Journal of Integrative Neuroscience

J. Integr. Neurosci. **2025**; 24(4): 25845
https://doi.org/10.31083/JIN25845

Review

Ferroptosis in Alzheimer's Disease: The Regulatory Role of Glial Cells

Jingyi Xu[1], Rongjing Shen[1], Mengting Qian[1], Zhengjun Zhou[2], Bingqing Xie[3], Yong Jiang[3], Yang Yu[1,4,*], Wei Dong[1,*]

[1]Key Laboratory of Medical Electrophysiology, Ministry of Education & Medical Electrophysiological Key Laboratory of Sichuan Province, Institute of Cardiovascular Research, Southwest Medical University, 646000 Luzhou, Sichuan, China
[2]Department of Neurosurgery, The Affiliated Hospital of Southwest Medical University, 646000 Luzhou, Sichuan, China
[3]Laboratory of Neurological Diseases and Brain Function, Institute of Epigenetics and Brain Science, The Affiliated Hospital of Southwest Medical University, 646000 Luzhou, Sichuan, China
[4]Department of Human Anatomy and Histoembryology, School of Basic Medical Sciences, Southwest Medical University, 646000 Luzhou, Sichuan, China
*Correspondence: yuyang80@swmu.edu.cn (Yang Yu); dongwei@swmu.edu.cn (Wei Dong)
Academic Editor: Gernot Riedel
Submitted: 25 July 2024 Revised: 11 October 2024 Accepted: 30 October 2024 Published: 24 April 2025

Abstract

Alzheimer's disease (AD) is a neurodegenerative disease characterized by the formation of amyloid plaques, neurofibrillary tangles and progressive cognitive decline. Amyloid-beta peptide (Aβ) monoclonal antibody therapeutic clinical trials have nearly failed, raising significant concerns about other etiological hypotheses about AD. Recent evidence suggests that AD patients also exhibit persistent neuronal loss and neuronal death accompanied by brain iron deposition or overload-related oxidative stress. Ferroptosis is a type of cell death that depends on iron, unlike autophagy and apoptosis. Inhibiting neuronal ferroptosis function is effective in improving cognitive impairment in AD. Notably, new research shows that ferroptosis in AD is crucially dependent on glial cell activation. This review examines the relationship between the imbalance of iron metabolism, the regulation of iron homeostasis in glial cells and neuronal death in AD pathology. Finally, the review summarizes some current drug research in AD targeting iron homeostasis, many novel iron-chelating compounds and natural compounds showing potential AD-modifying properties that may provide therapeutic targets for treating AD.

Keywords: ferroptosis; Alzheimer's disease; glial cells; neuron; lipid peroxidation

1. Introduction

Iron is an essential metal cofactor that plays a vital role in many physiological functions in the body. Various physiological processes are regulated by iron in the brain, including functions that contribute to myelin formation, neurotransmitter synthesis and antioxidant enzymes [1]. Maintaining homeostasis of iron is crucial for maintaining human health, as both iron deficiency and iron overload can be harmful. It has been demonstrated that iron is essential for the normal function of neurons, oligodendrocytes, astrocytes and microglia in the central nervous system (CNS) [2]. Abnormal iron metabolism can increase blood-brain barrier (BBB) permeability and neuroinflammation, promoting neurodegenerative processes [3]. Ferroptosis is a novel type of iron-dependent cell death caused by iron overload, which results in iron-dependent accumulation of lipid peroxides and the production of reactive oxygen species (ROS) [4]. This may be a novel mechanism for inducing neuronal death in neurodegenerative diseases such as Alzheimer's disease (AD).

There is increasing evidence that iron overload and homeostasis dysregulation of iron contribute to neurodegeneration in AD and that dysregulation of metal homeostasis is associated with cell activation and death processes [5,6]. In an earlier study, histochemistry showed a striking accumulation of iron (III), localized with iron (II) cyanide, which was closely related to senile plaques, neurofibrillary tangles, and neuropil threads; the iron associated with this lesion promotes *in situ* oxidation and catalyze H_2O_2-dependent oxidation, indicating that iron accumulation may be an important factor in oxidative damage in AD [7]. Patients with moderate cognitive impairment (MCI) and AD have higher levels of brain iron deposition, according to quantification using susceptibility-weighted imaging [8]. Further evidence suggests that disruption of iron homeostasis and elevated ferritin levels in the cerebrospinal fluid (CSF) are linked to the progression from MCI to AD [9]. Additionally, a meta-analysis involving 2174 patients with AD and 2931 healthy controls showed decreased levels of iron in the blood and increased ferritin in the CSF of patients with AD when compared to levels in controls, suggesting that iron and iron-associated proteins are associated with the risk of AD [10]. Notably, whole-exome sequencing identified protein-coding variants associated with brain iron in 29,828 individuals, revealing several insights into the relationship between brain iron accumulation and AD and identifying multiple genes associated with brain iron accumulation levels [11]. These studies demonstrated a strong correlation between the pathophysiology of AD and iron homeostasis disturbance.

Recently, most research on iron-mediated neurodegenerative diseases has focused on neurons, ignoring the role of non-neuronal cells, in regulating pathological processes. Indeed, in an environment of iron metabolism disorder AD, the crosstalk between glial cells and neurons may form positive feedback, astrocyte reactive hyperplasia and amyloid-beta peptide (Aβ) activation of microglia, resulting in a self-amplifying inflammatory response in the AD process [2,12,13]. This suggests that iron deposition-induced ferroptosis, glial cell activation and neuroinflammation may be potential underpinnings of AD pathogenesis.

2. AD Pathogenesis

AD is a neurodegenerative disease that stands out as a prominent health problem for elderly individuals worldwide. It has become evident that AD is not only linked to its hallmark lesions—the accumulation of Aβ and development of neurofibrillary tangles (NFT) consequent to the hyperphosphorylation of tau protein but also to other concurrent pathologies [14]. Currently, the exact pathogenesis of AD is complex and still not fully understood, as it is influenced by factors such as genetics, aging, nutrition and a person's environment [15]. The complexity of the clinical measurement of underlying pathogenesis also poses a challenge to characterizing the pathology of AD and the fact that most medications only alleviate the symptoms and usually fail to achieve the desired outcome [15]. Indeed, the underlying biological mechanisms implicated in the pathogenesis of AD are also involved in abnormal protein dynamics, oxidative stress, neuroinflammation, disturbances of metal-ion homeostasis and bioenergetics [16].

3. Iron Dysregulation in AD

Aberrant iron uptake, excretion and storage in neurons increases intracellular labile iron pools (LIP) and Fenton responses during the regulation of iron homeostasis [17]. The primary regulator of intracellular iron metabolism is the iron regulatory protein (IRP) response element (IRE) regulatory system [18]. In an intracellular environment deficient in iron, IRP binds to ferritin and homologous IRE in the untranslated region of transferrin receptor 1 (*TfR1*) mRNA to promote ferritin mRNA translation inhibition and stabilize *TfR1* mRNA to prevent intranuclear catabolic events [19]. However, in iron-rich cells, IRP does not bind to the IRE, enhances ferritin synthesis, permitting degradation of *TfR1* mRNA and the extracellular transport of Fe^{3+} by transferrin (Tf) to cells, subsequently reducing Fe^{2+} [20,21]. Fe^{2+} are then transported from endosomes to the cytoplasm via divalent metal transporter 1 (DMT1), which is regulated by homeostasis of LIP [22]. DMT1 is used for normal neuronal metabolism and is partially stored in ferritin to protect neurons from excess iron [23]. When excess H_2O_2 in the cell interacts with Fe^{2+}, it starts the Fenton reaction, which causes intracellular lipid peroxidation to produce ROS and ferroptosis [24]. Notably, iron export in neurons is mediated by iron-exporting transmembrane protein ferroportin1 (Fpn1) through the Fpn1/Hephaestin and Fpn1/Ceruloplasmin (CP) pathways [25,26]. Alterations to this pathway induce iron retention, leading to memory impairment [27,28]. Simultaneous Fe^{2+} and Fe^{3+} imaging shows their enrichment in the brains of mice with AD [29]. Moreover, increased ferritin heavy chain (FTH) and ferritin light chain expression were found in the brains of AD patients, suggesting that LIP is increased in AD, confirming that iron can be used as a biomarker for AD [5].

Aβ deposition and hyperphosphorylated Tau protein tangles are AD's two main pathological features. Autopsy and magnetic resonance imaging have shown significant iron deposition around senile plaques [30] and at sites of cortical Tau accumulation [31], suggesting potential crosstalk between iron and senile plaques and neurogenic fiber tangles. Iron-Aβ complexes are formed in the Amyloid Precursor Protein (APP)/Presenilin genes 1 (PS1) animal, as shown by submicron resolution X-ray microscopy, indicating a direct correlation between Aβ and iron [32]. Aβ is produced by the amyloid precursor protein (APP) and an IRE in the 5′ untranslated region of the APP transcript regulates APP levels [33]. It has been shown that higher cellular iron levels in AD pathology cause increased APP translation and Aβ generation [34]. Interestingly, APP can interact with and stabilize Fpn1 to facilitate iron export and maintain the homeostasis of iron concentration [35]. Silencing/mutation of APP leads to abnormal Fpn1 function and inefficient neuronal output of iron, which further leads to iron accumulation, suggesting that APP/Fpn1 plays an important role in the regulation of iron homeostasis in the brain [36]. Furthermore, in the context of aging, Fpn1 exhibits age-dependent down-regulation [37], as demonstrated in the APPswe/PS1dE9 mouse model and in brain tissue from AD patients [28]. The degradation of APP involves two pathways, mainly involving three secretases: α, β, and γ [38]. Under normal physiological conditions, APP is processed by α-secretase to produce non-toxic forms of P3, Aβ16 and Aβ17-40/42; on the downside, when iron is overloaded in cells, β and γ secretases promote APP cleavage to form Aβ1-40 and Aβ1-42 fragments, leading to neurotoxic amyloid proteins, inducing cell damage and death [39]. It is also noteworthy that Aβ also promotes the reduction of Fe^{3+} to Fe^{2+} to be a potential source of low-oxidation-state iron, leading to oxidative damage to Aβ and surrounding molecules and further deposition of Aβ into senile plaques [40]. Additionally, the affinity of Aβ for iron increases after aggregation, leading to additional neuronal cytotoxicity [41]. The above studies suggest that AD pathophysiology is significantly influenced by the interplay between APP, Aβ and iron metabolism.

The tau protein is a significant component of neurogenic fibrillary tangles, mediating iron efflux from cells and excess iron colocalizes with tau in neurogenic fibrillary tan-

gles [31]. Autopsy study finds colocalization of iron and tau in neurons carrying NFT associated with progressive neurodegeneration [42]. Neuronal iron overload causes tau hyperphosphorylation by activating protein kinases, such as glycogen synthase kinase-3β, cyclin-dependent protein kinase-5 and mitogen-activated protein kinases amongst others, inhibiting protein phosphatase 2A [43,44], while treatment with the iron chelator desferrioxamine alleviates iron-induced tau hyperphosphorylation [45]. Under normal physiological conditions, tau protein can transport APP to cell membranes, thereby stabilizing Fpn1 and promoting iron efflux [46]. However, due to over-modification and cleavage of APP by secreted enzymes, APP is unable to reach the cell surface properly, which results in a decrease in Fpn1 levels and iron accumulation within neurons and NFT [47,48]. Notably, increased levels of oxidative stress mediated by iron regulatory imbalance may also promote tau oligomerization by binding to cysteine containing mercapto-cysteine [49]. Moreover, in a cell culture model, iron may lead to hyperphosphorylation and aggregation of tau proteins through iron binding motifs in tau proteins as well as dysregulation of insulin signaling [50]. More importantly, it has been demonstrated that age-induced neurodegeneration is caused by iron accumulation in the cortex, substantia nigra and hippocampus of tau mutant mice [47]. APP/PS1 mice with iron feeding showed impaired cognitive function, accompanied by increased in Aβ accumulation and phosphorylation of tau expression [51]. Inhibition of iron-induced hippocampal tau phosphorylation [52] and APP production processing in APP/PS1 mice is induced by treatment with the iron chelator desferrioxamine (DFO), thereby inhibiting Aβ deposit formation [53] and reversing iron-induced memory impairment [52]. Different models of AD show a strong association between iron accumulation with Aβ deposition and tau phosphorylation. However, the up- and downstream molecular mechanisms among these three in this potentially relentless cycle remain unclear. Despite insufficient data from human studies, targeting iron homeostasis with therapies improves AD pathology, as one important mechanism controlling the early pathological development of AD is iron metabolism.

Dysregulation of iron metabolism in AD has been demonstrated mainly in preclinical studies. Studies have found that Fpn1 is downregulated in AD patients and APP/PS1 animal models, while genetic absence of Fpn1 resulted in hippocampus atrophy and memory impairment. However, administration of specific iron chelating inducer significantly reduces neuronal death and memory deficits caused by Aβ aggregation, while restoration of Fpn1 ferroptosis and memory deficits in APP/PS1 mice [28]. Additionally, ferritinophagy-mediated ferroptosis is a key mechanism leading to neurodegenerative disease [54]. An essential component of the body's regulation of iron metabolism is the iron store protein ferritin; nuclear receptor coactivator 4 (NCOA4) and ferritin-containing iron cooperate in iron-deficient cells to mediate the release of iron from the ferritin storage pool through the ferritinophagy pathway [55]. The ferritinophagy process promotes ferroptosis and ferritin degradation within the lysosome and dysfunction of ferritinophagy is an important factor contributing to iron accumulation in senescent cells, this can lead to elevated total iron levels within affected brain regions, especially in AD pathology [56,57].

Calcium-mediated oxidative stress is largely inseparable from iron, as both iron and Ca^{2+} play key roles in neuronal function, such as ROS production, mitochondrial homeostasis, and synaptic plasticity [58]. Iron-induced neuronal ROS production alters Ca^{2+} signaling, which in turn affects synaptic plasticity and hippocampus-dependent memory formation [59,60]. In the mouse hippocampal neuronal cell line HT-22, excess iron leads to mitochondrial fragmentation and increased Ca^{2+} levels, which in turn stimulates the Ca^{2+}-dependent phosphatase calcineurin and neuronal cell death [61]. In primary hippocampal neurons, iron-induced ROS increase promotes the release of calcium in the endoplasmic reticulum (ER) and subsequent mitochondrial fission may lead to neuronal dysfunction [62]. Thus, mitochondria as a potential target for the treatment of neurodegenerative processes induced by abnormal iron metabolism. Notably, the crosstalk between iron, ROS, and Ca^{2+} signaling is bidirectional, as many proteins involved in cellular antioxidant defense and ROS production are dependent on Ca^{2+}. The aberrant increase in intracellular Ca^{2+} promotes the uptake of mitochondrial Ca^{2+} by mitochondrial Ca^{2+} unidirectional transporters, resulting in more ROS production, which may further increase an unstable iron pool [63]. A primary hippocampal neuronal study has reported an influx of iron through Ca^{2+} channels, resulting in altered intracellular iron content [64]. A sustained increase in Ca^{2+} flux regulates the immunological profile of ferroptosis [65]. Overall, current evidence suggests that the coordinated interrelationship between excess iron and abnormal Ca^{2+} signaling is most likely to occur in neurodegeneration, particularly AD, as abnormal calcium signaling is a central issue in AD pathology [66–68].

4. Ferroptosis in AD

Several pathological features found in AD patients are highly correlated with ferroptosis, including elevated levels of free iron [8], lipid peroxidation [69] and defects in antioxidant systems such as glutathione peroxidase 4 (*GPX4*), glutathione (GSH), and cystine/glutamate antiporter system (system Xc^-) [70]. System Xc^-, composed of the light chain Solute Carrier Family 7 Member 11 (*SLC7A11*) and heavy chain Solute Carrier Family 3 Member 2 (*SLC3A2*), is an important glutamate transporter in the CNS for the cellular uptake of cystine in exchange for intracellular glutamate [71]. In the context of AD, compensatory uptake of cystine leads to poor glutamate clearance in the synaptic cleft, causes excitatory neurotoxicity through system

Xc^-, enhances lipid peroxidation and leads to ferroptosis and the development of AD [72,73]. Additionally, GSH is an important intracellular antioxidant that prevents iron-dependent oxidation, which is a crucial biological process in ferroptosis, primarily by binding to Fe^{2+} in unstable LIP [74]. Reduced GSH levels have been found in the occurrence and progression of AD [75]. Further, γ-glutamylcysteine ethyl ester, a precursor to GSH, was found to increase intracellular GSH content, thereby inhibiting neuronal toxicity triggered by an Aβ-induced decline in GSH levels [76] and these findings suggest a strong link between dysregulation of GSH levels and AD pathology. Another predisposing factor associated with ferroptosis in AD is GPX4. GPX4 has been shown to be a key regulatory enzyme in AD-associated ferroptosis and has been shown to repair lipid hydroperoxides in membranes and inhibition of GPX4 is one of the key factors in the pathogenesis of ferroptosis-associated AD [77]. Indeed, knockout of the GPX4 gene in the brain leads to a number of features associated with AD pathology, for example, Gpx4BIKO mice exhibit cognitive deficits and hippocampal neurodegeneration, including reduced levels of NeuN, synaptophysin and Synaptosome Associated Protein 25 (SNAP25) and a significant decline in learning ability and memory in mice over time [78]. Additionally, studies have shown that GPX4 deletion upregulates β-secretase activity and leads to increased Aβ production [79], overexpression of the GPX4 gene in 5xFAD mice reduced cognitive impairment and markedly enhanced learning and memory [77]. Further, mutations in presenilin genes 1 and 2 (*PS1* and *PS2*) mediate autosomal dominant familial AD lesions; mutations in *PS1* and *PS2* cause AD lesions by repressing GPX4 expression and deregulating ferroptosis [80]. These findings suggest that ferroptosis is involved in AD lesions and the search for drugs t targeting Xc^-, GSH and GPX4 systems represents an important direction in AD research. Notably, the aging brain expresses high quantities of polyunsaturated fatty acids, which are favored substrates for lipid peroxidation during ferroptosis and increase vulnerability to the consequences of ferroptosis [81]. Moreover, one important regulator of ferroptosis is nuclear factor erythroid 2-related factor 2 (Nrf2), Nrf2 activates to protect cells and tissues from ferroptosis by regulating significant genes, such as those involved in iron and glutathione metabolism, against oxidative stress caused by excess iron [82]. Research has demonstrated that *Nrf2* mRNA expression is significantly lower in AD patients and animal models, and that Nrf2 deficiency speeds up the production of Aβ and β-secretase 1 (BACE1) expression [83]. More importantly, the expression of Nrf2 decreases with age, suggesting that it may contribute to the development of AD by promoting ferroptosis stress sensitivity [84].

Apolipoprotein E (*APOE*) allele variants are the most significant genetic risk for disseminated AD and *APOE* variants, leading to Aβ deposition, hippocampal atrophy and abnormal brain metabolic function [85]. Ferritin levels in CSF have been found to be positively correlated with *APOE-ε4* expression and negatively correlated with both MCI and AD [86]. In this context, Duro *et al*. [87] found an association between *APOE-ε4*, intracortical iron and brain function. Indeed, elevated extracellular iron levels upregulate *APOE-ε4* expression in neurons and accelerate intracellular polyunsaturated fatty acids (PUFA) accumulation [88], providing a suitable environment for lipid peroxidation and ferroptosis, which leads to increased extracellular Aβ deposition and exacerbation of AD [89]. Notably, glial cell dysfunction is thought to contribute to amyloid accumulation and synaptic loss in AD and Haney *et al*. [90] found that both a large number of lipid droplets accumulate in glial cells and their synaptic pruning function may be regulated by the *APOE* allele. Moreover, a recent research has revealed that APOE is a potent inhibitor of ferroptosis that activates the Phosphatidylinositol-3-kinase/ Protein kinase B (PI3K/AKT) pathway and inhibits the autophagic degradation of ferritin (ferritinophagy) thereby avoiding lipid peroxidation mediated by iron [57]. Although the study of APOE in brain iron regulation needs to be further developed, iron seems to provide a bridge between APOE and AD, which supports a further theoretical basis for the study of the pathomechanisms of AD.

Ferroptosis in AD is accompanied by multiple pathologic changes. A variety of other manifestations associated with ferroptosis have been identified in various neurological diseases mediated by neuroinflammation, and damage-associated molecular patterns. These include the ROS generated during ferroptosis events that activate glial cells by activating neuroimmune pathways, which subsequently lead to the production of various inflammatory cytokines that promote the development of neurological diseases [91]. Novel drugs that target inflammation have shown effective intervention against ferroptosis. One study found that dimethyl fumarate attenuates neuroinflammation and ferroptosis by mediating the inflammatory central node nuclear factor-κB (NF-κB) signaling pathway and ameliorates bivascular occlusion-induced cognitive impairment in rat chronic cerebral hypoperfusion models [92]. Similarly, silybin exerts neuroprotective effects on STZ-induced sporadic AD models by downregulating ferroptosis injury and thereby downregulating downstream stimulator of interferon genes (STING)-mediated neuroinflammation [93]. Indeed, a recent study indicates that ferroptosis is associated with the activation of inflammation, including the activation of multiple inflammation-related signaling pathways, including the Janus kinase-signal transducer and activator of transcription (JAK-STAT), NF-κB, inflammasome, cyclic Guanosine Monophosphate–Adenosine Monophosphate (GMP-AMP) synthase-stimulator of *IFN* genes (*cGAS-STING*) and Mitogen-Activated Protein Kinase (MAPK) pathways [94]. Targeting these inflammation-related pathways may

provide intervention for ferroptosis, especially in AD, as one of the important features of AD pathogenesis is neuroinflammation [95].

Various pathways, including iron metabolism, redox status, lipid and sugar metabolism, the metabolism of cytotoxic amino acids and mitochondrial activity may regulate the process of ferroptosis [4]. Major markers of ferroptosis, dysregulation of ferritosis, lipid peroxidation and ROS production have long been identified in the brain and animal models of AD patients [96]. A recent transcriptomic study has identified differential expression of genes associated with ferroptosis in AD in different glial cells and neurons [97], suggesting that the pathogenic process of ferroptosis in AD may include glial cells. Though it's yet unknown exactly how ferroptosis occurs in neurons, non-neuronal cells such as glia are integral to mediating ferroptosis to neurons [17]. When activated, glial cells can induce ferroptosis by disrupting iron homeostasis, releasing proinflammatory factors, altering amino acid metabolism and raising levels of oxidative stress, which are associated with many organ injuries and degenerative diseases [98,99]. For instance, neurofilament light chain, a pathologic marker for various neurological disorders, including AD, is part of the axonal cytoskeletal protein complex and FTH may be released into the extracellular space while reflecting the senescent state of microglia. After acting on microglia with various neurofilament light chain concentrations, the secretion of FTH-containing exosomes by microglia increased and stimulated peroxidation of membrane lipid and neuronal loss involved in neuronal ferroptosis [100]. Although iron homeostasis and ferroptosis are crucial in causing AD neuronal death, how they interact and lead to neurodegeneration remains poorly understood. Therefore, the pathological processes of iron metabolism disruption and associated cell death urgently require further investigation in the brain.

5. The Role of Glial Cells in Regulating Ferroptosis in AD

Microvascular endothelial cells (BMECs), astrocytes, microglia and pericytes together constitute the BBB [101]. The BBB is an effective protective filter for the brain as it regulates iron entry, separating cerebral iron homeostasis from whole-body homeostasis. Expressed on the luminal side of cerebral capillaries, TfR1 mediates iron uptake in the brain and binds circulating transferrin to promote the transfer of iron to BMECs through the TfR1-mediated endocytosis mechanism [3]. Notably, hepcidin is a peptide hormone implicated in the regulation of Fpn1 and brain iron metabolism. It has been shown that hepcidin is expressed in cortical neurons, glial cells and BMECs and plays an important role in the regulation of iron homeostasis [102]. Hepcidin binds to Fpn1 in the cell membrane of BMECs, promotes the internalization and degradation of Fpn1 and blocks the passage of iron into the brain through the BBB [103]. It was shown that hepcidin expression levels were reduced in AD patients and APP transgenic mice, whereas hepcidin treatment of cultured BMECs and neurons resulted in a reduction of iron input (TfR1 and DMT1) and output (Fpn1) proteins, which reduced iron uptake in neurons [104]. Furthermore, in a recent study of the APP/PS1 mouse model, it has been shown that hepcidin overexpression in astrocytes induces a reduction in iron levels in cortical and hippocampal neurons, with significant improvements in cognition and Aβ plaque aggregation, leading to a reduction in oxidative stress and neuroinflammation, but more importantly, a reduction in neuronal death [105]. Additionally, it was found that iron, transferrin and ferritin levels in astrocytes, microglia and oligodendrocytes change during aging [106]. This means that glial cells play an important role in the regulation of iron in the brain. In fact, aging mediates inflammation and BBB damage, which is responsible for the uneven and unbalanced distribution of brain iron and the main cause of neurodegeneration, while aging-dependent brain iron accumulation may be due to changes in ferritin levels that impair its homeostasis, which in turn activates glial cells, induces cytokine release and propagates neuroinflammation.

Glial cells are not only the primary support cells for neurons but are active participants in neuronal network formation and information processing in the CNS [107]. Extensive research has demonstrated that the crucial role of ferroptosis in the inflammatory response. Ferritin synthesis is regulated by proinflammatory cytokines, including interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor α (TNF-α), and interferon-gamma (IFN-γ), which affect iron storage in cells and tissues [108]. Microglia first induce ferroptosis and may do so by producing inflammatory factors, including interleukin-8 or IL-1β [109]. Astrocyte-neuron interactions protect neurons from ferroptosis, these include enhanced expression of GSH, Nrf2 and catalase to counteract redox stress associated with excess free iron [110,111]. For example, in the resting state, the ferroptosis inhibitor Nrf2 is efficiently activated by brain-derived neurotrophic factor in astrocytes and regulates metabolic cooperation between astrocytes and neurons [112]. Thus, dysregulation of neuronal interactions in astrocytes may induce neuronal ferroptosis. Additionally, in the setting of iron deficiency, astrocytes and microglia are able to release iron bound to ferritin and support oligodendrocytes during myelination [113,114]. Conversely, in the setting of iron overload, oligodendrocytes overexpress ferritin, providing important antioxidant defenses to neurons [115]. Uncontrolled glial activation and neuroinflammation are involved in the pathogenesis of AD [116]. In the brains of AD patients, reactive astrocytes accumulate around Aβ by phagocytosis of locally degenerated dendrites and synapses [117] and surround Aβ deposition in the form of glial scars [118]. Activated microglia and astrocytes induce neuronal death *in vitro* by releasing proinflammatory factors, nitric oxide (NO), ROS, and glutamate [119]. Moreover, in spo-

radic and preclinical AD patients, focal loss of oligodendrocytes in the neocortical gray matter is associated with Aβ plaque cores [120]. Indeed, glial cells regulate iron metabolism by expressing iron regulatory proteins to maintain normal myelin sheath function and neuronal recombination processes; when activated, they can influence AD pathology by inducing neuronal death through pathological processes such as disruption of iron homeostasis [2], release of various cytokines, alteration of protein metabolism, and increased levels of oxidative stress (Fig. 1). Thus, there is a need to gain insight into the interactions between glial cells and iron metabolism and neurodegenerative diseases, which may facilitate the exploration of therapeutic strategies for AD by restoring iron homeostasis and inhibiting oxidative stress.

6. Glia Activation Regulates Ferroptosis by Disrupting Iron Homeostasis

6.1 Microglia

As highly reactive immune cells in the brain, microglia play a critical role in regulating the iron metabolism in brain networks [121]. Proteins that regulate iron metabolism in microglia, including transferrin receptors (TfR), ferritin, divalent metal DMT1 and Fpn1, which mediate iron influx from BMECs and the brain interstitium control the amount of iron in neurons [122,123]. After being released from Tf, iron is translocated to the cytoplasm via DMT1 or other transporters [124]. Thus, microglia can internalize non-Tf-bound iron (NTBI) and Tf iron through different uptake pathways [125]. Microglia regulate their iron levels through the IRP and IRE signaling pathways, which control the expression of proteins related to iron metabolism; when intracellular iron levels are low, IRP binds to transferrin receptors and iron *IRE* in ferritin mRNA, leading to an increase in the expression of these proteins and promoting iron uptake and storage [125]. Under conditions of neuroimmune activation, the abundance of DMT1 on the surface of microglia and neurons is increased, and these cells are susceptible to ferroptosis due to iron overload induced by high levels of NTBI [126].

First, the microglia of activated cells can accumulate iron, leading to increased iron accumulation in the CNS within the brain [127]. The study reported that iron supplementation in newborn mice promotes neurodegeneration, leading to microglia activation, increased volume and reduced process length [128]. Second, proinflammatory cytokines mediated by NF-κB activate microglia in response to iron excess; Subsequently, microglia exacerbate iron accumulation in neurons by releasing proinflammatory cytokines [129]. When cultures of organotypic hippocampal cells were treated with ferrous ammonium sulfate, ferrous ammonium citrate, or ferrocene, there was a significant activation of microglia, accompanied by increased levels of ferritin expression in microglia and oligodendrocytes, as well as proinflammatory factors such as TNF-α, IL-1β and IL-6 [130,131]. Furthermore, ultra-high-resolution magnetic resonance imaging (MRI) showed the presence of microglia with iron-positive staining in AD patients' hippocampus [132]. Iron accumulation is also consistently found in activated microglia in the frontal cortex of AD patients and is normally located near the Aβ plaques [133]. Further research has found that increased iron levels may trigger and lead to iron-rich Aβ plaque formations, which promote microglia proliferation and toxicity accumulation [127]. Iron feeding elevates Aβ levels in SH-SY5Y (neuroblastoma cells) co-culture senescent microglia cells [134] and co-deposition of Aβ with iron has also been found in microglia of APP/PS1 mice [135]. Moreover, an earlier autopsy study has found strong immunopositivity for microglia ferritin in senile plaques in the hippocampal region of AD patients and subsequent in-depth studies found that increased microglia ferritin, as well as intracellular iron deposition, increased the level of oxidative stress in the cells themselves, leading to a tendency toward apoptosis [136]. Notably, when neurodegeneration has occurred, activated microglia remove extracellular iron by expressing more ferritin [137], which is accompanied by an increase in expression of the intracellular ferritin light chain iron storage protein [127], an increase in the release of proinflammatory factors [135,138] and finally infiltration with Aβ [127,139], meaning that that iron overload may trigger microglia metabolic and/or inflammatory responses [140].

In the APP/PS1 mouse, an inflammatory microglia phenotype was induced with IFN-γ and Aβ [135], inflammatory cytokines IL-6 and TNF-α increased DMT1 expression in microglia, thereby promoting iron sequestration in cells [141,142]. Subsequently, the expression of ferritin mRNA on the cell surface was upregulated, and transferrin mRNA was down-regulated, which further promoted iron accumulation in activated microglia; iron accumulation induced a shift toward a glycolytic metabolism, impaired their phagocytosis and weakened the clearance rate of Aβ and eventually led to Aβ deposition [135], resulting in a relentless cycle of AD. Interestingly, activated microglia also secrete the acute-phase protein lactoferrin, which interacts with APP to promote Aβ formation [143], promoting an increase in IL-1β expression in microglia in the setting of iron overload, thereby enhancing pro-inflammatory effects [138]. Additionally, through regulating the NF-κB signaling pathway, Aβ causes microglia to synthesize and secrete inflammatory IL-1β; iron treatment further enhanced the inflammatory response in microglia, while DMT1 inhibition protects microglia from Aβ-induced inflammation responses and IL-1β increases induced by Aβ were prevented by ROS inhibitors [138]. Intriguingly, in another study, iron deprivation culture experiments inhibited LPS-induced secretion of IL-1β and TNF-α from microglia and increased the expression of anti-inflammatory cytokine IL-10 [144]. In particular, IL-10 improves iron metabolism by inhibiting inflammatory factors, regulating the STAT3 signaling path-

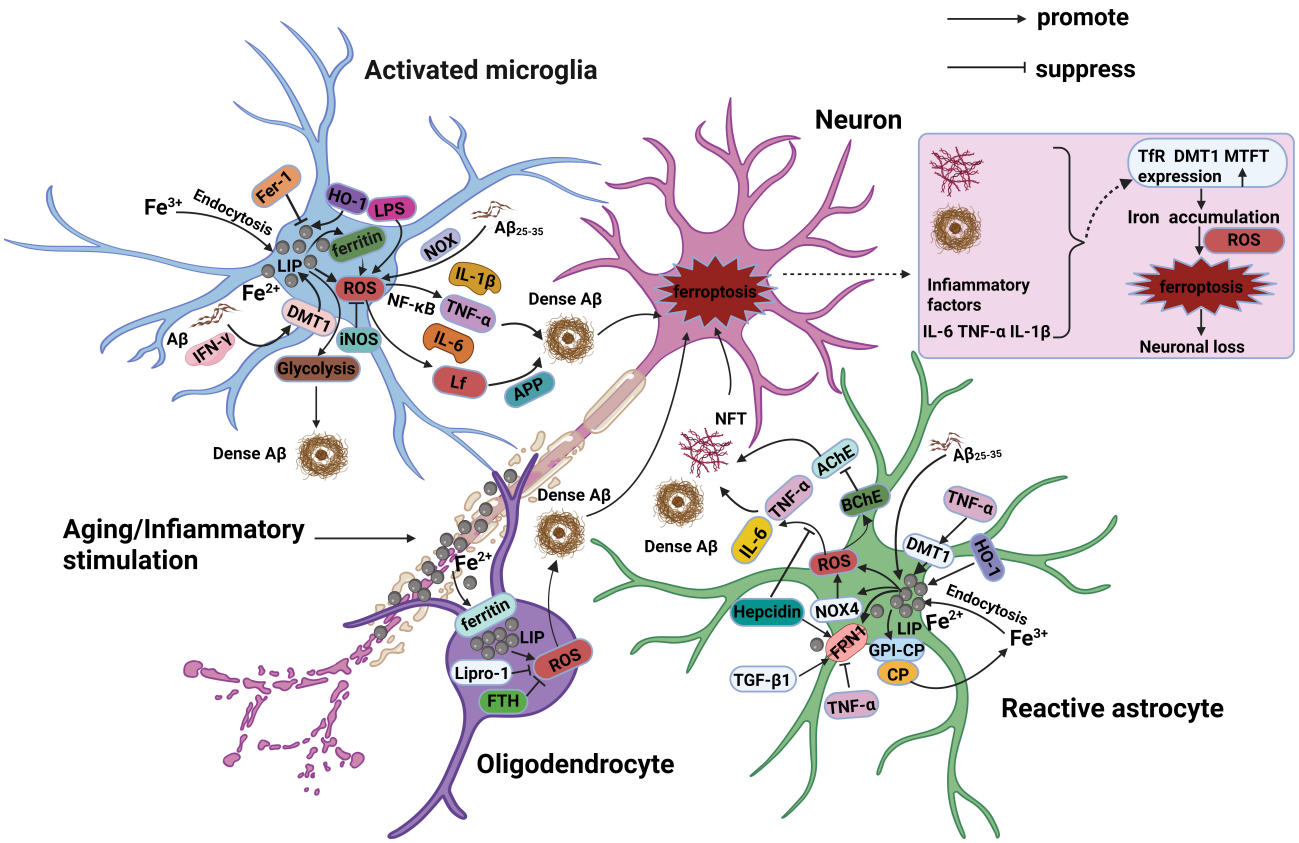

Fig. 1. Molecular mechanisms of glial cell ferroptosis regulation in AD. In an AD pathological setting, glial cells are exposed to elevated levels of iron, lipopolysaccharide and extracellular Aβ released by damaged neurons. (i) DMT1 and ferritin expression are upregulated in microglia, leading to increased intracellular iron stores. With continued iron uptake, LIP is formed. Iron induces ROS production and activates inflammatory factor release, promoting neuroinflammation, infiltrating Aβ plaques and promoting neuronal iron accumulation. Increased iron promotes microglia glycolytic pathways, reduces phagocytosis and leads to Aβ deposition. Extracellular Aβ promotes ROS production via NADPH-oxidase, further increasing DMT1 expression and promoting iron sequestration, forming a relentless cycle of iron, ROS and Aβ. (ii) High iron levels induce reactive astrocytes to produce ROS and release inflammatory factors to promote Aβ deposition and NFT formation. Inflammatory factors upregulate DMT1 expression and downregulate Fpn1 expression, further promoting iron sequestration. Hepcidin in astrocytes resist ROS-mediated inflammatory factor release and upregulate Fpn1 expression. CP protein regulates the dynamic balance of iron entering and leaving the cell. (iii) Activated oligodendrocytes release ROS to promote neuronal oxidative stress, upregulate ferritin expression, increase intracellular iron stores and provide antioxidant defense against iron-induced cytotoxicity by secreting ferritin heavy chains. Three types of glial cells change neuronal iron homeostasis in neuroinflammation, promote iron accumulation in neurons by releasing inflammatory factors, infiltrating Aβ plaques and NFT formation, triggering neuronal ferroptosis, resulting in neuronal loss. Abbreviations: ROS, reactive oxygen species; HO-1, heme oxygenase 1; DMT1, divalent metal transporter 1; NOX, NADPH-oxidase; LPS, lipopolysaccharide; IFN-γ, interferon-γ; TNF-α, tumor necrosis factor α; IL-1β, interleukin-1β; IL-6, interleukin 6; iNOS, inducible nitric oxidesynthase; Lf, lactoferrin; APP, amyloid precursor protein; Aβ, amyloid β-protein; NFT, neurofibrillary tangles; LIP, labile iron pool; Lipro-1, liproxstatin-1; FTH, ferritin heavy chains; BChE, butyrylcholinesterase; AChE, acetylcholinesterase; TGF-β1, transforming growth factor-β1; NOX4, NADPH Oxidase 4; GPI-CP, glycosylphosphatidylinositol-anchored proteins; MTFT, Mitochondrial ferritin; Fpn1, ferroportin1; TfR, transferrin receptors. This figure was drawn using Biorender (https://www.biorender.com).

way, downregulating hepcidin expression and suppressing TfR expression [145].

6.2 Astrocytes

Astrocytes, a component of the BBB, are thought to be critical regulators of redox-active metal-iron metabolism within the brain and they influence iron homeostasis by regulating the transfer of iron from the outer body into the CNS, as well as the inflow and outflow of iron between neurons and glial cells [146]. Since the terminal foot protrusions of astrocytes are closely linked to the luminal creation of BMECs, this may be the primary pathway for iron

to enter brain tissue via the Tf/TfR1 pathway [147]. Studies show astrocytes exhibit high levels of DMT1 and TfR1, as well as the iron oxidase CP, iron inflow and iron efflux proteins [148,149]. Among them, DMT1 is predominantly expressed in astrocytes associated with vascular endothelial cells, which play a major role in iron uptake [149]. Moreover, CP acts as an iron oxidase, oxidizes Fe^{2+} to Fe^{3+}, promotes iron efflux from cells to regulate iron homeostasis, inhibits lipid peroxidation mediated by the instability of the pool of intracellular Fe^{2+} and prevents neurotoxicity [150]; in the absence of physiological activity of CP proteins, Fe^{2+} cannot be oxidized, leading to a significant iron accumulation in astrocytes and loss of glial-derived growth factors essential for neurons [151]. CP knockout mice lead to progressive astrocyte and neuronal death and contribute to neurodegenerative processes [152]. According to recent research, the CSF of AD patients contains substantially less CP than normal [153]. In Aβ25-35-induced or transgenic APP expression-induced AD mouse models, knockout of the gene encoding CP increased memory impairment and iron accumulation and Aβ-induced hippocampal neuronal damage and iron levels were attenuated by injection of exogenous CP expression plasmids into the ventricles [154]. Notably, astrocytes appear to be primarily involved in the transport of iron rather than its accumulation, as they have the lowest metabolic prerequisites for iron in neuroglia [155]. However, in the case of brain aging, an increase in the number of iron-positive astrocytes can be observed, perhaps because iron is stored not only in ferritin but also in the mitochondria of astrocytes, iron overload mediates mitochondrial dysfunction and triggers oxidative stress [156].

Unlike CP, heme oxygenase-1 (HO-1) breaks down heme into carbon monoxide, free iron and biliverdin [157]. It acts as a sensor of mitochondrial iron chelation in astrocytes, and overexpression of HO-1 in astrocytes contributes to the pathological deposition of non-transferrin iron and adjacent neuronal damage. In contrast, using the iron chelator DFO effectively reduces the death of cultured astrocytes [158]. Furthermore, it was discovered that, in comparison to controls, HO-1 was substantially more immunoreactive in astrocytes and neurons in the cerebral cortex and hippocampus and it colocalized with neurogenic fibrous tangles and amyloid senile plaques in AD patients [159]. This suggests neuronal death in AD pathogenesis is related to elevated astrocyte expression of HO-1 and consequent iron accumulation. Within the brain's glia and white matter, butyrylcholinesterase (BChE) participates in cholinergic neurotransmission alongside acetylcholinesterase [160]. In AD mice, pathogenic Aβ and NFT were discovered to colocalize with BChE, indicating that this protein may be implicated in the etiology of AD [161]. In particular, the recent identification of a possible *IRE* in the 3′-UTR of BChE based on mRNA sequence analysis suggests that BChE may be regulated by iron metabolism, while further studies have found that BChE levels are iron-dependent and are expressed predominantly in brain astrocytes and BChE generated by reactive astrocytes can hasten the breakdown of acetylcholine in the aging brain, which causes cognitive function to deteriorate [160,162]. Additionally, ferroptosis is induced in astrocytes and may contribute to pathogenesis in the inner olfactory brain according to scRNA-seq study and astrocyte ferroptosis further accelerates mood and cognitive deficits in AD [163]. Moreover, TNF-α treatment of astrocytes increased DMT1 expression and decreased Fpn1 expression *in vitro*, whereas TGF-β1 treatment had no effect on DMT1 expression but increased Fpn1 expression in astrocytes [141], suggesting that iron metabolism in astrocytes is also regulated by cellular inflammatory factors in the CNS. Based on the previously listed AD models, astrocyte-bound or released proteins affect iron homeostasis, which in turn may affect ferroptosis. Thus, strategies targeting different protein expression in astrocytes may help prevent neuronal death, particularly via ferroptosis.

Further, given that astrocytes are Cu depots, dysregulation of Cu metabolism in the brain is characteristic of neurodegenerative diseases, including AD [164]. The cytotoxicity of copper disrupts mitochondrial integrity by aggregating lipoylated proteins and causing the loss of Fe-S cluster proteins, thereby triggering cuproptosis, leads to oxidative stress and mitochondrial dysfunction, which has something in common with the pathological mechanism of ferroptosis [165]. In fact, in addition to the mitochondrial tricarboxylic acid cycle, GSH is a common hub of ferroptosis and cuproptosis, albeit with different roles, in ferroptosis GSH acts as an antioxidant, preventing lipid peroxidation, while in cuproptosis it acts as a copper companion, binding copper to mitigate the aggregation of lipoylated proteins [166]. The depletion of GSH levels is a feature of brain aging and has been associated with the progression of neurodegenerative diseases, including impaired cognitive function and ferroptosis in AD patients [167]. Therefore, it may be speculated that cuproptosis and ferroptosis may have a cross talk in AD, but the upstream and downstream molecules that mediate the common pathological mechanism need to be further studied.

6.3 Oligodendrocytes

The brain's oligodendrocytes are the cells with the highest iron content. Iron is bound by oligodendrocytes as metabolic substrates for myelin synthesis and maintenance; the formation of myelin sheaths is correlated with both direct and indirect iron uptake [168]. Indeed, ferritin is found in AD patients, mainly in oligodendrocytes and myelinated axons of glial dystrophy [169]. By comparing cortical myelin formation profiles with Aβ deposition profiles, it was found that age-related myelin breakdown liberates iron release from oligodendrocytes, which promotes Aβ oligomerization in brain parenchyma [170]. White matter abnormalities due to myelin and oligodendrocyte damage have been shown to promote cognitive im-

pairment and AD pathogenesis [171]. Notably, one of the most susceptible cell types to oxidative stress is the oligodendrocyte due to its intrinsic iron-rich composition and low antioxidant concentration and as age increases, iron levels in the brain gradually increase and oligodendrocytes are highly susceptible to increased damage due to oxidative stress and DNA damage [172]. A recent MRI study of AD patients found a negative correlation between iron levels and myelin levels in key brain regions with age, suggesting that myelin breakdown may release large amounts of accumulated iron, further promoting myelin breakdown and neurodegeneration [173]. Additionally, FTH secreted by oligodendrocytes prevents oxidative damage and death caused by neuronal iron deposition [115]. In a multiple sclerosis model induced by cuprizone, ferritin's quick mobilization of iron causes ferroptosis, leading to oligodendrocyte loss and iron-mediated lipid peroxidation and demyelination [174]. This suggests that ferroptosis in AD may also be caused by lipid peroxidation and rapid ferritin mobilization-mediated oligodendrocyte loss, as oligodendrocyte demyelination is a natural source of iron for loading iron into neurons under conditions such as aging and pathological inflammation.

7. Glia Activation Induces Ferroptosis by Increasing Oxidative Stress

7.1 Microglia

Molecular mechanisms of ferroptosis in AD have been implicated in increased oxidative stress. Neuronal networks are attenuated by glial cells via a variety of pathways that inhibit the entry of excess ROS into neurons, with the targets they provide being valuable for restoring the degenerating metabolic status of neurons. Activation of microglia induces neuronal ferroptosis in AD through increased oxidative stress. One study found that Aβ25-35 induces excessive amounts of ROS in BV2 microglia through NADPH oxidase; when intracellular iron is depleted, Aβ25-35-induced ROS is inhibited [175]. Further research found that when primary neurons and microglia were co-cultured with iron and LPS, there was a significant decrease in the number of neuronal cells and a dose-dependent increase in ROS generation in the treated microglia, suggesting that iron significantly increased microglia ROS production and induced neurotoxicity and targeting NADPH oxidase may be a therapeutic direction for iron-induced microglia-related inflammation and neurotoxicity [176]. Moreover, in acute inflammatory injury and LPS-induced inflammation, increased microglia HO-1 expression, iron deposition and iron toxicity accumulation further increases ROS, decreased GPX4 expression, and enhanced oxidative stress in the brain, leading to cognitive impairment and behavioral disorder; in this context, these features are significantly improved and partially restored when the *HO-1* gene is knocked out, or iron chelators are used in mice, suggesting that inhibition of microglia HO-1 activity or application of iron chelators might be a potential therapeutic in slowing down AD progression [177]. According to a recent study, ferroptosis susceptibility is modulated by inducible nitric oxide synthase (iNOS)/NO•-enrichment in activated M1 macrophages/microglia. iNOS knockdown increased the sensitivity of macrophages and microglia to RAS-selective lethal 3 (RSL3) (ferroptosis agonist)-induced ferroptosis, however, this phenomenon was effectively inhibited by the use of ferrostatin-1 (a ferroptosis inhibitor), indicating that iNOS is a potent target for the regulation of inflammation and ferroptosis [178].

7.2 Astrocytes

When reactive, astrocytes release a variety of antioxidant molecules such as GSH, hepcidin and Nrf2, which are critical regulators in iron metabolism and oxidative stress neuroprotection [112,179,180]. Hepcidin is one of the key regulators of systemic iron homeostasis; astrocyte hepcidin regulates iron uptake at the BBB and hepcidin injection into the brain attenuates iron deposition [105]. In an Aβ-induced AD model, hepcidin treatment reduces Aβ-induced secretion of TNF-α and IL-6 in astrocytes, reduces neuroinflammation and pro-oxidative processes, the Aβ burden and AD symptoms can be alleviated by astrocyte hepcidin thereby protecting neighboring neurons from neurotoxicity [181,182]. Another study found that hepcidin overexpression in APP/PS1 transgenic mice astrocytes reduced iron deposition caused by Aβ25-35, significantly reduced oxidative damage and neuroinflammation in the hippocampus, further improving cognitive performance [105]. Additionally, ferroptosis of astrocytes caused by oxidative stress in AD such as lipid peroxidation, DNA oxidation and mitochondrial breakage in mouse astrocytes is encouraged by Nrf2 deficiency [183]. Another study found that NADPH oxidase 4 (NOX4) serves as a significant generator of ROS, that NOX4 is significantly elevated in astrocytes in the cerebral cortex and mitochondrial metabolism was impaired in APP/PS1 double transgenic mice through oxidative stress-induced lipid peroxidation, which promoted iron toxicity in astrocytes [12], NOX4 silencing alleviated mitochondrial abnormalities, decreased Aβ and p-Tau levels, enhanced cognition and lessened ferroptosis [184].

7.3 Oligodendrocytes

Oligodendrocyte death, dysfunction and/or demyelination occur in AD [185]. It has been estimated that oligodendrocytes operate at the highest metabolic rate among brain cells that consume a lot of oxygen to generate adenosine triphosphate to provide energy for the production of myelin sheaths, resulting in the production of hydrogen peroxide and other ROS [186,187]. Iron serves as an important cofactor in myelin synthesis; it provides raw material for myelin production and tends to trigger the Fenton reaction, leading to enhanced lipid peroxidation and promotion of ferroptosis [188]. Paradoxically, low antioxidant content

in oligodendrocytes such as GSH further amplifies ferroptosis. A study has shown that liproxstatin-1 prevents ferroptosis; the use of liproxstatin-1 not only restored the expression of GPX4, GSH and iron death inhibitory proteins, but also inhibited oligodendrocyte mitochondrial lipid peroxidation and GPX4-induced iron death in oligodendrocytes [189]. This suggests that antioxidants targeting ferroptosis with age may be the direction of research to target non-neuronal cells. Since iron accumulation is associated with many neurological diseases, exploring oligodendrocytes and AD pathogenesis in future studies should be encouraged.

8. Prospects of Targeted Ferroptosis in AD Therapy

8.1 Clinical Trials of Iron Chelators for the Treatment of AD

One key mechanism causing AD neurodegeneration is ferroptosis. Therefore, in patients with AD, targeting ferroptosis may be a promising treatment option. Inhibitors of ferroptosis with current applications for treating and preventing AD are emerging (Table 1, Ref. [73,105,190–214]). Therapeutic effects in AD models have been demonstrated by iron chelators that are used in clinical settings, such as DFO, deferiprone (DFP) and deferasirox [215,216]. In a 24-month, a single-blind trial of 48 patients with AD, intramuscular injection of DFO was found to reduce the rate of cognitive decline in these patients by 50% when compared to the normal controls [190]. DFO is challenging to transport across the BBB, has low bioavailability, the nasally administered DFO nanoparticles under investigation facilitate brain transport [217] and have a potential role in AD treatment. DFP readily crosses the BBB and chelates intracellular iron. It is currently being studied in a phase II randomized, double-blind, placebo-controlled clinical trial (ClinicalTrials.gov ID NCT03234686) designed to investigate the safety and efficacy of DFP in subjects with MCI, prodromal AD and mild AD [218]. DFP has a high safety profile, low systemic toxicity and is a viable strategy for anti-ferroptosis therapy in AD. Additionally, other iron chelators, such as chloroioquine and its derivatives, may also help with the treatment of AD by reducing tau and Aβ deposition and enhancing memory and cognition (Table 1). Chloroiodoquinoline and its derivatives are moderately mild iron chelators capable of chelating iron, zinc and copper and polybutylene terephthalate 2 (PBT2) is one of the chloroiodoquinoline derivatives that promotes Aβ degradation [219]. The tolerability and safety of PBT2 in AD treatment has been demonstrated in a randomized, double-blind, placebo-controlled phase IIa trial with reduced Aβ42 concentrations in CSF and improved cognition [220,221]. Due to the potential of chloroiodoquinoline in AD treatment, researchers have synthesized several derivatives or hybrids to treat AD that are effective [222]; For example, the flurbiprofen-chloroiodonol hybrid, which has recently been used for AD treatment, has been shown to prevent the accumulation of Aβ and it resists oxidation and anti-neuroinflammation [223]. Additionally, antioxidants targeting ferroptosis compounds currently under development with therapeutic potential for AD, including Vitamin E, Alpha-lipoic acid, Selenium, Ferrostatin-1, Hepcidin, Coenzyme Q10 (CoQ10), N-acetylcysteine and Dexmedetomidine. They have all been shown to inhibit lipid peroxidation and exhibit beneficial aspects in cell and animal models of AD therapy (Table 1).

8.2 The Role and Mechanism of Other Drugs in Regulating Ferroptosis in AD

Traditional metal chelators have a single function in terms of treatment and as previously mentioned that there may be crosstalk in the pathogenesis of AD with cuproptosis and ferroptosis, dual chelating agents like Cu chelators along with Fe chelatore, have also been studied in the treatment of AD. α-Lipoic acid is a metal ion (iron, copper) chelator with targeted ferroptosis, anti-inflammatory and antioxidant effects, which improves scopolamine-induced cognitive and memory deficits in rats by attenuating reactive astrocyte proliferation [224]. Additionally, it has been shown to act as a copper chelator to transfer copper from the extracellular to the intracellular milleu, to alleviate intracellular copper deficiency in AD neurons [225]. Similarly, salicylic acid has been widely used as an anti-inflammatory drug, and given its anti-neuroinflammatory effects in AD, researchers have developed a series of salicylamide derivatives with metal chelating Cu^{2+}, Fe^{2+} capabilities, exhibiting good activity to inhibit self and Cu^{2+}-induced Aβ aggregation [226]. Further, some natural compounds also have a potential role in targeting ferroptosis in AD. For example, curcumin has chelating activity against Fe^{3+}, Cu^{2+} and Zn^{2+} and has been shown to attenuate pathological alterations in AD, while curcumin inhibits neuroinflammation in APOE4 transgenic mice via the endoplasmic reticulum stress pathway [227] and regulates microglial (M1/M2) polarization by inhibiting the TLR4/NF-κB pathway and TREM2 expression in BV2 cells, thereby attenuating LPS-induced inflammation [228]. Ginkgolide B prevents cognitive impairment by reducing oxidative stress, inflammation and ferroptosis in senescence-accelerated P8 mice [229]. Multifunctional metal chelators are able to modulate multiple targets simultaneously and have shown promise in the treatment of metal-induced neurotoxicity, however, their exact mechanism has not been determined clinically and parameters such as chelation specificity, mode of administration, bioavailability, BBB penetration ability and drug toxicity, must be considered when selecting appropriate multiple metal chelation therapies, especially for the case of drug toxicity, which must exhibit the lowest possible toxicity levels when providing durable intervention for metal-related neurodegenerative diseases.

Table 1. Overview of available ferroptosis inhibitors in AD.

Sort	Drug candidates	Key results	References
Iron Chelators	Deferoxamine	Cognitive decline in AD patients slowed by 50%	[190]
	Deferiprone	Phase AD II clinical trials are ongoing; Reverses pathological brain iron accumulation; Reduces iron deposition, Aβ levels and cognitive impairment in rats	[191,192]
	Deferasirox	Blocks iron accumulation, reduces expression of ferritin and transferrin receptors; reverses changes in Aβ metabolism; alleviates Aβ-induced learning defects in AD rat model	[193,194]
	Clioquinol	Prevention of cognitive decline in 32 AD patients and reduction of plasma Aβ42 levels; reduces iron-associated Aβ42 aggregation	[195,196]
	M30	Reduces APP expression and Aβ production; alleviates cognitive impairment in APP/PS1 mice; Reduces brain iron accumulation, Aβ and tau levels	[197,198]
	HPO	Neuroprotective effect on Aβ-induced mouse cortical neurons	[199]
	Hydroxylated chalcones	Fights human neuroblastoma SH-SY5Y cells Aβ peptide aggregation and ferroptosis	[200]
	HLA20A	Reduces APP expression and Aβ production and reduces iron-induced Aβ aggregation	[201]
	Tacrine	Neuroprotective in neuroblastoma cells treatment with Aβ1-42 and ascorbate/iron stressors. AChE inhibition and antioxidant activity	[202,203]
	Schiff bases	Inhibit redox active metals and metal-induced Aβ aggregation	[204]
Antioxidants	Selenium	Inhibit ferroptosis. Key regulator of the activity of GPX4. Improvement of cognitive impairment in AD animal models	[205,206]
	Vitamin E	Lipophilic free radicals capture antioxidants, fight ferroptosis, improve lipid ROS to prevent iron denaturation in GPX4-deficient cells, slows cognitive deterioration in patients with AD	[207]
	Alpha-Lipoic Acid	Blocks tau induced iron overload and lipid peroxidation and improves cognitive function in AD patients. Slowed cognitive decline in 129 probable AD patients	[208,209]
	Ferrostatin-1	Prevents neuronal death and memory loss. Reduces iron deposition and neuronal degeneration. Improves long-term motor and cognitive function	[73,210]
	Liproxstatin-1	Aβ-induced memory improved in AD mice	[73]
	Hepcidin	Reduces iron and Aβ levels in the hippocampus and cortex of APP/PS mice, improves cognitive function in mice	[105]
	Polyphenols	Reduces iron accumulation, clears ROS, inhibits Aβ aggregation and P-tau, improves memory and cognitive function in APP/PS1 mice	[211,212]
	FSP1	A FSP1-CoQ10-NAD(P)H pathway, along with GPX4 and GSH, inhibits ferroptosis and phospholipid peroxidation	[213]
	NQO1	Inhibits lipid peroxidation and maintains antioxidant forms of α-tocopherol, ascorbic acid and CoQ10	[214]

AD, Alzheimer's disease; CoQ10, Coenzyme Q10; GSH, glutathione; GPX4, glutathione peroxidase 4; NQO1, NAD(P)H Quinone Dehydrogenase 1; FSP1, Ferroptosis suppressor protein-1; HPO, hydroxypyridin-4-ones.

Notably, some genes targeting Fe chelators along with the gene responsible for promoting ferroptosis or anti-ferroptosis genes should be considered. For example, NCOA4, as a selective autophagy receptor, has been identified to colocalize with endogenous LC3B and intracellular iron storage ferritin complexes. However, NCOA4-mediated ferritosis-induced ferroptosis dysfunction can accelerate the pathological process of AD [230], which suggests that targeting NCOA4-mediated ferritinophagy holds promise for preventing and treating AD. Recently, the role of Nrf2 as a key regulator against oxidative stress has attracted much attention. Nrf2 exerts an antiferroptosis role by regulating the expression of a large number of ferroptosis-related genes and key aspects of lipid metabolism, which play an important role in the development of AD, as brain cells are rich in lipid [231]. Future studies should examine the mechanisms of iron homeostasis dysregulation and ferroptosis, as well as the role of the Nrf2-regulated ferroptosis-related signaling pathway in the development of AD, both to determine new drugs that effectively treat AD and identify their key targets.

Despite the compelling evidence supporting iron's involvement in the pathogenesis of AD, it is unclear what roles iron play both upstream and downstream in the pathophysiology of AD. More recently, a growing number of iron-chelating compounds and antioxidants have been found to show potential therapeutic benefits. Although it is still unclear as to whether these ferroptosis inhibitors are effective in treating AD patients, their performance has demonstrated encouraging results in AD models and future research into the use of drugs with these potential therapeutic properties (e.g., iron chelators and multifunctional metal chelators) and their to entry into clinical trials, improved bioavailability and ability to effectively cross the BBB into the brain for practical physiological functions will be a significant issue in ferroptosis-mediated AD therapeutic pharmacology research.

9. Conclusions

Given an aging population, early detection of AD is essential. Notwithstanding substantial progress in understanding the etiology of AD, drug development therapeutic strategies based on these discoveries have very limited efficacy in altering the course of the disease. Consequently, there are compelling reasons to investigate new therapeutic approaches. Ferroptosis research has recently made rapid progress in understanding the pathophysiology of AD. Dysregulation of brain iron homeostasis exacerbates neurotoxicity and cognitive impairment. Thus, targeted ferroptosis inhibitors gain new momentum in the treatment of AD. Nevertheless, further study is required to pinpoint the exact cause of neurodegenerative diseases linked to ferroptosis. The current review elucidates the function of iron homeostasis between neuronal and glial cells in AD pathogenesis. Disturbed iron metabolism in glial cells mediates inflammation, oxidative stress and other pathological processes damaging neurons; iron deposition in neurons also leads to glial cell hyperactivation, accompanied by the release of proinflammatory factors and iron metabolism molecules by overactive microglia and astrocytes, mediating neuronal cell death in AD pathology. There are few studies on the mechanism of ferroptosis in oligodendrocytes in AD. Oligodendrocytes are high in iron content and tightly wrapped around neuronal axons; further study is necessary to investigate the ferroptosis induced by oligodendrocytes in AD neurons during aging.

In summary, ferroptosis is involved in the interaction between glial cells and neurons, thereby regulating the pathogenesis of AD. However, experimental animal models are the primary focus of current ferroptosis research and changes in ferroptosis in AD patients cannot be fully simulated. Comprehensive preclinical investigations are necessary to completely understand the precise molecular and cellular pathways of iron metabolism in AD neuronal degeneration, even while clinical trials assess the potential treatment benefits focused on ferroptosis.

Author Contributions

YY and WD conceived the perspective of the work. JX, RS, MQ, and BX drafted the manuscript. JX, ZZ, BX, and YJ designed the figure. RS and MQ collect and sort references. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This work was supported by the National Natural Science Foundation of China (31871031, WD), Ministry of Science and Technology of the People's Republic of China (2019YFE0120600), and Sichuan Science and Technology Program (2023NSFSC0593, YY; 2022YFS0615, BX), the Science and Technology Planning Project of Luzhou (2022-JYJ-140 to YY).

Conflict of Interest

The authors declare no conflict of interest.

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