The Association Between Ferroptosis and Neurodegenerative Diseases and Its Regulatory Mechanisms

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Abstract. Neurodegenerative diseases (NDDs) are characterized by specific damage to neurons in certain brain regions, and their pathogenesis is complex with the lack of effective early intervention methods. Ferroptosis is a novel iron-dependent form of cell death driven by lipid peroxidation. In recent years, it has been demonstrated to play an important role in the pathogenesis of NDDs. Multiple iron metabolism and lipid oxidation pathways are closely associated with classic pathological damage in the brain. This article systematically reviews the molecular mechanism of ferroptosis, combines three common diseases: Alzheimer's disease, Parkinson's disease, and Huntington's disease, to analyze their pathogenesis and the role of ferroptosis in it. At the same time, it summarizes the experimental results of various intervention methods targeting ferroptosis at the present stage, objectively summarizes the existing research shortcomings and transformation dilemmas in this field, which can provide theoretical references and new ideas for the mechanism analysis of NDDs and the development of targeted new drugs.

Keywords: Ferroptosis; Neurodegenerative diseases; Molecular mechanism.

1. Introduction

As the global population structure continues to age, the risk of neurodegenerative diseases (NDDs) has significantly increased, gradually becoming an important public health issue and a social and economic burden. However, the pathogenesis of these diseases is regulated by multiple levels and types of factors, and the molecular pathological mechanisms are complex. Currently, there is still no curative treatment available, so it is urgent to deeply analyze the pathogenesis process from a new perspective and promote research on effective intervention strategies [1]. NDDs are a type of chronic and progressive neurological disorders characterized by the progressive loss of neurons and the decline of their functions, often accompanied by clinical manifestations such as cognitive impairment and motor disorders. Ferroptosis is a novel type of regulated cell death, which is regulated by pathways such as amino acid metabolism, iron metabolism, lipid metabolism, autophagy, and mitochondrial activity, and ultimately leads to the accumulation of iron ions within the cells, causing oxidative-reductive imbalance and triggering cell death [2]. Since its discovery in 2012, a large number of studies have revealed the molecular mechanism of ferroptosis and its role in NDDs. Through gene database screening, it has been found that a large number of ferroptosis-related genes overlap with the genes related to NDDs [3]. Although different types of NDDs vary in pathogenic genes and clinical manifestations, their pathogenesis mostly concentrates on specific gene mutations, abnormal aggregation of pathogenic proteins, and independent pathways. However, more and more pathological evidence can confirm that there are common pathological features in the pathogenesis of various NDDs, including intracellular iron homeostasis imbalance, continuously elevated oxidative stress levels, lipid metabolism disorders, and significant impairment in the expression or function of the key regulatory protein GPX4 in ferroptosis. Thus, ferroptosis is not a unique cell death mode for a single disease, but a common mechanism that mediates neuronal damage and programmed death in various NDDs, playing a crucial regulatory role in NDDs.

Currently, the cutting-edge clinical treatment strategies mainly focus on the ferroptosis pathway, including three targeted directions: iron chelators, lipid peroxidation inhibitors, and GPX4 pathway activators. These provide new ideas for the early intervention of NDDs and new drug development. This article focuses on the molecular mechanism of ferroptosis and its core role in the pathogenesis

of Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD), summarizes the correlation between ferroptosis and NDDs. At the same time, it summarizes the research progress of targeted treatment and analyzes the existing shortcomings of current research, providing a summary and outlook for future research directions.

2. Molecular Mechanism of Ferroptosis

Ferroptosis is a type of cell death. It is triggered by an imbalance in redox reactions between oxidation and antioxidation, driven by the abnormal expression of various redox-active enzymes. The two core features are excessive accumulation of iron ions and lipid peroxides. Additionally, iron ions catalyze the Fenton reaction to produce reactive oxygen species (ROS), which also initiates ferroptosis. The accumulation of a large amount of ROS causes cellular oxidative stress [4].

2.1. Ferroptosis and Iron Metabolism

Iron exists in two ionic forms in the body: ferrous (Fe2+) and ferric (Fe3+), which are indispensable important trace elements in the body and participate in various physiological processes, including oxygen transport, electron transfer, and cellular metabolism, etc. Iron metabolism includes iron uptake, excretion, storage, and utilization, and is the "engine and master switch" of ferroptosis. Cells maintain the stability of intracellular iron levels by regulating iron metabolism. In the iron uptake stage, iron outside the cell mainly binds to transferring and enters the cell through endocytosis mediated by transferring receptor 1 (TFR1). After entering the cell, Fe3+ is reduced to free Fe2+, and in the iron storage stage, ferritin FTH1/FTL can seal free iron and inhibit oxidative damage. The ferroptosis-mediated iron protein autophagy activates NCOA4, which degrades iron protein and releases a large amount of iron ions. In the iron excretion stage, FPN is responsible for transporting excess iron ions out of the cell, and its downregulation or inhibition by ferrostatin will cause intracellular iron accumulation. When the intracellular free divalent iron ions increase abnormally, they can catalyze hydrogen peroxide to generate a large number of hydroxyl free radicals through the Fenton reaction, thereby causing oxidative damage, triggering the lipid peroxidation chain reaction on the cell membrane and accumulating to a lethal level, and ultimately inducing ferroptosis [5]. In summary, increased iron uptake, reduced iron storage, blocked iron excretion, or activation of ferroptosis-mediated iron protein autophagy can all promote ferroptosis.

2.2. Ferroptosis and Lipid Metabolism

The occurrence of ferroptosis also depends on lipid metabolism. The key process involves the peroxidation of polyunsaturated fatty acids (PUFAs). Among them, phosphatidylethanolamine (PE) containing arachidonic acid (AA) or adrenal acid (AdA) is the most susceptible to oxidation during lipid metabolism due to its unstable double allyl hydrogen atoms [6]. ACSL4 and LPCAT3, as key enzymes, can activate PUFAs such as AA and AdA and integrate them into the cell membrane phospholipids, making them more prone to oxidation. Subsequently, lipid peroxidases (ALOXs) and cytochrome P450 reductase (POR) catalyze chain-like peroxidation reactions of lipids, generating a large amount of toxic lipid peroxides. When the lipid peroxides exceed the cell's clearance capacity, they will cause cell membrane damage and ultimately trigger ferroptosis. The main antioxidant defense line in cells is composed of glutathione peroxidase 4 (GPX4), which can reduce lipid peroxides to non-toxic lipidsal, thereby terminating the peroxidation chain reaction. However, when the activity of GPX4 decreases or the supply of PUFA substrates is excessive, lipid peroxidation will become uncontrolled, leading to the occurrence of ferroptosis.

3. Ferroptosis and NDDs

3.1. Common Mechanisms

Since the discovery of ferroptosis in 2012, related research has continued to advance. Currently, the view that ferroptosis is involved in the occurrence and development of NDDs has been widely recognized. Ferroptosis may be the potential core mechanism of neuronal loss in various NDDs. Most NDDs share common pathological changes closely related to ferroptosis, mainly manifested as abnormal iron deposition in the brain, depletion of glutathione (GSH), and decreased activity of GP4. Simultaneously, there is significant lipid peroxidation and enhanced oxidative stress, ultimately leading to degenerative loss of neurons through ferroptosis.

3.2. Specific Mechanisms

3.2.1. AD

AD is a neurological disease characterized by progressive memory impairment and behavioral disturbances. Its core pathological feature is the deposition of Aβ amyloid plaques and excessive phosphorylation of tau protein. Studies have shown that in the hippocampus, cerebral cortex, and other key brain regions of AD patients and APP/PS1 mouse models, there is excessive iron deposition, and the iron content is positively correlated with the progression of AD and cognitive function decline [7]. Aging, ROS, and inflammatory factors are upstream triggers that significantly inhibit the function of the neuronal Xc^--GSH-GPX4 antioxidant pathway, reduce the activity of the SLC7A11 transporter, lead to insufficient cysteine intake, reduce GSH synthesis, and thereby decrease the activity of the core protective protein GPX4, damaging the neuronal antioxidant defense system, creating prerequisite conditions for ferroptosis. The imbalance of iron metabolism in the brain is the material basis for neuronal ferroptosis in AD. Under pathological conditions of AD, neurons overtake iron ions through the Tf, TfR1, and DMT1 pathways (Tf binds to TfR1 for endocytosis and releases iron ions, which are then transported to the cytoplasm by DMT1, forming the core pathway for cellular uptake of exogenous iron) and accumulate excessive divalent iron within the cell; at the same time, APP protein and phosphorylated tau protein inhibit the function of iron efflux protein FPN1, hindering iron efflux. Severe iron overload in the brain further promotes the occurrence of ferroptosis. At the same time, the occurrence of AD pathology and ferroptosis form a bidirectional vicious cycle. Aβ and phosphorylated tau protein can aggravate iron overload and oxidative damage, while excessive iron accumulation can, in turn, promote the abnormal modification and deposition of typical pathological proteins in AD.

3.2.2. PD

PD is the second most common NDD worldwide. Its pathological feature is the gradual loss of dopaminergic neurons in the substantia nigra compacta, accompanied by pathological aggregation of α-synuclein (α-syn). Neuroimaging and autopsy results have shown that PD patients have significant iron accumulation in the substantia nigra region, and the iron content in the remaining dopaminergic neurons is significantly increased [8]. After iron overload in the substantia nigra region triggers the Fenton reaction, the level of ROS increases sharply, thereby causing abnormal aggregation of α-syn, continuously damaging the mitochondrial structure and function, ultimately leading to the complete disintegration of the System xc^--GSH-GPX4 antioxidant defense system, triggering lipid peroxidation chain reactions, inducing iron death in dopaminergic neurons, and gradually and continuously presenting and worsening the related symptoms of PD. Recent studies have shown that iron death has a bidirectional vicious cycle relationship with other pathological features of PD, and α-syn can inhibit the antioxidant system, while the oxidative stress caused by iron death can reverse and accelerate the aggregation of α-syn, forming a vicious cycle [9]. In summary, iron death in PD drives lipid peroxidation through iron metabolism imbalance and together with other pathological features completes the pathogenic mechanism, and provides a theoretical basis for subsequent disease treatment.

3.2.3. HD

HD is a hereditary NDD characterized by the degeneration of neurons in the striatum and cerebral cortex. The clinical manifestations include dystonia, motor incoordination, and cognitive decline. Studies have shown that iron death plays a key driving role in its pathological process. In HD mice, there is an imbalance of oxidative stress, manifested as elevated lipid peroxidation levels [10] and decreased GSH levels [11]. This is the core prerequisite for iron death to occur, indicating that iron death plays a role in the pathogenesis of HD. At the same time, iron overload will further catalyze the lipid peroxidation chain reaction, exacerbating oxidative stress damage, forming a vicious cycle; the mutant Huntington protein will also damage mitochondrial function, promote ROS generation, and cause the failure of the System xc^--GSH-GPX4 defense system, ultimately inducing iron death in striatal neurons, amplifying the effect of iron death, and presenting and worsening the related symptoms of PD. These findings reveal the connection between iron death and HD pathology, and provide a theoretical basis for targeted iron accumulation, lipid peroxidation, and restoration of GPX4 activity for treatment.

4. Targeted Therapeutic Strategies and Prospects

4.1. Iron Chelators and Iron Homeostasis

Regional iron deposition in the brain is a common feature of NDDs. Therefore, reducing unstable iron content and restoring iron homeostasis is the main direction for treating NDDs. Chelators that restore iron homeostasis are suitable therapeutic drugs. Iron chelators can bind Fe3+ and Fe2+ with high affinity to form stable and non-toxic complexes, which can be excreted through urine or bile and redistribute iron to functional proteins lacking iron. This process not only reduces the generation of lipid peroxidation and minimizes damage by shrinking the unstable iron pool but also inhibits the Fenton reaction and reduces the generation of ROS. It protects neurons, and delays disease progression. Deferoxamine (DFO), deferoxaprole (DFP), and deferoxorin (DFX) are iron chelators approved by the US Food and Drug Administration for treating iron overload [12]. These compounds have been proven to chelate intracellular free iron, block iron retention caused by the Tf, TfR1, and DMT1 pathways, and can reduce iron accumulation in AD patients [13]. Although these iron chelators are recommended as first-line treatment for iron overload, each of them has clear side effects, such as gastrointestinal diseases, liver toxicity, kidney toxicity, and visual and auditory nerve toxicity. Therefore, more iron chelators that are better suited for regulating iron homeostasis need to be further explored and developed to assess their potential in treating NDDs in preclinical and clinical studies.

4.2. Inhibition of Membrane Phospholipid Peroxidation

Iron death is a form of cell death driven by membrane phospholipid peroxidation. In NDDs, membrane phospholipids rich in PUFAs are often over-oxidized, leading to the disruption of membrane integrity and the induction of neuronal death [14], promoting the development of diseases such as AD and PD. Therefore, targeting the inhibition of membrane phospholipid peroxidation has become an important strategy for treating NDDs. The therapeutic mechanisms targeting membrane phospholipid peroxidation can be mainly divided into two categories: One is to directly carry out lipid antioxidant intervention. Specific iron death inhibitors such as Ferrostatin-1 and Liproxstatin-1 can directly eliminate lipid free radicals, block the phospholipid peroxidation reaction, and inhibit neuronal iron death at the source. In addition, weakening the synthesis of membrane phospholipid peroxidation substrates is more preventive. By activating the Nrf2 antioxidant pathway and inhibiting the ACSL4 lipid synthesis enzyme, the generation of polyunsaturated phospholipids is reduced, and the initiation of the peroxidation chain reaction is blocked at the source. Targeted phospholipid peroxidation treatment can significantly improve motor disorders and cognitive decline, and compared with traditional anti-inflammatory and antioxidant drugs, this target is more specific and has no obvious off-target side effects. However, currently, such targeted drugs still have problems

such as low penetration through the blood-brain barrier and poor stability in the body, providing a direction for further development and becoming a breakthrough point for targeted treatment of NDDs.

5. Conclusion

To sum up, ferroptosis, as a novel type of cell death that is iron-dependent and driven by the peroxidation of PUFAs, is closely related to the occurrence and development of NDDs. Imbalance in iron homeostasis, weakened antioxidant system function, and lipid metabolism disorders are the main triggers of ferroptosis. Besides the typical pathogenic mechanisms such as abnormal deposition of pathogenic proteins and neuronal degeneration, ferroptosis can also react with aging and inflammatory factors, amplifying damage, and at the same time explains the specificity of the disease from a new perspective, filling the gap where traditional pathogenic mechanisms cannot explain the progression of the disease. Currently, relevant research is mainly conducted using cell and animal models, which limits the process of translating basic results into clinical applications. The existing intervention drugs also have problems such as weak penetration of the blood-brain barrier and insufficient specificity. Future research needs to further understand the regulatory mechanisms of ferroptosis in different NDDs, optimize existing intervention methods, and explore multi-target combined intervention schemes. In summary, targeting the ferroptosis pathway can provide new research ideas and breakthrough directions for the mechanism study and clinical prevention and treatment of NDDs.

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