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Review on Traditional Chinese Medicine with Treating Ischemic Stroke Based on Ferroptosis

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Abstract: ***Ischemic stroke is a cerebrovascular disease caused by local blood flow interruption, which is characterized by high mortality and disability. Its pathological mechanism is complex and includes multiple pathological factors and signaling pathways. Ferroptosis is a new therapeutic target discovered in recent years, as a new mode of death closely related to ischemic stroke. Based on the above background, this study aims to explore the mechanism of ferroptosis and the intervention effect of traditional Chinese medicine (TCM) on ferroptosis after ischemic stroke.***

Keywords: Ferroptosis, Ischemic stroke, Iron metabolism, Lipid peroxidation, Traditional Chinese Medicine.

1. Introduction

Ischemic stroke is also known as "stroke" in traditional Chinese medicine. It is the leading cause of death and disability in China. It will cause heavy economic and mental burdens to the family and society, and can also seriously affect the patient's quality of life [1]. According to statistics, the intravenous thrombolysis rate for acute ischemic stroke in China was only 5.64% in 2019-2020 [2]. The incidence of stroke in my country was 2.58% in 2019, showing an overall upward trend, and the mortality rate remains at a high level [3]. Age is an important risk factor for stroke, and the accelerated aging of my country's population indicates that effective prevention and treatment of stroke has become a research hotspot. Cell death is almost inevitable in the core area of cerebral ischemia, so the core treatment method in clinical practice is to open the blocked blood vessels as quickly as possible to save the ischemic penumbra. Recombinant tissue plasminogen activator (rt-PA) is one of the most important drugs for restoring blood flow [4]. However, intravenous thrombolytic therapy has strict restrictions on the onset time and contains many contraindications to thrombolysis. Only a small number of patients can restore blood flow through thrombolysis or surgery. Restoration of blood flow may also cause cerebral ischemia-reperfusion injury (CIRI), further aggravating brain tissue damage. The complex pathophysiological process of cerebral ischemia involves multiple mechanisms such as metabolic disorders, inflammation, blood-brain barrier disruption, and neuronal apoptosis. Ferroptosis is believed to play an important role in neurological diseases and will become a potential important therapeutic target for ischemic stroke. Traditional Chinese medicine is widely used in the treatment of ischemic stroke in clinic due to its advantages of high safety, multiple pathways and multiple targets. Studies have found that traditional Chinese medicine or its extracts can play a therapeutic role in ischemic stroke and inhibit ferroptosis by reducing iron overload, reducing oxide production, resisting lipid overoxidation and activating the antioxidant system. This article summarizes the occurrence and development of ferroptosis and the intervention effect of traditional Chinese medicine on ferroptosis after cerebral ischemia, providing a reference for the prevention and treatment of cerebral ischemia and the modernization of traditional Chinese medicine.

2. Ferroptosis Mechanism

Dixon [5] first proposed the concept of ferroptosis in 2012. The essence of ferroptosis is the process of cell death caused by excessive accumulation of iron ions, which induces lipid peroxidation and can be prevented by iron chelators or inhibition of cellular iron uptake. Ferroptosis is a cell death mode that is different from other known cell death modes such as necrosis, pyroptosis, and apoptosis in terms of morphology, biochemistry, genetics, and immunology. Ferroptosis is a morphological feature characterized by smaller mitochondria, increased membrane density, fewer or absent ridges, and even outer membrane rupture, with normal-sized nuclei but condensed chromatin; The biochemical characteristics are excessive deposition of intracellular iron ions and increased levels of membrane lipid peroxidation, and its occurrence is related to intracellular iron metabolism disorders, lipid peroxidation, and depletion of antioxidants.

2.1 Iron Overload Catalyzes Lipid Peroxidation

Iron is an important element for redox reactions in cells and is involved in many physiological processes such as metabolism, signal transduction and enzymatic reactions. Usually, cells maintain iron homeostasis by regulating the uptake, storage and release of iron. The balance of iron in cells is regulated by a variety of proteins. Extracellular free Fe^{3+} binds to transferrin (TF) to form a complex, which enters the cell through the transferrin receptor (TFR) on the cell membrane. The Fe^{3+} is reduced to Fe^{2+} and then stored in the cell in the form of ferritin or unstable iron pools. Ferroportin (FPN) is the only way for excess iron ions in cells to be excreted [6]. Excessive free iron ions in cells due to various reasons can induce the Fenton reaction to produce a large amount of ROS, consume antioxidants, and cause oxidative damage.

Studies have found that the ferroptosis inducer Erastin can induce cell death, and supplementation of exogenous iron increases the sensitivity of cells to Erastin [5]. The iron chelator deferoxamine (DFX) can prevent ferroptosis from occurring in cells by specifically binding to iron ions [7].

Lipid peroxidation, one of the core mechanisms of ferroptosis, is an important cause of cell death caused by cell membrane damage. Polyunsaturated fatty acids (PUFAs) are the main

raw materials for lipid peroxidation in ferroptosis [8]. Under the influence of reactive oxygen and multiple enzymes, the generated peroxidation product malondialdehyde (MDA) can damage proteins, DNA and other biological molecules [9]. Acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3) play important regulatory roles, mediating lipid peroxidation through enzymatic reactions [10]. During ferroptosis, ACSL4 and LPCAT3 are responsible for catalyzing the esterification of PUFAs, and polyunsaturated fatty acids are oxidized under the mediation of lipoxygenase (LOX) and cyclooxygenase (COX) to generate lipid peroxides [11]. Studies have shown that knocking down ACSL4 can alleviate ischemic brain damage, while promoting its expression will aggravate the damage and affect the synthesis of lipid peroxides [12]. The research of Karatas [13] showed that in animal models of cerebral ischemia, the expression level of LOX in the infarcted brain tissue increased, and inhibition of LOX could reduce neuronal mortality and promote recovery.

2.2 System Xc-/GSH/GPX4 Axis

There is a cystine/glutamate antiporter on the cell membrane, which is composed of two subunits, solute carrier family 7 member 11 (SLC7A11) and SLC3A2, namely System Xc-, which is the cell's defense system against oxidative damage. System Xc- can transport cystine into cells and transport glutamate out of cells. Cysteine that enters the cell is reduced to cysteine, which is then used to synthesize reduced glutathione (GSH). The raw materials for synthesizing the antioxidant GSH in cells include cysteine, glutamate, and glycine [10]. Glutathione peroxidase 4 (GPX4) is a peroxide degrading enzyme that has been shown to be a key protein in regulating ferroptosis. Its activity depends on the activity of glutathione and can enhance the ability of cells to resist ferroptosis. GSH, as a cofactor, participates in the clearance of lipid peroxides by GPX4 [14].

Rastin is a classic ferroptosis inducer. Studies have found that it targets System Xc-, weakening its ability to take up cystine. Due to the reduction of glutathione synthesis, GPX4 activity decreases and the cell's antioxidant capacity is reduced [15]. When glutamate is used to stimulate nerve cells, it can be observed that the influx of cystine decreases, resulting in cell death. Iron chelators can reverse this process, indicating that in the process of ferroptosis, System Xc- provides raw materials for the synthesis of glutathione, which is an important part of resisting ferroptosis [16]. The death of developing oligodendrocytes (OL) can cause periventricular softening. It has been reported that ferroptosis is involved in the process of periventricular softening. The use of Fer-1 (a synthetic antioxidant) can protect oligodendrocytes from death due to glutathione depletion [17]. Lipid peroxidation was observed in GPX4 knockout mice, suggesting that the protective effect of GPX4 on cells is achieved through anti-lipid peroxidation [18].

3. Ferroptosis and Ischemic Stroke

The pathological outcome of neuronal ferroptosis after cerebral ischemia is caused by the combined effects of various pathological factors, including oxidative stress, metabolic disorders, and inflammatory responses. The brain is characterized by being rich in iron and unsaturated fatty acids [19], which is why brain tissue is sensitive to ferroptosis. After cerebral ischemia, iron metabolism is impaired, which will cause an imbalance in the regulation of iron transporters and iron storage proteins. Studies have found that the levels of iron, TF, and TFR in the brain of patients with cerebral ischemia increase [20], prompting neurons to absorb iron and increasing the amount of free iron in cells, making cells more susceptible to ferroptosis. Inflammatory response after cerebral ischemia is another cause of iron overload. The inflammatory factor IL-6 can enhance the expression of hepcidin, a protein related to iron metabolism, through the JAK/STAT3 pathway, resulting in a decrease in the iron export protein FPN1 and a decrease in iron release, which will cause intracellular iron overload and thus lead to intracellular iron overload [21]. Excess iron generates more ROS through the Fenton reaction and increases the activity of LOX, further promoting lipid peroxidation and damaging cell structure. Under normal circumstances, System Xc- transports glutamate to the outside of the cell and cystine to the inside of the cell. However, after cerebral ischemia-reperfusion, glutamate and other excitatory amino acids flow out excessively, cystine is difficult to be taken up by cells, and cells lack cysteine, the precursor for synthesizing GSH, thereby inhibiting the GSH/GPX4 signaling pathway, depleting the antioxidants in the cell, and ultimately causing ferroptosis of neurons [22].

4. Traditional Chinese Medicine Regulates Ferroptosis

Ischemic stroke is classified as "stroke, hemiplegia, hemiplegia" and other diseases in traditional Chinese medicine. The main clinical manifestations include sudden coma, hemiplegia, crooked mouth and tongue, dysphasia and unilateral numbness.

Most doctors believe that the pathological factors of diseases are mainly caused by the obstruction of evil qi such as wind, fire, phlegm, blood stasis, and deficiency in the meridians. The fundamental pathogenesis lies in the disorder of qi and blood, which leads to disturbance of the brain and body, and dysfunction of the mind [23]. Although traditional Chinese medicine is widely used in clinical practice, its ingredients are complex and its mechanism of action is still unclear. Therefore, analyzing the mechanism of ferroptosis through traditional Chinese medicine theory is of great significance to clinicians and experimental research.

Based on "Toxin Damaging Brain Collaterals" Theory [24], it can be concluded that the key features of ferroptosis - iron overload and excessive accumulation of lipid peroxides - are the result of "toxins" caused by dysfunction of the internal organs, imbalance of yin and yang, and poor circulation of qi and blood. Ultimately, the "turbid toxins" damage the brain, manifested as the death of nerve cells and damage to nerve function.

4.1 Regulation of Ferroptosis by Chinese Herbal Compound or Extract

Chinese herbal extracts: Safflower yellow is a flavonoid derived from the traditional Chinese medicine safflower.

Studies have shown that Carthamin yellow can protect rats from cerebral ischemia-reperfusion injury by inhibiting the expression of NF-κB P65 in brain tissue and reducing the release of inflammatory factors [25]. Guo [26] found that Carthamin yellow pigment 40 mg/kg could inhibit the accumulation of iron ions and reactive oxygen species in the brain tissue of MCAO rats, while reducing the content of MDA. It enhanced the expression of GPX4, FTH1 and GSH, while inhibiting the activity of NF-κB/NLRP3 family-related factors in brain tissue, thereby reducing the concentrations of TNF-α, IL-1β and IL-6 and improving the inflammatory response.

Trillium tschonoskii Maxim (TTM) has the effects of calming the nerves, dispelling wind, and promoting blood circulation. Gao [27] found that 100 mg/kg of total saponins from Trillium tschonoskii Maxim (TST) can improve the learning and memory ability of rats, enhance antioxidant capacity, and reduce neuronal damage. Its ability to inhibit ferroptosis is related to the activation of GPX4 and SL7A11. It is reported that resveratrol, a natural antioxidant extracted from plants such as grapes and knotweed, has antioxidant, anti-inflammatory and anti-apoptotic effects and can significantly relieve brain edema, inhibit lipid peroxidation, reduce MDA and iron levels, and activate the P53/SLC7A11/GPX4 channel [28]. Another natural "estrogen" extracted from soybeans, Soybean isoflavones (SI), have been widely studied for their ability to cross the blood-brain barrier to exert neuroprotective effects. Rats pretreated with 120 mg/kg of SI showed that compared with the model group, the rats in the SI group had higher resistance to ferroptosis, more regular neuronal morphology, more complete blood-brain barrier structure, reduced Fe^{2+} and MDA levels, and increased GSH content and GPX4 expression [29]. Chrysin is a natural flavonoid compound that is widely present in propolis, skullcap, wood butterfly and other natural medicines. Shang [30] found that 50 mg/kg of chrysin significantly reduced the brain function of rats with transient cerebral ischemia. The contents of iron, malondialdehyde, and lipid peroxide in tissues and serum increased the mRNA and protein expression of SLC7A11 and GPX4, inhibited the expression of ACSL4, TFR1, and PTGS2, and improved iron metabolism disorders and oxidative damage. Salvia miltiorrhiza (SM) has the effect of promoting blood circulation and removing blood stasis. It contains multiple ingredients such as salvianolic acid B and tanshinone IIA. Ko's experiment [31] found that 200 mg/kg of Salvia miltiorrhiza extract reduced the long-term (28 days) mortality of tMCAO mice, increased taurine and total creatine content, inhibited ACSL4 expression, reduced the levels of lipid peroxidation products 4-HNE and MDA, and activated FPN1 to promote iron ion release. Ecdysterone (EDS) is the key active compound in Achyranthes bidentata Blume. Sun [32] created animal and cell models and found that EDS alleviated acute oxidative damage, and its mechanism was related to inhibiting ACSL4 to alleviate ferroptosis.

Compound traditional Chinese medicine: Buyang Huanwu Decoction is included in the book "Yilin Gaicuo" written by Wang Qingren, a famous doctor in the Qing Dynasty. It is composed of Astragalus as the main ingredient, supplemented by a variety of Chinese medicines for promoting blood circulation and removing blood stasis. It is based on the principle of invigorating qi and promoting blood circulation. It has been proven to improve blood circulation, resist inflammation, resist oxidative stress and promote nerve regeneration [33]. Cai [34] found that Buyang Huanwu Decoction intervention could alleviate pathological damage in brain tissue, reduce iron and MDA levels in brain tissue, increase GSH and GPX4 levels, and thus improve antioxidant capacity. Through network pharmacology methods, Zhao [35] discovered that the mechanism of Buyang Huanwu Decoction in intervening in ferroptosis in ischemic stroke is related to signaling pathways such as MAPK and PI3K-AKT. Tongqiao Huoxue Decoction has the functions of activating the SHH pathway to protect the blood-brain barrier (BBB) and inhibiting inflammation [36,37]. Ou [38] found that Tongqiao Huoxue Decoction can inhibit ferroptosis, and its mechanism is related to anti-oxidative stress, reducing ROS production, and promoting ACSL4 degradation.

Rao [39] used HSF1 and HSPB1 as the research entry point, and observed the iron content and iron metabolism-related proteins in the brain tissue of MCAO rats. He found that Naotai Fang may inhibit the expression of TFR1 by upregulating the HSF1/HSPB1 pathway, thereby reducing the absorption of iron by neurons. By increasing the expression of FTH1, the free iron ions in the cells are reduced, thereby inhibiting the iron death caused by lipid peroxidation caused by iron overload. Danloutablet (DLT) is a traditional Chinese medicine that has been shown to have a good therapeutic effect in protecting the cerebral vascular endothelium. Liu [40] speculated that COX2, GPX4 and SLC7A11 are key targets based on Network pharmacology and bioinformatics analyses. In in vivo and in vitro experiments, ischemia and hypoxia can upregulate the levels of COX2, GSSG and MDA, and DLT can reverse such changes.

4.2 Physical Therapy Regulates Ferroptosis

Acupuncture has a long history in China as a safe and effective treatment method. It is often used in the clinic to treat stroke-related diseases and their sequelae. Previous clinical research data have shown that acupuncture can improve the neurological function of stroke patients by improving blood flow and regulating related factors [41]. Experimental studies have shown that acupuncture can reduce infarct volume and improve neurological function scores after IS [42]. Mitochondrial damage is considered to be a morphological feature of neuronal ferroptosis. Shangguan [43] performed electroacupuncture treatment on the Zusanli and Quchi points of MCAO rats and found that the neurological function of the rats in the electroacupuncture group was improved compared with that in the model group. Transmission electron microscopy showed that the mitochondria of the cortical neurons in the ischemic side of the rats in the model group showed typical ferroptosis features, such as morphological atrophy, increased mitochondrial membrane density, and a significant reduction in vertebrae. The mitochondrial structure of the rat neurons treated with electroacupuncture was more complete, revealing the inhibitory effect of acupuncture on neuronal ferroptosis. Wu [44] performed electroacupuncture pretreatment on the Baihui point, Fengfu point, and Dazhui point of rats and found that the electroacupuncture pretreatment had a significant therapeutic effect on CIRI. Compared with the model group, the rats in the electroacupuncture group The expression of GSH and GPX4

is increased, and the expression of ACSL4, TFRC, 15-LOX and COX-2 is downregulated, thereby inhibiting neuronal ferroptosis. Wang [45] used iron metabolism as the starting point and observed that in rats with cerebral ischemia-reperfusion injury, iron input increased and iron excretion decreased. However, the "Xingnao Kaiqiao" method increased FPN1 expression, inhibited TFR1 and DMT1 levels, and reduced iron overload in the ischemia-reperfusion area of brain tissue, thus having an anti-iron overload effect.

5. Summary

At present, symptomatic treatments such as thrombolysis in clinical practice cannot completely relieve the pain of patients. Neurological damage and complex mechanisms after ischemic stroke are still a major problem. Ferroptosis involves many signaling pathways, genes, cytokines, which can also interact with each other. Only some regulatory targets can be described here. This article explains the mechanism of ferroptosis and connects it with various pathological factors after ischemic stroke, suggesting that ferroptosis mediates neurological damage in cerebral ischemia, providing a new direction for the treatment of cerebral ischemic damage. Traditional Chinese medicine is expected to become an effective means of treating ischemic stroke due to its unique advantages of comprehensive treatment and multiple targets, but its intervention mechanism is not yet fully clear. This study found through literature review that whether it is a traditional Chinese medicine compound or an extract, the regulatory effect of traditional Chinese medicine on various key targets of ferroptosis has been reported in cell experiments and animal experiments, providing new research ideas and treatment basis for the treatment of cerebral ischemic injury with traditional Chinese medicine.

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