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Review

Endothelial progenitor cells and revascularization following stroke

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ABSTRACT

Brain injury after ischemia induces the mobilization of endothelial progenitor cells (EPCs), a population of bone marrow-derived cells with angio-vasculogenic capabilities. These cells have been also tested in pre-clinical models and proposed for neurorepair therapy aiming to treat patients in the delayed phases of stroke disease. Promising results in the pre-clinical field encourage the translation into a clinical therapeutic approach. In this review, we will describe EPCs actions for enhanced revascularization and neurorepair, which on one hand are by their direct incorporation into new vascular networks/structures or by direct cell–cell interactions with other brain cells, but also to indirect cell–cell communication thorough EPCs secreted growth factors. All these actions contribute to potentiate neurovascular remodeling and neurorepair. The data presented in this review encourages for a deep understanding of the mechanisms of the cross-talks between EPCs and other brain and progenitor cells, which deserves additional investigations and efforts that may lead to new EPCs-based therapies for stroke patients.

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Contents

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1. Stroke disease and neurorepair

Ischemic stroke is a leading cause of mortality, long-time disability and morbidity in the world. Data from the World Health Organization confirms that stroke affects 15 million people worldwide each year; of these, 5 million people will die and another 5 million will survive with neurological deficits that limit their functional independence (http://www.who.org). Once a vascular occlusion in the brain happens, a complex chain of events develop at molecular and cellular level leading to irreversible tissue injury and cell death (Kalladka and Muir, 2014), if vascular occlusion is not resolved in a short period of time. As a consequence an ischemic core is formed as a result of irreversible cell necrosis not only affecting all the cellular elements like neurons, glial cells and blood vessels but also affecting the extracellular matrix components. The ischemic penumbra surrounding the ischemic core, transiently maintains a collateral blood supply sufficient for cell viability. However, tissue in the penumbral region could progresses to cellular death by expanding the core lesion without an appropriate restored perfusion and recanalization in time (Rha and Saver, 2007). In addition to early brain injury caused by the reduction of blood flow, post-ischemia reperfusion may worsen initial tissue damage by secondary damage by triggering an inflammatory response, blood–brain barrier breakdown and cell apoptosis (Lopez-Neblina et al., 2005). On the other hand, stroke also triggers a regenerative response such as the proliferation of endogenous neural progenitor cells, an increase in the number of immature neurons or an enhancement of peri-infarct angiogenesis, among other processes (Parent et al., 2002; Jin et al., 2001; Zhang et al., 2004), demonstrating the plastic nature of the brain in opposition to more classical views of passive dying brains.

The only proven effective drug treatment for acute ischemic stroke is thrombolysis with recombinant tissue plasminogen activator (rtPA), which was approved by the US in 1995 (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995), and now given to patients in a limited therapeutic time window of 4.5 h from symptoms onset (Hacke et al., 2008). Although thrombolysis with tPA is effective and lifesaving, only 2–5% of all stroke patients receive this treatment. Therefore, it is necessary to develop new stroke therapies that could be used to treat a large number of patients in the delayed phases to repair and rewire the injured tissue. The new concept for research in stroke therapy is that endogenous neurovascular plasticity and remodeling are also activated in the most-early phases of the ischemic event and participate in the functional recovery after stroke.

1.1. *Angiogenesis, neurogenesis and oligodendrogenesis after stroke*

The classical view of neurorepair as the replacement of death neurons has changed in the last decades for a more global understanding of the brain as a whole, including other cell types (glial cells, inflammatory cells and stem/progenitor cells) but also the extracellular matrix and their interactions. Therefore endogenous mechanisms of neurorepair include angio-vasculogenesis (formation of new blood vessels), gliogenesis (formation of new glial cells), neurogenesis (formation of new neurons), re-myelination (new myelin sheaths on demyelinated axons), among others. Immediately after stroke, some early functional recovery mechanisms can be attributed to the resolution of edema or inflammation, which are usually limited in time and extent, whereas other process including neurogenesis, angiogenesis and oligogenesis are involved in the longer-time recovery of neurological function and tightly regulated by many factors (Arvidsson et al., 2002). Thus, neurorepair of the damaged tissue to rewire neuronal networks and enhance neuronal regenerative mechanisms becomes one promising therapeutic approach that involves other remodeling steps. Several of those endogenous mechanisms are activated in minutes following the ischemic trigger in peri-infarct areas (Pepper, 1997; Carmichael, 2008) and several populations of newborn progenitor cells have been identified in remodeling areas (Carmichael, 2008; Ohab et al., 2006; Jin et al., 2006), such as neural progenitor cells (NPCs), endothelial progenitor cells (EPCs) or oligodendrogyte progenitor cells (OPCs).

Neurogenesis in the adult brain takes place in two areas: the hippo-campal sub-granular zone (SGZ) and sub-ventricular zone (SVZ) (Ohab et al., 2006; Ohab and Carmichael, 2008) which renew cells of the dentate gyrus and olfactory bulb, respectively. Neural stem cells (NSCs) reside in specific niches such as the SVZ, and display partial differentiation and enhanced proliferation with specific fates, for example to neuroblasts or oligodendrocyte progenitor cells (OPCs). After cerebral ischemia it has been observed that in those areas rich in neural progenitor niches these cells can proliferate, migrate and graft into the most peri-lesional brain areas where they can differentiate into new neurons or glial cells and renew the cell population (Ohab and Carmichael, 2008). For this to happen there must be signals that guide migrating neuroblasts to areas where cell renewal can take place. In this process, neurons facilitate each others migration in chains; astrocyte end-feets influence migration by surrounding and creating encased tube; blood vessels provide a path of neuronal migration by releasing some factors and acting as a physical scaffold (Gage, 2000; Arvidsson et al., 2002). It appears that peripheral areas of infarction, and no other healthy areas of the brain, present such signals. In these areas bordering the injured tissue, the induction of endogenous angiogenesis has been observed. Neuronal migration is influenced by cell-secreted factors and by cell-bound molecules including gamma-aminobutyric acid (GABA), vascular endothelial growth factors (VEGF), brain-derived neurotrophic factor (BDNF), polysialylated neuronal cell adhesion molecule (PSA-NCAM), matrix metalloproteinases (MMP), β1 integrins, angiopoietins (Ang) and extracellular matrix components (Kahle and Bix, 2012). Importantly, today we recognize the so-called neurovascular niche that promotes the coupling between angiogenesis and neurogenesis with the establishment of migratory neuroblasts in the peripheral infarction in co-localization with small blood vessels especially in areas with active vascular remodeling (Ohab et al., 2006) where an increase in growth factors such as stromal derived factor (SDF)-1 occurs days after stroke. Other authors have demonstrated that cerebral endothelial cells are activated by ischemia enhance NPC proliferation and differentiation mediated by VEGF receptor 2 (VEGFR2)