

Endogenous Neurogenesis, Oligodendrogenesis and Angiogenesis after Ischemic Brain Injury

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Abstract

Since strokes are a major cause of death and result in a drastic reduction in the quality of life, a new strategy to minimize ischemic-related damage is thus required. Recent evidence indicates that endogenous neural stem cells of the subventricular zone give rise to not only neurons but also oligodendrocytes, which can restore a disrupted neuronal network in post-ischemic brain, and various kinds of neurotrophic factors, such as EGF, are known to promote this process. To promote the functional recovery of post-stroke brain, angiogenesis is also essential. It has been suggested that circulating endothelial progenitor cells (EPCs) can play an important role in angiogenesis of the post-stroke brain. The number or function of EPCs can also be modulated by various kinds of factors. For example, VEGF, G-CSF and statins can increase EPC levels. In this review, we discuss the present knowledge of endogenous neurogenesis/oligodendrogenesis/angiogenesis and how to enhance their ability to restore the neuronal network through self-repair strategies.

Keywords: Neurogenesis; Oligodendrogenesis; Neural stem cells; Angiogenesis; Endothelial progenitor cells (EPCs)

Abbreviations: NPCs: Neural Progenitor Cells; OPCs: Oligodendrocyte Precursor Cells; EPCs: Endothelial Progenitor Cells; EGF: Epidermal Growth Factor; VEGF: Vascular Endothelial Growth Factor; G-CSF: Granulocyte Colony-Stimulating Factor

Introduction

Strokes are a major cause of death and result in a drastic reduction in the quality of life. The only effective therapeutic approach is thrombolysis with recombinant tissue plasminogen activator, and a new strategy to minimize ischemic-related damage is thus required. Over the past 10 years, regenerative therapy, which supplies new neurons or oligodendrocytes, has been extensively studied. Two tactics are proposed to supply new neurons or oligodendrocyte into the infarcted brain. One is the transplantation of extrinsic neural stem cells (NSCs) derived from stem cells such as embryonic stem (ES) cells and induced pluripotent stem (iPS) cells [1]. The other is the activation of intrinsic neural stem cells [2,3]. Although stem cell transplantation may be one promising method, tumorigenicity and rejection by immuno-response are potentially large hindrances for the application to a clinical setting. On the other hand, the endogenous capacity for regeneration now draws attention to the development of a novel therapeutic strategy for strokes. In addition, angiogenesis is also required to regenerate the neural network [4, 5]. In this article, we focus on endogenous neurogenesis/oligodendrogenesis/angiogenesis, and discuss current developments in this field with special emphasis on the therapeutic application for strokes (Table 1).

Intrinsic Neural Stem Cells and Neurogenesis

Persistent neurogenesis occurs in two restricted regions of the adult mammalian brain including the human brain: the subgranular zone (SGZ) of the hippocampal dentate gyrus [6] and the subventricular zone (SVZ) of the lateral ventricle [7]. In the SGZ, newly born neurons migrate into the granule cell layer and integrate into the neuronal network. In the SVZ, which is a thin cell layer in the lateral walls of lateral ventricles, NSCs continuously produce neural progenitor cells (NPCs) migrating into the olfactory bulb [8]. To discern whether the ischemic condition affects endogenous neurogenesis, we studied the temporal profile of NSC division, migration, and differentiation in the

SGZ and the SVZ in the transient forebrain ischemia gerbil model. We found that the ischemic condition increased the division of NSCs of the SGZ with a peak 10 days after ischemic induction, following which cells migrated into the granule cell layer and differentiated mainly into neuronal cells [9]. Furthermore, we also found that transient forebrain ischemia enhances NSC proliferation in the SVZ with a peak 10 days after ischemia, leading to the migration of more NPCs to the olfactory bulb [10]. These studies indicate that ischemic stimuli could increase the number of NSCs and resulted in enhanced neurogenesis in the two restricted lesions, the SGZ and the SVZ. Many researchers reported that newly born neurons can be found in the post-infarcted lesion including the striatum and cortex in another animal model, the transient focal ischemia model [11,12], which is a mimic model of human cardio-embolic stroke. To clarify whether SVZ NSCs supply new neurons to areas injured by ischemia, several study groups have performed region-specific cell labeling and long-term tracing experiments. SVZ-derived NPCs were also reported to migrate towards the injured striatum after middle cerebral artery occlusion (MCAO). A long-term tracing study revealed that the SVZ-derived NPCs differentiated into mature neurons in the striatum, in which they formed synapses with neighboring striatal cells [13] (Figure 1), implying that the SVZ is one of the harbors supplying newborn neurons to brain lesions damaged by focal ischemia.

Intrinsic Oligodendrogenesis and Future Therapeutic Strategy

In the adult brain, mature oligodendrocytes have been reported

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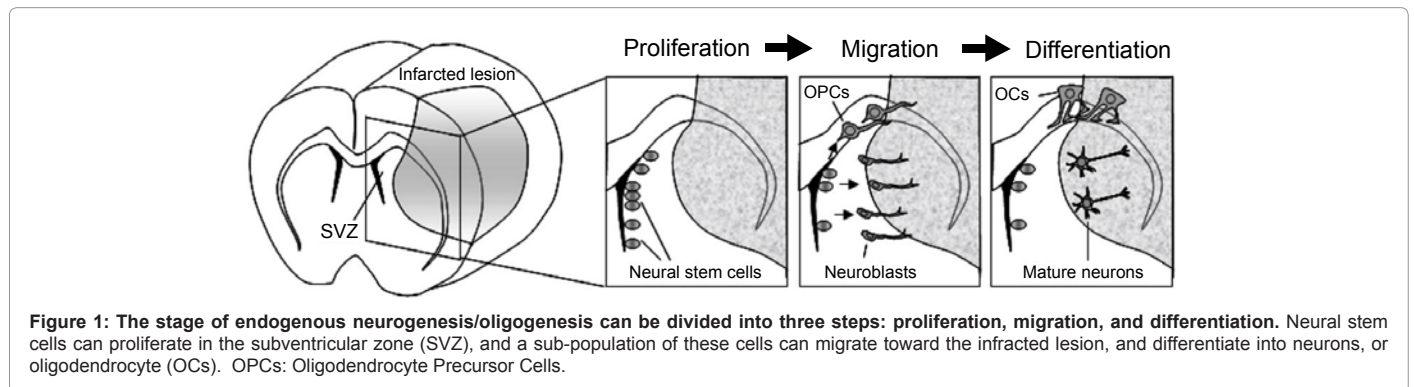
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Factor/Drug	Suggested effect	Reference
EGF	Increase both NPCs number and OPCs number	[21]
Asialo-erythropoietin	Promote the maturation of OPCs	[22]
VEGF	Increase EPCs number for angiogenesis	[30,31]
G-CSF	Increase EPCs number for angiogenesis	[32,45]
Statin	Increase EPCs number for angiogenesis Promoting re-endothelialization.	[40, 41]
Cilostazol	Increase EPCs number for angiogenesis	[43]

Table 1: Scientific evidence showing that the administrated factor/drug can enhance endogenous neurogenesis/oligodendrogenesis/angiogenesis.



to be produced from local oligodendrocyte precursor cells (OPCs) located in the brain parenchyma. Recent evidence indicates that SVZ neural stem cells also give rise to oligodendrocytes as well as neurons [14]. Menn et al. clearly demonstrated that SVZ astrocytes generate oligodendrocytes, which migrate to the corpus callosum and the white matter tract, by using GFAP-tva transgenic mice and avian retrovirus [15].

In the post-ischemic brain, newly born neurons and oligodendrocytes can be supplied from the SVZ, but this number may be too small for recovery of neurological functions. For example, newly born neurons could replace only 0.2% of the dead striatal neurons even in the rat MCAO model [11]. It has been reported that various kinds of neurotrophic factors including EGF [16], FGF2 [17], CNTF [18], IGF-1 [19] and NGF [20], can promote neurogenesis in animal models. Of note, EGF may be a promising drug candidate because it can increase the number of precursors, promoting not only neurogenesis, but also oligodendrogenesis [21]. A recent study indicated that asialo-erythropoietin promoted the maturation of SVZ-derived OPCs and the recovery of neurological function in a hypoxia ischemia mouse model [22]. However, the precise mechanisms that control the proliferation, survival, and/or neuronal maturation of intrinsic NSCs and their progeny must be known so as to use their intrinsic neural cell source for therapeutic purposes.

Endogenous Endothelial Progenitor Cells for Angiogenesis in the Ischemic Brain

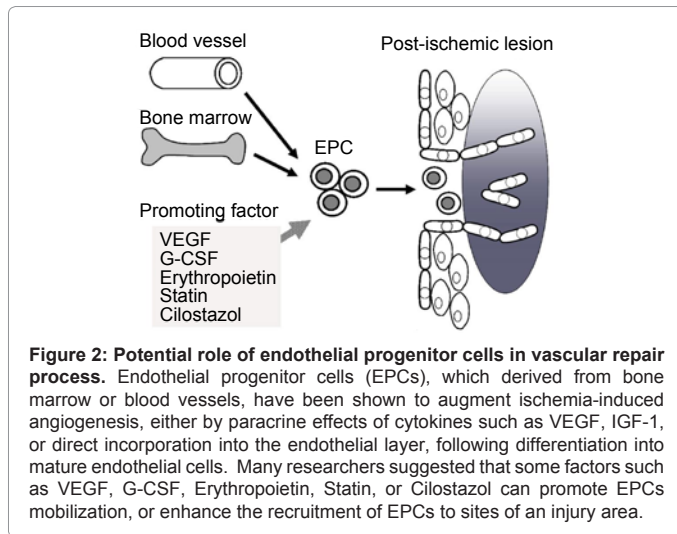
Several studies from human and experimental stroke models indicate that angiogenesis can occur in the adult brain after a stroke [23,24]. In the past, the migrated neighboring endothelial cells have been regarded as the main cell resource for the regeneration of injured endothelial cells. However, several research groups reported that bone marrow-derived cells can incorporate and differentiate into endothelial cells at the border of the infarct lesion of the focal cerebral ischemia murine model [25,26]. Hess et al. reported that 34% of vessels of the peri-infarcted area were bone marrow-derived cells [25]. It has also been reported that a number of circulating, very small embryonic-like

stem cells mobilized into peripheral blood in patients after a stroke [27]. These results indicate that bone marrow-derived endothelial cells can take part in angiogenesis, and can minimize the effects of an ischemic stroke.

However, increasing scientific reports suggest that there are non-bone marrow-derived cells, which can also give rise to endothelial cells [28]. Recently, tissue-resident stem cells, which were isolated from the heart, have been shown to be capable of differentiating into endothelial cells [29]. Therefore, at present, it seems unclear which organ is the main resource for endothelial progenitor cells (EPCs). However, regardless of the origin, the circulating endothelial progenitors in peripheral blood may play an important role in vascular remodeling after a stroke (Figure 2).

Therapeutic Strategy Promoting Repair of Endogenous Endothelial Progenitor Cells

As discussed above, much evidence exists to show that EPCs take part in angiogenesis in ischemic tissue. Therefore, many researchers have tried various kinds of agents in the ischemic animal model, and test whether such agents can enhance the mobilization of EPCs, leading to augmented angiogenesis. Firstly, VEGF has been reported to play an important role in angiogenesis through mobilization of EPCs in an animal model and in human subjects [30,31]. Zhang et al. reported that administration of recombinant human VEGF at 48 hours after the induction of ischemia enhanced angiogenesis in the peri-infarcted lesion and significantly improved neurological recovery in the rat model [24]. These results seem to suggest that VEGF can be a promising agent for minimizing ischemic-related injury, although issues regarding its utility as a therapeutic agent remain because administration of VEGF at 1 hour after ischemia increased blood brain barrier leakage, and worsened brain edema [24]. As another candidate, granulocyte colony-stimulating factor (G-CSF) also increased the number of circulating EPCs. To test whether G-CSF can promote angiogenesis, we administrated G-CSF to a focal ischemia rat model, and analyzed angiogenesis. We found that newly born endothelial cells were significantly increased in the G-CSF-treated group, compared



with the vehicle-treated group [32]. G-CSF has already been applied for idiopathic or chemotherapy-induced neutropenia and related indications such as bone-marrow harvesting, and seems to be a well tolerated drug [33]. Moreover, G-CSF can be administered to patients subcutaneously. Therefore, G-CSF is now regarded as a promising candidate for modulating ischemic-related injury. In addition, erythropoietin also increased peripheral blood EPCs in mice and in human patients [34]. Interestingly, estrogen, a female sex hormone, has been reported to increase the level of circulating EPCs [35,36]. Moreover, exercise also increased the number of EPCs in mice and in men, probably through up-regulation of VEGF and angiotensin [37,38]. The mechanism by which these factors augment EPCs is not fully understood. However, it has been reported that VEGF and exercise-induced mobilization of EPCs was blunted in endothelial nitric oxide synthase (eNOS) knock out mouse, suggesting that eNOS play an essential role in endothelial progenitor cell mobilization [39].

The first evidence for the pharmacological modulation of circulating EPCs by atheroprotective drugs came from studies with HMG-CoA reductase inhibitors (statins). Statins have been shown to increase the mobilization and re-endothelialization of EPCs in the balloon-injured arterial rat model [40]. Chen et al. reported that treatment with atorvastatin for 14 days, which started from 24 hours after a stroke, showed increased VEGF, VEGF receptor 2 and BDNF expression in peri-infarcted lesions, and showed a significant improvement in functional recovery compared with untreated controls [41]. In the myocardial infarction murine model of eNOS null mice, mobilization of statin-induced EPCs was not detected, indicating that eNOS appears to be critical for the mobilization of statin-induced EPCs [42]. In addition, statin treatment of human endothelial progenitors was reported to up-regulate the expression of endothelial integrin $\alpha 5 \beta 1$, which was associated with increased adhesive function of endothelial progenitors toward endothelial cells, indicating that statins may promote EPCs homing to the site of vascular injury [40]. Very recently, cilostazol, which is a selective inhibitor of phosphodiesterase 3, has attracted attention as another candidate for therapy. It has already been reported that cilostazol enhanced angiogenesis probably by promoting EPC mobilization both in the transient forebrain ischemia mouse model [43] and in the carotid balloon injury rat model [44]. In the future, EPCs need to be defined and the mechanisms involved in their beneficial effects need to be studied in detail.

Through new research, multiple novel neuronal self-repair strategies enhancing endogenous neurogenesis/oligodendrogenesis/angiogenesis should be proposed for clinical settings in the near future.

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