

Mechanisms of Postischemic Stroke Angiogenesis: A Multifaceted Approach

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Abstract: Ischemic stroke constitutes a significant global health care challenge, and a comprehensive understanding of its recovery mechanisms is imperative for the development of innovative therapeutic strategies. Angiogenesis, a pivotal element of ischemic tissue repair, facilitates the restoration of blood flow to damaged regions, thereby promoting neuronal regeneration and functional recovery. Nevertheless, the mechanisms underlying postischemic stroke angiogenesis remain incompletely elucidated. This review meticulously examines the constituents of the neurovascular unit, ion channels, molecular mediators, and signaling pathways implicated in angiogenesis following stroke. Furthermore, it delves into prospective therapeutic strategies informed by these factors. Our objective is to provide detailed and exhaustive information on the intricate mechanisms governing postischemic stroke angiogenesis, thus providing a robust scientific foundation for the advancement of novel neurorepair therapies.

Keywords: ischemic stroke, angiogenesis, signaling pathways

Introduction

Stroke ranks as the second primary cause of mortality worldwide.¹ Between 1990 and 2019, the incidence of stroke increased by 85.0%, while mortality increased by 43.0%.² Particularly in China, the burden of stroke is notably severe and represents a major threat to the health and lives of its citizens. According to data from 2020, the overall prevalence of stroke in China was 2.6%, with an estimated 17.8 million adults having experienced a cerebrovascular event.^{3,4} As the population ages, the incidence of stroke is projected to increase by 55.58%, the prevalence by 119.16%, and the mortality by 72.15% by 2030 compared to 2019 levels.⁵ Although the mortality rate of ischemic stroke has decreased in recent decades,⁶ more than half of survivors experience lasting disabilities, resulting in significant societal and economic burdens.⁷ Ischemic strokes are predominantly caused by thrombosis or embolism, which disrupts cerebral blood flow and leads to regions of hypoxia and glucose deprivation, referred to as the ischemic penumbra. In the absence of prompt reperfusion, neuronal cells within the penumbra undergo apoptosis, which contributes to the formation of the ischemic core.⁸ The onset of acute ischemic stroke rapidly inflicts substantial damage to cerebral tissue and neurons.⁹ Contemporary therapeutic strategies for acute ischemic stroke include intravenous thrombolysis, endovascular thrombectomy, and neuroprotective agents.¹⁰

Recombinant tissue plasminogen activator (rt-PA) remains the sole FDA-approved treatment for acute ischemic stroke, providing an approach for the dissolution of cerebral blood clots and reestablishment of cerebral perfusion, yielding prompt therapeutic outcomes.¹¹ Despite its effectiveness, the overall success rate for early thrombolytic intervention is disappointingly low. This low success rate is attributed to delays in administering treatment during the critical initial phase of stroke and the associated heightened risk of cerebral hemorrhage.¹² Furthermore, strokes caused by occlusions in major intracranial vessels, such as the internal carotid, middle cerebral, and basilar arteries, are

particularly recalcitrant to intravenous rt-PA treatment and have an unfavorable prognosis.¹³ Although endovascular thrombectomy improves recanalization rates in patients with ischemic stroke due to large artery occlusions, it has limited efficacy in cases of small vessel blockages. Moreover, surgical intervention can only be applied to specific patients.¹⁴ Neurological recovery depends on angiogenesis and neural plasticity. The development of new blood vessels is regulated by the coordinated actions of multiple angiogenic factors rather than a single factor. Although the last two decades have seen the preclinical assessment of numerous neuroprotective compounds, their translation into clinical practice has not been realized.¹⁵ The trajectory of neurofunctional recovery is intricately linked to angiogenesis and neuroplasticity.¹⁶ Present-day research is thus concentrated on the development of optimal neurorestorative pharmacological therapies.

In the field of ischemic stroke research, the phenomenon of angiogenesis is receiving increased scrutiny. Angiogenesis not only catalyzes axonal growth and neurogenesis but also plays an indispensable role in the rehabilitation of neurological function following stroke.¹⁷ Therefore, strategically enhancing the cerebrovascular system by promoting angiogenesis is viewed as a viable approach for stroke recovery.¹⁸ The relationships between the complex molecular mechanisms of poststroke neovascularization and potential therapeutic targets remain unclear. In addition, the long-term effects of induced angiogenesis, potential risks of abnormal vascular growth, and the absence of proven clinical applications of these insights pose significant challenges. No neurorehabilitation model grounded in angiogenesis research has effectively made the transition from experimental settings to clinical application. In recent years, an increasing number of studies on angiogenesis and stroke have been published, but the relationship between the molecular mechanisms mediating angiogenesis and potential therapeutic targets has received less attention and lacks a systematic summary. Further analysis of the relationship between the two would be beneficial in providing directions for further research.

Compared with the literature, our article focuses on the molecular mechanisms of poststroke angiogenesis, and by reviewing the literature, we propose possible therapeutic targets for poststroke angiogenesis to provide directions for future research.

Methods

Literature searches were conducted using the PubMed, Scopus, Web of Science, and Google Scholar databases. The search terms included “ischemic stroke”, “stroke”, “cerebral ischemia”, “angiogenesis”, and “neurovascular unit”, along with various combinations of these terms. The inclusion of studies was based on the relevance of the titles and abstracts to the research theme. Articles whose titles and abstracts did not align with the theme were excluded. This review did not impose any time restrictions, covering the literature published up to December 2023.

Ischemic Stroke and Angiogenesis

Acute ischemic stroke arises from the formation of an intravascular thrombus, precipitating a marked decrease in blood flow to the cerebral cortex and affecting collateral circulation. This phenomenon culminates in brain tissue necrosis and the manifestation of localized neuronal deficits.¹⁹ Ischemic conditions subject various cerebral regions to differing levels of blood supply diminution, which in turn induces ischemic injury within both the ischemic core and the surrounding penumbra.²⁰ The ischemic core is characterized by profound ischemia, resulting in the irreversible demise of cells and extensive neuronal damage. In contrast, penumbral cells, while compromised, do not suffer complete death and thus retain the capacity for recovery, positioning them as prime targets for therapeutic strategies.²¹ As such, the penumbra is increasingly recognized for its potential for recovery and has emerged as a focal point in the treatment of ischemic stroke.²² The intravenous delivery of rt-PA along with mechanical thrombectomy represent the gold standard reperfusion treatments and significantly increase the likelihood of functional recovery during the initial phase poststroke. Nevertheless, the sole reliance on immediate reperfusion therapy postischemic stroke is an oversimplification of treatment needs. The scope of care must be extended to encompass functional recovery in the subacute and chronic phases of stroke recovery.

Angiogenesis, the physiological process characterized by the proliferation and migration of endothelial cells (ECs), orchestrates the formation of a sophisticated capillary network, leading to the branching of new blood vessels from preexisting vessels.^{23,24} Angiogenesis is strongly associated with ischemic stroke, and angiogenesis is involved in stroke

prognosis. In the acute phase of stroke, angiogenesis can aggravate neurological injury,²⁵ and angiogenesis plays a protective role;²⁶ in the subacute and chronic phases, angiogenesis plays a protective role and improves the prognosis.^{27,28} The mechanism underlying the role of angiogenesis in different periods of stroke is not fully understood, and further in-depth studies are needed.

Poststroke, the ischemic penumbra releases angiogenic factors to initiate and regulate angiogenesis. Emerging evidence suggests that cerebral ischemia can induce transient angiogenesis; however, this phenomenon is not stable over the long term.²⁹ Current therapeutic strategies aim to maintain and promote the long-term stability of angiogenesis to ensure the maturation of new vessels. Enhanced angiogenesis is closely linked to the prolonged survival of stroke patients and improved outcomes in stroke mouse models.^{30,31} The initiation of angiogenesis occurs within the first 24 hours after stroke onset and can persist for weeks to months,³² significantly contributing to the repair of the compromised cerebrovascular system. Contemporary evidence increasingly supports the notion that angiogenesis, along with neurogenesis postischemic stroke, are integral to functional recovery.³³ Historical research dating back three decades established that angiogenic processes commence between 3 and 4 days following an ischemic insult in experimental models.³⁰ More recent analyses of brain tissues from stroke patients have revealed a notable augmentation in microvascular density within the penumbral zones compared to contralateral unaffected areas, a phenomenon directly associated with enhanced survival rates.³⁴ Consequently, the amplification of angiogenic activity is recognized as a crucial strategy for bolstering recovery outcomes and facilitating functional rehabilitation poststroke.³⁵

Tissue plasminogen activator (tPA) thrombolysis and endovascular thrombectomy are the two primary treatments used during the acute phase of ischemic stroke; these treatments reduce mortality and improve functional outcomes at three months poststroke.³⁶ Clinical studies have shown that tPA treatment can rapidly and directly reopen blocked vessels by dissolving thrombi and restoring blood flow.³⁷ tPA converts plasminogen to plasmin, which regulates angiogenesis directly by degrading matrix molecules and indirectly by activating extracellular matrix metalloproteinases and angiogenic growth factors, thereby beneficially influencing poststroke recovery.³⁸ Another mechanism of tPA-induced angiogenesis involves the use of fibrin as a cofactor to activate plasmin, whose degradation products stimulate EC proliferation and migration and enhance the angiogenic activity of vascular endothelial growth factor (VEGF).³⁹

Endovascular thrombectomy can lead to vascular remodeling, a crucial process in neovascularization after stroke. This process is influenced by various factors released under ischemic conditions, which can promote angiogenesis, potentially improving outcomes after stroke. Although evidence supporting increased angiogenesis is available, this process is primarily associated with reperfusion and tissue repair processes rather than direct evidence that thrombectomy itself promotes neovascularization.⁴⁰ Thus, further research is needed to specifically explore the direct effects of thrombectomy on angiogenesis.

The recovery of neurological function postischemic stroke involves multiple regenerative processes, namely, angiogenesis, neurogenesis, and axonal sprouting.⁴¹ These mechanisms work synergistically to facilitate neurological restoration. Astrocytes, for example, play multifaceted roles in promoting angiogenesis, neurogenesis, synaptogenesis, and axonal remodeling.⁴² Neurogenesis involves the proliferation, migration, and maturation of endogenous neural stem cells (NSCs) into fully developed neurons. Following ischemic stroke, the resultant ischemic injury triggers the proliferation of NSCs within the subventricular zone (SVZ) and hippocampus, which subsequently aids in the repopulation of neuronal cells in areas encircling the infarcted vasculature.⁴³ Angiogenesis contributes to neuronal remodeling through several mechanisms: it steers axonal sprouting under the guidance of VEGF secreted in response to neovascularization; it ensures the delivery of oxygen, nutrients, and trophic factors to NSCs migrating toward the peri-infarct zone; and it enhances NSC proliferation by modulating the expression of extracellular signals, such as hypoxia-inducible factor 1- α (HIF-1 α). Angiogenesis augments the oxygenation process and is crucial for supporting NSCs as they transition into mature neurons. Thus, angiogenesis and neuronal remodeling are mutually reinforcing phenomena that play crucial roles in optimizing the functional recovery of the brain following ischemic events.³¹

Cellular Regulation of Angiogenesis Following Ischemic Stroke

The neurovascular unit (NVU) is a complex system comprising multiple components that was first proposed by the National Institute of Neurological Disorders and Stroke in 2001. This transformative concept highlights the unique

interactions among neurons, astrocytes, and endothelial cells, emphasizing their critical roles in ischemic stroke.^{44,45} As research on the NVU has advanced, the synergistic actions of these components have been recognized as crucial for both brain function and pathological conditions, particularly during the recovery phase of ischemic stroke.

The brain, the most complex organ in the human body, ensures that nearly every neuron has its own blood supply.⁴⁶ Poststroke, the interactions between neurons and other cell types induce the formation of new connections, promoting the coupling of regional brain activity with blood flow and metabolism.⁴⁷ Newly formed vessels enhance the local cerebral blood supply, transporting oxygen, energy, and nutrients while helping to remove waste products generated by neurons, thus supporting the recovery and enhancement of neurological functions.⁴⁸

Astrocytes interact directly with neurons and capillaries through their endfeet, not only regulating the hemodynamics of cerebral microvessels but also forming cellular networks that support neuronal survival and repair.⁴⁹ They provide a physical scaffold and produce angiogenic factors during vascular development. After stroke, astrocytes actively interact with new vessels, and functional ablation of these vessels impairs new vessel formation.⁵⁰ Additionally, astrocytes secrete angiogenic factors that promote endothelial cell proliferation and neovascularization, thus improving the blood supply to ischemic areas and reducing the infarct size.⁵¹

Ischemic and hypoxic injuries activate endothelial cells, leading to the release of a significant amount of matrix metalloproteinases (MMPs), which cleave the extracellular matrix and basement membranes, creating space for new vessels.⁵² Elevated levels of VEGF increase vascular permeability, enhance angiogenesis, and facilitate the migration of activated endothelial cells to form new vascular networks.⁵³

Ion Channel Regulation of Angiogenesis Following Ischemic Stroke

Ion channels are widely expressed in various vascular cells, including endothelial cells, smooth muscle cells (SMCs), and fibroblasts.⁵⁴ During cerebral ischemia, rapid changes in these channels play crucial roles in signal transduction, hemodynamics, and angiogenesis.⁵⁵ Increasing evidence suggests that ion channels are intimately involved in the process of vascular formation.

For instance, in the rat middle cerebral artery occlusion (MCAO) model, inhibition of the TRPM4 channel not only maintains vascular integrity but also enhances angiogenesis, thereby significantly reducing the infarct size and facilitating functional recovery.⁵⁶ Furthermore, studies have indicated that the selective loss of TRPA1 expression in brain endothelial cells under hypoxic conditions exacerbates ischemic stroke-related brain tissue damage, suggesting that the activation of this channel is a novel adaptive response to hypoxia.⁵⁷ Additionally, excessive activation of the TRPM2 channel during the recovery period after spinal cord injury leads to increased apoptosis and weakened angiogenesis; however, inhibition of TRPM2 can improve endothelial cell survival and promote angiogenesis.⁵⁸ Moreover, the activity of K⁺ channels is directly linked to cell proliferation and cytokine production.⁵⁹ In models of acute myocardial infarction, the upregulation of the TRPV4 channel by growth differentiation factor 15 significantly promotes angiogenesis.⁶⁰

These studies not only deepen our understanding of the role of vascular ion channels in regulating vascular functions but also highlight their potential as therapeutic targets for clinical treatment. Currently, clinical trials targeting ion channels have begun for various diseases, including ischemic stroke, epilepsy, and headaches,^{61–63} opening new avenues for future research into poststroke angiogenesis.

Molecular Regulation of Angiogenesis in Ischemic Stroke

Vascular Endothelial Growth Factor (VEGF)

Vascular endothelial growth factor (VEGF) is a homodimeric, disulfide-bonded glycoprotein that is pivotal for driving angiogenic processes. VEGF plays a significant role in stimulating the proliferation of endothelial cells and has antiapoptotic effects. It concurrently enhances vascular permeability and cell migration, establishing itself as an indispensable regulator of the angiogenesis cascade.⁶⁴ The VEGF family encompasses a spectrum of isoforms, including VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PGF), each of which contributes to various aspects of vascular development.⁶⁵ VEGF-C and VEGF-D are specifically implicated in lymphangiogenesis.⁶⁶ The prototypical member of this family, VEGF-A, known ubiquitously as VEGF, is instrumental in angiogenesis and the modulation of

vascular diseases. VEGF-A is present in several isoforms, such as VEGF121, VEGF145, VEGF165, VEGF183, VEGF189, and VEGF206. Among these, VEGF165 is the most biologically significant and is primarily found in oncological pathologies.⁶⁷

In a variety of experimental ischemic stroke models, a well-documented increase in the expression of VEGF and its receptors has been observed following an ischemic event. The interaction between VEGF and its receptors is critical for the promotion of endothelial cell proliferation and migration, which are foundational processes in angiogenesis within the ischemic cerebral milieu.²⁴ HIF-1 α has emerged as a key regulatory molecule in this context that governs the expression of VEGF. The augmented levels of the VEGF-A mRNA observed under hypoxic conditions underscore the significance of the HIF-1 α /VEGF axis in modulating angiogenic activity.⁶⁸ Furthermore, HIF-1 α , along with other genes responsive to hypoxic stress, orchestrate VEGF expression, influencing the cascade of VEGF-mediated signaling pathways.⁶⁹

VEGF orchestrates a multitude of kinase activities through its interaction with VEGF receptors (VEGFR1 and VEGFR2), thereby exerting its angiogenic effect. VEGFR2 predominantly resides within neuronal and endothelial cells, indicating its central role in these cell types, while VEGFR1 is more widely distributed within the vascular system, encompassing the choroid plexus and neuroglial cells. This distribution pattern suggests that the role of VEGF extends beyond that of endothelial cells, influencing a variety of cellular functions.⁷⁰ Upon the binding of VEGF to its receptors, a cascade of downstream signaling pathways, including the PLC γ /PKC and the Ras/ERK/MAPK pathways, is activated,⁷¹ which are integral to the processes of endothelial cell proliferation and migration (Figure 1). Furthermore, VEGF is known to enhance vascular permeability, which is instrumental in the disruption of the endothelial cell cytoskeleton, thereby facilitating endothelial cell movement within the extracellular matrix.⁷²

The poststroke increase in VEGF expression is a natural response that plays pivotal roles in enhancing the proliferation of neural stem cells (NSCs)⁷³ and stimulating the growth and motility of vascular smooth muscle cells,⁷⁴ both of which are essential processes in angiogenesis. The endogenous synthesis of VEGF by endothelial cells is a cornerstone in the maintenance of vascular homeostasis.⁷⁵ Emerging research indicates that stem cell transplantation therapies augment the release of endogenous VEGF, thereby stimulating angiogenic activity in ischemic regions through the VEGF-VEGFR2 signaling axis.⁷⁶ However, despite the activation of various downstream pathways by exogenous VEGF via VEGFR2—such as the PI3K-Akt pathway, which is integral to cellular survival⁷⁵—exogenous VEGF cannot wholly substitute for the function of endogenous VEGF in endothelial cells. In these cells, the interaction of VEGF with VEGFR2 is critical for the phosphorylation of endothelial nitric oxide synthase (eNOS) by Akt, culminating in the production of nitric oxide (NO).⁷⁷ The synthesis of NO plays a crucial role in augmenting cerebral blood flow, thereby facilitating the repair of ischemic tissues.⁷⁸ Notably, at lower concentrations, NO can activate a broad spectrum of signaling pathways, including the ERK, Akt/mTOR, STAT, and Ras pathways, which are known to significantly promote tumor angiogenesis and metastasis.⁷⁹

The therapeutic application of VEGF in ischemic stroke is controversial, as VEGF functions as a double-edged sword. VEGF is acknowledged for its neuroprotective properties, principally through the facilitation of angiogenesis.⁸⁰ However, its involvement in the pathophysiology of stroke is complicated by its propensity to disrupt the blood–brain barrier (BBB), thus augmenting permeability and potentially aggravating cerebral edema.⁸¹ The intricacies underlying the dichotomous effects of VEGF—fostering angiogenesis on the one hand and increasing permeability on the other—remain insufficiently defined. Hypoxic conditions are widely accepted as the predominant trigger for VEGF upregulation. Notably, VEGF activity within the first 72 hours poststroke, corresponding to the subacute phase, is associated with heightened vascular edema and BBB permeability.^{82,83} Ghori et al reported that VEGF deficiency in a mouse model of middle cerebral artery occlusion (MCAO) led to significant vascular leakage, whereas VEGF overexpression appeared to maintain vascular integrity during the critical 72-hour poststroke window.⁸⁴ Despite these findings, clinical applications aimed at inducing VEGF expression have frequently encountered setbacks that are largely attributed to the absence of suitable experimental models. Consequently, optimizing the therapeutic potential of VEGF poststroke necessitates careful consideration of the timing of its administration.⁸⁵ Further investigative efforts are essential to unravel the complex interplay between VEGF and the myriad pathways that govern angiogenesis and neural restoration.

Research on angiogenesis following ischemic stroke has primarily focused on foundational studies, and clinical investigations are relatively limited. However, several clinical exploratory studies are currently progressing. The level of

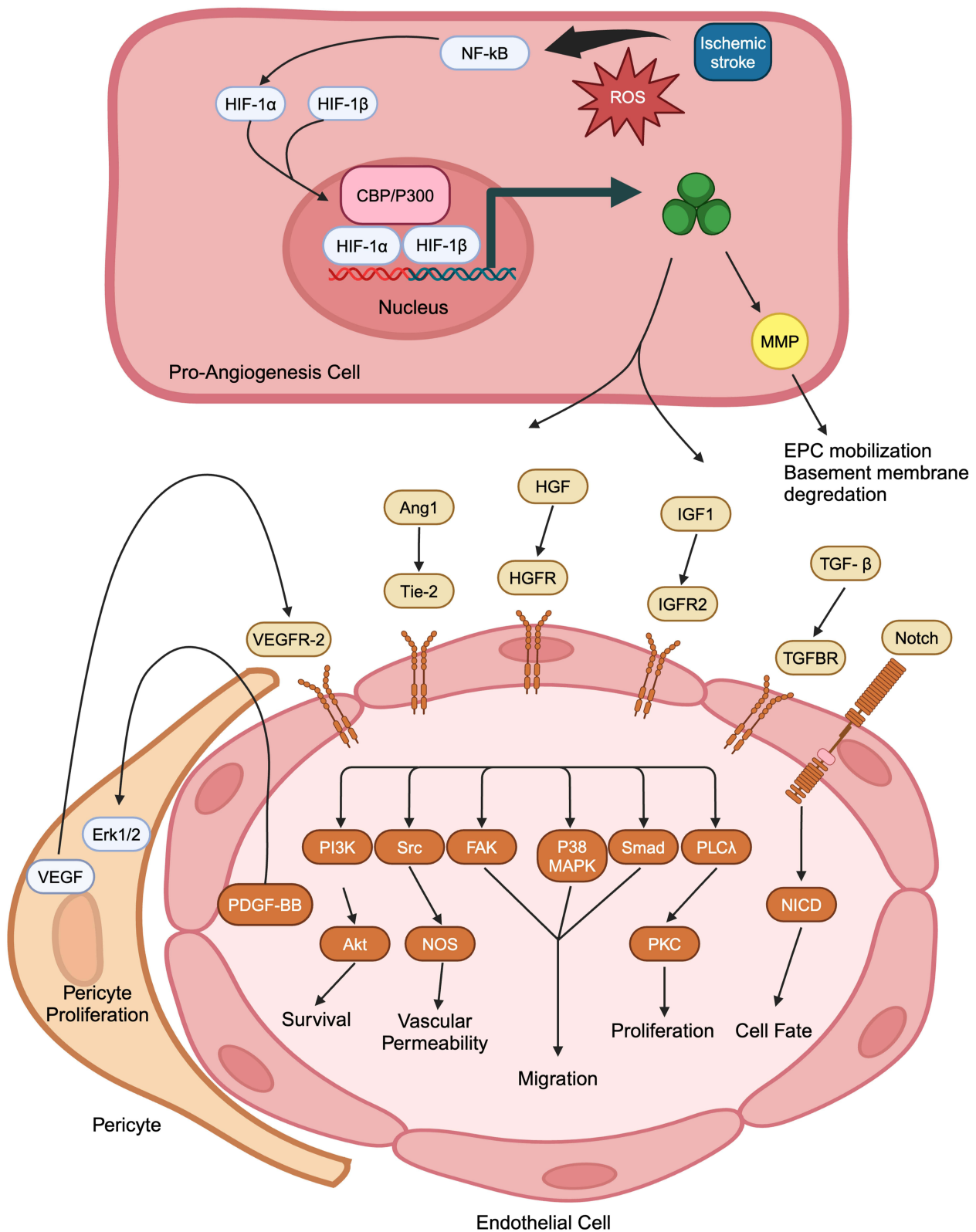


Figure 1 Pathways activating angiogenesis following ischemic stroke. This figure delineates the orchestrated signaling pathways that are activated in response to ischemic stroke and culminate in angiogenesis. Central to this process are hypoxia-inducible factors (HIF-1 α and HIF-1 β), which, upon activation by hypoxic conditions, translocate to the nucleus to drive the transcription of angiogenic genes. The PI3K/Akt/mTOR and MAPK/ERK pathways, which are activated by various growth factors, including VEGF, PDGF, and EGF, mediate downstream effects that lead to endothelial cell survival, proliferation, and migration, which are essential for new blood vessel formation. Matrix metalloproteinase (MMP) facilitates extracellular matrix breakdown, enabling endothelial progenitor cell mobilization. Additionally, the interplay between the Notch signaling pathway and VEGFR2 is depicted, indicating its importance in vascular remodeling and stability. This comprehensive representation underscores the complexity and multifactorial nature of poststroke angiogenesis. Created with BioRender.com.

VEGF could serve as a potential biomarker for assessing angiogenic activity during the recovery process after stroke.⁸⁶ Furthermore, ongoing efforts are devoted to developing therapeutic drugs targeting VEGF to promote angiogenesis and functional recovery in damaged brain tissue. In a prospective study involving patients, human urinary kallidinogenase was shown to enhance the expression of VEGF in stroke patients, improve cerebral perfusion, and thereby ameliorate stroke outcomes.⁸⁷ In a comparative prospective trial examining the effects of dl-3-n-butylphthalide (NBP) and human urinary kallidinogenase on the functional outcomes of ischemic stroke patients, both treatments were found to upregulate VEGF expression and significantly promote recovery in stroke patients.⁸⁸ In summary, these studies suggest that angiogenesis-promoting therapies have potential for treating chronic stroke. Modulating angiogenesis could serve as a potential therapeutic strategy to alleviate brain injury poststroke. However, this approach largely remains in the experimental stage, requiring further research into angiogenic factors, timing, delivery Methods, and monitoring long-term effects to ensure safety and sustained benefits.

Insulin-Like Growth Factor-1 (IGF-1)

Within the constellation of pathways that stimulate angiogenesis, insulin-like growth factor-1 (IGF-1) and its cognate receptor, IGF1R, constitute a critical axis for angiogenesis, neurogenesis, and neuroprotection—especially in the context of ischemic stroke.^{89,90} IGF-1 is instrumental in fostering neuronal proliferation, survival, and differentiation, underpinning these processes by enhancing synthetic metabolic activities.⁹¹ Empirical studies have shown that IGF-1 administration results in a substantial reduction in the infarct size and an amelioration of neurological deficits in rodent ischemic stroke models.⁹² IGF-1, which is produced by cerebral microvascular endothelial cells, mitigates neuronal damage caused by oxygen–glucose deprivation (OGD).⁹³ Furthermore, the overexpression of IGF-1 is associated with vascular remodeling and neurogenesis, thereby contributing to sustained functional recovery in mouse models of focal cerebral ischemia.⁹⁴ Endogenous IGF-1 is vital for poststroke recovery, and its augmentation through exogenous supplementation has shown promise in attenuating cerebral damage following stroke.⁸⁹ Postischemic phosphorylation of IGF1R in endothelial cells leads to the activation of downstream signaling molecules such as Akt, FAK, and MEK1/2, with a subsequent increase in the phosphorylation of effector proteins such as eNOS and ERK1/2 (Figure 1).⁹⁵ Additionally, ginsenoside F1 augments angiogenesis via the IGF-1/IGF1R pathway within endothelial cells.⁹⁵ IGF-1 is also implicated in the activation of pathways, including the MAPK, PI3K, and AKT pathways, which collectively promote angiogenesis.⁹⁶ Collectively, these findings underscore the pivotal role of IGF-1 in enhancing angiogenesis and fostering neurological recovery poststroke.

Erythropoietin (EPO)

Erythropoietin (EPO) is a glycoprotein hormone whose primary biosynthesis occurs in the fetal liver and adult kidneys, and it is chiefly associated with the regulation of erythropoiesis in response to oxygen deficits in the bloodstream.⁹⁷ Although EPO is traditionally recognized for its role in augmenting red blood cell production, the scope of its biological activities has expanded with advancing research, revealing its significant cytoprotective functions, particularly within cardiovascular pathophysiology.⁹⁸ The biological actions of EPO are mediated by its interaction with the erythropoietin receptor (EPOR), and the specificity of EPOR dictates whether EPO will exert hematopoietic or tissue-protective effects. The engagement of EPOR triggers critical intracellular signaling cascades responsible for cell survival, proliferation, differentiation, antiapoptotic responses, and neuroprotection.^{99,100} Notably, the EPO/EPOR complex activates several downstream pathways, including the PI3K and Ras/MAPK pathways, which are instrumental in cellular proliferation processes.¹⁰¹ Recent findings have shown that the binding of EPO to the EphB4 receptor initiates STAT3-mediated signaling, resulting in rhEPO-induced oncogenic activity.¹⁰² Moreover, the role of EPO in angiogenesis has been substantiated, as it promotes endothelial cell migration and proliferation,¹⁰³ with empirical support from both in vivo and in vitro studies.¹⁰¹

In rodent models of myocardial infarction, erythropoietin (EPO) has been shown to enhance cardiac function through its ability to downregulate the expression of Caspase-12, thereby exerting a cardioprotective effect.¹⁰⁴ Systemic administration of EPO is associated with a significant decrease in the infarct size following middle cerebral artery occlusion in rats, suggesting a protective role in cerebral ischemia as well.¹⁰⁵ Investigations into

the mechanisms underlying the effects of EPO have revealed that electroacupuncture at the GV26 acupoint can potentiate angiogenesis via the activation of both the EPO-mediated Src signaling pathway and the VEGF signaling pathway, with the former contributing to the upregulation of VEGF expression.¹⁰⁶ Additionally, *in vitro* assays have confirmed that EPO facilitates endothelial cell migration.¹⁰⁷ A randomized controlled trial revealed that in patients with acute symptomatic stroke, treatment combining cranial burr-hole surgery with erythropoietin significantly improved hemispheric perfusion parameters in patients with perfusion deficit strokes and increased the rate of arteriogenesis.¹⁰⁸

Under physiological conditions, the expression of the EPO receptor (EPOR) in the adult central nervous system is relatively low.¹⁰⁹ Nonetheless, in the presence of environmental enrichment or mild hypoxic stress, EPOR expression is upregulated, which has been implicated in neuronal protection against severe ischemic and hypoxic neuronal injury.¹¹⁰ Preconditioning with hypoxia prior to the induction of permanent MCAO has been shown to confer significant neuroprotection against focal ischemia in rats via brain-derived EPO.¹¹¹ Further studies revealed that recombinant human EPO (rhEPO) not only promotes astrocyte activation and reduces the population of M1 microglia but also promotes angiogenesis and neurogenesis postcerebral ischemia.¹¹²

Despite the accumulating evidence supporting the tissue-protective properties of EPO, the detailed mechanisms by which EPO facilitates angiogenesis and neuroprotection in ischemic stroke remain to be fully elucidated, necessitating more comprehensive investigations.

Hepatocyte Growth Factor (HGF)

Hepatocyte growth factor (HGF), comprising an alpha chain and a beta chain, was initially recognized as a mitogen for liver cells upon molecular cloning.¹¹³ Accumulating research now corroborates the multifunctionality of HGF, revealing its capacity to initiate a range of cellular activities, such as mitosis, motility, and morphogenesis. These activities underscore the versatility of HGF as a growth factor across various biological contexts, including cellular migration, angiogenesis, and antiapoptotic processes.^{114,115} The HGF/MET signaling axis has been identified as a direct activator of endothelial cells within tumorous tissues, spurring cellular motility and indirectly enhancing the secretion of proangiogenic factors such as VEGF.¹¹⁶ HGFs are expressed in neuro-microvascular endothelial cells, and their roles have been substantiated in diverse animal models,¹¹⁷ addressing conditions such as spinal cord injury and acute ischemia.¹¹⁴ After transient middle cerebral artery occlusion (tMCAO) in rats, HGF has been shown to augment angiogenesis and mitigate apoptosis *in vitro*.¹¹⁸ Further research revealed that HGF expression increases in rat brains during delayed reperfusion post-MCAO, reducing the infarct volume and neuronal apoptosis through the HGF/c-Met/STAT3/Bcl-2 pathway.¹¹⁴ Shang et al reported that HGF reinforces the BBB integrity, mitigates cerebral edema, and fosters endogenous repair and functional recovery after cerebral ischemia in rodent models, thereby significantly increasing angiogenesis poststroke.¹¹⁸ Additionally, a recent investigation reported that in a rat model of cerebral artery ischemia/reperfusion (I/R), HGF-modified human follicle-stimulating cells (HFSCs) ameliorated I/R injury through anti-inflammatory actions, BBB protection, angiogenic promotion, and enhanced neural recovery.¹¹⁹

The molecular intricacies of HGF-induced angiogenesis are linked to the VEGF and c-Met pathways. c-Met, the designated receptor for HGF, is ubiquitously expressed in endothelial cells and is pivotal for propagating signals that lead to endothelial cell proliferation and migration via the MAPK/ERK and STAT3 pathways (Figure 1).¹²⁰ In addition to its direct impacts on endothelial cells, HGF also orchestrates the recruitment and angiogenic incorporation of bone marrow-derived endothelial progenitor cells.¹²¹ HGF, through Ets-1 upregulation, mediates the elevated expression of IL-8 and VEGF.¹²² Moreover, HGF induces vascular smooth muscle cells (VSMCs) to secrete VEGF-A, thus indirectly fostering angiogenesis. The VEGF-A and HGF/Met signaling systems exhibit reciprocal effects, collaboratively engaging neuropilin to stimulate angiogenic processes.¹²³ HGF further modulates the inflammatory response by dampening NF- κ B activity and reducing MCP-1 production in endothelial cells, thus attenuating the proangiogenic effects of VEGF.¹²⁴ Mesenchymal stem cells (MSCs) have been shown to enhance angiogenesis via the secretion of an array of trophic factors, including VEGF-A, VEGF-C, bFGF, PGF, and HGF.^{125,126} Collectively, these findings delineate the essential regulatory role of HGF in the angiogenic cascade.

MicroRNAs (miRNAs)

MicroRNAs (miRNAs) are small noncoding RNA molecules, typically 20–24 nucleotides in length, and exert a profound influence on the posttranscriptional regulation of gene expression. These miRNAs are implicated in a myriad of cellular processes and pathological conditions, including metabolic pathways, cellular proliferation, differentiation, and apoptosis,¹²⁷ positioning them as potent biomarkers and therapeutic targets in ischemic stroke pathobiology.¹²⁸ The roles of miRNAs must be considered within specific cellular milieus, as their functions intimately depend on the surrounding cellular context. Studies have highlighted miRNAs as pivotal modulators of the pathophysiological mechanisms of cerebral ischemia and associated disorders,¹²⁹ including excitotoxicity, oxidative stress, inflammation, and cell death.¹³⁰ Recent research has also revealed the significant participation of miRNAs in the angiogenic response of postischemic brain tissue.¹³¹ For example, miR-210, whose expression is highly inducible by hypoxic conditions and regulated by HIF-1 α , has been shown to promote angiogenesis.¹³² Overexpression of miR-210 in the adult murine brain has been shown to facilitate focal angiogenesis by modulating regional VEGF concentrations. In addition, miR-210 is known to stimulate endothelial cell migration and the formation of tubular structures under hypoxic conditions *in vitro*.¹³³ Further investigations have shown that miR-107, which is markedly upregulated in the ischemic boundary zone (IBZ) following permanent middle cerebral artery occlusion (pMCAO) in rats, plays a critical role in vascular remodeling poststroke. Inhibition of miR-107 led to a reduction in the capillary density within the IBZ, indicating its role in angiogenesis. This effect was partly mediated by the downregulation of Dicer-1 and the subsequent upregulation of VEGF isoforms, such as VEGF165/VEGF164.¹³⁴ Additionally, the expression of miR-15a has been reported to increase significantly within the vasculature of the ischemic penumbra following cerebral ischemic events.¹³⁵

Conversely, a subset of miRNAs has been shown to inhibit angiogenesis following ischemic events. MiRNAs such as miR-15b, miR-16, and miR-20 have been shown to suppress VEGF expression, thereby exhibiting antiangiogenic properties in endothelial cell cultures.¹³⁶ In a murine model of MCAO, the miR-15a/16-1 cluster was found to inhibit the production of VEGFA and fibroblast growth factor 2 (FGF2), along with its receptor. Notably, endothelial deletion of miR-15a/16-1 resulted in elevated cerebral VEGF levels and augmented neovascularization within ischemic brain tissue.¹³⁷ Furthermore, miR-130a exerts antiangiogenic effects by downregulating the expression of growth arrest-specific homeobox (GAX) and homeobox A5 (HOXA5).¹³⁸ In contrast, the downregulation of certain miRNAs, including miR-27b, miR-92a, miR-155, and miR-493, is associated with enhanced angiogenic activity.¹³⁹

In summary, miRNAs represent a promising frontier for therapeutic intervention in postischemic stroke scenarios. However, the translation of these molecular insights into viable human therapies remains an unmet challenge. Future research endeavors are essential to navigate and overcome the existing barriers, thereby enabling the application of miRNA-based interventions in the treatment of human ischemic conditions.

Angiopoietins (Angs)

Angiopoietins (Angs), key angiogenic mediators, play a fundamental role in angiogenesis within the brain tissue after stroke. The Ang family primarily comprises angiopoietin-1 (Ang-1) and angiopoietin-2 (Ang-2). Ang-1, a glycosylated protein, binds to the Tie-2 receptor, exerting regulatory effects on endothelial cell survival and vascular permeability through Tie-2-mediated signaling (Figure 1).¹⁴⁰ In contrast, Ang-2 functions as a natural antagonist of Ang-1, counteracting the role of Ang-2 in vascular stabilization and maturation.¹⁴¹ Upon receptor engagement, angiopoietins trigger multiple signaling cascades, including the PKB/Akt, ERK1/2, and SAPK/JNK cascades. These pathways facilitate angiogenesis and upregulate the expression of genes related to cellular proliferation, migration, invasion, and tubular structure formation.^{142,143} Angiopoietins thus promote cellular growth, proliferation, and neovascular formation through the activation of the ERK1/2, SAPK/JNK, and PI3K/Akt-related pathways (Figure 1).¹⁴⁴

Chan et al elucidated the antiangiogenic function of fibulin-5, showing its inhibitory effect on endothelial cell survival and interference with the Ang-1/TIE-2 signaling axis.¹⁴⁰ Additionally, Ang has been recognized to stimulate endothelial cell proliferation by acting in concert with VEGF and fibroblast growth factor (FGF) to regulate angiogenesis.¹⁴⁵ Recent investigations have highlighted the role of angiopoietins and endothelial precursor cells (EPCs) in enhancing neurological functions through their involvement in the recovery process following cerebral ischemia.¹⁴⁶ The activation of

angiopoietins also prompts fibroblasts to produce extracellular matrix proteins, aiding in wound healing processes.¹⁴⁴ In addition to their angiogenic roles, angiopoietins have been implicated in the pathology of other conditions, such as their association with excitotoxic motor neuron death in amyotrophic lateral sclerosis (ALS) and the discovery of mutations in the Ang gene in Parkinson's disease.^{147,148} These findings underscore the involvement of Angs not only in angiogenesis but also in a broader spectrum of physiological and pathological contexts. Nevertheless, research specifically targeting Angs in ischemic stroke remains relatively scarce, necessitating further exploration to fully understand their roles in the mechanisms underlying poststroke angiogenesis.

Transforming Growth Factor- β (TGF- β)

Transforming growth factor- β (TGF- β), a multifaceted peptide cytokine, is integral to both early embryonic development and adult homeostasis.¹⁴⁹ This cytokine is present in three isoforms—TGF- β 1, TGF- β 2, and TGF- β 3—and interacts with three distinct TGF- β receptors (TGFBR-1, TGFBR2, and TGFBR3), each eliciting specific biological effects. TGF- β engages various downstream signaling pathways, both SMAD and non-SMAD, to modulate protein expression under diverse physiological and pathological conditions. The binding of active TGF- β to TGFBR2 initiates the SMAD pathway, in which TGFBR2 phosphorylates TGFBR1, and the latter phosphorylates Smad2 and Smad3.¹⁵⁰ Additionally, TGF- β activates non-SMAD pathways, including Erk1/2, TRAF4/6, PAR6, and PI3K/AKT/mTOR, which are crucial for embryonic development and adult neuronal and vascular growth (Figure 1).¹⁵¹

TGF- β exerts regulatory control over a myriad of cellular functions, such as embryogenesis, angiogenesis, cellular proliferation, differentiation, and migration, while also inducing apoptosis in microvascular endothelial cells.¹⁵² In endothelial cells, TGF- β activates two distinct SMAD signaling pathways: the Smad2/3 and Smad1/5/8 pathways. The activation of ALK5 leads to Smad2/3 pathway engagement, which dampens endothelial cell proliferation, migration, and angiogenesis. Conversely, ALK1 activation triggers the Smad1/5/8 pathway, thereby promoting endothelial cell proliferation, migration, and tubular formation, which are conducive to angiogenesis.¹⁵³ Recent findings have shown that Coicis exerts neuroprotective effects on ischemic stroke by enhancing angiogenesis through the TGF- β /ALK1/Smad1/5 pathway, mitigating ischemia–reperfusion injuries.¹⁵⁴ Additionally, LRG1 has been implicated in exacerbating diabetic nephropathy by augmenting TGF- β /ALK1-induced angiogenesis.¹⁵³ Moreover, extracellular vesicles from astrocytes with hypoxic preconditioning have been found to stimulate angiogenesis and inhibit apoptosis in stroke models through the TGF- β /Smad2/3 pathway.¹⁵⁵ These findings revealed that TGF- β plays a nuanced, signaling-specific role in angiogenesis characterized by intricate signaling pathways and complex interactions, thereby significantly influencing angiogenic processes.¹⁵⁶ A deeper exploration of the mechanisms of TGF- β after ischemic stroke is essential to identify novel therapeutic avenues.

Platelet-Derived Growth Factors (PDGFs)

Platelet-derived growth factors (PDGFs) represent a class of serum-derived growth factors that include four homodimers—PDGF-AA, PDGF-BB, PDGF-CC, and PDGF-DD—and one heterodimer, PDGF-AB. These growth factors engage their corresponding receptors, PDGFR- α and PDGFR- β , to activate PDGF signaling pathways.^{157,158} Initially identified for their roles in various diseases, PDGFs have been increasingly recognized for their potential for neuroprotection following ischemic stroke.¹⁵⁹ Among the PDGF isoforms, the PDGF-BB homodimer has garnered substantial research interest due to its unique ability to bind all types of PDGFRs, thereby initiating diverse signaling cascades.¹⁶⁰ The PDGF-BB/PDGFR- β axis is particularly important for the maintenance of blood–brain barrier (BBB) integrity, both during development and in the adult brain.¹⁶¹ Increased expression of PDGF-BB/PDGFR- β has been observed in the central nervous system of both human and animal models of ischemic stroke.¹⁶² In cerebral ischemia, PDGFR- β expression increases around the infarct zone, contributing to the survival and proliferation of neighboring cells, partially through the Akt signaling pathway.¹⁶³

Previous research has indicated that asiatic acid can stimulate angiogenesis by upregulating the expression of VEGF and PDGF in human umbilical vein endothelial cells (HUVECs).¹⁶⁴ Animal model studies involving *in vivo* angiogenesis and hind limb ischemia have revealed that the combination of PDGF-AB and FGF-2 enhances the stability of newly formed vessels by attracting perivascular cells. This process can be significantly inhibited by anti-PDGFR- β antibodies,

highlighting the importance of the PDGF-AB/FGF-2 axis in vascular stabilization.¹⁶⁵ More recent investigations have shown that PDGFR- β signaling facilitates functional recovery following cerebral ischemia by promoting the recruitment, migration, and proliferation of perivascular cells.¹⁶⁶ These findings underscore the pivotal role of PDGF in accelerating functional recovery by stimulating neoangiogenesis in ischemic tissues.

In conclusion, PDGF is a critical mediator of angiogenesis, particularly in the context of neovascularization postischemic stroke. A deeper understanding of the role of the PDGF signaling pathway could elucidate its mechanisms in neuroprotection and functional recovery, potentially providing new therapeutic strategies. While this section has focused on some key molecules that promote angiogenesis, numerous other molecules also contribute to this process.

While the preceding sections have provided an overview of some key molecules implicated in the promotion of angiogenesis, such as PDGF, angiogenesis is a multifaceted process influenced by a wide array of molecular factors. Angiogenesis research is expansive, with numerous molecules playing varied and significant roles in this complex biological process. Table 1 provides a more comprehensive summary of other molecules that are also integral to angiogenesis. This table aims to encapsulate a broader range of molecular entities, each contributing uniquely to the angiogenic landscape, particularly in the context of postischemic stroke neovascularization and recovery. Such an inclusive approach underscores the diversity and intricacy of the molecular mechanisms driving angiogenesis, highlighting the potential for future research and therapeutic development in this dynamic area of study.

Angiogenesis Signaling Pathways Activated After Ischemic Stroke PI3K/Akt

The phosphoinositide 3-kinase (PI3K) complex, which comprises the p85 and p110 subunits, is instrumental in binding to Akt isoforms.¹⁸⁴ Akt, a critical downstream component of the PI3K signaling pathway, exists in three isoforms: Akt1, Akt2, and Akt3.¹⁸⁵ This pathway is pivotal for regulating a spectrum of cellular processes, including development, differentiation, survival, protein synthesis, and metabolism.¹⁸⁶ Upon activation, Akt migrates from the cytoplasm to the cell membrane, where it phosphorylates an array of downstream substrates that influence apoptosis, cell cycle regulation, and angiogenesis (Figure 1).^{187,188}

Table 1 Other Molecules

Molecule	Regulated Molecules/ Pathways	Functions	References
miRNA-24-1-5p	HIF-1 α	Angiogenesis	[167]
miRNA27-b	AMPK	Regulation of tube formation and migration	[168]
miRNA-107	Dicer-1	Angiogenesis	[134]
miRNA133-b	TGF- β (miR-206/RABEPK)	Regulation of neurovascular plasticity	[169]
miRNA-140-5p	VEGFA	Cell proliferation, migration and tube formation	[170]
miRNA-155	TGF- β /BMP, SMAD5, mTOR, NO	Improves cerebral blood flow and supports the microvasculature	[171]
miRNA-191	NF- κ B	Angiogenesis	[172]
Malat1	miRNA26-b, miRNA30-a, miRNA145	Protects the neurovascular unit	[173,174]
LncRNA-MEG3	ABCA1	Proliferation of vascular smooth muscle cells	[175]
AMPK	VEGFA	Increased microvascular density	[176]
BDNF	miRNA-181C	Endothelial cell proliferation	[177]
G-CSF	eNOS, Ang-2	Endothelial cell proliferation	[178]
eNOS	NO	Proliferation of endothelial cells, tube formation	[179]
SDF-1	CXCR4	Endothelial cell proliferation	[180]
FGF	SIP1	Endothelial cell proliferation	[181]
HB-EGF	VEGFA	Proliferation of endothelial cells, increased microvessel density	[182]
CXCL12	VEGFA	Proliferation of endothelial cells, tube formation, increased microvessel density	[183]

Research has shown that VEGF, through its interaction with cellular receptors and subsequent phosphorylation of AKT, activates mTOR, thereby augmenting VEGF expression and stimulating angiogenesis in ischemic brain tissues.¹⁸⁹ In ischemic stroke, the combined application of spleen-derived stem cells (SFs) and bone marrow-derived mesenchymal stem cells (BMSCs) has been shown to enhance angiogenesis and neurogenesis in the ischemic boundary zone (IBZ). This effect is mediated by the VEGF and BDNF-AKT/mTOR signaling pathways, resulting in reduced lesion volumes poststroke.¹⁹⁰ mTOR, acting as a sensor for hypoxia and nutrient levels, is crucial for processes such as cell cycle regulation, glycogen metabolism, and protein synthesis.¹⁹¹ Ginsenoside Rg1 has been shown to promote cerebral angiogenesis via the PI3K/Akt/mTOR pathway,¹⁹² while Buyang Huanwu decoction enhances VEGFR2 phosphorylation and angiogenesis in a mouse model of cerebral hemorrhage through the same pathway.¹⁹³ Notably, mTOR serves as an upstream regulator of HIF-1 α ,¹⁹⁴ and activation of the PI3K/Akt/mTOR pathway can activate HIF-1 α , leading to the regulation of VEGF expression.¹⁹⁵ In contrast, inhibition of this pathway has been shown to suppress tumor angiogenesis and growth.¹⁹⁶ Zhu et al reported that resveratrol impedes glioblastoma proliferation and angiogenesis by inhibiting the PI3K/Akt/mTOR pathway.¹⁹⁷ In the context of angiogenesis, Akt activation enhances endothelial nitric oxide synthase (eNOS) activity, leading to increased production of nitric oxide (NO), which in turn induces vascular dilation and increases vascular permeability.⁶⁴ Consequently, the neuroprotective role of the PI3K/Akt pathway in angiogenesis provides promising avenues for developing therapeutic strategies aimed at functional recovery following ischemic stroke.

Notch

The Notch signaling pathway is integral to a plethora of biological processes, including embryonic development and the maintenance of adult tissue homeostasis.¹⁹⁸ Similar to the VEGFR system, Notch signaling is pivotal in vascular development and morphogenesis. In mammals, the Notch family consists of four receptors (Notch1, Notch2, Notch3, and Notch4) and five ligands (Jagged-1, Jagged-2, DLL-1, DLL-3, and DLL-4). Activation of Notch receptors results in the release of the Notch intracellular domain (NICD), which migrates to the nucleus to initiate the transcription of genes that influence cell fate and angiogenesis.¹⁹⁹

During angiogenesis, a feedback regulatory mechanism occurs between Notch signaling and VEGFR receptor expression.²⁰⁰ For example, activation of the DLL-4 ligand can downregulate VEGFR-2 expression, whereas inhibition of the DLL-4 pathway results in the upregulation of VEGFR-2, potentially enhancing angiogenesis.²⁰¹ Moreover, the Notch ligand Jagged 2, which is activated by HIF-1 α , triggers the Notch signaling pathway, further promoting vascular development and angiogenesis (Figure 1).²⁰² Liang et al documented that miRNA-210 can modulate the HIF/VEGF/Notch pathway, which participates in angiogenesis after hypoxia.²⁰³ In addition, miRNA-137 has been reported to regulate the Notch signaling pathway, thereby facilitating angiogenesis and vascular formation in ischemic stroke models in rats.²⁰⁴ Studies have also indicated that treatment with ginsenoside R1 in a rat model of ischemic stroke reduces the expression levels of Notch pathway-related proteins, enhances angiogenesis, and improves cerebral blood flow. This finding suggested a potential angiogenic mechanism of ginsenoside R1 via the inhibition of Notch signaling.²⁰⁵ Despite these advances, the precise mechanisms through which the Notch signaling pathway mediates angiogenesis in the context of ischemic stroke remain to be fully elucidated.

Other Relevant Signaling Pathways

NF- κ B

The nuclear factor-kappa B (NF- κ B) family, comprising five members, is a pivotal transcription factor group involved in a myriad of physiological and pathological processes. These processes include angiogenesis, inflammation, cell proliferation, transformation, and tumorigenesis.^{206–208} Under ischemic conditions, NF- κ B activity can be upregulated by reactive oxygen species (ROS), leading to increased mRNA expression of HIF-1 α (Figure 1).²⁰⁹ Research has indicated that the inhibition of NF- κ B results in a reduction in the levels of angiogenic factors such as VEGF and interleukin-8 (IL-8), suggesting a proangiogenic role for NF- κ B.²¹⁰ Conversely, NF- κ B inhibition has been shown to induce apoptosis, suppress the proliferation of fibroblast-like synoviocytes, and inhibit angiogenesis in conditions such as arthritis.²¹¹ Recent studies have shown that certain agents, such as crocin, can impede angiogenesis and the migration of colorectal cancer cells by targeting NF- κ B and obstructing the TNF- α /NF- κ B/VEGF pathway.²¹² In the context of ischemic stroke,

NF- κ B inhibitors have been found to diminish SCF+G-CSF-induced axonal sprouting, synaptic formation, and angiogenesis in the ipsilateral sensorimotor cortex.²¹³ Additionally, RSSW enhances neurogenesis and angiogenesis poststroke in rats by inhibiting the TLR4/NF- κ B/NLRP3 inflammatory signaling pathway.²¹⁴ Although traditionally associated with inflammation, the specific role of NF- κ B in angiogenesis is emerging as a significant area of interest. Future research should focus on identifying the specific upstream stimuli and downstream target genes that are regulated by the NF- κ B pathway during angiogenesis. Such studies could reveal new therapeutic approaches for the treatment and management of ischemic stroke.

Jak/Stat3

Under ischemic conditions, angiogenesis is predominantly driven by the upregulation of VEGF expression, which has been observed to increase in the ischemic hemisphere postinjury and remain elevated for up to one month.²¹⁵ Studies suggest that the angiogenic efficacy of VEGF largely hinges on the JAK2/STAT3 and VEGF/Flk-1 pathways, which are affected by EPO and its receptor EPOR, culminating in increased expression of the endothelial marker CD31.²¹⁶

Earlier investigations revealed a link between the leptin R/Jak-STAT signaling pathway and leptin-induced angiogenesis in stroke and tumor contexts.¹⁷⁶ The recruitment of STAT3 to leptin R leads to its phosphorylation by JAK2, followed by dissociation and dimerization with the receptor. The STAT3 dimer then migrates to the nucleus, where it functions as a transcription factor by binding to specific promoter elements of target genes such as VEGF. This interaction induces the transcription of the VEGF mRNA, leading to increased VEGF expression. Subsequently, VEGF interacts with receptors on endothelial cells, initiating a cascade of downstream signaling pathways that promotes angiogenesis. Further research showed that leptin induces angiogenesis following cerebral hemorrhage by activating the leptin R/STAT pathway, thereby triggering the release of growth factors.²¹⁷

Recent advances have revealed that small extracellular vesicles derived from mesenchymal stem cells (MSCs) facilitate angiogenesis by activating STAT3, which simultaneously inhibits autophagy and reinforces blood–brain barrier (BBB) integrity by suppressing STAT3.²¹⁸ The impact of the STAT3 signaling pathway on the cerebral vasculature after ischemic stroke is multifaceted, encompassing a range of biological functions.²¹⁹ JAK2/STAT3 signaling plays dual roles: while its activation can promote inflammation, cell apoptosis, and oxidative stress, it also plays a significant role in stimulating angiogenesis. The nature of upstream stimuli and the characteristics of downstream target genes are crucial determinants of the functional outcomes of this signaling pathway. Consequently, a thorough investigation into the diverse roles of STAT3 postischemic stroke is imperative. Such research could provide novel insights for the diagnosis and therapeutic intervention of this complex condition.

Wnt/ β -Catenin Signaling Pathway

The Wnt signaling pathway, which comprises both noncanonical and canonical pathways, plays a pivotal role in a variety of cellular functions. Of particular interest is the canonical Wnt/ β -catenin pathway, which is crucial for angiogenesis, the maintenance of vascular homeostasis, and brain development.^{220,221} This pathway involves extracellular Wnt signaling molecules, transmembrane receptors, β -catenin, glycogen synthase kinase 3 beta (GSK3 β), T-cell factor/lymphoid enhancer factor (TCF/LEF), and other components. Activation of this pathway, particularly by Wnt3a, results in the translocation of a significant portion of β -catenin from the cytoplasm to the nucleus. In the nucleus, β -catenin interacts with the transcription factor TCF/LEF, leading to the activation of TCF4 and subsequent promotion of VEGF expression.^{222,223} Activation of the Wnt/ β -catenin pathway not only is vital for maintaining the integrity of the blood–brain barrier (BBB) but also plays a significant role in vascularization, often in concert with other angiogenesis-related factors.²²⁴ Experimental studies have shown that activation of the Wnt/ β -catenin pathway and an increase in β -catenin levels can enhance VEGF expression in endothelial cells.²²⁵ Additionally, some research suggests that scalp electroacupuncture stimulation may activate the Wnt/ β -catenin signaling pathway, thereby facilitating angiogenesis.²²⁶ In a mouse model of transient middle cerebral artery occlusion (tMCAO), treatment with oligomeric proanthocyanidins (OPCs) led to increased expression of Wnt7a and β -catenin in the brain, indicating the involvement of the Wnt/ β -catenin pathway in OPC-induced angiogenesis.²²⁷

In summary, the Wnt/ β -catenin signaling pathway has emerged as a key regulatory mechanism in cerebral angiogenesis, particularly after ischemic stroke. Its ability to modulate VEGF expression and contribute to the structural integrity of the BBB underscores its potential as a therapeutic target. The interaction of the pathway with various angiogenic factors and its activation through diverse stimuli, such as electroacupuncture, further highlight its multifaceted role in promoting vascularization and recovery in ischemic brain tissue. Continued research into this pathway is essential to fully comprehend its regulatory mechanisms and therapeutic potential in the context of ischemic stroke and brain repair.

MAPK/ERK

The MAPK/ERK signaling pathway is instrumental for a multitude of biological activities. By phosphorylating various substrates within the cytoplasm and nucleus, this pathway plays a significant role in processes such as angiogenesis, cellular migration, proliferation, and neuroprotection.^{228,229} Its involvement in both angiogenesis and neural regeneration is particularly crucial.

Empirical studies have shown that extracellular vesicles from MEC-1 cells can enhance the invasive, migratory, and angiogenic capacities of human umbilical vein endothelial cells (HUVECs) by modulating the Integrin β 1 (ITG β 1)-MAPK/ERK signaling cascade.²³⁰ In models of neural defects, astrocytes overexpressing VEGF-A have been shown to promote neural recovery, particularly by stimulating angiogenesis through the VEGF/VEGFR2/ERK signaling pathway.²³¹ Moreover, recent research has indicated that miRNA-26a can regulate the expression of HIF-1 α and VEGF via both the PI3K/AKT and MAPK/ERK signaling pathways, thereby promoting angiogenesis in vascular endothelial cells following cerebral ischemia.²³² At present, multicenter clinical and mechanistic studies based on the MEK/ERK/AP-1 pathway to explore the promotion of vascular neovascularization after ischemic stroke have entered the clinical research stage (ChiCTR2300078956); however, most of these molecules are still being investigated in exploratory experiments but show promise.

These findings underscore the critical role of the MAPK/ERK signaling pathway in mediating key aspects of the angiogenic response, particularly following ischemic events in the brain. The ability of this pathway to influence multiple aspects of cellular function and its interaction with various molecular mediators highlight its potential as a target for therapeutic strategies aimed at enhancing neural recovery and angiogenesis poststroke.

Outlook

The study of angiogenesis following ischemic stroke provides critical theoretical foundations for promoting vascular regeneration and functional recovery. This paper deepens our understanding of the regulatory mechanisms of angiogenesis poststroke, particularly emphasizing the roles of the neurovascular unit and ion channels. Future research should further explore how these ion channels specifically regulate intracellular calcium signaling and the potential neuroprotective effects of this process.

Various molecules and signaling pathways, including but not limited to VEGF, IGF-1, EPO, HGF, miRNAs, Ang, TGF- β , and PDGF, play pivotal roles in angiogenesis. Additionally, inflammatory mediators, adhesion molecules, neurotrophic factors, and proteases are closely associated with poststroke angiogenesis. However, the complex interactions and regulatory relationships among these elements, as well as their respective upstream and downstream signals, may either enhance or hinder angiogenesis.

Despite significant progress in elucidating the molecular mechanisms of ischemia-induced angiogenesis, many challenges remain due to the complex structure and metabolic activity of the brain. Applying *in vitro* signal transduction mechanisms to *in vivo* environments is not straightforward. The complexity and intertwined interactions of angiogenic pathways limit the effectiveness of studies of isolated pathways. Although VEGF plays a critical role in poststroke angiogenesis, further research is needed to understand its activation mechanisms and key targets for promoting vascular and neural functional recovery. Although the role of miRNAs in angiogenesis has been recognized, their specific functions in angiogenic pathways and regulatory mediators require in-depth investigation. Integrating bioengineering technologies to develop new therapies that precisely regulate angiogenesis using specific miRNAs or small-molecule drugs will provide more options for clinical treatment.

Cerebrovascular diseases involve multiple genes and factors, making single-target therapies potentially insufficient for comprehensive efficacy. Currently, various strategies to promote angiogenesis, including the use of endothelial progenitor cells, mesenchymal stem cells, growth factors, cytokines, and noncoding RNAs, are being explored. However, compared to antiangiogenic treatments for tumors, angiogenesis therapies for ischemic stroke have received relatively less attention, and treatment options remain limited. This finding underscores the importance of further research to identify new therapeutic targets and strategies.

Given the involvement of various cell types and complex molecular pathways in angiogenesis, future research should adopt a systems biology approach for in-depth mechanistic studies. Drawing from the application of small-molecule inhibitors in cancer treatment, exploring multitarget drugs for angiogenesis in ischemic stroke could be promising. Furthermore, fostering interdisciplinary collaboration between researchers in pharmacology and nanotechnology to develop more targeted and less side effect-prone therapeutic strategies will be a promising field. Despite numerous challenges, these studies are expected to significantly improve the treatment outcomes and quality of life of stroke patients in the coming decades.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

References

1. Kuriakose D, Xiao Z, Antonio L. Pathophysiology and treatment of stroke: present status and future perspectives. *Int J Mol Sci.* 2020;22:21. doi:10.3390/ijms22010021
2. Feigin VL, Stark BA, Johnson CO. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the global burden of disease study 2019. *Lancet Neurol.* 2021;20:795–820. doi:10.1016/S1474-4422(21)00252-0
3. Tu WJ, Zhao Z, Yin P, et al. Estimated burden of stroke in China in 2020. *JAMA Network Open.* 2023;6:e231455.
4. Tu WJ, Wang LD. China stroke surveillance report 2021. *Mil Med Res.* 2023;10:33. doi:10.1186/s40779-023-00463-x
5. Yao M, Ren Y, Jia Y, et al. Projected burden of stroke in China through 2050. *Chin Med J.* 2023;136:1598–1605. doi:10.1097/CM9.0000000000002060
6. Waziry R, Heshmatollah A, Bos D, et al. Time trends in survival following first hemorrhagic or ischemic stroke between 1991 and 2015 in the Rotterdam study. *Stroke.* 2020;51:Strokeaha119027198. doi:10.1161/STROKEAHA.119.027198
7. Donkor ES. Stroke in the 21(st) century: a snapshot of the burden, epidemiology, and quality of life. *Stroke Res Treat.* 2018;2018:3238165. doi:10.1155/2018/3238165
8. DeLong JH, Ohashi SN, O'Connor KC, Sansing LH. Inflammatory responses after ischemic stroke. *Semin Immunopathol.* 2022;44:625–648. doi:10.1007/s00281-022-00943-7
9. Balch MHH, Nimjee SM, Rink C, Hannawi Y. Beyond the brain: the systemic pathophysiological response to acute ischemic stroke. *J Stroke.* 2020;22:159–172. doi:10.5853/jos.2019.02978
10. Zhang Y, Shen L, Xie J, et al. Pushen capsule treatment promotes functional recovery after ischemic stroke. *Phytomedicine.* 2023;111:154664. doi:10.1016/j.phymed.2023.154664
11. Livingston MH, Mahant S, Connolly B, et al. Effectiveness of intrapleural tissue plasminogen activator and dornase alfa vs tissue plasminogen activator alone in children with pleural empyema: a randomized clinical trial. *JAMA Pediatr.* 2020;174:332–340. doi:10.1001/jamapediatrics.2019.5863
12. Kamalakannan S, Gudlavalleti ASV, Gudlavalleti VSM, Goenka S, Kuper H. Incidence & prevalence of stroke in India: a systematic review. *Indian J Med Res.* 2017;146:175–185. doi:10.4103/ijmr.IJMR_516_15

13. Lima FO, Furie KL, Silva GS, et al. Prognosis of untreated strokes due to anterior circulation proximal intracranial arterial occlusions detected by use of computed tomography angiography. *JAMA Neurol.* 2014;71:151–157. doi:10.1001/jamaneurol.2013.5007
14. Hankey GJ. Stroke. *Lancet.* 2017;389:641–654. doi:10.1016/S0140-6736(16)30962-X
15. Chamorro Á, Lo EH, Renú A, van Leyen K, Lyden PD. The future of neuroprotection in stroke. *J Neurol Neurosurg Psychiatry.* 2021;92:129–135. doi:10.1136/jnnp-2020-324283
16. Włodarczyk L, Cichon N, Saluk-Bijak J, Bijak M, Majos A, Miller E, Neuroimaging techniques as potential tools for assessment of angiogenesis and neuroplasticity processes after stroke and their clinical implications for rehabilitation and stroke recovery prognosis. *J Clin Med.* 2022;1:11. doi:10.3390/jcm12010011
17. Xie W, Huang T, Guo Y, et al. Neutrophil-derived cathelicidin promotes cerebral angiogenesis after ischemic stroke. *J Cereb Blood Flow Metab.* 2023;43:1503–1518. doi:10.1177/0271678X231175190
18. Paro MR, Chakraborty AR, Angelo S, Nambiar S, Bulsara KR, Verma R. Molecular mediators of angiogenesis and neurogenesis after ischemic stroke. *Rev Neurosci.* 2023;34:425–442. doi:10.1515/revneuro-2022-0049
19. Zhao Y, Zhang X, Chen X, Wei Y, Li Y, Liu N. Neuronal injuries in cerebral infarction and ischemic stroke: from mechanisms to treatment (Review). *Int J Mol Med.* 2022;49:49. doi:10.3892/ijmm.2022.5104
20. Bandera E, Botteri M, Minelli C, Sutton A, Abrams KR, Latronico N. Cerebral blood flow threshold of ischemic penumbra and infarct core in acute ischemic stroke: a systematic review. *Stroke.* 2006;37:1334–1339. doi:10.1161/01.STR.0000217418.29609.22
21. Ermine CM, Bivard A, Parsons MW, Baron JC. The ischemic penumbra: from concept to reality. *Int J Stroke.* 2021;16:497–509. doi:10.1177/1747493020975229
22. Jung S, Gilgen M, Slotboom J, et al. Factors that determine penumbral tissue loss in acute ischaemic stroke. *Brain.* 2013;136:3554–3560. doi:10.1093/brain/awt246
23. Dudley AC, Griffioen AW. Pathological angiogenesis: mechanisms and therapeutic strategies. *Angiogenesis.* 2023;26:313–347. doi:10.1007/s10456-023-09876-7
24. Zhu T, Wang L, Wang LP, Wan Q. Therapeutic targets of neuroprotection and neurorestoration in ischemic stroke: applications for natural compounds from medicinal herbs. *Biomed Pharmacother.* 2022;148:112719. doi:10.1016/j.biopha.2022.112719
25. Lin TN, Sun SW, Cheung WM, Li F, Chang C. Dynamic changes in cerebral blood flow and angiogenesis after transient focal cerebral ischemia in rats. Evaluation with serial magnetic resonance imaging. *Stroke.* 2002;33:2985–2991. doi:10.1161/01.STR.0000037675.97888.9D
26. Du K, Zhao C, Wang L, et al. MiR-191 inhibit angiogenesis after acute ischemic stroke targeting VEZF1. *Aging (Albany NY).* 2019;11:2762–2786. doi:10.18632/aging.101948
27. Feng XF, Li MC, Lin ZY, et al. Tetramethylpyrazine promotes stroke recovery by inducing the restoration of neurovascular unit and transformation of A1/A2 reactive astrocytes. *Front Cell Neurosci.* 2023;17:1125412. doi:10.3389/fncel.2023.1125412
28. Nguyen JN, Mohan EC, Pandya G, et al. CD13 facilitates immune cell migration and aggravates acute injury but promotes chronic post-stroke recovery. *J Neuroinflammation.* 2023;20:232. doi:10.1186/s12974-023-02918-3
29. Roll L, Faissner A. Influence of the extracellular matrix on endogenous and transplanted stem cells after brain damage. *Front Cell Neurosci.* 2014;8:219. doi:10.3389/fncel.2014.00219
30. Krupinski J, Kaluza J, Kumar P, Kumar S, Wang JM. Role of angiogenesis in patients with cerebral ischemic stroke. *Stroke.* 1994;25:1794–1798. doi:10.1161/01.STR.25.9.1794
31. Hatakeyama M, Ninomiya I, Kanazawa M. Angiogenesis and neuronal remodeling after ischemic stroke. *Neural Regen Res.* 2020;15:16–19. doi:10.4103/1673-5374.264442
32. Sun Y, Ding S, Fan Y, et al. MiR-429 inhibits the angiogenesis of human brain microvascular endothelial cells through SNAI2-mediated GSK-3 β / β -catenin pathway. *Comput Math Methods Med.* 2021;2021:6753926. doi:10.1155/2021/6753926
33. Rahman AA, Amruta N, Pinteaux E, Bix GJ. Neurogenesis after stroke: a therapeutic perspective. *Transl Stroke Res.* 2021;12:1–14. doi:10.1007/s12975-020-00841-w
34. Krupiński J, Kaluza J, Kumar P, Kumar S, Wang JM. Some remarks on the growth-rate and angiogenesis of microvessels in ischemic stroke. Morphometric and immunocytochemical studies. *Patol Pol.* 1993;44:203–209.
35. Marushima A, Nieminen M, Kremenetskaia I, et al. Balanced single-vector co-delivery of VEGF/PDGF-BB improves functional collateralization in chronic cerebral ischemia. *J Cereb Blood Flow Metab.* 2020;40:404–419. doi:10.1177/0271678X18818298
36. Badhiwala JH, Nassiri F, Alhazzani W, et al. Endovascular thrombectomy for acute ischemic stroke: a meta-analysis. *JAMA.* 2015;314:1832–1843. doi:10.1001/jama.2015.13767
37. Chen S, Zhang J, Li M, Zhou J, Zhang Y. Danhong injection combined with tPA protects the BBB through Notch-VEGF signaling pathway on long-term outcomes of thrombolytic therapy. *Biomed Pharmacother.* 2022;153:113288. doi:10.1016/j.biopha.2022.113288
38. Teng H, Chopp M, Hozeska-Solgot A, et al. Tissue plasminogen activator and plasminogen activator inhibitor 1 contribute to sonic hedgehog-induced in vitro cerebral angiogenesis. *PLoS One.* 2012;7:e33444.
39. Ismail AA, Shaker BT, Bajou K. The plasminogen-activator plasmin system in physiological and pathophysiological angiogenesis. *Int J Mol Sci.* 2021;23:337. doi:10.3390/ijms23010337
40. Liu J, Wang Y, Akamatsu Y, et al. Vascular remodeling after ischemic stroke: mechanisms and therapeutic potentials. *Prog Neurobiol.* 2014;115:138–156. doi:10.1016/j.pneurobio.2013.11.004
41. Zhang ZG, Chopp M. Neurorestorative therapies for stroke: underlying mechanisms and translation to the clinic. *Lancet Neurol.* 2009;8:491–500. doi:10.1016/S1474-4422(09)70061-4
42. Sun L, Zhang Y, Liu E, et al. The roles of astrocyte in the brain pathologies following ischemic stroke. *Brain Inj.* 2019;33:712–716. doi:10.1080/02699052.2018.1531311
43. Dillen Y, Kemps H, Gervois P, Wolfs E, Bronckaers A. Adult neurogenesis in the subventricular zone and its regulation after ischemic stroke: implications for therapeutic approaches. *Transl Stroke Res.* 2020;11:60–79. doi:10.1007/s12975-019-00717-8
44. Sato Y, Falcone-Juengert J, Tominaga T, Su H, Liu J, Ribatti D. Remodeling of the neurovascular unit following cerebral ischemia and hemorrhage. *Cells.* 2022;12:11. doi:10.3390/cells12010011
45. Iadecola C. The neurovascular unit coming of age: a journey through neurovascular coupling in health and disease. *Neuron.* 2017;96:17–42. doi:10.1016/j.neuron.2017.07.030

46. Zlokovic BV. Neurovascular mechanisms of Alzheimer's neurodegeneration. *Trends Neurosci.* 2005;28:202–208. doi:10.1016/j.tins.2005.02.001
47. Buxton RB, Frank LR. A model for the coupling between cerebral blood flow and oxygen metabolism during neural stimulation. *J Cereb Blood Flow Metab.* 1997;17:64–72. doi:10.1097/00004647-199701000-00009
48. Fang J, Wang Z, Miao CY. Angiogenesis after ischemic stroke. *Acta Pharmacol Sin.* 2023;44:1305–1321. doi:10.1038/s41401-023-01061-2
49. Freitas-Andrade M, Raman-Nair J, Lacoste B. Structural and functional remodeling of the brain vasculature following stroke. *Front Physiol.* 2020;11:948. doi:10.3389/fphys.2020.00948
50. Williamson MR, Fuertes CJA, Dunn AK, Drew MR, Jones TA. Reactive astrocytes facilitate vascular repair and remodeling after stroke. *Cell Rep.* 2021;35:109048. doi:10.1016/j.celrep.2021.109048
51. Feng N, Wang Z, Wu Y, et al. ADAMTS9-AS2 promotes angiogenesis of brain microvascular endothelial cells through regulating miR-185-5p/IGFBP-2 axis in ischemic stroke. *Mol Neurobiol.* 2022;59:2593–2604. doi:10.1007/s12035-021-02641-1
52. Yang Y, Rosenberg GA. Blood-brain barrier breakdown in acute and chronic cerebrovascular disease. *Stroke.* 2011;42:3323–3328. doi:10.1161/STROKEAHA.110.608257
53. Zhang Y, Liu L, Zhao X, Yan S, Zeng F, Zhou D. New insight into ischemic stroke: circadian rhythm in post-stroke angiogenesis. *Front Pharmacol.* 2022;13:927506. doi:10.3389/fphar.2022.927506
54. Ramirez GA, Coletto LA, Sciorati C, et al. Ion channels and transporters in inflammation: special focus on trp channels and TRPC6. *Cells.* 2018;7. doi:10.3390/cells7070070
55. Cheng J, Wen J, Wang N, Wang C, Xu Q, Yang Y. Ion channels and vascular diseases. *Arterioscler Thromb Vasc Biol.* 2019;39:e146–e156. doi:10.1161/ATVBAHA.119.312004
56. Loh KP, Ng G, Yu CY, et al. TRPM4 inhibition promotes angiogenesis after ischemic stroke. *Pflugers Arch.* 2014;466:563–576. doi:10.1007/s00424-013-1347-4
57. Pires PW, Earley S. Neuroprotective effects of TRPA1 channels in the cerebral endothelium following ischemic stroke. *Elife.* 2018;7. doi:10.7554/eLife.35316
58. Zhang S, Zhao J, Wu M, et al. Over-activation of TRPM2 ion channel accelerates blood-spinal cord barrier destruction in diabetes combined with spinal cord injury rat. *Int J Biol Sci.* 2023;19:2475–2494. doi:10.7150/ijbs.80672
59. Earley S, Brayden JE. Transient receptor potential channels in the vasculature. *Physiol Rev.* 2015;95:645–690. doi:10.1152/physrev.00026.2014
60. Wei BY, Hou JN, Yan CP, et al. Shexiang Baoxin Pill treats acute myocardial infarction by promoting angiogenesis via GDF15-TRPV4 signaling. *Biomed Pharmacother.* 2023;165:115186. doi:10.1016/j.biopha.2023.115186
61. Hong JM, Lee JS, Lee YB, et al. Nelonemaz for patients with acute ischemic stroke undergoing endovascular reperfusion therapy: a randomized phase ii trial. *Stroke.* 2022;53:3250–3259. doi:10.1161/STROKEAHA.122.039649
62. French JA, Porter RJ, Perucca E, et al. Efficacy and safety of XEN1101, a novel potassium channel opener, in adults with focal epilepsy: a phase 2b randomized clinical trial. *JAMA Neurol.* 2023;80:1145–1154. doi:10.1001/jamaneurol.2023.3542
63. Al-Khazali HM, Christensen RH, Dodick DW, Chaudhry BA, Burstein R, Ashina H. Hypersensitivity to opening of ATP-sensitive potassium channels in post-traumatic headache. *Cephalalgia.* 2023;43:3331024231210930. doi:10.1177/03331024231210930
64. Melincovici CS, Boşca AB, Şuşman S, et al. Vascular endothelial growth factor (VEGF) - key factor in normal and pathological angiogenesis. *Rom J Morphol Embryol.* 2018;59:455–467.
65. Wiszniak S, Schwarz Q, Broughton P, Bradshaw AD, DeLeon-Pennell KY. Exploring the intracrine functions of VEGF-A. *Biomolecules.* 2021;12:11.
66. Alitalo K, Tammela T, Petrova TV. Lymphangiogenesis in development and human disease. *Nature.* 2005;438:946–953. doi:10.1038/nature04480
67. Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. *Nat Med.* 2003;9:669–676. doi:10.1038/nm0603-669
68. Hu Q, Liu L, Zhou L, et al. Effect of fluoxetine on HIF-1 α -Netrin/VEGF cascade, angiogenesis and neuroprotection in a rat model of transient middle cerebral artery occlusion. *Exp Neurol.* 2020;329:113312. doi:10.1016/j.expneurol.2020.113312
69. Semenza GL. HIF-1: mediator of physiological and pathophysiological responses to hypoxia. *J Appl Physiol.* 2000;88:1474–1480. doi:10.1152/jappl.2000.88.4.1474
70. Hu Y, Zheng Y, Wang T, Jiao L, Luo Y. VEGF, a key factor for blood brain barrier injury after cerebral ischemic stroke. *Aging Dis.* 2022;13:647–654. doi:10.14336/AD.2021.1121
71. Koch S, Claesson-Welsh L. Signal transduction by vascular endothelial growth factor receptors. *Cold Spring Harb Perspect Med.* 2012;2:a006502.
72. Bootle-Wilbraham CA, Tazzyman S, Thompson WD, Stirk CM, Lewis CE. Fibrin fragment E stimulates the proliferation, migration and differentiation of human microvascular endothelial cells in vitro. *Angiogenesis.* 2001;4:269–275. doi:10.1023/A:1016076121918
73. Ruan L, Wang B, ZhuGe Q, Jin K. Coupling of neurogenesis and angiogenesis after ischemic stroke. *Brain Res.* 2015;1623:166–173. doi:10.1016/j.brainres.2015.02.042
74. Bhardwaj S, Roy H, Babu M, Shibuya M, Yla-Herttuala S. Adventitial gene transfer of VEGFR-2 specific VEGF-E chimera induces MCP-1 expression in vascular smooth muscle cells and enhances neointimal formation. *Atherosclerosis.* 2011;219:84–91. doi:10.1016/j.atherosclerosis.2011.07.103
75. Lee S, Chen TT, Barber CL, et al. Autocrine VEGF signaling is required for vascular homeostasis. *Cell.* 2007;130:691–703. doi:10.1016/j.cell.2007.06.054
76. Yu Y, Dai K, Gao Z, et al. Sulfated polysaccharide directs therapeutic angiogenesis via endogenous VEGF secretion of macrophages. *Sci Adv.* 2021;7. doi:10.1126/sciadv.abd8217
77. Mistry RK, Brewer AC. Redox regulation of gasotransmission in the vascular system: a focus on angiogenesis. *Free Radic Biol Med.* 2017;108:500–516. doi:10.1016/j.freeradbiomed.2017.04.025
78. Endres M, Laufs U, Liao JK, Moskowitz MA. Targeting eNOS for stroke protection. *Trends Neurosci.* 2004;27:283–289. doi:10.1016/j.tins.2004.03.009
79. Liu X, Zhang Y, Wang Y, Yang M, Hong F, Yang S. Protein phosphorylation in cancer: role of nitric oxide signaling pathway. *Biomolecules.* 2021;12:11. doi:10.3390/biom12010011

80. Theis V, Theiss C. VEGF - A stimulus for neuronal development and regeneration in the CNS and PNS. *Curr Protein Pept Sci*. 2018;19:589–597. doi:10.2174/1389203719666180104113937
81. Wang L, Astone M, Alam SK, et al. Suppressing STAT3 activity protects the endothelial barrier from VEGF-mediated vascular permeability. *Dis Model Mech*. 2021;2021:14.
82. Hermann DM, Zechariah A. Implications of vascular endothelial growth factor for postischemic neurovascular remodeling. *J Cereb Blood Flow Metab*. 2009;29:1620–1643. doi:10.1038/jcbfm.2009.100
83. Kilic E, Kilic U, Wang Y, Bassetti CL, Marti HH, Hermann DM. The phosphatidylinositol-3 kinase/Akt pathway mediates VEGF's neuroprotective activity and induces blood brain barrier permeability after focal cerebral ischemia. *FASEB j*. 2006;20:1185–1187. doi:10.1096/fj.05-4829fje
84. Ghorri A, Prinz V, Nieminen-Kehlä M, et al. Vascular endothelial growth factor augments the tolerance towards cerebral stroke by enhancing neurovascular repair mechanism. *Transl Stroke Res*. 2022;13:774–791. doi:10.1007/s12975-022-00991-z
85. Dziejko M, Derugin N, Wendland MF, Vexler ZS, Ferriero DM. Delayed VEGF treatment enhances angiogenesis and recovery after neonatal focal rodent stroke. *Transl Stroke Res*. 2013;4:189–200. doi:10.1007/s12975-012-0221-6
86. Alrafiah A, Alofi E, Almohaya Y, et al. Angiogenesis biomarkers in ischemic stroke patients. *J Inflamm Res*. 2021;14:4893–4900. doi:10.2147/JIR.S331868
87. Li J, Chen Y, Zhang X, Zhang B, Zhang M, Xu Y. Human urinary kallidinogenase improves outcome of stroke patients by shortening mean transit time of perfusion magnetic resonance imaging. *J Stroke Cerebrovasc Dis*. 2015;24:1730–1737. doi:10.1016/j.jstrokecerebrovasdis.2015.03.032
88. Guo Y, Abdoulaye IA, Liu F, et al. N-butylphthalide vs. human urinary kallidinogenase for the treatment of acute ischemic stroke: functional outcome and impact on serum VEGF and TNF- α expressions. *Ann Clin Lab Sci*. 2021;51:503–511.
89. Guan J, Bennet L, Gluckman PD, Gunn AJ. Insulin-like growth factor-1 and post-ischemic brain injury. *Prog Neurobiol*. 2003;70:443–462. doi:10.1016/j.pneurobio.2003.08.002
90. De Geyter D, De Smedt A, Stoop W, De Keyser J, Kooijman R. Central IGF-I receptors in the brain are instrumental to neuroprotection by systemically injected IGF-I in a rat model for ischemic stroke. *CNS Neurosci Ther*. 2016;22:611–616. doi:10.1111/ens.12550
91. Siddiqui EM, Mehan S, Bhalla S, Shandilya A. Potential role of IGF-1/GLP-1 signaling activation in intracerebral hemorrhage. *Curr Res Neurobiol*. 2022;3:100055. doi:10.1016/j.crneur.2022.100055
92. Liu XF, Fawcett JR, Thorne RG, DeFor TA, Frey WH. Intranasal administration of insulin-like growth factor-I bypasses the blood-brain barrier and protects against focal cerebral ischemic damage. *J Neurol Sci*. 2001;187:91–97. doi:10.1016/S0022-510X(01)00532-9
93. Wang J, Tang Y, Zhang W, et al. Insulin-like growth factor-1 secreted by brain microvascular endothelial cells attenuates neuron injury upon ischemia. *Febs j*. 2013;280:3658–3668. doi:10.1111/febs.12359
94. Zhu W, Fan Y, Frenzel T, et al. Insulin growth factor-1 gene transfer enhances neurovascular remodeling and improves long-term stroke outcome in mice. *Stroke*. 2008;39:1254–1261. doi:10.1161/STROKEAHA.107.500801
95. Zhang J, Liu M, Huang M, et al. Ginsenoside F1 promotes angiogenesis by activating the IGF-1/IGF1R pathway. *Pharmacol Res*. 2019;144:292–305. doi:10.1016/j.phrs.2019.04.021
96. Ashpole NM, Sanders JE, Hodges EL, Yan H, Sonntag WE. Growth hormone, insulin-like growth factor-1 and the aging brain. *Exp Gerontol*. 2015;68:76–81. doi:10.1016/j.exger.2014.10.002
97. Peng B, Kong G, Yang C, Ming Y. Erythropoietin and its derivatives: from tissue protection to immune regulation. *Cell Death Dis*. 2020;11:79. doi:10.1038/s41419-020-2276-8
98. Chateauvieux S, Grigorakaki C, Morceau F, Dicato M, Erythropoietin DM. erythropoiesis and beyond. *Biochem Pharmacol*. 2011;82:1291–1303. doi:10.1016/j.bcp.2011.06.045
99. Suresh S, Rajvanshi PK, Noguchi CT. The many facets of erythropoietin physiologic and metabolic response. *Front Physiol*. 2019;10:1534. doi:10.3389/fphys.2019.01534
100. Ureña-Guerrero ME, Castañeda-Cabral JL, Rivera-Cervantes MC, et al. Neuroprotective and neurorestorative effects of Epo and VEGF: perspectives for new therapeutic approaches to neurological diseases. *Curr Pharm Des*. 2020;26:1263–1276. doi:10.2174/1381612826666200114104342
101. Haine L, Yegen CH, Marchant D, Richalet JP, Boncoeur E, Voituron N. Cytoprotective effects of erythropoietin: what about the lung? *Biomed Pharmacother*. 2021;139:111547. doi:10.1016/j.biopha.2021.111547
102. Pradeep S, Huang J, Mora EM, et al. Erythropoietin stimulates tumor growth via EphB4. *Cancer Cell*. 2015;28:610–622. doi:10.1016/j.ccell.2015.09.008
103. Ribatti D, Presta M, Vacca A, et al. Human erythropoietin induces a pro-angiogenic phenotype in cultured endothelial cells and stimulates neovascularization in vivo. *Blood*. 1999;93:2627–2636. doi:10.1182/blood.V93.8.2627
104. Weng S, Zhu X, Jin Y, Wang T, Huang H. Protective effect of erythropoietin on myocardial infarction in rats by inhibition of caspase-12 expression. *Exp Ther Med*. 2011;2:833–836. doi:10.3892/etm.2011.280
105. Sirén AL, Fratelli M, Brines M, et al. Erythropoietin prevents neuronal apoptosis after cerebral ischemia and metabolic stress. *Proc Natl Acad Sci U S A*. 2001;98:4044–4049. doi:10.1073/pnas.051606598
106. Wang L, Sheng G, Cui J, et al. Electroacupuncture attenuates ischemic injury after stroke and promotes angiogenesis via activation of EPO mediated Src and VEGF signaling pathways. *PLoS One*. 2022;17:e0274620.
107. Maltaner RE, Schiappacasse A, Chamorro ME, Nesse AB, Vittori DC. Aquaporin-1 plays a key role in erythropoietin-induced endothelial cell migration. *Biochim Biophys Acta Mol Cell Res*. 2020;1867:118569. doi:10.1016/j.bbamer.2019.118569
108. Hong JM, Choi MH, Park GH, et al. Transdural revascularization by multiple burrhole after erythropoietin in stroke patients with cerebral hypoperfusion: a randomized controlled trial. *Stroke*. 2022;53:2739–2748. doi:10.1161/STROKEAHA.122.038650
109. Hernández CC, Burgos CF, Gajardo AH, et al. Neuroprotective effects of erythropoietin on neurodegenerative and ischemic brain diseases: the role of erythropoietin receptor. *Neural Regen Res*. 2017;12:1381–1389. doi:10.4103/1673-5374.215240
110. Ostrowski D, Heinrich R. Alternative erythropoietin receptors in the nervous system. *J Clin Med*. 2018;7. doi:10.3390/jcm7020024
111. Darlington TR, LaManna JC, Xu K. Effect of 3-Day and 21-day hypoxic preconditioning on recovery following cerebral ischemia in rats. *Adv Exp Med Biol*. 2021;1269:317–322.

112. Zhang SJ, Wang RL, Zhao HP, et al. MEPO promotes neurogenesis and angiogenesis but suppresses gliogenesis in mice with acute ischemic stroke. *Eur J Pharmacol.* 2019;849:1–10. doi:10.1016/j.ejphar.2019.01.066
113. Imamura R, Matsumoto K. Hepatocyte growth factor in physiology and infectious diseases. *Cytokine.* 2017;98:97–106. doi:10.1016/j.cyt.2016.12.025
114. Tang H, Gamdzyk M, Huang L, et al. Delayed recanalization after MCAO ameliorates ischemic stroke by inhibiting apoptosis via HGF/c-Met/STAT3/Bcl-2 pathway in rats. *Exp Neurol.* 2020;330:113359. doi:10.1016/j.expneurol.2020.113359
115. Zhang J, Jiang X, Jiang Y, et al. Recent advances in the development of dual VEGFR and c-Met small molecule inhibitors as anticancer drugs. *Eur J Med Chem.* 2016;108:495–504. doi:10.1016/j.ejmech.2015.12.016
116. Moosavi F, Giovannetti E, Saso L, Firuzi O. HGF/MET pathway aberrations as diagnostic, prognostic, and predictive biomarkers in human cancers. *Crit Rev Clin Lab Sci.* 2019;56:533–566. doi:10.1080/10408363.2019.1653821
117. Rosen EM, Lateral J, Joseph A, et al. Scatter factor expression and regulation in human glial tumors. *Int J Cancer.* 1996;67:248–255. doi:10.1002/(SICI)1097-0215(19960717)67:2<248::AID-IJC16>3.0.CO;2-7
118. Shang J, Deguchi K, Ohta Y, et al. Strong neurogenesis, angiogenesis, synaptogenesis, and antifibrosis of hepatocyte growth factor in rats brain after transient middle cerebral artery occlusion. *J Neurosci Res.* 2011;89:86–95. doi:10.1002/jnr.22524
119. Tang H, Zhang X, Hao X, et al. Hepatocyte growth factor-modified hair follicle stem cells ameliorate cerebral ischemia/reperfusion injury in rats. *Stem Cell Res Ther.* 2023;14:25. doi:10.1186/s13287-023-03251-5
120. Sengupta S, Sellers LA, Li RC, et al. Targeting of mitogen-activated protein kinases and phosphatidylinositol 3 kinase inhibits hepatocyte growth factor/scatter factor-induced angiogenesis. *Circulation.* 2003;107:2955–2961. doi:10.1161/01.CIR.0000077501.19266.E5
121. Yang Z-J, Xu S-L, Chen B, et al. Hepatocyte growth factor plays a critical role in the regulation of cytokine production and induction of endothelial progenitor cell mobilization: a pilot gene therapy study in patients with coronary heart disease. *Clin Exp Pharmacol Physiol.* 2009;36(8):790–796. doi:10.1111/j.1440-1681.2009.05151.x
122. Lee KH, Koh SA, Kim JR. Hepatocyte growth factor-mediated gastrin-releasing peptide induces IL-8 expression through Ets-1 in gastric cancer cells. *Oncol Res.* 2013;20:393–402. doi:10.3727/0965504013X13657689382770
123. Sulpice E, Plouët J, Bergé M, Allanic D, Tobelem G, Merkulova-Rainon T. Neuropilin-1 and neuropilin-2 act as coreceptors, potentiating proangiogenic activity. *Blood.* 2008;111:2036–2045. doi:10.1182/blood-2007-04-084269
124. Makarevich PI, Dergilev KV, Tsokolaeva ZI, et al. Angiogenic and pleiotropic effects of VEGF165 and HGF combined gene therapy in a rat model of myocardial infarction. *PLoS One.* 2018;13:e0197566.
125. Zhang Y, Zhang Y, Chopp M, Zhang ZG, Mahmood A, Xiong Y. Mesenchymal stem cell-derived exosomes improve functional recovery in rats after traumatic brain injury: a dose-response and therapeutic window study. *Neurorehabil Neural Repair.* 2020;34:616–626. doi:10.1177/1545968320926164
126. Moon GJ, Sung JH, Kim DH, et al. Application of mesenchymal stem cell-derived extracellular vesicles for stroke: biodistribution and microRNA study. *Transl Stroke Res.* 2019;10:509–521. doi:10.1007/s12975-018-0668-1
127. O'Brien J, Hayder H, Zayed Y, Peng C. Overview of MicroRNA biogenesis, mechanisms of actions, and circulation. *Front Endocrinol.* 2018;9:402. doi:10.3389/fendo.2018.00402
128. Falcione S, Kamtchum-Tatuene J, Sykes G, Jickling GC. RNA expression studies in stroke: what can they tell us about stroke mechanism? *Curr Opin Neurol.* 2020;33:24–29. doi:10.1097/WCO.0000000000000786
129. Jeyaseelan K, Lim KY, Armugam A. MicroRNA expression in the blood and brain of rats subjected to transient focal ischemia by middle cerebral artery occlusion. *Stroke.* 2008;39:959–966. doi:10.1161/STROKEAHA.107.500736
130. Khoshnam SE, Winlow W, Farbood Y, Moghaddam HF, Farzaneh M. Emerging roles of microRNAs in Ischemic Stroke: as Possible Therapeutic Agents. *J Stroke.* 2017;19:166–187. doi:10.5853/jos.2016.01368
131. Han B, Zhang Y, Zhang Y, et al. Novel insight into circular RNA HECTD1 in astrocyte activation via autophagy by targeting MIR142-TIPARP: implications for cerebral ischemic stroke. *Autophagy.* 2018;14:1164–1184. doi:10.1080/15548627.2018.1458173
132. Crosby ME, Devlin CM, Glazer PM, Calin GA, Ivan M. Emerging roles of microRNAs in the molecular responses to hypoxia. *Curr Pharm Des.* 2009;15:3861–3866. doi:10.2174/138161209789649367
133. Zeng L, He X, Wang Y, et al. MicroRNA-210 overexpression induces angiogenesis and neurogenesis in the normal adult mouse brain. *Gene Ther.* 2014;21:37–43. doi:10.1038/gt.2013.55
134. Li Y, Mao L, Gao Y, Baral S, Zhou Y, Hu B. MicroRNA-107 contributes to post-stroke angiogenesis by targeting Dicer-1. *Sci Rep.* 2015;5:13316. doi:10.1038/srep13316
135. Yin KJ, Hamblin M, Chen YE. Angiogenesis-regulating microRNAs and Ischemic Stroke. *Curr Vasc Pharmacol.* 2015;13:352–365. doi:10.2174/15701611113119990016
136. Hua Z, Lv Q, Ye W, et al. MiRNA-directed regulation of VEGF and other angiogenic factors under hypoxia. *PLoS One.* 2006;1:e116. doi:10.1371/journal.pone.0000116
137. Sun P, Zhang K, Hassan SH, et al. Endothelium-targeted deletion of microRNA-15a/16-1 promotes poststroke angiogenesis and improves long-term neurological recovery. *Circ Res.* 2020;126:1040–1057. doi:10.1161/CIRCRESAHA.119.315886
138. Chen Y, Gorski DH. Regulation of angiogenesis through a microRNA (miR-130a) that down-regulates antiangiogenic homeobox genes GAX and HOXA5. *Blood.* 2008;111:1217–1226. doi:10.1182/blood-2007-07-104133
139. Todoran R, Falcione SR, Clarke M, Joy T, Boghiozian R, Jickling GC. microRNA as a therapeutic for ischemic stroke. *Neurochem Int.* 2023;163:105487. doi:10.1016/j.neuint.2023.105487
140. Chan W, Ismail H, Mayaki D, et al. Fibulin-5 regulates angiopoietin-1/Tie-2 receptor signaling in endothelial cells. *PLoS One.* 2016;11:e0156994.
141. Beck H, Plate KH. Angiogenesis after cerebral ischemia. *Acta Neuropathol.* 2009;117:481–496. doi:10.1007/s00401-009-0483-6
142. Hoang TT, Raines RT. Molecular basis for the autonomous promotion of cell proliferation by angiogenin. *Nucleic Acids Res.* 2017;45:818–831. doi:10.1093/nar/gkw1192
143. Yu W, Goncalves KA, Li S, et al. Plexin-B2 mediates physiologic and pathologic functions of angiogenin. *Cell.* 2017;171:849–864.e25. doi:10.1016/j.cell.2017.10.005
144. Cucci LM, Satriano C, Marzo T, La Mendola D. Angiogenin and Copper Crossing in Wound Healing. *Int J Mol Sci.* 2021;23:22.

145. Kishimoto K, Liu S, Tsuji T, Olson KA, Hu GF. Endogenous angiogenin in endothelial cells is a general requirement for cell proliferation and angiogenesis. *Oncogene*. 2005;24:445–456. doi:10.1038/sj.onc.1208223
146. Gabriel-Salazar M, Morancho A, Rodriguez S, et al. Importance of angiogenin and endothelial progenitor cells after rehabilitation both in ischemic stroke patients and in a mouse model of cerebral ischemia. *Front Neurol*. 2018;9:508. doi:10.3389/fneur.2018.00508
147. Sebastià J, Kieran D, Breen B, et al. Angiogenin protects motoneurons against hypoxic injury. *Cell Death Differ*. 2009;16:1238–1247. doi:10.1038/cdd.2009.52
148. Steidinger TU, Slone SR, Ding H, Standaert DG, Yacoubian TA. Angiogenin in Parkinson disease models: role of Akt phosphorylation and evaluation of AAV-mediated angiogenin expression in MPTP treated mice. *PLoS One*. 2013;8:e56092.
149. Xu X, Zheng L, Yuan Q, et al. Transforming growth factor- β in stem cells and tissue homeostasis. *Bone Res*. 2018;6:2. doi:10.1038/s41413-017-0005-4
150. Vander Ark A, Cao J, Li X. TGF- β receptors: in and beyond TGF- β signaling. *Cell Signal*. 2018;52:112–120. doi:10.1016/j.cellsig.2018.09.002
151. Peng D, Fu M, Wang M, Wei Y, Wei X. Targeting TGF- β signal transduction for fibrosis and cancer therapy. *Mol Cancer*. 2022;21:104. doi:10.1186/s12943-022-01569-x
152. Jaykumar AB, Plumber S, Barry DM, et al. WNK1 collaborates with TGF- β in endothelial cell junction turnover and angiogenesis. *Proc Natl Acad Sci U S A*. 2022;119:e2203743119.
153. Hong Q, Zhang L, Fu J, et al. LRG1 promotes diabetic kidney disease progression by enhancing TGF- β -induced angiogenesis. *J Am Soc Nephrol*. 2019;30:546–562. doi:10.1681/ASN.2018060599
154. Du J, Yin G, Hu Y, et al. Coicis semen protects against focal cerebral ischemia-reperfusion injury by inhibiting oxidative stress and promoting angiogenesis via the TGF β /ALK1/Smad1/5 signaling pathway. *Aging (Albany NY)*. 2020;13:877–893. doi:10.18632/aging.202194
155. Zhang L, Wei W, Ai X, et al. Extracellular vesicles from hypoxia-preconditioned microglia promote angiogenesis and repress apoptosis in stroke mice via the TGF- β /Smad2/3 pathway. *Cell Death Dis*. 2021;12:1068. doi:10.1038/s41419-021-04363-7
156. Nakagawa T, Li JH, Garcia G, et al. TGF-beta induces proangiogenic and antiangiogenic factors via parallel but distinct Smad pathways. *Kidney Int*. 2004;66:605–613. doi:10.1111/j.1523-1755.2004.00780.x
157. Guérit E, Arts F, Dachy G, Boulouadnine B, Demoulin JB. PDGF receptor mutations in human diseases. *Cell Mol Life Sci*. 2021;78:3867–3881. doi:10.1007/s00018-020-03753-y
158. Pandey P, Khan F, Upadhyay TK, Seungjoon M, Park MN, Kim B. New insights about the PDGF/PDGFR signaling pathway as a promising target to develop cancer therapeutic strategies. *Biomed Pharmacother*. 2023;161:114491. doi:10.1016/j.biopha.2023.114491
159. Iihara K, Hashimoto N, Tsukahara T, Sakata M, Yanamoto H, Taniguchi T. Platelet-derived growth factor-BB, but not -AA, prevents delayed neuronal death after forebrain ischemia in rats. *J Cereb Blood Flow Metab*. 1997;17:1097–1106. doi:10.1097/00004647-199710000-00012
160. Evrova O, Buschmann J. In vitro and in vivo effects of PDGF-BB delivery strategies on tendon healing: a review. *Eur Cell Mater*. 2017;34:15–39. doi:10.22203/eCM.v034a02
161. Jayaraj RL, Azimullah S, Beiram R, Jalal FY, Rosenberg GA. Neuroinflammation: friend and foe for ischemic stroke. *J Neuroinflammation*. 2019;16:142. doi:10.1186/s12974-019-1516-2
162. Papadopoulos N, Lennartsson J. The PDGF/PDGFR pathway as a drug target. *Mol Aspects Med*. 2018;62:75–88. doi:10.1016/j.mam.2017.11.007
163. Dăng TC, Ishii Y, Nguyen V, et al. Powerful homeostatic control of oligodendroglial lineage by PDGFR α in adult brain. *Cell Rep*. 2019;27:1073–1089.e5. doi:10.1016/j.celrep.2019.03.084
164. Lin CM, Chiu JH, Wu IH, Wang BW, Pan CM, Chen YH. Ferulic acid augments angiogenesis via VEGF, PDGF and HIF-1 alpha. *J Nutr Biochem*. 2010;21:627–633. doi:10.1016/j.jnutbio.2009.04.001
165. Andrae J, Gouveia L, Gallini R, et al. A role for PDGF-C/PDGFR α signaling in the formation of the meningeal basement membranes surrounding the cerebral cortex. *Biol Open*. 2016;5:461–474. doi:10.1242/bio.017368
166. Nguyen QL, Okuno N, Hamashima T, et al. Vascular PDGFR-alpha protects against BBB dysfunction after stroke in mice. *Angiogenesis*. 2021;24:35–46. doi:10.1007/s10456-020-09742-w
167. Cui H, Yang A, Zhou H, et al. Thrombin-induced miRNA-24-1-5p upregulation promotes angiogenesis by targeting prolyl hydroxylase domain 1 in intracerebral hemorrhagic rats. *J Neurosurg*. 2020;134:1515–1526. doi:10.3171/2020.2.JNS193069
168. Yuan Y, Zhang Z, Wang Z, Liu J. MiRNA-27b regulates angiogenesis by targeting AMPK in mouse ischemic stroke model. *Neuroscience*. 2019;398:12–22. doi:10.1016/j.neuroscience.2018.11.041
169. Xin H, Wang F, Li Y, et al. Secondary release of exosomes from astrocytes contributes to the increase in neural plasticity and improvement of functional recovery after stroke in rats treated with exosomes harvested from MicroRNA 133b-overexpressing multipotent mesenchymal stromal cells. *Cell Transplant*. 2017;26:243–257. doi:10.3727/096368916X693031
170. Sun J, Tao S, Liu L, Guo D, Xia Z, Huang M. miR-140-5p regulates angiogenesis following ischemic stroke by targeting VEGFA. *Mol Med Rep*. 2016;13:4499–4505. doi:10.3892/mmr.2016.5066
171. Caballero-Garrido E, Pena-Philippides JC, Lordkipanidze T, et al. In vivo inhibition of miR-155 promotes recovery after experimental mouse stroke. *J Neurosci*. 2015;35:12446–12464. doi:10.1523/JNEUROSCI.1641-15.2015
172. Gu Y, Ampofo E, Menger MD, Laschke MW. miR-191 suppresses angiogenesis by activation of NF- κ B signaling. *FASEB j*. 2017;31:3321–3333. doi:10.1096/fj.201601263R
173. Li Z, Li J, Tang N. Long noncoding RNA Malat1 is a potent autophagy inducer protecting brain microvascular endothelial cells against oxygen-glucose deprivation/reoxygenation-induced injury by sponging miR-26b and upregulating ULK2 expression. *Neuroscience*. 2017;354:1–10. doi:10.1016/j.neuroscience.2017.04.017
174. Wang S, Han X, Mao Z, Xin Y, Maharjan S, Zhang B. MALAT1 lncRNA induces autophagy and protects brain microvascular endothelial cells against oxygen-glucose deprivation by binding to miR-200c-3p and upregulating SIRT1 expression. *Neuroscience*. 2019;397:116–126. doi:10.1016/j.neuroscience.2018.11.024
175. Wang M, Li C, Zhang Y, Zhou X, Liu Y, Lu C. LncRNA MEG3-derived miR-361-5p regulate vascular smooth muscle cells proliferation and apoptosis by targeting ABCA1. *Am J Transl Res*. 2019;11:3600–3609.
176. Avraham Y, Davidi N, Lassri V, et al. Leptin induces neuroprotection neurogenesis and angiogenesis after stroke. *Curr Neurovasc Res*. 2011;8:313–322. doi:10.2174/156720211798120954

177. Eyileten C, Sharif L, Wicik Z, et al. The relation of the brain-derived neurotrophic factor with MicroRNAs in neurodegenerative diseases and ischemic stroke. *Mol Neurobiol.* 2021;58:329–347. doi:10.1007/s12035-020-02101-2
178. Dela Peña IC, Yoo A, Tajiri N, et al. Granulocyte colony-stimulating factor attenuates delayed tPA-induced hemorrhagic transformation in ischemic stroke rats by enhancing angiogenesis and vasculogenesis. *J Cereb Blood Flow Metab.* 2015;35:338–346. doi:10.1038/jcbfm.2014.208
179. Zhou C, Kuang Y, Li Q, et al. Endothelial S1pr2 regulates post-ischemic angiogenesis via AKT/eNOS signaling pathway. *Theranostics.* 2022;12:5172–5188. doi:10.7150/thno.71585
180. Xiang Y, Yao X, Wang X, et al. Houshiheisan promotes angiogenesis via HIF-1 α /VEGF and SDF-1/CXCR4 pathways: in vivo and in vitro. *Biosci Rep.* 2019;2019:39.
181. Zou Y, Hu J, Huang W, et al. Non-mitogenic fibroblast growth factor 1 enhanced angiogenesis following ischemic stroke by regulating the sphingosine-1-phosphate 1 pathway. *Front Pharmacol.* 2020;11:59. doi:10.3389/fphar.2020.00059
182. Sugiura S, Kitagawa K, Tanaka S, et al. Adenovirus-mediated gene transfer of heparin-binding epidermal growth factor-like growth factor enhances neurogenesis and angiogenesis after focal cerebral ischemia in rats. *Stroke.* 2005;36:859–864. doi:10.1161/01.STR.0000158905.22871.95
183. Li Y, Chang S, Li W, et al. cxcl12-engineered endothelial progenitor cells enhance neurogenesis and angiogenesis after ischemic brain injury in mice. *Stem Cell Res Ther.* 2018;9:139. doi:10.1186/s13287-018-0865-6
184. Gu C, Zhang Q, Li Y, et al. The PI3K/AKT pathway—the potential key mechanisms of traditional Chinese medicine for stroke. *Front Med Lausanne.* 2022;9:900809. doi:10.3389/fmed.2022.900809
185. Dong C, Wu J, Chen Y, Nie J, Chen C. Activation of PI3K/AKT/mTOR pathway causes drug resistance in breast cancer. *Front Pharmacol.* 2021;12:628690. doi:10.3389/fphar.2021.628690
186. Sharma A, Mehan S. Targeting PI3K-AKT/mTOR signaling in the prevention of autism. *Neurochem Int.* 2021;147:105067. doi:10.1016/j.neuint.2021.105067
187. Lee JH, Kim C, Um JY, Sethi G, Ahn KS. Casticin-induced inhibition of cell growth and survival are mediated through the dual modulation of akt/mtor signaling cascade. *Cancers.* 2019;12:11. doi:10.3390/cancers12010011
188. Wang M, Zhang J, Gong N. Role of the PI3K/Akt signaling pathway in liver ischemia reperfusion injury: a narrative review. *Ann Palliat Med.* 2022;11:806–817. doi:10.21037/apm-21-3286
189. Kaya D, Gürsoy-Ozdemir Y, Yemisci M, Tuncer N, Aktan S, Dalkara T. VEGF protects brain against focal ischemia without increasing blood-brain permeability when administered intracerebroventricularly. *J Cereb Blood Flow Metab.* 2005;25:1111–1118. doi:10.1038/sj.jcbfm.9600109
190. Zhang Q, Zhao Y, Xu Y, et al. Sodium ferulate and n-butylidenephthalate combined with bone marrow stromal cells (BMSCs) improve the therapeutic effects of angiogenesis and neurogenesis after rat focal cerebral ischemia. *J Transl Med.* 2016;14:223. doi:10.1186/s12967-016-0979-5
191. Van den Beucken T, Koritzinsky M, Wouters BG. Translational control of gene expression during hypoxia. *Cancer Biol Ther.* 2006;5:749–755. doi:10.4161/cbt.5.7.2972
192. Chen J, Zhang X, Liu X, et al. Ginsenoside Rg1 promotes cerebral angiogenesis via the PI3K/Akt/mTOR signaling pathway in ischemic mice. *Eur J Pharmacol.* 2019;856:172418. doi:10.1016/j.ejphar.2019.172418
193. Cui HJ, Yang AL, Zhou HJ, et al. Buyang huanwu decoction promotes angiogenesis via vascular endothelial growth factor receptor-2 activation through the PI3K/Akt pathway in a mouse model of intracerebral hemorrhage. *BMC Complement Altern Med.* 2015;15:91. doi:10.1186/s12906-015-0605-8
194. Hudson CC, Liu M, Chiang GG, et al. Regulation of hypoxia-inducible factor 1 α expression and function by the mammalian target of rapamycin. *Mol Cell Biol.* 2002;22:7004–7014. doi:10.1128/MCB.22.20.7004-7014.2002
195. Patra K, Jana S, Sarkar A, Mandal DP, Bhattacharjee S. The inhibition of hypoxia-induced angiogenesis and metastasis by cinnamaldehyde is mediated by decreasing HIF-1 α protein synthesis via PI3K/Akt pathway. *Biofactors.* 2019;45:401–415. doi:10.1002/biof.1499
196. Karar J, Maity A. PI3K/AKT/mTOR Pathway in Angiogenesis. *Front Mol Neurosci.* 2011;4:51. doi:10.3389/fnmol.2011.00051
197. Zhu Y, Liu X, Zhao P, Zhao H, Gao W, Wang L. Celestrol suppresses glioma vasculogenic mimicry formation and angiogenesis by blocking the PI3K/Akt/mTOR signaling pathway. *Front Pharmacol.* 2020;11:25. doi:10.3389/fphar.2020.00025
198. Wang H, Zang C, Liu XS, Aster JC. The role of Notch receptors in transcriptional regulation. *J Cell Physiol.* 2015;230:982–988. doi:10.1002/jcp.24872
199. Guo M, Niu Y, Xie M, Liu X, Li X. Notch signaling, hypoxia, and cancer. *Front Oncol.* 2023;13:1078768. doi:10.3389/fonc.2023.1078768
200. Sun Y, Cheng X, Wang H, et al. dl-3-n-butylphthalide promotes neuroplasticity and motor recovery in stroke rats. *Behav Brain Res.* 2017;329:67–74. doi:10.1016/j.bbr.2017.04.039
201. Zhang P, Xu R, Guo Y, et al. DL-3-n-butylphthalide promotes dendrite development in cortical neurons subjected to oxygen-glucose deprivation/reperfusion. *Cell Biol Int.* 2018;42:1041–1049. doi:10.1002/cbin.10980
202. Pietras A, von Stedingk K, Lindgren D, Pählman S, Axelson H. JAG2 induction in hypoxic tumor cells alters Notch signaling and enhances endothelial cell tube formation. *Mol Cancer Res.* 2011;9:626–636. doi:10.1158/1541-7786.MCR-10-0508
203. Liang C, Ni GX, Shi XL, Jia L, Wang YL. Astragaloside IV regulates the HIF/VEGF/Notch signaling pathway through miRNA-210 to promote angiogenesis after ischemic stroke. *Restor Neurol Neurosci.* 2020;38:271–282. doi:10.3233/RNN-201001
204. Shi F, Dong Z, Li H, Liu X, Liu H, Dong R. MicroRNA-137 protects neurons against ischemia/reperfusion injury through regulation of the Notch signaling pathway. *Exp Cell Res.* 2017;352:1–8. doi:10.1016/j.yexcr.2017.01.015
205. Zhu T, Xie WJ, Wang L, et al. Notoginsenoside R1 activates the NAMPT-NAD(+)-SIRT1 cascade to promote postischemic angiogenesis by modulating Notch signaling. *Biomed Pharmacother.* 2021;140:111693. doi:10.1016/j.biopha.2021.111693
206. Baichwal VR, Baeuerle PA. Activate NF-kappa B or die? *Curr Biol.* 1997;7:R94–6. doi:10.1016/S0960-9822(06)00046-7
207. Yu H, Lin L, Zhang Z, Zhang H, Hu H. Targeting NF-kB pathway for the therapy of diseases: mechanism and clinical study. *Signal Transduct Target Ther.* 2020;5:209. doi:10.1038/s41392-020-00312-6
208. Tang S, Nie X, Ruan J, Cao Y, Kang J, Ding C. Circular RNA circNFKB1 promotes osteoarthritis progression through interacting with ENO1 and sustaining NF-kB signaling. *Cell Death Dis.* 2022;13:695. doi:10.1038/s41419-022-05148-2
209. Korbecki J, Simińska D, Gąssowska-Dobrowolska M, et al. Chronic and cycling hypoxia: drivers of cancer chronic inflammation through HIF-1 and NF-kB activation: a review of the molecular mechanisms. *Int J Mol Sci.* 2021;23:22. doi:10.3390/ijms23010022

210. Xie TX, Xia Z, Zhang N, Gong W, Huang S. Constitutive NF-kappaB activity regulates the expression of VEGF and IL-8 and tumor angiogenesis of human glioblastoma. *Oncol Rep.* 2010;23:725–732.
211. Xia ZB, Meng FR, Fang YX, et al. Inhibition of NF-kB signaling pathway induces apoptosis and suppresses proliferation and angiogenesis of human fibroblast-like synovial cells in rheumatoid arthritis. *Medicine.* 2018;97:e10920.
212. Bakshi HA, Quinn GA, Nasef MM, et al. Crocin inhibits angiogenesis and metastasis in colon cancer via TNF- α /NF-kB/VEGF pathways. *Cells.* 2022;12:11.
213. Cui L, Duchamp NS, Boston DJ, et al. NF-kB is involved in brain repair by stem cell factor and granulocyte-colony stimulating factor in chronic stroke. *Exp Neurol.* 2015;263:17–27. doi:10.1016/j.expneurol.2014.08.026
214. Li Y, Liang W, Guo C, et al. Renshen Shouwu extract enhances neurogenesis and angiogenesis via inhibition of TLR4/NF-kB/NLRP3 signaling pathway following ischemic stroke in rats. *J Ethnopharmacol.* 2020;253:112616. doi:10.1016/j.jep.2020.112616
215. Wang T, Soker S, Atala A, Siroky MB, Azadzi KM. Alterations in angiogenic growth factors and neuronal nitric oxide synthase expression in chronic cavernosal ischemia. *Int J Impot Res.* 2004;16:403–411. doi:10.1038/sj.ijir.3901186
216. Zhu H, Zou L, Tian J, Du G, Gao Y. SMND-309, a novel derivative of salvianolic acid B, protects rat brains ischemia and reperfusion injury by targeting the JAK2/STAT3 pathway. *Eur J Pharmacol.* 2013;714:23–31. doi:10.1016/j.ejphar.2013.05.043
217. Cui Q, Zhang Y, Tian N, et al. Leptin promotes angiogenesis via Pericyte STAT3 pathway upon intracerebral hemorrhage. *Cells.* 2022;12:11.
218. Xia Y, Ling X, Hu G, et al. Small extracellular vesicles secreted by human iPSC-derived MSC enhance angiogenesis through inhibiting STAT3-dependent autophagy in ischemic stroke. *Stem Cell Res Ther.* 2020;11:313. doi:10.1186/s13287-020-01834-0
219. Zhong Y, Yin B, Ye Y, et al. The bidirectional role of the JAK2/STAT3 signaling pathway and related mechanisms in cerebral ischemia-reperfusion injury. *Exp Neurol.* 2021;341:113690. doi:10.1016/j.expneurol.2021.113690
220. Cho C, Smallwood PM, Nathans J. Reck and Gpr124 are essential receptor cofactors for Wnt7a/Wnt7b-specific signaling in mammalian CNS angiogenesis and blood-brain barrier regulation. *Neuron.* 2017;95:1056–1073.e5. doi:10.1016/j.neuron.2017.07.031
221. Liu J, Xiao Q, Xiao J, et al. Wnt/ β -catenin signalling: function, biological mechanisms, and therapeutic opportunities. *Signal Transduct Target Ther.* 2022;7:3. doi:10.1038/s41392-021-00762-6
222. Jiang L, Yin M, Wei X, et al. Bach1 represses Wnt/ β -catenin signaling and angiogenesis. *Circ Res.* 2015;117:364–375. doi:10.1161/CIRCRESAHA.115.306829
223. Xu Y, Zhang G, Kang Z, Xu Y, Jiang W, Zhang S. Cornin increases angiogenesis and improves functional recovery after stroke via the Ang1/Tie2 axis and the Wnt/ β -catenin pathway. *Arch Pharm Res.* 2016;39:133–142. doi:10.1007/s12272-015-0652-1
224. Du J, Li J. The role of Wnt signaling pathway in atherosclerosis and its relationship with angiogenesis. *Exp Ther Med.* 2018;16:1975–1981. doi:10.3892/etm.2018.6397
225. Tang E, Wang Y, Liu T, Yan B. Gastrin promotes angiogenesis by activating HIF-1 α / β -catenin/VEGF signaling in gastric cancer. *Gene.* 2019;704:42–48. doi:10.1016/j.gene.2019.04.029
226. Shi S, Wang M, Liu X, Han S, Zhu P. Scalp electroacupuncture promotes angiogenesis after stroke in rats by activation of Wnt/ β -catenin signal pathway. *Evid Based Complement Alternat Med.* 2022;2022:1649605.
227. Wang LP, Pan J, Li Y, et al. Oligodendrocyte precursor cell transplantation promotes angiogenesis and remyelination via Wnt/ β -catenin pathway in a mouse model of middle cerebral artery occlusion. *J Cereb Blood Flow Metab.* 2022;42:757–770.
228. Wen X, Jiao L, Tan H. MAPK/ERK Pathway as a Central regulator in vertebrate organ regeneration. *Int J Mol Sci.* 2022;23(3):1464.
229. Song ZY, Wang F, Cui SX, Qu XJ. Knockdown of CXCR4 Inhibits CXCL12-induced angiogenesis in HUVECs through Downregulation of the MAPK/ERK and PI3K/AKT and the Wnt/ β -catenin pathways. *Cancer Invest.* 2018;36:10–18. doi:10.1080/07357907.2017.1422512
230. Geng HY, Feng ZJ, Zhang JJ, Li GY. Exosomal CLIC1 released by CLL promotes HUVECs angiogenesis by regulating ITG β 1-MAPK/ERK axis. *Kaohsiung J Med Sci.* 2021;37:226–235. doi:10.1002/kjm2.12287
231. Wu P, Tong Z, Luo L, et al. Comprehensive strategy of conduit guidance combined with VEGF producing Schwann cells accelerates peripheral nerve repair. *Bioact Mater.* 2021;6:3515–3527. doi:10.1016/j.bioactmat.2021.03.020
232. Liang Z, Chi YJ, Lin GQ, Luo SH, Jiang QY, Chen YK. MiRNA-26a promotes angiogenesis in a rat model of cerebral infarction via PI3K/AKT and MAPK/ERK pathway. *Eur Rev Med Pharmacol Sci.* 2018;22:3485–3492. doi:10.26355/eurrev_201806_15175