Chapter 4
Modulating Endogenous Adult Neural Stem Cells to Improve Regeneration in Stroke Brain

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Abstract Stroke is a major cause of death and disability globally. Experimental and clinical stroke studies have demonstrated that endogenous brain repair processes could be activated in the brain following stroke. However, the spontaneous brain repair process is constrained with limited improvement of neurological outcome. Neurogenesis, oligodendrogenesis, angiogenesis, axonal outgrowth, and synaptogenesis are major brain repair processes during stroke recovery. In adult rodents and human, there are endogenous neural stem cells that generate new neurons, astrocyte, oligodendrocyte, and NG2-glia under physiological or pathological conditions. Much progress has been made in preclinical studies on the roles of endogenous neural stem cells in brain repair processes in response to stroke. In this review, we will summarize recent progress on the cellular and molecular mechanisms underlying how endogenous adult neural stem cells contribute to neurogenesis and oligodendrogenesis, and their modulatory effects on angiogenesis and inflammation, which may play critical roles in brain repair and leads to improvement of neurological function after stroke.

Keywords Stroke • Neural stem cells • Neurogenesis • Oligodendrogenesis • Brain repair

Abbreviations

3V	Third ventricle
ANg	Angiopoietin
BDNF	Brain-derived neurotrophic factor
BMP	Bone morphogenetic protein

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CB2R	Cannabinoid type-2 receptor
CCR2	C-C chemokine receptor type 2
ChAT	Choline acetyl-transferase
CNS	Central nervous system
CNTF	Ciliary neurotrophic factor
CSPGs	Chondroitin sulfate proteoglycans
CX3CR1	CX3C chemokine receptor 1
CXCL12	C-X-C motif chemokine 12
CXCR4	C-X-C chemokine receptor type 4
DARPP-32	cAMP-regulated neuronal phosphoprotein
DCX	Doublecortin
DG	Dentate gyrus
ECM	Extracellular matrix
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
FGF10	Fibroblast growth factor 10
FGF2	Fibroblast growth factor 2
GABA	Gamma aminobutyric acid
GAD67	Glutamic acid decarboxylase
GAP43	Growth Associated Protein 43
GSK-3β	Glycogen synthase kinase-3β
HDACs	Histone deacetylases
IGF-1	Insulin-like growth factor 1
MCAO	Middle cerebral artery occlusion
MCP-1	Monocyte chemoattractant protein 1
MMPs	Matrix metalloproteases
mTORC1	Mechanistic target of rapamycin complex 1
Nf1	Neurofibromatosis type 1
NPCs	Neural progenitor cells
NSCs	Neural stem cells
OB	Olfactory bulb
P57kip2	Cyclin-dependent kinase inhibitor 1C
PDGF	Platelet-derived growth factor
PDGFR	Platelet-derived growth factor receptor α
Ptc-1	Patched 1
PV	Parvalbumin
RMS	Rostral migratory stream
Robo	Roundabout
ROCK	Rho-associated kinase
SDF-1	Stromal cell-derived factor 1
SGZ	Subgranular zone
Shh	Sonic hedgehog
siRNA	Short interfering ribonucleic acid
Smo	Smoothened

SVZ	Subventricular zone
TGF-α	Transforming growth factor-alpha
TIA	Transient ischemic attack
Tregs	Regulatory T cells
Usp9x	Ubiquitin-specific peptidase 9, X-linked
VEGF	Vascular endothelial growth factor

1 Introduction

Globally, stroke is the second leading cause of death and the third most common cause of disability [1]. There are three types of stroke: ischemic stroke, hemorrhagic stroke, and transient ischemic attack (TIA, also called a "mini-stroke"). Ischemic stroke is caused by obstruction within a blood vessel and accounts for 87% of all stroke cases, while hemorrhagic stroke occurs when blood vessel rupture. TIAs are caused by a transient clot or blockage in the brain. Although TIAs last only a few minutes and causes no permanent damage to the brain, they are indicative of the likelihood of a coming stroke and should be taken seriously. Only a small percentage of stroke patients benefit from thrombolysis and endovascular thrombectomy treatments due to the short window (4.5–6 h) of these treatments. As a result, a large population of stroke patients still suffer from permanent severe neurological deficits in stroke survivors. Thus, there is an urgent need to develop new therapies for stroke to enhance functional recovery.

Studies from experimental stroke and patients with stroke show that some degree of spontaneous neurological recovery occurs after stroke. However, this endogenous brain self-repair is not sufficient to restore neurological function after stroke [2, 3]. Endogenous brain repair involves a set of highly interactive processes during stroke recovery, such as neurogenesis and oligodendrogenesis, which is induced mostly by endogenous neural stem cells (NSCs). Coupling of neurogenesis and angiogenesis has been implicated in some recent stroke studies [2]. In addition, stroke-induced inflammation, which is characterized by the activation of resident microglia and infiltration of monocytes and lymphocytes, is a major causative factor for neurological deficits [4]. Recent studies also suggest that there is cross-talk between neural stem cells and immune cells in response to brain injury [5]. Therefore, a promising field of investigation is to focus on modulating endogenous adult neural stem cells and their interactions with other cellular processes such as angiogenesis and neuroinflammation to improve functional recovery following stroke. Understanding how endogenous stem cells are activated, differentiate, migrate, integrate, and restore neuronal circuitry will help us develop less invasive therapeutic interventions. Elucidation of the interactions of neurogenesis with other cellular processes such as angiogenesis and inflammation after stroke will provide additional information needed to modulate this process to improve brain recovery after stroke. In this review, we will provide an update on the recent

findings on the mechanisms underlying endogenous NSC-mediated neurogenesis and oligodendrogenesis and their modulatory effects on angiogenesis and inflammation after stroke.

2 NSCs Responses in Adult Brain Following Stroke

NSCs are multipotent stem cells that can self-renew, divide, and differentiate into new mature neurons, astrocytes, and oligodendrocytes. In the adult brain, there are three main neurogenic niches containing NSCs: the subventricular zone (SVZ) of the lateral ventricle, the subgranular zone (SGZ) in the dentate gyrus of the hippocampus, and the recently discovered hypothalamic stem cell niche [6] (Fig. 4.1). In these regions, there is a basal rate of neurogenesis in normal conditions. In response to stroke, endogenous NSCs are activated and participate in brain repair processes.

2.1 Radial Glial Cells (Type B Cells) in SVZ

The NSCs in the SVZ are termed as Type B cells. They divide slowly to generate transit-amplifying type C cells, which proliferate actively and further differentiate into neuroblasts (also named type A cells). Finally, these neuroblasts form chains and migrate via the rostral migratory stream into the olfactory bulb (OB), where they differentiate into granule cells or periglomerular interneurons. Adult NSCs in the SVZ also generate NG2-glia that migrates toward the gray and white matter. Focal cerebral ischemia stimulates SVZ NSC proliferation and neurogenesis in adult rodent, monkeys, and even human brains [7–10]. Augmented neuroblasts could migrate from the SVZ to ischemic sites and differentiate into neurons in

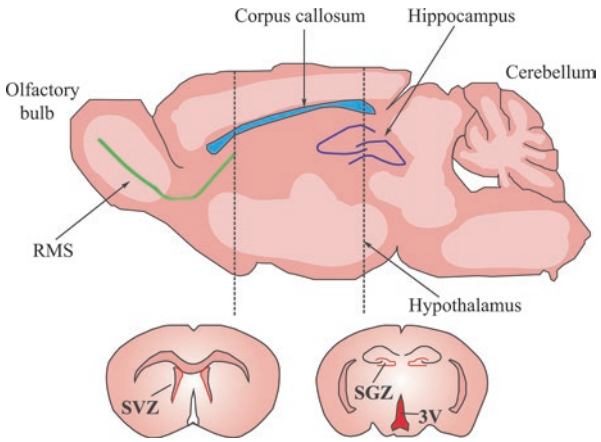

Fig. 4.1 Sagittal and coronal view of the adult rodent brain, illustrating the three niches where adult NSCs reside: the subventricular zone (SVZ), the subgranular zone (SGZ), and the recently described hypothalamic NSCs niche around the third ventricle

rodent middle cerebral artery occlusion (MCAO) models [11, 12]. In addition, stroke also induces oligodendrogenesis in the SVZ and the generated NG2-glia can migrate to the lesion site and differentiate into myelinating oligodendrocytes [13, 14]. Furthermore, activated SVZ NSCs give rise to a subpopulation of reactive astrocytes in the cortex that contribute to astrogliosis and scar formation [15]. Altogether, these data indicate that SVZ NSCs are a major therapeutic target for improving functional recovery after stroke.

2.2 Radial Glia-Like Cells (Type-1 Cells) in SGZ

SGZ NSCs are also known as type-1 cells or radial glia-like cells. These cells divide slowly and give rise to type-2 cells or transit-amplifying progenitors that could differentiate into neurons and astrocytes [16]. However, it is still a matter of debate whether these cells can spontaneously, that is without any exogenous manipulation, give rise to oligodendroglial cells. Indeed, either ectopical and elevated Ascl1 expression or inactivation of p57kip2, Nf1, Drosha, or Usp9x induce oligodendrogenesis in SGZ NSCs [17–21]. The function of neurogenesis derived from SGZ NSCs is associated with learning, memory, and cognition. Following a stroke, there is significantly enhanced proliferation of NSCs and neurogenesis in the SGZ of many species, such as rats, mice, monkeys, and humans [22]. Generally, the increased proliferation starts bilaterally at 3–4 days post-ischemia, peaks at 7–10 days, and returns to control levels by 3–5 weeks after the ischemia [22]. Recent studies show that hippocampal neurogenesis is responsible for some aspects of recovery following brain ischemia, such as learning and memory [23]. These data suggest that target SGZ NSCs might help to improve functional recovery after stroke.

2.3 Tanycytes

It has been recently demonstrated that NSCs also reside in the adult hypothalamus. The NSCs/NPCs of this region are termed as tanycytes, which express classical markers of neural precursor cells and multipotent cell markers, such as nestin, Sox2, UGS148, and FGF10 [6]. These tanycytes belong to ependymal glial cells and surround the lateral walls of the infundibular recess of the third ventricle. In response to peripheral signaling (i.e. CNTF, Leptin and high-fat diet), tanycytes are able to proliferate, migrate, and differentiate into neurons, such as arcuate pro-opiomelanocortin neurons and orexigenic and anorexigenic neurons [6, 24–27]. Importantly, tanycytes exhibited increased proliferation on the infarcted side on day 4 after ischemic stroke injury (MCAO model in rats) [28]. However, the functional role of tanycyte proliferation after stroke is still largely unknown.

3 Promoting Neurogenesis of Endogenous NSCs

Neurogenesis is a multistep process that includes proliferation, fate determination, migration, maturation, and survival of NSCs. Understanding the molecular mechanisms regulating these processes is essential for developing therapies to improve neurological recovery (Fig. 4.2). Many factors are involved in the regulation of adult NSCs, including growth factors, neurotransmitters, and chemokines. We will briefly summarize them in this review.

3.1 Proliferation

The initial response of NSCs following stroke is to increase proliferation, a process that is regulated by various intrinsic and extrinsic factors. The mechanism underlying stroke-induced proliferation of NSCs is unclear. Several hypotheses have been suggested as potential mechanisms to regulate proliferation of NSCs. Adult rodent stroke studies have shown that quiescent adult neural stem cells can be activated and recruited to an active pool to increase neurogenesis. As a response to stroke, an increased neurogenesis might result from transiently switching neural progenitors division from asymmetric to symmetric and from a reduction of the length of the cell cycle [29, 30]. Stroke can trigger the early expansion of the progenitor cell pool by shortening the cell-cycle length and retaining daughter cells within the cell cycle at an early stage after stroke. At a later stage, lengthening the cell cycle and the G1 phase leads to the daughter cells exiting the cell cycle and differentiating into neurons [31]. Several important pathways that may regulate the proliferation of NSCs and their early progeny have been identified.

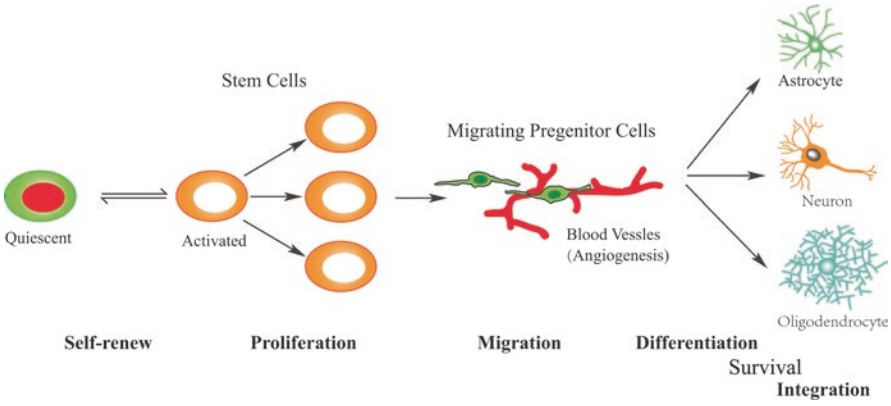

Fig. 4.2 Cellular and molecular processes that are involved in the maintenance of adult NSCs, generation of different lineages of cells and their integration in the brain after stroke

3.1.1 Sonic Hedgehog (Shh)

Shh is a secreted glycoprotein. It binds to its receptor Patched (Ptc-1) to de-repress Smoothened (Smo) and activate transcription factors of the Gli family. Shh signaling is required for SVZ NSC maintenance as conditional deletion of smoothened gene in adult SVZ NSC leads to decreased BrdU-positive cells and DCX+ neuroblasts in the SVZ [32]. Studies have found that stroke upregulates Shh signal in multiple cell types, such as neurons, reactive astrocyte, and SVZ neural progenitor cells [33, 34]. In vivo, blockage of the Shh signaling pathway with cyclopamine, a specific inhibitor of Smo, suppressed ischemia-induced proliferation of subgranular NPCs in the hippocampus [34]. Conditional deletion of shh genes in nestin-expressing cells leads to significantly more severe behavioral deficits in a cortical ischemic model [33]. Administration of cyclopamine also abolished carbamylated erythropoietin-induced neurogenesis [35]. These data suggests that Shh signaling is a key factor for NSC self-renewal or proliferation. Interestingly, at a lower dosage, delayed post-stroke treatment of Shh agonist improves functional recovery by enhancing survival of newly born neurons and angiogenesis [36] but not by increasing BrdU-positive cells at the NSC niche, suggesting that Shh signaling might play multiple roles in ischemia-induced neurogenesis and whether it enhances the proliferation or survival of the newly generated NSC progeny is dose-dependent.

3.1.2 Epidermal Growth Factor (EGF)/Fibroblast Growth Factors 2 (FGF2)

Studies have reported that FGF-2 and EGF expression in the brain increased significantly after ischemic stroke [37, 38]. Importantly, cerebral ischemia resulted in an increase in the number of EGF receptor (EGFR)-positive transit-amplifying cells (type C cells) in the SVZ [39]. Overexpression of FGF-2 significantly increased the proliferation of progenitor cells after ischemic stroke in both FGF-2-deficient mice and wild-type mice [40]. Meanwhile, in vivo infusion of EGF into adult mouse forebrain for 6 consecutive days resulted in a dramatic increase in the proliferation and the total number of subependymal cells and induced their migration away from the lateral ventricle walls into adjacent parenchyma [41]. Furthermore, infusion of EGF together with FGF-2 into the brain of adult rats was found to promote dentate gyrus (DG) and SVZ NPC proliferation after focal ischemic stroke [42, 43].

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

The progenitors in both the SVZ and DG show IGF-1 receptor expression [44]. In vitro studies demonstrate that IGF-1 stimulated the proliferation of cultured NPCs via activating the PI-3-kinase/Akt signaling pathway [45]. Following ischemic stroke, IGF-1 expression is increased in the activated astrocytes in the ischemic penumbra [44]. Inhibiting IGF-1 activity by intracerebroventricular infusion of

IGF-1 antibody significantly blocked the ischemia-induced neural progenitor proliferation [44]. *Exogenous* IGF-1 injection after ischemic stroke promoted neurogenesis [46]. Meanwhile, post-ischemic IGF-1 gene transfer in the peri-infarct region potently promoted neural and vascular regeneration in the chronic stage of cerebral infarction [47]. These results suggest that IGF-1 formed in the ischemic penumbra might be one of the endogenous diffusible factors that mediate post-ischemic neural progenitor proliferation.

3.1.4 Notch Signaling Pathway

Notch signaling is an evolutionarily conserved pathway that regulates cell-fate determination during development and maintains adult tissue homeostasis. Recent studies have shown that stroke increases the expression of Notch1 and Hes1 in SVZ cells [48]. Transient administration of Notch ligands to the brain of adult rats increases the numbers of newly generated precursor cells and improves motor skills after ischemic injury [49], while the blockage of the Notch pathway by short interfering ribonucleic acid (siRNA) against Notch or a gamma secretase inhibitor significantly blocked ischemia-induced cell proliferation in the SVZ [50]. These data suggest that the Notch signaling pathway mediates adult SVZ neural progenitor cell proliferation after stroke. Interestingly, it has recently been shown that striatal astrocytes can turn on nestin expression and generate neurons in stroke model through downregulation of Notch signaling, suggesting that Notch signaling might also suppress "NSC status" in mature astrocytes [51].

3.1.5 Other Regulators

Finally, other potential mediators of stroke-induced proliferation of NSCs in the neurogenic niches have been described. These include vascular endothelial growth factor (VEGF) [52], glial cell-derived neurotrophic factor (GDNF) [53], brain-derived neurotrophic factor (BDNF) [54], Wnt signaling, retinoic acid [55], bone morphogenetic protein [56], and microRNA [57, 58]. In addition, the communication between NSCs and other cell types also affects NSC proliferation after stroke. It has been reported that M2 phenotype microglia-derived transforming growth factor-alpha (TGF-α) is one of the key factors to enhance proliferation and neural differentiation of NSPCs after ischemic stroke [59]. Activated regulatory T cells (Tregs) enhanced SVZ NSC proliferation in normal and ischemic mice; blockage of IL-10 abolished Tregs-mediated NSC proliferation in vivo and in vitro [60]. Furthermore, astrocytic calcium waves are long-range signals capable of transmitting the occurrence of a brain injury to the SVZ, where they stimulate NSC proliferation and self-renewal and increase the migratory potential of NSPCs. It is shown that the Notch signaling pathway mediates effects of elevated calcium levels on NSPCs [61].

3.2 Migration

After stroke, following NSC proliferation, another critical biological process is the migration of these NSCs from neurogenic niches to the ischemic region. In the normal adult brain, SVZ neuroblasts migrate along the rostral migratory stream to the olfactory bulb. Lateral migration into the striatum and parenchyma is not observed in the rodent brain under normal condition. However, in the ischemic damaged brain, neuroblasts will migrate laterally into the ischemic injury region [11]. Although little is known about the molecular mechanisms underlying stroke-induced redirected migration, several potential mediators have been identified. These include stromal cell-derived factor 1 (SDF-1), monocyte chemoattractant protein 1 (MCP-1/CCL2), matrix metalloproteases (MMPs), cannabinoid type-2 receptor (CB2R), and β1 integrin. Further, the neurovascular niche within the SVZ and SDG is also a key regulator of neuroblast migration following stroke.

3.2.1 Stromal Cell-Derived Factor 1 (SDF-1)

SDF-1, also known as C-X-C motif chemokine 12 (CXCL12), is a chemokine protein that exerts biological functions by binding to its receptors CXCR4 and CXCR7. SDF-1 (CXCL12) is a member of the alpha (CXC) chemokine family which are involved in inflammatory responses [62]. SDF-1 and its receptor CXCR4 have been demonstrated to play an important role in the mobilization and homing of stem cells to bone marrow [63, 64]. Neuroblasts are reported to express CXCR4 [65]. During adult neurogenesis, SDF-1 is secreted by vascular endothelial cells and plays a role in the directional migration of neuroblasts in the CNS [65]. Following stroke, SDF-1 is upregulated by activated astrocyte and endothelial cells, subsequently guiding neuroblast migration toward the injured tissue [66–68]. In contrast, CXCR4 blockade blocks this pathology-directed chain migration [69].

3.2.2 Monocyte Chemoattractant Protein-1 (MCP-1)

MCP-1 is a member of the C-C chemokine family that regulates migration and infiltration of monocytes/macrophages [70]. Following cerebral ischemia, MCP-1 is induced in activated astrocytes and neurons within the injured tissue [71, 72]. The migrating neuroblasts in the ischemic brain express MCP-1 receptor CCR2. Infusion of MCP-1 into the normal striatum induced neuroblast migration to the infusion site [73]. In knockout mice that lacked either MCP-1 or its receptor CCR2, there was a significant decrease in the number of migrating neuroblasts from the SVZ to the ischemic striatum [73].

3.2.3 Matrix Metalloproteinases (MMPs)

Matrix metalloproteinases (MMPs) are members of the metzincin group of proteases that participate in several physiological processes, such as bone remodeling, angiogenesis, immunity, and wound healing [74]. Recent studies suggest that MMPs are involved in guiding neuroblast migration from the neurogenic region to the ischemic boundary [75]. Neuroblasts express MMP-3 and MMP−9. Inhibition of MMPs diminishes neuroblast migration after stroke [76, 77]. Moreover, MMP2 and MMP9 secreted by endothelial cells are also associated with neuroblast migration after stroke [78].

3.2.4 CB2R

The endocannabinoids (eCBs) 2-arachidonoylglycerol and anandamide are lipid signaling messengers involved in the homeostatic control of a large variety of functions of the nervous system through binding cannabinoid type-1 receptor (CB1R) and cannabinoid type-2 receptor (CB2R) [79]. CB2R is expressed in resident microglia, NG2-glia, and NSCs. CB2R is neuroprotective in acute experimental stroke by anti-inflammatory mechanisms [80]. *In vitro* studies show that CB2R promotes NSC proliferation via mTORC1 signaling [81]. Furthermore, in stroke, CB2R is required for neurogenesis by promoting neuroblast migration toward the injured brain tissue [82].

3.2.5 β1 Integrin

β1-class integrins are transmembrane receptors for several extracellular matrix (ECM) proteins such as laminin [83]. Under normal conditions, migrating neuroblasts generated in the adult SVZ express β1 integrin, which is required for their chain formation during RMS migration [84, 85]. Following stroke, laminin-β1 integrin signaling enables neuroblasts to form chains and migrate efficiently along vascular scaffolding in the post-stroke brain [86].

3.2.6 Neurovascular Niche

Stroke-induced directional migration of neuroblasts is closely associated with thin astrocytic processes and blood vessels, suggesting that blood vessels may act as a scaffold for neuroblast migration [87, 88]. Virally labeled SVZ NPCs were observed to migrate along both newly formed and pre-existing blood vessels toward the ischemic injured area. Live imaging showed that migrating SVZ NPCs have their leading process closely associated with blood vessels, suggesting that this interaction provides directional guidance for the NPCs [89]. In addition, vasculature promotes neuroblast migration via secreting various growth and chemotactic factors, including BDNF, MMPs, angiopoietins, and SDF-1 [22].

3.2.7 Other Regulators

Wnt3a, Angiopoitin (ANg)-1 and its receptor Tie 2, and Slit and its receptor (ROBO) also promote post-stroke neuroblast migration and behavioral recovery [66, 90, 91]. It also should be noted that stroke also induces inhibitory molecules to block the migration of neuroblasts. Glycogen synthase kinase-3β (GSK-3β) inhibition promoted proliferation of neural stem cells (NSCs) and migration of nascent doublecortin (DCX+) neuroblasts from the SVZ to the lesioned cortex [92]. Inhibition of Na^+-K^+-Cl^--co-transporter can increase migration of neuroblasts in the SVZ towards the infarct areas and improve sensorimotor recovery [93]. Stroke also induces chondroitin sulfate proteoglycans (CSPGs), which could block neuroblast migration through Rho-associated kinase (ROCK) activation [94, 95].

3.3 Survival, Differentiation, and Integration of Newborn Neurons

The long-term survival and functional maturation of newborn neurons following stroke are also crucial for neurological recovery. However, there are fewer studies that have examined the survival, differentiation, and integration of newborn neurons in the ischemic brain. The migration of SVZ neuroblasts to the lesion sites may persist for up to 1 year after ischemia [96], thus offering a long-term window for therapeutic manipulations. Ischemia-induced newly generated cells in the damaged areas express medium-size spiny neuronal marker dopamine- and cAMP-regulated neuronal phosphoprotein (DARPP-32) or neurotransmitter synthesizing enzymes such as glutamic acid decarboxylase (GAD67) and choline acetyl-transferase (ChAT) [11, 97, 98]. Moreover, ischemia-induced newly formed striatal GABAergic and cholinergic neurons could exhibit electrophysiological activity and functional synapses [97]. These data indicate that proliferating neuroblasts that migrate into the damaged areas following stroke are able to differentiate into a variety of functional neuronal cells. Compared to our knowledge of factors that promote adult neural precursor cell proliferation or migration, there is comparatively little known about factors that promote newborn neuron survival and integration in stroke. Intraventricular administration of EGF and albumin enhance the differentiation of newly born immature neurons into mature PV-expressing neurons, replacing more than 20% of PV+ interneurons lost after cerebral ischemia [99]. Complement-derived peptide C3a regulates neural progenitor cell migration and differentiation in vitro and C3a receptor signaling stimulates neurogenesis in unchallenged adult mice. Daily intranasal treatment of wild-type mice with C3a beginning 7 days after stroke induction robustly increased synaptic density and expression of Growth Associated Protein 43 (GAP43) in the peri-infarct cortex [100]. Post-stroke p53

inhibitor enhances the survival of NSCs and their progeny by inhibition of apoptosis in these cells through PUMA gene regulation [101]. Similarly, Shh agonist, delivered after stroke at a lower dose that did not affect BrdU-positive cells in SVZ and SGZ improved the long-term survival of YFP-labeled NSCs and their progeny in stroke model [36]. Some knowledge has been gained regarding factors that enhance newborn neuron integration and survival under normal physiological conditions, including the RhoA family of small GTPases, suppressor of cytokine signaling-2, neurotrophins, neurotransmitters (GABA and glutamate), and semaphorins [102]. Logically, we might get some implication from those factors and explore their roles after ischemic injury. However, it should be noted that the stroke-affected CNS environment is quite an inhibitory environment for newborn cell survival. Experimental studies have shown that only a small proportion of cells survive long enough to integrate into the damaged parenchyma after stroke [46, 68, 102, 103]. Thus, neuroprotective or anti-inflammatory strategies might need to be included with therapy to improve newborn neuron maturation, integration, or plasticity in stroke treatment.

4 Endogenous NSCs and Oligodendrogenesis

NG2-glia, also called oligodendrocyte precursor/progenitor cells and polydendrocytes, characterized by expression of chondroitin sulfate proteoglycan NG2 and platelet-derived growth factor receptor α (PDGFR α). It is widely distributed in the brain and can continuously produce differentiating and mature oligodendrocytes in the central neural system throughout the lifespan of the animals. Myelination of axons in the adult brain is critical for saltatory conduction, axonal integrity, neural plasticity, and circuitry function, which are important for functional recovery after stroke [104]. Stroke acutely leads to mature oligodendrocyte damage, resulting in myelin loss, which is associated with a loss of axons. Oligodendrogenesis is induced in the regions surrounding the lateral ventricles and peri-infarct areas during stroke recovery [105–107]. Studies demonstrate that stroke not only activates resident NG2-glia in white and gray matter, but also increases NG2-glia generation in the SVZ and attracts them to the ischemic area [108–111]. The newly generated NG2-glia could differentiate into mature myelinating oligodendrocytes in the peri-infarct areas, which is involved in the brain repair process [106]. Therefore, these studies suggest that NG2-glia generated by adult NSCs contribute to oligodendrogenesis after stroke. The process of SVZ NSC-mediated oligodendrogenesis is regulated by many intrinsic and extrinsic factors, therefore offering many pathways for potential therapeutic interventions to promote functional recovery following stroke.

4.1 Extrinsic Factors for Oligodendrogenesis

4.1.1 Shh

In addition to neurogenesis, Shh signaling regulates oligodendrogenesis by inducing transcription factor olig2 expression [112]. In the SVZ, there is a dorsal Shh-dependent domain producing many oligodendroglial lineage cells [113]. The blockage of Shh signal with cyclopamine could abolish cerebrolysin-enhanced oligodendrogenesis in stroke [114]. Bone marrow stromal cell transplantation stimulates oligodendrogenesis by activation of Shh/Gli1 pathway, which mediates subsequent functional recovery after stroke [115]. Thus, these data suggest that Shh signaling in SVZ plays an important role in mediating oligodendrogenesis in the ischemic brain.

4.1.2 Stromal-Derived Factor 1 (SDF-1)

SDF-1, has been shown to be able to promote neurogenesis and angiogenesis, leading to functional recovery in ischemic mice [116, 117]. Through binding with CXCR4 in NG2-glia, SDF-1 activates their proliferation, migration, and differentiation [118–120]. SDF-1 gene therapy at 1 week after ischemia promotes NG2-glia proliferation in the SVZ and further enhances their migration to the ischemic lesion area [121]. These data support that in addition to enhancing neurogenesis, SDF-1 promotes oligodendrogenesis as well after stroke.

4.1.3 Vascular Endothelial Growth Factor (VEGF)

VEGF is a signaling protein that is important for vasculogenesis and angiogenesis. The administration of VEGF improves neurological performance through mediating angiogenesis and survival of newborn neurons in the rat MCAO model [122]. Studies have shown that VEGF-C stimulates NG2-glia proliferation [123] while VEGF-A can induce NG2-glia migration via ROS and FAK-dependent mechanisms, but did not affect their proliferation and differentiation [124]. In the neonatal hypoxia-ischemia rat model, VEGF-A and VEGF-C are induced in the SVZ. Moreover, VEGF-C promotes the proliferation of both early and late oligodendrocyte progenitors through VEGFR-3 receptor [108]. These data suggest that besides promoting angiogenesis and neurogenesis, VEGF signaling is also involved in oligodendrogenesis after stroke.

4.1.4 Brain-Derived Neurotrophic Factor (BDNF)

BDNF is a well-known member of a neurotrophin family that regulates neuronal survival, synaptic plasticity, learning, and memory. Recent studies show that BDNF could promote the proliferation and differentiation of NG2-glia and is required for normal CNS myelination [125–127]. Astrocyte-derived BDNF supports oligodendrogenesis and regeneration after white matter ischemic injury or cuprizone-induced demyelination [128, 129]. BDNF administration improves functional recovery and promoting oligodendrogenesis and remyelination in rats subjected to ischemic stroke [130]. These data suggest that in addition to neuroprotective effects, BDNF plays important roles in white matter protection and remyelination after stroke.

4.1.5 Other Factors

There are many other factors regulating oligodendrogenesis under normal and pathological conditions [131]. For example, neuregulin-1 promotes NG2-glia survival and maintains NG2-glia in an immature state [132]. Platelet-derived growth factor (PDGF) is an important factor for maintaining NG2-glia proliferation and stimulating their differentiation into mature oligodendrocytes [133]. PDGF signaling in the SVZ promotes oligodendrocyte generation [134]. Insulin-like growth factor (IGF)-1 could promote the differentiation of adult NSCs into oligodendrocyte lineage cells through inhibiting BMP signaling [135]. Epidermal growth factor (EGF) induces the progeny of SVZ NSCs to migrate and differentiate into oligodendrocytes [136]. It has been reported that these above growth factors play positive roles in functional recovery after stroke [137]. However, the contribution of ischemia-induced oligodendrogenesis to functional recovery in stroke by these growth factors remains to be established.

4.2 Epigenetic Modulators and Stroke-Induced Oligodendrogenesis

Epigenetics is defined as the heritable changes in gene expression without a change in the DNA sequence [138]. Recent studies have shown that the multiple steps of oligodendrocyte generation (i.e., specific cell fates, proliferation, differentiation, and myelination) can be regulated through epigenetic mechanisms [139–141]. The epigenetic modulators of gene expression include post-translational modulations of nucleosomal histones, histone modification, chromatin remodeling enzymes, DNA methylation, and microRNAs [142]. Among them, we will mainly focus on miRNA and histone deacetylases (HDACs) in this review.

4.2.1 microRNAs

A number of miRNAs have been found to play a critical role in the proliferation or differentiation of OPCs into mature oligodendrocytes as well as myelination [143, 144]. miR-219 and miR-338 could promote NG2-glia differentiation into mature oligodendrocytes through suppressing the expression of PDGFRa, Sox6, Zfp238, FoxJ3, and NeuroD1 [145]. Stroke considerably increased miR-146a density in the corpus callosum and SVZ of the lateral ventricle of the ischemic hemisphere. In vitro, overexpression of miR-146a in neural progenitor cells (NPCs) significantly increased their differentiation into O4+ NG2-glia [146]. During development, miR17-92 cluster can regulate proliferation and survival of NG2-glia in the brain. In stroke, the miR17-92 cluster was significantly up-regulated in SVZ neural progenitor cells [147]. It could mediate the proliferation and survival of SVZ NPCs in the ischemic brain [148]. miR17-92 cluster-enriched exosomes could increase neural plasticity and functional recovery after stroke [149]. In addition, miR-23a, miR-9, and miR-200b are also likely involved in stroke-induced oligodendrogenesis by regulating serum response factor [150, 151]. Collectively, these findings suggest that miRNAs play an important role in stroke-induced oligodendrogenesis.

4.2.2 Histone Deacetylases (HDACs)

The administration of HDACs inhibitor suberoylanilide hydroxamic acid or TSA can confer protection against ischemia-induced brain injury [152, 153]. HDAC1 and HDAC2 are associated with oligodendrocyte differentiation and remyelination during brain development and disease [154–157]. In ischemic brains, there is increased expression of HDAC1 and HDAC2 proteins in NG2-glia [158]. In addition, blockage of HDACs with valproic acid considerably increased OPCs and new oligodendrocytes after stroke [159]. HDACs clearly play important roles in stroke-induced oligodendrogenesis.

5 The Implicating Effects of NSC-Mediated Neurogenesis and Oligodendrogenesis on Angiogenesis and Inflammation

Stroke continuously induces neuroblasts, which migrate to peri-infarct regions for at least 1 year [160]. The ablation of neuroblasts after stroke reduces ischemic brain repair and exacerbates functional recovery [161]. Experimental studies show that only a small fraction of neuroblasts derived from endogenous NSCs in the peri-infarct regions differentiate into mature neurons and survive [162–164]. Meanwhile, there is increased production of NG2-glia and some of them in the peri-infarct regions generate into mature myelinating oligodendrocytes after stroke [165–167].

These data suggest that stroke-induced neurogenesis and oligodendrogenesis might provide additional beneficial effects that are independent of cellular replacement of dead neurons and myelinating oligodendrocyte production to re-wire neuronal circuitry.

5.1 Angiogenesis

Angiogenesis is characterized by the formation of new vessels from existing blood vessels. Coupling and bi-directional regulation of neurogenesis and angiogenesis have been implicated both under normal and pathological conditions [2]. Both SVZ and SGZ niches have unique vasculature characteristics compared to non-neurogenic regions and adult NSCs extend their long processes to directly contact blood vessels, which enables the easy access of NSCs to molecules and factors in the blood [168]. Under the ischemic condition, it has been shown that angiogenic genes are upregulated rapidly after the onset of cerebral ischemia and the increased expression of angiogenic proteins can be sustained in the ischemic area for a prolonged period of time after stroke [169]. Both neurogenesis and angiogenesis have been suggested to contribute to the functional recovery after stroke [170] and the two critical biological processes might have synergistic effects and influence each other. Co-culture of ischemic neural progenitor cells with non-ischemic endothelial cells increases angiogenesis in vitro [171, 172] and co-culture of ischemic endothelial cells with non-ischemic NSCs increases progenitor cell proliferation and neuronal differentiation. On one hand, neuroblasts induced by stroke in the SVZ migrate along cerebral blood vessels to peri-infarct regions where angiogenesis occurs [96]. On the other hand, it is possible that NSC-derived progeny cells (neuroblasts and astrocytes) can regulate angiogenesis and help maintain the function and integrity of the newly generated blood vessels. Importantly, NG2-glia are also in close proximity to astrocyte, pericytes, or endothelial cells [173, 174]. It is an important component of the neurovascular unit in cerebral white matter [174]. NG2-glia and oligodendrocytes can act as a critical source of trophic factors [175, 176]. In addition, NG2-glia can support blood-brain barrier integrity by upregulating tight junction proteins via TGF-β1 signaling [177]. NG2-glia-specific TGF-β1-deficient mice exhibited cerebral hemorrhage and loss of BBB function [177]. It has been shown that signaling from NG2-glia to ECs plays an important role in angiogenesis during development. Wnt7a and Wnt7b secreted by hypoxic NG2-glia could increase the proliferation of endothelial cells and angiogenesis [178]. These data suggest close interaction and potentially synergistic effects of endogenous neurogenesis, oligodendrogenesis, and angiogenesis in stroke recovery.

5.2 Inflammation Modulation

Inflammation plays an important role in the pathogenesis of stroke, which contributes to neuronal death and impairs functional recovery. In the ischemic brain, there is activation of microglia, production of pro-inflammatory factors, and immune cell infiltration (i.e. neutrophils, monocyte/macrophages, T cells and B cells). Recent studies have shed new light on the interaction between endogenous NSCs and immune cells, such as microglia, T cells, and natural killer cells [179–182]. Both in vitro and after transplantation in vivo, NSCs can directly change inflammatory responses through releasing immunomodulatory factors [183–185]. However, it is still unknown whether endogenous NSCs in their native location have similar capacities under stroke conditions. Endocannabinoids are reported to play an important role in maintaining immune homeostatic balance within the host [186]. Anandamide, an endogenous cannabinoid, contributes to immune tolerance in the gut by promoting the presence of CX3C chemokine receptor 1 ($CX3CR1^{hi}$) macrophages, which are immunosuppressive [187]. In response to the excitotoxic damage occurring in stroke and epilepsy, SVZ NSCs can release endogenous endocannabinoids to exert a protective role for striatal neurons [188]. In the EAE model of multiple sclerosis, SVZ NSCs produce interleukin-15 and sustain functionally competent natural killer cells [180]. Studies have shown that there is an accumulation of natural killer cells in ischemic brain tissues [189–191]. These data suggest that endogenous NSCs maybe regulate stroke-induced inflammation through releasing immunomodulatory factors. In addition, NG2-glia and oligodendrocytes express a wide range of immunomodulatory molecules [192, 193], suggesting that endogenous NSCs might indirectly affect immune cell function and inflammation through regulating oligodendrogenesis. Further studies are needed to understand whether, when, and how endogenous NSCs can take over and locally manifest an immunomodulatory effect. It will help to develop novel therapies to promote functional recovery in stroke through modifying the immunomodulatory effects of endogenous NSCs.

6 Conclusion and Discussion

Brain repair processes after stroke are regulated by multiple cellular pathways, which include neurogenesis, oligodendrogenesis, angiogenesis, axonal sprouting, and synaptogenesis. The presence of endogenous NSCs in the adult brain and their capacity to generate new neurons, oligodendrocytes, and astrocytes raises hope that new therapeutic strategies can be designed based on appropriate modulation of endogenous NSCs in stroke. Over the past five decades, since its discovery, adult neurogenesis and NSCs have evolved into an established research field that has made substantial and promising progress as regenerative medicine for neurological disease. However, there are still many critical questions that need to be addressed.

The defining characteristics of stem cells are their ability to self-renew and to differentiate into various cell types. We have just started to appreciate the complexity and heterogeneity of adult NSCs. Balance and integration are important themes to consider when trying to modulate this process to improve brain recovery after injury. For example, adult NSCs have quiescent and activated states. Adult NSCs are largely quiescent in vivo, a state that recently has been recognized as not a passive state but rather maintained by active transcriptional regulation [194]. The mechanisms that trigger the activation of NSCs by entering multiple rounds of proliferation followed by potential terminal differentiation after brain injury are still unknown. Since the quiescent state is actively maintained by NSCs and might serve important roles to preserve these cells from metabolic stress and maintain genome integrity over a long lifetime, strategies that only target to enhance the activation and proliferation of NSCs might need to take cautions as these might have the risk of depleting quiescent NSCs over a prolonged period of time. In this regard, it is possible that treatment strategies that target the enhanced survival of NSCs and their progeny might be a better strategy as the majority of the newly born cells derived from NSCs fail to survive at weeks to months after stroke.

Similarly, the precise mechanisms that trigger differentiation of NSCs to different types of cells in vivo after brain injury are largely unknown. When cultured in vitro, adult NSCs are able to self-renew and differentiate into all three neuronal lineages [195]. However, under normal conditions, SVZ and SGZ cells generate different types of neurons and non-neuronal cells, suggesting that the microenvironment of the NSC niche might limit their differentiation potential. Adult NSCs are also capable of responding to a variety of brain injury by altered differentiation phenotypes as well as migration into the injured area instead of their "original path". What are the precise molecules and signals that direct the differentiation of these cells under the pathological condition? Knowledge in these areas will help us modulate the fate of these cells and help guide them to targeted areas to repair the brain. Substantial interests in the field have been focused on the neuronal differentiation of NSCs after injury; however, neuroblasts have been shown to play important roles through non-neuronal replacement mechanisms [2]. SVZ NSCs have also been reported to generate astrocytes that migrate to the injured cortex. Defects in this astrogenic process, which resulted in a shift in SVZ NSCs fate from glial cells to neuroblasts, resulted in abnormal glial scar formation and increased microvascular hemorrhage in stroke animals. In addition, although glial scar formation was previously considered as an inhibitory factor for axonal outgrowth, there is evidence indicating that the glial scar aids axonal outgrowth in spinal cord injury [196]. Therefore, strategies that aim to guide NSC differentiation towards a single cell type (neurons) might not provide desired effects in brain recovery. Considering the heterogeneity of astrocytes and their role in synapse formation and glial scar formation, whether reactive astrocyte derived from NSCs in stroke could affect axonal outgrowth and synaptogenesis also needs to be investigated. In addition, besides the role of producing new neurons and myelinating oligodendrocytes, it remains to be defined whether and how NSCs, NSC-derived neuroblasts, and NG2-glia contribute to angiogenesis and immunomodulation after stroke. Overall, understanding the

fundamental mechanisms underlying the endogenous NSC-mediated brain repair process will provide the basis for future endogenous NSC therapy for stroke. By elucidating the relationship and interactions of neurogenesis with other cellular and molecular processes such as angiogenesis, glial scar formation, and inflammation responses, it is possible that more effective therapies could be developed in the future to improve regeneration and functional recovery of the ischemic brain.

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