

Progress on the study of fibroblast growth factors as novel therapeutics in post-stroke cognitive impairment

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Abstract

Post-stroke cognitive impairment (PSCI) is one of the most common complications after stroke, which severely affects the daily life abilities and social function of patients. Fibroblast growth factor (FGF), as a regulator of homeostasis, participates in the regulation of cell metabolism and hormone secretion, and can increase cerebral blood flow and promote nerve repair which improves PSCI. Here, we will conduct a review on the typing, characteristics, and mechanism of action of FGF to further understand its function and mechanism in PSCI.

Keywords: Fibroblast growth factor; cognitive impairment, stroke

Introduction

Fibroblast growth factors (FGFs) are a class of multi-functional polypeptide molecules, including 23 family members, which are greatly distributed in various parts of the body. FGFs are involved in wound healing, angiogenesis, and neural stem cell proliferation and differentiation, which exert different biological effects under different physiological conditions and influence the whole process of wound healing. Post-stroke cognitive impairment (PSCI) refers to cognitive impairment that appears within six months after stroke events, which varies depending on the different characteristics like the type, volume, number, location, and severity of stroke, including multiple infarctions, cerebral infarction in strategic locations, subcortical ischemia, and cerebral hemorrhages. FGFs increase blood flow to the ischemic penumbra, inhibit vascular endothelial cell apoptosis, thereby mediating early inflammatory response after cell injury, increasing later active repair capacity, promoting angiogenesis and neurological functional recovery, which improve neurological function after stroke. The application of FGFs may open new avenues for PSCI treatment.

The emergence and current treatment of PSCI

Stroke is a common and frequently-occurring disease in the elderly population of the world, it is the second leading cause of death worldwide, affecting about 13.7 million people and leading to about 5.5 million deaths each year [1]. As societies age and stroke risk factors become generalized, the incidence and prevalence of stroke continue to increase and show a rapid increasing trend in low-income groups [2]. In China, there are over 2 million new stroke cases every year, among which people aged 20-45 years rise from 12.9% to 18.6% in the last 30 years [3]. Besides, the age-standardized attributable mortality rate has decreased by 36.2% over the same period, which results in a disability rate as high as 63.1%, leading to the highest disability rate of all diseases [4]. Around 1/3 of stroke survivors exist with varying degrees of PSCI, which severely affects the daily life and social function of patients [5].

The etiology and pathogenesis of post-stroke cognitive impairment are very complex, and are the result of multiple factors. Currently, it is mainly believed to be related to the interaction between vascular injury and neurodegeneration. Neurorestorative progression in stroke is often related to neurogenesis, angiogenesis, and synaptic plasticity. The neovascularization at the periphery of stroke lesions increases cerebral blood flow of ischemic border zone, which provides oxygen and nutrients for ischemic region and improves and restores neurological function [6]. Therefore, increasing angiogenesis may become a novel direction for PSCI treatment.

Currently, the drug treatment of PSCI mainly includes cholinesterase inhibitors (donepezil), calcium channel an-

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tagonists (nimodipine), and excitatory amino acid receptor antagonists (memantine, a NDMAR antagonists). Clinical research has demonstrated that donepezil improves overall functioning and self-care ability of patients, showing a role in improving mild and moderate cognitive dysfunction [45]. Nimodipine has been reported to have the effects of selectively dilating cerebral blood vessels and increasing cerebral blood flow, which can improve cognitive function of PSCI [7]. A previous study revealed that memantine improves cognitive impairment and mental status of patients with vascular dementia, but the role of memantine on PSCI needs further verification [8]. At present, in addition to drug treatment, the intervention including cognitive rehabilitation training and transcranial magnetic stimulation also exhibits certain efficacy for PSCI treatment. However, cognitive rehabilitation training is not only affected by patients' compliance and therapists' ability level, but also limited by therapeutic equipment such as transcranial magnetic stimulation, which leads to the uncertain effect of rehabilitation training. Therefore, it still lacks a certain effective intervention for PSCI treatment [9], and the role of FGF in repair related angiogenesis has been demonstrated in many studies. For example, targeted FGFR1 and FGFR2 knockout in mouse endothelial cells inhibits angiogenesis during wound healing, and it is expected to become a new clinical therapeutics for PSCI [10].

The definition, types, and mechanism of action of FGFs

Definition and types

FGFs, as a class of polypeptide growth factors, have multiple biological functions, including cell growth and differentiation, angiogenesis, embryonic development, wound healing, and mediating metabolism. FGFs have conserved core structure β -trilobate fold, that consists of 12 strands of β -thin sections arranged around the central axis into 3 similar lobes, of which 6 strands form an antiparallel β -barrel fold [11]. According to differences in sequence homology and development features, the FGF family can be classified into 6 subfamilies. Most FGFs are autocrine and paracrine factors, which mediate tissue and organ generation and metabolism during embryonic development [12]. FGFs are a group of structurally related polypeptide mitogen, including 23 different members. Except for acidic FGFs (aFGF, FGF-1) and basic FGF (bFGF, FGF-2), FGF family also includes int-2 (FGF-3), proto-oncogene products (FGF-4, FGF-5, FGF-6), keratinocyte growth factor (KGF, FGF-7), and androgen-induced growth factors (AIGF, FGF-8, GAF, FGF-9, FGF-10). Members of FGF family promote fibroblast proliferation and activation by stimulating collagen accumulation and endothelial cell differentiation [13]. Therefore, FGFs stimulate angiogenesis, thereby playing a critical role during cell repair. Fibroblast growth factor (FGF) and its receptor (FGFR) are conserved transmembrane growth factor receptors that are widely distributed in all vertebrate tissues, and FGFs and FGFRs share signal homology between their respec-

tive groups as well as with other signaling molecules. In humans, there are five known FGFRs, known as FGFR1 – FGFR4 and FGFR5 (also known as FGFR5). FGFR1 – FGFR4 is a typical growth factor receptor tyrosine kinase with an extracellular immunoglobulin (Ig) -like domain and an intracellular tyrosine kinase domain, while FGFR5 lacks an intracellular kinase domain. Different members of the FGF family bind to four different FGF receptors (FGFR1-FGFR4) and function in complementary ways. FGFR closely resembles other signaling receptors, including vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and other receptor tyrosine kinases. However, there are important differences between individual signaling molecules that can precisely control the entire process, including development, cell survival, differentiation, motility, angiogenesis, and carcinogenesis [14].

Characteristics

A majority of FGFs have a very broad mitogenic spectrum, which have multifarious activities and act as neurotrophic and angiogenic factors in vivo. FGFs are widely distributed in vascular endothelium, adrenal cortex, and fibroblast. FGF-5, FGF-8, FGF-9, and FGF-10 subfamilies combine extracellular matrix heparan sulfate and drive autocrine/paracrine mitogenic signaling axis to promote cell proliferation, while FGF-19, FGF-21, and FGF-23 do not directly promote proliferation [15]. The different members of FGF family bind to four distinct FGF receptors (FGFR1, 2, 3, 4) and act in a complementary manner, thereby producing multiple biological phenomena, such as development, differentiation, migration, survival, cell division and proliferation, and wound healing [16]. The majority of FGFs, as autocrine and paracrine factors, mediate tissue and organ generation during embryonic development, interact with heparin or heparin sulfate, enhance the activity and generation of brain cells and peripheral nerve cells, further exerting a role on PSCI repair [12]. FGFs maintains the activity and function of damaged cells surrounding lesions by inducing chemical activity and promoting angiogenesis, thereby reducing cell necrosis and improving ischemic/hypoxic injury states. FGFs further promote cell survival, which provide conditions for the maintenance and rehabilitation of injured tissue function and are effective in the rehabilitation of consciousness, language, and muscle strength. Thus, FGFs may play a role in PSCI and improve its prognosis [14].

The effects of FGFs on PSCI FGF-1 (aFGF)

Fibroblast growth factor-1 (FGF-1) is a typical member of the FGF family, which participates in various biological processes, including cell growth, proliferation, survival, and development. FGF-1 stimulates cellular signaling pathways like PKC/PLC γ , PI3K/Akt, and Ras/MAPK by combining and activating specific receptor FGFR [17]. Uchida *et al.* [18] found that the continuous expression of Fgf1b gene in the CA regions of the hippocampus after learning was related to the increase of memory strength, and Fgf1b was expressed specifically in the CA regions of

the hippocampus, indicating that the CA regions may be related to the establishment of memory strength. In addition, the levels of FGF-1 in the hippocampus were reduced by human intervention after intense memory training. The instantaneous memory of experiment subjects was not affected, but the long-term memory was decreased. Therefore, FGF-1 may be a necessary condition for the transformation of memory from instantaneous plasticity to strong enduring plasticity. Chang *et al.* [19] compared 97 cases of Alzheimer's disease (AD) patients carrying genomic variants of different FGF-1 and compared the effects of different genotypes on episodic memory impairment and hippocampus atrophy (HA). Next, they found that the clinicopathological relationship of AD exists genotype effects, and FGF-1 plays a role in episodic memory (EM) deficits. FGF-1 promotes neurodegenerative related neurons and synaptic dysfunction and enhances the invasion capacity of fibroblasts by promoting neuron survival, inhibiting neurotoxicity, and preventing nerve injury, further transforming to functional neurons and promoting the recovery of PSCI.

Hamed *et al.* [20] first explored the effects of acute intravenous administration of adipose-derived mesenchymal stem cells transfected with FGF-1 into mice with transient experimental ischemic stroke. The neurological functional recovery in cerebral ischemic regions, infarct size, and the expression of FGF-1 protein were determined, and the results found that FGF-1 treatment significantly improves neurological function, increases the intensity of FGF-1 protein in perinfarct area, while the infarct size and the apoptotic index are markedly decreased. All in all, acute intravenous administration of FGF-1 may become a new way for the treatment of PSCI in the future. Also, a genetic study revealed that FGF-1 may be involved in AD due to the obvious association of single nucleotide polymorphisms in FGF-1 gene, and the number of FGF-1-immunolabeled neurons decreases in AD patients, indicating that FGF-1 deficiency may be related to the pathophysiology of AD [21]. The increase of FGF-1 levels exerts a significant effect on glial cells and capillary proliferation, neurite outgrowth, and synapse formation. Therefore, FGF-1 may promote neuron and capillary repair, and improve its prognosis.

FGF-2 (bFGF)

Basic fibroblast growth factor (bFGF), as a member of FGF superfamily, plays a critical role in angiogenesis and neuron survival. FGF-2 may promote neural stem cells in the subgranular zone of hippocampal dentate gyrus and the subventricular zone of the lateral ventricle to generate new neurons. The function of FGF-2 is integrated into mature neural networks to promote the growth, differentiation, maintenance, and survival of new neurons and synapses, or to stimulate the growth of new blood vessels needed for brain tissue vascularization. New neurons may contribute towards stress response and adaptation, learning, and memory due to the sensitivity and high plasticity to environmental stimuli. The abnormal neurogenesis and the impairment of growth factor function, especially

hippocampus, are linked to the appearance of neurologic emotion and neurocognitive symptoms [22]. Lin *et al.* [23] explored the protective mechanism of FGF-2 on BBB by measuring the permeability of endothelial cell monolayers induced by oxygen and glucose deprivation/reoxygenation (OGD/R) and found that FGF-2 significantly reduces the permeability of primary human brain microvascular endothelial cell (HBMEC) monolayers induced by OGD/R and decreases the transendothelial electrical resistance. These data demonstrated that recombinant FGF-2 has a protective effect on BBB disruption in traumatic brain injury mice, suggesting that FGF-2 is a potential therapy for treating BBB damage in nervous system diseases. Seo *et al.* [24] investigated angiogenesis in ischemia/hypoxia-induced mouse brain damage model and measured FGF-2 expression in frontal cortex, striatum, and cerebellum. They further found that the levels of FGF-2 were significantly upregulated in the frontal cortex after 8 weeks of treatment, supporting that FGF-2 promotes endogenous angiogenesis and neurobehavioral functioning, which may be applied to the treatment of PSCI or other nervous system diseases.

FGF-10

FGF-10, a member of the FGF family, is a multifunctional growth factor, which has been extensively studied in the repair and wound healing after cerebral ischemic injury [25]. Li *et al.* [26] found that injection of FGF-10 into the lateral ventricle of middle cerebral artery occlusion (MCAO) mice significantly reduces infarct area (from 32% to 20%) and improves the neurological deficits, and the mechanism is related to decreased apoptosis. Also, FGF-10 improves cerebral blood flow in ischemic region and may have reparative effects on PSCI, thus being applied in the treatment of PSCI. Fang *et al.* [27] found obvious cerebral hemisphere edema in the ligation side 24 h after ligation of common carotid artery in neonatal mice to stimulate hypoxic/ischemic encephalopathy (HI). Also, they further demonstrated that intraperitoneal injection of FGF-10 markedly reduced brain edema, proving that FGF-10 treatment can significantly reduce brain damage after HI. Chen *et al.* [28] simulated spinal cord injury by resection of partial spinal cord in rats and performed immunofluorescence staining on the spinal cord tissues near the lesions. Further, they found that central gray matter and peripheral white matter are visibly damaged and anterior horn motor neuron loss is obvious in the traumatic spinal cord injury (SCI) group. While the necrotic cavity around the injured site was reduced and anterior horn motor neuron loss was decreased in the FGF-10 treatment group. These evidences indicate that FGF-10 has a protective effect on severe injury after SCI, suggesting that FGF-10 is a potential therapy for the treatment of central nervous system damage and has a certain application value for PSCI.

FGF-13

FGF-13 is a member of FGF homologous factor (FHF) subfamily, which is widely expressed in the central ner-

vous system. FGF-13 is located on X chromosomes, and FGF-13 deficiency results in Forssman-Lehmann syndrome. Therefore, FGF-13 is considered as a related gene of intellectual development. During brain development, FGF-13 mediates neuronal cell growth and development through stabilizing tubulin [29]. Poulian *et al.* [30] found delayed neuronal migration and severe mental retardation in FGF-13 knockdown mice, indicating that FGF-13 plays an essential role in establishing neural circuits in the cerebral cortex and achieving cognitive function. Yuan *et al.* [31] demonstrated that FGF-13 is essential for excitation/inhibition balance of synapse in FGF-13 deficiency and replication mouse model. FGF-13-related neural circuits control the emotion and cognitive behavior of autism and mental retardation, which exerts different effects on mediating emotion and cognitive behavior. Therefore, the dysregulated FGF-13 expression may have a broad effect on neuronal and synaptic homeostasis and nervous system functions, which serves a major role in PSCI. Voltage-gated sodium channels (VGSCs) in the axon initial segment (AIS) is critical in initiating action potentials effectively. Pablo *et al.* [32] employed gene knockout strategies and revealed that FGF-13 binds to VGSC in hippocampal

neurons to restrict its expression in somatic cell surface. Besides, experimental data indicated that FGF-13 and FGF-14 acts in concert to regulate VGSC polarization, further supports effective action potentials initiation, regulates outbreaks in the action potentials of neural cells, and stimulates the incidences of cognitive function, showing a certain positive influence on improving PSCI.

FGF-21

FGF-21 is a member of the endocrine FGF family [33], which has powerful polymetabolic effects [34]. Accumulating evidence has indicated that FGF-21 is involved in tissue injury and repair under various pathological conditions [35]. Jiang *et al.* [36] found that metabolic disorders improved in stroke mice after 14 days of daily treatment with recombinant human fibroblast growth factor 21 (rFGF-21) in a diabetic mouse model. Importantly, there was a significant reduction in white matter damage and neurological deficits between 6 h and 14 d of treatment with rFGF-21, indicating that FGF-21 has a protective effect on nervous system and may improve the prognosis of PSCI. Wang *et al.* [37] induced a mouse model with a high-fat diet and found that subcutaneous injection of

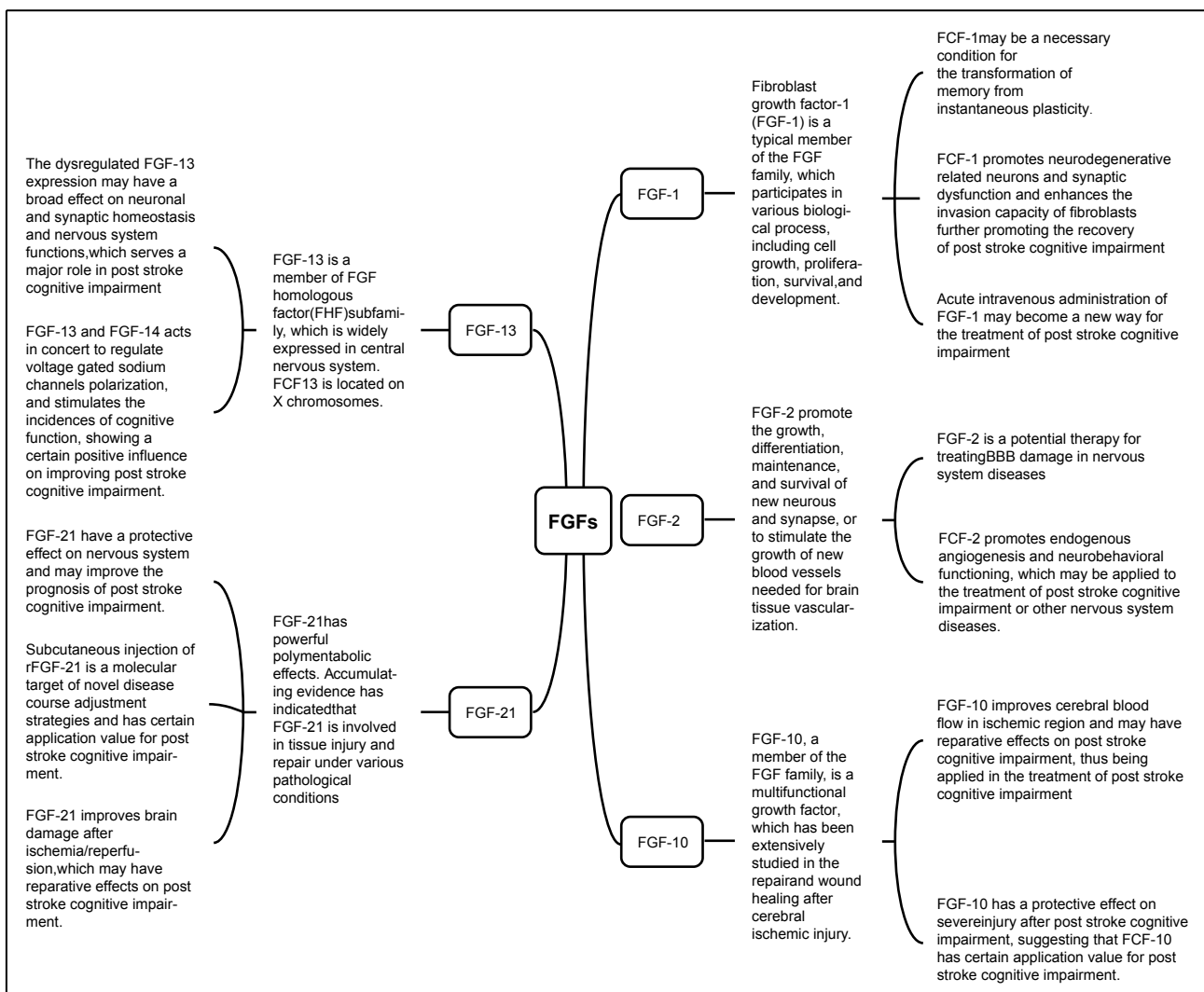


Figure 1. The effects of different FGFs on PSCI.

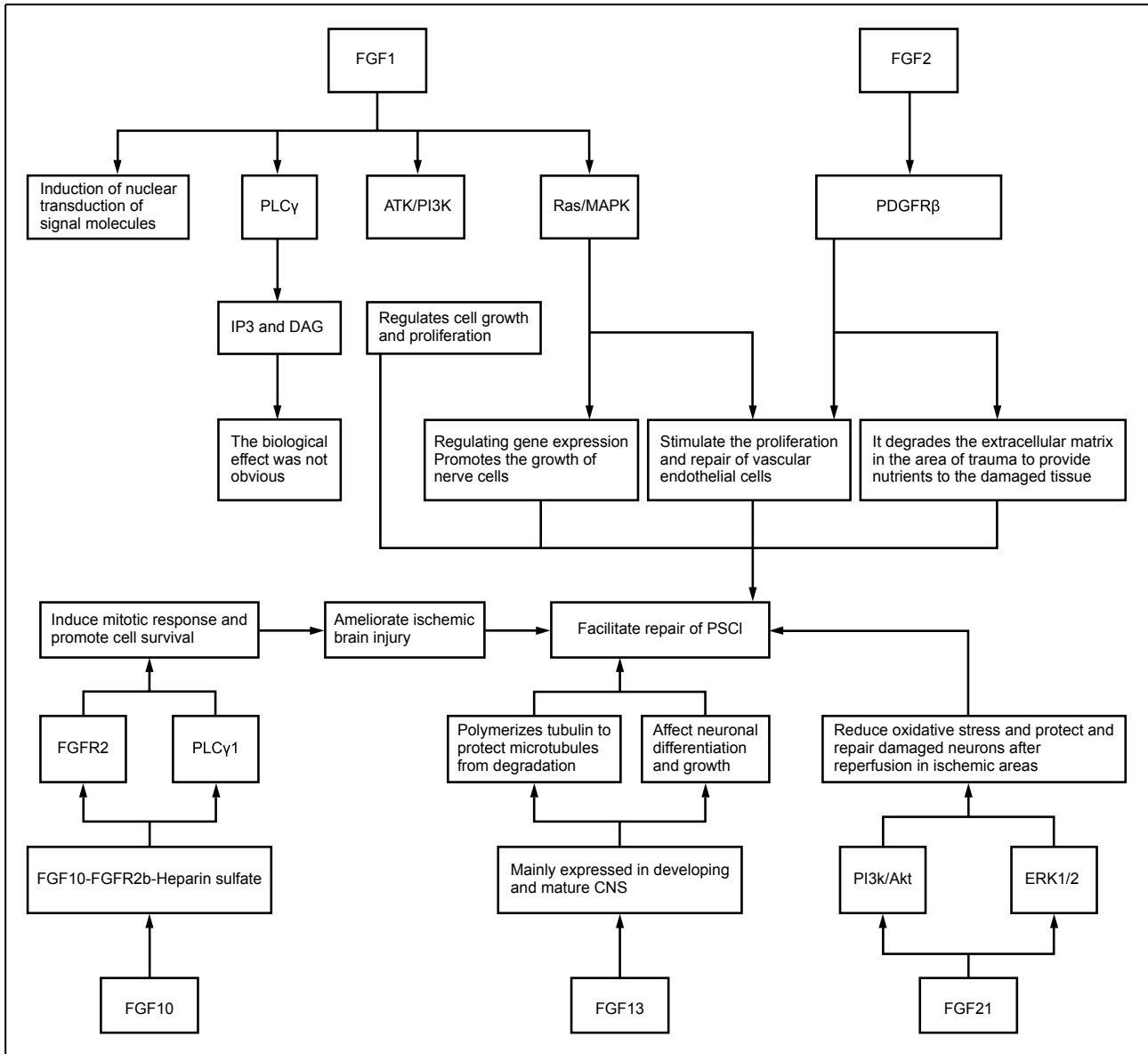


Figure 2. The pharmacological effects and mechanisms of FGFs in PSCI.

rFGF-21 significantly increases FGFR1 concentration in cerebrospinal fluid and enhances the levels of phosphorylated FGFR in brain tissues, suggesting that rFGF-21 can cross the blood-brain barrier (BBB) and functionally activate the FGF21-FGFR1 signaling pathway in the brain. Further, rFGF-21 can systematically inhibit inflammation, slow down the occurrence of brain edema, have a long effective window period in the injured site, and quickly activate the intracranial pathway, which is a molecular target of novel disease course adjustment strategies and has certain application value for PSCI. Yang *et al.* [38] in a study of ischemia/reperfusion rat model, revealed that FGF-21 decreases oxidative stress, protects and repairs injured neurons after ischemia/reperfusion, improves brain damage by activating ERK1/2 and PI3K/Akt signaling pathways, which may have reparative effects on PSCI. The related results are detailed in [Figure 1](#) and [Figure 2](#).

The mechanism of action of FGFs on improving PSCI

Brain function and plasticity rely on the establishment of neural circuits during development. Neuronal morphogenesis, cell migration, and synapse formation defects in the cerebral cortex cause mental retardation, cognitive deficit, and other symptoms [39]. Neural stem cells are mainly distributed in the subventricular and the dentate gyrus, and which actively proliferate in the subventricular and the dentate gyrus after traumatic brain injury, suggesting that the brain has the potential for the repair of injured cells and alleviates brain damage by promoting neural stem cell proliferation and division in these regions. The main method is to promote neural stem cell proliferation through mitogenic factors [9]. FGF is a type of effective stem cell mitogen involved in multiple cellular processes like stem cell differentiation, proliferation, anti-apoptosis, and angiogenesis. Secreted FGFs (FGF1-10 and FGF15-23) contain an N terminal signal peptide that promote the formation of axon branching by enhancing microtubules-severing. Prior study has demonstrated that injection of

FGF into damaged areas induces the proliferation and division of injured neural stem cells [46]. The injection of FGF into the animals obviously improve cognitive function, suggesting that FGF may promote PSCI recovery [40]. BBB disruption after stroke causes intracranial inflammatory response, brain edema, and central neurological impairment, thereby inducing PSCI. Huang *et al.* [41] found that FGF protects the integrity of BBB, controls the degree of brain edema, and repairs damaged nerves, thus reducing the occurrence of PSCI and improving its prognosis. It has been reported that supplementation with exogenous FGF-1, FGF-2 protects neuronal cells, increases transmitter release, thereby effectively alleviating the development of PSCI [42]. FGF-9 suppresses the apoptosis of striatal cells and ameliorates PSCI development through regulating ERKs signaling pathway [43]. Gimeno *et al.* [44] found that FGFs are expressed in various regions including the thalamus and the interthalamic boundary zone at the early neural development of mice and expressed in cochlea and midbrain at later stages. Further, they revealed that FGFs regulate the proliferation and survival of dorsal cell populations via mediating the mitogen responsiveness of dorsal neuronal precursor, suggesting that FGFs may also have the properties of morphogenesis in brain. Until today, there are plenty of studies supporting that FGF-related factors can maintain and repair injured nerve cells after stroke, and delay the progression of stroke and improve its prognosis, thereby preventing/improving PSCI [1].

Conclusions

The main cause of PSCI is impaired nervous system function resulted from the ischemia and hypoxia of brain cells. Until present, only intravenous thrombolysis is relatively effective for post-stroke rehabilitation but with a narrow time window, which limits its application. Currently, there still lacks effective measures to prevent and treat PSCI clinically, so it is of great significance to explore new drugs to ameliorate neuronal cell damage after stroke and to reduce the incidence of PSCI. FGFs control cells and hormones that are involved in metabolism. Also, FGFs have multiple targets of pharmacological effects in the treatment of ischemic stroke, including directly promoting neuronal survival, enhancing angiogenesis, preventing BBB from damage, and mediating microglia regulation, which can be utilized as effective drugs for stroke treatment and PSCI prevention. Although FGFs have not been applied in clinical practice, lots of animal experiments have proved that FGFs exert a role in nervous system rehabilitation, vascular repair, and synapses establishment. Consequently, FGFs are expected to be novel therapeutics for the prevention and treatment of PSCI in the future and are able to elevate the life quality of patients after stroke.

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