OLIGODENDROGENESIS AFTER CEREBRAL ISCHAEMIA AND TRAUMATIC BRAIN INJURY

Zheng Gang Zhang,[1] Michael Chopp[1,2]

1. Department of Neurology, Henry Ford Hospital, Detroit, Michigan, USA
2. Department of Physics, Oakland University, Rochester, Michigan, USA

Disclosure: This work was supported by National Institutes of Health Grants RO1 NS075156 (ZGZ) and AG037506 (MC). The content is solely the responsibility of the authors and does not necessarily represent the official view of the National Institutes of Health.
Received: 07.10.13 **Accepted:** 25.10.13
Citation: EMJ Neurol. 2013;1:26-31.

ABSTRACT

Stroke and traumatic brain injury (TBI) damage white and grey matter. Loss of oligodendrocytes and their myelin, impairs axonal function. Remyelination involves oligodendrogenesis during which new myelinating oligodendrocytes are generated by differentiated oligodendrocyte progenitor cells (OPCs). This article briefly reviews the processes of oligodendrogenesis in adult rodent brains, and promising experimental therapies targeting the neurovascular unit that reduce oligodendrocyte damage and amplify endogenous oligodendrogenesis after stroke and TBI.

Keywords: Cerebral ischaemia, traumatic brain injury, myelination, oligodendrocytes, oligodendrocyte progenitor cells.

INTRODUCTION

Stroke and traumatic brain injury (TBI) lead to white and grey matter damage and are leading causes of mortality and morbidity.[1-5] White matter mainly contains axons and oligodendrocytes, myelin forming cells, in the central nervous system (CNS).[1,3,5] Acute axonal injury is one of the most common pathological features of closed head injury.[3] Oligodendrocytes are vulnerable to ischaemic stroke.[1,6] Loss of oligodendrocytes and their myelin, impairs axonal function.[7] However, compared to investigations conducted in the area of neuroprotection, studies to reduce oligodendrocyte damage and to regenerate myelinating oligodendrocytes are few after stroke and TBI, which has impeded development of effective therapy for stroke and TBI.[1,8]

Emerging data indicate that in the adult rodent brain, new oligodendrocytes are generated to myelinate the previously unmyelinated axons in the cortical grey matter and subcortical white matter.[8-11] In addition to ensheathment of axons, which facilitates electrical conduction, oligodendrocytes in the adult brain contribute to neural plasticity and circuitry function.[8-11] New oligodendrocytes derived from non-myelinating oligodendrocyte progenitor cells (OPCs) are required to form myelin sheaths for sprouting axons during brain repair processes after brain injury, because mature oligodendrocytes do not proliferate in the adult brain and injured oligodendrocytes no longer form new myelin sheets.[7,12-16] Brain injury induces OPC proliferation, leading to a substantial increase in the number of OPCs. However, in the injured brain, OPCs do not effectively differentiate into myelinating oligodendrocytes.[8] Thus, it is imperative to elucidate the pathophysiology of white matter damage after stroke and TBI in order to develop therapies designed specifically to reduce oligodendrocyte damage and to enhance remyelination.

In light of the failures of neuroprotective therapies in clinical trials, promising new concepts suggest that therapies for brain injury should target the neurovascular unit.[17]

The neurovascular unit comprises of cerebral endothelial cells, astrocytes, neurons, and oligodendrocytes.[17,18] In this article, we will briefly review the processes of oligodendrogenesis in the adult rodent brain under normal and injured conditions, and experimental therapies targeting the neurovascular unit that reduce oligodendrocyte damage and amplify endogenous oligodendrogenesis after stroke and TBI.

AFTER STROKE AND TBI

Acute Oligodendrocyte Damage

OPCs comprise 3–9% of the total cell number in the adult CNS and are the majority of proliferating cells.[9,15,19] OPCs are locally present in the *corpus callosum*, the striatum, and the cortex, and are derived from neural progenitor cells in the subventricular zone (SVZ) of the lateral ventricle.[13,20-25] In the adult brain, OPCs continuously differentiate into mature oligodendrocytes to myelinate the previously unmyelinated axons throughout the grey and white matter.[7,9-11,15] Recent studies show that in addition to facilitating salutatory conduction, myelination in the adult brain contributes to maintaining axonal integrity, neural plasticity, and circuitry function.[8-11] For example, myelinating oligodendrocytes offset metabolic stress on neurons by providing trophic support to axons.[8,26]

Mature oligodendrocytes are acutely vulnerable to stroke, and damage of mature oligodendrocytes leads to the loss of myelin and axons.[1,6] However, there is a paucity of studies which characterise acute oligodendrocyte damage after TBI, although traumatic axonal injury has been intensively investigated.[3,27,28] Loss of myelinating oligodendrocytes exacerbates traumatic axonal injury, because myelinated axons are less vulnerable to damage compared to non-myelinated axons, following fluid percussion injury in the rat.[29] Injured oligodendrocytes no longer form new myelin sheets, and remyelination requires generation of new oligodendrocytes.[7,12-16] Thus, in addition to the neuroprotection, therapeutic approaches designed to reduce acute white matter damage may also require minimising mature oligodendrocyte injury. Mechanisms of oligodendrocyte injury include oxidative stress, excitotoxicity, proinflammatory cytokines, among others.[1,15] Clinical trials show that none of the neuroprotective drugs achieve clinical benefit for treatment of acute stroke and TBI, although neuroprotection has been demonstrated in experimental stroke and TBI.[3,4,30-32]

Stroke and TBI injure all brain cells, and a new integrative approach for treatment of stroke and TBI is emerging to restore the normal function of the neurovascular unit.[33,34] Treatment of acute stroke requires rapid restitution of cerebral blood flow (CBF) in the ischaemic cerebral microvascular bed, to preserve blood brain barrier (BBB) integrity, and to minimise ischaemic cell death.[32,35,36] Preclinical data support the concept of new therapies to target the neurovascular unit. For example, tissue plasminogen activator (tPA) is the only Food and Drug Administration (FDA) approved treatment for acute stroke (within 4.5 hours).[32,37] In addition to clot lysis, tPA induces brain haemorrhage and neurotoxicity, which limit its usage to a small minority of patients with acute stroke.[18,32] Experimental studies indicate that combination of tPA with neuroprotective agents or matrix metalloproteinase (MMP) inhibitors, substantially reduce the deleterious effects of tPA on disruption of the BBB and ischaemic cell damage.[18,38] Neuroprotective agents, or other agents that are to be used for the adjuvant treatment with thrombolysis, need to be safe without exacerbating brain injury, especially, brain haemorrhage.

Clinical data are emerging to examine the safety and efficacy of neuroprotective agents in conjunction with thrombolysis. Cerebrolysin®, a mixture of neurotrophic peptides, had a favourable outcome trend in patients with severe stroke when it was administered within 12 hours of the onset of stroke.[39] A recently published pilot clinical trial of combined treatment with tPA and Cerebrolysin® in acute ischaemic stroke including 119 patients with acute hemispheric stroke, has shown that this combination therapy is safe when tPA was administered within 3 hours of the onset of stroke, and Cerebrolysin® was given 1 hour after tPA treatment and subsequently daily for 10 consecutive days[40] [Combined Treatment With Alteplase (Rt-PA) and Cerebrolysin® in Acute Ischaemic Hemispheric Stroke (CERE-LYSE-1), www.clinicaltrials.gov, NCT00840671]. In addition, a clinical Phase III trial, Efficacy Study of Combined Treatment With Uric Acid and rtPA in Acute Ischaemic Stroke (Urico-Ictus, www.clinicaltrials.gov, NCT00860366), is currently underway to determine whether a combination therapy of uric acid and tPA is superior to a monotherapy of tPA

in patients with acute ischaemic stroke within 4.5 hours of symptom onset.[41,42] Uric acid is an endogenous product derived from the metabolism of purines and exerts neuroprotection by its antioxidant capacity.[41]

Another drug, a postsynaptic density-95 (PSD-95) protein inhibitor (NA-1), has marked potential for the combination therapy for patients with acute ischaemic stroke.[42] NA-1 substantially reduces ischaemic neuronal damage in rodent and primate models of stroke.[43,44] A published Phase II, randomised, double-blind, placebo-controlled trial showed that treatment of patients who underwent endovascular brain aneurysm repair, with NA-1 at the completion of aneurysm repair procedures, sustained fewer ischaemic infarcts than patients in the placebo group, as measured by diffusion-weighted MRI and fluid-attenuated inversion recovery MRI of the ischaemic lesion (Evaluating Neuroprotection in Aneurysm Coiling Therapy [ENACT] trial, www.clinicaltrials.gov, NCT00728182).[42,45] Although the effect of these combination therapies on oligodendrocyte injury has not been reported, one may expect that the integrative approach for treatment of acute brain injury may reduce oligodendrocyte damage.

Oligodendrogenesis During Brain Repair

Stroke and TBI are associated with chronically progressive cognitive impairment.[3,46-49] Myelination is essential for maintenance of the axon.[50,52] Failure of remyelination of axons after stroke and TBI could lead to axonal degeneration, and consequently, to cognitive impairment.[3,10,52,53] Remyelination involves oligodendrogenesis, during which new myelinating oligodendrocytes are generated by differentiated OPCs localised to the *corpus callosum* or derived from SVZ neural stem cells.[7,8,12-16] Loss of mature oligodendrocytes provokes remyelination.[50,54] Studies in the rodent indicated that stroke and TBI trigger a substantial increase in OPCs generated by actively proliferating OPCs not only in young but also in aged animals.[55-57] These OPCs are recruited to the injured tissue region and later some OPCs differentiate into myelinating oligodendrocytes, where sprouting axons are present.[12,55,56,58] However, endogenous oligodendrogenesis in response to stroke and TBI is limited.

The presence of inhibitory molecules predominantly blocks OPC differentiation into mature myelinating oligodendrocytes, which limits remyelination processes.[8,52] Treatment of stroke or TBI with mesenchymal stromal cells (MSCs) suppressed the expression of Nogo, an endogenous inhibitor of myelination, and was associated with substantial increases in mature oligodendrocytes in the peri-infarct striatum and *corpus callosum,* and with improvement of neurological outcome in the rodent 4 months after stroke.[34,59-65] These data suggest that the blockage of inhibitory molecules may enhance remyelination in the injured brain. Currently, there is a clinical Phase I safety trial to block a potent oligodendrocyte differentiation inhibitor, the LRR and Ig domain–containing Nogo receptor–interacting protein (LINGO-1), in multiple sclerosis (Safety Study of BIIB033 in Subjects With Multiple Sclerosis, www.clinicaltrials.gov, NCT01244139).[66,67] However, the relevance of LINGO-1 antagonist to enhance remyelination in the setting of stroke and TBI remains to be determined.

In addition to targeting oligodendrocyte differentiation inhibitors, preclinical studies show that therapies targeting the neurovascular unit increase endogenous oligodendrogenesis and axonal outgrowth after stroke and TBI.[34,55,62,66-68] Oligodendrogenesis couples with angiogenesis in the injured brain during the brain repair process.[34,69] *In vitro* studies show that cerebral endothelial cells may promote the proliferation of OPCs through the release of trophic factors, such as brain derived neurotrophic factor (BDNF) and basic fibroblast growth factor (bFGF).[69] Compounds that induce angiogenesis enhance the generation of oligodendrocytes. For example, EPO, in addition to regulating angiogenesis, promotes OPC differentiation into mature oligodendrocytes through interaction with its receptor EPOR.[70-74] Treatment of stroke with recombinant human EPO (rhEPO) induced sustained OPC proliferation and substantially amplified myelinating oligodendrocytes and increased myelinated axons in peri-infarct white matter, which was associated with improvement of neurological outcome.[66,75] Aging reduces oligodendrocytes in rodent and human brains.[54,76-78] Sildenafil, a potent phosphodiesterase type 5 (PDE5) inhibitor, induced cerebral angiogenesis after ischaemic stroke.[79,80] Moreover, the treatment of aged ischaemic mice with sildenafil markedly augmented new oligodendrocytes in peri-infarct *corpus callosum* and striatum.[55] These data suggest that even in aged animals, oligodendrogenic

potential is present in response to stroke and the treatment.

The Sonic hedgehog (Shh) signalling pathway regulates oligodendrogenesis and mediates OPC differentiation in the adult rodent brain.[81-85] Blocking of the Shh signalling pathway leads to a decrease of OPC proliferation and differentiation in a model of focal demyelination induced by lysolecithin in the *corpus callosum* of adult mice.[81] Stroke upregulates the Shh signal that is associated with the generation of new oligodendrocytes.[73,86] Compounds that amplify the Shh signals enhance oligodendrogenesis.[81,87] For example, treatment of stroke with Cerebrolysin® amplified the generation of OPCs and mature oligodendrocytes in white matter of the peri-infarct region.[87,88] Inhibition of the Shh signalling pathway abolished the therapeutic effect of Cerebrolysin® on brain remodelling, including oligodendrogenesis.[87] *In vitro* studies show that Cerebrolysin® induced upregulation of Shh expression in cerebral endothelial cells.[87] In addition to its action on oligodendrogenesis, the Shh pathway plays an important role in maintenance of BBB integrity.[89] Inactivation of the Shh pathway led to exacerbation of BBB leakage and demyelination in experimental autoimmune encephalomyelitis, a model of multiple sclerosis.[89] Collectively, these data suggest that amplification of the Shh signalling pathway has therapeutic potential for the enhancement of myelination after stroke and TBI.

CONCLUSION

Stroke and TBI induce demyelination which comprises of the functional unit of axon and oligodendrocyte. Remyelination involves oligodendrogenesis. Promising data, mainly derived from animal models of stroke and TBI, call for an integrative approach for minimising oligodendrocyte damage and amplifying oligodendrogenesis. Although the relevance of this approach in patients remains to be established, pilot clinical trials suggest that an integrative approach is achievable.

REFERENCES

1. Dewar D et al. Oligodendrocytes and ischemic brain injury. J Cereb Blood Flow Metab. 2003;23:263-74.
2. Cui X et al. Chemokine, vascular and therapeutic effects of combination Simvastatin and BMSC treatment of stroke. Neurobiol Dis. 2009;36:35-41.
3. Johnson VE et al. Axonal pathology in traumatic brain injury. Exp Neurol. 2013;246:35-43.
4. Smith DH et al. Therapy development for diffuse axonal injury. J Neurotrauma. 2013;30:307-23.
5. Demaerschalk BM et al. US cost burden of ischemic stroke: a systematic literature review. Am J Manag Care. 2010;16:525-33.
6. Pantoni L et al. Cerebral white matter is highly vulnerable to ischemia. Stroke. 1996;27:1641-6; discussion 1647.
7. Franklin RJ. Why does remyelination fail in multiple sclerosis? Nat Rev Neurosci. 2002;3:705-14.
8. Fancy SP et al. Myelin regeneration: a recapitulation of development? Annu Rev Neurosci. 2011;34:21-43.
9. Young KM et al. Oligodendrocyte dynamics in the healthy adult CNS: evidence for myelin remodeling. Neuron. 2013;77:873-85.
10. Fields RD. White matter in learning, cognition and psychiatric disorders. Trends Neurosci. 2008;31:361-70.
11. Zatorre RJ et al. Plasticity in grey and white: neuroimaging changes in brain structure during learning. Nat Neurosci. 2012;15:528-36.
12. Gregersen R et al. Focal cerebral ischemia induces increased myelin basic protein and growth-associated protein-43 gene transcription in peri-infarct areas in the rat brain. Exp Brain Res. 2001;138:384-92.
13. Menn B et al. Origin of oligodendrocytes in the subventricular zone of the adult brain. J Neurosci. 2006;26:7907-18.
14. Gensert JM et al. Endogenous progenitors remyelinate demyelinated axons in the adult CNS. Neuron. 1997;19:197-203.
15. McTigue DM et al. The life, death, and replacement of oligodendrocytes in the adult CNS. J Neurochem. 2008;107:1-19.
16. Franklin RJ et al. Remyelination in the CNS: from biology to therapy. Nat Rev Neurosci. 2008;9:839-55.
17. Silver B et al. Sildenafil treatment of subacute ischemic stroke: a safety study at 25-mg daily for 2 weeks. J Stroke Cerebrovasc Dis. 2009;18:381-3.
18. Lo EH et al. tPA and proteolysis in the neurovascular unit. Stroke. 2004;35:354-6.
19. Dawson MR et al. Ng2-expressing glial progenitor cells: an abundant and widespread population of cycling cells in the adult rat CNS. Mol Cell Neurosci. 2003;24:476-88.
20. Roy NS et al. Identification, isolation, and promoter-defined separation of mitotic oligodendrocyte progenitor cells from the adult human subcortical white matter. J Neurosci. 1999;19:9986-95.
21. Fancy SP et al. Increased expression of nkx2.2 and olig2 identifies reactive oligodendrocyte progenitor cells responding to demyelination in the adult CNS. Mol Cell Neurosci. 2004;27:247-54.
22. Nait-Oumesmar B et al. Progenitor cells of the adult mouse subventricular zone proliferate, migrate and differentiate into oligodendrocytes after demyelination. Eur J Neurosci. 1999;11:4357-66.
23. Picard-Riera N et al. Experimental autoimmune encephalomyelitis mobilizes neural progenitors from the subventricular zone to undergo oligodendrogenesis in adult mice. Proc Natl Acad Sci U S A. 2002;99:13211-6.
24. Ortega F et al. Oligodendrogliogenic and neurogenic adult subependymal zone neural stem cells constitute distinct lineages and exhibit differential responsiveness to Wnt signalling. Nat Cell Biol. 2013;15:602-13.

25. Rafalski VA et al. Expansion of oligodendrocyte progenitor cells following SIRT1 inactivation in the adult brain. Nat Cell Biol. 2013;15:614-24.

26. Nave KA. Myelination and the trophic support of long axons. Nat Rev Neurosci. 2010;11:275-83.

27. Flygt J et al. Myelin loss and oligodendrocyte pathology in white matter tracts following traumatic brain injury in the rat. Eur J Neurosci. 2013;38:2153-65.

28. Shaw K et al. TUNEL-positive staining in white and grey matter after fatal head injury in man. Clin Neuropathol. 2001;20:106-12.

29. Reeves TM et al. Myelinated and unmyelinated axons of the corpus callosum differ in vulnerability and functional recovery following traumatic brain injury. Exp Neurol. 2005;196:126-37.

30. Fisher M et al. Advanced imaging to extend the therapeutic time window of acute ischemic stroke. Ann Neurol. 2013;73:4-9.

31. Ginsberg MD. Current status of neuroprotection for cerebral ischemia: synoptic overview. Stroke. 2009;40:S111-4.

32. Zivin JA. Acute stroke therapy with tissue plasminogen activator (tPA) since it was approved by the U.S. Food and Drug Administration (FDA). Ann Neurol. 2009;66:6-10.

33. Lo EH et al. Mechanisms, challenges and opportunities in stroke. Nat Rev Neurosci. 2003;4:399-415.

34. Zhang ZG et al. Neurorestorative therapies for stroke: underlying mechanisms and translation to the clinic. Lancet Neurol. 2009;8:491-500.

35. Feuerstein GZ et al. Translational medicine for stroke drug discovery: the pharmaceutical industry perspective. Stroke. 2009;40:S121-5.

36. Chavez JC et al. Pharmacologic interventions for stroke: looking beyond the thrombolysis time window into the penumbra with biomarkers, not a stopwatch. Stroke. 2009;40:e558-63.

37. Bluhmki E et al. Stroke treatment with alteplase given 3.0-4.5 h after onset of acute ischaemic stroke (ECASS III): additional outcomes and subgroup analysis of a randomised controlled trial. Lancet Neurol. 2009;8:1095-102.

38. Sumii T et al. Involvement of matrix metalloproteinase in thrombolysis-associated hemorrhagic transformation after embolic focal ischemia in rats. Stroke. 2002;33:831-6.

39. Heiss WD et al. Cerebrolysin in patients with acute ischemic stroke in Asia: results of a double-blind, placebo-controlled randomized trial. Stroke. 2012;43:630-6.

40. Lang W et al. A prospective, randomized, placebo-controlled, double-blind trial about safety and efficacy of combined treatment with alteplase (rt-PA) and Cerebrolysin in acute ischaemic hemispheric stroke. Int J Stroke. 2013;8:95-104.

41. Amaro S et al. The URICO-ICTUS study, a phase 3 study of combined treatment with uric acid and rtpa administered intravenously in acute ischaemic stroke patients within the first 4.5 h of onset of symptoms. Int J Stroke. 2010;5:325-8.

42. Tymianski M. Novel approaches to neuroprotection trials in acute ischemic stroke. Stroke. 2013;44:2942-50.

43. Cook DJ et al. A translational paradigm for the preclinical evaluation of the stroke neuroprotectant Tat-NR2B9c in gyrencephalic nonhuman primates. Sci Transl Med. 2012;4:154ra133.

44. Cook DJ et al. Treatment of stroke with a PSD-95 inhibitor in the gyrencephalic primate brain. Nature. 2012;483:213-7.

45. Hill MD et al. Safety and efficacy of NA-1 in patients with iatrogenic stroke after endovascular aneurysm repair (ENACT): a phase 2, randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2012;11:942-50.

46. Moskowitz MA et al. The science of stroke: mechanisms in search of treatments. Neuron. 2010;67:181-98.

47. Nemetz PN et al. Traumatic brain injury and time to onset of Alzheimer's disease: a population-based study. Am J Epidemiol. 1999;149:32-40.

48. Gregoire SM et al. Cerebral microbleeds and long-term cognitive outcome: Longitudinal cohort study of stroke clinic patients. Cerebrovasc Dis. 2012;33:430-5.

49. Jokinen H et al. Longitudinal cognitive decline in subcortical ischemic vascular disease--the LADIS study. Cerebrovasc Dis. 2009;27:384-91.

50. Nave KA et al. Axon-glial signaling and the glial support of axon function. Annu Rev Neurosci. 2008;31:535-61.

51. Funfschilling U et al. Glycolytic oligodendrocytes maintain myelin and long-term axonal integrity. Nature. 2012;485:517-21.

52. Kremer D et al. The complex world of oligodendroglial differentiation inhibitors. Ann Neurol. 2011;69:602-18.

53. Lee Y et al. Oligodendroglia metabolically support axons and contribute to neurodegeneration. Nature. 2012;487:443-8.

54. Sim FJ et al. The age-related decrease in CNS remyelination efficiency is attributable to an impairment of both oligodendrocyte progenitor recruitment and differentiation. J Neurosci. 2002;22:2451-9.

55. Zhang RL et al. Sildenafil enhances neurogenesis and oligodendrogenesis in ischemic brain of middle-aged mouse. PLoS One. 2012;7:e48141.

56. Zhang RL et al. Ascl1 lineage cells contribute to ischemia-induced neurogenesis and oligodendrogenesis. J Cereb Blood Flow Metab. 2011;31:614-25.

57. Mandai K et al. Ischemic damage and subsequent proliferation of oligodendrocytes in focal cerebral ischemia. Neuroscience. 1997;77:849-61.

58. Ueno Y et al. Axonal outgrowth and dendritic plasticity in the cortical peri-infarct area after experimental stroke. Stroke. 2012;43:2221-8.

59. Liu Z et al. Bone marrow stromal cells enhance inter- and intracortical axonal connections after ischemic stroke in adult rats. J Cereb Blood Flow Metab. 2010;30:1288-95.

60. Chen J et al. Therapeutic benefit of intravenous administration of bone marrow stromal cells after cerebral ischemia in rats. Stroke. 2001;32:1005-11.

61. Lu D et al. Intraarterial administration of marrow stromal cells in a rat model of traumatic brain injury. J Neurotrauma. 2001;18:813-9.

62. Li Y et al. Gliosis and brain remodeling after treatment of stroke in rats with marrow stromal cells. Glia. 2005;49:407-17.

63. Shen LH et al. Intracarotid transplantation of bone marrow stromal cells increases axon-myelin remodeling after stroke. Neuroscience. 2006;137:393-9.

64. Shen LH et al. Down-regulation of neurocan expression in reactive astrocytes promotes axonal regeneration and facilitates the neurorestorative effects of bone marrow stromal cells in the ischemic rat brain. Glia. 2008;56:1747-54.

65. Chong SY et al. Neurite outgrowth inhibitor nogo-a establishes spatial segregation and extent of oligodendrocyte myelination. Proc Natl Acad Sci U S A. 2012;109:1299-304.

66. Zhang L et al. Erythropoietin amplifies stroke-induced oligodendrogenesis in the rat. PLoS One. 2010;5:e11016.

67. Morris DC et al. Thymosin beta4 improves functional neurological outcome in a rat model of embolic stroke. Neuroscience. 2010;169:674-82.

68. Xiong Y et al. Neuroprotective and neurorestorative effects of thymosin beta4 treatment initiated 6 hours after traumatic brain injury in rats. J Neurosurg. 2012;116:1081-92.

69. Pham LD et al. Crosstalk between oligodendrocytes and cerebral endothelium contributes to vascular remodeling after white matter injury. Glia. 2012;60:875-81.

70. Tsai PT et al. A critical role of

erythropoietin receptor in neurogenesis and post-stroke recovery. J Neurosci. 2006;26:1269-74.

71. Chen ZY et al. Endogenous erythropoietin signaling is required for normal neural progenitor cell proliferation. J Biol Chem. 2007;282:25875-83.

72. Shingo T et al. Erythropoietin regulates the in vitro and in vivo production of neuronal progenitors by mammalian forebrain neural stem cells. J Neurosci. 2001;21:9733-43.

73. Wang L et al. The Sonic hedgehog pathway mediates carbamylated erythropoietin-enhanced proliferation and differentiation of adult neural progenitor cells. J Biol Chem. 2007;282:32462-70.

74. Cervellini I et al. Erythropoietin (EPO) increases myelin gene expression in CG4 oligodendrocyte cells through the classical EPO receptor. Mol Med. 2013;19:223-9.

75. Jiang Q et al. Mri detects white matter reorganization after neural progenitor cell treatment of stroke. Neuroimage. 2006;32:1080-9.

76. Shen S et al. Epigenetic memory loss in aging oligodendrocytes in the corpus callosum. Neurobiol Aging. 2008;29:452-63.

77. Pelvig DP et al. Neocortical glial cell numbers in human brains. Neurobiol Aging. 2008;29:1754-62.

78. Shen S et al. Age-dependent epigenetic control of differentiation inhibitors is critical for remyelination efficiency. Nat Neurosci. 2008;11:1024-34.

79. Zhang R et al. Nitric oxide enhances angiogenesis via the synthesis of vascular endothelial growth factor and cGMP after stroke in the rat. Circ Res. 2003;92:308-13.

80. Zhang RL et al. Targeting nitric oxide in the subacute restorative treatment of ischemic stroke. Expert Opin Investig Drugs. 2013;22:843-51.

81. Ferent J et al. Sonic hedgehog signaling is a positive oligodendrocyte regulator during demyelination. J Neurosci. 2013;33:1759-72.

82. Ligon KL et al. The oligodendroglial lineage marker OLIG2 is universally expressed in diffuse gliomas. J Neuropathol Exp Neurol. 2004;63:499-509.

83. Arnett HA et al. bHLH transcription factor Olig1 is required to repair demyelinated lesions in the CNS. Science. 2004;306:2111-5.

84. Ligon KL et al. Olig gene function in CNS development and disease. Glia. 2006;54:1-10.

85. de Castro F et al . Regulation of oligodendrocyte precursor migration during development, in adulthood and in pathology. Cell Mol Life Sci. 2013;70:4355-68.

86. Liu XS et al. MicroRNA-17-92 cluster mediates the proliferation and survival of neural progenitor cells after stroke. J Biol Chem. 2013;288:12478-88.

87. Zhang L et al. Sonic hedgehog signaling pathway mediates cerebrolysin-improved neurological function after stroke. Stroke. 2013;44:1965-72.

88. Zhang C et al. Cerebrolysin enhances neurogenesis in the ischemic brain and improves functional outcome after stroke. J Neurosci Res. 2010;88:3275-81.

89. Alvarez JI et al. The Hedgehog pathway promotes blood-brain barrier integrity and CNS immune quiescence. Science. 2011;334:1727-31.