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Review

Research Progress on Basic Fibroblast Growth Factor (bFGF) and Ischemic Stroke

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Abstract Basic fibroblast growth factor (bFGF) is a multifunctional growth factor that promotes the differentiation of endothelial progenitor cells into vascular endothelial cells, facilitating the process of angiogenesis and the establishment of collateral circulation. Current studies have shown that bFGF can promote neuron survival and synaptic growth, acting as a mitogen for neurons, glial cells, and capillary endothelial cells, and it can counteract the neurotoxicity caused by excitatory amino acids and other harmful substances, thereby protecting neurons. This article reviews the research progress on bFGF and ischemic stroke, aiming to provide a theoretical basis for clinical treatment by fully understanding the role of bFGF in stroke.

Keywords: basic fibroblast growth factor; bFGF; ischemic stroke; progress.

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Introduction

Cerebrovascular disease is the third leading cause of death in Chinese residents, after cancer and heart disease【1】. Cerebrovascular disease includes ischemic stroke and hemorrhagic stroke, with ischemic stroke (or cerebral infarction) being one of the major diseases causing death and disability. Large vessel occlusion-induced ischemic stroke is often severe with a poor prognosis, placing a significant medical burden on individuals, families, and society【2】. Cerebral infarction mainly results from arterial occlusion, leading to a decrease in cerebral blood perfusion, causing ischemia and hypoxia in brain tissue within the affected blood supply area, as well as damage to neurons and glial cells【3】. Due to the high incidence, disability, mortality, and recurrence rates of cerebral infarction, it severely affects the health and quality of life of Chinese residents and brings significant economic burdens to families and society. The key to treating cerebral infarction is early revascularization to salvage the ischemic penumbra【4】. Current treatments include intravenous or arterial thrombolysis, mechanical thrombectomy, acute angioplasty, and anticoagulation therapy【5】. The selection of appropriate treatment strategies is crucial for the prognosis of cerebral infarction. Additionally, good collateral circulation is associated with greater benefits from thrombolysis and endovascular therapy【6】. Collateral vessels between intracranial and extracranial arteries can be established, including branches of the external carotid artery, internal carotid artery, and ophthalmic artery. Collateral circulation plays a critical role in maintaining perfusion in ischemic stroke, extending the therapeutic time window, and preventing irreversible damage【7】. Although significant progress has been made in the clinical diagnosis and treatment of cerebral infarction, brain

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damage in many patients cannot be fully reversed, leaving varying degrees of sequelae, which seriously affect the patient's work and quality of life【8】. Hence, collateral circulation plays a key role during the onset, progression, and recovery of cerebral infarction, and bFGF can promote angiogenesis, neurogenesis, and the development of collateral circulation. This article aims to summarize the research progress on bFGF in ischemic stroke, providing theoretical guidance for developing neuroprotective and therapeutic drugs for cerebral infarction.

bFGF and FGF

Fibroblast growth factors (FGFs) are a family of polypeptide molecules that act by binding to specific receptors on the cell membrane. The FGF family comprises at least 23 members, including FGF1 to FGF23. FGF1 (aFGF) and FGF2 (bFGF) are the most studied members, with aFGF having an acidic isoelectric point and bFGF being basic. They exhibit different activities in cell proliferation, angiogenesis, neural cell growth, survival, and wound healing【9】.

(Additional content includes sections on bFGF's role in angiogenesis, neural regeneration, and its specific functions related to ischemic stroke, among others.)

bFGF and Angiogenesis

bFGF has potent angiogenic activity and can promote vascular formation and neovascularization in cancers and chronic inflammatory diseases【17】【18】. Its reparative functions are based on its ability to stimulate cell proliferation and migration, promote angiogenesis, regulate inflammation, maintain cell stability, promote dedifferentiation, protect cells from apoptosis, and stimulate the expression of proteases【19】. Angiogenesis is crucial for the repair process, and fibroblast growth factors (FGF), vascular endothelial growth factors (VEGF), nerve growth factors, and others have anti-apoptotic and anti-inflammatory effects, promote stem cell survival, vascular formation, and neurogenesis, making them potential drugs for neuroprotection【20】. bFGF can induce a complex "angiogenic phenotype" in endothelial cells in vitro and produce an effective neovascular response and angiogenesis signal in vivo due to close crosstalk between pro-inflammatory agents【21】. While bFGF has not been conclusively proven as a physiological or pathological regulator of angiogenesis, it may operate through two mechanisms: (1) at the onset of angiogenesis, cells may release bFGF, which then stimulates new blood vessel formation in a paracrine manner, or (2) paracrine factors such as VEGF may stimulate the production of bFGF, which subsequently promotes bFGF-dependent autocrine activity【22】.

Additionally, bFGF may interact with various endothelial cell surface receptors, including tyrosine kinase receptors, heparan sulfate proteoglycans, and integrins, to exert its pro-angiogenic effects. bFGF can induce the expression of numerous inflammation-related genes in endothelial cells, including pro-inflammatory cytokines/chemokines and their receptors, endothelial adhesion molecules, and components of the prostaglandin pathway【23】.

In both in vivo and in vitro models of mammalian angiogenesis, research has shown that porcine adventitia-derived extracellular matrix (PAdv ECM) scaffolds have high utility for cardiovascular applications. In the presence of a bFGF inhibitor, the angiogenic potential of PAdv ECM scaffolds is completely abolished, strongly suggesting that bFGF is a key angiogenic signal

and a powerful regenerative factor in the adventitial ECM【24】.

Angiogenesis typically remains stable over time. However, in atherosclerosis, vascular endothelial cells leave their quiescent state and enter an activated state. bFGF can specifically stimulate vascular smooth muscle cells, inducing proliferation and dedifferentiation【25】. Since atherosclerosis is an inflammatory disease, angiogenesis may promote the growth of atherosclerotic lesions. While early clinical trials involving bFGF have shown that it can promote the formation of new collateral vessels to alleviate ischemia symptoms, bFGF-stimulated angiogenesis poses a dilemma, as it can lead to negative vascular effects such as atherosclerosis【26】. Studies have shown that knocking out the 18-kDa bFGF isoform significantly reduces atherosclerosis formation, diminishes aortic plaques, decreases macrophage infiltration, and suppresses oxidative stress in high-fat diet-fed mice【27】.

For the adverse effects of bFGF-induced angiogenesis, research has found inhibitors that can address this issue. Angiogenesis involves the formation of new blood vessels from pre-existing vessels and plays a key role in various physiological and pathological conditions. When the FGF2/FGFR1 pathway is highly expressed, VEGF-B can inhibit angiogenesis by suppressing this pathway【28】. Thus, future studies may focus on bFGF inhibitors to prevent the side effects of angiogenesis.

bFGF and Neural Regeneration

The neurovascular unit is not only an anatomical structure but also a functional unit of interaction and damage response between neurons, glial cells, and blood vessels under normal conditions【29】. bFGF's key functions in the nervous system include its roles in neurogenesis, axonal growth, developmental differentiation, and plasticity in adulthood【30】. By binding to heparan or heparan sulfate proteoglycans, bFGF activates FGFR, inducing diverse effects across different tissues and organs, including effective angiogenesis and important roles in central nervous system (CNS) differentiation and function. During development, high levels of bFGF are detected from the onset of neurodevelopment【31】.

In one experiment, combining a bFGF slow-release system with biodegradable nerve conduits showed that this system enhanced neurovascular formation and Schwann cell proliferation in a rat model【32】. Additionally, studies have found that FGF significantly enhances pMAPK signaling in the developing mouse cortex and converts cell fate from neurons to astrocytes via the MAPK pathway【33】. Thus, bFGF promotes neural regeneration in the CNS.

bFGF also plays a role in peripheral nerve regeneration. Specific extracellular matrix (ECM) conditions may help deposit neurotrophic factors, including FGFs, which aid peripheral nerve regeneration【34】. bFGF promotes axonal growth, impacting the regeneration of peripheral nerves through its influence on nerve cells, Schwann cells, and fibroblasts【35】.

To evaluate the effect of bFGF on peripheral nerve regeneration, nerve conduits coated with bFGF, SDF-1 gelatin, and SDF-1/bFGF gelatin showed that SDF-1 and bFGF dual-controlled release conduits could promote peripheral nerve regeneration【36】. Furthermore, studies have shown that the combination of bFGF and brain-derived neurotrophic factor (BDNF) enhances nerve recovery after peripheral nerve injury【37】. bFGF has also been found to induce nerve regeneration and sensory recovery following sciatic nerve crush injury【38】. Nerve regeneration can influence limb regeneration due to growth

factors such as BMP7, bFGF, FGF8, and SHH expressed in limb-targeting nerves【39】.

Improving synaptic plasticity is an effective method for alleviating neuropathic pain, and electroacupuncture has been found to upregulate bFGF expression【40】. FGF signaling plays a crucial role in regulating the proliferation and self-renewal of neural stem cells in vitro and in vivo【11】.

bFGF and Ischemic Stroke

Ischemic stroke induces coordinated endogenous neurogenesis and angiogenesis, contributing to brain repair. The underlying mechanisms that enhance endogenous neurogenesis and angiogenesis after stroke are becoming increasingly understood. Cerebral infarction promotes the proliferation of neural stem cells through the generation of various growth factors, including basic fibroblast growth factor (bFGF)【41】. In the developing central nervous system, bFGF may regulate the generation of neurons and astrocytes, as cells capable of producing both neurons and astrocytes contain FGFR1 protein and mRNA. FGFR1 has been shown to mediate the bFGF regulatory system in the central nervous system. During cortical development, bFGF plays an important role in cell proliferation and neurogenesis, with its biological function executed through downstream signaling pathways that bind to fibroblast growth factor receptors (FGFRs). The regulation of bFGF is primarily achieved through binding to FGFR1【42】.

bFGF is expressed during angiogenesis, neurogenesis, and neuronal survival. It decreases the permeability and apoptosis of human brain microvascular endothelial cells (HBMECs) subjected to oxygen-glucose deprivation/reperfusion (OGD/R) attacks by activating FGFR1 and the ERK pathway【43】. Previous research has shown that neurogenesis is not the only factor considered in stroke recovery; angiogenesis has also been proven to play a crucial role in improving neurological function post-stroke. More importantly, recent evidence suggests a highly probable interaction or interdependence between stroke-induced neurogenesis and angiogenesis. Additionally, pericytes in the central nervous system (CNS) have been recognized as an indispensable component of the neurovascular unit【41】.

Increased expression of platelet-derived growth factor receptor β (PDGFRβ) in CNS pericytes after cerebral ischemia has been observed. bFGF upregulates PDGFRβ expression, potentially enhancing PDGFRβ-mediated pericyte function following cerebral ischemia【44】. In the middle cerebral artery occlusion (MCAO) stroke model, the expression of bFGF and FGFR1 is induced in the ischemic penumbra following ischemic injury, exerting potent multi-potent trophic effects on central nervous system cells (including neurons, glial cells, and endothelial cells). Specifically, it promotes the survival of various brain neurons in vitro and protects these neurons from several neurotoxins, including excitatory amino acids, hypoglycemia, and calcium ion carriers【45】. For example, the intraventricular administration of bFGF can reduce infarct size after focal cerebral ischemia in rats.

Increasing experimental evidence shows that bFGF plays a key role in neurogenesis and angiogenesis during stroke recovery. In animal studies, bFGF treatment significantly improved neurobehavioral outcomes and produced better histological results in rats treated three months after ischemia. The study concluded that pre-ischemia treatment with bFGF increased the number of newborn neurons in the subventricular zone (SVZ) in aged rats【46】. In clinical studies examining angiogenic promoters and inhibitors in

the plasma of stroke patients receiving tPA therapy, FGF levels were found to correlate closely with stroke severity. Thus, FGF levels can be used as a reference indicator to estimate infarct size and clinical prognosis【47】.

Furthermore, bFGF promotes angiogenesis following ischemic stroke. bFGF mRNA and protein expression increases following neuronal injury, while endothelial cells can selectively delete the miR-15a/16-1 cluster, enhancing post-stroke angiogenesis and increasing ipsilateral ischemic brain blood flow by promoting vascular remodeling and stimulating the formation of new functional vessels. The mechanism behind this could be that endothelial cell-specific deletion of the miR-15a/16-1 cluster upregulates angiogenic factors such as VEGFA, FGF2, and their receptors VEGFR2 and FGFR1【48】.

Recent research has shown that enhancing endogenous neurogenesis is a potential therapeutic strategy for treating cerebral infarction, and bFGF treatment may benefit ischemic stroke by promoting the proliferation and neuronal differentiation of endogenous neural stem cells and progenitor cells (NSPCs)【49】. Another study found that an adeno-associated virus transduction system can induce bFGF expression, and using an adeno-associated virus as a vector can promote the expression of distal precursor and immature neuronal genes in the peri-infarct cortical region following cerebral infarction【50】.

In a mouse model of cerebral ischemia/reperfusion (I/R) injury, bFGF administration improved spontaneous activity and inhibited endoplasmic reticulum (ER) stress induced in the hippocampal CA1 region. The neuroprotective effects of bFGF involve the suppression of ER stress in ischemic oxidative damage models and in PC12 cells damaged by oxidative stress, indicating that bFGF has therapeutic potential in certain CNS diseases, including ischemic injuries【51】. In clinical studies evaluating the efficacy of bFGF treatment for ischemic stroke, patients were given intramuscular injections of recombinant bFGF. The results showed that bFGF treatment repaired damaged brain cells, reduced the size of cerebral infarctions, and improved the neurological symptoms of ischemic stroke patients【52】. In an experiment conducted by Lü Weili and colleagues on the expression of extracellular signal-regulated kinases (ERK) after cerebral ischemia-reperfusion in rats, it was found that bFGF reduced neuronal apoptosis in the cortex and hippocampus after cerebral ischemia and protected neural cells. The mechanism of action is likely through the MAPK protein kinase pathway, which increases ERK expression【53】. Since bFGF is an effective mitogen for stem cells, bFGF-enhanced neurogenesis contributes to cognitive recovery following traumatic brain injury (TBI)【54】. This property may be applied to the treatment of neurodegenerative diseases, including Alzheimer's disease (AD). As our understanding of neural stem cells and brain development deepens, developing strategies that harness neurogenic capabilities in these regions to repair damaged brains may become more feasible.

Summary and Prospects

Current research largely confirms the close relationship between bFGF and ischemic stroke, but its role is dual-sided. On the one hand, bFGF promotes angiogenesis and neural regeneration, but on the other hand, it may also facilitate the formation of atherosclerosis, which is detrimental to cerebral infarction recovery. In the future, further research on bFGF-driven angiogenesis and neural repair is needed to demonstrate its full potential. In the event of ischemic brain injury, appropriate timing and delivery methods to upregulate bFGF levels may have a

positive impact on the prognosis of ischemic stroke. In the coming years, deeper biochemical understanding of bFGF is expected, and as its mechanism of action becomes clearer, various novel bFGF-mediated drugs will likely enter clinical use, benefiting patients with cerebral infarction and providing new therapeutic approaches for ischemic stroke treatment.

Conflict of Interest

None.

Acknowledgments

None.

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