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Remyelination is critical for white matter stroke recovery

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Mini Review

Abstract: Stroke is a major cause of worldwide death and disability. Numerous events are triggered in the brain after stroke onset, which together lead to irreversible non-selective brain cells death, including neurons, endothelial cells, oligodendrocytes etc. The only sufficient clinical treatment, recombination tissue plasminogen activator (tPA), limits its administration in patients due to its very narrow treatment window and the risk of hemorrhage. Many studies have been carried out to find new therapeutic treatments, which are generally categorized into drugs/chemokine/cytokine treatment, stem cell therapy, gene therapy, stem cell-based gene therapy and other physical therapy. These studies are mainly focused on reduction of inflammatory response, protection of blood-brain barrier (BBB) integrity, and promotion of angiogenesis and neurogenesis. After stroke, white matter is more vulnerable to deprivation of glucose and oxygen. A very vital component of whiter matter is oligodendrocytes, which ensheath the axons to form myelin and ensure proper pulse signal transduction. However, the studies on how to protect the integrity of white matter myelin, and promote the remyelination after stroke are much fewer than those for angiogenesis and neurogenesis. Angiogenesis, neurogenesis, and remyelination are indispensable for neurobehavioral function recovery after stroke. The therapeutic treatments for remyelination should be treated as important as those for angiogenesis and neurogenesis during stroke recovery phase.

Key words: Stroke; treatment; remyelination; white matter.

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Stroke

Stroke is a leading cause of worldwide human death and disability (1, 2). It includes two types of stroke, ischemic stroke and hemorrhagic stroke. Ischemic stroke is induced by blood vessel occlusion with > 70% stroke incidence, while hemorrhagic stroke is induced by blood vessel rupture. After stroke, the brain is deprived of oxygen and glucose, which is vital for the neurons maintenance (3). The neurons will die from its vulnerability to stroke within minutes. Neurological deficits usually occur accompanying with the death of neurons after stroke onset (4). The only food and drug administration (FDA) approved clinical treatment is recombinant tissue plasminogen activator (rtPA) thrombolysis (5). rtPA is administrated intravenously in ischemic stroke patients for thrombolysis by breakdown of blood clots. However, very limited patients are timely treated with tPA due to its very narrow treatment window, only within 4.5 hours after stroke onset (6). Stoke triggers a process of pathophysiological events in brain, including energy failure, iron dyshomeostasis, inflammatory cytokines release, blood-brain barrier (BBB) disruption, immune response activation etc (7, 8). These events interrelate, coordinate and finally result in non-selective cell deaths, including neurons, astrocytes, oligodendrocytes, endothelial cells etc. The brain will continue deteriorating for several days, even months (9, 10). The early diagnosis is more important than post-stroke recovery treatment, but no very efficient tools for the clinicians to perform on the clinical patients. Near real time single-pair fluorescence resonance transfer analysis of mRNA transcripts for stroke-related gene expression may assist clinicians to treat patients with appropriate time-sensitive therapeutics (11, 12).

Recent treatments for stroke

A numerous preclinical experiments have been tried to ameliorate brain injury or to promote angiogenesis and neurogenesis in stroke injured brain. These therapeutic treatments can mainly be categorized into drugs/chemokine/cytokine therapy, stem cell therapy, gene therapy, stem cell-based gene therapy and other physical therapy. Drugs can reduce brain inflammation, protect BBB integrity, increase stem cells homing etc. For example, metformin, a widely used hypoglycemic drug, has been showed to protect brain injury, reduce inflammatory cells infiltration, and protect BBB integrity in ischemic mice (13). AMD3100, a well recognized antagonist of CXCR4 and widely applied to block CXCL12/CXCR4 signaling, has been demonstrated to suppress inflammatory response and reduce BBB permeability in ischemic mice (14). Granulocyte-macrophage colony-stimulating factor (GM-CSF), a hematopoietic cytokine, is demonstrated to act as a neuroprotective protein in central nervous system (CNS) (15). Besides, erythropoietin (EPO) (16), granulocyte colony-stimulating factor (G-CSF) (17) etc are considered as clinical candidates for their endogenous neuroprotective roles in stroke. Many other drugs/chemokine/cytokines are administrated to stroke animals, and also have been showed that they can promote angiogenesis and/or neurogenesis, such as interleukin-10 (IL-10) (18), vascular endothelial growth factor (VEGF) and brain-derived neurotrophic factor (BDNF) (19), in-

sulin growth factor-1 (IGF-1) (20), fluoxetine (21), inducible nitric oxide synthase (iNOS) (22) etc. Stem cells including embryonic stem cells (ESCs) (23), mesenchymal stem cells (MSCs) (24, 25), endothelial progenitor cells (EPCs) (26-28), neural stem cells (NSCs) (29, 30), vascular progenitor cells (VPCs) (31) have been showed that their transplantation into stroke animals ameliorated brain injury, either by releasing neurotrophic factors to protect brain or by cell integration into the injury site for cell replacement. A large number of genes has been selected for gene therapy of stroke, which include insulin growth factor-1 (IGF-1) (32), BDNF (33), stromal derived factor-1 (SDF-1, also named as CXCL12) (34), epidermal growth factor (EGF) (35), glial cell line-derived neurotrophic factor (GDNF) (36), hepatocyte growth factor (HGF) (37), hypoxia induced factor-1 (HIF-1) (38) etc. To some extent, these genes therapeutic treatments for stroke improved animals' behavioral function by either protecting brain against stroke injury or promoting brain recovery via enhancing angiogenesis and/or neurogenesis. Gene modified stem cells are aimed to enhance the cell function and viability. Many kinds of modified stem cells have been used to treatment of stroke. MSCs have been modified by BNDF (39), GDNF (40), HGF (37), placenta growth factor (PIGF) (41), VEGF (42), angiopoietin-1 (43, 44), CXCR4 (45) genes. NSCs were showed successfully modified by VEGF (46), neurotrophin-3 (47, 48), GDNF (49), BDNF (50), Akt-1 (51) genes. EPCs can be modified by VEGF (52), SDF-1/CXCL12 (53) etc. These gene modified stem cells are commonly showed their better beneficial effect on stroke recovery than stem cell treatments alone, but mainly focusing on promoting angiogenesis and/or neurogenesis. Besides these treatments, there are some other physical treatments to help patients to gain motor functions, such as acupuncture, electroacupuncture etc (54-56).

Stroke induced-white matter injury is vital for stroke recovery

Not only more than 25% ischemic strokes in humans happens in subcortical, but cortical infarcts also damage white matter (57). The white matter is composed mainly of axons and glial cells, but lacking of neuronal cell bodies or their dendrites. Besides blood vessel injury and neurons death, there is an important injury in brain white matter is myelin degradation, named as demyelination. Myelin wraps the axons to ensure fast nerve impulse conduction and is vital for maintenance of the axon cytoskeleton (58-61). Myelin is composed of mature oligodendrocytes. Because of the little collateral blood supply in the white matter, where the myelin is rich, the white matter is more vulnerable than gray matter to stroke attack (62-64). Oligodendrocyte progenitor cells (OPCs) harbor in the subventricular zone (SVZ) in adult brain. OPCs can proliferate, migrate and differentiate into mature oligodendrocytes to repair the injured myelin in white matter, which termed as remyelination (65, 66). However, the naïve remyelination is insufficient to help repair the damaged myelin. The axon-glia unit in the white matter should be considered as integrity when proper treatment was applied for stroke therapy (67).

White matter lesions often correlate with severe physical and mental disability. White matter lesion volume is positively related with the reduction of fine motor skills (68). In clinical patients, severe white matter lesions are a predictor for poor activities of daily living in the older stroke patients with mild neurological symptoms (69), and large deep white matter lesions in acute ischemic stroke patients, measuring by pretreatment diffusion-weighted MRI, indicate a signal for useless of recanalization in endovascular therapy (70). Meanwhile, subcortical white matter infarcts influence the risk of post-stroke fatigue and predict one year poor outcomes in stroke patients (71). Moreover, white matter changes due to arterial stiffness and hypoperfusion also lead to pulse pressure and cognitive decline in stroke and transient ischemic stroke patients (72). Some studies have showed that the lesion volume in the white matter is closely related with hospital admissions due to hip-fractures and trauma after ischemic stroke (73). Furthermore, motor skill learning and speech fluency are deteriorated by the white matter injury diffusion in chronic stroke patients (74, 75). Recognition memory impaired after white matter stroke in mice (76). White matter lesions are showed to be an independent predictor of stroke in elder people, but not any other vascular diseases (77). These studies show the important roles of white matter in stroke recovery. Since stroke induced white matter injury is strongly related with the recovery extent of patients, more and more work should not only focus on angiogenesis and neurogenesis, but also on myelin protection and remyelination.

Recently, several studies have been focused on how to improve remyelination process. Our previously data showed netrin-1 gene therapy (78) and SDF-1/CXCL12 gene therapy (34) can promote angiogenesis and neurogenesis. After that we further found that netrin-1gene therapy (79) and SDF-1/CXCL12 gene therapy (80) promoted remyelination after ischemic stroke in mice by enhancing the proliferation, migration and differentiation of OPCs, which also improved the animals' behavioral function. A few of stem cell treatment studies have been showed the restoration of the white matter injury in ischemic stroke. Intravenously administration of adipose-derived MSCs was showed the migration and implantation of MSCs in the brain as well as facility of axonal sprouting, remyelination and oligodendrogenesis. Meanwhile, MSC treated animals showed a smaller functional deficit, smaller lesion area, and less cell death (81). Another study also showed that combination treatment ischemic rats with Niaspan and bone marrow stem cells (BMSCs) increased white matter remodeling comparing with BMSCs treatment only (82). Although several pioneer studies have been done to promote the remyelination after stroke, more trials are needed to find the sufficient therapeutic treatments for remyelination after stroke.

Conclusion

Comparing with the lots of studies on promoting angiogenesis and neurogenesis after ischemic stroke, few studies have been done on enhancing remyelination. As a whole brain after stroke, angiogenesis, neurogenesis and remyelination should be treated the same important in the stroke treatments, with no one left behind. Each of them is indispensable for neurobehavioral function recovery.

Since stroke induced white matter injury deteriorates the neurobehavioral function, attention should also be paid to white matter injury and white matter recovery after stroke. The treatments on how to enhance the remyelination should also be treated as important as promoting angiogenesis and neurogenesis. Angiogenesis, neurogenesis, and remyelination should be paralleled to each other, when considering stroke recovery treatment.

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