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Function of neural stem cells in ischemic brain repair processes

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Abstract

Hypoxic/ischemic injury is the single most important cause of disabilities in infants, while stroke remains a leading cause of morbidity in children and adults around the world. The injured brain has limited repair capacity, and thereby only modest improvement of neurological function is evident post injury. In rodents, embryonic neural stem cells in the ventricular zone generate cortical neurons, and adult neural stem cells in the ventricular–subventricular zone of the lateral ventricle produce new neurons through animal life. In addition to generation of new neurons, neural stem cells contribute to oligodendrogenesis. Neurogenesis and oligodendrogenesis are essential for repair of injured brain. Much progress has been made in preclinical studies on elucidating the cellular and molecular mechanisms that control and coordinate neurogenesis and oligodendrogenesis in perinatal hypoxic/ischemic injury and the adult ischemic brain. This article will review these findings with a focus on the ventricular–subventricular zone neurogenic niche and discuss potential applications to facilitate endogenous neurogenesis and thereby to improve neurological function post perinatal hypoxic/ischemic injury and stroke.

Keywords

Hypoxic/ischemic injury, stroke, neural stem cells, brain repair

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Introduction

Hypoxic/ischemic (H/I) injury is the single most important cause of brain damage resulting from complications during birth, leading to permanent neurological deficits. Every year perinatal H/I injury afflicts approximately 1–2 per 1000 term births and roughly half of surviving preterm infants. Many of these infants suffer long-term handicaps that include learning disabilities, mental retardation, epilepsy, and cerebral palsy.[1]

Stroke remains a major cause of morbidity around the world.[2] Tissue plasminogen activator (tPA) is the only FDA approved treatment for patients with ischemic stroke onset within 4.5 h.[3,4] Successful randomized clinical trials show that endovascular thrombectomy with or without tPA is effective for ischemic stroke patients within 12 h after stroke onset, which suggest that rapid recanalization and reestablishing cerebral blood flow (CBF) can preserve vascular integrity, and minimize brain hemorrhage and parenchymal cell death.[5–8] However, most patients, even with effective thrombolysis will suffer neurological deficits during stroke recovery because the ischemic brain has limited repair capacity.[9]

Neurogenesis is essential for brain development and for repair of injured brain. Embryonic neural stem cells in the ventricular zone (VZ) generate cortical neurons.[10,11] In the adult mammalian brain, there are at least two neurogenic regions: the ventricular-subventricular zone (V/SVZ) of the lateral ventricle and the subgranular zone (SGZ) of the dentate gyrus.[12–16] Perinatal H/I injury induces acute neurogenesis.[17] Focal cerebral ischemia in the adult rodent promotes neurogenesis primarily in the V/SVZ and induces neuroblast migration from the V/SVZ to the ischemic boundary.[13,14,18–33] Newly generated neuroblasts are involved in functional recovery after stroke.[34] Stroke-induced neurogenesis has also been demonstrated in the adult human brain.[35–37] Much progress has been made

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on elucidating the cellular and molecular mechanisms that control and coordinate neurogenesis after perinatal H/I injury and in the adult ischemic brain. We will review these findings with a focus on the V/SVZ neurogenic niche and discuss potential applications to facilitate endogenous neurogenesis and thereby to improve neurological function post perinatal H/I injury and stroke.

Perinatal H/I injury and stroke-induced neurogenesis in the V/SVZ

During the embryonic stage, radial glial cells in the VZ are neural stem cells.[12,38] Actively dividing embryonic neural stem cells in the VZ contribute to cortical neurogenesis, whereas a population of quiescent embryonic neural stem cells constitute a majority ($\sim$73%) of adult neural stem cells.[38,39] Using whole-mount tissue preparation of adult rodent brain, in vivo studies show that glial fibrillary acidic protein (GFAP) positive neural stem cells in the SVZ directly contact the cerebrospinal fluid (CSF) by extending their apical processes anchored at the ependymal layer of the ventricular surface, while the stem cells also project their long basal processes to reach blood vessels in the SVZ just beneath the ependymal layer. Thus, these studies demonstrate the presence of adult neural stem cells in the V/SVZ, although embryonic VZ is replaced by an ependymal layer in the adult brain.[40,41] Moreover, in vivo studies using genetic approaches demonstrate coexistence of quiescent and activated GFAP positive neural stem cells in the V/SVZ, expressing phenotypes of GFAP/CD133 and GFAP/CD133/epidermal growth factor receptor (EGFR), respectively. Clonal analysis reveals that quiescent neural stem cells constitute the primary population of the cells responsible for adult neurogenesis. Upon activation, quiescent neural stem cells (type B cells) become actively proliferative and convert to short-live intermediate progenitor cells (type C cells), which, in turn, differentiate into neuroblasts (type A cells) and oligodendrocytes.[12,39,42–44]

Perinatal H/I injury induces proliferation of neural stem and progenitor cells as well as neuroblasts in the V/SVZ.[45–47] Using a multimarker flow cytometry approach, a study shows that perinatal H/I injury promotes neural progenitor cell proliferation, but reduces neural stem cell generation of neural progenitor cells,[17] which may contribute to transient neurogenesis induced by perinatal H/I injury (Table 1).

Experimental studies in early 2000 demonstrated that focal cerebral ischemia in the adult rodent induces neurogenesis in the ipsilateral V/SVZ. Newly generated neuroblasts in the V/SVZ migrate to the ischemic boundary where they exhibit neuronal phenotypes.[13,18,19,22] Stroke-induced neurogenesis is now well established.[25,32,54,55] Patients with stroke show an increase in neural progenitor cells and neuroblasts in the ischemic brain.[35–37,56,57] However, a study using genomic and carbon-14 dating approaches failed to demonstrate the presence of neurogenesis in the human neocortex after stroke.[58]

Studies on adult rodent ischemic brain show that stroke activates neural stem cells to proliferate in the V/SVZ.[14,48] For example, depletion of actively dividing neural progenitor cells, but not quiescent neural stem cells, in the V/SVZ using an antimitotic agent (cytosine-β-D-arabiofuranoside, Ara-C) leads to a rapid repopulation of neural progenitor cells and neuroblasts in the ischemic V/SVZ after termination of the Ara-C treatment, suggesting that neural stem cells regenerate ablated neural progenitor cells.[14] Subsequent studies based on the novel anatomical organization of the adult neural stem cells within the V/SVZ niche support this hypothesis by showing that stroke considerably increases GFAP positive neural stem cells at the center of a pinwheel structure composed of ependymal cells, and that these GFAP positive neural stem cells are actively proliferating. Proliferating neural stem cells in the V/SVZ are observed even 30 days after ischemia.[48] Together, these stroke studies along with clonal analysis data from non-stroke rodents suggest that in response to ischemic insult, quiescent adult neural stem cells in the V/SVZ can be activated and recruited to an active pool to increase the neurogenic process.

In addition to neural stem cells, stroke promotes proliferation of neural progenitor cells and neuroblasts.[13,17–19,22,46] Studies based on clonal analysis and whole-mount tissue preparation of the adult rodent brain demonstrate that in the non-ischemic V/SVZ, neural progenitor cells are actively dividing with a cell cycle ranging from 18 to 25 h, and doublecortin (DCX) positive neuroblasts have a cell cycle length of 18 h.[59,60]

Table 1. Comparison of neurogenesis and oligodendrogenesis between perinatal H/I injury and stroke.

Stem/progenitor cells	Perinatal H/I injury	Stroke	References
Proliferation	Short and transient↑ (weeks)	Long lasting↑ (months)	17, 34, 45, 46, 48
Differentiation	Neuroblasts, OPCs↑	Neuroblasts, OPCs↑	17, 47, 49–53
Migration	Neuroblasts to injured striatum	Neuroblasts and OPCs to injured striatum and CC	47, 49–53

The progenitor cells divide 3 times before converting into neuroblasts while neuroblasts undergo one to two time divisions prior to migrating out the V/SVZ.[43,61] Stroke transiently increases the percentage of dividing neural progenitor cells from 15 to 21% in non-ischemic V/SVZ to 31%.[59,60] Analysis of cell cycle phases of actively proliferating V/SVZ neural progenitor cells at the population level reveals that stroke reduces the cell cycle length of these mitotic cells from 19 h in non-ischemia to 11 h. Stroke-reduced cell cycle length likely results from a decrease of the G1 phase of the cell cycle, because the G2, M, and S phases are unchanged.[60,62] Stroke also induces rapid neuroblast proliferation, and newly generated neuroblasts in the ipsilateral V/SVZ migrate to the ischemic boundary, which can be noninvasively imaged by MRI.[13–15,63,64] These data indicate that shortening of the cell cycle length of neural progenitor cells also contribute to stroke-induced expansion of the progenitor pool and neurogenesis (Table 1).

Perinatal H/I injury and stroke-induced oligodendrogenesis

In addition to neuroblasts, neural stem cells in the V/SVZ generate oligodendrocyte progenitor cells (OPCs) that differentiate into myelin forming oligodendrocytes.[65,66] OPCs are vulnerable to perinatal H/I injury, leading to permanent white matter damage.[17,55] Fluorescence-activated cell sorting (FACS) analysis of perinatal V/SVZ neural progenitor cells reveals the presence of a heterogeneous population of NG2 (a marker of OPCs) positive neural progenitor cells, and that perinatal H/I injury promotes proliferation of subpopulations of NG2 positive neural progenitor cells.[17] These data suggest that perinatal V/SVZ neural progenitor cells generate OPCs in response to perinatal H/I injury. However, OPCs within the V/SVZ do not migrate toward H/I injured brain regions, while increased OPCs in the injured striatum originate from proliferating OPCs within the striatum.[47] It remains to be determined whether perinatal H/I injury-increased OPCs differentiate into myelinating oligodendrocytes.

In the adult rodent brain, OPCs originating from V/SVZ neural progenitor cells comprise 3–9% of the total cell number and distribute into the corpus callosum, the striatum, and the cortex.[65–67] OPCs continuously differentiate into mature oligodendrocytes to myelinate the previously unmyelinated axons throughout the gray and white matter, and myelination in adult brain contributes to maintaining axonal integrity, neural plasticity, and circuitry function.[68] OPCs also act as a surveillance network to detect brain injury.[69] Using a fate mapping strategy, studies demonstrate that stroke increases neural stem cell lineage OPCs and promotes these OPCs to differentiate into myelin forming oligodendrocytes in peri-infarct white matter.[49–53] These data suggest that OPCs generated by adult neural stem cells contribute to oligodendrogenesis after stroke.

Signaling pathways are involved in regulating perinatal H/I injury- and stroke-induced neurogenesis

The Notch receptors are transmembrane proteins activated by Delta and Jagged ligands. On activation, Notch triggers expression of transcription factors of hairy and enhancer of split (Hes) family.[70] The Notch signaling pathway plays a pivotal role in maintaining the embryonic neural stem cell pool and promotes gliogenesis.[71] Perinatal H/I injury upregulates Notch1, Hes5, and EGFR expression in neural progenitor cells prior to the injury-induced neural progenitor cell proliferation,[55] suggesting that the Notch pathway could mediate perinatal H/I injury-induced neurogenesis. Stroke also activates the Notch pathway in adult neural progenitor cells by upregulating Notch and Hes1 expression, leading to progenitor cell proliferation, whereas blockage of the Notch pathway abolishes stroke-increased progenitor cell proliferation.[72,73] In addition, inactivation of Notch signals promotes ischemic neural progenitor cells to generate neurons.[73] Interestingly, a recent study shows that inactivation of the Notch signaling pathway in striatal astrocytes triggers the astrocytes to enter the neurogenic program in response to stroke, leading to the generation of neurons in peri-ischemic regions. These data suggest that in addition to V/SVZ neurogenesis, striatal resident astrocytes meditated by the Notch signaling pathway may also contribute stroke-induced neurogenesis.[74]

Sonic hedgehog (Shh) is a member of the family of the hedgehog proteins. Shh binds to the transmembrane receptor protein, patched (ptc), which, activates smoothened (Smo), leading to expression of the Gli family of transcription factors. The Shh pathway regulates patterning and growth in a large number of tissues during embryogenesis.[75–77] The Shh pathway is coupled with the Notch signaling pathway and plays an important role in regulating progenitor cell proliferation and differentiation.[78,79] The Shh pathway mediates stroke-induced neurogenesis.[80] Stroke upregulates Shh expression in V/SVZ neural progenitor cells.[81] Inhibition of the Shh pathway reduces proliferation and differentiation of neural progenitor cells, whereas intraventricular infusion of exogenous Shh enhances stroke-induced neurogenesis.[81,82]

The bone morphogenic protein (BMP) and Wnt pathways also regulate neurogenesis and oligodendrogenesis. Overexpression of BMP7 in ependymal cells

inhibits neural progenitor cell proliferation and neuroblast production. Transgenic mice with overexpression of the BMP antagonist noggin driven by the neuron specific enolase promoter show increased oligodendrogenesis after perinatal H/I injury.[83] Leukemia inhibitory factor (LIF) has also been shown to regulate expansion of a subset of intermediate neural progenitor cells during acute recovery from neonatal H/I injury.[17] In addition, stroke alters Wnt gene expression in the V/SVZ.[84] Overexpression of Wnt3a by intrastriatal injection of lentivirus carrying Wnt3a increases stroke-induced neurogenesis.[85] Under non-ischemic conditions, overexpression of Wnt3 in adult SVZ neural progenitor cells increases OPCs.[49] However, the canonic Wnt pathway negatively regulates OPC differentiation.[86] Thus, the effect of the Wnt pathway in mediating ischemia-induced oligodendrogenesis remains to be investigated.

MicroRNAs and signaling pathways

MicroRNAs (miRNAs) are a family of short noncoding RNA molecules of 20 to 25 nucleotides. They regulate gene function by decreasing gene expression through mRNA destabilization and/or translational repression.[87] MiRNAs play an important role in neurogenesis and oligodendrogenesis.[88] Deletion of a miRNA biogenic machinery protein, Dicer, in nestin lineage neural stem cells is embryonic lethal, and ablation of Dicer in Olig 1 and 2 lineage cells impairs oligodendrogenesis.[89–91] Cre-inducible ablation of Dicer in NG2 lineage cells enhances OPC differentiation into myelinating oligodendrocytes in the corpus callosum after perinatal H/I injury.[92] In addition, perinatal H/I injury upregulates miR-338.[92] Elevation of miR-219 and miR-338 in OPCs promotes OPC differentiation into myelinating oligodendrocytes by repressing their target genes of platelet-derived growth factor receptor α (PDGFRα), Sox6, and Hes5, which inhibit OPC differentiation.[89,90] These data suggest that miRNAs play an important role in mediating oligodendrogenesis after perinatal H/I injury. Adult V/SVZ neural progenitor cells express miRNAs, and stroke induces robust alteration of miRNA profiles in these cells.[93–95] Stroke-altered miRNAs affect several signaling pathways including Notch, Shh, and Wnt.[93] For example, stroke increases miR-124a, the most abundant neuronal miRNA, expression in V/SVZ neural progenitor cells, and upregulated miR-124a inactivates Notch signaling by targeting a Notch ligand Jagged-1, which promotes neuronal differentiation.[96]

The miR17-92 cluster comprises a cluster of six miRNAs (miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, and miR-92a-1).[97] In the development of mouse neurocortex, the miR17-92 cluster controls neural progenitor cell proliferation by suppressing phosphatase and tensin homolog deleted on chromosome 10 (PTEN) and the transcription factor Tbr 2.[98,99] Ablation of the miR17-92 cluster in OPCs during brain development reduces their proliferation, indicating that this cluster affects oligodendrogenesis.[100] Stroke robustly increases miR17-92 cluster expression in V/SVZ neural progenitor cells. The Shh pathway likely triggers this upregulation because activation and blockage of the Shh pathway in V/SVZ neural progenitor cells increases and reduces miR17-92 expression, respectively. Overexpression of the miR17-92 cluster in V/SVZ neural progenitor cells enhanced stroke-induced progenitor cell proliferation, whereas attenuation of endogenous miR-17-92 cluster abolished the stroke-increased proliferation. Suppression of PTEN, that inhibits neural progenitor cell proliferation, by the miR17-92 cluster partially contributes to this process. Collectively, these data indicate that the Shh signaling pathway positively regulates miR17-92 cluster expression, while the upregulated miR-17-92 cluster represses its target gene PTEN, leading to expansion V/SVZ neural progenitor cell pools in response to stroke.[88,101]

In addition, miR-92 regulates bone morphogenetic protein (BMP) signals, while Wnt/β-catenin signaling represses Let 7.[102,103] Stroke downregulates Let-7 and miR-9 in neural progenitor cells[88] and these miRNAs regulate the TLX nuclear receptor to control the balance between the proliferation and differentiation of adult neural stem cells.[104] Thus, these data indicate that miRNAs and the signaling pathways in V/SVZ neural progenitor cells are closely connected and thereby regulate neurogenesis and oligodendrogenesis after brain injury, including perinatal H/I and stroke.

Coupling of neurogenesis and angiogenesis

Angiogenesis is the sprouting of new capillaries from preexisting blood vessels, involving endothelial cell proliferation, migration, tube formation, branching, and anastomosis.[105,106] The cerebral endothelial cells are linked by complex tight junctions that along with astrocytes form the blood–brain barrier (BBB).[105] In the SVZ, cerebral blood vessels form a planar vascular plexus that differs from the vascular structure in other brain regions. This planar vascular plexus permits small molecules to pass the BBB and to enter the SVZ.[107–109] Adult neural stem cells anchored on the ventricular surface extend their long processes to directly contact blood vessels within this plexus, while actively proliferating intermediate neural progenitor cells in the SVZ are localized to blood vessels.[109] In addition to this unique architecture, cerebral vasculature in the SVZ releases factors, such as integrin α6 and β1, to regulate

neural stem and progenitor cell biologic function,[107,108] indicating a coupling of cerebral blood vessels with neural stem cells in the adult V/SVZ neurogenic niche.[110] Stroke-increased neurogenesis is also coupled with angiogenesis. In the V/SVZ niche, stroke robustly increases neural stem cells and new blood vessels, while neural stem cells directly contact blood vessels in the SVZ.[48] Co-culture of cerebral endothelial cells harvested from ischemic brain with non-ischemic V/SVZ neural progenitor cells increases progenitor cell proliferation and neuronal differentiation, whereas culture of ischemic neural progenitor cells with non-ischemic cerebral endothelial cells promotes in vitro angiogenesis as measured by a capillary tube formation assay.[111] As a further reflection of vascular and V/SVZ neural progenitor and neuroblast interaction, stroke-increased neuroblasts in the V/SVZ migrate along cerebral blood vessels to ischemic boundary regions.[54,63,112–114] Suppression of stroke-induced angiogenesis by endostatin or a neutralizing antibody against the angiopoietin receptor, Tie2, substantially reduces neuroblast migration to the ischemic region.[54] Soluble molecules and their receptors mediate coupling of angiogenesis and neurogenesis, which include vascular endothelial growth factor (VEGF), angiopoietin-1 (Ang1), stromal-derived factor-1 α (SDF-1 α), and matrix metalloproteinases (MMPs) and receptors of VEGFR2, Tie2, and CXCR4.[54,63,111–114]

Emerging data indicate that exosomes play vital roles in intercellular communication by transferring contained proteomic and genomic materials between source and target cells. Exosomes are endosome-derived small membrane vesicles ($\sim$30–100 nm) and are released by cells in all living systems.[115] Treatment of non-ischemic endothelial cells with exosomes derived from ischemic V/SVZ neural progenitor cells enhances angiogenesis, whereas application of exosomes harvested from ischemic cerebral endothelial cells to non-ischemic neural progenitor cells augments neural progenitor cell proliferation and neuronal differentiation.[116] These data suggest that exosomes regulate coupling of neurogenesis and angiogenesis.

Therapies amplify stroke-induced neurogenesis

New neurons generated from the V/SVZ in the adult rodent integrate into local neuronal circuitry in the olfactory bulb and participate in processing of sensory information and olfactory memory.[12] Although V/SVZ derived new neurons in the ischemic boundary have been shown to exhibit electrophysiologic characteristics of mature neurons, their functional roles in brain repair remain uncertain.[117] In fact, only few new neurons survive in the peri-infarct region after stroke and no studies so far have conclusively shown that these neuroblasts mature into specific types of neurons that assemble into local circuits, suggesting that replacing dead neurons by V/SVZ derived new neurons does not primarily contribute to brain repair after stroke. However, there are substantial data that suggest a post stroke restorative role for neuroblasts, in that stroke robustly increases neuroblasts and this increase persists at least for 6 months after stroke.[31,48] In addition, specific ablation of neuroblasts after stroke substantially impairs brain repair and exacerbates functional recovery, suggesting that neuroblasts contribute to ischemic brain repair processes and functional outcomes.[34] These data suggest that in addition to differentiating into mature neurons, neuroblasts facilitate brain repair. Data from cell-based and pharmacologically based therapies strongly support this view.[118–121]

Among cell-based therapies, treatment of stroke with mesenchymal stromal cells (MSCs) substantially increases neurogenesis and angiogenesis and improves neurological function.[110,118,120–122] MSCs stimulate brain parenchymal cells to induce an array of molecules leading to amplifying processes of endogenous neurogenesis and angiogenesis. This parenchymal cell stimulation likely forms the cellular and molecular bases underlying the therapeutic effect of cell-based therapies. Pharmacological agents aimed at regulating these endogenous molecules also foster neurogenesis and angiogenesis and improve functional outcomes during stroke recovery.[123–134]

Conclusion

Embryonic quiescent neural stem cells comprise a majority of adult neural stem cells in the V/SVZ. Adult neurogenesis shares many features of embryonic neurogenesis. Much progress has been made to advance our knowledge in the field of V/SVZ neural stem cells in response to perinatal H/I injury and stroke. Perinatal H/I injury depletes neural progenitor cells, leading to reduction of neurogenesis and oligodendrogenesis, and consequently to impairment of cognitive and motor function. However, there is a subpopulation of neural stem cells that are resilient to H/I injury. Future studies need to investigate molecular mechanisms regulating function of this cell population, which may lead to development potential therapies to facilitate brain repair for perinatal H/I injury.

Adult V/SVZ neural stem cells are relatively resistant to stroke. However, stroke-induced neurogenesis is limited. Given the association of neurogenesis with neurological function, it will be important to investigate how the signaling pathways and miRNAs in neural stem cells and their progeny are modulated by stroke and how these cells communicate among themselves and

with other brain cells, and in turn regulate stroke-induced neurogenesis. These studies may provide not only novel insights into the function of neural stem cells but also new strategies for enhancement of stroke-induced neurogenesis and consequently means to improve neurological function.

Although preclinical studies have provided strong evidence that neurogenesis and oligodendrogenesis are essential to brain repair processes, the contribution of endogenous neural stem cells to repair processes in human perinatal H/I injury and stroke brains remains to be demonstrated.

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References

1. Wyatt JS, Gluckman PD, Liu PY, et al. Determinants of outcomes after head cooling for neonatal encephalopathy. *Pediatrics* 2007; 119: 912–921.
2. Lackland DT, Roccella EJ, Deutsch AF, et al. Factors influencing the decline in stroke mortality: a statement from the American Heart Association/American Stroke Association. *Stroke* 2014; 45: 315–353.
3. NINDS. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N Engl J Med* 1995; 333: 1581–1587.
4. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008; 359: 1317–1329.
5. Moskowitz MA, Lo EH and Iadecola C. The science of stroke: mechanisms in search of treatments. *Neuron* 2010; 67: 181–198.
6. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *New Engl J Med* 2015; 372: 1019–1030.
7. Campbell BC, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *New Engl J Med* 2015; 372: 1009–1018.
8. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *New Engl J Med* 2015; 372: 11–20.
9. Verheyden G, Nieuwboer A, De Wit L, et al. Time course of trunk, arm, leg, and functional recovery after ischemic stroke. *Neurorehabil Neural Repair* 2008; 22: 173–179.
10. Hinds JW and Ruffett TL. Cell proliferation in the neural tube: an electron microscopic and golgi analysis in the mouse cerebral vesicle. *Z Zellforsch Mikrosk Anat* 1971; 115: 226–264.
11. Chenn A and McConnell SK. Cleavage orientation and the asymmetric inheritance of Notch1 immunoreactivity in mammalian neurogenesis. *Cell* 1995; 82: 631–641.
12. Alvarez-Buylla A, Herrera DG and Wichterle H. The subventricular zone: source of neuronal precursors for brain repair. *Prog Brain Res* 2000; 127: 1–11.
13. Arvidsson A, Collin T, Kirik D, et al. Neuronal replacement from endogenous precursors in the adult brain after stroke. *Nat Med* 2002; 8: 963–970.
14. Zhang R, Zhang Z, Wang L, et al. Activated neural stem cells contribute to stroke-induced neurogenesis and neuroblast migration toward the infarct boundary in adult rats. *J Cereb Blood Flow Metab* 2004; 24: 441–448.
15. Jin K, Sun Y, Xie L, et al. Directed migration of neuronal precursors into the ischemic cerebral cortex and striatum. *Mol Cell Neurosci* 2003; 24: 171–189.
16. Parent JM. Injury-induced neurogenesis in the adult mammalian brain. *Neuroscientist* 2003; 9: 261–272.
17. Buono KD, Goodus MT, Guardia Clausi M, et al. Mechanisms of mouse neural precursor expansion after neonatal hypoxia-ischemia. *J Neurosci* 2015; 35: 8855–8865.
18. Zhang RL, Zhang ZG, Zhang L, et al. Proliferation and differentiation of progenitor cells in the cortex and the subventricular zone in the adult rat after focal cerebral ischemia. *Neuroscience* 2001; 105: 33–41.
19. Jin K, Minami M, Lan JQ, et al. Neurogenesis in dentate subgranular zone and rostral subventricular zone after focal cerebral ischemia in the rat. *Proc Natl Acad Sci USA* 2001; 98: 4710–4715.
20. Yoshimura S, Takagi Y, Harada J, et al. FGF-2 regulation of neurogenesis in adult hippocampus after brain injury. *Proc Natl Acad Sci USA* 2001; 98: 5874–5879.
21. Tonchev AB, Yamashima T, Zhao L, et al. Proliferation of neural and neuronal progenitors after global brain ischemia in young adult macaque monkeys. *Mol Cell Neurosci* 2003; 23: 292–301.
22. Parent JM, Vexler ZS, Gong C, et al. Rat forebrain neurogenesis and striatal neuron replacement after focal stroke. *Ann Neurol* 2002; 52: 802–813.
23. Liu J, Solway K, Messing RO, et al. Increased neurogenesis in the dentate gyrus after transient global ischemia in gerbils. *J Neurosci* 1998; 18: 7768–7778.
24. Iwai M, Sato K, Omori N, et al. Three steps of neural stem cells development in gerbil dentate gyrus after transient ischemia. *J Cereb Blood Flow Metab* 2002; 22: 411–419.
25. Iwai M, Sato K, Kamada H, et al. Temporal profile of stem cell division, migration, and differentiation from subventricular zone to olfactory bulb after transient forebrain ischemia in gerbils. *J Cereb Blood Flow Metab* 2003; 23: 331–341.

26. Schmidt W and Reymann KG. Proliferating cells differentiate into neurons in the hippocampal CA1 region of gerbils after global cerebral ischemia. *Neurosci Lett* 2002; 334: 153–156.
27. Tanaka R, Yamashiro K, Mochizuki H, et al. Neurogenesis after transient global ischemia in the adult hippocampus visualized by improved retroviral vector. *Stroke* 2004; 35: 1454–1459.
28. Kee NJ, Preston E and Wojtowicz JM. Enhanced neurogenesis after transient global ischemia in the dentate gyrus of the rat. *Exp Brain Res* 2001; 136: 313–320.
29. Yagita Y, Kitagawa K, Ohtsuki T, et al. Neurogenesis by progenitor cells in the ischemic adult rat hippocampus. *Stroke* 2001; 32: 1890–1896.
30. Zhu DY, Liu SH, Sun HS, et al. Expression of inducible nitric oxide synthase after focal cerebral ischemia stimulates neurogenesis in the adult rodent dentate gyrus. *J Neurosci* 2003; 23: 223–229.
31. Thored P, Arvidsson A, Cacci E, et al. Persistent production of neurons from adult brain stem cells during recovery after stroke. *Stem Cells* 2006; 24: 739–747.
32. Yamashita T, Ninomiya M, Hernandez Acosta P, et al. Subventricular zone-derived neuroblasts migrate and differentiate into mature neurons in the post-stroke adult striatum. *J Neurosci* 2006; 26: 6627–6636.
33. Tureyen K, Vemuganti R, Sailor KA, et al. Transient focal cerebral ischemia-induced neurogenesis in the dentate gyrus of the adult mouse. *J Neurosurg* 2004; 101: 799–805.
34. Wang X, Mao X, Xie L, et al. Conditional depletion of neurogenesis inhibits long-term recovery after experimental stroke in mice. *PLoS One* 2012; 7: e38932.
35. Jin K, Wang X, Xie L, et al. Evidence for stroke-induced neurogenesis in the human brain. *Proc Natl Acad Sci USA* 2006; 103: 13198–13202.
36. Macas J, Nern C, Plate KH, et al. Increased generation of neuronal progenitors after ischemic injury in the aged adult human forebrain. *J Neurosci* 2006; 26: 13114–13119.
37. Minger SL, Ekonomou A, Carta EM, et al. Endogenous neurogenesis in the human brain following cerebral infarction. *Regen Med* 2007; 2: 69–74.
38. Noctor SC, Martinez-Cerdeno V, Ivic L, et al. Cortical neurons arise in symmetric and asymmetric division zones and migrate through specific phases. *Nat Neurosci* 2004; 7: 136–144.
39. Furutachi S, Miya H, Watanabe T, et al. Slowly dividing neural progenitors are an embryonic origin of adult neural stem cells. *Nat Neurosci* 2015; 18: 657–665.
40. Morshead CM, Craig CG and van der Kooy D. In vivo clonal analyses reveal the properties of endogenous neural stem cell proliferation in the adult mammalian forebrain. *Development* 1998; 125: 2251–2261.
41. Mirzadeh Z, Merkle FT, Soriano-Navarro M, et al. Neural stem cells confer unique pinwheel architecture to the ventricular surface in neurogenic regions of the adult brain. *Cell Stem Cell* 2008; 3: 265–278.
42. Codega P, Silva-Vargas V, Paul A, et al. Prospective identification and purification of quiescent adult neural stem cells from their in vivo niche. *Neuron* 2014; 82: 545–559.
43. Calzolari F, Michel J, Baumgart EV, et al. Fast clonal expansion and limited neural stem cell self-renewal in the adult subependymal zone. *Nat Neurosci* 2015; 18: 490–492.
44. Tramontin AD, Garcia-Verdugo JM, Lim DA, et al. Postnatal development of radial glia and the ventricular zone (VZ): a continuum of the neural stem cell compartment. *Cereb Cortex* 2003; 13: 580–587.
45. Romanko MJ, Rothstein RP and Levison SW. Neural stem cells in the subventricular zone are resilient to hypoxia/ischemia whereas progenitors are vulnerable. *J Cereb Blood Flow Metab* 2004; 24: 814–825.
46. Yang Z and Levison SW. Hypoxia/ischemia expands the regenerative capacity of progenitors in the perinatal subventricular zone. *Neuroscience* 2006; 139: 555–564.
47. Dizon M, Szele F and Kessler JA. Hypoxia-ischemia induces an endogenous reparative response by local neural progenitors in the postnatal mouse telencephalon. *Dev Neurosci* 2010; 32: 173–183.
48. Zhang RL, Chopp M, Roberts C, et al. Stroke increases neural stem cells and angiogenesis in the neurogenic niche of the adult mouse. *PLoS One* 2014; 9: e113972.
49. Rafalski VA, Ho PP, Brett JO, et al. Expansion of oligodendrocyte progenitor cells following SIRT1 inactivation in the adult brain. *Nat Cell Biol* 2013; 15: 614–624.
50. Zhang RL, Chopp M, Roberts C, et al. Ascl1 lineage cells contribute to ischemia-induced neurogenesis and oligodendrogenesis. *J Cereb Blood Flow Metab* 2011; 31: 614–625.
51. Zhang RL, Chopp M, Roberts C, et al. Sildenafil enhances neurogenesis and oligodendrogenesis in ischemic brain of middle-aged mouse. *PLoS One* 2012; 7: e48141.
52. Li L, Harms KM, Ventura PB, et al. Focal cerebral ischemia induces a multilineage cytogenic response from adult subventricular zone that is predominantly gliogenic. *Glia* 2010; 58: 1610–1619.
53. Zhang L, Chopp M, Zhang RL, et al. Erythropoietin amplifies stroke-induced oligodendrogenesis in the rat. *PLoS One* 2010; 5: e11016.
54. Ohab JJ, Fleming S, Blesch A, et al. A neurovascular niche for neurogenesis after stroke. *J Neurosci* 2006; 26: 13007–13016.
55. Felling RJ, Snyder MJ, Romanko MJ, et al. Neural stem/progenitor cells participate in the regenerative response to perinatal hypoxia/ischemia. *J Neurosci* 2006; 26: 4359–4369.
56. Curtis MA, Kam M and Faull RL. Neurogenesis in humans. *Eur J Neurosci* 2011; 33: 1170–1174.
57. Marti-Fabregas J, Romaguera-Ros M, Gomez-Pinedo U, et al. Proliferation in the human ipsilateral subventricular zone after ischemic stroke. *Neurology* 2010; 74: 357–365.
58. Huttner HB, Bergmann O, Salehpour M, et al. The age and genomic integrity of neurons after cortical stroke in humans. *Nat Neurosci* 2014; 17: 801–803.
59. Schultze B and Korr H. Cell kinetic studies of different cell types in the developing and adult brain of the rat and the mouse: a review. *Cell Tissue Kinet* 1981; 14: 309–325.
60. Zhang RL, Zhang ZG, Lu M, et al. Reduction of the cell cycle length by decreasing G(1) phase and cell cycle

reentry expand neuronal progenitor cells in the subventricular zone of adult rat after stroke. *J Cereb Blood Flow Metab* 2006; 26: 857–863.
61. Ponti G, Obernier K, Guinto C, et al. Cell cycle and lineage progression of neural progenitors in the ventricular-subventricular zones of adult mice. *Proc Natl Acad Sci USA* 2013; 110: E1045–E1054.
62. Zhang RL, Zhang ZG, Roberts C, et al. Lengthening the G(1) phase of neural progenitor cells is concurrent with an increase of symmetric neuron generating division after stroke. *J Cereb Blood Flow Metab* 2008; 28: 602–611.
63. Zhang RL, LeTourneau Y, Gregg SR, et al. Neuroblast division during migration toward the ischemic striatum: a study of dynamic migratory and proliferative characteristics of neuroblasts from the subventricular zone. *J Neurosci* 2007; 27: 3157–3162.
64. Zhang ZG, Jiang Q, Zhang R, et al. Magnetic resonance imaging and neurosphere therapy of stroke in rat. *Ann Neurol* 2003; 53: 259–263.
65. Santra M, Chopp M, Zhang ZG, et al. Thymosin beta 4 mediates oligodendrocyte differentiation by upregulating p38 MAPK. *Glia* 2012; 60: 1826–1838.
66. Menn B, Garcia-Verdugo JM, Yaschine C, et al. Origin of oligodendrocytes in the subventricular zone of the adult brain. *J Neurosci* 2006; 26: 7907–7918.
67. Franklin RJ and Ffrench-Constant C. Remyelination in the CNS: from biology to therapy. *Nat Rev Neurosci* 2008; 9: 839–855.
68. McTigue DM and Tripathi RB. The life, death, and replacement of oligodendrocytes in the adult CNS. *J Neurochem* 2008; 107: 1–19.
69. Hughes EG, Kang SH, Fukaya M, et al. Oligodendrocyte progenitors balance growth with self-repulsion to achieve homeostasis in the adult brain. *Nat Neurosci* 2013; 16: 668–676.
70. Guentchev M and McKay RD. Notch controls proliferation and differentiation of stem cells in a dose-dependent manner. *Eur J Neurosci* 2006; 23: 2289–2296.
71. Gaiano NFG. The role of notch in promoting glial and neural stem cell fates. *Annu Rev Neurosci* 2002; 25: 471–490.
72. Wang LCM, Zhang RL, Zhang L, et al. The Notch pathway mediates expansion of a progenitor pool and neuronal differentiation in adult neural progenitor cells after stroke. *Neuroscience* 2009; 158: 1356–1363.
73. Wang L, Chopp M, Zhang RL, et al. The Notch pathway mediates expansion of a progenitor pool and neuronal differentiation in adult neural progenitor cells after stroke. *Neuroscience* 2009; 158: 1356–1363.
74. Magnusson JP, Goritz C, Tatarishvili J, et al. A latent neurogenic program in astrocytes regulated by Notch signaling in the mouse. *Science* 2014; 346: 237–241.
75. Ruiz i Altaba A, Sanchez P and Dahmane N. Gli and hedgehog in cancer: tumours, embryos and stem cells. *Nat Rev Cancer* 2002; 2: 361–372.
76. Goetz JA, Suber LM, Zeng X, et al. Sonic Hedgehog as a mediator of long-range signaling. *Bioessays* 2002; 24: 157–165.
77. Roberts DJ, Johnson RL, Burke AC, et al. Sonic hedgehog is an endodermal signal inducing Bmp-4 and Hox genes during induction and regionalization of the chick hindgut. *Development* 1995; 121: 3163–3174.
78. Androutsellis-Theotokis A, Leker RR, Soldner F, et al. Notch signalling regulates stem cell numbers in vitro and in vivo. *Nature* 2006; 442: 823–826.
79. Palma V, Lim DA, Dahmane N, et al. Sonic hedgehog controls stem cell behavior in the postnatal and adult brain. *Development* 2005; 132: 335–344.
80. Sims JR, Lee SW, Topalkara K, et al. Sonic hedgehog regulates ischemia/hypoxia-induced neural progenitor proliferation. *Stroke* 2009; 40: 3618–3626.
81. Liu XS, Chopp M, Zhang RL, et al. MicroRNAs in cerebral ischemia-induced neurogenesis. *J Neuropathol Exp Neurol* 2013; 72: 718–722.
82. Zhang L, Chopp M, Meier DH, et al. Sonic hedgehog signaling pathway mediates cerebrolysin-improved neurological function after stroke. *Stroke* 2013; 44: 1965–1972.
83. Dizon ML, Maa T and Kessler JA. The bone morphogenetic protein antagonist noggin protects white matter after perinatal hypoxia-ischemia. *Neurobiol Dis* 2011; 42: 318–326.
84. Morris DC, Zhang ZG, Wang Y, et al. Wnt expression in the adult rat subventricular zone after stroke. *Neurosci Lett* 2007; 418: 170–174.
85. Shruster A, Ben-Zur T, Melamed E, et al. Wnt signaling enhances neurogenesis and improves neurological function after focal ischemic injury. *PLoS One* 2012; 7: e40843.
86. Fancy SP, Chan JR, Baranzini SE, et al. Myelin regeneration: a recapitulation of development? *Annu Rev Neurosci* 2011; 34: 21–43.
87. Hammond SM, Bernstein E, Beach D, et al. An RNA-directed nuclease mediates post-transcriptional gene silencing in *Drosophila* cells. *Nature* 2000; 404: 293–296.
88. Liu XS, Chopp M, Zhang RL, et al. MicroRNA profiling in subventricular zone after stroke: MiR-124a regulates proliferation of neural progenitor cells through notch signaling pathway. *PLoS One* 2011; 6: e23461.
89. Zhao X, He X, Han X, et al. MicroRNA-mediated control of oligodendrocyte differentiation. *Neuron* 2010; 65: 612–626.
90. Dugas JC, Cuellar TL, Scholze A, et al. Dicer1 and miR-219 Are required for normal oligodendrocyte differentiation and myelination. *Neuron* 2010; 65: 597–611.
91. Kawase-Koga Y, Low R, Otaegi G, et al. RNAase-III enzyme Dicer maintains signaling pathways for differentiation and survival in mouse cortical neural stem cells. *J Cell Sci* 2010; 123(Pt 4): 586–594.
92. Birch D, Britt BC, Dukes SC, et al. MicroRNAs participate in the murine oligodendroglial response to perinatal hypoxia-ischemia. *Pediatr Res* 2014; 76: 334–340.
93. Liu XS, Zhang ZG, Zhang RL, et al. Stroke induces gene profile changes associated with neurogenesis and angiogenesis in adult subventricular zone progenitor cells. *J Cereb Blood Flow Metab* 2007; 27: 564–574.
94. Cheng LC, Pastrana E, Tavazoie M, et al. miR-124 regulates adult neurogenesis in the subventricular zone stem cell niche. *Nat Neurosci* 2009; 12: 399–408.

95. Akerblom M, Sachdeva R, Barde I, et al. MicroRNA-124 is a subventricular zone neuronal fate determinant. *J Neurosci* 2012; 32: 8879–8889.
96. Jones PMG, Healy L, Brown J, et al. Stromal expression of Jagged 1 promotes colony formation by fetal hematopoietic progenitor cells. *Blood* 1998; 92: 1505–1511.
97. Xiao C, Srinivasan L, Calado DP, et al. Lymphoproliferative disease and autoimmunity in mice with increased miR-17-92 expression in lymphocytes. *Nat Immunol* 2008; 9: 405–414.
98. Bian S, Hong J, Li Q, et al. MicroRNA cluster miR-17-92 regulates neural stem cell expansion and transition to intermediate progenitors in the developing mouse neocortex. *Cell Rep* 2013; 3: 1398–1406.
99. Nowakowski TJ, Fotaki V, Pollock A, et al. MicroRNA-92b regulates the development of intermediate cortical progenitors in embryonic mouse brain. *Proc Natl Acad Sci USA* 2013; 110: 7056–7061.
100. Budde H, Schmitt S, Fitzner D, et al. Control of oligodendroglial cell number by the miR-17-92 cluster. *Development* 2010; 137: 2127–2132.
101. Liu XS, Chopp M, Wang XL, et al. MicroRNA-17/92 cluster mediates the proliferation and survival of neural progenitor cells after stroke. *J Biol Chem* 2013; 288: 12478–12488.
102. Cai WY, Wei TZ, Luo QC, et al. Wnt/beta-catenin pathway represses let-7 microRNAs expression via transactivation of Lin28 to augment breast cancer stem cell expansion. *J Cell Sci* 2013; 126: 2877–2889.
103. Dews M, Fox JL, Hultine S, et al. The myc-miR-17 ~ 92 axis blunts TGF{beta} signaling and production of multiple TGF{beta}-dependent antiangiogenic factors. *Cancer Res* 2010; 70: 8233–8246.
104. Zhao C, Sun G, Li S, et al. A feedback regulatory loop involving microRNA-9 and nuclear receptor TLX in neural stem cell fate determination. *Nat Struct Mol Biol* 2009; 16: 365–371.
105. Risau W. Development and differentiation of endothelium. *Kidney Int Suppl* 1998; 67: S3–S6.
106. Carmeliet P. VEGF gene therapy: stimulating angiogenesis or angioma-genesis? [In Process Citation]. *Nat Med* 2000; 6: 1102–1103.
107. Shen Q, Wang Y, Kokovay E, et al. Adult SVZ stem cells lie in a vascular niche: a quantitative analysis of niche cell-cell interactions. *Cell Stem Cell* 2008; 3: 289–300.
108. Tavazoie M, Van der Veken L, Silva-Vargas V, et al. A specialized vascular niche for adult neural stem cells. *Cell Stem Cell* 2008; 3: 279–288.
109. Silva-Vargas V, Crouch EE and Doetsch F. Adult neural stem cells and their niche: a dynamic duo during homeostasis, regeneration, and aging. *Curr Opin Neurobiol* 2013; 23: 935–942.
110. Zhang ZG and Chopp M. Neurorestorative therapies for stroke: underlying mechanisms and translation to the clinic. *Lancet Neurol* 2009; 8: 491–500.
111. Teng H, Zhang ZG, Wang L, et al. Coupling of angiogenesis and neurogenesis in cultured endothelial cells and neural progenitor cells after stroke. *J Cereb Blood Flow Metab* 2008; 28: 764–771.
112. Tran PB, Ren D, Veldhouse TJ, et al. Chemokine receptors are expressed widely by embryonic and adult neural progenitor cells. *J Neurosci Res* 2004; 76: 20–34.
113. Robin AM, Zhang ZG, Wang L, et al. Stromal cell-derived factor 1alpha mediates neural progenitor cell motility after focal cerebral ischemia. *J Cereb Blood Flow Metab* 2006; 26: 125–134.
114. Zhang RL, Chopp M, Gregg SR, et al. Patterns and dynamics of subventricular zone neuroblast migration in the ischemic striatum of the adult mouse. *J Cereb Blood Flow Metab* 2009; 29: 1240–1250.
115. Lai CP and Breakefield XO. Role of exosomes/microvesicles in the nervous system and use in emerging therapies. *Front Physiol* 2012; 3: 1–14.
116. Pan W, Zhang X, Liu X, et al. Exosomes derived from ischemic cerebral endothelial cells and neural progenitor cells enhance neurogenesis and angiogenesis. *Stroke* 2016; 47(Suppl 1): AWMP39.
117. Hou SW, Wang YQ, Xu M, et al. Functional integration of newly generated neurons into striatum after cerebral ischemia in the adult rat brain. *Stroke* 2008; 39: 2837–2844.
118. Chopp M, Li Y and Zhang J. Plasticity and remodeling of brain. *J Neurol Sci* 2008; 265: 97–101.
119. Cramer SC and Riley JD. Neuroplasticity and brain repair after stroke. *Curr Opin Neurol* 2008; 21: 76–82.
120. Parr AM, Tator CH and Keating A. Bone marrow-derived mesenchymal stromal cells for the repair of central nervous system injury. *Bone Marrow Transplant* 2007; 40: 609–619.
121. Chopp M and Li Y. Treatment of neural injury with marrow stromal cells. *Lancet Neurol* 2002; 1: 92–100.
122. Borlongan CV, Glover LE, Tajiri N, et al. The great migration of bone marrow-derived stem cells toward the ischemic brain: therapeutic implications for stroke and other neurological disorders. *Prog Neurobiol* 2011; 95: 213–228.
123. Zhang R, Wang Y, Zhang L, et al. Sildenafil (Viagra) induces neurogenesis and promotes functional recovery after stroke in rats. *Stroke* 2002; 33: 2675–2680.
124. Zhang R, Zhang L, Zhang Z, et al. A nitric oxide donor induces neurogenesis and reduces functional deficits after stroke in rats. *Ann Neurol* 2001; 50: 602–611.
125. Chen J, Zhang ZG, Li Y, et al. Statins induce angiogenesis, neurogenesis, and synaptogenesis after stroke. *Ann Neurol* 2003; 53: 743–751.
126. Wang L, Zhang Z, Wang Y, et al. Treatment of stroke with erythropoietin enhances neurogenesis and angiogenesis and improves neurological function in rats. *Stroke* 2004; 35: 1732–1737.
127. Hossmann KA and Buschmann IR. Granulocyte-macrophage colony-stimulating factor as an arteriogenic factor in the treatment of ischaemic stroke. *Expert Opin Biol Ther* 2005; 5: 1547–1556.
128. Zhang L, Zhang Z, Zhang RL, et al. Tadalafil, a long-acting type 5 phosphodiesterase isoenzyme inhibitor, improves neurological functional recovery in a rat model of embolic stroke. *Brain Res* 2006; 1118: 192–198.

129. Chen J, Cui X, Zacharek A, et al. Niaspan increases angiogenesis and improves functional recovery after stroke. *Ann Neurol* 2007; 62: 49–58.
130. Nakano M, Satoh K, Fukumoto Y, et al. Important role of erythropoietin receptor to promote VEGF expression and angiogenesis in peripheral ischemia in mice. *Circ Res* 2007; 100: 662–669.
131. Tsai PT, Ohab JJ, Kertesz N, et al. A critical role of erythropoietin receptor in neurogenesis and post-stroke recovery. *J Neurosci* 2006; 26: 1269–1274.
132. Chen ZY, Asavaritikrai P, Prchal JT, et al. Endogenous erythropoietin signaling is required for normal neural progenitor cell proliferation. *J Biol Chem* 2007; 282: 25875–25883.
133. Iwai M, Cao G, Yin W, et al. Erythropoietin promotes neuronal replacement through revascularization and neurogenesis after neonatal hypoxia/ischemia in rats. *Stroke* 2007; 38: 2795–2803.
134. Li Y, Lu Z, Keogh CL, et al. Erythropoietin-induced neurovascular protection, angiogenesis, and cerebral blood flow restoration after focal ischemia in mice. *J Cereb Blood Flow Metab* 2007; 27: 1043–1054.