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REVIEW ARTICLE

Angiogenesis after ischemic stroke

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Owing to its high disability and mortality rates, stroke has been the second leading cause of death worldwide. Since the pathological mechanisms of stroke are not fully understood, there are few clinical treatment strategies available with an exception of tissue plasminogen activator (tPA), the only FDA-approved drug for the treatment of ischemic stroke. Angiogenesis is an important protective mechanism that promotes neural regeneration and functional recovery during the pathophysiological process of stroke. Thus, inducing angiogenesis in the peri-infarct area could effectively improve hemodynamics, and promote vascular remodeling and recovery of neurovascular function after ischemic stroke. In this review, we summarize the cellular and molecular mechanisms affecting angiogenesis after cerebral ischemia registered in PubMed, and provide pro-angiogenic strategies for exploring the treatment of ischemic stroke, including endothelial progenitor cells, mesenchymal stem cells, growth factors, cytokines, non-coding RNAs, etc.

Keywords: ischemic stroke; angiogenesis; endothelial progenitor cells; stem cells; secreted proteins

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INTRODUCTION

Stroke is the second leading cause of mortality and the leading cause of disability worldwide. It has high morbidity, mortality and disability rates, and its treatment methods are limited [1]. Stroke is a pathological condition that causes the cessation of blood supply to a portion of the brain, which results in abnormal blood dynamics, neurovascular function, and energy metabolism [2]. Ischemia or hemorrhage caused by a thrombus or systemic hypoperfusion can lead to the development of stroke [3]. Stroke is categorized into ischemic and hemorrhagic, wherein approximately 87% of cases are cerebral ischemia [4]. Currently, acute focal stroke is managed using three major approaches: neuroprotective, endovascular thrombectomy and thrombolytic therapy [3]. Theoretically, neuroprotection is a common strategy in treating ischemic and hemorrhagic stroke, and animal experimental models of stroke showed the effectiveness of neuroprotective drugs [5–7]. However, only a few have been proven clinically effective. Recent studies have shown that endovascular thrombectomy could improve recanalization rates in patients with ischemic stroke caused by large-artery occlusion, but surgical intervention could only be performed in select patients [8]. Additionally, the only FDA-approved drug for ischemic stroke treatment is tPA, which binds to fibrin via its lysine residue and activates the conversion of fibrinogen-bound plasminogen to plasmin, thereby achieving thrombolytic therapy [9]. However, its narrow therapeutic window (within 4.5 h after stroke) results in only 3%–5% of patients receiving timely treatment in practice, which hinders its better and broader clinical application [9]. Currently, no drugs can be used as a treatment for hemorrhagic stroke, which has a higher mortality rate [10]. Therefore, the pathological mechanism of stroke should be elucidated, and better drugs or methods should be available to treat stroke.

Neurovascular networks have been recently proposed, and the close communication between neurons and blood vessels is essential for brain function [11]. Certainly, angiogenesis is an important protective mechanism promoting nerve regeneration and functional recovery during stroke. Studies have shown that cerebral ischemia could induce transient angiogenesis [12]. Moreover, ischemic stroke treatment involves the promotion of angiogenesis in the peri-infarct area, which could effectively reduce the infarct volume, promote nerve cell survival and recover neurovascular network function [13]. With the development of stem cell technology and the discovery of molecular targets, cell and molecular therapies have been proposed, including stem cells such as endothelial progenitor cells (EPCs), mesenchymal stem cells (MSCs), and molecules such as vascular endothelial growth factor (VEGF), angiopoietin-1 (Ang1), microRNA, etc. This review summarized the cellular and molecular mechanisms affecting angiogenesis after cerebral ischemia in PubMed, and provided pro-angiogenic strategies to mainly explain ischemic stroke treatment, including EPCs, MSCs, growth factors, cytokines, non-coding RNAs (ncRNAs), etc.

ANGIOGENESIS AFTER ISCHEMIC STROKE

The most basic requirement in embryonic development is the development of blood vessels, which takes precedence over the development and differentiation of other tissues and organs, and guarantees reproductive function, wound healing and tissue injury and repair in adults [14]. Neovascularization occurs via two main cellular processes: vasculogenesis and angiogenesis [15]. Vasculogenesis, occurring mostly during embryonic blood vessel formation, refers to the differentiation of undifferentiated precursor cells (angioblasts) into endothelial cells (ECs), which assemble into the

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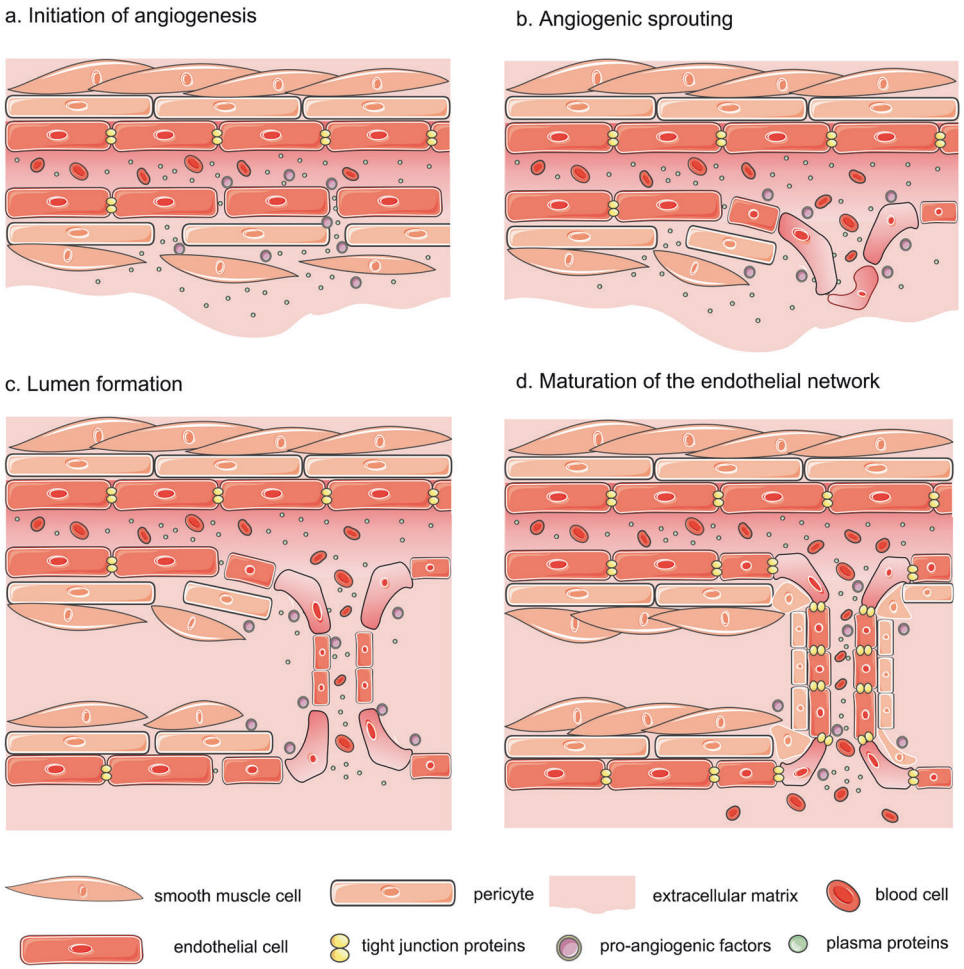

Fig. 1 Schematics of key steps in angiogenesis after ischemic stroke. a Pro-angiogenic molecules such as NO and VEGF induce local vasodilation, antagonize tight junctions between ECs, and initiate angiogenesis after ischemic stroke. Pericytes and smooth muscle cells are also loosened, resulting in extravasation of intravascular plasma proteins. **b** Activated ECs (graded pink) are induced to proliferate and migrate by a variety of angiogenic factors (VEGF, FGF, PDGF, αvβ3 integrin, etc.) to form subulate vascular buds. **c** Stimulated by VEGF, integrins (αvβ3 or α5) and other factors, activated EC continue to proliferate and migrate outwards, forming lumen with adjacent budding. **d** The newly formed lumen is not stable and needs to ensure endothelial cell survival and function, for example, tight junctions between ECs, orderly support of pericytes and smooth muscle cells, and deposition of the extracellular matrix.

primitive vascular network [14]. Angiogenesis refers to the growth of new vascular structures from existing blood vessels and involves various physiological and pathological processes in vivo, such as menstruation, pregnancy, wound healing, fracture repair, and "therapeutic angiogenesis" caused by ischemia [16]. More importantly, new blood vessels are mainly formed through angiogenesis in adults, although vasculogenesis has also been reported [3]. Angiogenesis has three main forms: remodeling of blood vessels to form smaller microvessels, sprouting angiogenesis, and arteriogenesis, which is the remedial formation of mature new arteries, increasing in length and width, from preexisting interconnected arterioles after arterial occlusion [17]. Evidence showed that angiogenesis after cerebral ischemia occurs through sprouting, which involves EC proliferation, migration, angiogenic sprouting and lumen formation, and endothelial network maturation [3] (Fig. 1).

After the development of stroke, the ischemic penumbra tissue releases a complex mix of angiogenic factors, such as VEGF, angiopoietins, platelet-derived growth factor (PDGF), angiogenin, transforming growth factors (TGFs), basic fibroblast growth factor (bFGF), matrix metalloproteinase (MMP), nitric oxide (NO), etc [18]. These angiogenic factors initiate and regulate angiogenesis, of which VEGF is a critical stimulator of angiogenesis. In humans, angiogenesis occurs 3–4 days after ischemic stroke [19]. Postmortem analyses of stroke patients showed an increased cerebral blood vessel density in the peri-infarct region compared with the contralateral normal area [19]. Moreover, blood vessel density in the ischemic border correlates with survival in stroke patients, and those with greater cerebral blood vessel density have better survival [19].

Initiation of angiogenesis after ischemic stroke

As the primary effector cells of the angiogenic response, ECs surrounding the infarcted brain area start to proliferate as early as 12–24 h after the development of ischemic stroke [20]. Moreover, VEGF upregulation in the peri-infarct region was described as early as 3 h after an ischemic insult, indicating that angiogenesis was initiated within hours of stroke onset [21]. Upon onset of ischemia stroke, VEGF and NO increase vascular permeability, leading to plasma protein extravasation that forms a temporary scaffold for endothelial cell migration [17]. For ECs to migrate from their resident sites, the contacts between ECs are loosened, and the support of the surrounding cells (pericytes and smooth muscle cells) is weakened, which ultimately leads to vascular instability [17]. After ischemic stroke onset, the reactive astrocytes restructure the extracellular matrix (ECM), leading to the formation of

ECM tracts that are used by migrating endothelial cells to establish new capillary buds [22, 23]. After establishing the sprouting path, VEGF binds to its receptors on vascular ECs to directly initiate an angiogenic response, promoting the proliferation and migration of endothelial cells [15].

Angiogenic sprouting after ischemic stroke
After initiation of angiogenesis, ECs are activated, which release proteases to degrade the ECM, and they proliferate and migrate to a distant space [3]. This process leads to vascular sprout formation, and depends on the involvement of various proteases and angiogenic cytokines, such as VEGF, placental growth factor (PLGF), Ang 1/2, FGF, PDGF, αvβ3 integrin, etc.

Lumen formation after ischemic stroke
After vessel sprouting, ECs accumulate continuously outward from the sprouting like solid cords, and the lumen is formed from the adjacent new budding [3]. Endothelial embedding and fusion with native vessels increase the vessel diameter and length in response to angiogenic factors, such as VEGF, Ang1, integrins (αvβ3 or α5), myocyte enhancer-binding factor 2 C, etc. Excessive matrix proteolysis may lead to cystic EC aggregation, which prevents lumen formation.

Maturation of the endothelial network after ischemic stroke
Endothelial network maturation includes the survival and differentiation of ECs in the neovascular lumen and vascular remodeling [24]. Studies showed that reduced endothelial cell survival led to vascular degeneration, which was detrimental to angiogenesis [17]. After the onset of ischemic stroke, ECs acquire special characteristics determined by the local tissue to adapt to the needs of the microenvironment [25]. For example, ECs involved in the exchange of substances in the endocrine glands differentiated into discontinuous and porous cells [26]. One of the most important parts of a mature endothelial network is remodeling, wherein new vessels are trimmed into capillary-like vessels that are organized irregularly into a structured branched vascular network [17]. Additionally, vascular smooth muscle cells and pericytes migrate around the blood vessels and contribute to ECM deposition. At this stage, various pro-angiogenic factors play an important role, such as VEGF, Ang and its receptor Tie, GTP-binding protein $G\alpha_{13}$, cell adhesion molecules, chemokine receptor 4, integrin α4, etc.

CELLULAR REGULATION OF ANGIOGENESIS AFTER ISCHEMIC STROKE

The vasculature in the brain originates from vasculogenesis during embryonic development and has some plasticity in adults. When cerebral ischemia occurs, various endogenous protective mechanisms are activated within a few minutes in the peri-infarct area, including angiogenesis, neurogenesis, glial cell infiltration, etc. After transient focal cerebral ischemia, a delayed increase was observed in cerebral blood flow and blood volume in the ipsilateral cortex, which may be related to angiogenesis [12]. Meanwhile, the cerebral ischemia-induced microvascular formation also promotes macrophage infiltration and clearance of necrotic tissue in the infarct area [13]. This enhanced angiogenesis in ischemic tissue is known as therapeutic angiogenesis. However, endogenous angiogenesis after ischemia was transient and completely disappeared weeks after ischemia. Endogenous angiogenesis was activated in the peri-infarct area in early cerebral ischemia [27]. Moreover, the remodeling area has different emerging progenitor cell populations [27, 28], such as EPCs, neural progenitor cells and oligodendrocyte progenitor cells (OPCs) [29]. Subsequently, evidence showed that various stem/progenitor cells had beneficial angiogenic effects [30], including embryonic stem cells (ESCs) [31], peripheral blood hematopoietic stem cells ($CD34^+$) [32], mesenchymal stem cells [33], neural stem/progenitor cells [34], oligodendrocyte precursor cells [35], human umbilical cord blood cells (huCBCs) [36], skin-derived progenitor cells (SKPs) [37], and EPCs [29].

EPCs
In an observational case-control study on 100 stroke patients, including 50 lacunar strokes and 50 cortical strokes, circulating EPCs were identified as potential biomarkers for the diagnosis and prognosis of cerebral ischemia [38]. EPCs play an important role in adult angiogenesis [39]. In response to the pathophysiological needs of neovascularization, EPCs could be mobilized from the bone marrow into the peripheral blood and differentiated into functional ECs, which participate in the neovascularization and blood vessel repair and remodeling [29].

The upregulation of high-mobility group box 1 caused by reactive astrocytes could induce the activation and accumulation of endogenous EPCs [40], promoting angiogenesis through chemokine (C-X-C motif) receptor 4 (CXCR4)/stromal cell-derived factor-1 (SDF-1) axis [41]. Interestingly, the secretome of EPCs from stroke patients promotes angiogenesis and endothelial tightness, thereby preventing vascular leakage caused by ischemia [42]. Moreover, the mobilization of endogenous EPCs might be beneficial to the repair of cerebral ischemia.

Furthermore, several studies reported that intravenous administration of EPCs [43–45] or transplantation of bone marrow-derived EPCs [46] or endothelial colony-forming cells [47], a homogeneous EPC subtype, could effectively promote neovascularization and improve functional repair after acute focal cerebral ischemia. The mechanism may involve increased plasma VEGF levels [44] and upregulation of hypoxia-inducible factor (HIF-1α) signaling [45], which reduce blood-brain barrier (BBB) leakage and degradation of tight junction proteins. Moreover, EPC transplantation induces vascular remodeling, which is related to MMP9 in the brain [48]. EPC-derived exosomes increase CD31 and VEGF expressions to promote angiogenesis and improve cerebral ischemic injury [49] (Table 1). Furthermore, a single EPC injection could prolong the lifespan of stroke-prone spontaneously hypertensive rats [50]. Additionally, EPCs played a role in promoting angiogenesis in a mouse model of permanent cerebral ischemia [51]. The chemokine CXCL12 promoted endothelial cell migration and tube formation through its receptor CXCR4 [52]. Therefore, VEGF expression, endothelial cell proliferation, and tube formation increased more significantly, which increases vessel density, if EPCs overexpressing chemokine *cxcl12* gene were used as a treatment for permanent damage caused by middle cerebral artery occlusion (MCAO) [51]. Although EPCs are the most important progenitor cells in angiogenesis, repair and remodeling after cerebral ischemia, and both endogenous EPC mobilization and exogenous EPC transplantation were effective, the exact mechanism has not been fully elucidated (Fig. 2).

MSCs
MSCs, also known as bone marrow stromal cells (BMSCs), are a class of stem cells found primarily in the bone marrow, and they can differentiate into various cell types in vivo, including osteoblasts [53], adipocytes [54], chondrocytes [55], hepatocytes [56], astrocytes [57], neurons [58], etc. MSCs can cross the BBB without damaging the brain's structural integrity [57], which has promoted the recent development of exogenous MSC transplantation in treating cerebral ischemia [33, 59]. Studies showed that intravenous administration of MSCs or human MSC cell line B10 in a rat model of focal cerebral ischemia could improve functional recovery by increasing the expression of neurotrophic factors, including insulin-like growth factor 1 (IGF-1), glial cell line-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), epidermal growth factor (EGF) and basic FGF [60, 61] (Table 1).

Table 1. Effects and mechanisms of cell transplantation therapy in cerebral ischemia.

Cell types	Effects	Mechanisms
EPCs; [43] bone marrow-derived EPCs; [46] ECFCs [47]	promoted cerebral neovascularization and neurovascular repair	increased HIF-1α signaling and plasma VEGF levels to reduce BBB leakage and tight junction protein degradation; [44, 45] related to MMP9; [48] increased the expression of CD31 and VEGF in the brain by secreting exosomes [49]
MSCs; [65, 68–70] human MSC cell line B10 [61]	enhanced the angiogenesis, induced functional improvement, reduced infarct volume, and neuroprotection	induced the expression of IGF-1, BDNF, EGF, and bFGF neurotrophic factors; [60] increased the expression and release of endogenous pro-angiogenic factors such as VEGF, Hes1, Ang1 and TGF-β1 in ischemic infarct area through Notch signaling; [65, 67, 68] increased expression of VEGF and Ang1 and their corresponding receptors Flk1 and Tie2 in MBECs or astrocytes; [69] transferred their functional mitochondria to stroke-injured ECs via nanotubes to improve endothelial cell function; [70] upregulated microRNA such as miR-21-5p, miR-210, and miR-126 to activate the PI3K/Akt/eNOS signaling pathway and induce the expression of pro-angiogenic factors, including VEGF, VEGFR2, Ang-1, Tie-2, EGF, and PDGF by secreting exosomes [84–86]
ESCs [31, 96]	promoted peri-infarct angiogenesis and decreased brain lesion	enhanced endogenous endothelial cell proliferation [31, 96]
iPSCs [98]	promoted angiogenesis	derived MSCs secreted extracellular vesicles that promote tube formation by inhibiting STAT3-dependent autophagy in ECs [98]
BMMNCs [99]	promoted arteriogenesis and angiogenesis	differentiated into smooth muscle cells and ECs mediated by cell-cell interaction mediated by endothelial gap junctions and the chemokine receptor CCR2 [100, 101]
$CD34^+$ cells [32, 102]	induced neuroplasticity and angiogenesis	increased β1 integrin expression [32]
NPCs/NSCs [34, 92]	facilitated angiogenesis	increased tight junction proteins and promoted Ang-1/Tie2 and VEGF/VEGFR2 signaling pathways in brain capillaries [34, 92]
ADSCs [104]	contributed to the migration length and tube extension in BMECs	down-regulated miR-181b-5p/TRPM7 axis by secreting exosomes [104]
hUCBCs [36]	promoted angiogenesis	increased the expression of BDNF, VEGF, Tie-2 and occludin [36]
hTPCs [105]	promoted angiogenesis and neurogenesis	increased the expression of LHX6, Olig1, PDGFRα, VEGFR1 and VEGFR2 [105]
hAFSCs [106]	improved cerebral vascular remodeling and angiogenesis	increased CD31, VEGF, vWF and α-SMA [106]
OPCs [35]	promoted angiogenesis and remyelination	facilitated endothelial β-catenin through Wnt7a [94]
SKPs [37]	promoted endogenous angiogenesis and neural stem cell proliferation	secreted bFGF and VEGF in the ischemic zone [37]
pericytes [117]	ameliorated neurovascular injury and promoted the formation of the blood-brain barrier	up-regulated the expression of NGF and NT3 through activating PDGFRβ/Akt; [117] secreted Ang-1 to activate its receptor Tie2 on the surface of ECs; [116] expressed and secreted other pro-angiogenic factors, including VEGF, TGFβ, angiopoietin, S1P and Notch signaling [21, 116, 118, 119]
microglia [122, 123]	regulated blood flow and promoted the proliferation and migration of ECs and angiogenesis	controlled purine release through PANX1 channel; [123] secreted the exosomes containing miRNA-26a; [124] stimulated Smad2/3 signaling from ECs by secreting extracellular vesicles enriched in TGF-β1; [125] released some pro-inflammatory cytokines, including MCP-1, TGF-α, TGF-β, G-CSF, FGF, IL-4, IL-6, IL-1β, which can also increase the expression of VEGF in ECs [126]

EPCs endothelial progenitor cells, *ECFCs* endothelial colony-forming cells, *MSCs* mesenchymal stem cells, *ESCs* embryonic stem cells, *iPSCs* induced pluripotent stem cells, *BMMNCs* bone marrow-derived mononuclear cells, *$CD34^+$ cells* peripheral blood stem cell, *NPCs/NSCs* neural progenitor/stem cells, *ADSCs* adipose-derived stem cells, *hUCBCs* human umbilical cord blood cells, *hTPCs* human placental trophoblast progenitor cells, *hAFSCs* human amniotic fluid stem cells, *OPCs* oligodendrocyte precursor cells, *SKPs* skin-derived progenitor cells.

Moreover, the transplanted MSCs increase various pro-angiogenic factor expression through autocrine and paracrine effects, and induce neovascularization and stability in the ischemic region [62, 63]. Accumulating evidence showed that BMSC transplantation after cerebral ischemia promotes angiogenesis and increases the expression and release of endogenous angiogenic factors such as VEGF, Hes1, Ang1 and TGF-β1 in ischemic infarct areas through Notch signaling [64–68] (Fig. 2). MSC-induced vascular stabilization might be mediated by increased VEGF and Ang1 expression and their corresponding receptors Flk1 and Tie2 in mouse brain ECs or astrocytes [69]. Interestingly, systemically delivered MSCs could transfer their

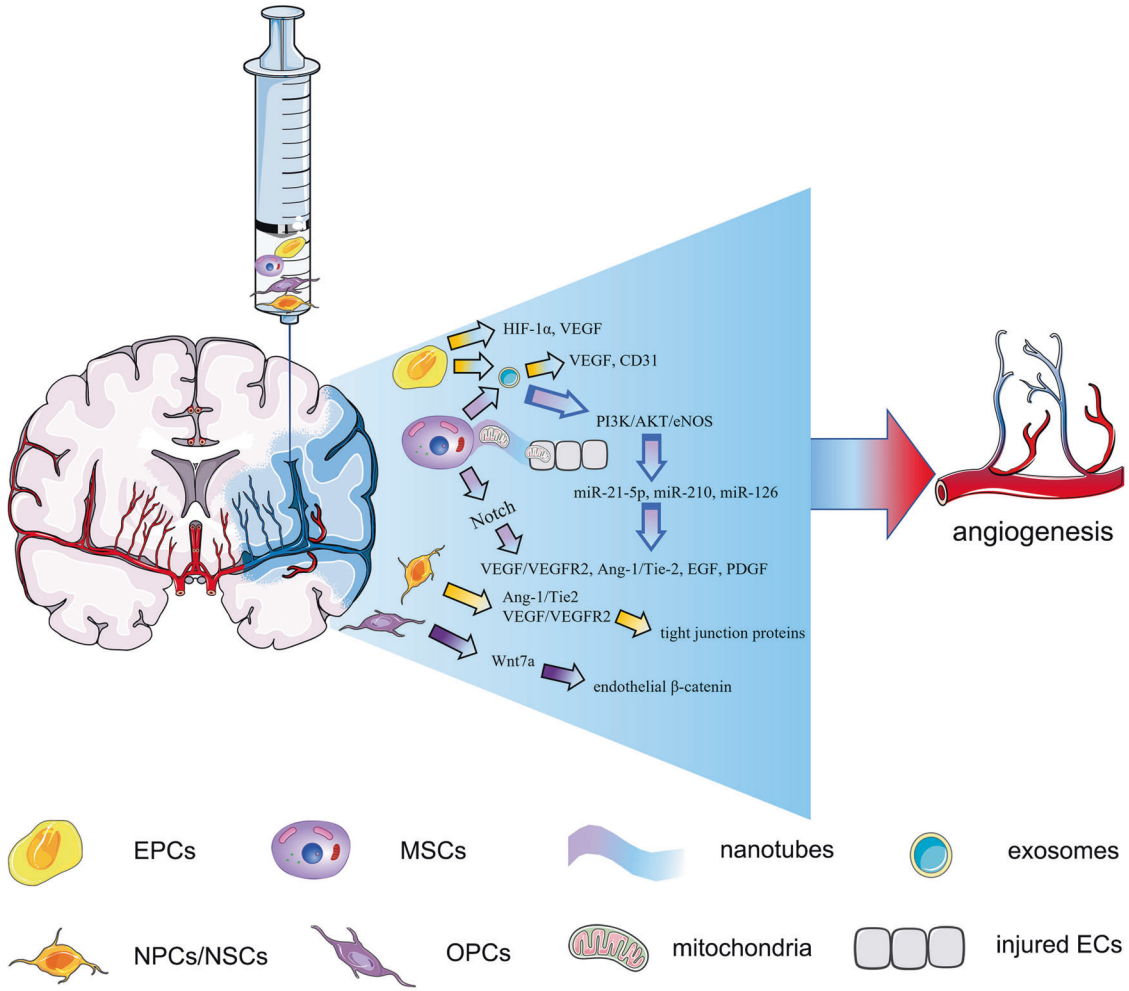

Fig. 2 Major stem cell therapies and its mechanisms for ischemic stroke. After stroke, the administered stem cells arrived the peri-infarct area and not only replaced the injured cells by directly differentiating into the corresponding ECs, neural cells, etc., but also promoted angiogenesis in the ischemic area through a variety of mechanisms. Endothelial progenitor cells could not only directly increase HIF-1α signaling and plasma VEGF levels, but also increase CD31 and VEGF expression by secreting exosomes in the brain. MSCs could promote angiogenesis in many ways, such as transferring their functional mitochondria to stroke-damaged ECs through nanotubes, and activating the PI3K/Akt/eNOS signaling pathway by secreting exosomes to up-regulate the expression of microRNAs and angiogenic factors. And the expression and release of endogenous angiogenic factors such as VEGF/VEGFR, Ang-1/Tie-2 and EGF in the peri-infarct zone were also increased through Notch signaling. NPCs/NSCs and OPCs could promote angiogenesis by increasing tight junction proteins in brain capillaries through Ang-1/Tie2 and VEGF/VEGFR2 signaling pathways, and by promoting β-catenin in ECs through Wnt7a.

functional mitochondria to stroke-injured ECs via nanotubes, thereby improving endothelial cell function and saving the cerebrovascular system [70] (Table 1, Fig. 2). A study evaluating the time window of MSC treatment showed that MSC treatment might have a beneficial effect through angiogenic mechanisms in the late stage of permanent MCAO (at least >1 month) in rats [71]. This might be related to the survival, migration, homing and implantation of transplanted cells in the lesion area. Therefore, methods promoting recruitment, survival and enhanced function of MSC around the ischemic core have been proposed. For example, gene modification of delivered MSCs to overexpress PLGF [72], CCL2 [73], thrombospondin-4 (TSP4) [74], CXCR4 [75], or Ang-1 [76] further enhanced the angiogenesis function of MSCs. Hypoxia-pretreated BMSCs enhanced the survival, homing, migration and differentiation of BMSCs through CXCL12/CXCR4 signaling [77] or upregulating HIF-1α and growth trophic factors, such as BDNF, GDNF, VEGF, FIK-1, EPO, EPOR, SDF-1, and CXCR4 [78]. Similarly, mild hypothermia could induce homing and angiogenesis of transplanted BMSCs to promote functional recovery and significantly reduce infarct size [79]. Combined therapy with drugs could also promote the beneficial effect of MSC treatment. Icariin and MSCs synergistically promote angiogenesis after transient MCAO by significantly increasing VEGF and BDNF expressions by activating the PI3K and ERK1/2 pathways [80].

Recent studies showed that BMSCs release secretome and extracellular vesicles to effectively promote angiogenesis [81]. Conditioned medium experiments showed that secretome from human embryonic MSCs promotes the partial recovery of focal ischemic injury by improving angiogenesis [82]. Extracellular vesicles, including exosomes and microvesicles, are nanoscale vesicles [83]. Exosomes and microvesicles are 30–100 and 40–1000 nm in diameter, respectively [83]. Exosomes derived from BMSCs promote angiogenesis and improve endothelial cell injury in ischemic stroke mice by microRNA upregulation, such as miR-21-5p [84], miR-210 [85], and miR-126 [86]. Subsequently, it activated the PI3K/Akt/eNOS signaling pathway and induced the expression of pro-angiogenic factors, such as VEGF, VEGFR2, Ang1, Tie2, EGF, and PDGF [84–86] (Fig. 2). However, MSC-derived extracellular vesicles also improved cerebral angiogenesis and

neurogenesis after stroke and prevented post-ischemic immunosuppression [87, 88] (Table 1). Gregorius et al. showed that the small extracellular vesicles produced by hypoxia-induced MSCs could promote cerebral vasculogenesis and brain remodeling in mice after focal cerebral ischemia by regulating miRNAs related to angiogenesis in human cerebral microvascular ECs, including up-regulation of miR-126-3p, miR-140-5p, and let-7C-5p, and the down-regulation of miR-186-5p, miR-370-3p, and miR-409-3p [89]. Moreover, microvesicles from MSCs treated with normal rat brain extract (NBE-MSC-MVs) and stroke-induced rat brain extract (SBE-MSC-MVs) were significantly better than untreated MSC-MVs in improving inflammation and enhancing angiogenesis and neurogenesis [90].

Neural stem cells

Neural stem cells (NSCs) are derived from neural tissue, and they can self-renew and differentiate into neurons, astrocytes and oligodendrocytes [91]. To enhance angiogenesis and repair damaged nerve tissue, endogenous NSCs proliferate, migrate, and differentiate into neurons and astrocytes in the hippocampus and cerebral cortex during ischemic brain injury [91]. Intravenous injection of neural progenitor/stem cells could promote Ang1/Tie2 and VEGF/VEGFR2 signaling pathways in brain capillaries, and increase tight junction proteins to facilitate angiogenesis [34, 92, 93] (Fig. 2). Moreover, OPC transplantation promotes angiogenesis and remodeling in ischemic stroke by acting on endothelial β-catenin through Wnt7a [35, 94] (Fig. 2).

Additional stem cells

Various experimental and clinical models showed the therapeutic effects of stem cell transplantation on brain injury, including ESCs, induced pluripotent stem cells (iPSCs), bone marrow-derived cells (BMDCs), NSCs, etc [95]. Systemic transplantation of ESCs or embryonic NSCs enhances endogenous endothelial cell proliferation to promote angiogenesis in the peri-infarct areas [31, 96]. iPSCs have been shown to derive different cell types to improve functional recovery after ischemia [97], and iPSC-derived MSCs could secrete extracellular vesicles that promote tube formation and angiogenesis by inhibiting signal transducer and activator of transcription-3 (STAT3)-dependent autophagy in ECs during brain ischemia [98] (Table 1). Bone marrow-derived mononuclear cells (BMMNCs) can differentiate into smooth muscle cells and ECs to promote arteriogenesis and angiogenesis in rats [99]. The mechanism may be mediated by cell-cell interaction mediated by endothelial gap junctions [100] and the chemokine receptor CCR2 [101]. Because BMMNCs are a rich source of human hematopoietic stem cells, peripheral blood stem cell ($CD34^+$) transplantation for stroke has also been considered [102]. Shyu et al. showed that transplanted $CD34^+$ cells increase β1 integrin expression to promote angiogenesis in chronic ischemic rats [32] (Table 1).

In addition, SKPs could secrete bFGF and VEGF in the ischemic zone to promote endogenous angiogenesis and NSC proliferation [37] (Table 1). Moreover, the mechanism by which adipose-derived stem cells promote cerebral vascular remodeling was exosomes secretion containing microRNA-181b-5p, which downregulated the expression of transient receptor potential melatonin 7 [103], and contributed to the migration length and tube extension in brain microvascular endothelial cells [104]. Other stem cells are also used in vascular remodeling and angiogenesis after cerebral ischemia, such as hUCBCs [36], human placental trophoblast progenitor cells [105] and human amniotic fluid stem cells [106].

With the development of stem cell culture technology, three-dimensional (3D) organ-like tissues, also known as organoids, provide promising models for studying organogenesis and disease [107]. An organoid is an in vitro 3D cellular cluster derived from ESCs or iPSCs that can self-renew and self-organize [108, 109]. Organoids may facilitate stem cell therapies because they contain stem and progenitor cells. Studies showed that the grafting of cerebral organoids into the mouse cortex could form functional vascular connections with the mouse cortex [110–112]. We also confirmed that cerebral organoid transplantation promoted neurogenesis, angiogenesis and neurological recovery in stroke rats [113]. Notably, because cerebral organoids contain various nerve cell types, their regulation mechanism in angiogenesis has not been fully clarified.

Pericytes

BMDCs promote angiogenesis after cerebral ischemia [114, 115]. However, the BMDC cell type supporting vascular remodeling after cerebral ischemia is still unclear. Kokovay et al. used GFP expression to trace the role of transplanted BMDCs in recipient mice, and found that BMDCs with vascular remodeling did not have endothelial cell markers, but expressed desmin and vimentin, which ultimately identified these cells as pericytes [115]. Pericytes may be derived from the bone marrow, and they are involved in vascular remodeling after cerebral ischemia [115]. Pericytes play an important role in the early and late stages of new blood vessel formation to help angiogenic sprouting and maintain the vascular lumen composed of ECs. Therefore, pericytes need to constantly communicate with ECs and exchange information [116]. PDGF receptor-β (PDGFRβ) was specifically expressed in pericytes around the infarction area in the rat MCAO model and gradually increased over time [117]. Meanwhile, PDGF-B expression is also upregulated in ECs in peri-infarct areas and further phosphorylates Akt in peripheral pericytes with high PDGFRβ expression [117]. PDGFRβ-Akt signaling in pericytes upregulates NGF and neurotrophin-3 expression, thereby improving neurovascular injury after stroke [117]. Ang1 secreted by pericytes also activates Tie2 on the surface of ECs and promotes BBB formation [116]. Furthermore, after cerebral ischemia, pericytes also express and secrete other pro-angiogenic factors, such as VEGF, TGFβ, angiopoietin, sphingosine-1-phosphate (S1P) and Notch signaling [21, 116, 118, 119] (Table 1). Subsequently, ECs regulate angiogenesis and ECM remodeling through STAT3 to improve long-term recovery after ischemic stroke [120].

Microglia

Microglia, macrophage-like cells residing in the central nervous system, have similar functions to macrophages, with two opposite phenotypes, M1 and M2. M1 microglia mainly secrete pro-inflammatory cytokines and exert a pro-inflammatory effect, whereas M2 microglia secrete anti-inflammatory cytokines to exert an anti-inflammatory effect [121]. Studies showed that perivascular microglia promote vascular collapse in the cerebral ischemic penumbra region [121, 122]. Subsequently, capillary-associated microglia control purine release through the PANX1 channel to regulate blood flow and vascular dilatation [123] (Table 1).

Furthermore, pretreatment of primary microglia with oxygen-glucose deprivation (OGD) or BV2 cell stimulation with interleukin-4 (IL-4) polarized them into the M2 phenotype and promoted angiogenesis and endothelial tube formation after ischemic stroke by secreting extracellular vesicles [124, 125]. The exosomes released from IL-4-polarized BV2 cells contain miRNA-26a to function [124], whereas hypoxia-induced microglia release vesicles enriched in TGF-β1 to stimulate Smad2/3 signaling from ECs to induce angiogenesis [125]. Additionally, microglia could secrete some pro-inflammatory cytokines, which increases VEGF expression in ECs, promotes the proliferation and migration of ECs and angiogenesis, including MCP-1, TGF-α, TGF-β, granulocyte colony-stimulating factor (G-CSF), FGF, IL-4, IL-6, IL-1β, etc [126] (Table 1).

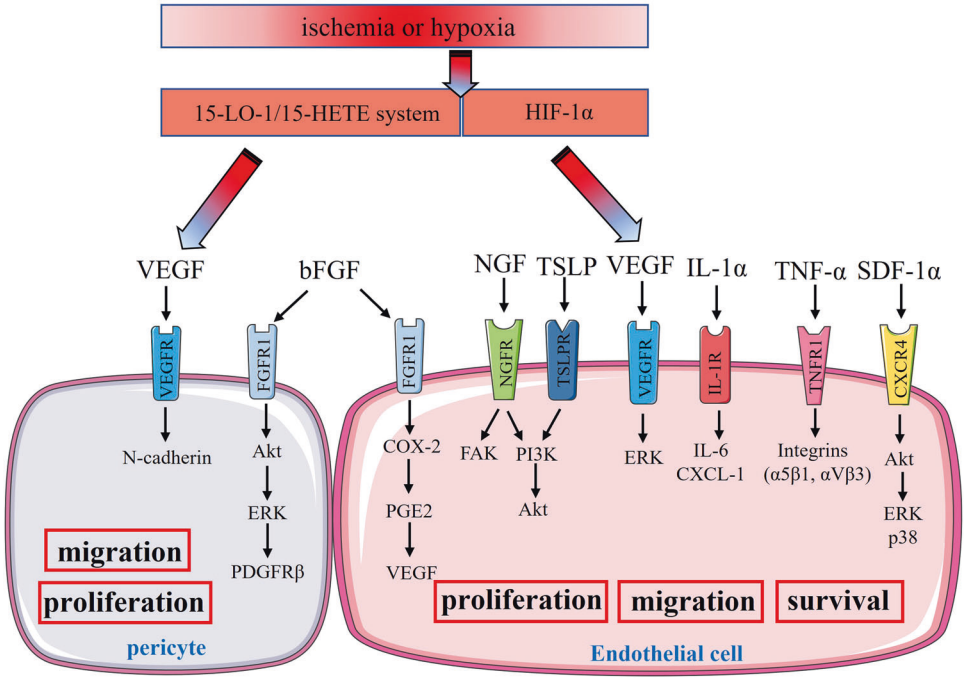

Fig. 3 Major factors and signaling pathways of angiogenesis after cerebral ischemia. Ischemia or hypoxia resulting from cerebral ischemia increased VEGF expression by upregulating HIF-1α and 15-LO-1/15-HETE systems, and subsequently VEGF promoted pericyte coverage of ECs by increasing N-cadherin expression on brain capillaries. NGF promoted angiogenesis by activating p-focal adhesion kinase (FAK) or PI3K/Akt signaling pathways after ischemic stroke, and similar pathways had also been found in TSLP and its receptor TSLPR. IL-1α, TNF-1α and SDF-1α also promoted angiogenesis by activating the expression of downstream genes through their receptors, respectively.

MOLECULAR REGULATION OF ANGIOGENESIS AFTER ISCHEMIC STROKE

During and after cerebral ischemia, cerebral blood vessels become unstable, vascular cells become relaxed, and ECs gradually proliferate, migrate and sprout, and angiogenesis occurs [15]. In this series of processes, different cell types and molecules mediating the crosstalk between cells are involved. These molecules regulate the biological behavior of various cells in a complex and coordinated manner and influence angiogenesis after stroke. Meanwhile, each molecule regulating angiogenesis shows its unique regulation mode and function. These factors, including growth factors, cytokines, angiogenic mediators, microRNAs, etc., mediate endothelial cell proliferation and migration, as well as tube formation and stability.

Growth factors

Accumulating data showed the involvement of several growth factors in angiogenesis after ischemic stroke, including bFGF, NGF, PDGF, BDNF, TGF-β1, and VEGF.

Mammals have five VEGF isoforms, such as VEGF-A, VEGF-B, VEGF-C, VEGF-D and PLGF, of which VEGF-A is the most original and most potent for angiogenesis [127]. VEGF-A acts via its receptors VEGFR1 and VEGFR2 in vascular ECs. Because of the low kinase activity of VEGFR1, VEGF-A angiogenesis is mainly achieved through its highly homologous VEGFR2 [128]. In 1996, two articles reported the importance of VEGF for embryonic angiogenesis [129, 130]. In 1998, a study showed that VEGF was significantly upregulated in the ischemic penumbra region after focal cerebral ischemia [131]. Mechanistically, HIF-1α and HIF-2α increased VEGF expression through ischemia or hypoxia [127, 132, 133] (Fig. 3). In addition, the transcriptional coactivator PGC-1α, independent of hypoxia response pathways and HIFs, strongly regulates VEGF expression and hindlimb angiogenesis in cultured muscle cells and skeletal muscle in vivo [134]. Moreover, specific p53 inhibition by pifithrin-α could lead to increased VEGF expression and angiogenesis after cerebral ischemia [135]. 15-Lipoxygenase (15-LO) catalyzes 15(S)-hydroxyeicosatetraenoic acid (15-HETE), major metabolite of arachidonic acid [136]. The 15-LO-1/15-HETE system was upregulated in cell models induced by OGD and a mouse model of MCAO, which also increased VEGF expression and promoted endothelial cell migration and microvessel formation after ischemic stroke [137] (Fig. 3). Endogenous VEGF was upregulated during or after cerebral ischemia to participate in angiogenesis through multiple different mechanisms. Therefore, exogenous administration of VEGF or in combination with indirect vasoreconstructive surgery could stimulate angiogenesis, reduce infarct size, and improve neurovascular function after chronic cerebral hypoperfusion [138, 139]. Furthermore, intraventricular injection of recombinant human VEGF also promotes pericyte coverage around the ECs and stabilizes neovascularization by increasing N-cadherin expression on cerebral capillaries [140] (Fig. 3). However, only a few studies support the mechanism of the VEGF/VEGFR cascade in regulating angiogenesis under the pathophysiological conditions of stroke. The combination of VEGF and Ang-2 leads to BBB leakage and promotes angiogenesis by increasing MMP-9 activity and inhibiting ZO-1 expression [141]. Interestingly, VEGF-B promotes the proliferation and differentiation of C2C12 myoblasts and skeletal muscle development through the PI3K/Akt signaling pathway regulated by VEGFR1 [142]. In VEGFR2-expressing neurons, PGC-1α increases VEGF expression and induces downstream PI3K/Akt and MEK/ERK signaling pathways to protect hippocampal neurons from apoptosis [143]. However, increased VEGF expression in OGD-induced ECs activates ERK signaling via its receptor Flk-1 but induces cell death [144] (Fig. 3), suggesting that the same signaling molecules mediate different effects in different cell types.

In 1991, bFGF, a heparin-binding growth factor, was discovered, and bFGF intraventricular administration could promote

cerebrovascular neovascularization after chronic cerebral ischemia [145]. Recent mechanistic studies found that intranasal administration of non-mitogenic FGF1 could activate the S1P receptor 1 (S1PR1) signaling pathway through its receptor FGFR1 and promote angiogenesis after stroke in vivo [146]. COX-2 expression is upregulated in in vitro cerebral microvascular ECs treated with bFGF, which promotes prostaglandin E2 (PGE2) production and increases VEGF expression in an autocrine manner [147] (Fig. 3). In addition, treadmill training increases bFGF expression in the ischemic brain, which further improves neurogenesis and angiogenesis through the caveolin-1/VEGF signaling pathway [148]. Interestingly, FGFR1 expression is up-regulated in intracerebral pericytes after cerebral ischemia or hypoxia [149]. With the administration of inhibitors, stroke-induced increased bFGF expression and upregulated PDGFRβ expression in pericytes of ischemic hemispheres by activating Akt/ERK signaling pathway via its receptor FGFR1, and improved BBB function after cerebral ischemia [149] (Fig. 3).

Angiogenesis after cerebral ischemia is also promoted by neurotrophins, originally found to induce neurogenesis, such as BDNF [150], hepatocyte growth factor [151], mesencephalic astrocyte-derived neurotrophic factor [152], PDGF [153], heparin-binding epidermal growth factor-like growth factor [154], TGF-β1 [155, 156], and growth differentiation factor 11 belonging the TGF-β superfamily and its downstream signaling molecule activin-like kinase 5 [157]. NGF also promotes angiogenesis by activating p-focal adhesion kinase (FAK) or PI3K/Akt signaling pathway after ischemic stroke [158, 159] (Fig. 3).

Cytokines

After the onset of stroke, cells, such as microglia and astrocytes are activated in the brain, and immune cells in the periphery, such as macrophages, also infiltrate into the brain, which releases cytokines, such as IL-8 [160], IL-6 [161], IL-1α [162], tumor necrosis factor-α (TNF-α) [163], galectin-3 (Gal-3) [164], Gal-1 [165], SDF-1α [166], G-CSF [167, 168], thymic stromal lymphopoietin (TSLP) [169], axon guidance factor netrin-1 [170, 171] and netrin-4 [172]. Although their mechanisms were different, these upregulated cytokines promote angiogenesis in ischemic brain regions.

Although IL-6 and IL-8 are members of the interleukin family, their mechanism of action is different. IL-8 promotes angiogenesis after ischemic stroke by increasing VEGF expression in human bone marrow MSCs via the PI3K/Akt and MAPK/ERK signaling pathways [160], whereas, IL-6 knockout decreases STAT3 activation and gene expression related to angiogenesis, such as *Cxcl4, Thbs1, Anxa2* and *Adamts1*, leading to decreased vessel density [161]. Compared with IL-1β, IL-1α has more potential to induce endothelial cell activation after cerebral ischemia [162]. IL-1α increases CXCL-1 and IL-6 expression via its receptor IL-1R, and promotes the migration and proliferation of ECs and tube-like structure formation [162] (Fig. 3). In addition, TNF-α, another pro-inflammatory cytokine, upregulates α5β1 and αVβ3 integrin expression via tumor necrosis factor receptor 1 (TNFR1), inducing endothelial cell proliferation and angiogenesis [163] (Fig. 3). Moreover, TSLP activates the PI3K/Akt pathway in human umbilical vein endothelial cells via its receptor TSLPR to promote cell proliferation, migration and tube extension [169] (Fig. 3).

Gal-3, an important angiogenic cytokine, is mainly derived from activated microglia and astrocytes, and it infiltrates macrophages in the brain after ischemic stroke [173]. Increased Gal-3 expression induces integrin-linked kinase/p-Akt/ERK1/2 signaling to promote microglial migration and angiogenesis [164, 174]. SDF-1α has also been involved in the mobilization of hematopoietic stem cells from the bone marrow to the periphery [166]. Shyu et al. showed that intracerebral injection of SDF-1α increased the arrival of BMDCs to damaged brain areas and increased pro-angiogenic factor expression, such as VEGF, BDNF, and GDNF in peri-infarct areas [166]. SDF-1α overexpression with the adeno-associated virus in mouse models of MCAO also showed that SDF-1α activates Akt, ERK, and p38 pathway through its receptor CXCR4 but not JNK [175] (Fig. 3).

Angiogenic mediators

In addition to the above cytokines that directly promote endothelial cell proliferation and migration, many important signaling molecules, such as the Ang1-Tie2 signaling pathway [176], Jagged1-Notch1 signaling pathway [177], HIF-1α/VEGF, Nrf2/HO-1/eNOS, EPO/EPOR, integrin family systems, etc., mediate angiogenesis after cerebral ischemia.

Angiopoietin has been identified in four different subtypes, including Ang-1, Ang-2, Ang-3 and Ang-4, with Ang-1 and Ang-2 being the most widely studied [178]. Ang-1 mediates the proliferation, migration and survival of ECs and reduces BBB leakage through its tyrosine kinase receptor Tie-2 during angiogenesis [176, 179]. Moreover, estradiol and its receptor estrogen receptor-α increase Ang1 levels in the brain under basal conditions or in stroke-induced brain damage, further increasing capillary density [180]. In contrast, Ang2 antagonizes Tie2 and disrupts the connections between ECs, leading to cell death and vascular destruction [181]. However, Ang2 and VEGF induce BBB destruction and promote angiogenesis by increasing MMP-9 activity and inhibiting ZO-1 expression after cerebral ischemia [16, 141]. Angptl [182] and Angpt4 [183], members of the angiopoietin-related protein family, improve cerebral microvascular function after cerebral ischemia. Mechanically, Angpt4 maintains the integrity of the brain endothelial barrier by increasing the stability of the VEGFR2-VE-cadherin complex [183].

MMP9 overexpression or increased endogenous metalloproteinase membrane type 1-metalloprotease levels induced by treadmill exercise improves microvessel density after cerebral ischemia by degrading collagen IV, a major component of the basal lamina [184, 185]. Besides, Yang et al. found that MMPs damage the tight junction between ECs in early cerebral ischemia; thus, early inhibition of MMP may be beneficial to the recovery of BBB after stroke by affecting the expression of extraendothelial tight junction proteins, such as ZO-1 and claudin-5 associated with pericytes and astrocytes [186].

In addition, the expression of Notch1 and its ligands Jagged1 and delta-like ligand (DLL) significantly increases in the infarct area after cerebral ischemia [187]. Subsequently, the Notch intracellular domain in ECs dissociates from the cell membrane and translocates to the nucleus to form a complex with RBPJ protein to further activate the transcription of Notch target genes [177]. Our previous studies showed that nicotinamide phosphoribosyltransferase (NAMPT) stimulates angiogenesis after ischemic stroke [188]. Mechanistically, NAMPT, a key rate-limiting enzyme for NAD^+ salvage synthesis, modulates DLL4/Notch signaling in endothelial progenitor cells via NAD^+/SIRT1 in a mouse model of hind-limb ischemia [189].

Furthermore, more studies have shown that integrins such as β1, α5β1 and αvβ3 play important roles in regulating angiogenesis and inflammation after cerebral ischemia [190]. The strong upregulation of αvβ3, α5β1 and their ligand fibronectin in the ischemic penumbra stimulated the proliferation of vascular ECs [191], which was mediated by TNFR1 during ischemia-induced angiogenesis [192].

The most direct biochemical response of cerebral ischemia was inducing increased oxidative stress levels in the brain [193]. Additionally, reactive oxygen species derived from NADPH oxidase 2 regulate angiogenesis via the PI3K/Akt/NF-κB signaling pathway after focal cerebral ischemia [194]. Signaling molecules, such as HIF/VEGF [195] and Nrf2/HO-1, were associated with oxidative stress-related angiogenesis after stroke. Therefore, targeting these two signaling pathways was affected by many molecules, including Int6 [196], intelectin-1 [197], x-box binding protein l

splicing [198], PTEN [199], hemopexin [200], immunoproteasome subunit low molecular mass peptide 2 [201], sestrin2 [202], sphingosine kinase 1/S1P [203], C1q/LAIR1 [204], etc. Of these, Nrf2 activated by sestrin2 could also regulate the interaction between p62 and Keap1 by increasing p62 expression to induce angiogenesis after ischemic stroke [205]. Furthermore, erythropoietin (Epo) regulates HIF-1α and eNOS expression by activating the AMPK-KLF2 signaling pathway through its receptor Epo-R to promote the development of new blood vessels after ischemia in vitro and in vivo [206–208]. Exogenous supplementation of NO also mediates angiogenesis in the ischemic brain through the cGMP and VEGF pathways [209]. Similarly, H_2S activates the PI3K/Akt signaling pathway, which stimulates the expression and release of VEGF and Ang1 in astrocytes and promotes the proliferation and migration of ECs and lumen formation after cerebral ischemia [210].

Recent studies showed that the metabolic level in the brain changed in a cascade manner after cerebral ischemia. In the infarcted penumbra, ischemia and hypoxia rapidly increased succinate levels, stimulated G protein-coupled receptor (GPR91) localized in neurons or astrocytes, and increased the expression of pro-angiogenic factors, such as VEGF, Ang1, IL-6, and IL-1β, through PGE2 and its receptor EP4 [211]. In addition, the administration of recombinant pyruvate kinase isoform M2 improves angiogenesis after cerebral ischemia by upregulating STAT3 and FAK expression [212]. Therefore, the changes in metabolic levels affected by cerebral ischemia may explain the progress of angiogenesis from the perspective of metabolism.

The following other molecules also regulate angiogenesis after cerebral ischemia: estrogen [213], kallikrein [214–216], endostatin [217], leptin [218], leucine-rich-α2-glycoprotein 1 [219], developmental endothelial locus-1 [220], TSP-1 and TSP-2 [221], src and src-suppressed C kinase substrate [222], adiponectin [223], endothelin B receptor [224], sonic hedgehog [225–227], vasoactive intestinal peptide [228], TRPM4 [229], transient receptor potential cation channel subfamily V member 4 [230], pentraxin 3 [231], prostaglandin E1 [232], repulsive guidance molecule a [233], guanosine [234], prostaglandin-endoperoxide synthase [235], glucagon-like peptide 1 [236], ephrinB2 [237], SorCS2 [238], mast cell-expressed membrane protein 1 [239], CELSR1 [240], c-type lectin family 14 member A [241], apelin-13 [242], thrombomodulin [243], RTN4/S1PR2 [244], lactate and GPR81 [245], GPR124 [246], and histamine H 3 receptor [247].

ncRNAs

Recently, ncRNAs were identified [248], and studies showed alteration of ncRNA levels during or after stroke, which also affected angiogenesis [249]. ncRNA, including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), are functional RNA molecules that regulate the expression and function of different genes through different mechanisms [250, 251]. Of these, miRNAs and lncRNAs have been studied the most and were recently found to regulate angiogenesis after cerebral ischemia by affecting the levels of angiogenesis factors (Table 2).

PERSPECTIVE

The brain is one of the most heavily perfused organs in the body. Almost every neuron has its own independent supply of blood vessels [252], suggesting a subtle relationship between neurons and blood vessels, known as the neurovascular network [253]. Blood vessels carry oxygen, energy, and nutrients to nourish neurons for proper function. Subsequently, blood vessels carry the waste neurons release, a series of physiological processes contributing to healthy brain function. Thus, previous therapies aimed solely at neuroprotection for stroke have become inadvisable.

Because of the importance of blood vessels in neurovascular units, angiogenesis in the treatment of cerebral ischemia has been considered and recognized. Nerve cells including NSCs and microglia, promote angiogenesis through multiple mechanisms, and angiogenesis also improves the interaction between neurons and glial cells during and after stroke. Thus, it promotes neurogenesis and improves nerve function. By contrast, providing nutritional support to the nerves is beneficial for glial cells [254].

Although this review summarized several roles and mechanisms in regulating angiogenesis after cerebral ischemia, most of them have not been fully explained, and several therapeutic approaches for inducing angiogenesis have limitations. The use of anti-VEGF/VEGFR drugs is popular in cancer treatment, with multiple FDA-approved drugs, such as bevacizumab, sorafenib, sunitinib, pazopanib, ramucirumab, lenvatini, fruquintini, anlotinib hydrochloride, etc [255, 256]. Although single molecular target drugs have shown significant efficacy in experimental animal models, they are not ideal for cerebral ischemia treatment because stroke is a complex disease. Therefore, molecular targets combined with cell therapy have been proposed and studied, such as CXCL12 gene overexpression in EPCs [51], and Ang-1, PlGF, TSP4, CCL2 or CXCR4 gene overexpression in MSCs [72–76]. Studies are still ongoing for the clinical application of novel microRNAs and lncRNAs.

Cell therapy is relatively superior compared with molecular targets. After reaching the peri-infarct area, the administered stem/progenitor cells could rescue or replace some of the injured cells to perform some functions, such as promoting angiogenesis, protecting neurons, and maintaining BBB homeostasis [33]. Otherwise, the injected stem/progenitor cells release secretome and extracellular vesicles to apply their pro-angiogenic effects. MSC-derived extracellular vesicles can induce the repair of ischemic stroke by upregulating the expression of various pro-angiogenic factors, such as VEGF, EGF, PDGF, Ang1, microRNA, etc [81, 88]. Although stem cell therapy is being investigated in clinical trials worldwide, several issues remain. Cell therapy requires several criteria, including the selection of which stem or progenitor cells (EPCs, MSCs, NPCs/NSCs, etc.) are better for treating stroke; the determination of the therapeutic window and the degree or stage of cerebral ischemia that is suitable for cell therapy; and the determination of the dosage, methods, and time of administration of cell therapy in clinical practice. In animal experiments, MSC transplantation therapy has different delivery methods, including intraventricular stereoscopic injection [257], intravenous injection [258], intra-arterial injection [259], and intranasal injection [260]. Furthermore, whether animal and clinical trials can be better matched remains to be resolved. Thus, some issues for cell therapy should be identified and resolved.

More importantly, the survival of cell transplantation is a key issue that needs attention and consideration of its therapeutic potential. With the development of materials science, biomaterials combined with cell therapy enhance the survival and differentiation of transplanted stem cells and improve neurological function in experimental stroke [261]. For example, hydrogel materials could serve as matrix mimics, such that temporary ECM is provided when placed in the peri-infarct area to enhance endogenous repair mechanisms [262]. Moreover, NPC transplantation with hydrogel/heparin/hyaluronan promotes the survival of NPCs and reduces inflammatory infiltration after transplantation [263]. Furthermore, the emergence of organoid technology has also promoted cell transplantation to a new level. Organoids consist of organ-specific stem/progenitor cells and mature cells that exhibit similar organ functionality as the tissue of origin [264]. Compared with transplants of dissociated NPCs, transplanted cerebral organoid exhibits enhanced cell survival and robust vascularization after ischemic stroke [110–112]. However, these are still experimental, and further clinical applications are worth looking forward to.

Table 2. Effects and mechanisms of non-coding RNAs (ncRNAs) in angiogenesis after cerebral ischemia.

Years	ncRNAs	Effects	Mechanisms
2012	miR-210	+	induced ECs to migrate and form capillary-like structures through activating notch signaling pathway [265]
2014	miR-376b-5p	–	inhibited HIF-1α-mediated VEGFA/Notch1 signaling pathway [266]
2015	miR-107	+	directly down-regulated Dicer-1, thereby increased expression of endothelial cell-derived VEGF (VEGF165/VEGF164) [267]
2015	miR-487b	+	directly targeted and regulated the 3′ untranslated regions of thrombospondin 1 (THBS1) mRNA [268]
2015	miR-296	+	upregulated VEGF expression and downregulated Notch1 [269]
2015	miR-155	+	decreased the expression of AT1R and VEGFR2 [270]
2016; 2017	LncRNA Meg3	–	activated notch signaling pathway; [271] increased NOX4 expression by interacting with p53, further inhibited the expression of HIF-1α and VEGF [272]
2016	miR-140-5p	–	directly targeted the 3′ untranslated region of VEGFA and inhibited its expression [273]
2016	miR-150	–	negatively regulated the expression of VEGF [274]
2016	miR-493	–	increased the expression of macrophage migration inhibitory factor (MIF) [275]
2017	lncRNA HIF1A-AS2	+	facilitated the activation of HIF-1α/VEGFA/Notch1 cascades by sponging to miR-153-3p [276]
2017	miR-195	–	negatively regulated the expression of VEGFA [277]
2017	miR-146a/b	+	down-regulated the TRAF6 and IRAK1 expressions and promoted proliferation, migration and angiogenesis ability of EPCs [278]
2018	LncRNA SNHG12	+	suppressed endothelial cell injury induced by OGD/R by targeting miR-199a; [279] regulated miR-150/VEGF pathway [280]
2018; 2019	miR-126; miR-126-3p, miR-126-5p	+	improved the migration of EPCs via the SDF-1/CXCR7 signaling pathway; [281] directly inhibited its target PTPN9 and activated AKT and ERK signaling pathways [282]
2018	miR-132	+	suppressed the NF-κB pathway and promoted the VEGF pathway [283]
2018	miR-210	+	decreased SOCS1 and increased STAT3 and VEGF-C expression in EPCs [284]
2018	miR-377	–	directly inhibited the expression of VEGF and EGR2 [285]
2018	miR-940	–	down-regulated the expression level of VEGF [286]
2018	miR-26a	+	up-regulated the expression of HIF-1α via activating the AKT and ERK1/2 pathway, thus mediated the transcriptional activity of VEGF [287]
2018	miR-27b	–	inhibited the activation of AMPK [288]
2018	LncRNA SNHG1	+	regulated the expression of HIF-1α and VEGF through miR-199a [289]
2018	miR-103	–	directly targeted VEGF and lead to the down-expression of VEGF [290]
2019	LncRNA MALAT1	+	regulated VEGF expression through the 15-LOX1/STAT3 signaling pathway [291]
2019	LncRNA MIAT	–	promoted HMGB1 expression by competitively binding to miR-204-5p in cerebral microvascular endothelial cell (CMECs) [292]
2019	lncRNA NEAT1	+	promoted the expression of VEGFA, SIRT1 and BCL-XL by targeting miR377 in BMECs [293]
2019	miR-384-5p	+	negatively regulated the expression of DLL4, which further downregulated the Notch signaling pathway in endothelial progenitor cells (EPCs) [294]
2019	miR-153	+	activated the SHH signaling pathway through lipid-coated Patch (PTC) [295]
2019	miR-191	–	inhibited its direct target vascular endothelial zinc finger 1 (VEZF1) at the post-translational level [296]
2019; 2020	miR-103a	–	regulated microvascular endothelial cell injury through targeting and negatively regulating AXIN2; [297] suppressed angiogenesis through targeting and negatively regulating X-linked inhibitor of apoptosis protein (XIAP) [298]
2020	LncRNA Meg8	+	increased the expression of VEGFA via negatively regulating miR-130a-5p of BMECs [299]
2020	miR-221	+	interacted directly with PTEN to regulate the PI3K/AKT pathway and promoted HUVECs function [300]
2020	miR-15a/16-1	–	suppressed VEGFA/VEGFR2 and FGF2/FGFR1 at the translational level, respectively, by directly binding to untranslated sequences (3′-UTRs) of those mRNAs in endothelium [301]
2020	miR-874-3p	+	inhibited CXCL12 expression by activating the Wnt/β-catenin pathway [302]
2021	miR-203	–	suppressed endothelial cell fuction through targeting to the 3′-UTR of SLUG, a zinc finger transcriptional repressor [303]
2021	miR-202-3p	+	increased the expression of vWF and VEGF through interacting with TLR4 [304]
2021	miR-191-5p	–	directly targeted and inhibited BDNF [305]
2022	LncRNA DHFRL1-4	–	regulated the expression levels of bFGF, VEGF, Wnt3a and GSK-3β [306]
2022	LncRNA ZFAS1	–	sponged miR-144-5p to modulate FGF7 [307]

miR microRNA, *LncRNA* long non-coding RNA, +: promoted angiogenesis, –: inhibited angiogenesis

CONCLUSIONS

We reviewed several physiological and pharmacological pathways and potential mechanisms of the regulation of angiogenesis after cerebral ischemia. However, we lack a detailed understanding of potential treatment strategies for ischemic brain injury and their limitations. In the future, the underlying mechanisms of angiogenesis, as well as neurovascular units after stroke, should be explored.

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ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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