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Therapeutic strategy against ischemic stroke with the concept of neurovascular unit

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ABSTRACT

Stroke is one of the leading causes of death and disability globally. Although thrombolytic therapy by t-PA and mechanical thrombectomy have improved outcomes of ischemic stroke patients, both of these approaches are applicable to limited numbers of patients owing to their time constraints. Therefore, development of other treatment approaches such as developing neuroprotective drugs and nerve regeneration therapy is required to overcome ischemic stroke. The concept of the neurovascular unit (NVU) was formalized by the Stroke Progress Review Group of the National Institute of Neurological Disorders and Stroke in 2001. This concept emphasizes the importance not just of neurons but of the interactions between neurons, endothelial cells, astroglia, microglia and associated tissue matrix proteins to investigate the pathological condition of ischemic stroke. Many reports have been published about these interactions. This review focuses on the roles of cells that surround cerebral vasculature, especially endothelial cells, and reports therapeutic strategies against ischemic stroke from four points of view including angiogenesis, neurotrophic effects, protection of NVU components and regenerative therapy.

1. Introduction

Although neuroprotection has been validated in experimental animal stroke models, many neuroprotective drugs have failed to show an effect against ischemic stroke in clinical trials(Davis et al., 2000; Gelmers and Hennerici, 1990; Horn and Limburg, 2001; O'Collins et al., 2006; Savitz and Fisher, 2007). Such results show the limit of therapy focused only on neurons for the treatment of stroke. One of the reasons of this limitations is that in the acute phase of stroke, free radical and matrix metalloproteinase 9 (MMP-9) dissolve the basement membrane of vascular endothelial cells and endfeet of astrocytes depart from cerebral vessels, this breaks down the blood-brain barrier (BBB) and shuts off the neuronal function (Yamashita et al., 2009). In this situation, the concept of the neurovascular unit (NVU) consisting of neurons, astrocytes and vascular endothelial cells was proposed in 2001 as a new strategy for stroke treatment recently microglia, pericytes and oligodendrocytes also play important roles to functional maintenance of NVU (Lo et al., 2003; Moskowitz et al., 2010). This concept emphasizes that a focus on all these components and investigation of intercellular signaling and signaling between cells and extracellular matrix are essential to clarify all the fact about ischemic stroke. Concerning the relationship between astrocytes and neurons, astrocytes decompose glucose to lactate and supply it to neurons for adenosine triphosphate (ATP) synthesis (Pellerin and Magistretti, 1994). After sublethal ischemia, astrocytes upregulate P2X7 receptors and HIF-1α and play a role in inducing ischemic tolerance(Hirayama et al., 2015). In ischemic lesions, microglia touch their processes with synapses longer than usual and restore or remove the injured synapses (Wake et al., 2009, 2013).

Pericytes are more vulnerable than neurons to ischemia (Tachibana et al., 2017). Ischemia to pericytes causes microcirculatory no-reflow phenomena and enlarges infarction volume even if recanalization of an occluded artery is achieved (Yemisci et al., 2009). As seen above, the relationship between the components of an NVU has been reported. However, the importance of the relationship between vascular endothelial cells and neurons for the treatment of ischemic stroke remains to be clarified. In this review, we detail how cerebral vascular especially vascular endothelial cells work with neurons in the NVU for the treatment of ischemic stroke, focusing on angiogenesis, neurotrophic effects, preserving the BBB and regenerative therapy (Fig. 1).

2. Angiogenesis

Promoting angiogenesis is one of the most important strategies for functional recovery after stroke (Beck and Plate, 2009; Guo et al.,

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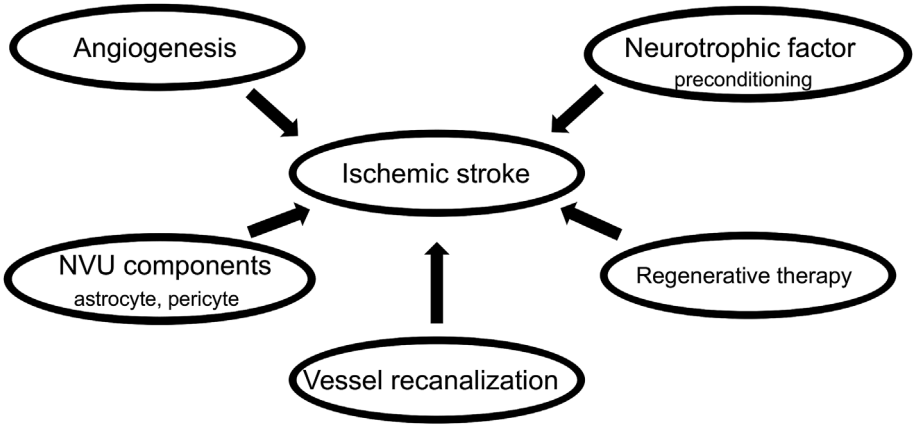

Fig. 1. Strategies against Ischemic stroke.

2008). In rodent middle cerebral artery occlusion (MCAO) models, endothelial cells surrounding the infarcted brain area start to proliferate as early as 12–24 h after ischemia (Hayashi et al., 2016; Kagiyama et al., 2003; Schoch, 2002). At the gene level, many angiogenesis-related gene expressions following stroke have been reported including vascular endothelial growth factor (VEGF), placenta growth factor (PLGF), neuropilins, angiotensin, and angiopoietins (Beck and Plate, 2009). Angiogenesis helps to restore oxygen and glucose supply to the affected brain area. Moreover, new blood vessels induce neuroblast migration from the subventricular zone (SVZ) to the degenerating striatum and cause neurogenesis (Thored et al., 2006; Yamashita et al., 2006). Stroke changes the molecular profiles of vascular endothelial cells in the peri-infarct cortex in which neuroblast migration occurs after stroke (Abumiya et al., 1999; Stumm et al., 2002). In 2006 Ohab et al. advocated a new concept, the neurovascular niche, which appears in the peri-infarct cortex after stroke and in which newly born neuroblasts are intimately entangled with endothelial cells (Ohab et al., 2006). In this report, neuronal regeneration and migration from GFAP-expression progenitor cells in the SVZ into the neurovascular niche in the peri-infarct cortex were shown to have occurred after stroke (Ohab et al., 2006). Blood vessels in this niche upregulate stromal-derived factor 1(SDF1) and angiopoietin 1 (Ang1). SDF1 and Ang1 promote post-stroke neuroblast migration and neuronal regeneration after stroke (Ohab et al., 2006).

3. Neurotrophic effect

Cerebral endothelial cells are not just tubes for delivering oxygen and glucose to neurons, but they also secrete neurotrophic factors that can be directly neuroprotective in the ischemic situation (Guo et al., 2008) (Ozaki et al., 2016). Guo et al. showed the trophic effect of the vascular endothelial cells by in vitro research (Guo et al., 2008). In this report, primary cortical neurons in the cell culture died when they were exposed to 8 h of hypoxia followed by 16 h of reoxygenation, but cell death was significantly ameliorated in neurons cocultured with either primary mouse cerebral endothelial cells or a human brain endothelial cell line or treated with conditioned media from cerebral endothelial cells (Guo et al., 2008). Moreover they revealed that brain-derived neurotrophic factor (BDNF) produced by endothelial cells is one of the neurotrophic factors against ischemia and β-1 integrin and integrin-linked kinase (ILK) signaling keep BDNF production (Guo et al., 2008).

Ischemic preconditioning (IPC) is the process by which exposure to sublethal ischemia provides tolerance against a long ischemic period (Dirnagl et al., 2009). This phenomenon has been verified by many organs (Adam, 2014; Y. Liu and Downey, 1992; Peralta et al., 2003). In the brain, from around 1990 IPC has been reported as an effective strategy for the treatment of ischemic stroke (Kitagawa et al., 1990) (Kirino et al., 1991). Hundreds of genes are either upregulated or downregulated by IPC (Bernaudin et al., 2002; Stenzel-Poore et al., 2003). Stenzel-Poore et al. reported gene expression changes in the mouse brain by IPC (MCAO model) using microarray analysis (Stenzel-Poore et al., 2003). In this report, IPC was shown to change the expression of genes related to the suppression of metabolic pathways, immune responses, ion-channel activity, and blood coagulation similar to neuroprotective strategies in hibernation (Stenzel-Poore et al., 2003). Activation of transcription factors such as hypoxia-inducible factor (HIF), nuclear factor kappa B (NF-κB) and cyclic AMP-responsive element binding protein (CREB) has reported (Bergeron et al., 2000; Blondeau et al., 2001; Mabuchi et al., 2001). Among these molecules, HIF is one of the key regulators of the genomic response by IPC (Dirnagl et al., 2009). HIF-1α, one of the HIF family, is activated by preconditioning and contributes to ischemic tolerance (Bergeron et al., 2000). Astrocyte, one of the components of NVU, contributes to ischemic tolerance. Hirayama et al. reported that P2X7 receptors of astrocytes were upregulated by IPC and HIF-1α in astrocytes upregulated by activated P2X7 receptors induced ischemic tolerance (Hirayama et al., 2015). We reported that endothelial cells also contribute to ischemic tolerance by IPC (Ozaki et al., 2016). Endothelial cells detect shear stress by blood flow and transmit signals to the interior of the cells resulting in changes in gene expression (Davies, 1995). The P2X4 receptor is the most abundantly expressed P2X receptor subtype in vascular endothelial cells (Yamamoto et al., 2003), and it detects shear stress by blood flow and contributes to ATP influx and flow induced Ca^{2+} influx in endothelial cells. {Yamamoto:2000dh} (Yamamoto et al., 2005) We focused on this phenomenon. We considered IPC, 15 min MCA occlusion and reperfusion in mice, as a changes of fluid shear stress. P2X4 receptors of cerebral vascular endothelial cells detected the changes in fluid shear stress and upregulated expression of osteopontin, a neuroprotective molecule, resulting in ischemic tolerance acquirement (Ozaki et al., 2016) (Meller et al., 2005). The role of endothelial cells and astrocytes in ischemic tolerance remains unclear and needs to be further investigated.

4. Protect the components of NVU

Astrocytes are a key target for considering relationship between derebral vascular and neurons, because they are the most abundant subtypes of glial cells (Z. Liu and Chopp, 2016) and almost all vascular endothelial cells in the brain are surrounded by foot process of the astrocytes and interact with neurons through astrocytes (Mathiisen et al., 2010). Astrocytes can survive longer than neurons against oxygen-glucose deprivation (OGD) in culture media which is an in vitro model of ischemia (Almeida et al., 2002). Further, in the animal stroke model, astrocytes can also survive longer than neurons(Gürer et al., 2009). Therefore, revealing the pathway by which astrocytes rescue neurons may help neuronal survival in ischemic stroke. Although

reactive astrocytes increase in the injured brain, including in ischemic stroke, the role of reactive astrocytes is not fully understood. In the negative side, proliferation of reactive astrocytes forms a glial scar and creates inhibitory environments for axonal outgrowth in the peri-infarct area after stroke (Hira et al., 2018). Moreover, reactive astrocytes release inflammatory cytokines such as TNF-αand TGF-β (Tuttolomondo et al., 2008) and free radicals such as NO(Buskila et al., 2005). These molecules cause neuronal death and increase infarction volumes in ischemic stroke. However, at the same time, reactive astrocytes have a positive effect for neuroprotection. Following ischemia, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and VEGF are released by reactive astrocytes and promote axonal outgrowth and angiogenesis (Silver and Miller, 2004). Hayakawa et al. reported that astrocytes donate mitochondria to neurons and contribute to the recovery of neurons after stroke (Hayakawa et al., 2016). Recently, Hira et al. reported that astrocyte-derived exosomes with prostaglandin D2 synthase expression contribute to axonal outgrowth and functional recovery after stroke by rat MCAO models (Hira et al., 2018). According to the glial scar, reactive astrocyte, main component of the glial scar, play a crucial role in wound healing and functional recovery after spinal cord injury by localizing inflammation and issue damage (Okada et al., 2006). Endothelial progenitor cells (EPCs), identified by Asahara et al., are marrow derived stem cell and have a potential to differentiate to endothelial cell (Asahara et al., 1997). EPCs contribute to attenuate ischemic damage and improves motor function after stroke (Fan et al., 2010). Reactive astrocytes upregulate the expression of HMGB1 and cause EPC migration to cerebral vessels. This contributes the recovery of motor function after stroke (Hayakawa et al., 2012).

Pericytes are also one of the components of the NVU. In response to neuronal excitation, pericytes activated by glutamic acid and NO dilated cerebral vessels and increase cerebral blood flow (Peppiatt et al., 2006) (Lourenço et al., 2014). However, ischemia to pericytes causes microcirculatory no reflow phenomena and enlarge infarction volume even if recanalization of an occluded artery can achieve (Yemisci et al., 2009). In the ischemic circumstance, endothelial cells secret PDGF-B and attract PDGFRβ positive pericytes (Arimura et al., 2012), resulting in BBB reconstruction and edema reduction (Arimura et al., 2012). PDGF-B increase extracellular matrix proteins in pericytes (Makihara et al., 2015). Few days after ischemic stroke, PDGFR-β positive pericytes differentiate to fibroblast-like cells and secret fibronectin and collagen resulting in fibrosis and reduction of infarction volume (Göritz et al., 2011) (Makihara et al., 2015). Moreover, PDGFRβ positive cells, activated by PDGF-B, produce neurotrophic factors such as NGF and NT-3 and contribute to neuronal survival (Caplan and Correa, 2011). As set out above, the role of pericytes is important to maintain microcirculation for preventing progression of infarct lesion. The endothelial cells also play important roles to keep microcirculation in the ischemic stroke. Yagita et al. reported that Rho-kinase is activated in the endothelial cells of brain microvessels in the early period after induction of ischemia and cause endothelial dysfunction and microcirculatory disturbances in the ischemic lesion (Yagita et al., 2007). They also demonstrated that Rho-kinase inhibitor fasudil treatment after induction of ischemia attenuated these disorders (Yagita et al., 2007).

Tissue-type plasminogen activator (t-PA) is one of the most effective and reliable agents for acute ischemic stroke. The effectiveness for acute ischemic stroke within 4.5 h from onset was proven by a large clinical randomized trial (Hacke et al., 2008). However, t-PA is a double-edged sword. Fatal intracerebral hemorrhage caused by t-PA has been reported (Emberson et al., 2014; IST-3 collaborative group et al., 2012; Wardlaw et al., 2012). Plasmin, activated by t-PA, upregulates some types of matrix metalloproteinases (MMPs). MMPs resolve extracellular matrix and break down the BBB resulting in intracerebral hemorrhage (Jin et al., 2010). MMP-9 activated by t-PA causes basement membrane collagen IV breaks, detaches astrocyte endfeet from the basement membrane and breaks the BBB (Yamashita et al., 2009). Thus in present age that t-PA becomes one of the effective treatments, we must not only protect neurons but also the components of the NVU. The free radical scavenger Edaravone was reported as a neuroprotective agent against ischemic stroke. (Edaravone Acute Infarction Study Group, 2003) Edaravone suppresses accumulation of lipid peroxidation products and oxidative DNA damage resulting in the elimination of inflammation after ischemic stroke (Zhang et al., 2005). In the context of the NVU, Edaravone prevents the activation of MMP-9 and oxidative damage caused by t-PA. In addition, Edaravone protects collagen IV, suppresses detachment of astrocyte endfeet and preserves the BBB (Yamashita et al., 2009). Thus Edaravone prevents intracerebral hemorrhage after t-PA treatment. In the clinical settings, Edaravone combined with t-PA and administered within 4.5 h of acute ischemic stroke lowered the incidence of symptomatic intracerebral hemorrhage after t-PA administration (Yamaguchi et al., 2017). As well as Edaravone, inhibition of VEGF signaling pathway by an anti-VEGF neutralizing antibody also attenuated MMP-9 activation and degradation of the BBB (Kanazawa et al., 2011). Angiopoietin-1 (Ang-1) is known to bind to the receptor Tie-2, which is expressed in various types of cells such as neurons, endothelial cells and pericytes (Davis et al., 1996). Ang-1 contributes the survival of endothelial cells and vascular stability (Gamble et al., 2000; Kim et al., 2000). Ang-1 positive vessel density was decreased when t-PA treatment was given after the therapeutic window. Administering Ang-1 decreased hemorrhagic formation and cerebral edema due to BBB damage after t-PA treatment (Kawamura et al., 2014).

5. Regenerative therapy

Although thrombolytic therapy by t-PA and mechanical thrombectomy has improved the outcomes of ischemic stroke patients, both of these approaches are applicable to limited numbers of patients owing to their time constraints (Campbell et al., 2015; Jovin et al., 2015; Saver et al., 2015) (Nogueira et al., 2018). In such a circumstances, cell based regenerative therapies have been developed as novel strategies for ischemic stroke. Experimental animal ischemic stroke models with embryonic stem cells (ES cells), induced pluripotent stem cells (iPS cells), bone marrow stem cells, neural stem cells and mesenchymal stem cells have been reported (Bliss et al., 2007; Chen et al., 2010; Kelly et al., 2004; X.−Y. Liu et al., 2014; Modo et al., 2002; Quittet et al., 2015). Some human studies of cell therapies for chronic stroke have demonstrated efficacy and adequate safety (Wechsler et al., 2018).

iPS cells have the advantage of sparing the damage induced by immune rejection and avoiding the ethical limitations of obtaining pluripotent cells from human embryos. These pluripotent cells can be differentiated into various neural cell type including neurons, oligodendrocytes and astrocytes (Bain et al., 1995; Chau et al., 2014; Reubinoff et al., 2001). Engraftment of IPS cells in ischemic stroke models of rodents ameliorates the neuronal outcomes (Chen et al., 2010; Oki et al., 2012; Tornero et al., 2013). But, potential to develop a tumor following engraftment is major concern of iPS cells (Yamashita et al., 2011).

Mesenchymal stem cells can be obtained from several tissue sources including bone marrow, adipose tissue, umbilical cord and dental pulp. Most cell-based clinical trials for stroke use mesenchymal stem cells (Marei et al., 2018). Because the method of their collection and culture is relatively established. Some clinical trials have revealed their feasibility and safety (Bang et al., 2005; Lee et al., 2010). Multiliniage-differentiating stress enduring (Muse) cells, one of the mesenchymal stem cells, have attracted attention for their non-tumorigenic behavior (Kuroda et al., 2010; Wakao et al., 2011). Uchida et al. reported feasibility and effectivity of the MUSE cell transplantation at rodent ischemic stroke models (Uchida et al., 2015, 2017). In these reports, MUSE cells were stereotaxically transplanted into the ischemic cortex and peri-ischemic lesions (Uchida et al., 2017, 2015). Clinical trial of MUSE cells in ischemic stroke is currently ongoing.

EPCs that can differentiate into vascular endothelial cells were first

isolated from peripheral blood of adults in 1997 (Asahara et al., 1997). EPCs, derived from bone marrow, attach to ischemic tissues, then migrate to the stromal microenvironment and promote vasculogenesis around the ischemic core (Murasawa and ASAHARA, 2005). Clinical studies of EPC transplantation for arteriosclerosis obliteration (ASO) and ischemic cardiac disease have been reported (Rafii and Lyden, 2003). The angiogenic ability and neurotrophic effect of EPCs were reported in this article (Rafii and Lyden, 2003). In experimental animal models, cell therapy with EPCs against ischemic stroke has also been reported (Fan et al., 2010; Iskander et al., 2013; Liao et al., 2017; Nakamura et al., 2012; Ohta et al., 2006; Rafii and Lyden, 2003; Rouhl et al., 2008; Takizawa et al., 2016). In these reports, sources of EPCs, ischemic stroke models and timing and route of administration are all different to each other. Ohta et al. reported 90 min transient MCAO model in rats. In that report, autologous rat-bone -marrow-derived EPCs were transplanted intra-arterially from the internal carotid artery 2 h after MCAO. EPC transplantation increased cortical blood flow at 48 h after MCAO and this therapy reduced infarction volume and improved neurological deficits (Ohta et al., 2006). Iskander et al. reported 2 h transient MCAO model in rats. In that report, human umbilical-cord-blood (UCB) derived CD133-positive EPCs were transplanted intra venously 24 h after MCAO and this therapy induced angiogenesis and neurogenesis in the stroke-affected hemisphere and reduced the infarction volume. They used the magnetically labeled cells and tracked by magnetic resonance imaging (MRI). MRI performed at days 1, 7, 14 after MCAO showed accumulation of transplanted cells in the stroke-affected hemispheres (Iskander et al., 2013). To investigate if treatment with EPCs or their secreted factors potentiate angiogenic and neurogenesis after ischemic stroke, Rosell et al. administered cell-free conditioned media obtained from EPCs to mice a day after MCAO (Rosell et al., 2013). Conditioned media contained growth factors such as VEGF, fibroblast growth factor (FGF-b), platelet derived growth factor (PDGF-bb). In the conditioned media group, capillary density was significantly increased compared with a vehicle media group and post-ischemia forelimb strength was significantly improved (Rosell et al., 2013). They showed a possibility for cell-free therapy against ischemic stroke.

Thus, in experimental animal models, cell therapy with endothelial progenitor cell (EPCs) against ischemic stroke has been verified for its feasibility. However, clinical trials have never been reported. The future clinical trials are awaited.

6. Conclusions

Vascular endothelial cells play important roles in ischemic stroke, such as angiogenesis, neurotrophic effect and ischemic tolerance by ischemic preconditioning. In addition, EPCs have a potential to treatment option in clinical settings. Pericytes and Astrocytes also act against ischemic stroke. Thus, the components of NVU affect each other and save neurons. So, we must considerate whole components of NVU and investigate multiple effects of these cells.

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