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Research Advances in Traditional Chinese Medicine Treatment for Ischemic Stroke via Regulation of Programmed Cell Death

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Abstract: ***Ischemic stroke (IS) is an acute cerebrovascular event caused by cerebral vascular occlusion, leading to cerebral tissue ischaemia and hypoxia, which in turn triggers neuronal cell death and corresponding neurological deficits. Multiple forms of programmed cell death contribute to its pathological progression. Traditional Chinese medicine exerts effects through multiple pathways, targets, and levels. In recent years, an increasing number of studies have demonstrated that traditional Chinese medicine can improve stroke outcomes by regulating programmed cell death. This paper reviews relevant research with the aim of providing new insights and directions for the prevention and treatment of IS using traditional Chinese medicine.***

Keywords: Ischemic stroke, Programmed death, Chinese medicine monomer, Compound Chinese Medicines**.**

1. Introduction

Ischemic stroke (IS), as a prevalent disorder of the central nervous system, accounts for approximately 80% of all cerebrovascular diseases. This condition not only ranks as the second leading cause of death globally but also stands as the primary factor contributing to long-term functional impairment. Furthermore, it is recognised as the second most common cause of dementia. The extensive programmed cell death in the IS is a pivotal factor underpinning the high rates of mortality and disability. During the progression of IS, the excessive activation of multiple cell death pathways induces and amplifies neuroinflammation and oxidative stress, creating a vicious cycle that perpetually damages the ischaemic penumbra and thereby accelerates disease progression. Therefore, research into the regulation of post-IS programmed cell death represents a key therapeutic target for mitigating brain injury, promoting neurological recovery, and improving patient outcomes [1].

Traditional Chinese medicine, adopting a holistic approach, exerts multi-targeted, multi-pathway, and multi-level effects, with a long history of treating ischaemia. Increasing research indicates that traditional Chinese medicine can exert neuroprotective effects by regulating programmed cell death in brain cells following ischaemia, such as pyroptosis, autophagy, apoptosis, and ferroptosis [2]. This paper reviews the impact of post-stroke cellular programmed death on pathological progression, summarising recent domestic and international research on traditional Chinese medicine's neuroprotective effects through regulating post-stroke cellular programmed death. It aims to provide evidence for the clinical application and further investigation of traditional Chinese medicine's regulation of cellular programmed death.

2. Cellular Programmed Cell Death Following Ischaemic Stroke and Its Implications

2.1 Apoptosis and Its Impact on Ischaemic Stroke

Apoptosis is a genetically regulated form of programmed cell death and one of the most fundamental mechanisms of cellular demise. Its characteristic morphological features include a reduction in cell volume, fragmentation of the nucleus, and condensation of chromatin, ultimately leading to cellular inactivation. As a vital physiological regulatory process, apoptosis plays a pivotal role in the development and growth of organisms. However, in pathological conditions, either insufficient or excessive apoptosis will lead to disease progression. Apoptosis primarily follows two core signalling pathways: one is the intrinsic pathway, also known as the mitochondrial pathway. Its pivotal step involves the oligomerisation of pro-apoptotic proteins (such as Bak/Bax) within the B-cell lymphoma 2 (Bcl-2) family, which subsequently triggers a caspase cascade reaction, ultimately resulting in cell death. The other pathway is the extrinsic route, also known as the death receptor pathway, which relies on a caspase cascade activated by membrane receptors such as tumour necrosis factor receptor (TNFR) 1, death receptors, or Toll-like receptors (TLRs). Following ischaemic stroke, cerebral cells undergo ischaemia and hypoxia, activating the expression of related apoptotic genes and inducing neuronal cell death through these pathways. Within the ischaemic core, neuronal death is predominantly necrotic; however, in the ischaemic penumbra, apoptosis is the predominant pathway leading to delayed neuronal loss. Consequently, effective inhibition of apoptotic signalling pathways is crucial for preserving the penumbra and improving stroke outcomes.

2.2 Cytotoxicity and Its Impact on Ischaemic Stroke

Pyroptosis is a form of programmed inflammatory cell death characterised morphologically by cellular swelling, nuclear condensation with intact nuclear envelope, and random chromatin aggregation. Upon inflammasome activation, it promotes cleavage of the GSDMD protein—a member of the pyroptosis-related membrane domain (PRMD) family—by Caspases (primarily Caspase-1/4/5/11). The resulting N-terminal domain forms pores in the cell membrane. This pore formation induces cell lysis through osmotic pressure, releasing inflammatory mediators such as IL-1β and IL-18,

thereby powerfully driving the inflammatory response. Pyroptosis primarily occurs within the ischaemic penumbra, where the release of substantial inflammatory factors constitutes a pivotal mechanism in driving neuroinflammation following ischaemia. Neuroinflammation is intrinsically linked to the onset and progression of ischaemia, representing a critical pathophysiological mechanism in this condition. Following an ischaemic stroke, damage-associated molecular patterns (DAMPs) released from damaged or necrotic cells mediate subsequent caspase activation and GSDMD cleavage. This process ultimately leads to pore formation in the cell membrane, facilitating the release of mature inflammatory cytokines IL-1β and IL-18 into the extracellular space, thereby executing pyroptosis. Following ischaemic stroke, pyroptosis exacerbates stroke injury through a vicious cycle of 'inflammation-death-reinflammation'. Pyroptotic neurons and glial cells release mature inflammatory cytokines such as IL-1β and IL-18, which further induce pyroptosis in surrounding healthy cells. This continuously amplifies inflammatory signals, leading to irreversible neurological damage [3].

2.3 Autophagy and Its Impact on Stroke

Mitochondrial autophagy serves as the core mechanism for cellular quality control of mitochondria, ensuring the normal functioning of cellular energy metabolism by eliminating dysfunctional mitochondria. The PINK1-Parkin pathway represents the most classical mechanism for inducing mitochondrial autophagy. Its key hallmarks include the stable accumulation of PINK1 on the mitochondrial membrane, the recruitment and activation of Parkin, and the colocalisation of autophagy adaptor proteins (such as p62/SQSTM1) with LC3-II. The severity of ischaemic stroke is closely correlated with the level of mitochondrial autophagy activation. Early, moderate clearance serves as a cellular self-protective mechanism; however, when injury is excessive or ischaemia persists, this process becomes unregulated, transforming from a protective mechanism into a destructive process that exacerbates damage by accelerating neuronal apoptosis [4].

2.4 Ferroptosis and Its Impact on Ischemic Strok

Ferroptosis is an iron-dependent form of programmed cell death, characterised cytologically by mitochondrial shrinkage, increased membrane density, and reduced or absent cristae. Its fundamental biochemical hallmark is the loss of activity in the core antioxidant enzyme GPX4 under conditions of intracellular iron overload. This failure prevents the repair of lipid peroxides, triggering a lethal cascade of lipid peroxidation that ultimately disrupts the cell membrane structure, leading to cell death. Following ischaemic stroke, ferroptosis significantly impacts prognosis by exacerbating oxidative damage to neurons. The underlying mechanism of this process primarily involves the deposition of iron within the ischaemic core and penumbra, in conjunction with the occurrence of lipid peroxidation, which subsequently leads to the rupture of cell membranes and the expansion of infarct size. Consequently, the targeting of the ferroptosis pathway has emerged as a potential therapeutic strategy for mitigating brain injury in stroke [5].

3. Traditional Chinese Medicine Intervenes in Ischemic Stroke by Modulating Programmed Cell Death

IS is fundamentally a network-related disorder, with the occurrence of post-stroke cascade reactions being the primary cause of its poor prognosis. In recent years, an increasing number of studies have demonstrated that regulating multiple forms of programmed cell death following IS can improve its prognosis. Traditional Chinese medicine (TCM), with its multi-targeted and multi-pathway effects, has a long history of treating stroke. Recent research has revealed that TCM can regulate programmed cell death after IS to enhance its prognosis [6].

3.1 Active Constituents of Traditional Chinese Medicine

Baicalin, one of the primary active constituents of the traditional Chinese medicinal herb Scutellaria baicalensis, belongs to the class of natural flavonoid compounds. Research indicates that baicalin exerts neuroprotective effects by inhibiting oxidative stress through promoting the deacetylation of SLC7A11, and by regulating the Bcl-2/Bax/Cyt-C/Caspase-3 pathway to suppress apoptosis [7]. Rhodiolol is the primary active component derived from Rhodiola rosea, belonging to the phenylethanol glycoside class. Research indicates that cells in an OGD/R model treated with rhodiolol exhibit reduced infarct size and improved histopathology. This effect is primarily mediated by rhodiolol's inhibition of apoptosis (manifested as enhanced Caspase-3 cleavage and downregulation of the Bax/Bcl-2 ratio) and its reduction in malondialdehyde (MDA) formation [8]. Methyl lotus seed heart alkaloid constitutes the primary component of lotus seed hearts. Research has demonstrated that methyl lotus seed heart alkaloid mitigates neuroinflammation and oxidative stress damage induced by ischaemia-hypoxia by targeting the pyroptosis pathway. It achieves this through inhibiting the activation of the Caspase-1/ASC/GSDMD signalling axis and reducing the maturation and release of IL-1β and IL-18 [9]. Berberine (berberine hydrochloride) is an isoquinoline alkaloid extracted from traditional heat-clearing Chinese herbs such as Coptis chinensis. Modern pharmacological research has revealed its diverse pharmacological activities, including hypoglycaemic, lipid-regulating, anti-inflammatory, and cardiovascular protective effects, demonstrating multi-targeted action characteristics. Research indicates that berberine inhibits the activation of the NF-κB signalling pathway, thereby downregulating the expression of IL-1β and IL-18—key pyroptosis-inducing factors transcriptionally regulated by NF-κB—ultimately mitigating neuronal pyroptosis [10]. Research indicates that baicalin may enhance cellular survival by activating the AMPK pathway, thereby mitigating mitochondrial dynamic impairment following ischaemic stroke and regulating mitochondrial autophagy [11]. Research indicates that crocin can inhibit the accumulation of Fe^{2+} and reactive oxygen species (ROS) in cortical neurons of MCAO model rats, while enhancing the expression of GPX4, TfR1, and FTH1 in the brain and elevating serum levels of GSH and SOD. This suppresses ferroptosis following ischaemic stroke, thereby exerting neuroprotective effects [12].

3.2 Compound Chinese Medicines

Buyang huanwu decoction is a classical formula for treating stroke, possessing the efficacy of invigorating qi, promoting blood circulation, and unblocking meridians. Modern research indicates that its neuroprotective effects are associated with the regulation of apoptosis-related proteins, significantly increasing the Bcl-2/Bax protein ratio in brain tissue and upregulating the expression level of the transcription factor Creb1 [13]. Zhachong Shisanwei Pills constitute a classic Tibetan medicinal formula for treating rheumatic arthralgia and hemiplegia following stroke. Research indicates that these pills effectively inhibit apoptosis by upregulating the Bcl-2/Bax ratio, significantly suppressing the activation of Caspase-9 and Caspase-3, and inhibiting the cleavage of poly (ADP-ribose) polymerase (PARP), thereby improving the prognosis of ischaemic stroke [14]. Taohong Siwu decoction is formulated by enriching the traditional Four Substances decoction with peach kernels and safflower, significantly enhancing its capacity to invigorate blood circulation and resolve blood stasis. Research indicates that this decoction suppresses cell pyroptosis by downregulating NLRP3, Caspase-1, ASC, and GSDMD expression levels in MCAO/R rats, thereby exerting neuroprotective effects [15]. Xiao-xu-ming decoction is a commonly used traditional Chinese medicine formula for ischaemic stroke, possessing effects of dispelling wind and fortifying the body's vital energy, promoting blood circulation and resolving stasis, and unblocking the meridians. Research indicates its neuroprotective effects may primarily stem from regulating the mitochondrial p53 signalling pathway, which helps enhance membrane potential and mitigate ischaemia-induced mitochondrial structural damage [16]. Nortifang may be employed in the treatment of ischaemic stroke. Research indicates that Nortifang effectively ameliorates neurological damage in rat models of ischaemic stroke, with its mechanism closely associated with the inhibition of ferroptosis. Naotaifang concurrently downregulates the TFR1/DMT1 pathway to reduce iron uptake whilst upregulating the SCL7A11/GPX4 pathway to enhance antioxidant capacity. This dual-pathway synergistic reduction in intracellular iron levels exerts a neuroprotective effect [17].

4. Summary and Outlook

The pathophysiological mechanisms of ischaemic stroke exhibit characteristic networked features, manifesting as extensive dynamic interactions and cascading reactions between diverse molecular pathways and cellular events. The excessive activation of programmed cell death following stroke constitutes a significant factor influencing its prognosis. Traditional Chinese medicine exerts its effects through multiple targets, pathways, and levels of action. It can improve stroke outcomes by regulating the excessive activation of programmed cell death following ischaemia. However, it remains unclear whether it can improve stroke outcomes by influencing interactions that regulate programmed cell death in different cells, and there are few high-quality clinical trials examining how traditional Chinese medicine modulates programmed cell death following ischaemia. In future research, multi-omics integrated analysis may be combined with molecular interaction detection techniques to investigate the mechanisms by which traditional Chinese medicine modulates interactions between different cell death pathways during the treatment of inflammatory bowel disease. At the clinical research level, high-quality studies can be conducted through precise patient recruitment combined with multicentre collaboration to enhance the influence of traditional Chinese medicine in stroke treatment. In summary, traditional Chinese medicine exerts its effects through multiple targets, pathways, and levels, demonstrating significant value in the management of ischaemic stroke.

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