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REVIEW

Metabolic Regulatory Networks in Ferroptosis During Alzheimer's Disease, Mechanisms of Glial Cell Action, and Pathological Correlations with Neuritic Plaques

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Abstract: Alzheimer's disease (AD) is a neurodegenerative disease with a complex pathological mechanism, which is still poorly understood. Ferroptosis is a type of non-apoptotic programmed cell death. Many recent studies have found that ferroptosis is closely related to the occurrence and development of AD. This article explains the main theoretical basis of ferroptosis in the pathological development of AD, and systematically analyzes the synergistic pathological network of multiple pathways caused by iron metabolism disorder, abnormal lipid peroxidation, and abnormal amino acid metabolism. This article mainly focuses on the dual regulation mechanism and molecular mechanism of microglia, astrocytes, and oligodendrocytes in the process of ferroptosis. This article studies the two-way relationship between neuritic plaques (NP) and ferroptosis, and the relationship between NP and dystrophic neurites, inflammatory response, and abnormal tau phosphorylation. Based on the existing research, we propose several unanswered questions and possible targeted research directions to provide a theoretical reference for the study of AD pathogenesis and the exploration of intervention strategies.

Plain Language Summary: Alzheimer's disease is a serious brain condition that causes memory loss. One major cause of this disease is the buildup of too much iron in the brain. This excess iron harms brain cells and leads to their death. We call this specific type of cell death "iron-driven cell death."

Brain cells do not work alone. They are helped by many support cells. In Alzheimer's disease, these support cells also get damaged by the extra iron. When they fail, they cannot protect the brain anymore. This makes the disease worse. Harmful protein clumps form in the brain. These clumps hurt memory and thinking skills.

Scientists have found that certain transport systems in the brain move iron and other chemicals. Sometimes, these systems work too hard or not well enough. This imbalance causes more damage. For example, too much of a chemical called glutamate can hurt nerve cells.

This review elucidates how iron, support cells, and these transport systems work together to cause Alzheimer's disease. We also discuss new ideas for treatment. Doctors might be able to stop this iron-driven cell death. They could also fix the problems in support cells. These new methods might help slow down the disease. Our goal is to find better ways to protect the brain and help patients live healthier lives.

Keywords: ferroptosis, Alzheimer's disease, glial cells, neuritic plaques, pathogenesis

Introduction

The most common neurodegenerative disease in the contemporary world is Alzheimer's disease (AD), characterized by the progressive deterioration of cognition accompanied by decreased memory function and emotional regulation.[1] Two

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pathogenic mechanisms fundamental to this disease are the hyperphosphorylation of the microtubule-associated protein tau (p-tau) and amyloid-beta (Aβ) plaque deposition, which result in neurofibrillary tangles (NFT) and neuritic plaques (NP), respectively. Together, they exacerbate the progression of AD along with other pathological features such as the neuroinflammatory response.[2] With the continuous growth of the aging population, AD has developed into an emerging global public health issue. Despite the considerable advances in AD pathogenesis in recent years, many questions remain to be answered, and there is currently no effective and feasible targeted intervention for treating AD in clinical practice.[3] Although there have been some achievements in the development and research of small-molecule drugs targeting Aβ or p-tau, the drugs are mainly concentrated in the exploration stages and have significant limitations. Therefore, this indicates that AD may involve a more complex and multi-level regulatory network.[4]

As a new type of non-apoptotic programmed cell death, ferroptosis is mainly induced by lipid peroxidation, iron ion accumulation, and redox balance disorder.[5] It has been proven in recent studies that ferroptosis has an important influence on the pathogenesis of AD.[6] Autopsy results show that the iron content in neurons in the brain tissue of AD patients in some areas is significantly increased. Iron accumulation can increase the reactive oxygen species (ROS) level through the Fenton reaction, which aggravates the damage of lipid peroxidation, and ultimately leads to iron-induced neuronal death.[7,8] There is a relationship between many factors, such as abnormal amino acid metabolism, glial cell dysfunction, and NP deposition. These factors are closely related to ferroptosis and play an important role in the AD pathological process. On the basis of the above reasons, this paper reviews comprehensively the metabolic regulatory network of ferroptosis in AD, the dual regulation function of glial cells, and the pathological relationship of NP with ferroptosis. This paper summarizes the current research progress and key points and aims to provide theoretical support for the development of diagnostic methods and therapeutic strategies for AD targeting ferroptosis.

Homeostasis Dysregulation and Ferroptosis: A Core Regulatory Axis in the Pathological Process of AD

The Regulatory Network of Intracerebral Iron Homeostasis and Its Physiological Significance

As an integral trace element, iron is fundamental for the synthesis of DNA, transportation of oxygen, and functioning of the electron transport system of the mitochondria.[9] Iron directly influences the metabolism of glial cells and the activity of neurons in the central nervous system (CNS). Consequently, it influences the physiology of the brain as a whole.[10] The brain's ability to maintain a dynamic equilibrium of the "absorption - transport - storage - release" cycle is pivotal in achieving a steady concentration and homeostasis of iron ions. The meticulous control of this system is one of the fundamental conditions that enables the optimal operational capacity of neurons and glial cells.[11]

As shown in Figure 1, the absorption of dietary iron mainly occurs in the proximal duodenum. The intestinal epithelial cells take up non-heme iron and heme iron through different pathways. Non-heme Fe^{3+} is first reduced to Fe^{2+} by brush border enzyme duodenal cytochrome B (Dcytb), and then transported into the cells through divalent metal transporter 1 (DMT1). Meanwhile, dietary heme (contains heme iron) enters the cells through heme carrier protein 1 (HCP1) and is dehydrated by Heme Oxygenase-1 (HO-1) to release Fe^{2+} inside the cells.[12]

As illustrated in Figure 2, once inside the enterocyte, Fe^{2+} is exported across the basolateral membrane into the bloodstream by ferroportin (FPN1).[13] In the bloodstream, the membrane-bound ferroxidase hephaestin (HEPH) oxidizes Fe^{2+} to Fe^{3+}, enabling it to bind to transferrin (Tf) for transport.[14] This complex transfers iron to the cerebrospinal fluid (CSF) through endocytosis at transferrin receptor 1 (TfR1) in the blood-brain barrier (BBB) to keep the brain functioning with free iron.[15]

Glial cells and neurons employ the TfR1/DMT1 pathway to access the Fe-Tf complex and satisfy the basal metabolic demands, while cytoplasmic ferritin (FT) stores excess free iron to mitigate oxidative harm, and FT autophagy is the central regulator of this entire process, to prevent oxidative damage caused by free iron.[16]

It is the select NCOA4-autophagy pathway that degrades FT granules to release the cellular Fe^{2+} that is exported through FPN1 to achieve dynamic cellular iron balance regulation.[17] The iron response element (IRE) binding proteins (IRPs) can bind to the FT mRNA IRE (5'-IRE) to reduce the level of FT within the cells, inhibiting the cellular iron

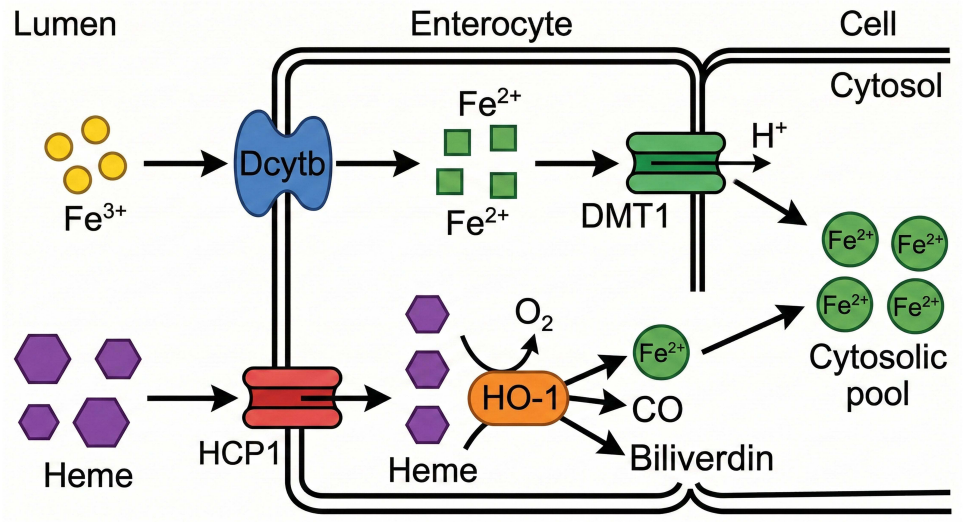

Figure 1 Mechanisms of dietary iron absorption in enterocytes.
Notes: Two iron uptake pathways: Non-heme Fe^{3+} → reduced by Dcytb to Fe^{2+}→ imported via DMT1; Heme → transported by HCP1 → degraded by HO-1 → releases Fe^{2+}, biliverdin, CO. Both feed the cytosolic iron pool.
Abbreviations: Dcytb, duodenal cytochrome b; DMT1, divalent metal transporter 1; HCP1, heme carrier protein 1; HO-1, heme oxygenase-1; Fe^{2+}/Fe^{3+}, ferrous/ferric iron; CO, carbon monoxide.

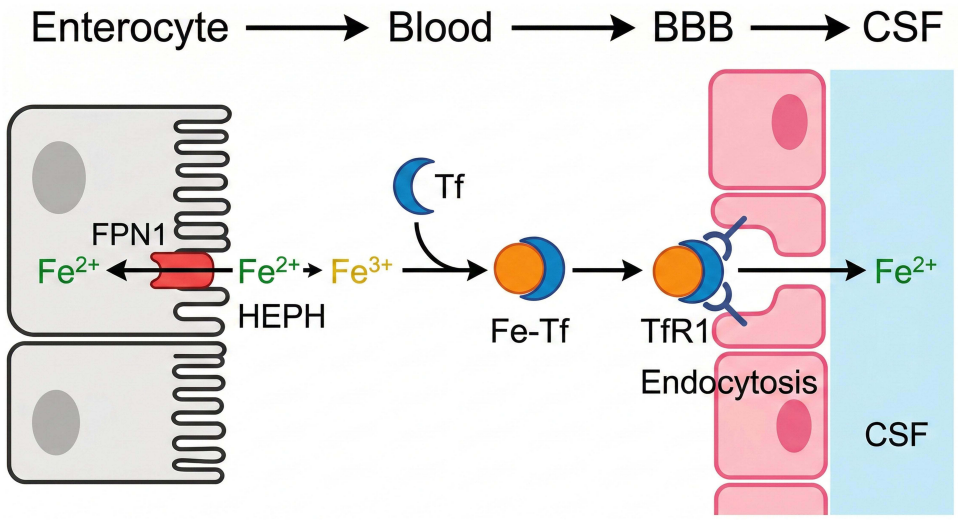

Figure 2 Iron export from enterocytes to brain via Tf.
Notes: Dietary iron exits enterocytes via FPN1 as Fe^{2+}, is oxidized to Fe^{3+} by HEPH, and loaded onto Tf for systemic transport. At the BBB, the Fe-Tf complex binds TfR1 and enters endothelial cells via endocytosis for delivery to the CSF.
Abbreviations: FPN1, Ferroportin 1; HEPH, Hephaestin; Tf, Transferrin; TfR1, Transferrin Receptor 1; BBB, Blood-Brain Barrier; CSF, Cerebrospinal Fluid.

deficient (CID). At the same time, the activated IRPs can be combined with the FPN1 mRNA IRE (3'-IRE) to stabilize the mRNA and promote its translation. This process eventually upregulates the expression of FPN1 and promotes the export of iron.[18] A schematic representation is provided in Figure 3.

Even though there is a growing body of research describing the governing regulatory mechanisms of iron homeostasis in the brain, the differential expression and regulatory mechanisms of the iron regulatory proteins and other iron metabolism molecules in various brain regions of patients with AD pathology remain an understudied area. Furthermore, the interlinking mechanisms between the regulatory network of iron homeostasis and the other pathways, particularly pathways of metabolism of amino acids and lipids, are yet to be defined.

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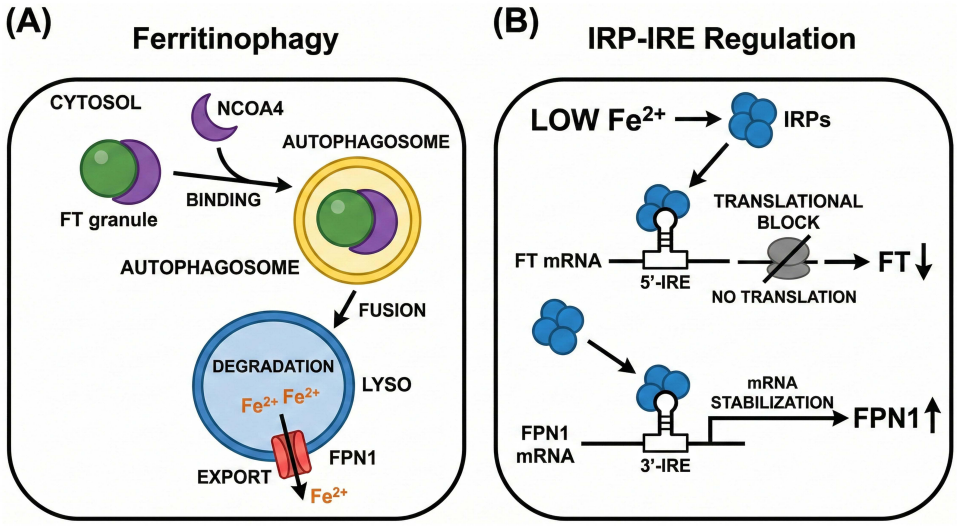

Figure 3 Ferritinophagy and IRP-IRE cross-regulation.
Notes: (**A**) Ferritinophagy: In the cytosol, NCOA4 binds FT granules → delivers them to autophagosomes → fusion with lysosomes → degradation releases Fe^{2+}→ exported via FPN1. (**B**) IRP-IRE regulation: Low Fe^{2+} activates IRPs → bind 5'-IRE on FT mRNA → translational block → ↓ FT; simultaneously bind 3'-IRE on FPN1 mRNA → mRNA stabilization → ↑ FPN1. This dual mechanism ensures iron release and retention during deficiency.
Abbreviations: FT, ferritin; NCOA4, nuclear receptor coactivator 4; FPN1, ferroportin 1; IRP, iron regulatory protein; IRE, iron-responsive element; LYSO, lysosome. ↑, increased/upregulated; ↓, decreased/downregulated.

Biological Characteristics and Core Molecular Mechanisms of Ferroptosis

Ferroptosis, a novel cell death modality, was identified by Dixon et al in 2012. Surging intracellular iron ion concentrations, noticeably increased membrane lipid peroxidation reactions, redox imbalance, and necrosis-like morphological changes, such as reduced mitochondrial volume, increased surface area, and damaged cristae, are the features of ferroptosis.[19] Ferroptosis has its own molecular regulatory mechanism, which is different from the classical apoptosis or pyroptosis pathways. The "iron metabolism disorder, accelerated lipid peroxidation, decreased antioxidant capacity" pathway is typical of ferroptosis and plays a pivotal role in the physiological process of AD patients.[20]

In the state of iron overload, free Fe2+ can produce a large amount of ROS through the Fenton reaction to attack polyunsaturated fatty acids (PUFAs) in the cell membrane directly, thereby causing structural damage to the cell membrane and leading to lipid oxidation damage.[21] At the same time, an excess of iron in the brain also activates related cytokines such as lipoxygenase (ALOX5/12/15) and prolyl hydroxylase (EGLN), which further disrupt the redox homeostasis and accelerate the pathological process of lipid peroxidation.[22]

Impaired cystine/glutamate reverse transport system (System Xc^-) is the main cause of oxidation imbalance. The synthesis of glutathione (GSH) is injured due to a decrease in intracellular cystine uptake.[23] GSH is an important cofactor of glutathione peroxidase 4 (GPX4) activity. When GSH is depleted, the lipid peroxide (L-OOH) scavenging activity of GPX4 declines sharply, causing damage to cell membrane structure, disturbing cellular functions and accelerating ferroptosis.[24] Recent reports have demonstrated that ferroptosis is an indispensable process in the development and progression of a number of neurodegenerative diseases, especially AD. Ferroptosis is closely interlinked with two key pathological processes: Aβ aggregation and p-tau hyperphosphorylation. Both of these processes are closely related to the complex molecular regulation network. These results provide critical empirical evidence and theoretical reference to understand the fundamental mechanism of AD.

Metabolic Regulatory Networks in AD

Iron Metabolism Dysregulation: The Pathological Initiator of AD Ferroptosis

Iron Accumulation Mediated by Dysfunction of FT and FPN1

Imbalances in iron homeostasis occur due to the abnormal storage of iron in the FT and the impaired iron efflux in the brain FPN1. These two phenomena create a pathological cycle of "uncontrolled iron storage and impaired iron efflux,"

leading to further iron overload in AD.[25,26] FT consists of a heavy chain (FT heavy chain 1, FTH1) and a light chain (FT light chain, FTL). FTH1 possesses a ferrous oxidase function and can oxidize the free Fe^{2+} (ferrous form) to Fe^{3+} (ferric form) for further encapsulation and storage within the protein shell. This mechanism prevents free iron oxidative damage. FTL contributes to the structural stability of the complex storage of iron.[27]

There are differential neuronal and glial FTH1/FTL expression and functional modulation in the pathophysiological stages of AD across various brain regions.[28] There is documented evidence of increased oxidative stress and Aβ aggregation in the brain of AD patients.

As depicted in Figure 4, excessive Aβ activates the RNA-binding activity of IRP1, leading to the inhibition of ubiquitination and degradation of IRP2. This increases the IRP2's binding to the 5' IRE of the mRNA, impairs the protein translation of FTH1/FTL, and causes dysregulation of intracellular iron, resulting in the accumulation of labile iron.[29] The Fenton reaction with unbound Fe^{2+} can lead to formation of high levels of ROS, worsening damages from peroxidation of lipids, and causing dysfunction of mitochondria and triggering the related apoptotic pathways, all of which aggravate symptoms of cognitive decline.[30]

Hepcidin is an important regulatory factor, which controls the iron balance in the human body, by inducing the degradation of FPN1. Figure 5 depicts that the imbalance of the Hepcidin-FPN1 axis plays a vital role in the brains of AD patients.[31] Studies have shown that the level of Hepcidin in the brains of AD patients has increased notably, and this increase is particularly obvious in the Braak stages III to VI of AD patients. At the same time, in the hippocampus of AD patients, FPN1 mRNA also decreases, and there was an evident negative correlation between Hepcidin and FPN1.[32] In the CNS, the chronic neuroinflammatory environment unique to AD drives Hepcidin, leading to the upregulation of Hepcidin. For example, in the context of neuroinflammation, the IL-6/JAK2/STAT3 pathway is activated, which can promote the expression of Hepcidin.[33] Additionally, in the environment of inflammation or oxidative stress in the body, microglia (MG) and astrocytes (AST) will enter activated states. Subsequently, they will further release inflammation-related factors, especially TNF-α, IL-6, and BMPs. These factors stimulate the overexpression of Hepcidin in neurons and glial cells.[34]

The increase in Hepcidin leads to the post-translational downregulation of FPN1. After binding to FPN1, Hepcidin can trigger the endocytosis and lysosomal degradation of FPN1 via ubiquitin-mediated degradation by inducing the E3 ubiquitin ligase RNF217.[35] This process will eventually block the outflow of iron, leaving a large amount of iron in the cell. This mechanism partially explains the paradox of systemic iron deficiency co-occurring with severe cerebral iron overload in AD patients.[36] The intracellular iron accumulation caused by the Hepcidin-FPN1 axis provides a basis for

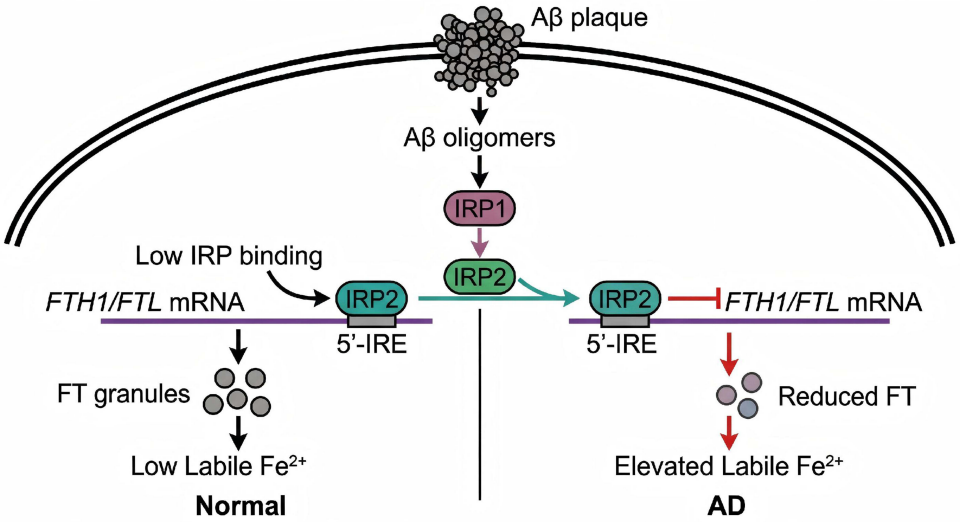

Figure 4 FT dysregulation and iron accumulation in AD neurons.
Notes: Aβ oligomers activate IRP1 → stabilize IRP2 → IRP2 binds 5'-IRE of FTH1/FTL mRNA → blocks translation → ↓ ferritin granules → ↑ cytosolic labile Fe^{2+}.
Abbreviations: AD, Alzheimer's Disease; Aβ, Amyloid-beta; IRP1/2, Iron Regulatory Protein 1/2; FT: Ferritin; FTH1/FTL, Ferritin Heavy/Light Chain; 5'-IRE, 5'-Iron Responsive Element; FT, Ferritin; Fe^{2+}, Ferrous iron.

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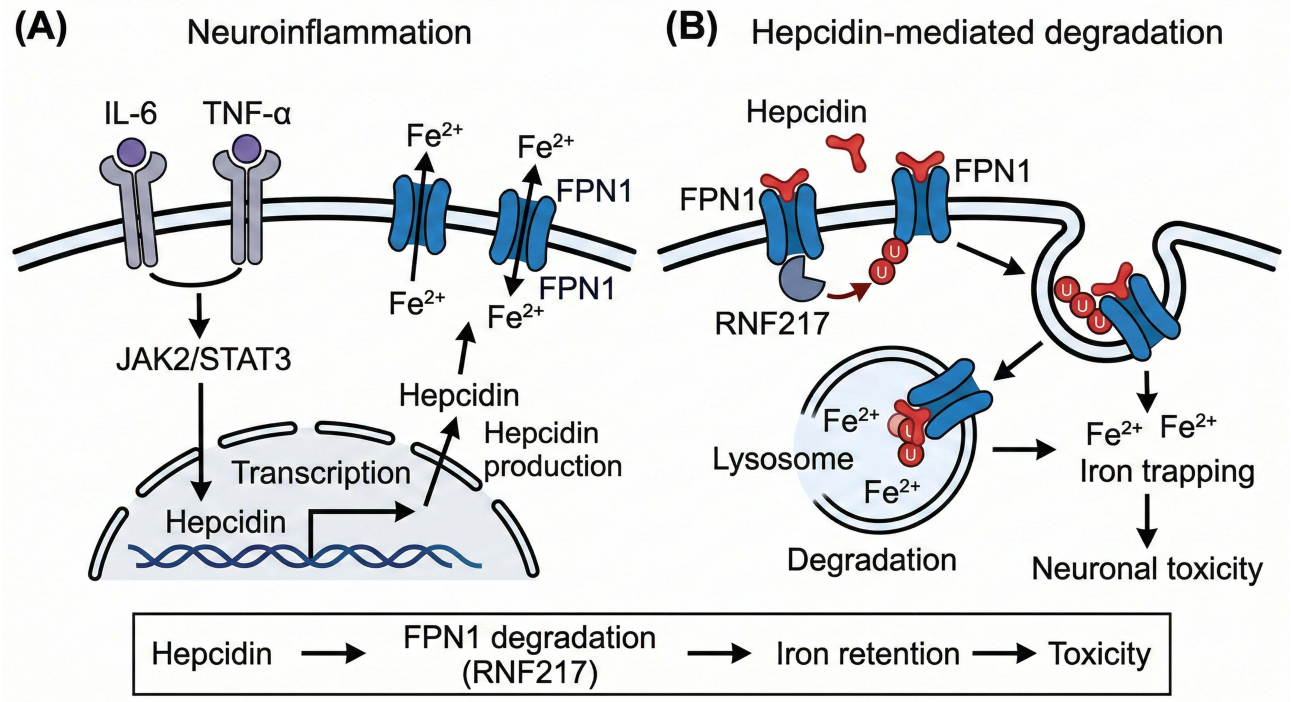

Figure 5 Hepcidin-FPN1 degradation traps iron in AD brain.
Notes: (**A**) Neuroinflammation (IL-6/TNF-α) induces Hepcidin transcription via JAK2/STAT3. (**B**) Hepcidin binds FPN1, triggering RNF217-mediated ubiquitination and lysosomal degradation, leading to Fe^{2+} retention and neuronal toxicity.
Abbreviations: IL-6, Interleukin-6; TNF-α, Tumor Necrosis Factor-alpha; JAK2/STAT3, Janus Kinase 2 / Signal Transducer and Activator of Transcription 3; FPN1, Ferroportin 1; RNF217, Ring Finger Protein 217; Fe^{2+}, Ferrous iron.

Fenton reactions, lipid peroxidation, and ultimate ferroptosis. Therefore, the Hepcidin-FPN1 axis shows a key connection between neuroinflammation and iron-mediated neurotoxicity.

In addition to Hepcidin, other factors can also affect FPN1. At the cellular level, the IRP/IRE system can further reduce the cellular iron export by inhibiting the translation of FPN1, exacerbating the iron accumulation in the brain.[37]

The impaired iron storage capacity of FT (FTH1/FTL) and malfunctioning brain FPN1 in AD patients disrupt CNS iron homeostasis through several synergistic pathways. It is worth noting that the interactions among these mechanisms may form a vicious cycle, causing iron overload and ferroptosis to continue to accelerate, and further accelerating the loss of neurons and the decline of cognitive function.

Disruption of Brain Iron Homeostasis by Blood-Brain Barrier Damage

BBB is an essential anatomical structure for CNS iron homeostasis and is composed of capillary endothelial cells, basement membrane, pericytes and glial cells.[38] Endothelial cell TJs maintain the dynamic balance of the brain microenvironment. It blocks peripheral iron ions from entering brain tissue.[39] The BBB system plays an important role in the precise control of brain iron metabolism by modulating the expression of the TfR1, internalization of the TR-Fe transport complex and endosomal pH of endothelial cells to regulate the transmembrane transport of Tf-Fe and NTBI.[40]

In the brains of AD patients, the downregulation of tight junction proteins occludin and claudin-5, red blood cell extravasation and perivascular deposition of hemolytic fibrinogen are typical manifestations of BBB dysfunction. These changes are closely related to oxidative stress, neuroinflammation and Aβ deposition in AD.[41] Studies have found that Aβ fibrils and oligomers are directly toxic to the BBB and disrupt its structural integrity and functional stability. This disrupts the transmembrane transport of iron and destabilizes the equilibrium of brain iron distribution.[42,43] The permeability of the BBB increases, and Tf-Fe complexes from the peripheral circulation enter the brain abnormally. The simultaneous up-regulation of TfR1 and down-regulation of FPN1 significantly increases the efficiency of iron ion uptake and inhibits iron efflux, which further aggravates iron deposition in brain tissue.[44] Oxidative damage induced by

imbalance of iron metabolism in intracellular compartments not only disrupts the structure of the neurons, but also reciprocally aggravates BBB vascular barrier dysfunction. This vicious cycle forms the chain of "BBB dysfunction - iron deposition increasing - ferroptosis deepening - BBB degradation sustained" and provides a new molecular biological explanation for the pathogenesis of AD.[45]

The initial trigger of this cyclical mechanism has been a topic of controversy in academic circles. At this point, it remains unknown whether iron overload first leads to BBB dysfunction and subsequently accelerates the Aβ pathological process, or Aβ deposition precedes BBB injury and iron overload. In-depth research on the dynamic development patterns and interaction mechanisms of these factors is urgently needed for future research to improve the theoretical model and advance the field.

Lipid Peroxidation: A Core Pathological Effect in AD Ferroptosis

The Driving Role of Polyunsaturated Fatty Acid Metabolic Abnormalities

The most frequent site for lipid peroxidation is the cell membrane, where phospholipids contain PUFAs. PUFAs are essential for lipid peroxidation because they are the most susceptible to reactive ROS due to the many double bond sites in their structures.[46,47] The most common PUFAs are arachidonic acid (ARA), docosahexaenoic acid (DHA), and adrenic acid (AA). The peroxidation of PUFAs is very damaging because it not only causes severe and irreversible damage to membranes and cell death, but the peroxidation of a given membrane phospholipid can also perpetuate its membrane-damaging effects and propagate across the cell membrane.[48] When the load of PUFAs exceeds the safe buffering capacity of the lipid droplets, or when these stored n-3 and n-6 PUFAs undergo peroxidation, they will produce strong cytotoxicity. This toxicity is proportional to the number of double allyl double bonds, making PUFAs one of the main drivers of ferroptosis.[49]

In the case of a patient with AD, cPLA2 is stimulated as a result of Aβ deposits interacting with the membranes of phospholipids. This interaction promotes the degradation of phospholipids in the membrane, thereby producing a large number of free PUFAs, which aggravate the conditions of ferroptosis and iron accumulation.[50] At the same time, acyl-CoA synthase long-chain family member 4 (ACSL4) recognizes PUFAs, particularly ARA and AA. Once ARA and AA are recognized, ACSL4 binds to and activates these PUFAs into PUFA-CoA esters. These esters are able to induce and propagate ferroptosis through the modification of phospholipid membranes and via serving as substrates for lipid peroxidation.[51] The clinical data obtained from AD patients indicate a significant increase in the expression of ACSL4 and a concomitant decrease in the overall concentration of PUFAs in the hippocampus. This is indicative of the fact that ACSL4 possibly contributes to the worsening of the condition by elevating the PUFA that has been activated. This in turn increases the production of lipid radicals ($ROO\cdot$) and exacerbates the pathological changes that are iron-dependent.[52]

An enzyme called LPCAT3 has been characterized as a lipase. LPCAT3 primarily performs catalysis on the esterification of membrane lipids to activated PUFA-CoA. In doing so, LPCAT3 produces phospholipid compounds that are enriched with PUFA (PUFA-PLs). These PUFA-PLs induce alterations in the structural membrane and the distribution of the various regions of the cell.[53] Increased activity of LPCAT3 results in the extracellular accumulation of LPLs, free ARA, and an increase in the presence of bioactive free molecules. This is due to the release of ARA from the cell membrane into the extracellular space.

Increased storage of free fatty acids and their derivatives readily triggers lipid peroxidation stress and increases oxidative damage and neuroinflammation in the brains of patients with AD.[54]

Increased PUFA metabolism abnormalities in AD have been attributed to an increase in ferroptosis. However, the specific molecular mechanisms and the regulatory networks pertaining to different types of PUFA and PUFA-ferroptosis in AD are largely missing. Additionally, the effects of PUFAs may be limited, or influenced, by cell type and microenvironment, indicating that there is more work to be done to advance our understanding of this theory.

Accumulation of Lipid Peroxides and Cytotoxic Effects

Lipids represent an important part of cell membranes. The excess oxidation of lipids leads to covalent alteration of proteins and nucleic acids, alteration of the physical properties of biological membranes, and severe injury to the cell.[55] $A\beta_{-42}$ is a hydrophobic oligopeptide capable of embedding in the lipid bilayer structure during the AD pathological

process and allows ROS to abstract the unstable allylic hydrogen atoms from PUFAs in the lipid bilayer, releasing electrons, ultimately initiating a chain reaction called lipid peroxidation.[56]

In this reaction, which includes initiation, propagation and termination phases, various lipid peroxidation derivatives, such as malondialdehyde (MDA) and 4-hydroxy-2-nonenal (4-HNE), are formed.[57] This leads to profound cytotoxicity, disruption of the neuronal ion balance, the function of mitochondria and other subcellular organelles, and eventually leads to ferroptosis-related signaling pathways.[58]

The abnormal iron metabolism in the brains of affected AD patients leads to increased intracellular free Fe^{2+} concentrations. Fe^{2+} catalyzes the Fenton reaction to convert H_2O_2 into a large number of hydroxyl radicals (· OH).[59] The · OH then abstracts a hydrogen atom from the double allyl methylene group of PUFAs on cell membranes to produce carbon-centered lipid radicals (L ·).[60] L · can further react with O_2 to form LOO · , which then continuously reacts with other PUFAs, forming a chain reaction to form additional L · and L-OOH, promoting the L · /L-OOH recurrent oxidation process and initiating a lipid peroxidation chain reaction in the brain tissue, producing a large number of free radical derivatives,[61] as illustrated in Figure 6.

This further directly disrupts the membrane structural stability, through oxygenated fatty acid cleavage and cyclization, damaging membrane fluidity and selective permeability, ultimately leading to membrane rupture.[62]

With the progression of lipid peroxidation, the mechanical properties of the cell membrane also change. Experimental data indicate that the elastic modulus of natural lipids in the native state is about 200 N m^{-1}. However, in fully oxidized bilayer membrane systems, the elastic modulus falls to about 50 N m^{-1}. This continuous dynamic change plays an important role in triggering neuronal apoptosis.[63]

Moreover, lipid peroxidation products destroy the integrity of organelle membranes, including mitochondria and the endoplasmic reticulum, leading to high carbonyl stress in nonneuronal cellular IMR-90 cells, interfering with the tricarboxylic acid cycle and electron transport chain activities, and ultimately contributing to mitochondrial dysfunction and subsequent ferroptosis.[64]

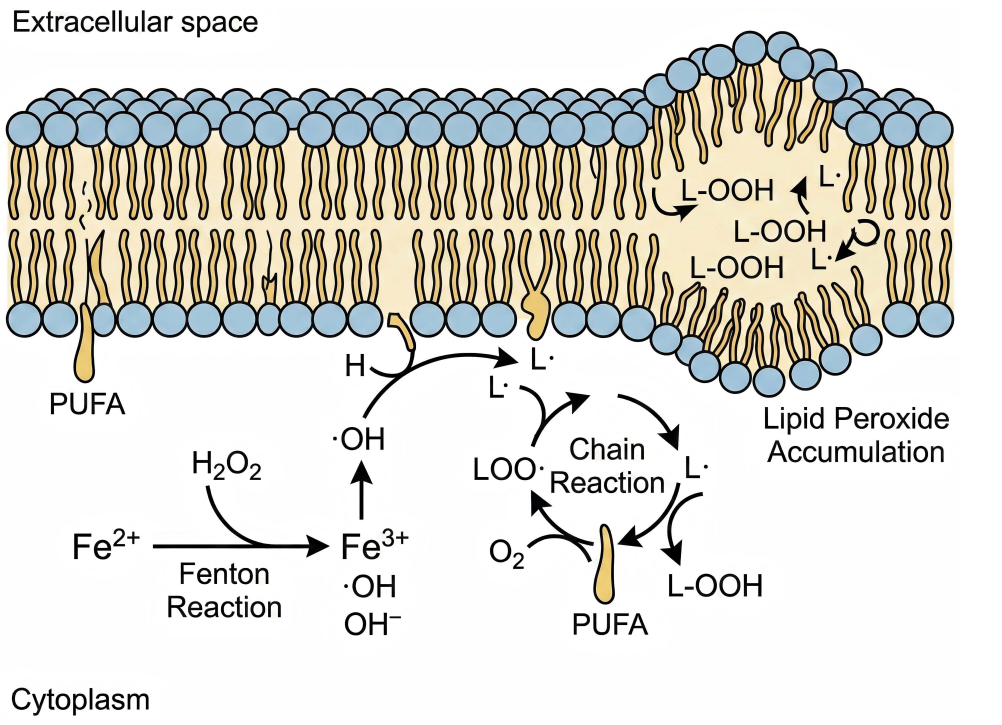

Figure 6 Iron-driven lipid peroxidation in neuronal membranes.

Notes: Iron overload in AD drives Fenton reaction–mediated lipid peroxidation, generating · OH that initiate a PUFA oxidation chain reaction, producing cytotoxic L-OOH.

Abbreviations: AD, Alzheimer's disease; Fe^{2+}, ferrous iron; H_2O_2, hydrogen peroxide; · OH, hydroxyl radical; PUFAs, polyunsaturated fatty acids; L · , lipid radical; LOO · , lipid peroxyl radical; L-OOH, lipid hydroperoxide.

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The accumulation of lipid peroxidation products is not only one of the basic pathological features of ferroptosis in AD but also one of the important factors that indirectly promote the disease process by regulating downstream signaling pathways. Endoplasmic reticulum (ER)-associated oxidative stress markers, MDA and 4-HNE, activate the MAPK/NF-κB pathway, upregulate the expression levels of neuroinflammatory factors such as TNF-α, and further aggravate the inflammatory response in the CNS.[65,66] Therefore, these pathways are of great theoretical value for the deep research of the regulatory mechanisms of lipid peroxidation in AD.

Amino Acid Metabolism: A Key Antioxidant Regulatory Mechanism in AD Ferroptosis

Physiological Functions and Regulatory Mechanisms of System Xc^-

System Xc^- is an amino acid transporter made of the heavy chain SLC3A2 and light chain SLC7A[11] on the cell membrane.[67] System Xc^- is vital for intracellular redox balance and for protection against ferroptosis. The reverse transport action of System Xc^- is driven by SLC7A11, which electroneutrally co-transports intracellular glutamate (Glu) out of the cell and imports cystine from the outside.[68] Once imported, cystine is rapidly reduced to cysteine by intracellular reductases, providing the essential substrate for GSH synthesis. SLC3A2, by tethering SLC7A11 to the plasma membrane, increases the protein stability of SLC7A11.[69] The synthesis of GSH needs cysteine which enters the cell. GSH works with GPX4, and together they remove lipid peroxides and protect the cell from oxidative stress and ferroptosis.[70] The molecular interplay between neuroinflammation and ferroptosis is summarized in Figure 7.

Also, cysteine as a precursor of other biomolecular antioxidants like taurine and hydrogen sulfide increases the cellular antioxidant capacity.[71]

Aside from substrate concentration, the activity of System Xc^- is influenced by several transcription factors, epigenetic changes, energy metabolism, signaling pathways of neuroinflammation, and more.[72,73] The state and functions of System Xc^- will change under the influence of various mechanisms, exerting different biological effects, and demonstrating great flexibility and cell specificity in neurodegenerative pathologies.[74,75]

Regulatory Role of the GSH/GPX4 Pathway in Ferroptosis of AD

The main intracellular antioxidant defense system consisting of GSH and GPX4 is crucial for ferroptosis and lipid peroxidation protection. GSH, a condensation product of Glu, cysteine, and glycine, is the most abundant non-protein thiol in the cytoplasm. Its active thiol group (-SH) is the predominant means for it to participate in various redox reactions.[76] This compound is highly effective in scavenging pro-oxidants and free radicals, generating the crucial non-

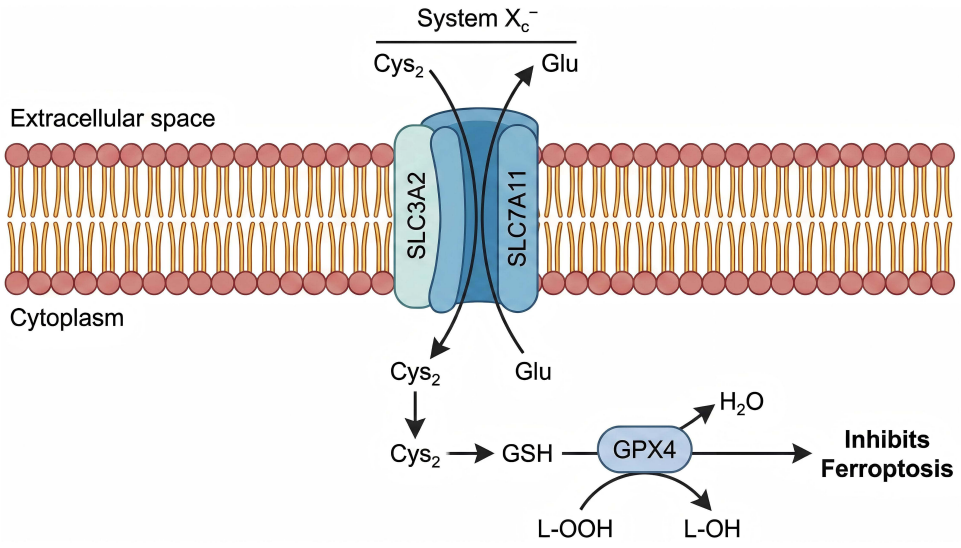

Figure 7 System Xc^-–GSH–GPX4 axis against ferroptosis.
Notes: Cysteine imported via System Xc^- fuels GSH synthesis, enabling GPX4 to detoxify lipid hydroperoxides and suppress oxidative membrane damage.
Abbreviations: System Xc^-, cystine/glutamate antiporter; SLC7A11, solute carrier family 7 member 11; SLC3A2, solute carrier family 3 member 2; GSH, glutathione; GPX4, glutathione peroxidase 4; L-OOH, lipid hydroperoxide.

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enzymatic antioxidant functions for the maintenance of the structural stability of biological membranes.[77] GPX4 is a multifunctional selenium-dependent enzyme that utilizes GSH as a cofactor to convert L-OOH to lipid alcohol (L-OH). This step terminates the chain reaction of lipid peroxidation to prevent the occurrence of harmful changes in the cell membrane structure.[78]

Defective GSH/GPX4 pathways in AD brains reduce the ability of the antioxidant system to inhibit ferroptosis, leading to accelerated neuronal loss.[79] Magnetic resonance spectroscopy and measurements of quantitative magnetic susceptibility show substantial depletion of GSH in AD brains, and low GSH is closely related to axonal injury and atrophy.[80] Inhibition of System Xc^- transport function impairs cysteine uptake in AD brains, blocking GSH synthesis and thereby decreasing GPX4 activity. Under these circumstances, the lipid peroxides cannot be cleared in a timely manner. Their accumulation leads to damage to cell membranes and organelle membrane structures, ultimately resulting in ferroptosis.[81] Conditional knockout mouse models of GPX4 also demonstrate that maintaining normal GPX4 expression in various cell types is critical to preventing ferroptosis-associated tissue injury, sterile inflammation and abnormal immune responses.[82]

The research indicates that GPX4 has various complex biological functions beyond the antioxidant enzymes, which play an important role in neuroprotective mechanisms. Previous evidence has shown that GPX4 deficiency leads to abnormal increases in mitochondrial superoxide radical production and dramatically increases the expression of various chemokines (CCL19, CCL6) and proinflammatory mediators (IL-1β),[83] suggesting that GPX4 participates in the formation of neuroinflammation by regulating the immune response and influencing microenvironment homeostasis. The dysregulation of the GSH-GPX4 signaling pathway may also aggravate cognitive impairment in AD patients through the synergistic effect of the "oxidative stress-inflammation-ferroptosis" triad.

It is worth noting that System Xc^- mainly regulates ferroptosis in AD patients through the GSH/GPX4 pathway. However, some factors can directly affect System Xc^- to directly interfere with the occurrence of ferroptosis, such as TP53, which can directly induce cellular ferroptosis by damaging System Xc^- independently of the GSH/GPX4 pathway.[84]

Impairment of the GSH/GPX4 pathway function is a key mechanism of ferroptosis in AD. However, the mechanism of the initiating factors affecting the pathway in AD, such as the malfunction of System Xc^-, selenium deficiency, and oxidative stress, needs further clarification.[85] In addition to its function of clearing lipid peroxides, the non-canonical functions of GPX4 in regulating inflammatory responses and immune cell functions also need to be further explored through specific knockout or overexpression experiments.

Pathological Significance of System Xc^- Overexpression

Inhibition of System Xc^- and the disruption of the GSH/GPX4 pathway have traditionally been viewed as the main drivers of ferroptosis and cognitive impairment in patients with AD. However, in the last decade, numerous studies using brain autopsies and animal models have documented the upregulation of the light chain subunit expression of System Xc^- in the brain tissues of patients with late-stage AD.[86] Such findings are in direct contradiction to the earlier hypothesis that System Xc^- inhibition would reduce the cellular antioxidant capacity.

Therefore, this might indicate that the System Xc^- function has a dual nature. While early inhibition of System Xc^- may reduce the cellular antioxidant defenses, in later stages, overactivation of System Xc^- may lead to excitotoxicity.

A study shows that $A\beta_{25–35}$ activates the Nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway, which leads to a robust upregulation of the System Xc^- related protein expression in the hippocampus. Although Nrf2 has classically been associated with antioxidant functions, in the particular AD-related pathology context, the dysregulated Nrf2 hyperactivation leads to System Xc^- overexpression which, in turn, enhances the outflow of Glu.[87]

The large extent of Glu released results in signaling hypersensitivity of NMDA receptors that contain the NR2B subunit, which causes an aberrant calcium influx and subsequent mitochondrial dysfunction. This shifts oxidative stress to excitotoxic neuronal damage, worsening ferroptosis and damaging the structural components of synapses.[88]

In normal physiological activity, System Xc^- function is controlled by internal mechanisms, which result in low concentrations of Glu in the extracellular space. Such a condition sustains normal levels of AMPA receptors on postsynaptic membranes and facilitates synaptic plasticity.[75]

In contrast, abnormal potentiation of System Xc^- function causes above normal levels of Glu to be released into the extracellular space.[89] Pathologically high levels of Glu in the extracellular space cause synaptic transmission to be less efficient. Through negative feedback, System Xc^- transport function is inhibited. The overall process finally creates a feedback loop.[90]

The Dual Role of System Xc^-: Balancing Ferroptosis and Excitotoxicity

As shown in Figure 8, there seems to be a contradiction between ferroptosis due to inhibition of System Xc^- and excitotoxicity due to upregulation of System Xc^-. This contradiction precisely reflects the environmental dependence and "double-edged sword" characteristics of this special transporter protein in the pathogenesis of AD.

On the one hand, System Xc^- is very important for the uptake of cystine and the subsequent synthesis of GSH. When System Xc^- is suppressed or downregulated, the GSH in the cell is rapidly depleted, which leads to GPX4 inactivation and disrupts regulation of lipid peroxidation, eventually making neurons and glial cells very prone to ferroptosis.[91] This condition can often be observed in the early stages of AD or in specific brain areas where the antioxidant defense system is damaged.

On the other hand, the reverse transport function of System Xc^- can link the uptake of cystine with the release of Glu. Due to chronic neuroinflammation and the effects of AST (common in advanced AD), overexpression or over-activation of System Xc^- can lead to excessive increase in extracellular Glu content.

This phenomenon of "Glu overflow" will excessively stimulate NMDA receptors on neurons, leading to excessive accumulation of calcium ions and excitotoxicity. This will not only further exacerbate the death of neurons, but may also cause secondary ferroptosis through mediating mitochondrial dysfunction.[92]

Therefore, there is a delicate balance in the physiological role played by System Xc^-: insufficient activity of System Xc^- leads to GSH exhaustion, causing ferroptosis; and excessive activity of System Xc^- leads to extracellular Glu accumulation, causing excitotoxicity. Future treatment strategies should focus more on restoring this balance, rather than simply inhibiting or activating this transporter.

In the brains of AD patients, the function of System Xc^- is not only dynamic, but also related to the cell type. The functional differences of this protein transporter in MG, AST, and neurons still need to be further clarified. These studies will provide a solid theoretical support for the future development of more refined and targeted System Xc^- intervention methods for clinical translation.

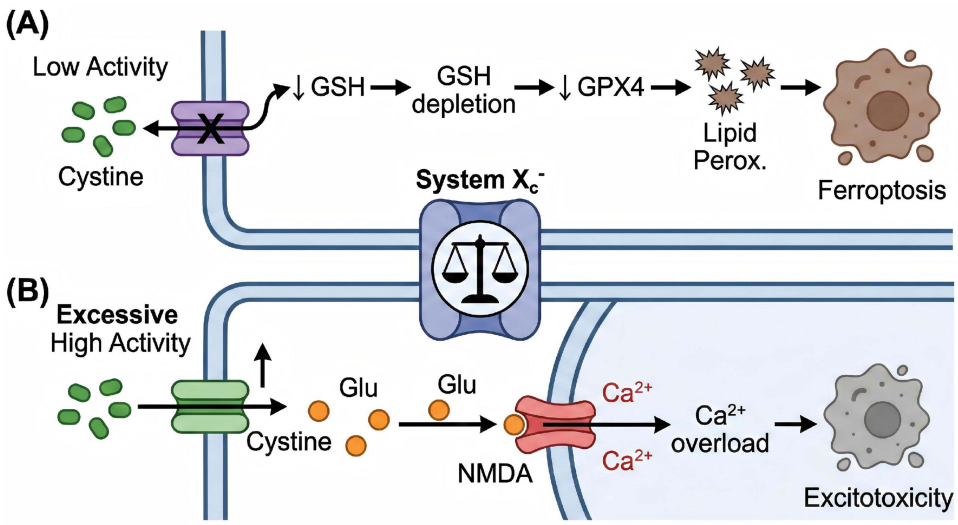

Figure 8 The dual nature and cell-specific roles of System Xc^- in AD.
Notes: (**A**) Low activity of System Xc^- reduces cystine uptake → ↓ GSH synthesis → GSH depletion → ↓ GPX4 → lipid peroxidation accumulation → ferroptosis. (**B**) Excessive/high activity of System Xc^- increases Glu efflux → overstimulates NMDA receptors → Ca^{2+} overload → excitotoxicity. The central balance icon represents the opposing outcomes depending on System Xc^- activity level.
Abbreviations: System Xc^-, cystine/glutamate antiporter; GSH, glutathione; GPX4, glutathione peroxidase 4; Glu, glutamate; NMDA Rec., N-methyl-D-aspartate receptor; Ca^{2+}, calcium ion. ↑, increased/upregulated; ↓, decreased/downregulated.

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The Dual Regulatory Role of Glial Cells in AD Ferroptosis

MG: Core Regulators of Inflammation and Iron Accumulation

MG, the brain's first line of defense, play a complex and context-dependent role in AD-related ferroptosis, usually promoting the occurrence of ferroptosis under chronic inflammatory conditions.[93] MG are known to maintain CNS iron homeostasis by phagocytosing apoptotic neurons and clearing excess iron under normal conditions.[94] However, the deposition of Aβ plaques causes a proteomic change in AD's defining pathological state, affecting the cell's receptor or lysosomal proteome. This transforms MG into a pro-inflammatory (M1) state. There is a consequent increase in the release of IL-6, IL-1β, TNF-α, and other ROS.[95]

The pro-inflammatory mediators as a direct effector cause neuronal injury, and through the downregulation of SLC7A11 and GPX4, they inhibit the GSH-GPX4 axis, which increases lipid peroxidation and the resultant injury.[96] For instance, IL-6 acts as a central driving factor of iron dyshomeostasis and lipid peroxidation in the CNS, primarily by inducing Hepcidin expression which degrades FPN1, thereby trapping iron within cells and triggering ferroptosis.[97] ROS trigger the Fenton reaction and the Haber-Weiss cycle to produce unbounded free iron (Fe^{2+}), while they also cause NCOA4-mediated FT autophagy. This again increases the iron content within the cells, which predisposes the cells to the process of ferroptosis.[98]

As noted in Table 1, in recent studies, multiple newly identified pathways might be implicated in MG activation and in the progression of AD. Evidence indicates that the CD36-Nrf2-GPX4 axis in MG is a key node for lipid regulation within the CNS. Under physiological conditions, CD36 signaling activates Nrf2 to counteract lipid peroxidation. However, prolonged oxidative stress in AD eventually overloads and dysfunctions this defense system, leading to Nrf2 depletion, GPX4 downregulation, and subsequently ferroptosis.[99,100] Characteristic MG-induced NLRP3 inflammasome activation leads to the reduction of Nrf2, which is responsible for the maintenance of ferroptosis resistance, thereby resulting in further neurodegeneration and aggravating the toxic consequences of abnormal iron sequestration.[101,102] Gp91phox is known as a member of the NADPH oxidase 2 (NOX2) subunit. Studies show that MG Gp91phox overexpression induces the most rapid neuronal ferroptosis, and its overexpression is closely linked to the cognitive decline of experimental animals.[103]

Table 1 MG Molecular Regulators Linking Neuroinflammation, Oxidative Stress, and Ferroptosis in AD

Molecular Target	Primary Function in MG	Mechanism Related to Ferroptosis	Downstream Effects	References
CD36	Oxidized lipid scavenger	↑ Lipid overload; ↓ Nrf2/GPX4 defense	↑ Lipid ROS; ↑ Microglial ferroptosis; ↑ Neuroinflammation	[95]
NLRP3 inflammasome	Pro-inflammatory signaling hub	Reduces Nrf2 expression; disrupts redox balance	↑ Neurodegeneration; exacerbates iron sequestration	[96, 97]
Gp91phox	Catalytic subunit of NADPH oxidase	Generates ROS via superoxide production	Rapid induction of neuronal ferroptosis; cognitive decline in animal models	[98]
FoxO3a	Transcription factor for stress resistance	Regulates catalase/MnSOD; modulates HO-1 and FoxO3a/ATG-dependent autophagy	Alters ROS clearance; influences iron metabolism and apoptosis	[99, 100]
α7nAChR	Cholinergic anti-inflammatory receptor	Suppresses Nrf2 and GPX4 expression	Worsens ferroptosis; interacts with TfR-FT-FPN iron axis	[101]
RSL3	Pharmacological inducer (not endogenous)	Inhibits GPX4 via TXNRD1/selenoprotein pathway	Drives pathological MG polarization; amplifies ferroptosis	[102, 103]

Notes: All entries represent experimentally observed effects in MG or MG–neuron co-culture systems relevant to AD models.
Abbreviations: CD36, Cluster of Differentiation 36; GPX4, Glutathione Peroxidase 4; MG, Microglia; Nrf2, Nuclear Factor Erythroid 2-Related Factor 2; NLRP3, NOD-, LRR- and Pyrin Domain-Containing Protein 3; ROS, Reactive Oxygen Species; TfR, Transferrin Receptor; FT, Ferritin; FPN, Ferroportin; TXNRD1, Thioredoxin Reductase 1; ↑, increased/upregulated; ↓, decreased/downregulated.

FoxO3a in MG affects antioxidant-induced and enzymatic (catalase and MnSOD) modulation of ROS, which alters the incidence of ferroptosis and oxidative stress.[104] FoxO3a in MG also regulates iron homeostasis and apoptosis in the CNS via FoxO3a/ATG-dependent autophagy and the HO-1 signaling pathway.[105]

The MG Alpha-7 nicotinic acetylcholine receptors (α7nAChR) also act on the "Tf receptor-FT-FPN" axis, which suggests a multi-layered interaction, pointing to potential cross-talk with other systems. α7nAChR are known to lower Nrf2 and GPX4 levels, and this can worsen cellular ferroptosis.[106] RSL3 is one of the most studied inducers of ferroptosis, as it inhibits GPX4 via the selenoprotein TXNRD1.[107] RSL3 is one of the most studied compounds with homeostatic disruption in MG models, where it drives pathological MG polarization.[108] Among MG polarization and ferroptosis, RSL3 may be one of the most important regulatory components.

In conditions of cellular injury, the imbalance of iron homeostasis drives MG polarization toward the M1 (pro-inflammatory) phenotype. This is coupled with the release of neurotoxic agents from MG, which results in local neuroinflammation.

Influencing MG polarization and neuroinflammation, the ferroptosis inducer DSP-4 in animal models led to increased manifestations of neuroinflammation and MG polarization.[109] This provides evidence of a potential synergistic action between MG over-activation and ferroptosis, leading to a positive feedback loop which may increase damage to the structures of the CNS and impair cognitive functioning.

There are, however, aspects regarding MG's role in ferroptosis that can be described in positive terms. M2 MG regulate Wnt/β-catenin signaling, increases β-catenin levels, and alleviates damage from ferroptosis in neurons, as seen with secreted M2 MG exosomes (M2-Exos).[110,111] M2 MG can counteract with $A\beta_{1-42}$-associated reduction of GSH, increases the GSH level and associated neural structures GSH, increases synaptic plasticity, and preserves the neural structures.[112] The granule protein precursor (PGRN) produced in the MG lysosomes, improves the GSH/GPX4 system and subsequently inhibits ferroptosis.[113]

A major strategy may involve the modulation of MG polarization for the management of ferroptosis in AD. Future studies should explore the techniques aimed at specific MG subtypes and prospective therapeutic roles.

AST: Essential Defenders in Antioxidant Defense and Iron Transport

The majority of glial cells in the brain are AST. By regulating the cellular antioxidant homeostasis pathway and regulating the iron transport pathway, AST have a vital role in the process of AD cellular ferroptosis.[114] Figure 9 demonstrates that AST primarily polarize into two phenotypes: A1 (neurotoxic) and A2 (neuroprotective). A1-type AST promote STAT3 phosphorylation through the CXCL10/CXCR3 pathway, inhibit the expression of SLC7A11, reduce the level of intracellular GPX4, promote lipid peroxidation, and aggravate GPX4-GSH-dependent ferroptosis.[115] A2-type AST secrete various neuroprotective factors, significantly promoting neuronal survival, lowering the level of LCN2 in AST, inhibiting neuronal ferroptosis, and maintaining the normal structure of neurons.[116]

In terms of antioxidant defense, as a key regulator of intracellular iron metabolism, FTH1 heavy chain has a vital role in antioxidant defense pathways. It has been found that FTH1 becomes exhausted or downregulated in AST tissue from certain regions of the brain in patients with AD.[117] Dysfunction of FTH1 promotes ferroptosis by enhancing FT degradation. The accumulation of free iron leads to mitochondrial damage, redox imbalance, and eventually to neuronal degeneration and cognitive decline.[118]

SAT1 participates in AST lipid peroxidation, causing cells to be stressed by ROS and resulting in the disorder of the redox balance through increased ROS production.[119] Molecules of the Notch1 pathway (N1IC) also participate in the mitochondrial remodeling of AST, promoting lipid peroxidation, increasing ROS production, and reducing GSH.[120] Neural tissue is highly susceptible to ferroptosis in the above circumstances due to the redox imbalance of mitochondria.[121] Brain-derived neurotrophic factor (BDNF) can activate Nrf2 by cleaving the TrkB and p75NTR receptor complex in AST. Then, AST can deliver mRNA and proteins carried by exosomes into neurons, enhancing the resistance of neurons to oxidative stress.[122] Lactoferrin (Lf) is overexpressed to relieve oxidative damage induced by ferroptosis by decreasing intracellular iron accumulation, preventing GPX4 degradation due to chaperone-mediated autophagy (CMA), and upregulating the expression of GPX4.[123]

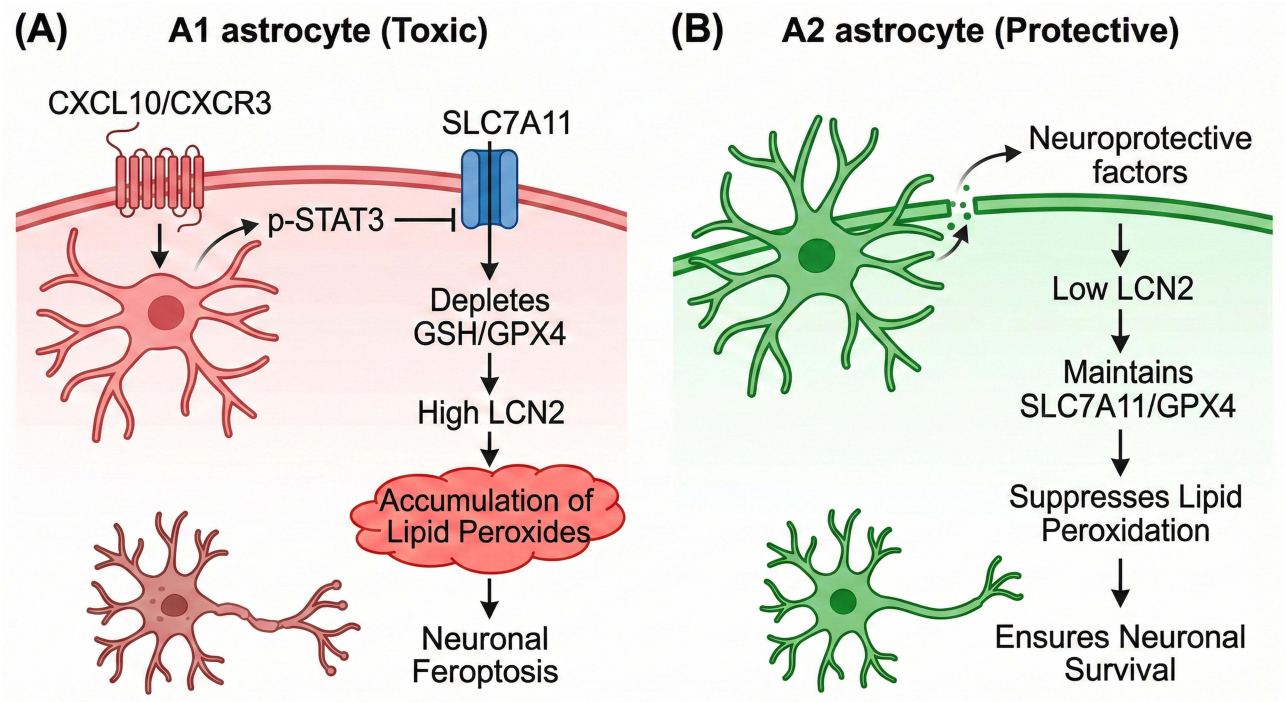

Figure 9 A1 vs. A2 astrocytes: opposing regulation of ferroptosis in AD.
Notes: (**A**) Toxic A1 astrocytes: CXCL10/CXCR3 → p-STAT3 → ↓ SLC7A11 → ↓ GSH/GPX4 → ↑ LCN2 → lipid peroxides → neuronal ferroptosis. (**B**) Protective A2 astrocytes: Neuroprotective factors → ↓ LCN2 → ↑SLC7A11/GPX4 → lipid peroxidation → neuronal survival.
Abbreviations: A1/A2, reactive astrocyte subtypes; CXCL10/CXCR3, C-X-C motif chemokine ligand 10 / receptor 3; p-STAT3, phosphorylated STAT3; SLC7A11, solute carrier family 7 member 11; GSH, glutathione; GPX4, glutathione peroxidase 4; LCN2, lipocalin-2.

As for the regulation of iron transport, AST highly express Hepcidin and FPN1. AST release related biomolecular signals to rapidly communicate brain iron demand to endothelial cells.[124] AST can uptake excess iron released by neurons, convert excess iron to FT for storage, and transport iron to other cells via FPN1, thus, establishing an "AST-neuron" iron transport network.[125]

AST-secreted FT directly regulates the expression of FPN1 in brain BMVECs, which is a mechanism critical for maintaining normal intracerebral iron levels. Dysregulation of this mechanism leads to abnormal iron transport and iron accumulation in the brain, thereby initiating iron-induced neuronal death.[126]

As for the AD pathological condition, neuroinflammatory factor levels rise significantly in the CNS. This change could influence the level of FT in AST, thereby regulating the FPN1 expression and iron content in the brain.[127]

In addition, even under AD pathological conditions, AST still have the capacity for efficient iron transport and recycling. AST buffer rapid abnormal iron accumulation in the brain by regulating iron uptake and release, and slow down synaptic activity by regulating the iron concentration in the synaptic environment, thus, partially suppressing iron-induced neuronal death.[128] AST and their FPN1 can also directly intervene in the expression of oligodendrocyte precursor cell (OPC) by regulating iron transport-related processes. Therefore, they regulate the level of neurotrophic factors, including FGF-2 and IGF-1, and indirectly promote the regeneration of myelin in neural structures, improving memory, and learning functions in AD patients.[129]

The protection of AST in the ferroptosis of AD mainly involves the antioxidant and iron transport pathways. However, the regulation of A1/A2 polarization and the conversion conditions in AD have not been adequately studied.

Oligodendrocytes: Myelin Protection and Iron-Sensitive Target Cells

Oligodendrocytes (OL) are crucial to myelin formation in the CNS. Their disruption is closely associated with cognitive decline in AD.[130] Given the fact that iron is important in OL synthesis of myelin basic protein (MBP), OL biosynthesis processes are quite iron demanding.[131] Therefore, OL keep significantly greater quantities of iron compared to other glial

cells, making them more prone to ferroptosis.[132] In the context of AD, Aβ deposition results in OL damage, which initiates a cascade of events: Aβ-induced lipid peroxidation creates a disruption to OL constituents and their myelinating roles, finally leading to a reduction in myelin and axonal signaling.[133] In addition, demyelination contributes to the pathological progression of Aβ by the unleashing of free iron, which is pathological to AD.[134] On the other hand, a decline in OL GPX4, the enzyme responsible for ROS detoxification, diminishes the ability of OL to perform their function and increases their vulnerability to ferroptosis.[135] Fenton reactions, which are caused by excessive iron, can quickly trigger ferroptosis in OPCs, which delays myelin remodeling and increases cognitive decline.[136]

It has been suggested that reduced levels of AKR1C1 may, via specific miRNA-directed signaling pathways, increase the risk of ferroptosis in OL as a result of neuroinflammation in the CNS.[137] Reduced expression of the promoter for the palmitoyltransferase, DHHC5, in OL leads to the palmitoylation of the TfR1 C98 cysteine residue, which activates the ferroptosis functions of TfR1 and causes myelination deficits and the advancement of the neurodegenerative disease.[138] OL themselves are also extremely sensitive to exogenous neuroinflammation and oxidative stress, which amplify the effects of ferroptosis via certain molecular pathways, and in so doing, exacerbate the myelin damage and the progression of the disease.

In studies involving AD pathology, AST and MG frequently interact with OL-associated ferroptosis. There is a signaling pathway with OL where AST are the central communicators. AST can also enhance OL regeneration through the down-regulation of the Nrf2 pathway in conjunction with regulation of cholesterol metabolism.[139] AST can support the normal functioning of OL by buffering excessive iron. However, under conditions of chronic inflammation and iron overload, AST themselves become more susceptible to ferroptosis and their buffering capacity declines. The loss of this iron buffering capacity exposes OL and neurons to iron-related stress environments, accelerating cell death.[140,141] Hyperpolarized MG cells increase the expression of LCN2. LCN2 is a quintessential proferroptotic factor that is under the feedback CSF1/CSF1R regulation and promotes the apoptosis of OL and the degradation of cognitive function.[142] Such synergistic interactions across cell types could constitute more complex regulatory systems to advance AD pathology.

The AD ferroptosis pathology aspects concerning OL remain ambiguous in multiple areas. Primarily, the OL ferroptosis and the damage to the myelin sheath cross-causally, or cross-sequential, relation is speculative. Secondly, there is insufficient examination of the OL polarization state under various pathological conditions and its relation to ferroptosis. There is a need for further investigation into ascertaining whether OL possess polarization attributes as AST and MG, and clarifying the ways in which OL affect ferroptosis.

Pathological Interactions and Molecular Mechanisms Between NP and Ferroptosis

The Differential Roles of NP and Diffuse Plaques in Ferroptosis During AD

Not all senile plaques in AD are harmful in the AD pathology. These senile plaques can be divided into two main types: NP and diffuse plaques (DP). Figure 10 shows that these two plaque types have significant differences in pathological significance, iron metabolism, and susceptibility to ferroptosis. NP are linked with the start of AD and cognitive impairment. They are also seen as vital markers in the Braak staging for AD.[143] On the other hand, DP are usual in the brains of the elderly with normal cognition, and they are seen as things considered benign age-related changes. The building up of DP by itself is not enough to make dementia happen, and its part in the pathologic change of AD is very limited.[144]

In the brains of AD patients, NP have a lot of iron build-up, with iron levels much higher than nearby tissues.[145] On the other hand, the build-up of DP does not cause iron overload in itself or in the nearby tissues. This difference may be due to the fibrillar structure of Aβ in NP, which can bind more iron than the non-fibrillar structure in DP.[146]

The high iron content in Aβ fibers within NP promotes Fenton chemistry, generating ROS, which in turn induces lipid peroxidation and ferroptosis in surrounding neurons and glial cells.[147] In contrast, DP lack sufficient iron accumulation, making the surrounding environment less conducive to the reactions required for ferroptosis.

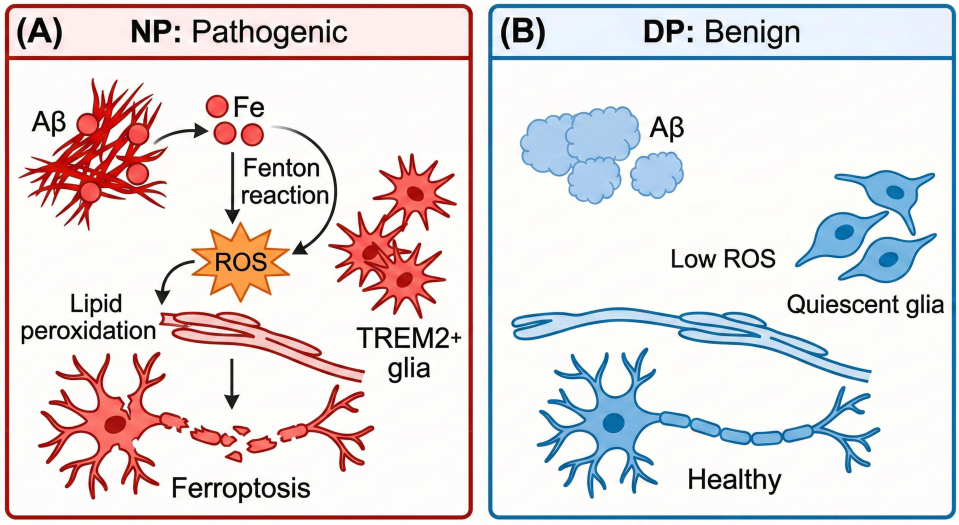

Figure 10 Differential roles of NP and DP in ferroptosis.
Notes: (**A**) Pathogenic NP: Iron-bound fibrillar Aβ triggers Fenton reaction → ROS/lipid peroxidation → TREM2+ glial activation → ferroptosis. (**B**) Benign DP: Non-fibrillar Aβ with no iron accumulation results in low ROS, quiescent glia, and healthy neurons.
Abbreviations: NP, Neuritic Plaque; DP, Diffuse Plaque; Aβ, Amyloid-beta; Fe, Iron; ROS, Reactive Oxygen Species; TREM2, Triggering Receptor Expressed on Myeloid cells 2.

MG and AST gather around NP under the regulation of TREM2. By aggregating, they can cause chronic inflammation and interfere with iron metabolism. DP, on the other hand, do not significantly activate glial cells, which is also an important reason why their effect on AD pathology is very limited.[148]

These differences suggest that we should focus more on NP and the iron overload around it in AD-related research. Compared with DP, in the brains of AD patients, analyzing the interaction between NP and ferroptosis is of more significance for understanding the pathological development of AD.

NP and Ferroptosis: A Bidirectionally Promoting Pathological Cycle

NP is mainly composed of $A\beta_{1-42}$ or $A\beta_{1-40}$ oligomers and fibrous aggregates. They are usually surrounded by dystrophic neurites (DN) with autophagy lysosomes. NP is one of the main pathological features of AD.[149] As summarized in Table 2, there is a two-way propulsion between NP and ferroptosis, and they are jointly involved in the pathological process of AD.[150]

On the one hand, NP can promote the occurrence of ferroptosis in many ways. Aβ oligomers directly bind to TfR1 and FPN1 on the cell membrane of neurons, inhibiting iron transport, damaging normal iron metabolism, and ultimately causing iron accumulation and ferroptosis. This is regarded as an upstream trigger of neurotoxic programmed cell death.[151] In addition, $A\beta_{1-42}$ can reduce Fe^{3+} to Fe^{2+} and generate large amounts of ROS through the Fenton reaction, which causes redox homeostasis imbalance and leads to ferroptosis.[152] Moreover, NP can inhibit peripheral cell proliferation through the CD36/PINK/PARKIN signaling pathway (initiates mitochondrial autophagy-dependent ferroptosis and simultaneously damages the blood-brain barrier), thereby increasing AD iron accumulation and ferroptosis-related damage.[153] Abnormal NP deposition may also inhibit the GSH/GPX4 pathway by downregulating the expression of SLC7A[11] and GPX4, while inhibiting the expression of NCOA4 to ultimately increase the vulnerability of neural structures to ferroptosis.[154]

On the other hand, ferroptosis is also conducive to NP formation. On the other hand, ferroptosis also helps NP formation. The power of iron to join with amyloid proteins helps NP aggregation, which makes neuronal toxicity stronger.[155] When the CNS is overloaded with iron, furin will decrease and the activity of β-secretase will increase. This change promotes the amyloid processing of amyloid precursor protein (APP). This leads to the depletion of APP and the deposition of NP through the IRP/IRE system.[156] Too much loss of APP will make the control of FPN1 function on the cell membrane by APP weaker, so it stops the iron transport across the membrane, and makes more iron build up.[157]

Table 2 Bidirectional Molecular Mechanisms Linking NP and Ferroptosis in AD

Direction	Core Mechanism	Key Molecular Targets	Reference
NP→Ferroptosis (Trigger)	Iron Transport Blockade: Aβ oligomers bind transporters, trapping iron intracellularly.	TfR1, FPN1	[151]
	Direct Redox Reaction: $A\beta_{1-42}$ reduces Fe^{3+} to Fe^{2+}, driving Fenton chemistry and ROS.	$A\beta_{1-42}$, Fe^{2+}/Fe^{3+}, ROS	[152]
	Mitochondrial Damage: Activates mitophagy pathway, damaging BBB & promoting iron retention.	CD36, PINK1, PARKIN	[153]
	Antioxidant Suppression: Downregulates GSH synthesis and ferritinophagy, increasing vulnerability.	SLC7A11, GPX4, NCOA4	[154]
Ferroptosis→NP (Amplifier)	Enhanced Aggregation: Iron directly binds amyloid, stabilizing plaque nuclei.	Iron, Aβ proteins	[155]
	Amyloidogenic Shift: Iron overload alters enzyme balance (↓Furin, ↑BACE1) via IRP/IRE.	Furin, β-secretase, IRP/IRE	[156]
	Loss of Regulation: APP depletion reduces FPN1 modulation, worsening iron overload.	APP, FPN1	[157]
	Inflammatory Feedback: Cell death releases DAMPs, activating NF-κB to drive Aβ aggregation.	DAMPs, NF-κB, Cytokines	[158]
	Impaired Clearance: Inflammation induces MMPs, degrading the Aβ phagocytosis machinery.	Microglia, MMPs	[159, 160]

Notes: The table summarizes experimentally observed interactions where NP triggers ferroptotic pathways and, conversely, ferroptosis amplifies NP progression.
Abbreviations: NP, Neuropathology (primarily Aβ plaques); TfR1, Transferrin Receptor 1; FPN1, Ferroportin 1; Aβ, Amyloid-beta; ROS, Reactive Oxygen Species; BBB, Blood-Brain Barrier; GSH, Glutathione; GPX4, Glutathione Peroxidase 4; NCOA4, Nuclear Receptor Coactivator 4; BACE1, Beta-secretase 1; IRP/IRE, Iron Regulatory Proteins/Iron Responsive Elements; APP, Amyloid Precursor Protein; DAMPs, Damage-Associated Molecular Patterns; NF-κB, Nuclear Factor kappa-light-chain-enhancer of activated B cells; MMPs, Matrix Metalloproteinases; ↑, increased/upregulated; ↓, decreased/downregulated.

Neuronal injury caused by ferroptosis leads to the leakage of intracellular things (DNA, RNA, proteins), this activates the IKK/IκB/NF-κB signaling pathway, and leads to the release of pro-inflammatory factors, helping Aβ get together and NP deposition.[158]

In addition, MG inflammation caused by ferroptosis releases matrix metalloproteinases (MMPs), which can degrade a lot of Aβ scavenging proteins. This process reduces the phagocytosis and clearance efficiency of Aβ and exacerbates the formation of NP.[159,160]

The research showed that the brain-penetrant ferroptosis inhibitor Ferrostatin-1 and high-dose treatment with ascorbic acid can reduce NP deposition in 5XFAD mouse models by promoting the metabolism of GSH and reducing cellular oxidative stress. These results suggest that ferroptosis is a major regulator of NP formation.[161]

The bidirectional regulatory relations between NP and ferroptosis have become an important entry point for the research of AD pathogenesis. The precise molecular targets and basic roles are still unknown, although this model plays an important role as a guide to understanding disease pathophysiology. These issues will be further clarified by intensive research on the signaling pathways through which NP induces ferroptosis, as well as the specific biological mechanisms through which ferroptosis promotes NP deposition, which will broaden our pathological understanding of disease and provide a scientific basis for the development of targeted NP and ferroptosis therapies.

NP and DN: Pathological Correlation of Structural Damage

DN are a large number of swollen and dystrophic abnormal neurites that appear around NP. DN are related to ferroptosis and the decrease in signal transmission found in the brains of AD patients.[162] Aβ oligomers in neurofibrillary can interact with the APP on the axon membrane. This interaction activates glycogen synthase kinase 3β (GSK-3 β), which in turn causes abnormal phosphorylation of the nerve membrane. This phenomenon can make axons become swollen, forming a beaded structure (namely DN), and it can also cause abnormal axon transport function.[163] Aβ-induced ferroptosis causes the breakdown of the integrity of the synaptic membrane, which leads to the abnormal release of transmitters and causes an acceleration of calcium influx, all of which promote the formation of DN and the dysfunction of axonal signaling.[164] Aβ/APP fragments that are misfolded and accumulate in neuronal autophagolysosomes, the so-called

"erroneous molecules", cause neurotrophic swelling and morphological changes of the plasma membrane in neurites. Such phenomena have been confirmed to correlate with the pathology of DN.[165]

Under typical circumstances, MG in the brains of AD patients can transform into a phenotypic state known as neurodegenerative phenotype microglia (MGnD). This specific MGnD phenotype is known to promote the densification of amyloid plaques, decrease DN, and improve the cognitive function, at least partially.[166] However, when the NP load reaches a specific threshold, MG will aggregate around the NP to create a barrier, and in the process lose their protective function due to depletion or sustained autophagy. At this stage, MG are considered to be overly activated, and due to the MG's release of substantial amounts of ROS and neuroinflammatory mediators, the situation is made worse by the activation of ferroptotic pathways as well as the conversion of normal neurites into DN, which further diminishes the number of neurites and the conduction dysfunction.[167] According to research, there is a loss of function or prolonged hyperfunction of TREM2 in MG in the brains of patients suffering from AD. This abnormal expression causes an increase in p-tau-related DN within a certain pathway and a concomitant increase of tau burden surrounding NP, which is known to worsen neurostructural damage and the process of ferroptosis.[148,168]

The reciprocal influences and pathological connections between DN and NP shed new light on the AD-related neurodegeneration molecular mechanisms. A combination of the specific biomarker analysis for DN throughout the disease continuum with an emphasis on spatial distribution and dynamics and the mechanistic analysis of DN in the regulation of ferroptosis may open up more fundamental avenues in AD research.

NP and Neuroinflammatory Response: Synergistic Activation of Inflammation and Ferroptosis

Numerous studies have shown that NP is one of the main sources of neuroinflammatory damage in the CNS, and the neuroinflammation induced by NP is an essential aspect of the pathogenesis of neurodegenerative diseases. Importantly, there exists a synergistic "inflammation activation-ferroptosis amplification" interaction between NP and ferroptosis.[169]

As noted in Figure 11, Aβ fibrils in NP can activate NLRP3 inflammasomes in MG cells through the TLR4 signaling pathway, activate NF-κB, caspase-1 and MAPK signaling pathways, thereby inducing the accumulation of neurotoxins and ROS, and disrupting intracellular redox homeostasis.[170,171] These neuroinflammatory molecules inhibit the protein expression of SLC7A11 and GPX4, and increase the concentration of p53 and ACSL4, thereby reducing antioxidant capacity and accelerating the progression of ferroptosis.[172] The increase in ROS also promotes the accumulation of iron through Fenton reactions, and a positive feedback mechanism is formed by continuously activating the relevant inflammatory signaling pathway.

Previous studies have shown that AST produce a large amount of complement protein C3 under NP stimulation. The activation of C3 directly leads to neuroinflammation through synapse damage, and enhances the phagocytic function of macrophages through the C1q/C3 pathway, thereby promoting the risk of iron absorption and apoptosis.[173] Iron overload causes abnormal mitochondrial membrane permeability, the release of mtDNA and the downregulation of IAP, thereby intensifying the effect of NP deposition and the inflammatory microenvironment in the CNS.[174]

The extensive deficiency of ferroptosis-related enzyme GPX4 in the CNS can reduce the stability of Nrf2 protein and create a favorable environment for the transcriptional upregulation of cellular inflammatory factor genes, which may involve the dynamic changes of RNA polymerase II in the Nrf2 promoter region.[175,176] This abnormally activates AST, MG, and macrophages, thus exacerbating NP deposition and neuroinflammation.[177] It is thought that a positive feedback regulation exists between inflammation and ferroptosis, through signaling pathways such as NF-κB, JAK/STAT, cGAS-STING and MAPK, which synergistically accelerate the formation of AD pathological features.[178,179]

Recent research has provided new evidence of the mechanism of synergistic activation between neuroinflammation and ferroptosis, and their relationship with NP. However, further research is necessary to clarify the specific mechanisms of action of important regulatory molecules in the interaction between neuroinflammation and ferroptosis, such as inflammatory mediators, ROS and iron metabolism molecules.

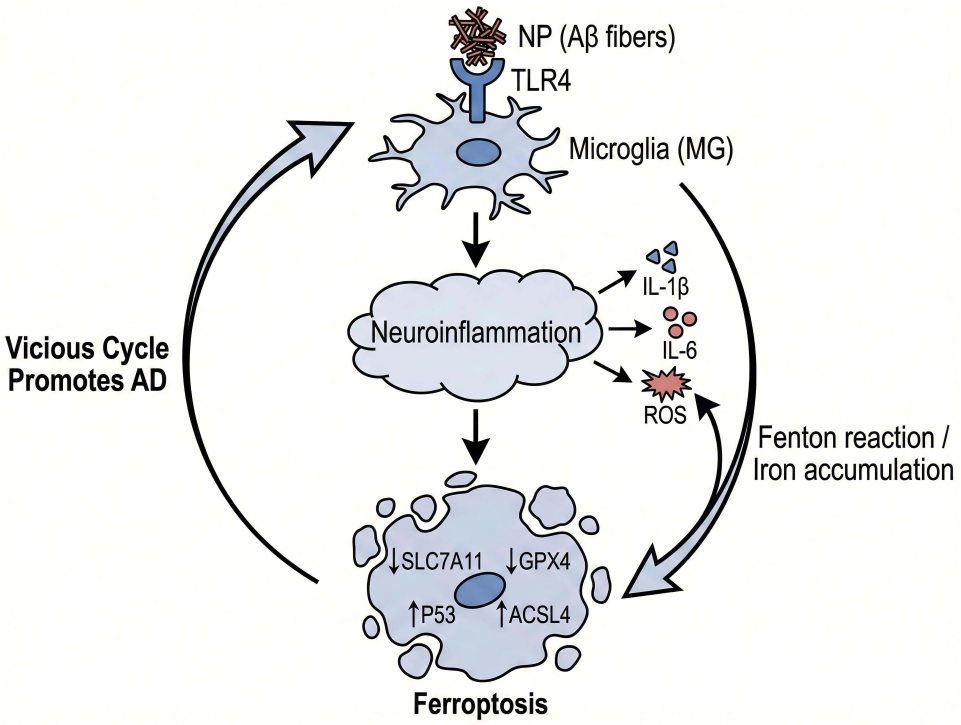

Figure 11 A cycle linking neuroinflammation and ferroptosis in AD.
Notes: Aβ fibrils activate microglial TLR4, triggering neuroinflammation that suppresses SLC7A11 and GPX4, promotes p53/ACSL4, and drives ferroptosis. ROS and iron accumulation further amplify inflammation, creating a self-sustaining loop that accelerates AD progression.
Abbreviations: AD, Alzheimer's disease; Aβ, amyloid-beta; NP, neuroplaque; MG, microglia; TLR4, toll-like receptor 4; ROS, reactive oxygen species; SLC7A11, solute carrier family 7 member 11; GPX4, glutathione peroxidase 4; p53, tumor protein p53; ACSL4, acyl-CoA synthetase long-chain family member 4. ↑, increased/upregulated; ↓, decreased/downregulated.

NP and p-Tau Phosphorylation: Molecular-Level Interactions

p-tau is mainly located in the axons of CNS neurons, serving as a microtubule-associated protein.[179] Hyperphosphorylated p-tau, which is unable to effectively stabilize the microtubules, aggravates NFT aggregation and simultaneously leads to autophagy defects and abnormal mitochondrial autophagy, thus leading to neuronal death.[180] In addition to the formation of NFT, under the condition of iron overload, p-tau+ pre-tangle neurons experience droplet-like degeneration. The p-tau droplets formed can be wrapped by Aβ, which in turn ultimately form NP.[181] NP and p-tau have an intimate intermolecular interaction, which may explain the relationship between NP and p-tau and the negative effect on cognition in neurodegenerative diseases, such as AD.

Furthermore, although NP is not enough to induce the conformational changes of p-tau, it is a necessary precondition for p-tau pathology.[182] In the presence of other pathological risk factors, such as p-tau repeat domain, or p-tau fragments, NP can promote the development of p-tau pathological changes.[183] p-tau aggregated in NP is one of the characteristic manifestations of AD p-tau pathology. In addition to directly damaging the structure of neural networks, this form of p-tau can initiate and support the propagation and seeding of various tau pathologies in different brain regions.[184] The diffusion process spreads from the origin site (generally the medial temporal lobe) to the target area, eventually diffusing throughout the whole cortex and destroying the neural network.[185] Iron overload and the neuronal degeneration caused by ferroptosis are known to be one of the most critical causes of NP formation. The various associations between NP and p-tau offer new directions for exploring the link between ferroptosis and p-tau.[186]

GSK-3β has core regulatory roles in the AK/GSK-3β signaling pathway, which mediates the regulatory effect of GSK-3β on ferroptosis and NP deposition.[187] Notably, GSK-3β can also precisely regulate the phosphorylation of p-tau via Ser199, Ser396 and Ser404.[188] Therefore, there is an intrinsic relationship between ferroptosis, NP deposition and p-tau phosphorylation, but the mechanism underlying this relationship remains to be further explored.

Current findings suggest that p-tau and NP form complex interactive networks and are co-involved in ferroptosis. Integrating the functional patterns of such key elements will be promising for a systematic clarification of the disease pathogenesis in the future.

Summary and Perspective

This paper is a systematic exposition of the core theoretical foundation of ferroptosis in AD, the features of its metabolic regulation network, the regulatory dual role of glial cells, and the pathological correlation pattern between ferroptosis and neuropathological changes.

The above research demonstrates that a multi-pathway synergistic network consisting of disorders in iron metabolism, abnormality in lipid peroxidation and imbalance in amino acid metabolism is the core pathological mechanism of ferroptosis in AD. MG, AST and OL regulate ferroptosis in AD through different molecular mechanisms and establish a complex regulatory system. There is a bidirectionally positively reinforcing pathological cycle between NP and ferroptosis. They interact with neurotrophic axons, neuroinflammation and tau phosphorylation to jointly promote the development of AD pathology.

Despite the significant progress on ferroptosis in AD, there are still some hot scientific questions worthy of discussing: Firstly, what are the expression patterns of key molecules of ferroptosis in different pathological stages and what is their correlation with the clinical manifestations of the disease? Secondly, what are the specific regulatory mechanisms of ferroptosis in different cells (neuron, glial cell) and the interaction network? Thirdly, little is known about the pathological meanings of cross-regulation among ferroptosis and other cell death pathways (apoptosis, pyroptosis) in AD.

Future research should focus on three aspects: Firstly, in order to promote early diagnosis and dynamic evaluation of the disease, we should first determine the biomarkers that are closely related to ferroptosis in AD together with in vivo imaging methods; Secondly, it is only by studying the regulatory mechanisms of ferroptosis in different cells under special conditions so as to identify the key regulatory molecular control points and intervention techniques that precision medicine will be promoted; Thirdly, more research on the connections among ferroptosis and other types of cell death will provide a theoretical basis for the development of multi-target therapy.

We believe that as the mechanisms of ferroptosis in AD become more clear, the results of these studies will yield new theoretical insights into the pathologic mechanisms of AD, provide an important basis for the development of high-efficiency, targeted therapeutic strategies for AD, and ultimately achieve real clinical gains for AD patients.

Abbreviations

4-HNE, 4-hydroxy-2-nonenal; Aβ, Amyloid-beta; ACSL4, Acyl-CoA synthase long-chain family member 4; AD, Alzheimer's disease; ALOX, Lipoxygenase; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; APP, Amyloid precursor protein; ARA, Arachidonic acid; AST, Astrocyte(s); BBB, Blood-brain barrier; BDNF, Brain-derived neurotrophic factor; cGAS-STING, Cyclic GMP-AMP synthase–stimulator of interferon genes; CID, Cellular iron deficient; CMA, Chaperone-mediated autophagy; CSF, Cerebrospinal fluid; CNS, Central nervous system; DCYTB, Duodenal cytochrome B; DMT1, Divalent metal transporter 1; DN, Dystrophic neurite(s); DHA, Docosahexaenoic acid; DP, diffuse plaques; EGLN, Prolyl hydroxylase; ER, Endoplasmic reticulum; FT, Ferritin; FTH1, Ferritin heavy chain 1; FTL, Ferritin light chain; FPN1, Ferroportin 1; FoxO3a, Forkhead box O3a; Glu, Glutamate; GPX4, Glutathione peroxidase 4; GSH, Glutathione; GSK-3β, Glycogen synthase kinase 3β; HCP1, Heme carrier protein 1; HEPH, hephaestin; HO-1, Heme oxygenase-1; IKK/IκB/NF-κB, Inhibitor of nuclear factor kappa-B kinase / Inhibitor of kappa B / Nuclear factor kappa-light-chain-enhancer of activated B cells; IRE, Iron response element; IRP, Iron regulatory protein; JAK/STAT, Janus kinase / Signal transducer and activator of transcription; LCN2, Lipocalin-2; L-OH, lipid alcohol; L-OOH, Lipid peroxide; LOO, Lipid peroxyl radical; LPCAT3, Lysophosphatidylcholine acyl-transferase 3; L·, Carbon-centered lipid radical; MAPK, Mitogen-activated protein kinase; MBP, Myelin basic protein; MDA, Malondialdehyde; MG, Microglia; MGnD, Neurodegenerative phenotype microglia; miR, microRNA; MMP, Matrix metalloproteinase; NCOA4, Nuclear receptor coactivator 4; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; NFT, Neurofibrillary tangle(s); NMDAR, N-methyl-D-aspartate receptor; NOX2, NADPH oxidase 2;

NP, Neuritic plaque(s); Nrf2, Nuclear factor erythroid 2-related factor 2; NTBI, Non-transferrin-bound iron; OL, Oligodendrocyte(s); OPC, Oligodendrocyte precursor cell; p-tau, Hyperphosphorylated tau; PUFA, Polyunsaturated fatty acid; PUFA-PL, PUFA-enriched phospholipid; ROS, Reactive oxygen species; SAT1, Spermidine/spermine N1-acetyltransferase 1; SLC3A2, Solute carrier family 3 member 2; SLC7A11, Solute carrier family 7 member 11; SN, Substantia nigra; System Xc^-, Cystine/glutamate antiporter; Tf, Transferrin; TfR1, Transferrin receptor 1; TLR4, Toll-like receptor 4; TNF-α, Tumor necrosis factor-alpha; TrkB, Tropomyosin receptor kinase B; TXNRD1, Thioredoxin reductase 1.

Data Sharing Statement

All data generated or analysed during this study are included in this article.

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Disclosure

The authors report no conflicts of interest in this work.

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