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Targeting Angiogenesis and White Matter Repair for Enhanced Functional Recovery after Acute Ischemic Stroke: A Focus on the Roles of Glial Cells

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Running Head: Glial cell-mediated angiogenesis and WM in AIS

Abbreviation:

AIS, acute ischemic stroke; BBB, blood-brain barrier; CAMP, cathelicidin antimicrobial peptide; CCR5, chemokine C-C-Motif Receptor 5; CXCL12, C-X-C Motif Ligand 12 (CXCL12); CXCR4, CXC chemokine receptor 4; ECs, endothelial cells; EPO, erythropoietin; Evs, extracellular vesicles; GGF2, glial growth factor 2; HIF, hypoxia-inducible factor; HMGB1, High Mobility Group Box-1; HT, hemorrhagic transformation; IGF-1, insulin-like growth factor 1; IL-10, interleukin 10; IL-1β, interleukin-1β; MCAO, medial cerebral artery occlusion; MG/MΦ, microglia and macrophages; MMP, matrix metalloproteinase; NG2, neural/glial antigen 2; OGD, oxygen-glucose deprivation; OLs, oligodendrocytes; OPCs, oligodendrocyte precursor cells; PAR1, protease-activated receptor 1; ROS, reactive oxygen species; TGF-β，transforming growth factor-β; TJPs, tight junction proteins; TNF-α, tumor necrosis factor-α; tPA, tissue plasminogen activator; TREM2, triggering receptor expressed on myeloid cell-2; VEGF, vascular endothelial growth factor; ZNT3, zinc transporter 3.

Abstract

Neural network connections require adequate blood flow to deliver sufficient oxygen and glucose. Acute ischemic stroke (AIS) significantly impairs neural function due to insufficient blood flow, leading to diffuse microvascular dysfunction and compromised white matter integrity, both indicators of poor prognosis. Post-stroke neural recovery hinges on promoting neovascularization around the infarct and restoring white matter integrity. Therefore, strategies to enhance angiogenesis and white matter repair are crucial for post-stroke neuro-rehabilitation. Emerging research highlights the pivotal roles of activated microglia, astrocytes, and oligodendrocyte precursor cells in facilitating neurogenesis, angiogenesis, and neural functional recovery following cerebral ischemia. In this review, we explore the mechanisms by which these neuroglial cells contribute to angiogenesis and white matter repair after AIS. We also propose potential therapeutic strategies that target the intricate interactions at the glial cell-endothelial cell interface. A deeper understanding of oligovascular signaling in ischemic conditions could unveil novel therapeutic targets for improving outcomes after AIS.

Keywords: angiogenesis, blood-brain barrier, glial cells, ischemic stroke, white matter.

Introduction

Acute ischemic stroke (AIS) is one of the major diseases with high rates of disability and fatality worldwide. Currently, the thrombolytic tissue plasminogen activator (tPA) is the only drug approved by the US food and drug administration (FDA) for the treatment of AIS. However, the narrow treatment time window (~4.5 hours), the risk of cerebral hemorrhagic transformation (HT) following thrombolysis, and the high mortality rate after HT have significantly limited its clinical use[1]. Despite promising results in animal experiments, all neuroprotection drugs tested so far for stroke have failed in clinical trials[2]. Consequently, there is an urgent need to restore neural function in stroke patients to improve their quality of life significantly.

After AIS, the brain can spontaneously recover some neural function, but this recovery is often only partial[3]. Current research into neurological repair post-stroke largely focuses on gray matter, which is rich in neuronal cell bodies and dendrites[4]. However, despite this focus, no approved drugs have been developed that specifically target gray matter to enhance recovery. Moreover, it is important to recognize that stroke also significantly damages white matter, which consists of the axons (long extensions of neurons) that form connections between brain regions. White matter damage can account for up to half of the infarct volume, worsen stroke symptoms, and lead to a poorer prognosis[5]. This suggests that repairing white matter integrity could be a crucial strategy for promoting functional recovery. Several cellular players are involved in white matter repair, including astrocytes, microglia, and interactions between endothelial cells (ECs) and oligodendrocytes (OLs)[6]. Additionally, disruption of the blood-brain barrier (BBB) is a key factor in pathological white matter damage[7].

Angiogenesis, the formation of new blood vessels, is a crucial response to brain injury. It helps stabilize blood flow, supports the survival of neurons, promotes brain plasticity, and aids in neurological recovery[8]. Studies have shown that the extent of angiogenesis around the damaged brain tissue after stroke is a significant indicator of patient prognosis and survival[8]. In addition, restoring the integrity of the BBB after ischemic stroke is essential for the development of mature and functional blood vessels. In fact, new blood vessel formation is

critical for the recovery of neural function following stroke. This makes promoting effective angiogenesis in the area surrounding the infarct a promising therapeutic strategy for improving neurological recovery following AIS. Evidence increasingly points to the importance of glial cells in facilitating angiogenesis[9]. Furthermore, the interactions between existing blood vessels, OLs, and oligodendrocyte precursor cells (OPCs) are vital for maintaining the health and function of white matter[6]. For instance, clinical studies have shown that following an acute stroke diffuse microvascular dysfunction and the loss of white matter integrity are predictors of unfavorable outcomes[10]. In this review, we first address BBB damage and repair following ischemic stroke. Then, we examine the contributions of white matter repair and angiogenesis to functional recovery after ischemic stroke. Subsequently, we explore the roles of glial cells in regulating both angiogenesis and white matter repair. Finally, we propose integrating white matter repair with angiogenesis as a therapeutic strategy after AIS.

Angiogenesis and BBB repair-mediated vascular remodeling after ischemic stroke

BBB damage after ischemic stroke

BBB is a complex structure composed of ECs, astrocytes, pericytes, the basement membrane, components of the extracellular matrix, and tight junction proteins (TJPs)[11]. These ECs are core anatomical structures that interact with various types of cells in the central nervous system (CNS). The ECs within the BBB are tightly bound by TJPs, resulting in a distinct lumen[12].

BBB dysfunction is one of the hallmarks of ischemic stroke. The integrity of the BBB is crucial, and its disruption is a primary pathological basis for the development of vasogenic cerebral edema and hemorrhagic transformation following acute stroke[13]. This breakdown is also a key factor contributing to pathological damage to white matter[14]. Protecting the integrity of the BBB has been shown to improve cognitive and motor function after AIS. Several therapeutic strategies have demonstrated promise in ameliorating BBB damage. For example, inhibition of D1 receptor-mediated endogenous tPA upregulation can alleviate BBB injury after AIS[15]. Moreover, inhibition of autophagy can decrease ischemia-induced occludin degradation and loss of BBB integrity[16]. Nicotine treatment has been shown to ameliorate BBB damage

after AIS by regulating endothelial scaffolding protein Pdlim5[17], and glial growth factor 2 (GGF2) treatment alleviates ischemia and reperfusion-damaged integrity of the BBB[18]. It is of note that structural and functional recovery of the BBB after stroke is critical to prognosis. Compounds like Omega-3 polyunsaturated fatty acids[19] and the immunomodulator 2-Methoxystypandrone[20] have been reported to improve neurological function in aged mice by promoting the restoration of BBB integrity (Table).

The role of angiogenesis in neural functional recovery after ischemic stroke

After a cerebral infarction, the affected brain area is often filled with empty, unperfused microvessels, a phenomenon that's especially pronounced in older patients[8]. Although microvascular density in the ischemic region increases significantly around 14 days post-stroke, cerebral blood flow remains considerably lower than in healthy areas[21]. This suggests that the newly formed microvessels are not effectively transporting blood. Furthermore, studies in rats have shown that the density of newly formed blood vessels (angiogenesis) around the infarcted area actually decreases between 30 and 60 days after ischemia-reperfusion[22], which suggests that this temporary network of microvessels is not sustained long-term.

Restoring blood flow to damaged brain areas is a critical strategy for promoting neurological recovery after stroke, and the reconstruction of the vascular network is the primary way to achieve this[23]. For example, in mice, the establishment of cerebral collateral circulation due to hypoxia can reduce the adverse consequences of ischemic stroke by increasing cerebral blood perfusion[24]. Two-photon studies have further shown that the formation of new blood vessels contributes to the recovery of motor function after stroke by restoring cerebral blood perfusion around the infarct area[25].

Angiogenesis, the growth of new blood vessels, is a natural defense mechanism. It helps to restore the supply of oxygen and nutrients to affected brain tissue after AIS. Ischemic stroke-induced angiogenesis is a complex and dynamic process involving various vascular components, including ECs, pericytes, and extracellular matrix. This process, along with vascular remodeling, occurs around the peri-infarction area of the ischemic hemisphere after

AIS[26]. Beyond simply providing essential materials and energy for neural regeneration and secreting neurotrophic factors and chemokines to support the survival of new neurons, angiogenesis after stroke also serves as a scaffold, guiding the migration of neural precursor cells to the injured brain area, thereby facilitating structural repair and functional remodeling of brain tissue[27]. Previous studies have shown that cerebral ischemia increases neurogenesis, with newly generated neurons in the subventricular zone migrating toward the ischemic border, where angiogenesis is active [28].

Pathologic analysis and brain imaging studies of patients with cerebral infarction in the subacute and chronic phases have revealed that the extent of angiogenesis and vascular network reconstruction in the ischemic penumbra directly influences patients' long-term survival rates[8]. Promoting cerebral angiogenesis can significantly enhance neurological recovery after stroke, while disrupting it after stroke can hinder neural functional recovery. For example, conditional knockout of microRNA-15a/16-1[29] or neutrophil-derived cathelicidin antimicrobial peptide (CAMP)[30]. can regulate target genes to promote angiogenesis and vascular network reconstruction after stroke, leading to improved neurological outcomes. In addition, Kaempferol has shown promise in promoting angiogenesis in the peri-infarct cortex. It does this by enhancing the proliferation, migration, and lumen formation of endothelial cells through hypoxia inducible factor-1α (HIF-1α)/vascular endothelial growth factor-A (VEGF-A) signaling pathway[31].

Despite these promising results, current strategies aimed at improving angiogenesis, even with factors like VEGF, can be a double-edged sword. While they can promote angiogenesis after cerebral infarction[26], their effects are often countered by impaired vascular maturation and increased vessel permeability. This hindrance prevents the formation of stable lumens and effective blood perfusion. Furthermore, it can severely compromise BBB integrity, which exacerbates cerebral edema or hemorrhagic transformation and can potentially worsen post-stroke outcomes[26].

Given that angiogenesis in ischemic infarcts regulates cerebral blood flow, neuronal

repair and regeneration, patient functional recovery, and the re-establishment of synaptic connections between neuronal cells, it is crucial for neurological function recovery after stroke[8]. Consequently, effective angiogenesis in the peri-infarction area is now considered a significant therapeutic target for promoting neural functional recovery after AIS[3].

The role of BBB repair in neural functional recovery after ischemic stroke

Angiogenesis after stroke offers very limited therapeutic benefit for clinical prognosis unless the new vessels become functional and perfused. For example, while angiogenic factors such as VEGF supplements can stimulate the growth of new blood vessels, they may not result in the formation of mature, functional vessels. This can lead to increased BBB leakage and vasogenic edema[26]. Therefore, strategies that promote angiogenesis should also prioritize repairing the integrity of the BBB to ensure the newly formed blood vessels are both mature and functional[26] (Fig. 1). The maturation of vascular barrier function, essential for effective cerebral blood perfusion, relies on the formation of tight junction proteins, pericyte coverage, and a stable basal membrane between neovascular endothelial cells[26]. BBB integrity repair is not solely dependent on endothelial cell proliferation and migration; it also critically requires pericyte recruitment and adhesion. Pericytes are vital not only for regulating cerebral blood perfusion after stroke but also for mediating post-stroke basement membrane remodeling, which plays a significant role in tissue repair and functional recovery following ischemic stroke[32]. Myeloid-driven endothelial cell-to-pericyte transdifferentiation accelerates post-stroke BBB recovery and exerts neuroprotective effects[33]. Interestingly, delayed administration of atorvastatin may help restore neurological function by promoting pericyte coverage and BBB integrity repair after ischemic stroke[34].

White matter integrity repair after ischemic stroke

White matter injury after ischemic stroke

White matter is particularly vulnerable to ischemia (reduced blood flow) because it has a lower blood supply than gray matter, and the deep white matter has limited collateral circulation[14]. Following ischemic stroke, white matter damage can be observed in the adult brain for several

days. The main manifestations include OL damage, nerve demyelination, and axonal injury[3]. Damage to the white matter of the brain is a serious consequence of ischemic stroke, significantly impacting neurological function. Ischemia-induced reductions in the integrity of local or remote white matter are known to contribute to cognitive decline in stroke patients. This is a considerable concern, as approximately 64% of stroke patients, with up to one-third developing dementia[35]. Furthermore, cerebral white matter damage, often linked to chronic hypoperfusion, is a common histologic feature in patients with stroke and cerebrovascular disease [36], and it has been shown that enhancing OL autophagy can alleviate white matter injury and cognitive impairment induced by chronic cerebral hypoperfusion in rats[37].

Promotion of oligodendrocyte differentiation facilitates white matter integrity repair after ischemic stroke

Promoting the restoration of white matter integrity is a significant factor in neurological recovery (Fig. 1), with evidence suggesting that it could be a powerful therapeutic strategy. For example, studies have shown that Nogo receptor antagonists can facilitate recovery by repairing white matter[38], and rosiglitazone, a drug for diabetes, similarly enhances functional recovery by improving white matter integrity[39]. Thus, therapies that aim to increase white matter repair hold promise for promoting functional recovery after AIS[14].

Myelin, produced by OLs in the CNS, is crucial for neuronal health. Myelin defects due to the absence or dysfunction of OLs are often seen after ischemic stroke, and can lead to neuronal loss and functional impairment[40]. A key characteristic of ischemic white matter injury is the disruption of myelin structures, which is further exacerbated by impaired recruitment or differentiation of OPCs[41]. OPCs are fundamental to the brain capacity for myelin repair. While OPCs differentiate into myelin-forming OLs during development, a pool of immature OPCs persists throughout the adult brain, including the subventricular zone. These adult OPCs continuously generate new oligodendrocytes in the white matter. In cases of brain injury and neurological disorders, adult OPCs are recognized as a key component of the endogenous response that contributes to the recovery of brain function. Upon receiving demyelinating

signals, OPCs actively proliferate and migrate to the injured regions. Their differentiation into mature oligodendrocytes and subsequent remyelination highlights the potential role of OPCs in myelin repair after injury[42]. While residual OPCs typically tend to proliferate and differentiate into OLs to mitigate white matter injury in demyelinating diseases[43], this process may be significantly hindered after ischemic stroke.

Although ischemic stroke induces endogenous oligodendrogenesis, which is vital for maintaining axonal structure and function. Animal and human studies have shown that the adult brain's capacity for self-repair is limited. Numerous approaches aimed at preserving or increasing OPC numbers to promote OLs differentiation and myelin regeneration have been taken for improving white matter integrity and neurological function after ischemic stroke [3]. For example, interleukin 10 (IL-10) is a cytokine that plays a role in reducing neuroinflammation and preventing OPCs loss and white matter damage by reducing lipid reactive oxygen species (ROS)[44]. Necrostatin-1, a programmed necrosis-specific inhibitor, has been reported to promote neurological recovery after ischemic stroke by protecting neural/glial antigen 2 (NG2) cells[45], and rosiglitazone, a diabetes drug, promotes white matter integrity repair and functional recovery with significant NG2 cell proliferation[39]. Melatonin treatment has also been reported in the literature to improve neurological function after stroke, accompanied by neurogenesis and a significant increase in NG2 cells around the infarct area[46] (Table).

Regulation of angiogenesis and white matter integrity repair by microglia cells/ macrophages after ischemic stroke

Neuroglial cells play important roles in neuroinflammation and neuroimmune response in post-stroke neural injury and repair. Microglia have a dual effect: they can worsen brain damage, yet they also play a role in promoting brain repair[47].

Role of microglia in angiogenesis and BBB repair after stroke

Role of microglia in BBB destruction after AIS

After ischemic stroke, microglia are activated, characterized by a debranching morphology with

contractile processes and enlarged cell bodies. These activated microglia tend to cluster around the vasculature, which can result in vessel disintegration and upregulation of phagocytic CD68 expression in the penumbra[48], a region of salvageable brain tissue. One of the critical consequences of microglial activation after stroke is the impairment of BBB integrity. Microglia contribute to this damage by upregulating pro-inflammatory cytokines, such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α)[13]. Evidence suggests that mitigating these microglial responses can be beneficial. For example, selective depletion of resident microglia in the early phase after ischemic stroke or modulation of microglia-mediated inflammatory responses has been shown to alleviate brain damage[49] (Fig. 2).

There are several therapeutic approaches aiming to protect the BBB by modulating microglial activity. For example, melatonin attenuates ischemia- and reperfusion-impaired BBB integrity by inhibiting high mobility group box-1 (HMGB1)-mediated microglia activation[13] and GGF2 significantly alleviates I/R-induced BBB damage by inhibiting microglial cell activation and upregulation of inflammatory factors[18]. TNF-α-induced endothelial apoptosis secreted by M1 microglia leads to BBB destruction after ischemic stroke. Anti-TNFα (infliximab) reduces endothelial necrotic apoptosis and BBB leakage[50]. Lipid nanoparticles targeting M2 microglia induced IL-10 production and enhanced M2 polarization of microglia, restored the damaged BBB after stroke[51] (Table).

Role of microglia in angiogenesis and BBB repair after AIS

Microglia are intimately involved in the brain's response to ischemic stroke, particularly in the process of angiogenesis. Following a stroke, microglia are often found clustered around blood vessels, forming perivascular clusters and phagocytic structures. Microglia exhibit different functional states, broadly categorized as M1 and M2. M1 microglia can release neuroinflammatory and neurotoxic mediators, but M2 microglia can promote neurogenesis and angiogenesis by secreting insulin-like growth factor 1 (IGF-1), VEGF and brain-derived neurotrophic factor (BDNF)[52], highlighting that they have reparative capacity in inducing neovascularization after stroke. There is a strong correlation between angiogenesis and

microglia recruitment and activation after ischemic stroke. Various interventions and observations underscore microglia's pro-angiogenic potential. For example, microglia dynamic activity is closely related to capillary blood flows around their cell bodies after photothrombosis-induced ischemia[53], and extracellular vesicles derived from hypoxia-preconditioned microglia promote angiogenesis in stroke mice[54]. In addition, interleukin 4 (IL-4)-polarized microglia may attenuate ischemic stroke-induced injury by promoting angiogenesis via exosomes[55], and salvianolic acid C inhibits microglia polarization, promotes endothelial cell proliferation, angiogenesis, maintains BBB integrity, and exerts neurorestorative functions in cerebral ischemia[56]. Furthermore, energy-restricted-mediated upregulation of SIRT6 inhibits microglia activation and enhances angiogenesis in cerebral ischemia by suppressing TXNIP[57] and oxygen-glucose deprivation (OGD)-pretreated and intra-arterially administered microglia may cross the BBB, secrete remodeling factors in the brain parenchyma, and exert pleiotropic therapeutic effects by promoting angiogenesis and axonal growth[58].

The role of microglia in post-stroke white matter integrity repair

Microglia-mediated inflammatory response

Microglia are continuously triggered during cerebral ischemia and exhibit heterogeneity. In the acute phase of ischemia, microglia polarize toward early anti-inflammatory and protective phenotypes, followed by a chronic deleterious pro-inflammatory phenotype in the later stages of the disease. Pro-inflammatory microglia secrete pro-inflammatory cytokines that exacerbate white matter damage by exacerbating OLs death and demyelination[59], and microglial TLR4-dependent autophagy can result in ischemic white matter damage via STAT1/6 pathway[60]. Protease-activated receptor 1 (PAR1) and PAR3 act as 3K3A-APC inhibitors of microglia responses and protect white matter and OLs from ischemic injury[61]. Other interventions also demonstrate protective effects. Minocycline protects white matter development from oxygen toxicity by blocking microglia morphology and IL-1β release and protecting OLs[62].

The phagocytic activity of microglia in white matter integrity repair after AIS

The removal of myelin debris after white matter injury is a critical step for successful myelin regeneration. This process, known as demyelination, clears the way for OPCs to be recruited and mature into new OLs, which are responsible for producing myelin. Microglia are central to this regenerative process. They foster an environment conducive to pro-myelin OPC responses by secreting regenerative factors, altering the extracellular matrix, and phagocytosing inhibitory myelin debris. The efficiency of myelin debris removal can be enhanced by various mechanisms. For example, impairments in microglial function can severely hinder recovery. Triggering receptor expressed on myeloid cell-2 (TREM2) KO mice exhibit reduced numbers of activated microglia and phagocytes, leading to decreased phagocytosis and exacerbating ischemic injury[63]. Additionally, lactolipid globule-epidermal growth factor 8 is a microglia phagocytosis-associated protein that enhances microglia phagocytosis to promote the differentiation of OPCs[64]. Finally, the efficient clearance of myelin debris by microglia is vital. The clearance of myelin debris by microglia is severely blocked, affecting axon and myelin integrity. Thus, the phagocytic activity of microglia is important not only for regional clearance but also for effective myelin regeneration[65].

Role of secreted molecules from microglia in white matter integrity repair after AIS

Several secreted molecules from microglia are known to be involved in the microglia-mediated repair of white matter damage after AIS. It has been found that selective deletion of microglia Na/H exchanger-1 (Nhe1) can accelerate restorative microglia-OLs communication by stimulating BDNF secretion to exert an effect on white matter myelin formation[66]. In addition, the CD11c microglia population expresses characteristic myelin genetic profiles, enabling them to play a fundamental role in white matter repair during the recovery phase of stroke[67]. Interleukin 33 (IL33) and its receptor ST2 (interleukin 1 receptor-like 1) can regulate microglia activity, protect OLs and OPCs from ischemic injury, and improve white matter integrity[68]. Many genes upregulated in microglia stimulated by Regulatory T cell (Treg) encode cell-released factors that promote oligodendrocyte generation and white matter repair[69]. M2 microglia-derived extracellular vesicles promote proliferation, survival, and maturation of

OPCs, oligodendrogenesis, and white matter repair after ischemic stroke[70].

The role of macrophages in BBB and white matter integrity after AIS

In addition to microglia, infiltrating monocyte-derived macrophages (MoDM) are another key mediator of immune responses in the brain. For example, activating the neuroprotective phenotype of macrophages and enhancing TJP expression in the brain can facilitate neurovascular remodeling during stroke recovery[71], and macrophages can accelerate the clearance of myelin debris, which in turn promote myelin regeneration after stroke[72].

Microglia and macrophages (MG/MΦ) can drive angiogenesis and oligodendrogenesis via a paracrine mechanism. For example, permanent depletion of MG/MΦ via antagonism of the colony-stimulating factor 1 receptor resulted in loss of poststroke angiogenesis and oligodendrogenesis [73]. In addition, targeted ablation of signal transducer and activator of transduction 1 in MG/MΦ can promote white matter recovery after ischemic stroke[74], and IL-13 can improve the white matter integrity after ischemic stroke by promoting the polarization of MG/MΦ[75]. Furthermore, TGFα in MG/MΦ can preserve oligodendrocyte lineage cells and improve white matter integrity after cerebral ischemia[76]. Of note, C-C-motif receptor (CCR2) deficiency in monocytes impairs angiogenesis and functional recovery after ischemic stroke in mice[77] and transplantation of monocyte-derived macrophages (RAMf) into stroke-affected mice improves white matter integrity and vascular repair [78].

Regulation of angiogenesis and white matter integrity repair by astrocytes after ischemic stroke

Astrocytes are the most abundant cell type in the CNS, and astrocytes are a key structural and functional part of the synaptic and neurovascular unit and communicate with neurons, OLs, and ECs[79]. Astrocytes provide many housekeeping functions, including structural support, BBB formation, neuronal metabolism, extracellular environment maintenance, cerebral blood flow regulation, cell-cell communication stabilization, neurotransmitter synthesis, and defense against oxidative stress[11]. Inhibition of reactive astrocytes with fluorocitrate ameliorates learning and memory impairment in ischemic stroke rats[80].

Role of astrocytes in angiogenesis and BBB repair after AIS

Dual role of astrocytes in BBB integrity after AIS

Astrocytes are critical in maintaining the BBB and regulating brain health. Their terminals, rich in gap junction channels, form a perivascular pathway around blood vessels, facilitating intercellular transport between adjacent endfeet[81]. The endfeet of astrocytes also wrap around the brain blood vessels, helping to maintain the tight junctions of the BBB and preventing harmful substances from entering the brain tissue. Beyond structural support, astrocytes secrete factors vital for BBB stability and repair, including glial fibrillary acidic protein and VEGF[82]. They also contribute to BBB integrity through the secretion of Wnt, which mediates Wnt/β-catenin activity in both ECs and astrocytes [83]. However, astrocytes can also hurt BBB integrity. Ischemic stroke can induce astrocytes to transform into the A1 phenotype with neurotoxic properties, exacerbating brain damage[84]. After ischemic stroke, these A1-reactive astrocytes release pro-inflammatory factors IL-1β and TNF-α, which modulate the inflammatory response and increase BBB permeability, while cottonseed oil can reduce the activation of A1 phenotype neurotoxic astrocytes, inhibit the inflammatory response, and attenuate post-ischemic stroke injury[85]. In addition, astrocytes release chemokines that recruit immune cells to the site of injury, further affecting the integrity of the BBB[86](Fig. 2).

Role of astrocyte in angiogenesis after AIS

Astrocytes play a crucial role in protecting preexisting blood vessels and promoting vascular repair and remodeling after stroke. During the repair phase of cerebral ischemia, proliferating reactive astrocytes migrate to the edge of the injury area[87]. Astrocytes and ECs interact closely, and genes that are involved in vascular repair are upregulated in astrocytes after injury. Increasing the levels of HIF-1α, VEGF-A, and VEGF-R2 in astrocytes promotes angiogenesis during cerebral ischemic repair[88]. Astrocyte HMGB1 enhances IL-6 differentiation through the PI3K/AKT signaling pathway to promote post-stroke angiogenesis and functional recovery[89]. Imaging study shows that astrocytes actively bind to new vessel segments after stroke, and specific ablation of proliferating astrocytes in the peri-infarct cortex leads to failure of the

vascular remodeling response and long-term blood flow defects[87]. HMGB1 in astrocytes can promote endothelial progenitor cell-mediated neurovascular remodeling during stroke recovery[90]. In addition, astrocyte HMGB1-mediated post-stroke depression and anxiety-like behavior inhibition were also found to promote angiogenesis and functional recovery[89].

The role of astrocytes in post-stroke white matter integrity repair

The role of astrocyte-mediated phagocytosis of myelin debris in white matter injury and repair

Astrocytes also play a crucial role in maintaining healthy myelin formation. It has been shown that accumulation of lipid droplets or myelin membrane-like debris is observed in the lysosomes of astrocytes, suggesting that astrocytes are also involved in the maintenance of myelin homeostasis by phagocytosis of myelin[108]. Astrocytes recognize myelin debris for phagocytosis via receptors such as cytosolic low-density lipoprotein-receptor-related protein 1 and multiple EGF-like structural domain 10 (MEGF10)[91]. However, over-activated astrocyte cells can lead to excessive myelin phagocytosis, which may result in secondary brain damage (Fig. 2). Astrocyte lipid carrier protein-2 is responsible for myelin uptake by astrocytes through binding to lipoprotein-receptor-related protein 1, exacerbating demyelination and cognitive impairment[92].

Role of astrocyte-induced secreted molecules in white matter repair

Astrocytes are crucial in regulating the development of OPCs related to the process of myelin regeneration. BDNF expression plays an important role in oligodendrocyte-lineage cell-cell interactions in myelin homeostasis[93]. During endogenous recovery from white matter ischemic injury, astrocytes support OPCs maturation by secreting BDNF[94]. Several neurotrophic and growth factors, including neurotrophic factor-3, platelet-derived growth factor, and ciliary neurotrophic factor, are essential for OLs proliferation and differentiation.

However, the role of astrocytes is not always straightforward. For example, OGD induces activation of astrocytes, and exosomes from astrocytes under hypoxic conditions can inhibit proliferation while promoting differentiation and migration of OPCs *in vitro*[95]. Moreover, pericyte medium significantly enhanced the ability of astrocyte medium to promote OPC

differentiation and myelin formation[96]. Astrocyte tumor necrosis factor receptor 2 activation induces chemokine C-X-C Motif Ligand 12 (CXCL12) expression in demyelination, thereby promoting OPCs proliferation and differentiation[97]. Despite these supportive roles, evidence also suggests that astrocytes can impede myelin repair. Stroke initially induces an initial proliferative and repair response in OPCs, but this response is inhibited by inhibin A secreted by reactive astrocytes, thereby blocking myelin repair and recovery[98]. Additionally, astrocyte-derived chemokine C-X-C Motif Ligand 5 (CXCL5) exacerbates white matter damage and cognitive decline after cerebral ischemia by inhibiting microglia phagocytosis of myelin debris[99]. Astrocytes can also cause OPCs maturation arrest in impaired white matter integrity by inducing cyclooxygenase 2-prostaglandin E2 signaling[100]. Overall, these studies suggest that the activation status of astrocytes may determine the outcome of myelin formation.

Role of interactions between oligodendroglial cells and endothelial cells in angiogenesis and white matter integrity repair after ischemic stroke

Intercellular interactions between endothelial cells and OLs are also important for maintaining brain function, especially in the white matter. In addition to astrocytes and pericytes, a subset of OPCs is also close to the vasculature, and in this microenvironment, or so-called oligovascular niche, brain endothelial cells and OPCs communicate closely to maintain the BBB and to maintain OPCs homeostasis[101]. In white matter, stroke recovery should be based on re-establishing connections. During recovery after stroke, axons must be appropriately regenerated to re-normalize neuronal network connections, and blood vessels must be repaired to regain metabolic supplies of oxygen and glucose, as the "wiring and plumbing" theory has been proposed by Arai and Lo[101].

Oligodendroglial-endothelial interactions regulate angiogenesis after ischemic stroke

In the brain, neural cells and blood vessels form a complex network of interconnections. In addition to pericytes and astrocytes, OLs-lineage cells monitor the BBB and ECs[102]. For example, OPCs can damage the BBB by secreting matrix metalloproteinase 9 (MMP-9) during white matter injury caused by chronic cerebral hypoperfusion[103].

OPCs transplantation can promote oligodendrogenesis, angiogenesis, which reduces infarct volume in early ischemia and cerebral atrophy volume in recovery, and induced angiogenesis promotes OPCs migration and myelin remodeling, improving ischemic stroke prognosis[104]. OPC-encoded HIF can induce postnatal white matter angiogenesis and can directly stimulate endothelial cell proliferation, and OPC-specific HIF1/2α loss of function leads to insufficient callosal angiogenesis and catastrophic axonal loss[105]. Treatment with hypoxic OPC-conditioned medium 5 times daily, starting 2 days after ischemic stroke, promotes post-stroke angiogenesis and improves functional impairment[6]. After white matter injury, mature OLs secrete a well-known angiogenic factor, MMP-9, to promote vascular remodeling[106]. Hypoxic OPCs secreted a greater amount of pro-angiogenic factors, such as VEGF and angiopoietin-1[107]. Although astrocytes and pericytes are regulators of BBB maturation and maintenance, OPCs also play a key role in promoting BBB integrity by upregulating TJPs through transforming growth factor-β (TGF-β) signaling[108].

Oligodendroglial-endothelial interactions regulate white matter repair after ischemic stroke

The regeneration of OLs and the maturation of OPCs depend on the number of local angiogenesis in this brain, and microvascular dysfunction and loss of white matter integrity predict a poor prognosis in patients with acute ischemic stroke[10]. OLs may act as sensors of white matter injury and maintain white matter homeostasis by secreting angiogenic factors[106]. In addition, OPCs migration requires physical interaction with the vascular endothelium[109]. Endothelial cells-derived from human induced pluripotent stem cells benefit myelin protection and regeneration by increasing the proliferation, migration, and differentiation of OPCs through secreted soluble factors BDNF[110]. Factors released by brain endothelial cells activate Src and Akt signaling to maintain OPCs proliferation[111]. Deletion of the interferon gene stimulator of the endothelium perturbs metabolic homeostasis in endothelial cells and increases interleukin 17D production, thereby inhibiting OLs development and myelin formation[112]. Endothelial caveolin-1 restores normal vascular-OPCs interactions, promotes oligodendrogenesis, and attenuates ischemic myelin damage[113]. In addition, endothelial cells exert myelin debris

clearance through the degradation of phagocytosed myelin debris by the autophagy-lysosomal pathway[114].

The effect of OPC-neuron interaction on the integrity of BBB and white matter

In the nervous system, the only known neuron-glial synapse is the one between neurons and OPCs. These neuron-OPC synapses are dynamically assembled and use Ca^{2+} signaling to play a key role in the CNS[115]. OPCs affect white matter impairment by differentiating into OLs for myelin formation, but they can also form synaptic connections with neurons or secrete factors that regulate neuronal function. Neurons themselves promote oligodendrocyte differentiation, remyelination, and improve working memory in mice after ischemic white matter injury[116]. Additionally, neurons regulate the BBB and neurovascular coupling[117], as seen with the neuronal zinc transporter ZNT3, which can regulate ischemic stroke-induced BBB damage[118].

Coupling of white matter repair and angiogenesis as a therapeutic strategy after ischemic stroke

Therapies in basic research have targeted vascular remodeling or white matter integrity repair after ischemic stroke to alleviate neurological deficits[26, 40]. Long-term neural functional recovery is strongly associated with angiogenesis and oligodendrogenesis[119]. However, drugs that can effectively promote neural functional repair are still lacking. Therefore, the therapies could target the interaction between glial cells and endothelial cells to promote neovascularization and white matter repair.

Growth factors that can stimulate angiogenesis and oligodendrogenesis

Several studies have shown that neuroprotective agents have an important role in white matter repair and revascularization after ischemic stroke. Microglia and astrocytes release a variety of neuroprotective agents, including erythropoietin (EPO), VEGF, and glial cell-derived neurotrophic factor, all of which can reduce injury after ischemic stroke. For example, minocycline and EPO can reduce oligodendrocyte apoptosis, promote myelin regeneration, and improve white matter integrity[120], and EPO can also promote endothelial cell proliferation and migration and stimulate angiogenesis by upregulating VEGF expression[121]. In addition,

atorvastatin can promote the induction of VEGF and BDNF post-stroke angiogenesis and brain plasticity, and enhance functional recovery[122], and delayed recombinant fibroblast growth factor 21 (rFGF21) administration can improve cerebrovascular remodeling and white matter repair after stroke in diabetic mice [123].

Extracellular vesicles (EVs)

EVs, which can transfer a wide range of molecules such as lipids, nucleic acids, and proteins, serve as a new platform for complex intercellular communication[124]. EVs of astrocyte cell origin are actively involved in cerebral angiogenesis, neural synapse regeneration, maintenance of neurohomeostasis, and neuroprotection after stroke[125]. Astrocyte-derived exosomes can exert pro-angiogenic, neurogenic, and synaptogenic effects through the release of VEGF and FGF-2[126]. Astrocyte-derived EVs accelerate OPC proliferation by upregulating cell cycle protein D1 via laminin Beta 2 [127]. *In vitro*, experimental studies show that astrocyte-derived exosomes improve OPC differentiation and migration in the OGD/R model[95]. Extracellular vesicles derived from inflammatory microglia inhibit myelin regeneration, whereas extracellular vesicles produced by pro-regenerative microglia are effective in promoting myelin repair. A microglia depletion model suggests that injection of regenerating microglia-derived EVs rescues OPCs differentiation and functional recovery[128]. In addition, endothelial cell-derived EVs can promote nerve regeneration by activating the PI3K/AKT/PTEN signaling pathway[129]. Brain endothelium-derived EVs attenuate BBB permeability and improve neurological function by regulating caveolin-1-dependent ZO-1 and claudin-5 endocytosis[130] and anti-inflammatory effects[131] after ischemic stroke.

Chemokine receptor antagonists or chemokine inhibitors

Studies have shown that activation of the C-C motif chemokine 5 (CCL5)-chemokine C-C-motif receptor 5 (CCR5) signaling pathway significantly promotes neuroinflammation and neurological deficits after ischemic stroke[132]. CCL2 and CCL5 have been shown to cause leukocyte recruitment, which induces disruption of the BBB, thereby exacerbating cerebral ischemia/reperfusion injury[132]. Inhibition of CCR5 or CXCR4 chemokine pathways attenuates

inflammatory white matter injury. A novel CCR5 antagonist, A14, significantly inhibited reactive proliferation of post-stroke glial cells, reduced infiltration of peripheral immune cells, and promoted repair after ischemic stroke[133]. Maraviroc (CCR5 antagonist) and plerixafor (AMD3100), a CXC chemokine receptor 4 (CXCR4) antagonist, improve recovery after traumatic brain injury[134]. In the OGD/R model, interleukin 1 receptor antagonist (IL-1RA) prevents acute brain injury by inhibiting neutrophil migration through inhibition of astrocyte CXCL1 expression[135]. Maraviroc down-regulates the expression of pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) in microglia and attenuates the neuroinflammatory response after cerebral ischemia/reperfusion injury[136].

Anti-inflammatory drugs

Inflammatory responses after ischemic stroke play an important role in white matter injury and BBB disruption. On one hand, microglia and astrocytes activate and release pro-inflammatory factors (e.g., TNF-α, IL-1β, and IL-6) and chemokines, which exacerbate white matter injury. On the other hand, by disrupting proteins that tightly connect endothelial cells in the BBB and the components of the basement membrane, inflammatory factors increase vascular permeability. The Wnt/β-catenin pathway activator TWS119 promotes angiogenesis after ischemic stroke by modulating microglia to an anti-inflammatory phenotype[137]. Levetiracetam stimulated angiogenesis and functional recovery after cerebral ischemia mediated by anti-inflammatory and anti-apoptotic activities as well as induced expression of heat shock protein 70 (HSP70), VEGF, and HIF-1α[138]. L-4F, an economical apolipoprotein A member I mimetic peptide, reduces macrophage infiltration and neuroinflammation, providing a recovery strategy for stroke by promoting neurovascular and white matter remodeling[139].

Regulation of related phagocytosis signaling molecules

Astrocyte- and microglia-mediated phagocytosis has regulatory effects on pathological repair after injury. Astrocytes and microglia recognize and phagocytose necrotic cell debris, apoptotic neurons, and damaged myelin debris, thereby reducing toxic accumulation and inhibiting the spread of secondary inflammation [140]. Pentoxifylline promotes myelin debris phagocytosis by

microglia and attenuates white matter damage by upregulating Mer receptor tyrosine kinase (Mertk) expression in the bilateral common carotid artery stenosis model and primary cultured microglia[141]. Overexpression of macrophage scavenger receptor 1 leads to increased phosphorylation of Akt via histamine receptor H1, which promotes myelin debris clearance accelerated by phagocytosis of myelin debris by microglia[142]. Notably, prolonged or dysregulated phagocytosis may lead to undesirable consequences, and thus precise regulation of the spatiotemporal balance of phagocytosis is a key target for promoting neural repair.

Factors to consider when stimulating angiogenesis and white matter repair

The impact of comorbidities

The presence of comorbidities significantly impacts angiogenesis, white matter repair, and the overall therapeutic window following a stroke. While angiogenesis can promote neural functional recovery after stroke, patients with conditions such as diabetes and obesity often face complications.

Diabetes, for instance, can trigger dysfunctional and uncontrolled angiogenesis in the cerebral vascular system, which may lead to a hemorrhagic conversion and toxic edema[143]. This can worsen cognitive and motor impairments, delaying recovery after ischemic stroke[143]. Furthermore, diabetes can exacerbate white matter damage of cerebral ischemia[144], as high-glucose conditions can cause microglia/macrophages to adopt a pro-inflammatory state. This, in turn, inhibits the differentiation of OPCs, thereby impairing white matter repair[145].

Obesity can also negatively affect angiogenesis[146] and is linked to impaired white matter integrity[147]. In fact, previous studies have shown a negative correlation between obesity and white matter integrity[147]. Additionally, obesity can significantly increase stroke-induced brain edema, which results in worsened long-term recovery[148]. This suggests that weight loss may be a beneficial strategy to normalize pre-stroke glucose metabolism, reduce post-stroke complications in diabetic populations, and improve functional recovery [149].

Translational Challenges: rodents vs. humans

Significant differences between rodents and humans, particularly in the brain composition and structure, present challenges for translating stroke repair research. In rodents, white matter constitutes only about 10% of the brain volume[150]. In contrast, it makes up roughly 45% of the

human brain volume[150]. The human brain also has a more complex white matter network. This substantial difference means that white matter damage has a far more pronounced impact on cognitive and motor functions in humans than in rodents, directly influencing the translational potential of stroke repair research findings.

Conclusion

In summary, glial cells not only perform multiple functions in the microvasculature, such as promoting neovascularization and maintaining BBB integrity, but also play a crucial role in repairing white matter integrity after cerebral ischemia. In particular, glial cells systematically drive neurological recovery by secreting various growth factors and mediating debris removal through phagocytosis. This highlights the importance of investigating glial cell interactions, both among themselves and with endothelial cells, as a therapeutic target.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' contributions

WD, WL, YS, PG drafted the manuscript, WD prepared the figures and table. CG, PG and XJ revised the manuscript. All authors agreed on the final manuscript.

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Figure legends

Fig 1. Angiogenesis, BBB and white matter repair are essential for neural functional recovery after ischemic stroke. Erythropoietin (EPO), vascular endothelial growth factor (VEGF), and insulin-like growth factor 1 (IGF-1) which promote endothelial cell proliferation and stimulate angiogenesis, improve BBB repair. In addition, brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and fibroblast growth factor (FGF) promote proliferation, survival, and maturation of OPCs, oligodendrogenesis, and white matter repair after ischemic stroke.

Fig 2. Role of microglia and astrocytes in the BBB and white matter integrity after stroke. A1-reactive astrocytes and M1 microglia release pro-inflammatory factors (IL-1β, TNF-α, iNOS, IL-6, IL-12, IL-23), which modulate the inflammatory response and increase BBB permeability, exacerbating OLs death and demyelination. The phagocytic activity of microglia and astrocytes removes myelin debris and promotes myelin integrity. A2 reactive astrocytes and M2 microglia release anti-inflammatory (TNF-β, IL-1α, COX-2, IL-10, IL-4) and growth factors (VEGF, BDNF, CNTF, PDGF, NT-3) that promote differentiation of OPCs and angiogenesis, improving the BBB and white matter integrity after ischemic stroke.

Table. Therapeutic strategies for white matter repair and angiogenesis after ischemic stroke.

Table 1: Therapeutic strategies for white matter repair and angiogenesis after ischemic stroke

Outcome	Theraputic strategy	Molecular targets/signal pathway	Dose	Injection Method	References
Reduced BBB damage	Glial growth factor 2 (GGF2)	Inhibition of microglia activation and upregulation of inflammatory factors	50 ng/kg/day	Tail vein injection	Wang et al,. 2023
	Nicotine	Regulation of the endothelial scaffolding protein pdlim5	4.5 mg/kg/day	Subcutaneous injection	Hu et al,. 2023
	Melatonin	Inhibiting HMGB1-Mediated Microglia Activation	15 mg/kg/day	Intraperitoneal injection	Chen et al,. 2022
	Neuroserpin	Reduction of ischemia-induced upregulation of endogenous tPA	20 μmol/L, 3 μL	Infused into striatum	Wang et al,. 2020
	Melatonin	Activation of MT2 melatonin receptor to reduce oxidation/inflammation	10 mg/kg/day	Intraperitoneal injection	Chern et al,. 2012
	infliximab	Ameliorating endothelial necroptosis, BBB destruction	5 mg/kg/day	Tail vein injection	Chen et al,. 2019
	M2 microglia-targeting lipid nanoparticle	Inducing IL-10 production and enhance the M2 polarization of microglia.	0.6 mg/kg mRNA	Tail vein injection	Gao et al,. 2024
	3-methyladenine	Inhibition of autophagy reduces OGD-induced degradation of occludin.	0.3mg / kg/day	Tail vein injection	Kim et al,.2020
	2-Methoxystypandrone	Limiting inflammation and oxidative stress by impairing NF-κB signaling	50 μg/kg/day	Intraperitoneal injection	Chern et al,. 2014
	Cottonseed oil	Reduced A1 phenotype neurotoxic astrocyte activation, inhibit the inflammatory response	1.3 ml/kg/day	Subcutaneous injection	Liu et al,. 2020
Angiogenesis	Omega-3 polyunsaturated fatty acids		4%/day	Fed	Cai et al,. 2017
	Kaempferol	HIF-1α/VEGF-A/Notch1 signaling pathway	50 mg/kg/day	Intragastric injection	Zhang et al,. 2025
	recombinant CAMP peptide	Promoting increased expression of angiogenesis-related genes	2 mg/kg/day	intracerebroventricular injection	Xie et al,. 2023
	Exosomes of endothelial progenitor cells		50 μg	Tail vein injection	Wang et al,. 2020
	Extracellular vesicles from hypoxia-preconditioned microglia	TGF-β/Smad2/3 pathway	10 μg	Femoral vein injection	Zhang et al,. 2021
	Atorvastatin	Induction of VEGF and BDNF	10 mg/kg /day	Subcutaneous injection	Chen et al,. 2005
	Salvianolic acid C	Suppressing microglial cell M1 polarization	10 mg/kg /day	Intragastric injection	Shen et al,.2022
	Microglia preconditioned by oxygen-glucose deprivation	Secretion of VEGF, MMP-9 and TNF-β promotes M2 microglia polarization.	1×10^6/cell	External carotid artery infusion	Masato et al,. 2017
	TWS119	Modulating the anti-inflammatory phenotype of microglia	10 mg/kg /day	Intraperitoneal injection	Song et al,.2019
	L-4F	Reduced macrophage infiltration and neuroinflammation.	16 mg/kg/day	Subcutaneous injection	Zhou et al,.2022
	Levetiracetam	Mediated by anti-inflammatory and anti-apoptotic activities as well as induced expression of HSP70, VEGF, and HIF-1α	150 mg/kg/day	Intraperitoneal injection	Yao et al,.2021
Reduced myelin loss	IL-10	Reduction of lipid ROS to prevent OPC loss and white matter damage.	4×10^9 v.g./mL virus in 2 μL	Infused into striatum	Wu et al,. 2024
	Necrostatin-1	Inhibition of RIPK1, RIPK3, MLKL and P-MLKL expression significantly reduced necroptosis in OPCs.	0.04 mg/kg/day	Ventricular injection	Chen et al,.2018
	Rapamycin	Enhancing autophagy reduces the death of mature oligodendrocytes	3mg / kg/day	Intraperitoneal injection	Wang et al,. 2023
	Melatonin	Activation of MT2 melatonin receptor to reduce oxidation/inflammation	10 mg/kg/day	Intraperitoneal injection	Chern et al,. 2012
	3K3A-activated protein C	Activation of protease-activated receptor 1 (PAR1) and PAR3 protects oligodendrocytes.	0.2 mg/kg/day	Tail vein injection	Huuskonen et al,. 2022
	Minocycline	Blocking hyperoxia-induced microglia morphological changes and IL-1β release.	45 mg/kg/day	Intraperitoneal injection	Schmitz et al,.2014
	Pentoxifylline	Facilitated microglial phagocytosis of myelin debris by up-regulating the expression of Mertk	50 mg/kg/day	Intraperitoneal injection	Zheng et al,. 2022
Remyelinatio n	NgR(OMNI)-Fc	Blocking the Nogo signaling pathway	1.05 μg	Stereoscopic positioning	Sozmen et al,. 2016
	Rosiglitazone	Promoteing oligodendrocyte formation and microglia M2 phenotype polarization.	3 mg/kg/day	Intraperitoneal injection	Han et al,. 2015
	Erythropoietin	Promoting myelin formation by enhancing the proliferation of oligodendrocyte lineage cells	5000 U / kg/day	Intraperitoneal injection	Shumilov et al,. 2023
	Lactolipid globule-epidermal growth factor 8	Enhancing microglia phagocytosis to promote the OPCs differentiation.	400 nL	Bilateral CC injections	Dong et al,. 2024
	M2 microglia-derived extracellular vesicles	miR-23a-5p promotes OPC proliferation, survival and maturation	100 μg	Tail vein injection	Li et al,. 2022
	Endothelial cell-derived exosomes	Promoted Survival, Proliferation and Motility of Oligodendrocyte Precursor Cells	20 μL 50 μg/mL	under the epineurium of the sciatic nerve by using a micro syringe	Kurachi et al,. 2016
	L-4F	Reduced macrophage infiltration and neuroinflammation.	16 mg/kg/day	Subcutaneous injection	Zhou et al,.2022

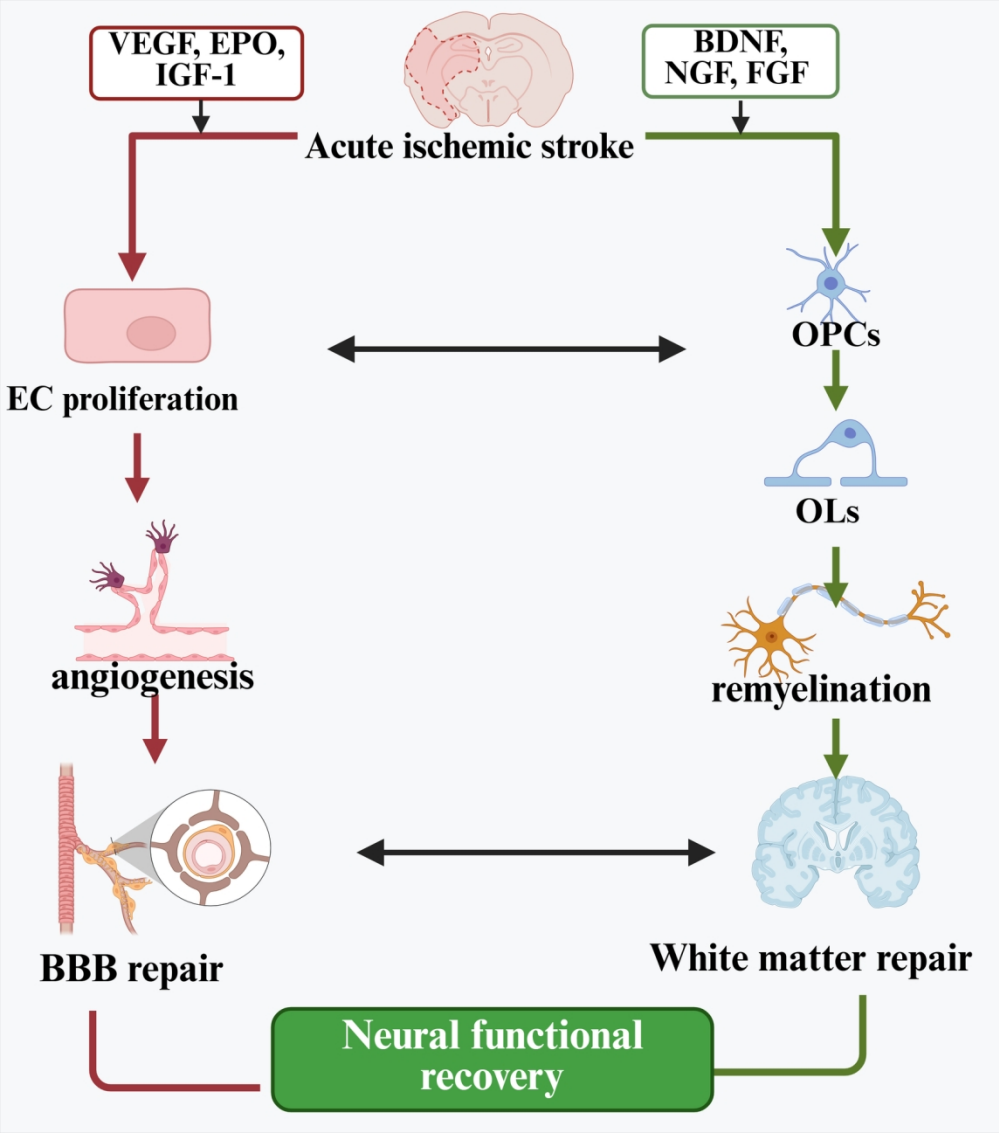

Fig.1

143x162mm (300 x 300 DPI)

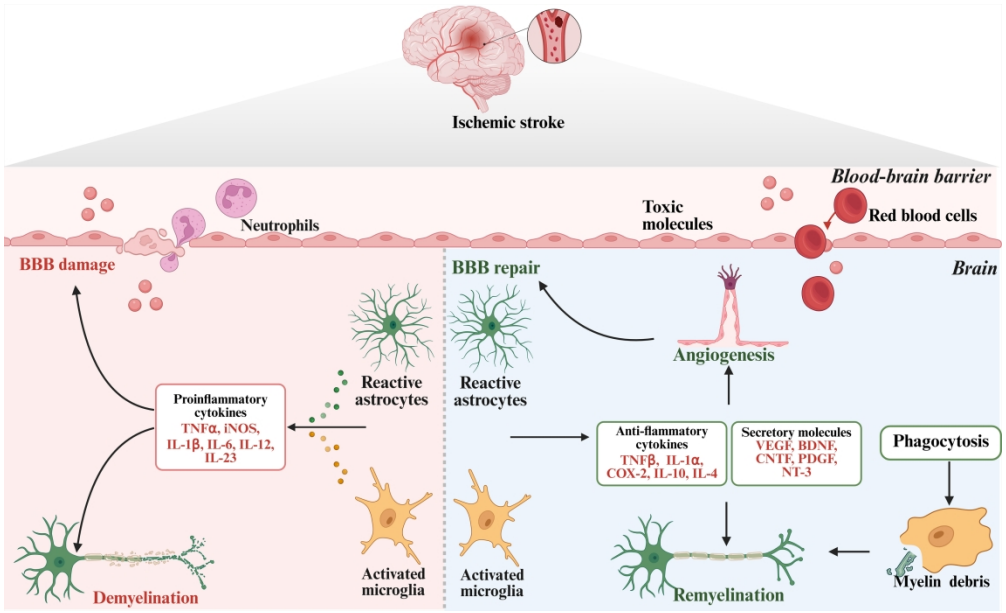

Fig.2

280x169mm (300 x 300 DPI)