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Role of Ferroptosis in Cerebral Ischemia-Reperfusion Injury

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Abstract: Ferroptosis is a novel form of non-apoptotic cell death that has been widely studied in recent years and is involved in a variety of pathophysiological processes. The core treatment goal of ischemic stroke is to restore blood flow as early as possible, while the pathological mechanism of reperfusion injury after restoring blood flow is complex, involving oxidative stress, calcium overload, and inflammatory response. In recent years, more and more studies have found that ferroptosis mediation is involved in the occurrence and development of cerebral ischemia-reperfusion injury. This paper elaborates on the concept, mechanisms, and regulation of ferroptosis, detailing its role in cerebral ischemia-reperfusion injury and potential inhibition strategies. The aim is to deepen the understanding of ferroptosis in this pathological process and provide insights for possible targeted therapies.

Keywords: Ferroptosis; Ischemic stroke; Reperfusion injury; Targeted therapy

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1. Introduction

Stroke is one of the leading global causes of death and disability, ranking as the second leading cause of mortality and the primary cause of adult disability worldwide. With its elevated disability, recurrence, and fatality rates, this condition presents a major public health risk and stands as one of the most pressing disease burdens globally. Timely and effective restoration of cerebral blood flow is critical for patient survival and is typically achieved through thrombolysis or thrombectomy. However, numerous studies have demonstrated that reperfusion itself can exacerbate tissue damage, leading to further deterioration of the patient's condition and, in severe cases, death. This pathological process is known as cerebral ischemia–reperfusion injury (CIRI) [1, 2]. Therefore, it is necessary to seek treatments to reduce CIRI. CIRI involves complex pathophysiological processes, and its mechanism is extremely complex, which is related to multiple links such as inflammatory response and oxidative stress, as well as various modes of cell death such as apoptosis, pyroptosis, and programmed necrosis [3].

Among them, ferroptosis is closely related to CIRI and has emerged as a potential therapeutic target in

acute ischemic stroke [4–6]. Iron death, unlike apoptosis, necrosis, and autophagy, is a form of iron-dependent cell death characterized by excessive accumulation of lipid peroxides leading to oxidative damage of the cell membrane and ultimately causing cell death [7]. Ferroptosis is closely related to many diseases, such as tumors, neurodegenerative diseases, renal impairment, and ischemia-reperfusion injury [8]. Ferroptosis has emerged as a novel mode of cell death implicated in cerebral ischemia–reperfusion injury (CIRI). Fang *et al.* reported iron accumulation in the injured brain regions of rats subjected to ischemia–reperfusion, while Tuo *et al.* observed significant iron deposition in the brain tissue of rats with unilateral transient middle cerebral artery occlusion (MCAO) [9, 10]. Notably, treatment with the ferroptosis inhibitor ferrostatin-1 was shown to reduce cerebral infarct volume and improve behavioral outcomes in MCAO models. It has been revealed that cerebral ischemia-reperfusion induces ferroptosis in neurons, while inhibition of ferroptosis attenuates CIRI [11, 12]. These studies all suggest that ferroptosis is strongly associated with brain injury.

Studies have shown that targeted therapies can inhibit ferroptosis through several mechanisms, including reducing iron overload, decreasing reactive oxygen species (ROS) production, suppressing lipid peroxidation, and activating endogenous defense signaling pathways. These interventions have demonstrated potential in mitigating cerebral ischemia–reperfusion injury (CIRI). Ferroptosis is expected to be an important potential target for CIRI intervention. In this paper, the pathological mechanism of ferroptosis in CIRI and the progress of targeted therapy for ferroptosis are discussed to provide new ideas for the mechanism study and clinical prevention and treatment of CIRI.

2. Overview of iron deaths

2.1. Concept of iron death

Iron is an indispensable trace element in the human body. Low or high iron content and abnormal distribution in the body will affect the physiological function of the body. Ferroptosis is a novel form of programmed cell death first identified and named by Dixon *et al.* [13]. It is characterized by intracellular iron accumulation, which activates lipid peroxidation, leading to cell membrane rupture. This process also affects the mitochondria, resulting in mitochondrial atrophy, increased density of the mitochondrial bilayer membrane, reduction or loss of cristae, and ultimately, cell death.

Iron death is an iron-dependent mode of programmed cell death, which is different from apoptosis, necroptosis, and autophagy. The main hallmarks of ferroptosis are: iron accumulation and unrestricted "phospholipid peroxidation" in the cell membrane. Peroxidation products destroy the integrity of the membrane and thus induce cell death. It is a series of processes leading to cell death by iron metabolism disorders and massive accumulation of lipid peroxidation products. Ferroptosis is an iron-dependent non-apoptotic cell necrosis due to excessive accumulation of ferric iron, glutathione depletion, and lipid peroxidation [14].

Ferroptosis differs from other types of cell death because it does not trigger DNA fragmentation or follow typical apoptotic or necrotic pathways. Instead, it is defined by iron-dependent lipid peroxidation and dysregulated iron metabolism, resulting in cellular membrane damage and eventual cell rupture. Under certain pathological factors or drug induction, intracellular iron uptake increases, iron-dependent Fenton reaction intensifies, cellular antioxidant capacity decreases, fatal peroxide accumulation is produced, and ultimately, cell death occurs.

2.2. Rationale for iron death

The mechanism of ferroptosis involves multiple intracellular processes, mainly including iron metabolism disorders, lipid peroxide accumulation, imbalance of amino acid antioxidant system, and cell membrane damage. Ferroptosis is based on abnormal accumulation of intracellular free iron. When iron metabolism is imbalanced (e.g., increased iron intake, decreased storage, or blocked efflux), free iron accumulates in excess intracellularly, leading to iron death, mainly through the following mechanisms:

(1) Accumulation of iron ions

Iron ions enter the cell through transporters (e.g., transferrin receptor, TFR1) and are stored by iron storage proteins (e.g., ferritin) or excreted through iron-releasing proteins (e.g., ferroportin). In iron death, an imbalance in iron metabolism leads to excessive intracellular iron concentrations.

(2) Lipid peroxidation

Iron ions are involved in the generation of reactive oxygen species (ROS), especially free radicals such as hydrogen peroxide (HO), which react with polyunsaturated fatty acids on the cell membrane to form lipid peroxidation products, such as 4-hydroxydiallyl peroxide (4-HNE). These peroxides can damage cell membranes and cause cell rupture. Therefore, metabolic processes such as iron absorption, transport, storage, utilization, and excretion are closely related to the occurrence of iron death.

3. The relationship between ferroptosis and cerebral ischemia-reperfusion injury

Restoration of blood flow is the most critical aspect of stroke treatment; however, paradoxically, reperfusion following ischemia can exacerbate brain tissue damage. Ischemia represents the initial phase of reperfusion injury. During the hypoxic stage, anaerobic metabolism becomes predominant, resulting in the accumulation of lactic acid, reduced synthesis and increased consumption of adenosine triphosphate (ATP), and subsequent cellular energy failure. These metabolic disturbances lead to calcium ion (Ca^{2+}) overload, mitochondrial dysfunction, and activation of inflammatory responses, collectively contributing to further neuronal injury.

In the refilling stage, the rapid recovery of blood flow supplied oxygen gas to the oxygen-deficient group, and also promoted the production of reactive oxygen species (ROS) at the same time. Reactive oxygen species (ROS) can damage various intracellular biomolecules, impair cellular functions, and induce inflammatory responses. In addition, ROS contribute to the formation of thrombi, thereby exacerbating cellular injury. In them, ROS pass through and interact with cell membrane lipids, causing lipid peroxidation, which damages cell membrane structure and leads to dysfunction, a process closely related to iron death [15]. Studies have shown that after cerebral ischemia, the blood-brain barrier (BBB) is disrupted and the permeability of cerebral microvascular endothelial cells increases, which in turn promotes the massive entry of iron from the blood into the brain parenchyma, resulting in iron overload [16].

In addition, under pathological conditions of ischemia and hypoxia, the acidic environment in brain tissue can reduce the binding capacity of iron and TF, and a large amount of free iron ions are released. Free iron ions released promote iron uptake by neurons, resulting in abnormally high intracellular iron content [17]. Intracellular iron ionomers are heterogenously accumulated, and ROS are generated by passing through the Finton reaction or the Haber-Weiss reaction, which in turn oxidizes polyunsaturated fatty acids in lipids, causing the accumulation of polyunsaturated fatty acid peroxides, resulting in cell membrane destruction and mitochondrial damage [18, 19].

The above process is central to the development of ferroptosis and is associated with oxidative stress response in IRI. The intracellular antioxidant system can reverse lipid peroxidation and prevent the accumulation of lipid peroxides, thereby inhibiting ferroptosis. Consequently, the mechanism of ferroptosis in cerebral ischemia-reperfusion injury involves three key processes: iron metabolism, lipid peroxidation, and antioxidant defense. The following are the specific mechanisms of iron death:

3.1. Iron metabolism disorders and cerebral ischemia-reperfusion injury

Iron death is based on disturbances in iron metabolism, particularly accumulation of intracellular free iron. Iron can enter cells via the iron transporter receptor (TFR), be stored in ferritin, or be expelled from cells via iron expulsion protein (FPN). When there is a disruption in iron regulation, excess iron builds up within cells, increasing its reactivity with oxygen and leading to the production of free radicals.

Iron is an essential trace element in the human body. Circulating Fe^{3+} binds to transferrin and is transported into cells via the transferrin receptor (TFR). Once inside the cell, Fe^{3+} is reduced and released into the labile iron pool (LIP) within the cytosol. Excess iron is stored in ferritin, where it remains in a bound and non-toxic form [20]. The labile iron pool within cells primarily consists of free Fe^{2+}, which is highly reactive and unstable. Through the Fenton reaction, Fe^{2+} catalyzes the production of hydroxyl radicals that readily react with polyunsaturated fatty acids in cellular and plasma membranes, leading to the generation of large amounts of lipid reactive oxygen species (ROS) and ultimately resulting in cell death. Membrane ferroportin 1 (FPN1) is currently the only known iron export protein responsible for transporting Fe^{2+} outside the cell [21].

Promoting intracellular iron import and breakdown of iron derivatives and inhibiting iron export can cause Fe^{2+} overload in labile iron pools. Accumulated Fe^{2+} generates ROS by reacting with H_2O_2 or O_2, causing lipid peroxidation damage and cellular iron death. Iron deposition has previously been reported to occur in the thalamus and basal ganglia of patients with cerebral ischemia, and subsequent studies have found that iron, transferrin, and transferrin receptor levels in the brain are increased to varying degrees after ischemia [22–24]. These findings suggest that neuronal cells increase their own iron intake by up-regulating the expression of transferrin and T FR during ischemic brain injury, which leads to an increase in free Fe^{2+} content in the cells, which is clinically characterized by iron deposition in ischemic injured areas of the brain. Neuronal cells showed a decrease in iron excretion in addition to increased iron intake during reperfusion in ischemic stroke.

Tuo *et al.* found that cerebral ischemia-reperfusion injury significantly suppresses tau protein expression, which has been previously reported to play a key role in iron efflux in neural cells. Tau protein mediates the interaction between the membrane iron exporter ferroportin (FPN) and amyloid precursor protein (APP), thereby facilitating normal iron excretion [25, 26]. Ischemic brain injury also affects the efflux capacity of the membrane iron transporter (FPN) after tau protein is inhibited. Increased intracellular free Fe^{2+} content activates the ferroptosis pathway due to increased iron intake and decreased iron excretion. On the one hand, excessive Fe^{2+} strengthens the Finton reaction and produces a hydroxyl group from the base; the synthesis of another square Fe^{2+} reference with lipoxygenase catalyzes the production of lipid peroxides [27].

Iron death is dependent on iron, and proteins involved in the maintenance of iron homeostasis play an important role in the regulation of iron death. Dysregulation of these proteins results in elevated intracellular iron concentrations, promoting the accumulation of lipid peroxides through two primary mechanisms. First, the iron-dependent Fenton reaction facilitates the generation of reactive oxygen species (ROS), whereby redox-active ferrous iron (Fe^{2+}) catalyzes the conversion of hydrogen peroxide into highly reactive hydroxyl radicals

and hydroxide ions. These ROS then directly promote the formation of phospholipid hydroperoxides (PLOOH). Additionally, iron overload activates iron-dependent enzymes, such as iron-containing lipoxygenases (LOX) and cytochrome P450 oxidoreductase. These enzymes, particularly LOX, drive the production of phospholipid hydroperoxides, thereby promoting the increased occurrence of iron death, reduced iron storage, and limited paste outflow. This results in intracellular iron accumulation, further increasing iron-related reactive oxygen species and lipid peroxide, which leads to iron death.

3.2. Lipid peroxidation and cerebral ischemia-reperfusion injury

Lipid peroxidation is the core process of iron death, while polyunsaturated fatty acids (PUFAs) are the main substrates of peroxidation, especially arachidonic acid (AA) and epinephrine. Iron ions promote lipid peroxidation and form lipid peroxide by generating free radicals. Oxidized lipids can disrupt the structure of the cell membrane, impairing its integrity and leading to dysregulation of cellular function, ultimately resulting in cell death. Several studies have now shown that PUFAs, such as arachidonic acid and adrenic acid, are specific substrates for PLOOH synthesis and play an important role in the development of iron death, and thus, the increase of these PUFAs increases the risk of iron death. The destruction of cell membranes by lipid peroxidation products is an important marker of iron death. Peroxidized lipid products can lead to structural and functional dysfunction of the cell membrane, forming membrane pores, resulting in the leakage of cellular contents, which in turn triggers cell rupture and death. During iron death, unsaturated fatty acid phospholipids are oxidized to lipid peroxides by reactive oxygen species (ROS) and lipoxygenase [28] . Lipoxygenase is not the sole catalytic enzyme for lipid peroxidation, and studies have shown that reduced nicotinamide adenine dinucleotide phosphate oxidase and cytochrome P450 oxidoreductase also play key roles in lipid peroxidation during iron death [29, 30].

Gubern *et al.* investigated the association between ACSL4 and brain ischemic injury and found that brain ischemic injury was able to induce miR-347 upregulation which in turn suppressed ACSL4 expression [31]. Increased expression of 12/15 lipoxygenase (12/15 - LOX) has been found in mouse models of ischemic stroke, and these studies point to 12/15-LOX mediated increased lipid peroxide levels and associated with neuronal cell damage [32, 33]. It has been suggested that the level of 12/15-LOX is regulated by glutathione in ischemic stroke, and that decreased glutathione in ischemic brain tissue contributes to the activation of 12/15-LOX [34]. Both 12/15-LOX and ACSL4 are increased in ischemic stroke, so inhibiting ferroptosis by regulating lipoxygenase and ACSL4 has the potential to be a new target for the treatment of ischemic stroke.

3.3. Imbalance of antioxidant system and cerebral ischemia-reperfusion injury

Under normal conditions, cells possess a well-coordinated antioxidant system that plays a crucial protective role by effectively scavenging excessive reactive oxygen species (ROS) and preventing the onset of lipid peroxidation. The main antioxidant enzymes include glutathione peroxidase (GPX4), superoxide dismutase (SOD) and catalase (CAT), which are selenium-containing enzymes expressed in mammalian cells and play a central role in resistance to iron death. Glutathione (GSH), as an important non-enzymatic antioxidant, can react with peroxides to form non-toxic products, thereby alleviating the effects of oxidative stress.

GPX4 catalyzes the conversion of reduced glutathione (GSH) into oxidized glutathione (GSSG), which reduces phospholipid hydroperoxides (PL-OOH) to phospholipid alcohols (PL-OH), thereby protecting membrane lipids from oxidative damage. For GPX4 to effectively inhibit ferroptosis, proper functioning of the

GSH synthesis pathway is essential. Glutathione (GSH), as a small antioxidant molecule, changes from reduced to oxidized form under the action of glutathione peroxidase 4 (GPX4), while converting lipid peroxides to the corresponding alcohols. Inhibition of GSH synthesis and reduction of GPX4 activity promotes the accumulation of lipid peroxides, which leads to ferroptosis in cells [35]. It has been suggested that enhancing the function of the antioxidant system may be an effective strategy to suppress iron death, which provides a new direction for the treatment of related diseases [36, 37].

In addition, panthenol (CoQH2)/ferroptosis-suppressor-protein 1 (FSP1) system and tetrahydrobiopterin (BH4)/GTP cyclohydrolase 1 (GCH1) system are two novel and independent ferroptosis antioxidant systems independent of GSH/GPX4. The FSP1/CoQ10 pathway acts as an independent system, and the FSP1/CoQ10 pathway cooperates with the GSH/GPX4 pathway to inhibit iron death. However, the coenzyme Q10/iron death inhibitory protein 1 (FSP1) system plays an antioxidant role through coenzyme Q10 and is able to capture lipid peroxyl radicals and prevent excessive oxidation of membrane lipids. FSP1 converts ubiquinone (CoQ) to the lipophilic radical trapping agent CoQH2, preventing the peroxidation of unsaturated fatty acids in lipid bilayers [38]. As a result, cells will become more susceptible to ferroptosis when this system fails.

The GCH1/BH4 pathway represents an independent ferroptosis suppression system. As a potent membrane-associated radical-trapping antioxidant, BH4 selectively shields phospholipids containing diunsaturated fatty acyl chains, functioning either alone or synergistically with vitamin E. Additionally, BH4 indirectly suppresses lipid autoxidation by contributing to CoQ10 biosynthesis. GCH1 protein is involved in the regulation of ferroptosis by synthesizing BH4 to prevent the autoxidation of the acyl residues of polyunsaturated fatty acids [39]. However, ferroptosis occurs when the antioxidant defense system of the cell fails, resulting in the inability of lipid peroxidation products to be removed, thereby driving the progression of ferroptosis.

4. Potential therapeutic targets for iron death

Iron death is a ROS-dependent form of cell death driven by iron-mediated Fenton reactions, which generate reactive oxygen species that oxidize polyunsaturated fatty acid-containing phospholipids, ultimately inducing lipid peroxidation. Cellular defense against this process primarily involves two key antioxidant systems that catalyze lipid peroxide reduction. The occurrence of ferroptosis is regulated by several key molecules, and the following are some important regulators:

(1) GPX4 (glutathione peroxidase 4): GPX4 is an important antioxidant enzyme capable of inhibiting lipid peroxidation. Functional restriction of GPX4 promotes the development of iron death, and therefore, GPX4 is an important suppressor of iron death.

(2) System Xc- (Cysteine/Glutamate exchange system): System Xc- is a transporter responsible for intracellular and extracellular cysteine and glutamate exchange. Cysteine is a precursor for glutathione synthesis, whereas glutathione has ROS scavenging effects. When the function of System Xc- is impaired, glutathione synthesis is inhibited and ferroptosis occurs.

(3) FSP1 (Ferroptosis Suppressor Protein 1): FSP1 is a suppressor of iron death, which inhibits ferroptosis by reducing the occurrence of oxidative stress.

Iron metabolism, lipid metabolism and redox pathways regulate ferroptosis together, so currently therapeutic drugs mainly affect bioactive molecules of ferroptosis by targeting the core molecules of these three pathways, and small molecule inhibitors or inducers against ferroptosis have been widely used in preclinical

practice, and become new therapeutic hotspots by regulating iron death.

4.1. Iron chelators

Iron is a crucial factor in the induction of lipid peroxidation and iron death. Common iron chelators, such as deferoxamine (DFO), the potent antioxidants deferoxamine mesylate (DFOM), and 2,2-bipyridyl (2,2-BP), can inhibit ferroptosis by chelating intracellular non-heme iron, reducing free iron ion levels [40]. In a rat model, DFO treatment reduced brain injury following transient focal ischemia and improved neurological recovery [41].

It has been documented that iron chelators such as 2,2-dipyridyl and deferoxamine can inhibit injury in a rat model of ischemic brain injury [42, 43]. These studies further suggest that free iron and its related ferroptosis pathways play an important role in the regulation of neuronal cell injury, while iron chelators may inhibit the opening of iron damage-related signaling pathways by directly binding extracellular free iron. However, in terms of intervention of iron efflux, Ding *et al.* inhibited the increase of ferritin and the decrease of FPN protein in neural cells by down-regulating Hepcidin using small interfering RNA in a rat cerebral ischemia-reperfusion model [44]. This therapeutic approach mitigates the declining iron export capacity in neuronal cells and identifies novel therapeutic targets for cerebral ischemia-reperfusion injury intervention.

4.2. Antioxidants

Because both 12/15-LOX and ACSL4 expression are increased in ischemic stroke, ferroptosis can be inhibited and cell damage can be alleviated by regulating lipoxygenase and ACSL4. In a mouse model of transient global ischemia, treatment with the selective 5-LOX inhibitor zileuton significantly reduced levels of inflammatory cytokines and chemokines and ameliorated brain injury [45].

Lip-1 and Fer-1 have been identified as classical ferroptosis inhibitors used in vitro and in vivo. These two compounds are also categorized as radical-trapping antioxidants (RTAs). Xu *et al.* demonstrated that Fer-1 could upregulate GPX4 and reduce ROS levels by inhibiting the cyclooxygenase-2/prostaglandin E2 (COX-2/PGE2) signaling pathway, thereby suppressing ferroptosis in CIRI and improving neurological outcomes [46]. Baicalein, a polyphenolic compound, was shown to inhibit both iron accumulation and lipid peroxidation, thus alleviating brain injury following ischemia in mice [47].

In 2007, Lapchak *et al.* found that baicalein was able to inhibit 15-LOX, thereby reducing brain cell injury [48]. These findings not only facilitate the development of novel ferroptosis-inhibiting therapeutics, but also offer innovative approaches and promising treatment strategies for cerebral ischemia-reperfusion injury (CIRI). Intervention of lipid peroxidation through 12/15-LOX and upstream regulators such as ACSL4 represents a promising strategy to suppress ferroptosis and warrants further in-depth investigation.. The pharmacokinetic study of these inhibitors in vivo may become a future research hotspot.

4.3. Intervention of an antioxidant system

System Xc- and GPX4 play a key role in iron death, while regulatory intervention for system Xc- and GPX4 can play an important role in ischemic brain injury. GPX4 acts as an important endogenous antioxidant, and its up-regulation can inhibit iron death, thereby protecting neurons in the brain from injury. It has been demonstrated that the trace element selenium (Se), as an important component of GPX4, can promote GPX4 expression, and then inhibit the occurrence of ferroptosis [49]. In addition, carvacrol upregulated GPX4 in the ferroptosis pathway, thereby reducing lipid peroxide damage [50]. It has been demonstrated that compound

Naotaifang extract can increase the expression of GPX4 and SLC7A11, thereby inhibiting ferroptosis in nerve cells [51].

5. Prospects

The high morbidity, disability, and mortality of ischemic stroke still cause great pressure on families and society, and it has become urgent to explore the therapeutic target of ischemia-reperfusion injury. Iron death, as a novel programmed cell death mode, is involved in the pathophysiological process of ischemia-reperfusion injury in a variety of organs and has been confirmed by many scholars to play a key role in the process of ischemia-reperfusion injury. Although ferroptosis in cerebral ischemia-reperfusion injury is a hot research field, there are still many urgent problems to be solved. First, the pathological mechanisms by which ferroptosis is involved in and aggravates CIRI are complex and diverse, and the specific mechanisms need to be studied in depth. Secondly, the pathological progression of cerebral ischemia-reperfusion injury (CIRI) involves multiple cell death modalities, including ferroptosis, apoptosis, necrosis, and pyroptosis, which interact through various signaling pathways. In addition, the specific molecular targets of ferroptosis inhibitors in the context of CIRI remain unclear, raising important questions regarding how ferroptosis can be selectively modulated in this condition. Therefore, elucidating the specific regulatory mechanism of ferroptosis in CIRI and how to effectively regulate ferroptosis and clarify the target of ferroptosis inhibitors will provide new research ideas and treatment strategies for the treatment of cerebral ischemia-reperfusion injury.

6. Conclusion

Ferroptosis plays a critical role in cerebral ischemia-reperfusion injury (CIRI), yet its precise mechanisms and interactions with other cell death pathways remain unclear. Further research is needed to elucidate the specific regulatory mechanisms of ferroptosis in CIRI and identify targeted inhibitors, which could provide novel therapeutic strategies for mitigating ischemic stroke damage. Addressing these challenges will advance the development of effective treatments for CIRI.

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