HHS Public Access

Author manuscript

Trends Mol Med. Author manuscript; available in PMC 2016 September 01.

Published in final edited form as:

Trends Mol Med. 2015 September ; 21(9): 543–548. doi:10.1016/j.molmed.2015.07.005.

Promoting brain remodeling to aid in stroke recovery

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

[1]Department of Neurology, Henry Ford Hospital, Detroit, Michigan, U.S.A

[2]Department of Physics, Oakland University, Rochester, Michigan, U.S.A

Abstract

Endogenous brain repair after stroke involves a set of highly interactive processes, such as angiogenesis, neurogenesis, oligodendrogenesis, synaptogenesis and axonal outgrowth, which together orchestrate neurological recovery. During the past several years, there have been advances in our understanding of miRNAs and histone deacetylases (HDACs) in brain repair processes after stroke. Emerging data indicate the important role of exosomes for intercellular communication in promoting coupled brain remodeling processes. These advances will likely have a major impact on development of restorative therapies for ischemic brain repair, consequently leading to improvement of neurological function. In this review, we provide an update on our current understanding of cellular and molecular mechanisms of miRNAs, exosomes, and HDACs in brain restorative processes after stroke.

Keywords

Neurorestorative therapy; Stroke recovery; miRNAs; Exosomes

Brain remodeling during stroke recovery

Stroke is a major cause of morbidity around the world, although stroke mortality has been declining [1]. Treatment of stroke has traditionally focused on reducing ischemic cell death. Although this approach has been validated in experimental stroke, clinical trials have shown that none of neuroprotective drugs tested achieve clinical benefit for treatment of acute stroke [2]. Tissue plasminogen activator (tPA) is the only FDA approved treatment for patients with ischemic stroke (see Glossary) onset within 4.5 hours [3,4]. The failure of the clinical trials provides insight that neuroprotective therapies for acute stroke need to target restoration of neurovascular function by rapidly reestablishing cerebral blood flow (CBF) in the ischemic cerebral microvascular bed, preserving vascular integrity, and minimizing brain hemorrhage and parenchymal cell death [2]. This concept has been supported by the three

Corresponding author: Zheng Gang Zhang (zhazh@neuro.hfh.edu).

recently successful randomized clinical trials showing that endovascular thrombectomy with or without tPA is effective for ischemic stroke patients within 12 hours after stroke onset by inducing rapid recanalization and increasing tissue reperfusion [5–7]. However, there is a paucity of therapeutic options for enhancement of stroke recovery. Most patients, even with effective thrombolysis will suffer neurological deficits, although limited spontaneous functional improvement has been observed during stroke recovery [8]. Endogenous brain repair after stroke involves a set of highly interactive processes, such as angiogenesis, neurogenesis, oligodendrogenesis, synaptogenesis and axonal outgrowth, which in-concert orchestrate neurological recovery [9,10]. MiRNAs (see Glossary), short noncoding RNA molecules of 20 to 25 nucleotides, are involved in physiological and pathophysiological functional regulation by decreasing gene expression through mRNA destabilization and/or translational repression [11]. miRNA-target interactions are cell type dependent [12]. During the past several years, there have been advances in our understanding of cellular levels of miRNAs in brain repair processes after stroke. Intercellular communication of miRNAs via exosomes (see Glossary), small lipid microvesicles, to promote brain repair has been demonstrated [10,13,14]. In addition, studies have shown potential roles of individual histone deacetylases (HDACs) (see Glossary) in stroke-induced oligodendrogenesis and axonal remodeling, as well as an interplay between HDACs and miRNAs [15]. These advances will likely have a major impact on development of restorative therapies for ischemic brain repair, consequently leading to improvement of neurological function. In this review, we provide an update on our current understanding of cellular and molecular mechanisms of miRNAs, exosomes, and HDACs in neurovascular remodeling processes after stroke.

Cerebral angiogenesis and miRNAs

Induction of angiogenesis couples to other brain remodeling events post stroke and subsequently leads to improvement of functional outcome. Although the role of miRNAs in mediating angiogenesis has been extensively studied, few studies have investigated how miRNAs in cerebral endothelial cells regulate stroke-induced angiogenesis. Rodent and human cerebral endothelial cells express abundant miRNAs including angiogenesis-regulatory miRNAs, also termed as AngiomiRs [16,17]. Overexpression of miR-210 in the adult non-ischemic mouse brain induced angiogenesis which was associated with increased vascular endothelial growth factor (VEGF) expression [18]. Stroke substantially altered endothelial miRNA profiles in a rat model of middle cerebral artery occlusion [19]. Among them, expression of miR-139 and miR-335 was downregulated by approximately 60% and 90%, respectively, compared to expression in non-ischemic endothelial cells. Reduction of miR-139 and miR-335 was closely associated with stroke-induced angiogenesis. *In vitro*, down- and up-regulation of miR-139 and miR-335 in cerebral endothelial cells promoted and inhibited, respectively, angiogenesis assessed by a capillary tube formation method via directly targeting the serine/threonine protein kinase paralogs Rock1 and Rock2 [19]. In addition, study in the mouse model of focal cerebral ischemia showed upregulation of miR-15a in cerebral vessels in the peri-infarct region seven days after stroke [17]. Overexpression of miR-15a in endothelial cells led to reduction of stroke-induced angiogenesis [17]. miR-15a inhibited fibroblast growth factor 2 (FGF2) and VEGF in

endothelial cells [17]. Collectively, these studies highlight the important role of endothelial miRNAs as promoting and suppressing stroke-induced angiogenesis.

Adult neurogenesis and miRNAs

The adult rodent brain contains neural stem cells at least in the two regions, the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone of the dentate gyrus [20,21]. Focal cerebral ischemia mainly increases neurogenesis in the SVZ, and newly generated neuroblasts migrate from the SVZ to the ischemic boundary regions [22]. Stroke induced neurogenesis has also been reported in humans [23]. The effect of neuroblasts on the ischemic brain extends beyond the replacement of damaged neurons. Ablation of stroke-induced neuroblasts in transgenic mice exacerbates ischemic damage and worsens neurological outcome during stroke recovery [24], indicating that newly generated neuroblasts are involved in the brain repair process.

MiRNAs play an important role in the regulation of adult neurogenesis [25]. Emerging experimental data show that stroke robustly altered miRNA profiles in adult SVZ neural progenitor cells [25]. Bioinformatics analysis revealed that stroke-altered miRNAs selectively affected several signaling pathways including Notch (see Glossary) and sonic hedgehog (Shh)[22]. One of downregulated miRNAs in the neural progenitor cells affected by stroke was miR-124a, which regulates neuronal differentiation in adult neural stem cells by targeting the SRY-box transcription factor Sox9 under physiological conditions. After stroke, downregulation of miR-124a dramatically increased neural progenitor cell proliferation, whereas upregulation of miR-124a promoted neuronal differentiation and blocked proliferation. The effect of miR-124a on progenitor cell proliferation and differentiation was mediated via targeting Jagged-1 (JAG1) which is a ligand of the Notch receptor [25]. The Notch signaling pathway plays a pivotal role in maintaining the neural stem cell pool [26]. In the ischemic brain, activation of the Notch pathway by stroke increases neural progenitor cell proliferation, whereas blockage of the Notch pathway abolishes stroke-increased progenitor cell proliferation [27]. Collectively, these data suggest that miR-124a in neural progenitor cells mediates adult neurogenesis either by targeting SOX9 or the Notch signaling pathway under non-ischemic and ischemic conditions.

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) and is transcribed as a single polycistronic unit [28]. Germline deletion of the miR17-92 cluster in humans causes microcephaly and skeletal abnormalities [29]. The miR17-92 cluster is robustly increased in SVZ neural progenitor cells after stroke, and this miR cluster regulates stroke-induced neurogenesis by enhancing progenitor cell proliferation. [25,30]. Phosphatase and tensin homolog deleted on chromosome 10 (PTEN) is one of the validated genes targeted by the miR17-92 cluster, and is known to negatively regulate embryonic neural stem cell proliferation and survival [31–37]. Thus, suppression of PTEN by the cluster may contribute to the miR-17-92 cluster-augmented proliferation of neural progenitor cells. Studies in cultured SVZ neural progenitor cells and in ischemic animals showed that activation of the Shh signaling pathway in these progenitor cells triggers stroke-upregulated miR-17-92 cluster [30]. Attenuation of endogenous Shh by siRNA and addition of exogenous Shh down-and up-

regulated the miR17-92 cluster expression in cultured SVZ neural progenitor cells, respectively [30]. Blockage of the Shh pathway in ischemic animals suppressed the ischemia-upregulated miR17-92 cluster expression and reduced neural progenitor cell proliferation [30]. In contrast, administration of exogenous Shh to stroke animals further upregulated the miR17-92 cluster expression in SVZ neural progenitor cells [30]. The Shh pathway regulates neural progenitor cell proliferation and differentiation [38,39]. Thus, these data suggest that activation of the Shh pathway by stroke upregulates miR17-92 cluster expression that leads to neural progenitor cell proliferation via reduction of PTEN levels.

There are many other miRNAs altered by stroke in neural progenitor cells, such as Let-7 and miR-9, among others, which have been implicated in neural stem cell function by regulating bone morphogenetic protein (BMP) and Wnt signaling [25]. Future studies are warranted to determine the role of these miRNAs in mediating proliferation and differentiation of neural progenitor cells in stroke-induced neurogenesis.

Oligodendrogenesis, axonal remodeling and miRNAs

Oligodendrocyte progenitor cells (OPCs) are present in adult rodent brain and continuously differentiate into mature myelinating oligodendrocytes in the grey and white matter throughout life [40–42]. Mature oligodendrocytes are vulnerable to cerebral ischemia. Once they are injured, oligodendrocytes no longer generate myelin, leading to impairment of axonal function [43,44]. New oligodendrocytes are required to form myelin sheaths for sprouting axons during brain repair processes after stroke, because mature oligodendrocytes do not proliferate in the adult brain. However, during stroke recovery, newly generated oligodendrocytes have been detected in peri-infarct grey and white matter where sprouting axons are present [45–47]. These new oligodendrocytes result from differentiation of OPCs.

MiRNAs play a pivotal role in controlling processes of OPC generation and differentiation [48]. For example, during development overexpression of miR-219 and miR-338 in OPCs promotes oligodendrocyte differentiation by repressing targeting genes including platelet-derived growth factor receptor α (PDGFRα) and Sox6 [49,50]. Stroke substantially downregulated miR-9 and miR-200b expression in the corpus callosum, and time points of downregulation of these two miRNAs were closely associated with an increase of mature oligodendrocytes [51]. In cultured OPCs, elevation and reduction of miR-9 and miR-200 led to inhibition and promotion of OPC differentiation, respectively [51]. Both miRNAs suppressed the transcription factor serum response factor (SRF) [51]. These data suggest that miR-9 and miR-220 mediate the processes of OPC differentiation after stroke.

Limited axonal growth occurs in the peri-infarct region during stroke recovery [46,52]. Chondroitin sulfate proteoglycans (CSPGs) produced by reactive astrocytes inhibit axonal regrowth after stroke. For example, cortical injections of chondroitinase ABC (ChABC), a bacterial enzyme that degrades CSPG glycosylated sugar chain, promote motor function in a model of focal cortical ischemia by enhancing remodeling of the excitatory cortical circuitry [53]. Recent *in vitro* studies indicate that miRNAs in distal axons locally mediate axonal outgrowth by regulating their targeted proteins localized to the axon for the response of the growth cone to guidance cues [54]. Addition of CSPGs to cultured cortical neurons inhibited

axonal growth and substantially altered axonal miRNA profiles [55]. Elevation of axonal miR-29c by CSPGs reduced axonal integrin β1 protein and activated RhoA signals. In contrast, reduction of miR-29c levels in axons increased axonal integrin β1 (ITGB1) levels and inactivation of RhoA signals, leading to overcoming CSPG inhibition of axonal growth [55]. Moreover, elevation of the miR-17-92 cluster in axons of cortical neurons promoted axonal growth by suppressing axonal PTEN proteins and inactivation of mTOR signals [56]. Together, these data suggest that axonal miRNAs play an important role in mediating axonal growth.

Oligodendrogenesis, axonal remodeling and HDACs

HDACs are a large family of enzymes, divided into four major classes (I–IV), that regulate histone acetylation levels by catalyzing the removal of acetyl moieties from lysine residues in histone tails. Histone deacetylation consequently leads to compaction of chromatin and gene repression [57,58]. DNA methylation and histone deacetylation are involved in stroke recovery [59,60]. Emerging data show that different classes of HDACs and individual HDAC isoforms within the same class may play non-overlapping roles in stroke-induced oligodendrogenesis and axonal remodeling. During brain development, activity of HDAC classes I and II is essential for oligodendrocyte differentiation [61,62]. For example, inhibition of HDAC1 and HDAC2, class I HDACs, in oligodendrocyte lineage cells leads to reduction of OPCs and mature oligodendrocytes [62,63]. In adult brain, HDAC1 and HDAC2 are mainly localized to nuclei of OPCs under non-ischemic conditions [15]. Stroke increased nuclear HDAC 1 and HDAC2 proteins in OPCs, which were accompanied by reduction of the acetylation levels of histones H3 and H4 in OPCs, suggesting that nuclear HDAC1 and HDAC2 are active in OPCs [15]. Inhibition of HDAC activity by a pan HDAC inhibitor, valproic acid, significantly increased stroke-induced oligodendrogenesis and neurogenesis [64]. These data indicate that HDACs are involved oligodendrogenesis and neurogenesis in the ischemic brain, however, the role of HDACs 1 and 2 in oligodendrogenesis remains to be determined.

HDACs 4 and 5 are normally localized to the cytoplasm where they cannot directly access chromatin [65]. In response to external stimuli, they shuttle to the nucleus and regulate gene expression [65]. Stroke robustly induces neuronal nuclear shuttling of HDAC4 across all layers of the peri-infarct cortex during stroke recovery [66]. The nuclear shuttling of HDAC4 appears to be specific, because stroke does not induce nuclear shuttling of HDAC5, and nuclear shuttling of HDAC4 is not detected in astrocytes and oligodendrocytes. Neuronal nuclear shuttling of HDAC4 was positively and significantly correlated with increased dendritic and axonal densities, suggesting that the neuronal nuclear shuttling of HDAC4 is involved in the process of promoting neuronal remodeling [66]. These data also highlight the complexity of HDACs in brain remodeling after stroke, and the importance of developing therapies to specifically block and enhance individual HDACs for promoting brain repair after stroke.

HDACs also mediate angiogenesis. Inhibition of HDAC activity blocks tumor-induced angiogenesis [67]. Interestingly, the nuclear shuttling of HDAC5 in human umbilical vein endothelial cells (HUVACs) blocks in vitro angiogenesis by suppressing expression of

FGF2 and Slit2 genes [68], suggesting that HDAC5 is a repressor of angiogenesis. However, the role of individual HDACs in stroke-induced angiogenesis remains to be investigated.

Exosomes and brain remodeling

Exosomes are endosome-derived small membrane vesicles (~30–100 nm) and are released by cells in all living systems [69]. Exosomes play vital roles in intercellular communication by transferring contained proteomic and genomic materials, as well as proteins, mRNAs and miRNAs, between source and target cells [69]. Transferred biological materials are functional in target cells [69]. Thus, one would expect that exosomes released by ischemic brain and by cells remote from the stroke are likely involved in highly interwoven brain remodeling processes. Cell-based therapy, in particular bone marrow mesenchymal cells (MSCs), promotes brain remodeling and improves neurological outcome. MSC therapy is already in clinical trials for stroke (https://clinicaltrials.gov). Emerging data indicate that therapeutic benefits of MSCs on stroke and traumatic brain injury (TBI) recovery are at least in-part mediated by exosomes released from MSCs. For example, intravenous administration of exosomes derived from MSCs to rats subjected to middle cerebral artery occlusion or TBI substantially improved neurological function by promoting neurovascular remodeling during stroke recovery [13,70]. MiR-133b targets connective tissue growth factor (CTGF) and RhoA, that are known to suppress neurite growth [14]. Stroke significantly downregulated miR-133b in the brain, whereas administration of MSCs upregulated miR-133b in the ischemic brain [14]. Moreover, administration of MSCs with increased and reduced miR-133b to ischemic rats enhanced and inhibited neurite outgrowth, respectively. *In vitro* studies showed that ischemic brain tissue elevated miR-133b levels in MSC-released exosomes. In the brain, CTGF is mainly expressed by astrocytes [71]. The treatment of astrocytes with the exosomes containing high levels of miR-133b downregulated CTGF expression, while incubation of neurons with the exosomes reduced RhoA expression and promoted neurite outgrowth [72]. In addition to miR-133b, elevation of the miR17-92 cluster in MSC-exosomes promoted axonal growth of cultured embryonic cortical neurons by targeting the PTEN signaling pathway [56]. MSC-exosomes contain more than 700 miRNAs and the majority of them are bound to argonaute 2 (Ago2, Zhang *et el*., unpublished data), an important component of the RNA-induced silencing complex. Reduction of Ago2 in MSC-exosomes abolished exosome-enhanced axonal growth of cultured embryonic cortical neurons [73]. Moreover, internalization of the exosomes into the neurons appears to occur through endocytosis with target cell membranes, because the internalization is blocked by botulinum neurotoxin type A which inhibits neuronal cytosis (Zhang *et al*., unpublished data). Collectively, these data suggest that MSC-exosomes are a promising therapy for improvement of neurological outcome, and that delivered-miRNAs within the MSC-exosomes become functional in target brain cells and facilitate neurovascular remodeling in the ischemic brain.

In addition to miRNAs, exosomes also transfer proteins to target cells. For example, exosomes released by oligodendrocytes transfer proteolipid protein (PLP) and Sirtuin-2 (SIRT2) proteins into the neurons, leading to improvement of neuronal viability under conditions of cell stress[74]. Moreover, exosomes released by postnatal oligodendrocytes inhibit myelination by activating the Rho-ROCK-myosin signaling in target cells [75].

These emerging data highlight the important role of exosomes for intercellular communication in mediating interwoven brain remodeling processes, and the use of exosomes as vehicles to deliver special biological materials, in particular miRNAs, for amplifying brain restorative events, consequently leading to improved functional outcome.

Concluding remarks and future perspectives

Non-coding RNAs (including miRNAs), HDACs and exosomes are emerging as important players in mediating neurorestorative events after stroke and neural injury [22,59,60,72,76,77]. In addition to decreasing gene expression through mRNA destabilization and/or translational repression, miRNAs regulate transcription through epigenetic mechanisms and mediate exosome production [78,79]. Conversely, intercellular communication is mediated by exosome delivery of miRNAs and proteins to target cells. Investigating and elucidating the interplay among miRNAs, HDACs and exosomes that are involved in brain remodeling at the cellular level may lead to development of therapies for stroke and neural injury. However, current strategies for miRNA-targeting, HDAC inhibition, and exosome therapeutics are not cell-type specific, and cell-targeted delivery of these processes would augment their therapeutic potential. By fusing the neuron-specific RVG peptide to an exosomal membrane protein, Lamp2b, a recent study demonstrated that intravenous injection of these exosomes specifically targeted neurons, microglia and oligodendrocytes in the brain [80]. Furthermore, the neurorestorative process in the ischemic brain is regulated by multiple cellular pathways that act in concert. Engineering exosomes containing several miRNAs or proteins to simultaneously target multiple pathways could facilitate brain remodeling and improve neurological function after stroke, TBI, and possibly also neurodegenerative disease. Although there are multiple challenges in development of cell type specific miRNA-targeting, HDAC inhibition, and exosome therapeutics (Box 1), emerging data hold promise to bring these therapies to clinical fruition for stroke recovery.

Box 1

Outstanding questions

- What are the cellular signals by which the ischemic brain is able to affect the content and quantity of exosomes released by brain parenchymal cells and by remote organs?
- Which cell specific miRNAs and HDACs contribute to facilitate brain remodeling in the ischemic brain?
- Can we generate tailored exosomes to target specific brain cells?
- How do specific miRNAs, siRNAs, and/or proteins carried by exosomes affect profiles of endogenous genes and proteins in the brain?

Acknowledgments

Grant support: NIH, R01 NS 088656 (MC) and R01 NS079612 (ZG).

Glossary

Exosomes	endosome-derived small membrane extracellular vesicles (~30–100 nm) that participate in intercellular communication by transferring contained proteomic and genomic materials
HDACs	a class of enzymes that remove acetyl moieties from lysine residues in histone tails, leading to compaction of chromatin and gene repression
Ischemic stroke	an obstruction within a blood vessel supplying blood to the brain, which accounts for approximately 87 percent of strokes
miRNAs	a family of short noncoding RNA molecules of 20 to 25 nucleotides, decreasing gene expression through mRNA destabilization and/or translational repression
Notch signals	Notch receptors are transmembrane proteins activated by Delta and Jagged ligands that regulate neurogenesis

References

1. Lackland DT, Roccella EJ, Deutsch AF, Fornage M, George MG, et al. Factors influencing the decline in stroke mortality: a statement from the American Heart Association/American Stroke Association. Stroke. 2014; 45:315–353. [PubMed: 24309587]
2. Moskowitz MA, Lo EH, Iadecola C. The science of stroke: mechanisms in search of treatments. Neuron. 2010; 67:181–198. [PubMed: 20670828]
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. [PubMed: 7477192]
4. Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008; 359:1317–1329. [PubMed: 18815396]
5. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015; 372:1019–1030. [PubMed: 25671798]
6. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med. 2015; 372:1009–1018. [PubMed: 25671797]
7. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med. 2015; 372:11–20. [PubMed: 25517348]
8. Verheyden G, Nieuwboer A, De Wit L, Thijs V, Dobbelaere J, et al. Time course of trunk, arm, leg, and functional recovery after ischemic stroke. Neurorehabil Neural Repair. 2008; 22:173–179. [PubMed: 17876069]
9. Zhang ZG, Chopp M. Neurorestorative therapies for stroke: underlying mechanisms and translation to the clinic. Lancet Neurol. 2009; 8:491–500. [PubMed: 19375666]
10. Li Y, Liu Z, Xin H, Chopp M. The role of astrocytes in mediating exogenous cell-based restorative therapy for stroke. Glia. 2014; 62:1–16. [PubMed: 24272702]
11. Bartel DP. MicroRNAs: target recognition and regulatory functions. Cell. 2009; 136:215–233. [PubMed: 19167326]
12. Nam JW, Rissland OS, Koppstein D, Abreu-Goodger C, Jan CH, et al. Global analyses of the effect of different cellular contexts on microRNA targeting. Mol Cell. 2014; 53:1031–1043. [PubMed: 24631284]

13. Xin H, Li Y, Cui Y, Yang JJ, Zhang ZG, et al. Systemic administration of exosomes released from mesenchymal stromal cells promote functional recovery and neurovascular plasticity after stroke in rats. J Cereb Blood Flow Metab. 2013; 33:1711–1715. [PubMed: 23963371]
14. Xin H, Li Y, Buller B, Katakowski M, Zhang Y, et al. Exosome-mediated transfer of miR-133b from multipotent mesenchymal stromal cells to neural cells contributes to neurite outgrowth. Stem Cells. 2012; 30:1556–1564. [PubMed: 22605481]
15. Kassis H, Chopp M, Liu XS, Shehadah A, Roberts C, et al. Histone deacetylase expression in white matter oligodendrocytes after stroke. Neurochem Int. 2014; 77:17–23. [PubMed: 24657831]
16. Anand S. A brief primer on microRNAs and their roles in angiogenesis. Vasc Cell. 2013; 5:2. [PubMed: 23324117]
17. Yin KJ, Hamblin M, Chen YE. Angiogenesis-regulating microRNAs and Ischemic Stroke. Curr Vasc Pharmacol. 2015; 13:352–365. [PubMed: 26156265]
18. Zeng L, He X, Wang Y, Tang Y, Zheng C, et al. MicroRNA-210 overexpression induces angiogenesis and neurogenesis in the normal adult mouse brain. Gene Ther. 2014; 21:37–43. [PubMed: 24152581]
19. Teng H, Chopp M, Liu X, Wang X, Zhang Z. Stroke alters expression of miRNAs and ROCK signaling in cerebral endothelial cells. Neuroscience. 2013 2013 337.21/U6.
20. Alvarez-Buylla A, Herrera DG, Wichterle H. The subventricular zone: source of neuronal precursors for brain repair. Prog Brain Res. 2000; 127:1–11. [PubMed: 11142024]
21. Gage FH, Ray J, Fisher LJ. Isolation, characterization, and use of stem cells from the CNS. Annu Rev Neurosci. 1995; 18:159–192. [PubMed: 7605059]
22. Liu XS, Chopp M, Zhang RL, Zhang ZG. MicroRNAs in Cerebral Ischemia-Induced Neurogenesis. J Neuropathol Exp Neurol. 2013; 72:718–722. [PubMed: 23860031]
23. Huttner HB, Bergmann O, Salehpour M, Racz A, Tatarishvili J, et al. The age and genomic integrity of neurons after cortical stroke in humans. Nat Neurosci. 2014; 17:801–803. [PubMed: 24747576]
24. Wang X, Mao X, Xie L, Sun F, Greenberg DA, et al. Conditional depletion of neurogenesis inhibits long-term recovery after experimental stroke in mice. PLoS One. 2012; 7:e38932. [PubMed: 22723908]
25. Liu XS, Chopp M, Zhang RL, Tao T, Wang XL, 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. [PubMed: 21887253]
26. Gaiano NFG. The role of notch in promoting glial and neural stem cell fates. Annu Rev Neurosci. 2002; 25:471–490. [PubMed: 12052917]
27. Wang LCM, Zhang RL, Zhang L, Letourneau Y, Feng YF, Jiang A, Morris DC, Zhang ZG. The Notch pathway mediates expansion of a progenitor pool and neuronal differentiation in adult neural progenitor cells after stroke. Neuroscience. 2009; 158:1356–1363. [PubMed: 19059466]
28. Xiao C, Srinivasan L, Calado DP, Patterson HC, Zhang B, et al. Lymphoproliferative disease and autoimmunity in mice with increased miR-17-92 expression in lymphocytes. Nat Immunol. 2008; 9:405–414. [PubMed: 18327259]
29. de Pontual L, Yao E, Callier P, Faivre L, Drouin V, et al. Germline deletion of the miR-17 approximately 92 cluster causes skeletal and growth defects in humans. Nat Genet. 2011; 43:1026–1030. [PubMed: 21892160]
30. Liu XS, Chopp M, Wang XL, Zhang L, Hozeska-Solgot A, et al. MicroRNA-17–92 Cluster Mediates the Proliferation and Survival of Neural Progenitor Cells after Stroke. J Biol Chem. 2013; 288:12478–12488. [PubMed: 23511639]
31. Gregorian C, Nakashima J, Le Belle J, Ohab J, Kim R, et al. Pten deletion in adult neural stem/progenitor cells enhances constitutive neurogenesis. J Neurosci. 2009; 29:1874–1886. [PubMed: 19211894]
32. Groszer M, Erickson R, Scripture-Adams DD, Dougherty JD, Le Belle J, et al. PTEN negatively regulates neural stem cell self-renewal by modulating G0–G1 cell cycle entry. Proc Natl Acad Sci U S A. 2006; 103:111–116. [PubMed: 16373498]

33. Groszer M, Erickson R, Scripture-Adams DD, Lesche R, Trumpp A, et al. Negative regulation of neural stem/progenitor cell proliferation by the Pten tumor suppressor gene in vivo. Science. 2001; 294:2186–2189. [PubMed: 11691952]
34. Li L, Liu F, Ross AH. PTEN regulation of neural development and CNS stem cells. J Cell Biochem. 2003; 88:24–28. [PubMed: 12461771]
35. Li L, Liu F, Salmonsen RA, Turner TK, Litofsky NS, et al. PTEN in neural precursor cells: regulation of migration, apoptosis, and proliferation. Mol Cell Neurosci. 2002; 20:21–29. [PubMed: 12056837]
36. Otaegi G, Yusta-Boyo MJ, Vergano-Vera E, Mendez-Gomez HR, Carrera AC, et al. Modulation of the PI 3-kinase-Akt signalling pathway by IGF-I and PTEN regulates the differentiation of neural stem/precursor cells. J Cell Sci. 2006; 119:2739–2748. [PubMed: 16787946]
37. Zheng H, Ying H, Yan H, Kimmelman AC, Hiller DJ, et al. p53 and Pten control neural and glioma stem/progenitor cell renewal and differentiation. Nature. 2008; 455:1129–1133. [PubMed: 18948956]
38. Marti E, Bovolenta P. Sonic hedgehog in CNS development: one signal, multiple outputs. Trends Neurosci. 2002; 25:89–96. [PubMed: 11814561]
39. Wang L, Zhang ZG, Gregg SR, Zhang RL, Jiao Z, et al. The Sonic hedgehog pathway mediates carbamylated erythropoietin-enhanced proliferation and differentiation of adult neural progenitor cells. J Biol Chem. 2007; 282:32462–32470. [PubMed: 17804404]
40. Young KM, Psachoulia K, Tripathi RB, Dunn SJ, Cossell L, et al. Oligodendrocyte dynamics in the healthy adult CNS: evidence for myelin remodeling. Neuron. 2013; 77:873–885. [PubMed: 23473318]
41. Fields RD. White matter in learning, cognition and psychiatric disorders. Trends Neurosci. 2008; 31:361–370. [PubMed: 18538868]
42. Zatorre RJ, Fields RD, Johansen-Berg H. Plasticity in gray and white: neuroimaging changes in brain structure during learning. Nat Neurosci. 2012; 15:528–536. [PubMed: 22426254]
43. Pantoni L, Garcia JH, Gutierrez JA. Cerebral white matter is highly vulnerable to ischemia. Stroke. 1996; 27:1641–1646. discussion 1647. [PubMed: 8784142]
44. Dewar D, Underhill SM, Goldberg MP. Oligodendrocytes and ischemic brain injury. J Cereb Blood Flow Metab. 2003; 23:263–274. [PubMed: 12621301]
45. Zhang RL, Chopp M, Roberts C, Jia L, Wei M, et al. Ascl1 lineage cells contribute to ischemia-induced neurogenesis and oligodendrogenesis. J Cereb Blood Flow Metab. 2011; 31:614–625. [PubMed: 20736965]
46. Ueno Y, Chopp M, Zhang L, Buller B, Liu Z, et al. Axonal outgrowth and dendritic plasticity in the cortical peri-infarct area after experimental stroke. Stroke. 2012; 43:2221–2228. [PubMed: 22618383]
47. Gregersen R, Christensen T, Lehrmann E, Diemer NH, Finsen B. 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; 138:384–392. [PubMed: 11460777]
48. He X, Yu Y, Awatramani R, Lu QR. Unwrapping myelination by microRNAs. Neuroscientist. 2012; 18:45–55. [PubMed: 21536841]
49. Zhao X, He X, Han X, Yu Y, Ye F, et al. MicroRNA-mediated control of oligodendrocyte differentiation. Neuron. 2010; 65:612–626. [PubMed: 20223198]
50. Dugas JC, Cuellar TL, Scholze A, Ason B, Ibrahim A, et al. Dicer1 and miR-219 Are required for normal oligodendrocyte differentiation and myelination. Neuron. 2010; 65:597–611. [PubMed: 20223197]
51. Buller B, Chopp M, Ueno Y, Zhang L, Zhang RL, et al. Regulation of serum response factor by miRNA-200 and miRNA-9 modulates oligodendrocyte progenitor cell differentiation. Glia. 2012; 60:1906–1914. [PubMed: 22907787]
52. Rosenzweig S, Carmichael ST. Age-dependent exacerbation of white matter stroke outcomes: a role for oxidative damage and inflammatory mediators. Stroke. 2013; 44:2579–2586. [PubMed: 23868277]

53. Gherardini L, Gennaro M, Pizzorusso T. Perilesional treatment with chondroitinase ABC and motor training promote functional recovery after stroke in rats. Cereb Cortex. 2015; 25:202–212. [PubMed: 23960208]
54. Iyer AN, Bellon A, Baudet ML. microRNAs in axon guidance. Front Cell Neurosci. 2014; 8:78. [PubMed: 24672429]
55. Zhang Y, Chopp M, Liu XS, Kassis H, Wang X, et al. MicroRNAs in the axon locally mediate the effects of chondroitin sulfate proteoglycans and cGMP on axonal growth. Dev Neurobiol. 2015
56. Zhang Y, Ueno Y, Liu XS, Buller B, Wang X, et al. The MicroRNA-17-92 Cluster Enhances Axonal Outgrowth in Embryonic Cortical Neurons. J Neurosci. 2013; 33:6885–6894. [PubMed: 23595747]
57. Kouzarides T. Chromatin modifications and their function. Cell. 2007; 128:693–705. [PubMed: 17320507]
58. Jenuwein T, Allis CD. Translating the histone code. Science. 2001; 293:1074–1080. [PubMed: 11498575]
59. Qureshi IA, Mehler MF. The emerging role of epigenetics in stroke: II. RNA regulatory circuitry. Arch Neurol. 2010; 67:1435–1441. [PubMed: 21149808]
60. Felling RJ, Song H. Epigenetic mechanisms of neuroplasticity and the implications for stroke recovery. Exp Neurol. 2015; 268:37–45. [PubMed: 25263580]
61. Shen S, Casaccia-Bonnefil P. Post-translational modifications of nucleosomal histones in oligodendrocyte lineage cells in development and disease. J Mol Neurosci. 2008; 35:13–22. [PubMed: 17999198]
62. Shen S, Sandoval J, Swiss VA, Li J, Dupree J, et al. Age-dependent epigenetic control of differentiation inhibitors is critical for remyelination efficiency. Nat Neurosci. 2008; 11:1024–1034. [PubMed: 19160500]
63. Ye F, Chen Y, Hoang T, Montgomery RL, Zhao XH, et al. HDAC1 and HDAC2 regulate oligodendrocyte differentiation by disrupting the beta-catenin-TCF interaction. Nat Neurosci. 2009; 12:829–838. [PubMed: 19503085]
64. Liu XS, Chopp M, Kassis H, Jia LF, Hozeska-Solgot A, et al. Valproic acid increases white matter repair and neurogenesis after stroke. Neuroscience. 2012; 220:313–321. [PubMed: 22704966]
65. Grozinger CM, Schreiber SL. Regulation of histone deacetylase 4 and 5 and transcriptional activity by 14-3-3-dependent cellular localization. Proc Natl Acad Sci U S A. 2000; 97:7835–7840. [PubMed: 10869435]
66. Kassis H, Shehadah A, Chopp M, Roberts C, Zhang ZG. Stroke Induces Nuclear Shuttling of Histone Deacetylase 4. Stroke. 2015; 46:1909–1915. [PubMed: 25967576]
67. Ellis L, Hammers H, Pili R. Targeting tumor angiogenesis with histone deacetylase inhibitors. Cancer Lett. 2009; 280:145–153. [PubMed: 19111391]
68. Urbich C, Rossig L, Kaluza D, Potente M, Boeckel JN, et al. HDAC5 is a repressor of angiogenesis and determines the angiogenic gene expression pattern of endothelial cells. Blood. 2009; 113:5669–5679. [PubMed: 19351956]
69. Lai CP, Breakefield XO. Role of exosomes/microvesicles in the nervous system and use in emerging therapies. Front Physiol. 2012; 3:228. [PubMed: 22754538]
70. Zhang Y, Chopp M, Meng Y, Katakowski M, Xin H, et al. Effect of exosomes derived from multipluripotent mesenchymal stromal cells on functional recovery and neurovascular plasticity in rats after traumatic brain injury. J Neurosurg. 2015; 122:856–867. [PubMed: 25594326]
71. Jones EV, Bouvier DS. Astrocyte-secreted matricellular proteins in CNS remodelling during development and disease. Neural Plast. 2014; 2014:321209. [PubMed: 24551460]
72. Xin H, Li Y, Chopp M. Exosomes/miRNAs as mediating cell-based therapy of stroke. Front Cell Neurosci. 2014; 8:377. [PubMed: 25426026]
73. Zhang Y, Chopp M, Katakowski M, Liu X, Zhang Z. Exosomes derived from mesenchymal stromal cells promote axonal outgrowth. Stroke. 2015; 46:A67.
74. Fruhbeis C, Frohlich D, Kuo WP, Amphornrat J, Thilemann S, et al. Neurotransmitter-triggered transfer of exosomes mediates oligodendrocyte-neuron communication. PLoS Biol. 2013; 11:e1001604. [PubMed: 23874151]

75. Bakhti M, Winter C, Simons M. Inhibition of myelin membrane sheath formation by oligodendrocyte-derived exosome-like vesicles. J Biol Chem. 2011; 286:787–796. [PubMed: 20978131]

76. Bhalala OG, Srikanth M, Kessler JA. The emerging roles of microRNAs in CNS injuries. Nat Rev Neurol. 2013; 9:328–339. [PubMed: 23588363]

77. Zhang R, Chopp M, Zhang ZG. Oligodendrogenesis after cerebral ischemia. Front Cell Neurosci. 2013; 7:201. [PubMed: 24194700]

78. Li Z, Rana TM. Therapeutic targeting of microRNAs: current status and future challenges. Nat Rev Drug Discov. 2014; 13:622–638. [PubMed: 25011539]

79. Barteneva NS, Maltsev N, Vorobjev IA. Microvesicles and intercellular communication in the context of parasitism. Front Cell Infect Microbiol. 2013; 3:49. [PubMed: 24032108]

80. Alvarez-Erviti L, Seow Y, Yin H, Betts C, Lakhal S, et al. Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes. Nat Biotechnol. 2011; 29:341–345. [PubMed: 21423189]

Highlights

- miRNAs mediate neurovascular remodeling processes after stroke.
- HDACs are implicated in the process of stroke-induced remodeling of axons and myelin.
- Exosomes regulate intercellular communication in neurovascular remodeling.
- Exosomes as vehicles to deliver biological materials amplify brain restorative events.

Table 1

Molecules, exosomes and their cellular functions that are involved in brain remodeling

Molecules/vesicles	Target genes/cells	functions	Refs
miRNAs			
miR-9	SRF	oligodendrogenesis	51
Mir-15a	FGF2, VEGF	angiogenesis	17
miR-17-92	PTEN	neurogenesis, axonal growth	30,56
miR-29c	ITGB1	axonal growth	55
miR-124	JAG1	neurogenesis	25
miR-133	CTGF, RhoA	neurite outgrowth	14
miR-139	Rock1, Rock2	angiogenesis	19
MiR-200	SRF	oligodendrogenesis	51
miR-219	PDGFRα, SOX6	oligodendrogenesis	50
miR-335	Rock1, Rock2	angiogenesis	19
miR-338	PDGFRα, SOX6	oligodendrogenesis	49
HDACs			
HDAC1	oligodendrocytes	oligodendrogenesis	15,61,62
HDAC2	oligodendrocytes	oligodendrogenesis	15,61,62
HDAC4	neurons	axonal remodeling	66
HDAC5	endothelial cells	angiogenesis	68
Exosomes			
MSC-exosomes	neurons	axonal growth	73