapeutic drugs.
central nervous system (CNS) [30,46,47]. Guo and coworkers reported iron deposition in microglia in the SN and globus pallidus in a non-human primate PD model induced by α-syn fibril injection, and this was aggravated upon additional neurotoxin paraquat treatment [30]. Second, proinflammatory cytokines released by microglia exacerbated neuronal iron deposition. When organotypic hippocampal cultures were exposed to ferrous ammonium sulfate, ferric ammonium citrate (FAC), or ferrocene, microglial activation became evident, accompanied by increased expression of ferritin in microglia and oligodendrocytes as well as the release of proinflammatory factors including interleukin (IL)-6, IL-1β, and tumor necrosis factor (TNF)-α [48,49]. Mechanistic studies showed significantly upregulated expression of the iron-import proteins divalent metal transporter 1 (DMT1), iron regulatory protein 1 (IRP1), and transferrin receptor 1 (TfR1), and downregulated expression of the iron-export protein ferroportin 1 (FPN1) [49,50], indicating that neuroinflammation regulates the
expression of these iron-related transporters, and modulates iron accumulation in the CNS.

Microglial HO-1 overexpression in aged wild-type mice contributes to neurotoxic iron deposition in the brain, whereas DFX normalizes iron deposition as well as inflammatory and behavioral alterations [11]. These studies in PD rodent and primate models suggest that activated microglia may increase iron overload in the nervous system. Therefore, targeting ferroptosis, preventing microglial iron deposition, and anti-inflammatory treatments may have potential therapeutic value in the early stages of PD.

Astrocytes

As a blood–brain barrier (BBB) component, astrocytes regulate iron homeostasis in the brain by controlling iron influx from the periphery to the CNS and between neurons and glia [51]. Astrocytes mediate the transport of various types of iron, including transferrin–Fe (Tf–Fe), non-transferrin-bound iron (NTBI), and heme iron [52], mainly by cascades of protein interactions, especially ceruloplasmin (CP). In the brain, CP mainly binds to the astrocyte membrane in the form of glycosylphosphatidylinositol-anchored proteins (GPI-CP). Iron can be taken up into astrocytes via DMT1 and passed on to astrocytic proteins, including FPN1 and CP [51], which colocalize on the surface of cells [53]. The ferroxidase activity of CP can effectively oxidize Fe^{2+} into Fe^{3+}, thus promoting iron efflux from cells and inhibiting Fe^{2+}-mediated lipid peroxidation [53]. Approximately 80% of CP ferroxidase activity was lost in the SN of PD patients [54]. In MPTP-induced PD mouse models, depletion of the gene encoding CP aggravated the death of DA neurons [55], and peripheral infusion of CP attenuated SN iron deposition and neurodegeneration [54]. In the 6-OHDA lesioned mouse models, both mRNA and protein levels of CP in the SN on the lesion side were decreased, suggesting that decreased CP expression and subsequent iron accumulation participate in neuronal death in PD [56]. In contrast to the effect of CP, HO-1 overexpression in mature astrocytes led to iron deposition in the striatum, and deferiprone (DFP), a widely used membrane-permeant iron chelator, can improve behavioral abnormalities in GFAP.HMOX mice.

Table 1. Ferroptosis-related genes in PDa

| Gene   | Function                                                                 | Refs |
|--------|--------------------------------------------------------------------------|------|
| ACSL4  | ACSL4 converts free fatty acids into fatty-CoA esters                     | [69] |
| DJ1    | DJ-1 maintains cysteine and GSH biosynthesis through the trans-sulfuration pathway | [16,92] |
| FTH1   | FTH1 inhibits ferroptosis through ferritinophagy in the 6-OHDA model of PD | [93] |
| GPX4   | GPX4 reduces membrane phospholipid hydroperoxides and suppresses ferroptosis | [10,94] |
| IL13, IL13RA1 | The interaction of IL-13 with IL-13Ra1 increases the susceptibility of mouse DA neurons to oxidative stress | [35] |
| PLA2G6 | Phospholipase iPLA_β3 averts ferroptosis by eliminating a redox lipid death signal | [17] |
| mIR-335 | mIR-335 enhances ferroptosis through the degradation of FTH1             | [96] |
| Nrf2   | Nrf2 is directly or indirectly involved in modulating ferroptosis, including metabolism of GSH, iron, and lipids, as well as mitochondrial function | [72] |
| TP53   | Inhibition of p53 upregulates SLC7A11 and GPX4                           | [97] |
| SQSTM1 | High p62 expression inhibits ferroptosis by promoting Nrf2 nuclear transfer and upregulating HO-1 expression | [9] |
| SLC7A11 | Codes for xCT that regulates GSH levels                                  | [20] |
| SNX5   | Silencing of SNX5 lowers the level of ferroptosis in 6-OHDA-induced PC12 cells | [36] |
| Trx1   | Trx-1 overexpression inhibits the decrease of GPX4 and GSH and the increase of ROS | [23] |

Abbreviations: FTH1, ferritin heavy chain 1; IL-13, interleukin-13; IL-13Ra1, interleukin-13 receptor α1; PLA2G6, Ca^{2+}-independent phospholipase A2 (encoded by PLA2G6/PNPLA9); SLC7A11, solute carrier family 7 member 11; SNX5, sorting nexin 5; Trx-1, thioredoxin-1.
Brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) released by astrocytes are also involved in neuronal iron metabolism. In primary cultured ventral mesencephalic neurons treated with 6-OHDA, BDNF and GDNF inhibited iron uptake by reducing DMT1 expression, leading to reduced iron accumulation in cultured neurons [58]. In the PD models listed previously, proteins either binding to or released by astrocytes affect iron metabolism, which could subsequently influence ferroptosis. Therefore, strategies targeting astrocytic protein expression might prevent neuronal death, especially via ferroptosis.
Oligodendrocytes
Oligodendrocytes are the cells containing most iron in the CNS [47] because myelination and metabolic enzyme activity require the participation of iron [59]. Quantitative analyses showed that iron accumulation in DA neurons and glial cells of postmortem PD brains was significantly increased, and the iron content of Olig2-positive oligodendrocytes was increased by a factor of ~2.5 [47]. In addition, oligodendrocytes provide an antioxidant defense system for neurons against iron-induced cytotoxicity by secreting ferritin heavy chain [60]. Rapid iron mobilization from ferritin triggered ferroptosis and caused oligodendrocyte loss and demyelination in a cuprizone-induced model of multiple sclerosis (MS) [59]. It is conceivable that lipid peroxidation and oligodendrocyte loss mediated by rapid mobilization of ferritin may also contribute to ferroptosis in DA neurons. Therefore, under pathological conditions such as demyelination, oligodendrocytes became a natural pool for loading iron to neurons, given the close physical contact between the two.

Glial activation induces ferroptosis of neurons via increasing oxidative stress
Increased oxidative stress has been shown to be a key molecular mechanism of ferroptosis in PD [61]. Because glia act via different pathways to attenuate oxidative stress in neuronal networks and prevent excessive amounts of ROS from entering neurons, they could represent valuable targets to restore the metabolic status of degenerating neurons.

Microglia
Activated microglia are chronic sources of cytokines and ROS production that accelerate DA neuron death [62]. NADPH oxidase (NOX) is the primary source of ROS production from activated microglia and contributes to DA neuron degeneration [63]. Targeting NOX can inhibit microglial activation [62] and erastin-induced ferroptosis in rhabdomyosarcoma (RMS) cells [64]. It has been shown that inhibition of microglia-derived oxidative stress protects DA neurons in MPP+-lesioned rats [65]. Primary rat microglia activated by phorbol myristate acetate (PMA) treatment induced superoxide-mediated release of iron from ferritin, leading to iron-dependent lipid peroxidation [66], the key feature of ferroptosis. Furthermore, in response to inflammatory signals, inducible nitric oxide synthase (iNOS) in microglia was significantly upregulated to resist ferroptosis by decreasing 15-lipoxygenase (15-LOX) activity [67]. Moreover, inhibition of the production of microglial proinflammatory cytokines and lipid peroxidation by knocking down acyl-CoA synthetase long-chain family member 4 (ACSL4) in an ischemic stroke model prevented ferroptosis in neurons [68]. Similar neuroprotective effects on ACSL4 were observed in the MPTP-induced PD model [69].

Astrocytes
Reactive astrocytes release various antioxidant molecules such as GSH, metallothioneins (MTs), and Nrf2 that are key neuroprotective regulators of iron homeostasis and oxidative stress. Extracellular MTs secreted by astrocytes have radical-scavenging properties owing to their abundant thiol groups and can protect DA neurons from quinone toxicity [70]. Nrf2 is a transcription factor that upregulates detoxification enzymes including GSH synthesis enzymes, quinone reductase 1 (NQO-1), and MTs. Many studies have shown that Nrf2 activation in astrocytes can protect DA neurons against oxidative stress [71]. In addition, activation of Nrf2 in astrocytes by BDNF was reported to protect neurons against iron-mediated ferroptosis [72], and modulation of Nrf2 transcription by DJ-1 was shown to impair the neuroprotective effects of astrocytes against stress inducers in a coculture system [73]. The antioxidant effects of astrocytes against ferroptosis may suggest a new strategy to inhibit ferroptosis by focusing on astrocytes and non-neuronal cell populations rather than solely on neurons.
Oligodendrocytes
Oligodendrocytes consume a large amount of oxygen and ATP to produce myelin, which leads to the formation of hydrogen peroxide and other reactive oxygen species [74]. As a cofactor of myelin synthase, iron in oligodendrocytes plays a crucial role in myelin production and triggers the formation of hydroxyl radicals through the Fenton reaction [75,76]. These free radicals are effective inducers of lipid peroxidation and can even induce ferroptosis [59]. This effect is further amplified by the low content of GSH in oligodendrocytes. Oligodendrocytes might be involved in DA neuron ferroptosis in PD. However, few studies have addressed the role of oligodendrocytes in the pathology of PD, and further investigations will be necessary to explore the potential role of oligodendrocytes in PD pathogenesis.

Mechanisms of iron transport between glia and neurons
We have discussed in the preceding text how iron can be deposited in both glia and neurons. More importantly, all three types of glia represent backup storage sites for excess iron, which may be transferred to neurons and induce ferroptosis. Is there a specific route for iron transport between glia and neurons? Proteins regulating iron metabolism can transmit between cells via the secretion of vesicles, such as exosomes released from multivesicular bodies (MVBs) that can carry ferritin–iron cores. Iron export via MVBs can promote ferroptosis resistance in mammalian epithelial and breast carcinoma cells [77,78] (see Outstanding questions). Although transfer of iron between glia and neurons has not been demonstrated directly, iron transmission between cells through extracellular vesicles is well documented. Furthermore, Tfr was shown to be transported between cancer cells through tunneling nanotubes (TNTs) [79] which are reported to exist between glia and neurons. Lastly, it is possible that iron transfers between cells by binding to other proteins. Iron can bind to α-syn [31], which was shown to propagate between cells potentially through endocytosis [80], exosomes [81], and tunneling nanotubes [82]. Iron transfer between glia and neurons represents a possible mode of glia–neuron crosstalk in mediating disease progression. Transmission of iron could be part of the mechanism of glia activation–induced neurodegeneration. To halt further progress of disease pathology, inhibiting glia–neuron iron transfer warrants investigation.

The potential value of targeting ferroptosis in the treatment of PD
Emerging evidence suggests that iron deposition and ferroptosis may be important mechanisms for neurodegeneration in PD and may serve as targets for preventing disease progression. In fact, in both preclinical experiments and clinical practice, ferroptosis inhibitors have shown promising effects (Table 2). DFP reduced SN iron deposition and progression of motor handicap in PD patients in Phase II randomized double-blind placebo-controlled clinical trials (NCT00943748, NCT01539837) [83,84]. Although there were some adverse events (such as a decline in white cell counts, gastrointestinal upset, muscular, joint pain) in both trials, these promising results prompted the launch of a large Phase II European multicenter, parallel-group, placebo-controlled randomized clinical trial to evaluate the global effect of DFP in PD patients (NCT02655315). In addition, antioxidants targeting ferroptosis, including N-acetyl cysteine (NAC) (NCT02212678, NCT02445651, NCT02445651) [85–87], GSH (NCT02424708), vitamin E (IRCT201604035623N73) [89], and CoQ10 (NCT01892176) [90] have also shown beneficial effects in PD patients. Although the evidence for the efficacy of these ferroptosis inhibitors in PD is far from being conclusive, they have considerable potential for the treatment of neurodegenerative disease and merit further exploration. Other metal chelators have also given promising results in clinical trials. Cu(II)ATSM exerted a positive effect by preventing lipid peroxidation in a Phase I dose-escalation study in early idiopathic PD patients (NCT03204929) [91]. Given its favorable properties, such as oral bioavailability and accessibility to the brain, Cu(II) ATSM may be a promising drug for clinical applications in PD.

Clinician’s corner
Nose-to-brain drug delivery
Systemic administration of deferiprone (DFP), a membrane-permeant iron chelator, leads to inefficient transfer across the blood–brain barrier (BBB) and can lead to nonspecific toxicity. Although direct transfer of drugs from the nasal cavity to the brain has some limitations, such as low drug permeability through the nasal mucosa, the nose-to-brain route bypasses the BBB and can deliver drugs directly to the brain.

Iron imaging as a diagnostic tool
Iron deposition in the substantia nigra (SN) is a prominent feature of PD. Therefore, monitoring iron deposition in the early stages of PD is crucial for early diagnosis and treatment. Available evidence suggests that quantitative susceptibility mapping (QSM) is a promising tool in investigating PD.

Ferroptosis inhibitors
Clinical trials of ferroptosis inhibitors including DFP (NCT00943748, NCT01539837), the copper-containing small molecule Cu(II)ATSM (NCT02870634), glutathione (GSH; NCT02424708), N-acetyl cysteine (NAC; NCT02445651), coenzyme Q10 (CoQ10; NCT01892176), and vitamin E (IRCT201604035623N73) have shown some beneficial effects in PD patients. Although the efficacy of these ferroptosis inhibitors in clinical applications is often inconclusive, further exploration is warranted.

Anti-inflammatory drugs combined with iron chelators
Recent evidence suggests that proinflammatory microglia sequester iron in a non-bioavailable form that is not accessible to iron chelators. Therefore, the combination of anti-inflammatory drugs with iron chelators might be a better approach to increase chelator efficacy.
Concluding remarks
The past decade has seen rapid progress in exploring the biochemical mechanism of ferroptosis. Multiple studies have demonstrated that ferroptosis can aggravate neurotoxicity and brain injury. The application of ferroptosis-specific inhibitors in PD treatment has therefore gained momentum because these ferroptosis inhibitors can rescue neuronal death and represent novel therapeutic targets in PD.

The causal relationship between iron deposition and neuronal degeneration remains an open question. One hypothesis is that iron deposits in the glia and then affects the function of neurons, causing lipid peroxidation and inducing neuronal atrophy, even if the iron level is low in neurons at that stage. This hypothesis is supported by the finding that iron deposition in microglia precedes DA neuronal degeneration after intranasal α-syn fibril treatment [30]. Another hypothesis suggests that iron deposits in neurons cause overactivation of glia that transfer more iron to the neurons, accompanied by toxic substance release from overactive microglia and astrocytes, that jointly trigger neuronal cell death [48, 49]. Only a few studies on ferroptosis in oligodendrocytes have been reported. The importance of analyzing iron content in oligodendrocytes and subsequent ferroptosis induction in neurons cannot be ignored because oligodendrocytes are tightly packed around the neurons. In conclusion, ferroptosis may play a role in the interaction between glia and neurons and thus modulate the pathogenetic process of PD. Although several clinical trials are already underway to evaluate the benefits of iron chelation or ferroptosis targeting, extensive preclinical research will be necessary to fully understand the roles of glia–neuron crosstalk and ferroptosis in PD.

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Table 2. Clinical trials targeting ferroptosis in PD

| Agents       | Trial phase and identifier number | Key results                                                                 | Refs |
|--------------|-----------------------------------|------------------------------------------------------------------------------|------|
| DFP          | Phase II NCT00943748              | Reduced SN iron overload and progression of motor handicap in PD patients. | [83] |
| DFP          | Phase II NCT01539837              | Iron content in the SN was reduced in 3 of 14 patients with PD               | [84] |
| NAC          | Phase II NCT02212678              | No significant increase in brain GSH. Blood catalase and GSH/GSSH were significantly increased, while MDA and 4-HNE were unchanged | [85] |
| NAC          | Phase not applicable NCT02445651  | In the NAC group, increased DAT binding was observed in the caudate and putamen, along with improved PD symptoms | [86] |
| NAC          | Phase II NCT01427517              | NAC boosts brain and blood GSH in Gaucher and PD patients.                  | [87] |
| GSH          | Phase II NCT02424708              | Improvements of motor handicap observed in the high-dose group               | [88] |
| GSH          | Phase II NCT01177319              | No improvements in Parkinsonian signs and symptoms in the GSH group compared to the placebo group | [89] |
| ω3 Fatty acids and vitamin E | Phase II IRCT201604035623N73 | Improved symptoms and increased GSH concentration | [90] |
| CoQ10        | Phase II NCT01892176              | Well tolerated; improvements in PD-related symptoms                          | [90] |
| CoQ10        | Phase III NCT00740714             | No signs of clinical benefit                                                 | [100] |
| Cu(II)ATSM   | Phase II NCT03204929              | Significant reduction in disease severity and improved quality of life in PD patients | [91] |

Outstanding questions
In which cell type is iron first deposited in the brain – neurons, microglia, astrocytes, or oligodendrocytes?

How is ferroptosis regulated, in addition to the classical pathways of lipid peroxidation and amino acid metabolism?

Is neuroinflammation a promising target for controlling iron availability to neurons through glial activation?

Because exosomes might mediate iron delivery between glia and neurons, does downregulation of exosome release counteract iron accumulation in neurons?
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Declaration of interests
The authors declare no conflicts of interest.

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