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Progress and Application of Ferroptosis Mechanisms in Neurological Diseases

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Abstract: *Ferroptosis is a form of cell death triggered by intracellular lipid peroxidation or iron ion accumulation. Cells undergoing ferroptosis exhibit disrupted mitochondrial membrane potential, mitochondrial swelling, and increased density of mitochondrial cristae. In neurological diseases, research has found that neurodegenerative diseases and cerebral ischemic injury can induce ferroptosis in neurons. Ferroptosis plays a significant role in neurological diseases. Recently, studies have discovered that ferroptosis inhibitors can improve neural function, although the specific regulatory network of ferroptosis remains unknown. In this review, we focus on several regulatory mechanisms of ferroptosis, including the Xc- system regulation, lipid metabolism, and mitochondrial involvement, and also discuss its applications in neurological diseases.*

Keywords: *Ferroptosis, Neurological disease, Xc- System, Lipid metabolism, Mitochondria*

1. Introduction

Recent studies have shown that cell death includes new programmed death patterns such as necrosis, apoptosis, and autophagy[1].When cells undergo necrosis, their membranes lose integrity and swell, allowing intracellular components to leak into the extracellular matrix, which triggers an inflammatory response. In contrast, during apoptosis, the cell membrane remains intact, and in the late stages, apoptotic cells fragment into apoptotic bodies[2].The term “ferroptosis" oined in 2012, representing an iron-dependent cell death mode characterized by the accumulation of intracellular iron ions and lipid peroxidation, discovered after necroptosis and apoptosis[3].Ferroptosis is characterized morphologically by reduced mitochondrial size, increased mitochondrial membrane density, and a decrease or disappearance of mitochondrial cristae. Early studies indicated that the morphological features of ferroptosis resemble those of necrosis, such as loss of plasma membrane integrity and swelling of cells and organelles [4].Cell death due to ferroptosis can be triggered through the regulation of certain transport proteins and the inhibition of antioxidant enzymes. In iron-rich tissues , iron-induced damage is common, and ferroptosis further deteriorates organ function[5].

Ferroptosis is a form of cell death induced by oxidative stress and is associated with various diseases such as traumatic brain injury, hemorrhagic stroke, and Parkinson's disease (PD) [6]. In patients with PD, brain imaging and pathological studies have shown that iron deposition in the brain is associated with the loss of dopaminergic (DA) neurons. Research indicates that the relationship between iron-dependent ferroptosis in the brain, the activation of glial cells, and neurodegeneration is the basis of the pathogenesis of PD [7]. After cerebral hemorrhage occurs, cells undergo various forms of cell death. Studies have shown that the Hb released after cerebral hemorrhage is metabolized into ferrous/iron in microglia, leading to the production of reactive oxygen species (ROS). When iron is released from microglia, it generates hydroxyl radicals, thereby disrupting neural function [8]. Research has found that in the Amyotrophic lateral sclerosis (ALS) mouse model, the early characteristic of glutathione peroxidase 4 (GPX4) deficiency appears in the brain and spinal cord. GPX4 combats the formation of lipid peroxides and thereby resists ferroptosis. Overexpression of GPX4 can improve the motor function of mice and prolong their lifespan. This reveals that in ALS, ferroptosis of cells is closely related to the motor function of mice [9]. Thus, the regulation of ferroptosis represents a promising target for the investigation and potential treatment of neurological disorders.

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2. Inhibition of System Xc- Mediated Ferroptosis

The amino acid transport system Xc- is one of the important antioxidant systems in the body[10] ,it is a transporter for Cys and Glu, promoting the synthesis of glutathione (GSH), thereby preventing lipid peroxidation and ferroptosis. GSH or thioredoxin reductase 1 (TrxR1) reduces cystine to cysteine, which is then used to synthesize glutathione. GPX4 reduces phospholipid hydroperoxide (PLOOH), and a decrease in intracellular GPX4 activity leads to the decomposition of PLOOH by ferrous ions, causing ferroptosis. Studies have shown that activating transcription factor 3 (ATF3) inhibits Xc-, promoting erastin-induced ferroptosis. Moreover, ATF3 inhibits the activity of the catalytic subunit xCT/Solute Carrier Family 7 Member 11 (SLC7A11)[11]. Xc- is composed of SLC7A11 and the regulatory subunit 4F2 (4F2hc)/Solute Carrier Family 3 Member 2 (SLC3A2). SLC7A11 enhances the activity of the Xc- system and increases the cell's resistance to ferroptosis. Activating transcription factor 4 (ATF4) and nuclear factor erythroid 2-related factor 2 (Nrf2) induce the synthesis of SLC7A11. The key rate-limiting enzymes for GSH synthesis are mainly GSS and GCLC. GSS catalyzes the formation of GSH from γ-glutamylcysteine (γ-GC), and Nrf2 can upregulate the expression of GSS and GCLC. Selenium and isopentenyl pyrophosphate (IPP) promote the expression of GPX4, and GPX4 can also regulate Nrf2[12].

Studies have found that in hemorrhagic brain injury in rabbits, mice and humans, Glu significantly increases, and glutaminase inhibitors reduce the number of degenerative neurons around the hematoma[13]. In subarachnoid hemorrhage (SAH), inhibiting BECN1 and SLC7A11 can enhance antioxidant capacity, inhibit ferroptosis, and improve brain edema. In a mouse model of ischemic stroke, down-regulating SLC7A11 can inhibit neuronal death induced by cerebral ischemia/reperfusion. [10] Additionally, research has shown that SAH-induced brain injury depletes Xc- and GPX4, leading to increased reactive oxygen species and neuronal death in the hippocampus of rats, and reducing ubiquitinated SLC3A2, SLC7A11 and GPX4 can lower the expression of reactive oxygen species and the level of lipid peroxides [14]. In Hypoxic-ischemic encephalopathy (HIE), catalpol inhibits the Nrf2/system Xc-/GPX4 axis, thereby inhibiting neuronal ferroptosis and protecting cells from hypoxic-ischemic injury [15].Leucine-rich repeat protein kinase 2 (LRRK2) regulates ferroptosis by modulating Xc/GSH/GPX4, and inhibiting LRRK2 can prevent SHSY5Y cell death [16].

3. Lipid metabolism in Ferroptosis

Lipid peroxidation of the cell membrane is an indispensable process in ferroptosis. Polyunsaturated fatty acids (PUFAs) are responsible for lipid peroxidation in ferroptosis. Cells need to absorb essential amino acids from the blood and lymph of the body, then synthesize PUFAs, and then enter the cell membrane, promoting lipid peroxidation through enzymatic or non-enzymatic mechanisms. In the ferroptosis signaling pathway, doubly and triply oxygenated arachidonic acid (AA)- and adrenic acid (AdA)-containing PE species (C18:0/C20:4 and C18:0/C22:4) are the four most crucial phospholipids. In GPX4 KO mice, the expression of oxidized phospholipids increases, but it decreases after treatment with ferroptosis inhibitors. Acyl-CoA synthetase long-chain family member 4 (ACSL4) combines long-chain fatty acids with coenzyme A to generate fatty acyl-CoA esters and form phospholipids. The absence of ACSL4 can resist ferroptosis induced by the absence of GPX4. In addition, PUFA-CoA mainly enters the endoplasmic reticulum (ER) through lysophosphatidylcholine acyltransferase 3 (LPCAT3), which prefers PC and PE as substrates. LOX directs oxygen to combine with PUFAs, promoting lipid peroxidation. Studies have shown that inhibitors of 12/15-LOX can inhibit ferroptosis, but 5-LOX is not related to ferroptosis in cells. Studies have shown that p53 upregulates 15-LOX through spermine N1-acetyltransferase 1 (SAT1), increasing the sensitivity of cells to ferroptosis. 15-LOX binds to Raf kinase inhibitory protein (RKIP1) to regulate the Raf-1-mediated mitogen-activated protein kinase (MAPK) signaling pathway. In addition, NOXs can promote lipid peroxidation. Among them, NOX1 binds to DPP4, and NOX2 and NOX4 can activate the Hippo pathway effector taafazzin (TAZ) to promote erastin-induced ferroptosis. POR is a membrane-bound enzyme required for the transfer of electrons from NADPH to cytochrome P450, which accelerates the cycle between ferrous and ferric iron and may promote lipid peroxidation. Peroxisomal biogenesis factor 10 (PEX10), peroxisomal biogenesis factor 3 (PEX3), alkyldihydroxyacetone phosphate synthase (AGPS), and fatty acyl-CoA reductase (FAR1) have been identified as essential for ferroptosis[17].

In the brains of patients with Alzheimer's Disease (AD), there is excessive accumulation of iron, and the levels of lipid peroxidation products and Aβ peptide plaques increase simultaneously in the

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body. Research has found that apolipoprotein E can modify the affinity of intracellular iron-binding proteins, inhibit the autophagic degradation of ferritin, and thereby suppress cellular lipid peroxidation and ferroptosis [18]. Neurons release fatty acids through exocytosis, eliminating the accumulation of peroxidized fatty acids and iron in cells, thereby inhibiting ferroptosis in neurons[19] .In patients with Parkinson's Disease (PD), the striatum is rich in polyunsaturated fatty acids (PUFAs) and iron. Studies have shown that arachidonic acid (AA) modifies PUFAs in dopaminergic neurons and affects the occurrence of ferroptosis in neurons. Iron and AA can promote ferroptosis in dopaminergic neurons, while inhibiting ACSL4, ALOX15 or ALOX15B can protect cells from ferroptosis[20] .NADPH oxidase 4 (NOX4) promotes ferroptosis in astrocytes by inducing lipid peroxidation in AD patients[21]. In a mouse model of sepsis-associated encephalopathy (SAE), the expression of S-100β and neuron-specific enolase (NSE) in the hippocampus increases, while in mice treated with deferoxamine (DFO), the expression of S-100β and NSE in the hippocampus decreases. Moreover, iron ion accumulation occurs in the hippocampus of SAE mice, while the iron ion level in the hippocampus of DFO-treated mice is reduced. SAE brain injury leads to a significant increase in the levels of hippocampal phosphatidylethanolamine-binding protein (PEBP) and 15-LOX, and a significant decrease in GPX4[22].

4. Mitochondria are involved in ferroptosis

Mitochondria are involved in various cellular signaling pathways, such as oxidative stress, apoptosis, iron metabolism, etc. In ferroptosis, mitochondria play a significant role. The accumulation of ROS in mitochondria increases the cell's sensitivity to ferroptosis. Studies have found that inhibiting SLC7A11 or depriving cystine leads to a decrease in ROS clearance and an increase in intracellular glutamate content, which is converted to α-ketoglutarate (α-KG), promoting ferroptosis by enhancing the tricarboxylic acid cycle. In pancreatic cancer, endoplasmic reticulum protein stimulator (STING1) promotes mitochondrial ROS production and lipid peroxidation through mitochondrial fusion. It has been found that inhibiting the function of mitochondrial complex III and mitochondrial uncoupling agents can inhibit cystine deprivation-induced ferroptosis. The mitochondrial tricarboxylic acid cycle is also involved in the process of cellular ferroptosis. The activity of α-ketoglutarate (α-KG) dehydrogenase complex (KGDHC) can inhibit ferroptosis, and supplementing α-KG and the downstream metabolites of 2-oxoglutarate dehydrogenase complex (OGDC) can simulate the role of glutamine in cystine deprivation-induced ferroptosis. In erastin-induced ferroptosis, glycolytic flux is reduced, promoting mitochondrial oxidative phosphorylation and ferroptosis. In ferroptosis, the expression levels of hexokinase II, platelet-type phosphofructokinase, and pyruvate kinase M2 are significantly decreased. Mitochondrial respiratory enzymes also participate in the process of cellular ferroptosis. Fumarate hydratase (FH) can promote cystine deprivation-induced ferroptosis. Erastin weakens the regulation of tubulin on the function of voltage-dependent anion-selective channel (VDAC), and the mitochondrial membrane potential increases due to the opening of VDAC, promoting the production of mitochondrial ROS. Excessive accumulation of mitochondrial calcium ions leads to the opening of the mitochondrial permeability transition pore, resulting in a decrease in mitochondrial membrane potential and ATP consumption. Protochlorophyll oxidoreductase and cytochrome b5 reductase 1 (CYB5R1) transfer to downstream proteins, generating active hydroxyl radicals and causing lipid peroxidation. O-GlcNAcylation promotes the release of iron from ferritin, and the released iron is transported to mitochondria, promoting mitochondrial autophagy and the release of iron from mitochondria, thereby promoting ferroptosis. In addition, studies have shown that mitochondrial DNA stress can activate STING1/transmembrane protein 173 (TMEM173) and also activate cyclic GMP-AMP synthase (cGAS)/STING1 to promote autophagy-dependent ferroptosis. Targeted removal of ROS in mitochondria can inhibit ferroptosis. Erythropoietin can inhibit Xc- in cells with mitochondrial DNA depletion, protecting cells from ferroptosis. Studies have found that the AMP-activated protein kinase (AMPK)/FoxO3a signaling pathway regulates the activity of mitochondria to regulate the occurrence of ferroptosis. Fatty acid β-oxidation in mitochondria reduces polyunsaturated fatty acids (PUFAs) and lipid peroxidation. The lipid transporter StAR-related lipid transfer domain protein 7 (STARD7) transports CoQ to the cell membrane, preventing iron oxidation[23].Research has found that cells with mitochondrial deficiency do not have resistance to ferroptosis induced by GPX4 inhibitors. However, mitochondrial uncouplers do not inhibit lipid peroxidation and ferroptosis. Therefore, GPX4 inhibition-induced ferroptosis does not require mitochondrial function[24]. Studies have shown that doxorubicin (DOX) leads to the down-regulation of GPX4, causing lipid peroxidation through the mitochondrial DOX-Fe2+ complex, thereby inducing mitochondrial-dependent ferroptosis in cardiomyocytes[25].

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Mitochondrial transplantation is a novel approach for treating ferroptosis in cells. In hippocampal HT22 cells and primary cortical neurons (PCN), mitochondrial transplantation enhances the activity of mitochondrial complexes, metabolic activity, and cell survival rate, reduces the accumulation of lipid peroxides in cells, and protects neuronal activity[26]. Mitochondrial quality control, including mitochondrial fission and fusion, mitochondrial biogenesis, and mitophagy, is the cornerstone for maintaining the integrity and stability of morphology, quantity, and function. Studies have found that disrupted mitochondrial quality control promotes ferroptosis through mitochondrial fission and fusion. Mitochondrial transfer via mesenchymal stem cells restores the mitochondrial pool through mitochondrial fusion, thereby inhibiting the occurrence of ferroptosis[27]. The mitochondrial calcium uniporter (MCU) transports calcium ions into the mitochondrial matrix. Inhibiting MCU can prevent mitochondrial dysfunction and protect HT22 cells, human dopaminergic neurons, and mouse primary cortical neurons from ferroptosis[28]. Cerebral ischemia/reperfusion (I/R) injury leads to excessive oxidative stress in the body. UBIAD1 is an antioxidant enzyme that catalyzes the production of coenzyme Q10 and vitamin K in the Golgi apparatus and mitochondria. I/R injury causes ferroptosis in neurons. UBIAD1 improves the functional disorders of mitochondria and the Golgi apparatus, ameliorates the morphological changes of mitochondria and the Golgi apparatus, and inhibits the accumulation of mitochondrial lipid peroxides and the occurrence of ferroptosis[29]. During cerebral ischemia, DNA oxidation occurs earlier than DNA breakage, and the generated reactive oxygen species (ROS) disrupt mitochondrial function, leading to cell ferroptosis. Studies have shown that p53 contributes to mitochondrial respiration and promotes ferroptosis in neurons. In cerebral ischemia, the opening of the mitochondrial permeability transition pore leads to mitochondrial swelling and mitochondrial dysfunction, promoting ferroptosis in neurons. Mitochondrial dysfunction leads to the activation of iron regulatory protein 1 (IRP1) to regulate β-amyloid precursor protein (APP) mRNA, promoting ferroptosis in PD neurons[30]. Research has found that diacetylmorphine (DA) exposure activates mitophagy and upregulates protein kinase Cδ (PKCδ), leading to the downregulation of GPX4 expression. Inhibiting PKCδ can restore the expression level of GPX4 in rats and improve their behavior[31].

5. Conclusions

Ferroptosis, as a newly discovered form of cell death, its specific regulatory mechanism remains to be explored. In neurological diseases, the regulation of ferroptosis is expected to become a therapeutic target. By modulating the regulatory mechanism of ferroptosis, regulating the process of ferroptosis or mitochondrial biological functions, neurons can be protected. With the deepening understanding of the regulatory process of ferroptosis, lipid peroxidation and mitochondrial function, the regulation of ferroptosis may offer new opportunities for the treatment of neurological diseases. Notably, ferroptosis can also affect cellular immune activities. How to apply ferroptosis to the diagnosis and treatment of human diseases remains a major challenge in the future.

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