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Insight into the potential role of ferroptosis in neurodegenerative diseases

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Ferroptosis is a newly discovered way of programmed cell death, mainly caused by the accumulation of iron-dependent lipid peroxides in cells, which is morphologically, biochemically and genetically different from the previously reported apoptosis, necrosis and autophagy. Studies have found that ferroptosis plays a key role in the occurrence and development of neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease and vascular dementia, which suggest that ferroptosis may be involved in regulating the progression of neurodegenerative diseases. At present, on the underlying mechanism of ferroptosis in neurodegenerative diseases is still unclear, and relevant research is urgently needed to clarify the regulatory mechanism and provide the possibility for the development of agents targeting ferroptosis. This review focused on the regulatory mechanism of ferroptosis and its various effects in neurodegenerative diseases, in order to provide reference for the research on ferroptosis in neurodegenerative diseases.

KEYWORDS

ferroptosis, iron, Alzheimer's disease, neurodegenerative diseases, treatment

Introduction

Iron is involved in oxygen transport and cellular respiration, DNA synthesis and cell division, cellular metabolism and neurotransmission, which are essential for maintaining the body's function and daily metabolism. The ability of iron to circulate in an oxidative state in the body is fundamental to its biological function, and excess iron can lead to oxidative stress damage to biomolecules, as well as cellular dysfunction. However, with the increase of age, the accumulated iron in the brain will increase the risks of neurodegenerative diseases (Belaidi and Bush, 2016; Eid et al., 2017).

Ferroptosis is an iron-dependent, novel cell death mode, which is significantly different from apoptosis, cell necrosis and autophagy. The main mechanism is that under the action of ferrous iron or lipoxygenase, iron catalyzes liposomal peroxidation of highly expressed unsaturated fatty acids on cell membranes, thereby inducing cell death (Dixon et al., 2012; Nikseresht et al., 2019). The morphological features of ferroptosis are mitochondrial atrophy, increased bilayer membrane density, and loss of mitochondrial inner membrane cristae, with the intact cell membrane remaining and the normal size

of the nucleus, as well as no chromatin condensation (Alborzina et al., 2018; Ou et al., 2022). Numerous studies have shown that ferroptosis is also related to a reduction in the expression of glutathione and glutathione peroxidase 4 (GPX4) in the antioxidant system of cells (Zhan et al., 2022; Zhao et al., 2022; Zhu et al., 2022). Lipid peroxides cannot be metabolized by the reduction reaction catalyzed by GPX4, and lipids are oxidized by ferrous iron in Fenton reaction to generate a large amount of reactive oxygen species to promote ferroptosis (Alborzina et al., 2018; Torii, 2018; He et al., 2020). Therefore, the essence of ferroptosis is the metabolic disorder of intracellular lipid oxides, which are then abnormally metabolized under the catalysis of iron ions to produce a large amount of lipids to destroy the intracellular redox balance and attack biological macromolecules, triggering programmed cell death (Figure 1).

In recent years, studies have found that ferroptosis plays an extremely important role in neurodegenerative diseases with a common regulatory mechanism. This review will focus on

ferroptosis and neurodegenerative diseases, such as Alzheimer's disease (AD), vascular dementia (VD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS) and traumatic brain injury (TBI), as well as the potential therapeutic effects of targeting ferroptosis (Table 1).

Mechanisms of ferroptosis

Transport and storage of iron in the brain

The neuronal iron metabolism related protein, TfR1 (transferrin receptor protein 1), is highly expressed on the surface of neurons (Giometto et al., 1990). Similar to BMECs, iron enters neurons through clathrin-mediated phagocytosis of holo-Tf/TfR1, and exits endosomes in the form of reduced Fe²⁺ through DMT1 (Burdo et al., 2001). NTBI (Non-transferrin-bound iron) can also enter neurons independently of Tf in a DMT1 (Divalent metal transporter 1)-dependent manner.

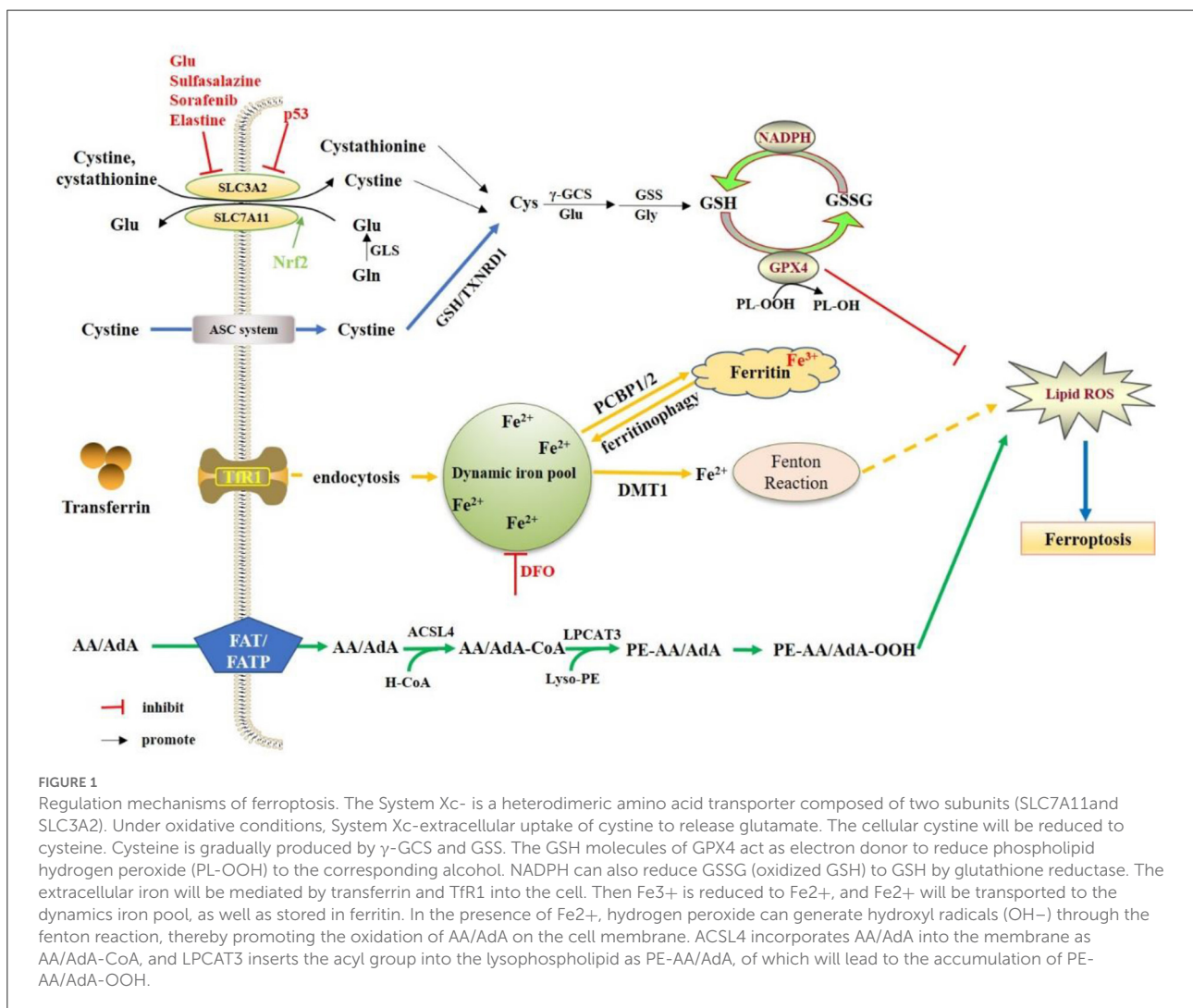


TABLE 1 Targeting ferroptosis for the potential treatment of neurodegenerative diseases.

Diseases	Types	Name	Potential mechanism
AD	Iron chelators	DFO	Improve the excretion of iron, reduce the content of iron in the body and its pathological deposition in various organs
		DFP	
	Quinoline derivatives	Clioquinol	Downregulate the expression of β and γ secretases and APP in the brain, degrade oligomeric tau and reduce tau tangles
	Antioxidants	Vitamin E	Reduce lipid peroxidation and attenuate iron morphology
		a-LA	Block iron overload, lipid peroxidation and inflammation
		Se-containing compounds	Upregulate GPX4 to inhibit iron toxicity
	Hepcidin	Hepcidin	Inhibit FPN1, TFR1 and DMT1 to reduce neuronal iron uptake and release
GBH	GBH	Inhibit lipid peroxidation and restore the expression of ferritin GPX4, HO-1, COX-2 altered by RSL3	
VD	Antioxidants	Fer-1	Inhibit ROS levels and downregulate Nrf2 and GPX4
	Thiazolidinedione	ROSI	Inhibits ACSL4 activity, reduce lipid peroxidation and oxidative stress
PD	Iron chelator	DFP	Reduce oxidative stress and increase dopamine activity
	Quinoline derivatives	Clioquinol	Chelate iron and antioxidant
HD	Iron chelator	DFO	Improve the excretion of iron, reduce the content of iron in the body and its pathological deposition in various organs
	Antioxidant	Fer-1	Inhibit oxidative lipid damage
TBI	Iron chelators	DFO	Reduce the iron overload, and relieve acute oxidative brain injury
		HBED	
	Ferroptosis inhibitor	Liproxstatin-1	Reduce cerebral edema and blood-brain barrier permeability

Prion protein (PrP^C), as the ferredoxin partner of DMT1, mediates the uptake of PrP^C/DMT1 in the plasma membrane in the form of a complex of iron ions (Shih et al., 2003; Tripathi et al., 2015). Brain iron deficiency and increased holo-Tf uptake can be found in PrP^C knockout mice (Singh, 2014). In the brain, divalent iron ions are normally metabolized in the neuronal cytoplasm, and stored in ferritin in the form of trivalent iron ions. When neurons are iron deficient, ferritin can be degraded by lysosomes, releasing stored iron to meet the normal physiological needs of neurons (Connor et al., 1992; Mancias et al., 2014; Raha et al., 2022). Studies have shown that ferritin in the brain increases with age (Belaidi et al., 2018), which is positively correlated with cognitive dysfunction. The etiology of cognitive dysfunction in the elderly is closely related to the iron overload. Iron homeostasis can also be regulated at the translation level. Iron regulatory protein 2 (IRP2), an RNA binding protein, controls the translation of a group of mRNAs involved in iron homeostasis. In the untranslated regions (UTRs) of genes encoding a variety of iron regulatory molecules (including DMT1 and TFR1), the IRP1 and IRP2 bind to the iron response elements (IREs). In an iron-deficient state, the combination of IRP2 and IREs can maximize intracellular iron levels. When the iron content increases, the extracellular iron regulatory pathway (IRE/IRP system) will be activated to weaken the iron overload state (Rouault, 2006; Sanchez et al., 2007; Hentze et al., 2010). In

addition, nuclear receptor coactivator 4 (NCOA4) can degrade ferritin to mediate iron autophagy, and release free iron in the process, which can also lead to an increase in intracellular Fe²⁺ and ferroptosis (Li W. Y. et al., 2021). Iron-responsive element-binding protein 2 (IREB2) is a regulator of iron metabolism, which can up-regulate the expression of ferritin light chain and ferritin heavy chain in the cytoplasm during iron metabolism, and alleviate erastin-induced ferroptosis (Mishima, 2022). Nuclear factor E2-related factor 2 (Nrf2) can reduce the expression of TFR1, regulate iron metabolism, maintain the balance of intracellular iron homeostasis, and limit the production of reactive oxygen species (ROS), thereby reducing ferroptosis (Li S. W. et al., 2021).

The role of the glutamate/cysteine antiporter in ferroptosis

Cystine uptake by the glutamate/cysteine antiporter (System Xc⁻), including a 12-pass transmembrane protein transporter solute carrier family 7 member 11 (SLC7A11) and a single-channel transmembrane regulatory protein solute carrier family 3 member 2 (SLC3A2), is inhibited in ferroptosis (Dixon et al., 2012). Thus, inhibition of the System Xc⁻ results in the depletion of intracellular cysteine (Ma et al., 2021).

Cysteine plays an important role in the biosynthesis of glutathione (GSH). GSH, as a substrate of GPX4, is required for its lipid repair function. GSH depletion through cysteine starvation results in the loss of GPX4 activity, as well as the accumulation of unrepaired lipid peroxides and iron toxicity (Angeli et al., 2014). GPX4 converts reduced glutathione to oxidized glutathione (GSSG) to reduce lipid hydrogen peroxide to the corresponding alcohol or free hydrogen peroxide to water (Gaschler et al., 2018). Selenium (Se) is a key regulator of GPX4 activity. Wild-type GPX4 containing Se can effectively reduce peroxides to the corresponding alcohols, thereby preventing ferroptosis (Ingold et al., 2018). GSH is also a natural ligand for Fe²⁺ in the labile iron pool (LIP), which is an exchange pool for loosely ligated iron in neurons (Hider and Kong, 2011), and glutathione binds Fe²⁺ in LIP to prevent iron oxidation, which not only maintains Fe²⁺ solubility but also prevents Fe²⁺ from acting as a catalyst to generate a potent oxidant, hydroxyl radical, from physiologically available hydrogen. Therefore, direct inhibition of GSH synthesis triggers ferroptosis.

The role of lipid peroxidation in ferroptosis

Lipid metabolism is also closely related to ferroptosis. Nitrogen oxides (NOXs) provide a source of accumulation of ROS in erastin-induced iron sickness, and it has been reported to modulate the sensitivity of tumor cells to erastin (Dixon et al., 2012). On the other hand, the production of membrane lipid peroxidation is also a source of ROS, which drives iron toxicity. The abundance and location of polyunsaturated fatty acids (PUFAs) determine the degree of lipid peroxidation that occurs in cells, and lead to ferroptosis. The most susceptible lipids are phospholipids containing polyunsaturated fatty acids (PUFA-PLs), which can lead to subsequent cell death (Doll et al., 2017). Free PUFAs need to be esterified to form membrane phospholipids and oxidized to iron ion signals to synthesize lipid signals, especially phospholipids containing phosphatidylethanolamine (PE) and arachidonic acid or epinephrine moieties (Kagan et al., 2017). In the membrane lipid environment, PUFAs are specifically peroxidized in iron toxicity (Doll et al., 2017; Kagan et al., 2017). There are three main classes of lipid oxidases: cyclooxygenases (cox), cytochrome p450s (CYPs), and lipid oxidases (LOXs), of which LOX enzymes have been found to be most important for ferroptosis. LOXs are a class of non-heme iron-containing enzymes that catalyze the deoxygenation of PUFAs (Shintoku et al., 2017).

Relationship between ferroptosis and neurodegenerative diseases

AD

In addition to β -amylose deposition and accumulation of intracellular neurofibrillary tangles (NFTs) composed of tau proteins, abnormal deposition of iron in the brain is a common feature of AD. The effects of iron on AD have been attributed to its interaction with AD pathological central proteins (amyloid precursor protein and tau protein) and/or through iron-mediated generation of prooxidative molecules such as hydroxyl radicals. However, the source of iron accumulation in brain pathologically relevant regions and its contribution to AD remain unclear. The potential reason for iron accumulation is that senescent cells within tissues increase with age, and these cells trigger inflammation and contribute to various pathologies associated with aging. The accumulation of iron makes aging tissues susceptible to oxidative stress, leading to cellular dysfunction and ferroptosis. In addition, elevated brain iron levels are associated with AD progression and cognitive decline. Elevated brain iron levels, a hallmark of AD, can be pharmacologically modulated to mitigate the effects of age-related dysregulation of iron balance and improve disease outcomes (Masaldan et al., 2019a).

A meta-analysis involving 300 AD cases in 19 studies reported that iron levels were significantly elevated in multiple regions of the cerebral cortex, although iron levels varied across regions and studies (Tao et al., 2014). Iron accumulation may be detrimental, as elevation of iron itself may lead to neurodegeneration (Schneider et al., 2012), possibly by inducing oxidative stress and ferroptosis (Stockwell et al., 2017). High brain iron levels, cerebrospinal fluid ferritin (Ayton et al., 2015, 2017a), and quantitative susceptibility maps have been found to have the potential to predict AD clinical severity and cognitive decline (Ayton et al., 2017b). The relationship between postmortem brain iron levels and AD clinical and pathological diagnosis, severity, and rate of cognitive decline in the 12 years preceding death was also investigated in 209 AD patients. It was found that the iron content in the brains of AD patients was significantly increased, and it was significantly related to cognitive function. Therefore, cortical iron may contribute to the deterioration of cognitive function in AD underlying proteinopathies by inducing oxidative stress or ferroptosis, or by being associated with inflammatory responses (Ayton et al., 2020). Another study found that iron deposition in the frontal lobe, parietal lobe, temporal lobe, caudate nucleus, putamen, globus pallidus, cingulate cortex, amygdala, and hippocampus of AD patients was higher than that of healthy controls (Tao et al., 2014), and histological differences in the intensity of iron accumulation in the frontal cortex of AD subtypes can be used

not only to distinguish sporadic (late-onset) from familial (early-onset) (Bulk et al., 2018a), but also to correlate with disease severity (van Duijn et al., 2017; Bulk et al., 2018b).

The accumulation of iron has been proven to accelerate the deposition of senile plaques and the generation of neurofibrillary tangles (Becerril-Ortega et al., 2014; Kim et al., 2018). Autopsy evidence and MRI analysis provide evidence that there was substantial iron deposition not only in senile plaques (James et al., 2017), but also at sites of cortical tau protein accumulation (Spotorno et al., 2020), suggesting a potential interaction of iron with senile plaques and neurofibrillary tangles. Perturbation of iron homeostasis is one of the key factors in A β deposition. High intracellular iron concentration enhances the IRP/IRE interaction and induces upregulation of APP. The enzymes that cleave APP are called α - and β -secretases, which are tightly balanced and regulated by furin (Silvestri and Camaschella, 2008; Guillemot et al., 2013). In the presence of iron excess, more β -secretase is activated when α -secretase is inhibited by furin injury (Silvestri and Camaschella, 2008). Up-regulated APP is cleaved by more β -secretase A β 40/42, accelerating A β deposition. At the same time, the application can no longer assist FPN1, resulting in impaired iron efflux and aggravated iron deposition (Ward et al., 2014). It was suggested that in the absence of redox metals, A β is nontoxic, and the aggregation of A β requires the participation of metals (Li et al., 2013; Belaidi and Bush, 2016). Soluble A β binds to Fe $^{3+}$ when extracellular iron increases, removing excess iron, but it is difficult to separate after interaction. A β can promote the reduction of Fe $^{3+}$ to Fe $^{2+}$, and ROS released in the process make A β easily and rapidly to deposit and form more senile plaques (Ha et al., 2007). The interaction of iron with APP and A β greatly increased the rate and extent of senile plaque formation (Rottkamp et al., 2001). Therefore, iron deposition could be included in the "A β cascade hypothesis" of AD (Peters et al., 2018). Iron can also interact with tau protein. Decreased soluble tau protein in the brains of AD patients increases cerebral iron deposition by inhibiting FPN1 activity (Lei et al., 2012). Conversely, high-iron diet led to cognitive decline in mice, abnormally increased neuronal tau phosphorylation, and abnormal expression of insulin pathway-related proteins. Insulin supplementation reduces iron-induced tau phosphorylation (Wan et al., 2019), suggesting that iron deposition may lead to tau hyperphosphorylation by interfering with insulin signaling. *In vivo* studies have found that iron can participate in tau hyperphosphorylation by activating the cyclin-dependent kinase 5 (CDK5)/P25 complex and glycogen synthase kinase 3 β (GSK-3 β) (Guo et al., 2013). Excessive intracellular Fe $^{2+}$ -induced generation of oxygen free radicals can also promote tau hyperphosphorylation by activating extracellular signal-regulated kinase 1/2 (Erk1/2) or mitogen-activated protein kinase (MAPK) signaling pathways (Chan and Shea, 2006; Munoz et al., 2006).

Glial activation and neuroinflammation have been shown to be prominent features of AD pathology (Newcombe et al., 2018; Leng and Edison, 2021). Microglia are highly responsive cells that respond to increased iron levels in the brain. When iron levels are elevated in the brain, microglia are activated (Meng et al., 2017) with increased volume and decreased length (Rathnasamy et al., 2013; Donley et al., 2021). Iron may activate microglia *via* nuclear factor-kb (NF-KB)-mediated pro-inflammatory cytokines (Meng et al., 2017). Upon activation, more ferritin will be expressed to remove extracellular iron (Streit et al., 2022), leading to intracellular iron retention (Kenkhuis et al., 2021), increased TNF α expression (Holland et al., 2018), and eventual infiltration as a β -plaque (Peters et al., 2018; Kenkhuis et al., 2021). It can also interact with APP to promote the formation of A β (Tsatsanis et al., 2021). Conversely, in an environment with elevated iron levels, A β formation leads to increased IL-1 β expression in microglia, exacerbating pro-inflammatory effects (Nnah et al., 2020). Astrocytes are highly resistant to metal-induced toxicity in the brain (Kress et al., 2002), serving as a key cell type for maintaining the homeostasis of the extracellular environment and supporting normal neuronal function (Abbott et al., 2006). Under the high-iron environment, the levels of glutathione, catalase, and manganese superoxide dismutase are significantly elevated in astrocytes to counteract oxidative stress (Iwata-Ichikawa et al., 1999; Shih et al., 2003). However, astrocytes were found to be activated by increased glial fibrillary acidic protein (GFAP) (Kress et al., 2002). Activated astrocytes release inflammatory mediators, induce oxidative stress, and promote the formation of A β and tau tangles, hindering A β clearance (Dolotov et al., 2022).

Abnormal expression of GPX4 mRNA and its protein levels was found in AD patients and mouse brains (Yoo et al., 2012; da Rocha et al., 2018). In glial cells, mild hypoxia can reduce the level of GSH, which is used for GPX4 biosynthesis (Makarov et al., 2006). In a mouse model of AD, GSH expression was reduced in the cortex and positively correlated with cognitive decline (Karelson et al., 2001). GSH levels in the frontal lobe and hippocampus may serve as biomarkers for predicting AD and mild cognitive impairment (Karelson et al., 2001; Ayton et al., 2020). xCT activity determines GSH availability, and subsequent GPX4 activity in the brain (Ashraf et al., 2020). Furthermore, studies have found that most of the proteins involved in ferroptosis can be regulated by Nrf2 (Habib et al., 2015; Lane et al., 2021). The genes of interest included FPN1, GSH and SLC7A11 encoding xCT. The level of Nrf2 in the brain decreases with age, as well as in AD patients (Osama et al., 2020), so the brain of AD patients is more prone to ferroptosis (Habib et al., 2015). GPX4 expression has been reported to be reduced in both AD mouse models and AD patient brains (Ansari and Scheff, 2010; Yoo et al., 2010). GPX4 knockout mice were shown to have significant hippocampal neuronal loss and cognitive impairment (Yoo et al., 2010;

Hambright et al., 2017). A diet deficient in vitamin E, an antioxidant with anti-ferroptosis activity, simultaneously results in hippocampal neurodegeneration and worsens behavioral dysfunction; the ferroptosis inhibitor liproxstatin 1 improves cognitive function and neurodegeneration in mice (Hambright et al., 2017). In addition to animal models, autopsy results of AD patients showed down-regulation of GPX4, up-regulation of arachidonic acid 12/15 lipoxygenase (ALOX15), and enhanced lipid peroxidation, and 4-hydroxynonenal (4-HNE) in AD patient brains was elevated (Yoo et al., 2010). 4-HNE has the potential to modify proteins involved in antioxidant and energy metabolism, promoting A β deposition and fibrogenesis (Seibt et al., 2019). These results indicate that ferroptosis plays a key role in AD, which can cause neuronal loss and cognitive decline. Therefore, modulating brain iron metabolism and reducing neuronal ferroptosis may be a promising approach for the treatment of AD.

Deferoxamine (DFO) and deferiprone (DFP) are commonly used clinical iron chelators. The clinical efficacy of DFO in the treatment of AD is as high as 50%. However, the side effects, such as weight loss and loss of appetite (Mclachlan et al., 1991), limit its clinical application. Besides, DFO is difficult to pass through the blood-brain barrier (BBB) (Ward et al., 1995; Ben Shachar et al., 2004), which could be solved by intranasal administration of DFO nanoparticles (Rassu et al., 2015). Compared to DFO, DFP could cross the BBB and is safer (Gallie and Olivieri, 2019). In a randomized controlled trial, DFP improved neurological scores and iron-related neurological symptoms (Abbruzzese et al., 2011; Klopstock et al., 2019).

Quinoline and its derivatives, which could chelate with iron, zinc, and copper, have the potential to improve cognition, reduce A β deposition, and promote A β degradation in AD animal models (Grossi et al., 2009; Crouch et al., 2011). Clioquinol could downregulate β and γ secretase and APP expression in the brain (Wang et al., 2012), as well as degrade oligomeric tau protein and reduce tau tangles (Lin et al., 2021). Besides, clioquinol has been proven to slow down cognitive decline in patients with severe AD and reduce A β 42 in cerebrospinal fluid (Ritchie et al., 2003). Studies have also found that vitamin E (an antioxidant) can reduce lipid peroxidation in the brain, reduce iron morphology on neurons, and improve cognitive function in GPX4 knockout mice. However, in a randomized clinical trial, vitamin E showed no benefit in patients with AD or mild cognitive impairment (Farina et al., 2017), while it could accelerate cognitive decline (Lloret et al., 2009). Therefore, the application of vitamin E in AD remains questionable, and more clinical trials are needed to determine its effect. Alpha-lipoic acid (a-LA) was also proven to improve cognitive impairment, slow cognitive decline (Fava et al., 2013), block iron overload, lipid peroxidation, and inflammatory responses in AD patients (Zhang et al., 2018). Se is present in various proteins in the body, such as GPX4, and has antioxidant activity. Se-containing compounds may inhibit iron toxicity by upregulating

GPX4 and improve cognitive function in AD patients (Gwon et al., 2010; Cardoso et al., 2019). Ferrostatin-1 (Fer-1) is a common ferritin inhibitor and a free radical scavenger, which is much more effective than phenolic antioxidants (Miotto et al., 2020). Fer-1 could alleviate angiotensin II-induced astroglial inflammation and iron degeneration by inhibiting ROS levels and downregulating Nrf2 and GPX4 (Li S. J. et al., 2021). In the treatment of AD, Fer-1 was shown to ameliorate neuronal death and memory impairment *in vitro* and *in vivo* (Bao et al., 2021).

Hepcidin can reduce iron transport across the BBB and prevent iron overload in the brain. In cultured microvascular endothelial cells, hepcidin significantly inhibits the expression of FPN1, TfR1 and DMT1, and reduce iron uptake and release by neurons (Du et al., 2015). Hepcidin can reduce the iron level of mouse astrocytes and hippocampal neuron glial cells, reduce the formation of A β plaques, and improve mouse cognitive function (Xu et al., 2020). The recombinant adenoviruses carrying the hepcidin gene could also reduce iron deposition and oxidative stress levels in the brain (Gong et al., 2016). Insamgobonhwan (GBH) can inhibit the impairment of β -amyloid on cognitive function *in vivo*, and also inhibit cell death and lipid peroxidation *in vitro* cells. In addition, GBH restores ferritin GPX4, HO-1. The expression of COX-2 can improve cognitive dysfunction in mice, and it also has certain potential in AD treatment (Yang et al., 2022).

VD

The main cause of VD is chronic cerebral hypoperfusion (CCH) caused by chronic cerebral blood flow (CBF) and a variety of vascular pathologies. These include atherosclerosis, arteriosclerosis, infarcts, white matter (WM) changes, and microbleeds (Calabrese et al., 2016; Kalaria, 2018). Researchers have demonstrated that amino acid metabolism is related to ferroptosis and that CCH can cause neuronal depolarization to release excess glutamate during the pathogenesis of VD, resulting in excitotoxicity, and high levels of glutamate inhibit the function of System Xc⁻. Glutamate excitotoxicity is also a pathological mechanism of iron toxicity, and iron chelation prevents excitotoxic cell death (Krzyzanowska et al., 2014; Liu et al., 2016; Frank et al., 2021). Nuclear factor erythroid 2 related factor 2 (Nrf2) is a fundamental regulator of cellular antioxidant defense systems, which regulates the expression of multiple antioxidant response element-dependent genes, including NADPH-quinone oxidoreductase 1 (NQO1), heme oxidoreductase 1 (HMOX1), ferritin heavy chain 1 (FTH1), FPN1, GSH, and GPX4 (Kerins and Ooi, 2018; Milkovic et al., 2019; Sarutipai boon et al., 2020). Studies have shown that the expression level of Nrf2 is directly related to the susceptibility to iron poisoning. Increased expression of Nrf2 inhibits ferroptosis, and decreased expression promotes ferroptosis (Sun Y. R. et al., 2020; Fan et al., 2021; Nishizawa et al., 2022). Studies have

shown that, on the one hand, Nrf2 promotes the expression of glutathione and GPX4 strengthens the function of the antioxidant system, and on the other hand, Nrf2 can also reduce intracellular iron accumulation by promoting the expression of ferritin and the simultaneous release of FPN1 storage and export. iron, thereby preventing iron poisoning (Yang et al., 2017; Kasai et al., 2019). The Nrf2 regulatory network plays a fundamental role in different mouse models of cerebral ischemia. Although the expression of Nrf2 is controversial in different studies, the neuroprotective effect of enhanced Nrf2/ARE activation has been demonstrated in different studies (Park et al., 2018; Liu et al., 2019, 2020). At the same time, NRF2 overexpression can improve cognitive dysfunction (Yang et al., 2014; Qi et al., 2018; Mao et al., 2019), suggesting that it may be related to the inhibition of iron poisoning, and the GSH metabolic network is a bridge connecting iron poisoning and VD.

CCH can also lead to massive iron deposition. Bilateral common carotid artery occlusion is the most commonly used experimental model for VD. In the study, it was found that CCH leads to iron deposition in the rat brain, and a large amount of iron deposition leads to neuronal death caused by oxidative stress. Among them, the CA1 area has the most iron deposition and neuronal death (Li et al., 2012; Du et al., 2018). Abnormal brain iron and iron ion deposition are closely related to cognitive dysfunction, and iron ion deposition has been confirmed in AD, PD, HD and other neurodegenerative diseases. It plays an important role in sexually transmitted diseases (Chen L. et al., 2019; Thomas et al., 2020; Xu et al., 2020). It has also been shown that a wide range of abnormal iron deposits in the cortex of patients with subcortical ischemic VD, especially in the lateral caudate nucleus, putamen, globus pallidus, and frontal cortex, correlate closely with the severity of cognitive impairment (Liu et al., 2015; Sun C. Y. et al., 2020). Model of cerebral ischemia-reperfusion injury confirmed that iron accumulation in the ischemic precursor is a novel mechanism of stroke injury, leading to neuronal death. Iron chelators attenuate ischemia-reperfusion injury in animal models (Tuo et al., 2017), indicating that iron-induced ferroptosis may be the underlying mechanism of VD neuron loss.

The oxidative stress produced by CCH has been proven to be one of the main pathogenic mechanisms leading to VD (Du et al., 2017; Lee et al., 2021), and studies have shown that blood lipid levels in VD patients are significantly higher than those in AD patients, suggesting lipid peroxidation. Having an important impact on the pathophysiology of VD, MDA levels may be a hallmark of VD (Gustaw-Rothenberg et al., 2010). Lipid peroxidation and ROS accumulation are key processes that induce iron toxicity (Dixon and Stockwell, 2014). LOX causes lipid peroxidation by catalyzing polyunsaturated fatty acids in phospholipid membranes, and inhibition of LOX inhibits ferroptosis (Kagan et al., 2017; Doll et al., 2019). During cerebral

ischemia, the extensive increase in 12/15-LOX in brain tissue is an important cause of neuronal cell death and neurological damage. Inhibition of 12/15-LOX can reduce neuronal cell death and brain edema, and improve neurological prognosis (Piao et al., 2008; Pallast et al., 2010; Yigitkanli et al., 2017). In addition, NOX also plays an important role in lipid peroxidation. NOX1 expression was increased in hippocampal neurons during CCH, leading to lipid peroxidation and oxidative stress. It is an important cause of hippocampal neuronal degeneration and cognitive impairment (Choi et al., 2014). Lipid peroxidation caused by NOX is also one of the links of ferroptosis. NOX1 inhibitors have different effects on erastin-induced ferroptosis in Calu-1 cells and HT-1080 cells, and have a partial effect on HT-1080 cells (Dixon et al., 2012; Wang et al., 2021).

Thiazolidinediones such as rosiglitazone (ROSI), a drug for the treatment of diabetes, can selectively inhibit ACSL4 activity and thereby inhibit ferroptosis (Angeli et al., 2017; Doll et al., 2017). ACSL4 is widely expressed in brain tissue, especially in the hippocampal CA1 region, and the expression of ACSL4 is gradually increased during cerebral ischemia (Kassan et al., 2013; Peng et al., 2021). Rosiglitazone (ROSI) has been shown to reduce lipid peroxidation and oxidative stress injury in hippocampal neurons during CCH, protecting brain function (Sayan-Ozacmak et al., 2012). Multiple studies have shown that long-term use of pioglitazone in patients with insulin-dependent diabetes reduces the risk of dementia in nonpsychiatric patients (Heneka et al., 2015; Lu et al., 2018).

PD

PD is the second most common neurodegenerative disease. It is common in middle-aged and elderly people with neurodegenerative diseases. Some PD patients also have cognitive dysfunction. In the late stage of PD, patients often have severe cognitive dysfunction such as dementia. Abnormal intracranial iron deposition is thought to be one of the pathogenic mechanisms of PD (Langkammer et al., 2016; An et al., 2018; Chen Q. et al., 2019), and iron induces the formation of Lewy bodies through oxidative stress pathway, which aggregates α -synuclein (Takahashi et al., 2007). Li et al. (2018) found that the iron content of the substantia nigra pars compacta in PD patients may gradually increase during the progression of PD and manifest as more significant iron deposition in the middle and late stages of the disease. Relatedly, observation of changes in its iron deposition may serve as a potential marker for monitoring disease progression. Substantia nigra iron deposition is also related to the cognitive function of patients (Liu et al., 2017). The QSM CP value of the left substantia nigra on MRI was negatively correlated with the ADL score. The CP value of the left frontal white matter was negatively correlated with the HAMD score, CP value of left

substantia nigra and CP value of left frontal lobe were positively correlated with MOCA score, and CP value of left frontal lobe white matter was positively correlated with MMSE score. SWI reflects abnormal iron deposition in the brain through CP value, which can be used for the diagnosis of PD, but has little significance for disease staging, and can be used to study the mechanism of PD cognitive dysfunction and depression (Xiong et al., 2020). Quantitative analysis of susceptibility-weighted imaging (SWI) found that PD patients with mild cognitive impairment had increased iron concentrations in the globus pallidus and head of the caudate nucleus (Kim et al., 2021). Iron is also widely deposited in the premotor cortex, prefrontal lobe, insula, cerebellum, pons and other parts of PD patients (Acosta-Cabronero et al., 2017; Chen L. et al., 2019), which are all related to apathy and rapid eye movement sleep behavior disorder (RBD) and other non-motor symptoms. There was a metabolic disorder of iron in the cerebrospinal fluid of patients with PD combined with apathy and PD combined with RBD (Hu et al., 2015; Wang et al., 2016). Serum iron has also been found to be associated with anxiety in PD patients (Xu et al., 2018). In addition, Masaldan et al. (2019b) found that the abnormal accumulation of iron in PD may be closely related to the changes of iron regulatory proteins.

Alpha-synuclein (a-syn), as a key player in tyrosine hydroxylase-dependent dopamine synthesis and other dopamine metabolic processes (Do Van et al., 2016; Belarbi et al., 2017), may play a role in iron regulation (Duce et al., 2010; Zhou and Tan, 2017). In the presence of a copper catalyst, a-syn has ferredoxinase potential, which, when combined with Fe³⁺ and converted to Fe²⁺, binds to the C-terminus of a-syn (Davies et al., 2011). Iron also increases the formation of non-normal fibers, a major event in PD (Abeyawardhane et al., 2018). Furthermore, GSH was found to be decreased in a mouse model of MPTP (Feng et al., 2014), while GSH depletion enhanced MPP⁺ toxicity in substantia nigra dopaminergic neurons (Wullner et al., 1996).

DFP has also been found to be neuroprotective in patients with early PD (Do Van et al., 2016). The MPP⁺-induced SH-SY5Y (a commonly used PD model) cell line is not programmed cell death and shares some similarities with iron toxicity: both involve lipid peroxidation and can be inhibited by DIM and Fer-1 suppressed. Results showed that iron chelators not only inhibited iron toxicity, but also protected dopamine neurons from cell death (Abeyawardhane et al., 2018). In a transgenic mouse model of PD, clioquinol was able to prevent the loss of substantia nigra cells due to the ability of clioquinol to chelate iron (Billings et al., 2016). Zeng et al. (2021) found that GPX4 in PD cells significantly decreased and ROS increased significantly after administration of ferric ammonium citrate, which in turn induced ferroptosis and led to neuronal death, while administration of iron chelators could inhibit ferroptosis and protect neurons.

HD

HD is a progressive neurodegenerative disease characterized by rapid involuntary movements and cognitive impairment, ultimately leading to death, due to expansion of CAG repeats in the Huntingtin (HTT). The pathological hallmark of HD is iron accumulation and abnormal levels of glutamate and glutathione (Skouta et al., 2014; Agrawal et al., 2018). It has also been reported that plasma samples from HD patients have lower levels of GSH (Klepac et al., 2007) and lower GPX activity in erythrocytes, so the pathogenesis of HD may be related to ferroptosis. In a mouse model of HD, nitropropionic acid-treated mice also exhibited reduced global (cytoplasmic and mitochondrial) GSH reduction, suppressed hippocampal and cortical glutathione s-transferase (GST) function, and exhibited an HD phenotype (Klivenyi et al., 2000). Although the underlying mechanism by which mutant huntingtin causes neurodegeneration is unclear, the ability of huntingtin to induce oxidative damage has been demonstrated. A study found that Fer-1 treatment at 10 nM, 100 nM, and 1 μ M protected neurons labeled with yellow fluorescent protein (YFP) and expressed by biotransfection with a pathogenic repeat (73Q) The huntingtin exon 1 fragment (mN90Q73) induces cell death. The number of medium spiny neurons (msnn) was significantly increased compared to controls (Skouta et al., 2014). The iron chelator DFO was protective and improved cognition in R6/2 mice, a mouse model of HD (Yang et al., 2016). Fer-1 can inhibit oxidative lipid damage and cell death in a cellular model of HD (Skouta et al., 2014).

ALS

ALS is a neurodegenerative disease affecting motor neurons in the cortex, spinal cord, and brainstem, and clinically manifests as progressive muscle atrophy and weakness in the extremities and trunk. The pathogenesis of ALS is unknown, and neither is the treatment of the disease. The most common type of dementia associated with ALS is frontotemporal dementia (FTD), a progressive non-AD dementia syndrome characterized by localized frontal and temporal lobe degeneration (Ringholz and Greene, 2006; Heidler-Gary and Hillis, 2007; Bede et al., 2018; Iridoy et al., 2019). Iron deposition was observed in the spinal cord of a mouse model of ALS (Golko-Perez et al., 2017). Abnormal iron deposits are found in ALS patients, and iron deposits were found in the motor cortex of the patient's brain at autopsy (Kwan et al., 2012). The lipid peroxidation of erythrocytes in ALS patients is significantly increased, while the content of GSH is decreased (Babu et al., 2008). The concentration of glutamate is higher, and the accumulation of glutamate can cause neuronal cell toxicity, which indicates that ferroptosis is directly involved in the

pathogenesis of ALS mechanism. At the same time, motor neurons in ALS mice are very sensitive to GPX4 knockout-induced cell death (Conrad et al., 2018). At present, the only approved treatment for ALS in the United States and the European Union is the anti-excitatory amino acid toxicity drug Riluzole, which is a glutamate antagonist, which can inhibit the release of presynaptic glutamate and inhibit nerve endings. It can inhibit the neurotoxicity of excitatory amino acids by inhibiting the neurotoxicity of excitatory amino acids. It has a certain effect on ALS patients with bulbar palsy or limb paralysis as the first symptom, can delay the progression of ALS, and can clearly prolong the survival time and postponement of tracheostomy (Gurney et al., 1998).

TBI

TBI is recognized as a disease with high mortality and complex survival, which is the main environmental risk factors for the development of neurodegenerative diseases. Complications of TBI are mainly motor function, cognitive function, and social dysfunction, which cause a serious burden on patients, family members and society, and age is an important factor affecting the prognosis of TBI (Griesbach et al., 2018; Fraser et al., 2019; Ritzel et al., 2019). Iron is considered to be an important agent of secondary injury after traumatic brain injury and can induce peroxidation and inflammation (Ayton and Lei, 2014). Studies have shown that after experimental brain trauma in rats, the production of lipid peroxidation products is significantly enhanced, the consumption of GSH and ascorbic acid is significantly increased (Bayir et al., 2002), and the activity of GPX is decreased (Xu et al., 2014). Elevated levels of 15-HpETE-PE after traumatic brain injury led to ferroptosis in the cerebral cortex and hippocampus, accompanied by increased expression of 15LO2 (a catalyst for the formation of protoferroporphyrin 15-oh-eicosapentaenoic acid) and depletion of GPX4, leading to cognitive impairment, effectively suggesting the possibility of ferroptosis (Wenzel et al., 2017).

Iron chelators such as DFO may improve cognitive function after traumatic brain injury (Khalaf et al., 2019). N,N'-bis(2-hydroxybenzyl)ethylenediamine-N,N'-diacetic acid hydrochloride (HBED) is a unique iron chelator that not only crosses the BBB, but also reduces the improvement and recovery of motor impairment and cognitive function after TBI in rats (Khalaf et al., 2019). The ferroptosis inhibitor Liproxstatin 1 can reduce brain edema and BBB permeability caused by TBI, improve motor and learning and memory impairment caused by TBI in rats, and significantly improve anxiety and cognitive function caused by TBI (Xie et al., 2019).

Discussion

Ferroptosis is a newly discovered form of cell death manifested by iron overload, accumulation of lipid peroxidation, and ROS. The current research preliminarily showed that ferroptosis plays an important role in neurodegenerative diseases. Clinically, ferroptosis can be induced by the following methods and exert a neuroprotective effect: exogenous lipid supplementation promotes lipid peroxidation in cells; inhibition of GPX4 and expression of GSH; construction of nano-drug delivery system to supplement hydrogen peroxide and iron ions to promote Fenton reaction of tumor cells, etc. Therefore, ferroptosis is a potential target for the treatment of neurodegenerative diseases. However, the exploration of ferroptosis still faces many problems to be solved. First, the study of ferroptosis in cognitive dysfunction-related diseases is still in its infancy, and its underlying molecular mechanisms remain unclear. Although iron overload and lipid peroxidation can cause ferroptosis, their involvement in ferroptosis-related regulatory targets such as DMT1, FPN1, or iron uptake proteins needs to be further investigated. Second, there is no specific ferroptosis marker to comprehensively and extensively study its process, and which are the key executive molecules of ferroptosis remain unclear. Finally, it is known that abnormal iron metabolism can cause ferroptosis, and whether other metal elements induce ferroptosis remains to be explored.

In addition, ferroptosis is different from other forms of cell death, but these different forms of cell death are not independent of each other. The various forms of cell death are likely to be interconnected and form a network to participate in the regulation of cell death. Studies have found (Sun et al., 2018; Chen et al., 2021) that ferroptosis is closely related to apoptosis, and ferroptosis, autophagy and apoptosis can synergistically promote cancer cell death. Therefore, further studies on the relationship and mechanism between ferroptosis and other known cell death pathways are still needed in the future, which may be helpful for the treatment of cognitive dysfunction-related diseases. In addition, ferroptosis inhibitors contain some traditional ROS scavengers, but compared with traditional ROS scavengers, ferroptosis inhibitors can block iron-catalyzed ROS generation, activate oxidative stress, and induce cell death. It can only clear the accumulated ROS in cells and has a weak inhibitory effect on ferroptosis, and cannot completely block the occurrence of ferroptosis in cells. Various types of ferroptosis inducers and inhibitors have been found, but ferroptosis regulators generally suffer from low bioavailability and adverse reactions. Therefore, screening of ferroptosis-related drugs and traditional Chinese medicines with few adverse effects on normal tissues and high target specificity is crucial for the development of ferroptosis.

In conclusion, with the gradual deepening of ferroptosis research, the research on targeted drugs and new drug targets

for ferroptosis is of great significance for the prevention and treatment of diseases in the future. At the same time, more and more experimental studies have confirmed the role of ferroptosis in neurodegenerative diseases, which provides more possibilities for the discovery of potential therapeutic drugs and therapeutic targets for neurodegenerative diseases, and also provides help to further explain the pathogenesis of neurodegenerative diseases. However, the research on ferroptosis in neurodegenerative diseases is still in its initial stage, and there are many unexplained problems, and more experiments are needed to deepen its understanding.

Author contributions

YJi and ZZ conceived the study. KZ, SL, CR, YS, LT, and YJia performed literature searching and summary. YJi, HZ, and YJia wrote the manuscript. YJia and ZZ edited the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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