

The evolving role of neuro-immune interaction in brain repair after cerebral ischemic stroke

Xin Wang | Wei Xuan | Zi-Yu Zhu | Yan Li | Hao Zhu | Ling Zhu | Dan-Yun Fu |
Li-Qun Yang | Pei-Ying Li  | Wei-Feng Yu

Department of Anesthesiology, Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China

Correspondence

Pei-Ying Li and Wei-Feng Yu, Department of Anesthesiology, Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China.
Emails: peiyingli.md@gmail.com (PL); ywf808@yeah.net (WY)

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Summary

Stroke is the world's leading cause of disability with limited brain repair treatments which effectively improve long-term neurological deficits. The neuroinflammatory responses persist into the late repair phase of stroke and participate in all brain repair elements, including neurogenesis, angiogenesis, synaptogenesis, remyelination and axonal sprouting, shedding new light on post-stroke brain recovery. Resident brain glial cells, such as astrocytes not only contribute to neuroinflammation after stroke, but also secrete a wide range of trophic factors that can promote post-stroke brain repair. Alternatively, activated microglia, monocytes, and neutrophils in the innate immune system, traditionally considered as major damaging factors after stroke, have been suggested to be extensively involved in brain repair after stroke. The adaptive immune system may also have its bright side during the late regenerative phase, affecting the immune suppressive regulatory T cells and B cells. This review summarizes the recent findings in the evolving role of neuroinflammation in multiple post-stroke brain repair mechanisms and poses unanswered questions that may generate new directions for future research and give rise to novel therapeutic targets to improve stroke recovery.

KEYWORDS

brain repair, immune response, neuroinflammation, regeneration, stroke

1 | INTRODUCTION

As the leading cause of disability in adults, cerebral ischemic stroke is frequently accompanied by long-lasting neurological deficits that significantly impair the quality of life for stroke patients.¹ The brain may undergo self-repair events at late stage of stroke, which allows stroke patients to regain some part of their sensorimotor functions.²⁻⁴ Unfortunately, the self-repair capacity is very limited, and therapeutic strategies that can sufficiently restore stroke patients' lost neurological functions are still lacking.^{2,5} Neuroinflammation is a promising new brain repair target after stroke for the following four reasons: (a) the long-lasting cross talk between the peripheral

immune system and the ischemic brain provides a wide therapeutic window and thus offers an opportunity to enhance the brain repair during the late phase of stroke; (b) inflammatory responses are fundamentally involved in multiple brain repair mechanisms which work in concert to orchestrate neurological recovery; (c) recent research on neuroinflammation has improved our understanding of the contribution of inflammatory cell infiltration to ischemic brain injury; (d) the finding of alternative phenotypes of microglia/macrophage, neutrophils, and astrocytes after stroke.^{6,7}

This review introduces the recent findings in the evolving role of neuroinflammation in multiple post-stroke brain repair mechanisms, which hold promise for generating new novel therapeutic targets

Wang and Xuan are contributed equally to this work.

to improve and accelerate the brain tissue repair and functional recovery.

2 | THE ROLE OF NEUROINFLAMMATION IN MULTIPLE BRAIN REPAIR MECHANISMS FOLLOWING CEREBRAL ISCHEMIC INJURY

In response to cerebral ischemic stroke, both resident glial cells in the brain and peripheral immune cells are activated, inducing various immune cells to infiltrate into the injured brain. The cross talk between the peripheral and resident inflammatory cells forms a vicious cycle, leading to a series of detrimental consequences and resulting in a secondary brain damage from augmented neuroinflammation.⁸⁻¹⁰ The immune cells participating in neuroinflammation are a large family, consisting of various types of cells and their responses toward acute ischemic attack and late phase brain repair are complex and can persist into late repair phase of cerebral ischemic injury.^{11,12} Both innate immune cells such as local microglia, newly infiltrated macrophages and adaptive immune cells, such as CD4⁺ T cells, CD8⁺ T cells, remain activated in the late phase of ischemic stroke.¹¹⁻¹³

In the late phase of stroke, multiple endogenous brain repair processes are occurring in the ischemic brain. It is emerging that immune responses in the late phase of stroke mainly affect the functional and structural repair elements, including neurogenesis, new born neuron migration, formation of novel synapses, and neuronal networks, axonal spouting, remyelination, and neurovascular unit remodeling.

2.1 | Neuroinflammatory responses are profoundly engaged in post-stroke neurogenesis

2.1.1 | Ischemic stroke initiates neurogenesis in the adult brain

Neurogenesis is a physical phenomenon that persists the whole lifetime and is an important and promising step toward the recovery and restoration of brain function after stroke and other neurodegenerative diseases.¹⁴⁻¹⁸ The generation and maturation of de novo neurons require multiple steps, including neuronal progenitor cells (NPCs) mobilization, proliferation, neuronal migration, neuron maturation, and synaptic reconstruction. Multipotent NPCs support self-renewal and differentiation and reside within specialized niches in the adult mammalian CNS.¹⁹ One of the best characterized niches is the subventricular zone (SVZ), a layer of cells lying immediately under the ependymal lining of the lateral ventricles.²⁰ Neuron generation mostly happens in the SVZ and the subgranular zone (SGZ) of the hippocampus.²¹ The SVZ has great potential for neurogenesis, both in rodents and humans, and contains three major stem cell types; B, C, and A. The CNS stem cells (type B cells) display an astrocyte-like phenotype and express glial fibrillary acid protein (GFAP). They can also give rise to intermediate transit amplifying progenitors (type C cells), which

lose the immunoreactivity of GFAP and acquire the expression of the distal-less homeobox (Dlx)-2.^{22,23} These type C cells can, in turn, differentiate into neuroblasts (type A cells) that express the polysialylated form of neural cell adhesion molecule in addition to doublecortin, and migrate to the olfactory bulb. The cell lineage differentiation pathway proceeds from type B, through type C, to type A cells, with the type B cell believed to be the self-renewing CNS stem cell.²⁴ After proliferation, the newly born neuroblasts migrate from the generation zone to the injurious areas and differentiate into mature neurons.^{25,26}

2.1.2 | Neuroinflammation is fundamentally engaged in neurogenesis and affects the proneurogenic microenvironment after stroke

Neuroinflammation participates in almost every step of the above-mentioned ischemic brain repair, including neurogenesis.²⁷⁻³¹ Microglia activation, and possibly M1 phenotype development, augments post-stroke neuroinflammation and may decrease neurogenesis.³²⁻³⁵ Persistent brain inflammation also extensively alters the proliferative and migratory properties of SVZ-resident NPCs in vivo, leading to significant accumulation of nonmigratory neuroblasts within the SVZ germinal niche.²⁹ But injured CNS neurons can benefit from active or passive immunization with CNS myelin-associated antigens. Peripheral immune cell infiltration and inflammation in the ischemic brain also drastically changes the microenvironment for brain repair and impairs the proneurogenic homeostasis after stroke,³⁶ which is believed to be a prerequisite for the development, and survival of de novo generated neurons.^{27,28,37,38} In the ischemic stroke model, the neurogenesis after stroke also depends on T lymphocytes subgroups, different subgroup deficient plays different effect on neurogenesis.³⁹ Exogenous stem cell therapy confers superior antiinflammatory effects and the robust antiinflammatory action is considered as an important requirement to improve neurogenesis and other regenerative processes after stroke.^{40,41}

Therefore, neuroinflammation is crucial for endogenous neurogenesis and it plays dual roles on endogenous neurogenesis after cerebral ischemic stroke. Brain glial cells and distinct components of the peripheral immune system can either promote or impair the post-stroke neurogenesis by their specific phenotypes as discussed below.

2.1.3 | Post-stroke responses from resident brain glial cells and neurogenesis

Microglia, resident brain immune cells, are responsible for immune surveillance and clearing up dead/apoptotic neurons through phagocytosis.⁴²⁻⁴⁴ After cerebral ischemic injury, microglia are stimulated and secrete a number of signaling factors into the brain.⁴⁵ Neurogenesis is thereby influenced through the milieu of secreted factors.²⁸ Microglia can secrete pro-inflammatory factors such as tumor necrosis factors- α (TNF- α)^{46,47} and neurotrophic factors

such as insulin growth factors (IGF) and brain-derived neurotrophic factor (BDNF), both of which can reduce inflammation and exert neuroprotective effects.⁴⁸⁻⁵¹ The complex role of microglia in neurogenesis is also due to its modulatory nature.^{27,49,52} Under different stimulations, microglia may polarize into either of two phenotypes that conduct drastically different pathophysiological behaviors.⁵³ Although there is a growing concern for the limitations of the terminology of M1/M2 phenotype, the dual role of microglia/macrophage in promoting inflammation and resolution can be mediated by distinct gene expression programs and distinct phenotypes.^{54,55} The “classically activated” M1 type is destructive and promotes brain injury by releasing pro-inflammatory mediators, such as IL-1, IL-6, and IL-12, and nitric oxide.^{6,56} M1 microglia have been suggested to inhibit differentiation of neural stem cells (NSCs).⁵⁷ Inhibiting M1 microglia using minocycline, a selective inhibitor of M1 microglia, is protective through promoting neurogenesis and functional

recovery after stroke.^{58,59} However, microglia depletion using dual colony-stimulating factor 1 receptor/c-kit inhibitor PLX3397 exacerbates neurological deficits,⁴⁹ indicating that there are different phenotypes of microglia that may promote brain recovery, which is now termed as the “alternatively activated” M2.^{52,56,60,61} In addition to secreting anti-inflammatory factors, M2 cells also support neurogenesis by promoting neuron proliferation and brain repair.^{27,62,63} The M2 polarized microglia are able to produce specific trophic factors that increase neural precursor cell proliferation and neuroblast migration.^{27,60,64}

Astrocytes account for nearly half of the brain cells.⁶⁵ Although astrocytes are not typical immune cells, they can function as inflammatory cells and produce inflammatory factors affecting the post-stroke immune responses.^{66,67} In addition, astrocytes provide energy and structural support, glucose metabolism, take up excessive molecules in the extracellular matrix,^{68,69}

TABLE 1 Neurotrophic factors secreted by astrocytes for post-stroke brain repair

Major findings	Study	Model	Key factors
Neurogenesis			
Improve behavioral impairment	Okoreeh et al, (2017) ⁶⁶	Aging female rats with 90 min ischemic stroke	Insulin like growth factor (IGF)-1
Proliferation factors	Kalani et al, (2008) ⁷⁰	Neural stem cells	Wnt signaling
	Otaegi et al, (2006) ⁷¹	Mouse olfactory bulb stem cells	Insulin-like growth factor I (IGF-I)
	Shetty et al, (2005) ⁷²	Hippocampus of aging rats	Fibroblast growth factor-2 (FGF-2)
	Bartkowska, (2007) ⁷³	Embryonic cortical precursor cell	TRK signaling
	Quesseveur, (2013) ⁷⁴	Mice hippocampal astrocytes	Brain-derived neurotrophic factor (BDNF)
	Kang et al, (2013) ⁷⁶	Subventricular zone in stoked mice	Ciliary neurotrophic factor (CNTF)
Axonal remodeling of corticospinal tract (CST)	Magnusson et al, (2014) ⁸¹	Striatum of stroked mouse	Notch signaling
	Liu et al, (2014) ⁷⁸	Cerebral cortical photothrombotic stroke	GFAP/vimentin
Transdifferentiate into functional new neurons	Duan et al, (2015) ⁸⁰	Striatal astrocytes in MCAO rats	
Neurovascular unit remodelling			
Limit neuroinflammation	Cekanaviciute et al, (2014) ¹¹⁵	Mice where TGF β signaling is inhibited specifically in astrocytes	Transforming growth factor-beta (TGF β)
Synaptogenesis			
Synaptogenesis promoter	Tournell et al, (2006) ¹⁶⁹	Astrocytes cultured with hippocampal rat neurons	Agrin
	Christopherson et al, (2005) ¹⁷⁰ and Lin et al, (2003) ¹⁷¹	Immature astrocytes in vitro and in vivo	Thrombospondins (TSPs)-1 and -2
Synaptic plasticity modulator	Choi et al, (2016) ¹⁶⁶	Stroke model of rat	Ephrin-A1 and ephrin-A5
Axon sprouting			
Axonal sprouting stimulator	Ren et al, (2000) ¹⁹⁵	Rats underwent MCA	Bone morphologic protein(BMP)
	Choi et al, (2016) ¹⁶⁶	Rose Bengal-treated rats underwent focal cortical infarcts	Ephrin-A1 and ephrin-A5
Remyelination			
Support myelination	Nash et al, (2011) ²³³	Astrocytes plated on poly-L-lysine	Ciliary neurotrophic factor (CNTF)
Decreased demyelination	Wang et al, (2017) ²³⁷	mouse brain	CD59

and actively participate in neuronal proliferation, maturation, and survival.^{37,38,65,67} They stimulate neurogenesis by secreting prodifferentiation factors such as Wnt⁷⁰ and proproliferation factors such as insulin growth factors (IGF),^{71,72} BDNF,^{73,74} glia-derived neurotrophic factor (GDNF), nerve growth factor (NGF), basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), ciliary neurotrophic factor (CNTF), and erythropoietin (EPO).⁷⁵⁻⁷⁷ Deletion of astrocytic intermediate filament proteins, GFAP and Vimentin were shown to severely impair stroke recovery.⁷⁸ Reactive astrocytes also secrete the neuroblast attracting chemokines such as stromal cell-derived factor-1 after brain ischemic injury, which contributes to guiding migrating neuroblasts to the infarcted brain area.⁷⁹ The influence of astrocytes on post-stroke neurogenesis is not limited to the trophic factors as shown in Table 1. Resident astrocyte-derived neurons could transdifferentiate into morphologically mature and functional neurons, and the newly generated neurons could form new synapses, which possessed typical neuronal morphology and electrophysiological activity.⁸⁰ It has been shown that striatal astrocytes possess the ability to either produce neuroblasts or acquire NSC-like properties by expressing NSC related proteins such as nestin, Sox2, and DCX after stroke.^{80,81} Reduced

Notch1 signaling was essential for triggering striatal astrocytes to enter the neurogenic program.⁸¹

2.1.4 | Peripheral immune cells that participate in neurogenesis after stroke

Apart from resident glial cells, peripheral immune cells, such as T cells, can infiltrate into the ischemic brain via the compromised blood brain barrier (BBB) or choroid plexus⁸² and indirectly promote neurogenesis and microglia activity by producing IL-4 or low-level IFN- γ , respectively.^{62,83} However, the subgroups of T cells that promote neurogenesis were not identified. In fact, there are huge discrepancies with respect to cytokine production from Th1 or Th2 cells and the ratio of Th1/Th2 cells can even affect stroke severity.⁸⁴ Th17 cells and $\gamma\delta$ T cells produce pro-inflammatory cytokines and chemokines,^{85,86} usually impairing neurogenesis.^{87,88} However, it is recently suggested that IL-17A secreted by $\gamma\delta$ T cells unexpectedly promoted neuronal differentiation via p38 mitogen-activated protein kinase in cultured NPCs.⁸⁹ Regulatory T cells (Tregs) are one special subset of Th2 cells that have been shown to negatively regulate neuroinflammation alleviating post-stroke brain damage.⁹⁰⁻⁹⁵ Injecting activated Tregs, a

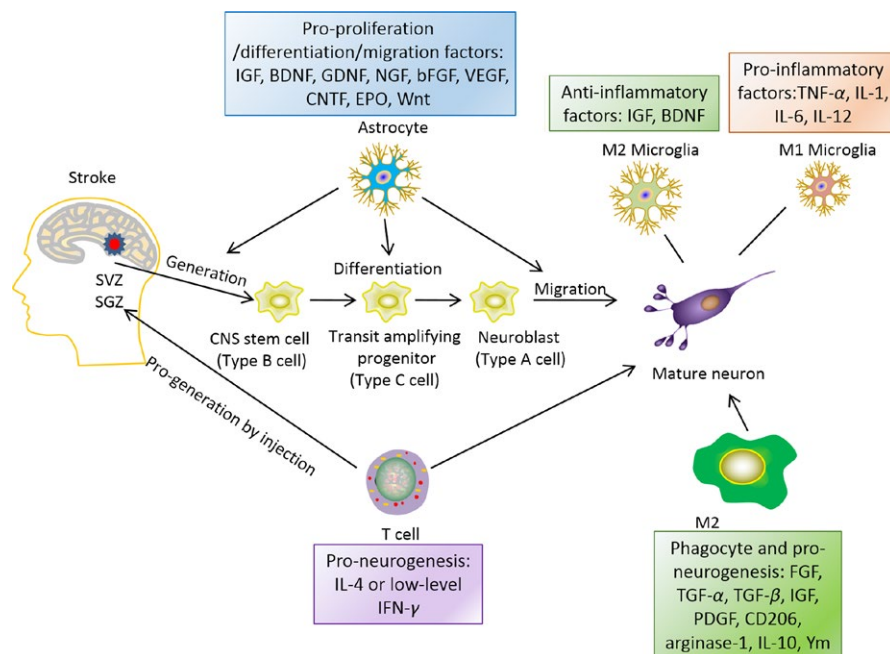


FIGURE 1 Neuro-inflammation and neurogenesis. Astrocytes can affect the generation, differentiation and migration of de novo generated neurons by secreting pro-neurogenic factors, such as insulin growth factor (IGF), glia-derived neurotrophic factor (GDNF), nerve growth factor (NGF), basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), ciliary neurotrophic factor (CNTF), erythropoietin (EPO) and Wnt. Microglia can affect neurogenesis in their distinct phenotype, M2 phenotype produces anti-inflammatory factors, such as IGF, BDNF; while M1 phenotype secretes pro-inflammatory factors, such as: TNF- α , IL-1, IL-6, and IL-12. T cells can also promote neurogenesis and maturation of neuroprogenitor cells by producing IL-4 or low level IFN- γ . M2 macrophages in the periphery can produce factors, such as fibroblast growth factor (FGF), TGF- α (transforming growth factor- α), TGF- β , IGF, PDGF (platelet driven growth factor), CD206 (cluster of differentiation 206, mannose receptor), arginase-1, IL-10, and Ym, all above factors have been shown to promote maturation of newly generated neurons

special subset of T cells, into the left lateral ventricle of ischemic mouse brain was shown to enhance neural stem cell proliferation in the SVZ.⁹⁶

Macrophages are another type of peripheral immune cell that can infiltrate into the ischemic brain and promote neurogenesis exhibit a prorecovery profile through their M2 phenotype.⁹⁷⁻⁹⁹ They produce members of fibroblast growth factor (FGF), transforming growth factor- α and β (TGF- α and TGF- β), insulin-like growth factor (IGF), and platelet derived growth factor (PDGF) families⁹⁷ and antiinflammatory cytokines, such as CD206, arginase-1, IL-10, and Ym.¹⁰⁰ Other than these cytokines, the phagocytic activity of macrophages also helps to provide a microenvironment receptive to brain repair.²⁷ It is now recognized that macrophages play important roles in neurogenesis.¹⁰¹ They can produce neurotrophic factors that promote neuron progenitor proliferation, the migration of neuroblast cells and maturation of the newly born neurons.^{102,103} Therefore, the special macrophage M2 phenotype is becoming recognized as an important promotor of post-stroke brain repair.^{104,105}

Collectively, the impact of neuro-immune cross talk on the post-stroke neurogenesis process largely depends on the activated immune cell subsets or the specialized phenotypes of the inflammatory cells (Figure 1). Apart from neurogenesis, understanding how the interactions between the neuro- and immune systems

affects the migration and maturation of newly born neurons is still largely unknown and thus warrants further investigation.

2.2 | Neuroinflammation and neurovascular unit remodeling

2.2.1 | Neurovascular unit remodeling after ischemic stroke

The neurovascular unit a complex interplay of biochemical and molecular mechanisms involving practically any cell type of the brain.¹⁰⁶ After ischemic stroke, disruption of the normal vasculature leads to neuronal ischemia and cascades of pro-inflammatory responses that eventually exacerbates ischemic brain injury.^{107,108} Angiogenesis, the growth of new blood vessels, could be interpreted as a natural defense mechanism helping to restore oxygen and nutrient supply to the affected brain tissue.¹⁰⁹ In this context, angiogenesis and structure reconstruction are necessary and important steps towards function restoration.¹¹⁰⁻¹¹² Soon after ischemic attack, endothelial cells proliferate and migrate to the impaired region under the regulation of angiogenic growth factors to form a new microvasculature structure,¹¹³ while the perilesional vascular reactivity remains elevated until 21 days after stroke.¹⁰⁸ Angiogenesis relies heavily on the coordination

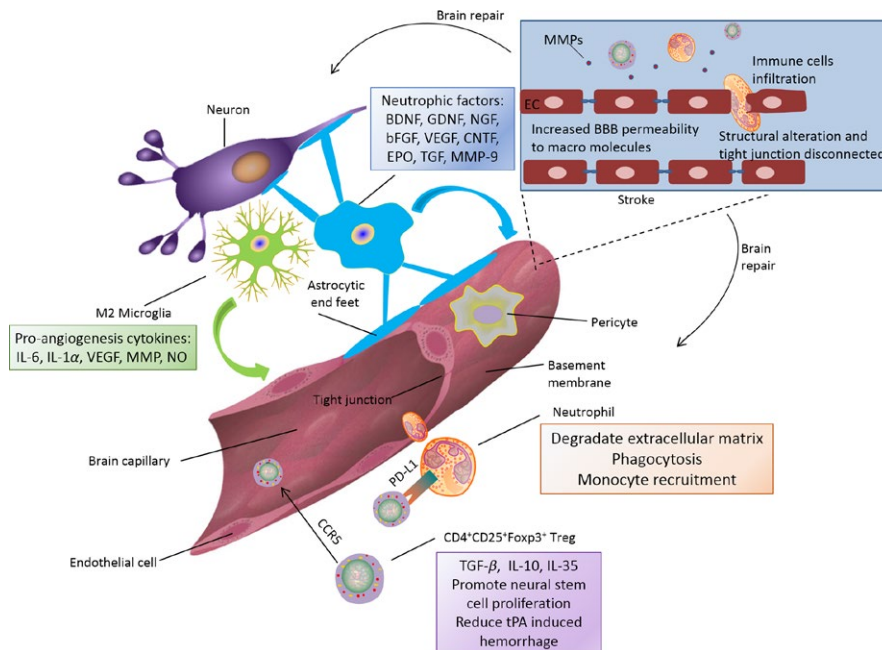


FIGURE 2 Neurovascular unit remodeling after stroke. Microglia in M2 phenotype can generate proangiogenesis factors such as IL-6, interleukin-1 α , vascular endothelial growth factor (VEGF), matrix metalloproteinase (MMP) and nitric oxide. In chronic phase of stroke, astrocytes can promote neuronal survival and neurovascular unit remodeling by producing brain-derived neurotrophic factor (BDNF), gliaderived neurotrophic factor (GDNF), nerve growth factor (NGF), basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), ciliary neurotrophic factor (CNTF), erythropoietin (EPO), transforming growth factors (TGF) and matrix metalloproteinase 9 (MMP9). Neutrophils assist neurovascular unit repair through extracellular matrix degradation, phagocytosis, monocyte recruitment. CD4+CD25+Foxp3+ Tregs can release anti-inflammatory cytokines of TGF- β , IL-10 and IL-35. They can also promote neural stem cell proliferation and reduce tissue plasminogen activator (tPA)-induced haemorrhage. CD4+CD25+Foxp3+ Tregs can be recruited to ischemic blood brain barrier by CCR5 and alleviate BBB disruption through the expression of PD-L1

of proangiogenic and antiangiogenic factors,^{7,75,76,114-117} in which the neuro-immune crosstalk by microglia, astrocytes, and peripheral immune cells is actively involved (Figure 2).

2.2.2 | Resident glial cells and post-stroke neurovascular unit remodeling

Local resident microglia can secrete proangiogenesis cytokines such as interleukin-6 (IL-6),¹¹⁸ IL-1 α ,¹¹⁹ vascular endothelial growth factor (VEGF),¹²⁰ matrix metalloproteinase (MMP)^{121,122} and nitric oxide.^{123,124} The role of microglia on the post-stroke neurovascular unit largely depends on the phenotype of microglia. Microglia can interact with endothelial cells through integrin Mac1 and the endocytic receptor, low density lipoprotein receptor-related protein 1 (LRP1) and induce BBB permeability in the thrombotic stroke model.¹²⁵ On the other hand, induction of the M2 phenotype in activated microglia is effective in promoting BBB remodeling, possibly by enhancing tight junction protein expression during stroke recovery.⁷

Astrocytes are a major component of BBB and thus play critical roles in supporting neurovascular unit remodeling during the BBB repair phase after cerebral ischemia.^{79,126-128} Activated astrocytes can persistently produce neurotrophic factors, including BDNF, GDNF, NGF, bFGF, VEGF, CNTF, EPO, TGF and so on to support neuronal survival and neurovascular unit remodeling in the chronic phase of stroke.^{7,75,76,114-116,129} Deletion of GFAP and Vimentin, the two major astrocytic intermediate filament proteins, were shown to severely impair stroke recovery.⁷⁸ Astrocytes may also be an important cellular source of MMP-9 essential for the remodeling of neurovascular structure and functional recovery in the late phase of stroke (7-14 days after stroke).¹³⁰

2.2.3 | Peripheral immune cells and post-stroke neurovascular unit remodeling

In addition to the resident glial cells, certain subsets of peripheral immune cells also contribute to BBB repair after stroke. The M2 macrophages also produce proangiogenesis factors such as VEGF, IL-8,¹³¹ IGF-1, and TGF- β .¹³² Therefore, M2 macrophages are also a promising target to enhance angiogenesis and neurovascular unit remodeling after stroke.

Although the detrimental role of neutrophils on the BBB damage in the acute phase of stroke is well established,¹³³⁻¹³⁷ neutrophils may also have a beneficial effect in neurovascular repair after stroke. The degradation of extracellular matrix by neutrophils should induce the release of growth factors, which are normally bound to the extracellular matrix in the zymogen form, such as vascular endothelial growth factor (VEGF) and transforming growth factor (TGF)- β .¹³⁸ Neutrophils clear away dead cells, debris, and bacteria through phagocytosis, thus providing a better microenvironment for repair.^{139,140} Moreover, neutrophils promote monocyte recruitment into the extracellular matrix and phagocytotic function, leading to the clearance of their own.^{141,142} It has recently been highlighted that neutrophils can polarize toward the beneficial N2 phenotypes

in the setting of stroke by activating the nuclear peroxisome proliferator-activated receptor (PPAR)- γ .¹⁴³ So far the mechanism of neutrophil-promoted neurovascular repair after stroke is largely unknown. It will be intriguing to investigate whether neutrophils may transform into a protective phenotype to promote the neural network remodeling after stroke. In addition to the direct role of neutrophils on brain recovery after stroke, the ability of neutrophils to infiltrate the brain makes it a potential candidate for drug delivery into the brain.¹⁴⁴

CD4⁺CD25⁺Foxp3⁺ Tregs are a special subset of regulatory T cells that have been identified as an intrinsic protective factor after cerebral ischemic injury.^{12,93,136,145,146} CD4⁺CD25⁺Foxp3⁺ Treg cells constitute 10% of peripheral CD4⁺ T cells¹⁴⁷ and are essential for maintaining immunological self-tolerance and promote immunosuppressive features through releasing antiinflammatory cytokines, such as TGF- β , IL-10 and IL-35.¹⁴⁸ In response to cerebral ischemic injury, CD4⁺CD25⁺Foxp3⁺ Tregs can be directly activated at the surface chemokine receptor CCR5, allowing Tregs to be recruited to the BBB. At the BBB, these Tregs exert early protection against BBB disruption through interacting with neutrophils through the surface expression of PD-L1,^{12,90,136} and secreting IL-10 to protect against neuroinflammatory responses.^{93,149} The protection of Tregs on BBB disruption after stroke can also be utilized to ameliorate tissue plasminogen activator-induced brain hemorrhage after stroke by inhibiting neutrophil-derived MMP-9 and endothelial derived-CCL2.^{150,151} In addition, CD4⁺CD25⁺Foxp3⁺Tregs have also been regarded as a promising regulatory candidate of brain repair processes by dampening excessive immune responses and also promote the survival of newly generated neuroblasts.¹⁴⁸ Brain infiltration of endogenous CD4⁺CD25⁺Foxp3⁺Tregs after cerebral ischemia corresponds with the brain repair phase which occurs about 7 days after stroke.^{27,93} Injecting Tregs into the left lateral ventricle of the ischemic mouse brain promoted neural stem cell proliferation via secreting IL-10, suggesting a brain repair effect of Tregs in the late phase of stroke.⁹⁶ However, due to the complex function of regulatory cells in immune homeostasis,¹⁴⁶ divergent findings have been described for the role of Tregs in stroke models.¹⁵²

Despite considerable findings on the association of peripheral immune cells and the BBB disruption after stroke, it still remains largely unknown how the immune cells participate in the remodeling of neurovascular unit in the late phase of stroke.

2.3 | Neuroinflammation and post-stroke synaptogenesis

2.3.1 | Synaptogenesis and synaptic rearrangement after cerebral ischemic stroke

Transient global ischemia or hypoxia can induce impairment of spatial learning and memory, which may result from gradual loss of synapses, dysregulation of synaptic adhesion, apoptotic neuronal cell death, and insufficient synaptic repair in the dorsal hippocampus CA1 area.^{153,154} Synaptic degradation begins after global ischemic attack and proceeds during the reperfusion period, less than half

of the synapses survive 7 days after ischemic stroke.¹⁵³ The loss of synapses is accompanied by reduction in axon terminal volumes and synaptic vesicle numbers which is initiated as early as 2 hours after the cerebral ischemia induced by left carotid occlusion.¹⁵⁵

2.3.2 | Inflammatory regulation of synaptogenesis by brain glial cells after stroke

Synaptogenesis is an important form of brain repair after cerebral ischemic stroke.^{156,157} It involves formation of a neurotransmitter release site in the presynaptic neuron, a receptive field at the postsynaptic partners and the precise alignment of pre- and postsynaptic specializations.¹⁵⁸⁻¹⁶⁰ The regulation of post-stroke synaptogenesis is complicated and still not fully understood. Recent research suggests that the resident glial cells are essential regulators for synapse formation and modulation during CNS development,^{79,161-164} after traumatic brain injury¹⁶⁵ and cerebral ischemic stroke.¹⁶⁶ The interaction of astrocytic processes with the pre- and postsynaptic terminals forms a “tripartite synapse”, which is important for synaptic dysfunction and neuronal death.¹⁶⁷ Ischemic neurons express lipocalin-2, which functions as a “help me” signal to transform the glial cells into their prorecovery phenotypes.¹⁶⁸ Hippocampal neurons grew more synapses when cocultured with astrocytes, which is possibly mediated by agrin—a known synaptogenesis promoter derived from astrocytes.¹⁶⁹ Physiologically, thrombospondins (TSPs)-1 and -2 are two major factors produced

by immature astrocytes to promote synaptogenesis during brain development¹⁷⁰ and their expression is usually reduced in the adult brain. However, elevation of TSP-1 and TSP-2 were observed in a rat ischemic stroke model, and this might be one of the mechanisms underlying post-ischemic astrocyte induced synaptogenesis.¹⁷¹ During synaptogenesis, an impressive degree of plasticity is retained through morphological and molecular rearrangements in the pre- and postsynaptic compartments that underlie the strengthening or weakening of synaptic pathways, which is termed as synaptic plasticity.¹⁷² The upregulation of ephrin-A1 and ephrin-A5 in activated astrocytes of the corticospinal tract 2 weeks after stroke is believed to modulate synaptic plasticity in stroke recovery.¹⁶⁶ In response to ischemic injury in adult brains, striatal resident reactive astrocytes can differentiate from GABAergic and cholinergic neurons into functional mature neurons, and form synapses to receive inputs from surrounding neurons.^{80,173} The above evidence suggests that astrocytes have pleiotropic mechanisms to enhance synaptogenesis after stroke (Figure 3).

Microglia are also actively involved in brain development, especially in synaptic remodeling.¹⁷⁴⁻¹⁷⁶ Microglia play an essential role in synaptic pruning by engulfing synaptic debris.¹⁷⁷ Deprivation of microglia resulted in abnormal synapse maturation in mice.¹⁷⁸ Microglia not only regulate synaptic pruning in the developing brain,¹⁷⁸ but also the functional state of synapses at the ischemic terminals.¹⁷⁹ However, whether different microglial phenotypes affect synaptic remodeling after ischemic stroke needs to be clarified.

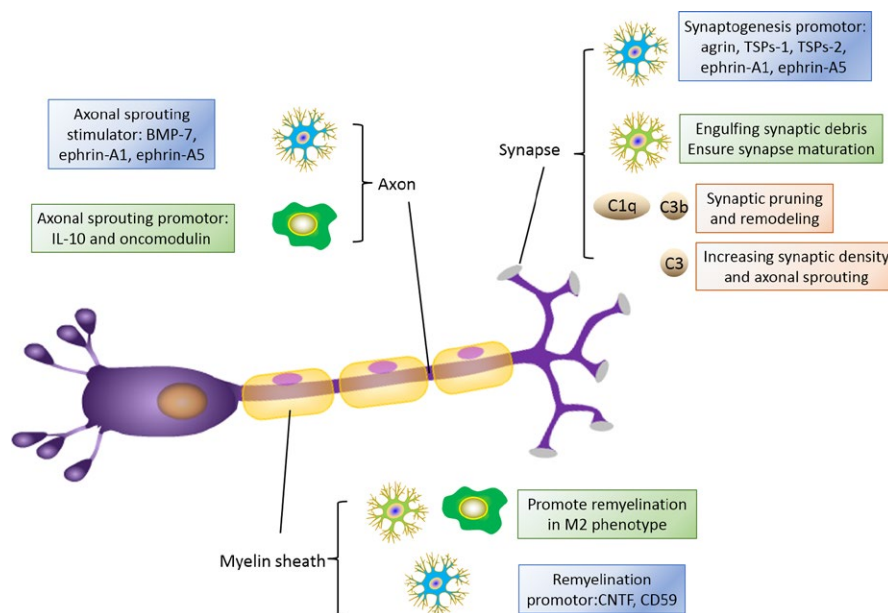


FIGURE 3 Interaction of immune cells with synaptogenesis, axonal regrowth and myelin sheath repair. In terms of synaptogenesis, astrocytes are beneficial by secreting agrin, thrombospondins (TSPs)-1 and -2, ephrin-A1 and ephrin-A5. Microglia is important in synaptic pruning by engulfing synaptic debris and ensure synapse maturation. Complement system exert their positive effects on synaptic pruning and remodeling, along with increasing synaptic density and axonal sprouting. For axonal sprouting, astrocytes can produce stimulating factors like bone morphologic protein 7 (BMP 7), ephrin-A1 and ephrin-A5. Macrophages promote axonal sprouting through IL-10 and oncomodulin release. M2 microglia and macrophage have been found to promote remyelination and may help to repair white matter injury. Astrocytes may also promote remyelination by expressing CD 59 and ciliary neurotrophic factor (CNTF)

2.3.3 | The emerging role of complement system in post-stroke synaptogenesis

The emerging role of the complement system in synaptogenesis and neural network plasticity opens new conceptual avenues for considering complement interception as a potential therapeutic modality for improving brain repair after stroke.^{180,181} The complement system is the innate immune response to foreign objects triggering a proteolytic cleavage cascade. It is activated by the classical, lectin, or alternative pathways.^{182,183} The classical and lectin pathways can be activated by antibodies, apoptotic cells, or polysaccharides. C1q is the target recognition protein of the classical complement pathway.¹⁸³ The alternative pathway can be activated spontaneously and functions to amplify the other pathways. All pathways converge with the formation of a C3 convertase and the cleavage of C3 to produce C3a and C3b. C3 cleavage also leads to cleavage of C5 to yield C5a and C5b.¹⁸² Distinct complement effectors appear to play multifaceted roles in brain homeostasis by regulating synaptic pruning in the retinogeniculate system and sculpting functional neural circuits in the brain.¹⁸⁴ C1q can bind neuronal pentraxins, a family of acute immune response proteins involved in clustering α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors at the postsynaptic cleft. This activation removes their stabilizing ability on dendritic spine receptors. This would ultimately decrease the amount of communication between the pre- and postsynapses resulting in synaptic weakening.¹⁸⁵ Astrocyte-mediated activation of C1q results in downstream activation of C3b, which then deposits on neurites, thus "tagging" them for elimination. Mice lacking either C1q or C3 show increased synaptic connectivity and enhanced epileptiform activity due to failed synaptic pruning.^{81,186} Unlike the detrimental impact of C1q and C3b on the brain plasticity, C3a was recently shown to enhance neural plasticity by increasing synaptic density and axonal sprouting.¹⁸⁷ Consistent with the beneficial role of C3a in neural plasticity, genetic ablation of complement receptor 3 (CR3) and C3 or pharmacological perturbations of these proteins results in microglial dysfunction and deficits in synaptic remodeling.¹⁷⁴ Furthermore, disrupting microglia-specific CR3/C3 signaling resulted in sustained deficits in synaptic connectivity.¹⁷⁴

With the above evidence showing close relationships of the complement system with the synaptic connectivity and the pathogenesis of cerebral ischemic injury (Figure 3),¹⁸² it is reasonable to expect that the complement system may potentially have crucial impacts on the post-stroke brain function recovery.

2.4 | Axonal sprouting and regrowth after ischemic stroke and the role of neuroinflammatory responses

Axonal sprouting is a process in which sprouts grow out of axons and is an important step toward recovery after ischemic stroke.^{188,189} It can be detected in the penumbra three weeks after the ischemic attack,¹⁹⁰ and last for several months.^{191,192} Ischemia and reperfusion injury leads to production of numerous cytokines and free radicals, which thereafter activate immune cells and subsequent destructive

casades. Activated astrocytes are fundamentally involved in post-ischemic repair, not only in angiogenesis and synaptogenesis, but also in induction of axonal sprouting.¹⁹³ There are several special cytokines that have been identified to involve in post-ischemic axonal sprouting. Bone morphologic proteins (BMP) are a family of growth factors that promotes cell differentiation. It is also a powerful stimulator for dendritic development.¹⁹⁴ Ren et al found that intracisternal injection of BMP-7 was associated with better behavior performance in mice and that the underlying mechanism may be axonal sprouting stimulated by BMP-7.¹⁹⁵ Growth and differentiation factor (GDF) is another important factor which enhances axonal sprouting through TGF- β signaling.¹⁹² The upregulation of ephrin-A1 and ephrin-A5 in activated astrocytes of the corticospinal tract 2 weeks post injury is also believed to modulate axonal reorganization in stroke recovery.¹⁶⁶

Activated macrophages and microglia after stroke are also important players in axonal sprouting (Figure 3).^{196,197} The M1 phenotype inhibits axonal growth by secreting destructive signals such as interferon- γ (IFN- γ)¹⁹⁸ and promoting dendrite retraction.¹⁹⁹ M2 cells, in particular the M2 macrophage, on the other hand, is a potent promoter of axonal sprouting by secreting protective factors such as IL-10 and oncomodulin.^{200,201} However, the role of microglia on axonal sprouting after cerebral ischemic stroke still warrants further investigation due to the conflicting evidence suggesting that microglia are irrelevant for neuronal degeneration and axonal regeneration after acute neuronal injury.²⁰²

2.5 | Interaction between post-stroke inflammation and remyelination

Myelin sheath is an important cellular component that mediates conductance of action potentials in the central nervous system. It also has important functions in regulating axon diameters and influencing axonal transport.^{203,204} Cerebral ischemic stroke causes long-lasting demyelination, which contributes significantly to long-term sensorimotor and cognitive dysfunction.²⁰⁵⁻²⁰⁷ Remyelination is a repair process to restore myelin sheath around axons after demyelination.^{208,209} This process is initiated by oligodendrocytes.^{210,211} It relies on proliferation and maturation of oligodendrocyte progenitor cells to become functional oligodendrocytes, which produces the myelin sheath to conduct action potentials from neurons to neurons.^{212,213} Improving remyelination has been repetitively shown to improve post-stroke neural behavioral function.²¹⁴⁻²²¹ Although the role of immune cells on post-stroke demyelination and remyelination are still obscure, studies in experimental allergic encephalomyelitis (EAE) and other demyelination disease models provide evidence showing correlation of demyelination and remyelination with the infiltration of different immune cells, including neutrophils, mast cells, microglia, macrophages, and nature killer (NK) cells.²²²⁻²²⁷ Neutrophils and mast cells appear to promote demyelination through degranulation.^{222,223} While microglia and NK cells may contribute to remyelination.²²⁴⁻²²⁷ Oligodendrocyte differentiation was promoted when cocultured with M2 microglia/macrophage in vitro, and was

inhibited in M2 microglia/macrophage-depleted EAE animals.²²⁷ Demyelination was exacerbated in EAE animals when microglia M2 polarization was inhibited.²²⁸ However, the M1 type macrophage, together with the Th17 cells are involved in the demyelination in the animal model of sclerosis.²²⁹ The evidence of macrophage's impact on white matter integrity is also conflicting. It may attack oligodendrocyte precursor cells thus hinder remyelination.²³⁰ However, macrophage depletion in female rats resulted in significant decrease in oligodendrocyte remyelination following lysolecithin-induced demyelination.²²⁶ Simply depleting peripheral immune cells by splenectomy did not change immune responses to myelin basic protein and stroke outcome.^{4,231} Therefore, the influence of peripheral immune cells, such as macrophages and resident microglia on remyelination is highly dependent on the dominant phenotype.

Astrocytes can affect post-stroke remyelination by secreting different extracellular matrix proteins, including laminin, vitronectin, fibronectin (Fn) and tenascin-C (TnC).²³² It has been shown that astrocytes grown on TnC exhibit a quiescent phenotype and are unable to support myelination in vitro.²³³ The production of Fn by astrocytes, although not directly toxic to oligodendrocyte progenitor cells (OPCs) or oligodendrocytes, has a negative impact on OPC differentiation.²³⁴ On the other hand, lipids synthesized by astrocytes are essential for oligodendroglial myelination.²³⁵ Astrocytes inhibition has been shown to exacerbate demyelination and delay remyelination processes after ischemic brain injury.²³⁶ Downregulating CD59 in astrocytes increases demyelination in the mouse brain.²³⁷ However, the role of astrocyte in remyelination is controversial.²³⁸ In addition to extracellular matrix proteins, astrocytes are also important producers of a myriad of factors that can hinder OPC differentiation and remyelination,²³⁹ such as high molecular weight hyaluronan (HA).²⁴⁰ HA accumulation has been identified in remyelination failure in MS mouse models.²⁴¹ Astrocytes are also engaged in myelin phagocytosis in diseases with characteristic myelin injury such as multiple sclerosis. The myelin debris taken up by astrocytes may increase the nuclear localization of NF- κ B and chemokine expression which in turn results in recruitment of immune cells.²³⁸

3 | SUMMARY AND CONCLUSIONS

Recent studies on neuroinflammation and the exquisitely coordinated regenerative events have led to a better understanding of their interaction. Neuroinflammation, including glial cell activation and peripheral immunological changes persist through the late stage of stroke, when multiple brain repair processes take place and thus contributes significantly to functional neurological recovery after stroke. Pleiotropic factors can be secreted from both resident glial cells and peripheral immune cells in response to ischemic stroke and change the microenvironmental cues for brain regenerative processes. Distinct phenotypes of microglia/macrophage or neutrophils may have distinct effects on brain repair. However, the engagements of neuro-immune cross talk in neural plasticity after cerebral ischemic stroke are just beginning to be understood and

merit further investigation. Understanding these biological events may provide a great opportunity for developing novel stroke recovery therapies, which may substantially reduce the clinical and societal burden of stroke in those disabled survivors.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Pei-Ying Li  <http://orcid.org/0000-0002-5721-9914>

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