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Review

De-routing neuronal precursors in the adult brain to sites of injury: Role of the vasculature

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ABSTRACT

Neurogenesis in the adult brain occurs predominantly in the two regions, the subventricular zone (SVZ) bordering the lateral ventricle and subgranular zone (SGZ) of the hippocampus. The neuronal precursors are produced in the specialized microenvironment called neurovasculature niche. Recent evidences indicate that in addition to neurogenesis promoting environment, vasculature also serves as a substrate for migration for these newly generated cells. Importantly, under some pathological condition, including stroke, neurogenesis is enhanced in the adult brain. Newly generated neuronal precursors migrate to the sites of injury along the blood vessels and try to integrate to the damaged brain circuitry. This self-healing capacity of the adult brain is, however, insufficient to produce a noticeable amelioration in the affected neuronal network since only a tiny proportion of cells succeed to integrate and survive. Here we review the mechanisms of neuronal recruitment into the post-stroke regions with particular attention to the guidance of neuronal precursors along the blood vessels. We also outline some of the molecular factors that have been used or have a potential to be employed to improve the cell recruitment into the sites of injury.

1. Introduction

Neurogenesis is an ongoing process that under normal conditions in the healthy uninjured adult brain, takes place in the subventricular zone (SVZ) of the lateral ventricles and in the dentate gyrus (DG) of the hippocampus. Newborn neurons generated locally in the subgranular zone (SGZ) of the DG mature and integrate into the existing neuronal network in the overlying granule cell layer (van Praag et al., 2002). By contrast, progenitors originating from the SVZ have to migrate all along the rostral migratory stream (RMS) before reaching their final position in the olfactory bulb (OB), where they differentiate into inhibitory gabaergic and dopaminergic interneurons and integrate into local circuitry (Alvarez-Buylla and Garcia-Verdugo, 2002; Doetsch and Hen, 2005; Kornack and Rakic, 2001; Luskin, 1993). Adult neurogenesis occurs in all mammalian species studied to date, including human and non-human primates (Bedard et al., 2002; Bedard and Parent, 2004; Gould et al., 1998; Kornack and Rakic, 1999, 2001; Ming and Song, 2005; Pencea et al., 2001a).

In addition to these constitutively operating neurogenic sites, under some pathological conditions, including stroke, neurogenesis is enhanced in the adult brain and neuronal precursors migrate to the site of injury (Ming and Song, 2005; Ohab and Carmichael, 2008). These new cells can differentiate, mature and survive for several weeks. While this natural self-renewal ability of the brain gives a lot of hope for cell replacement therapies, only a small number of dying neurons can be replaced without any intervention (Arvidsson et al., 2002). In order to improve the self-repair capacity of the adult brain, it is crucial to understand the mechanisms that govern the proliferation, migration, maturation and survival of adult neuronal precursors under normal and pathological conditions. This knowledge will be important for the development of new strategies for cell replacement therapies.

Several excellent reviews have highlighted the different aspects of post-stroke neurogenesis (Lichtenwalner and Parent, 2006; Lindvall et al., 2004; Nakatomi et al., 2002; Ohab and Carmichael, 2008; Parent, 2003; Sharp et al., 2002; Zhang et al., 2005). This review focuses on the mechanisms of migration of neuronal precursors derived from SVZ–RMS–OB pathway to the site of injury with particular attention to the role of blood vessels in the migration/recruitment process.

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2. Adult neurogenesis following stroke

Neurogenesis in the SVZ and SGZ is increased under many pathological conditions. The middle cerebral artery occlusion (MCAO) in mice and rat, widely used animal models for stroke, induces a substantial increase of neurogenesis in the SVZ (Arvidsson et al., 2002; Jin et al., 2001, 2003; Kokaia and Lindvall, 2003; Parent, 2003; Parent et al., 2002b; Zhang et al., 2004a,b, 2001) and the SGZ (Arvidsson et al., 2001; Jin et al., 2001; Kokaia and Lindvall, 2003; Parent, 2003). Interestingly, analysis of post-mortem brain samples from patients who suffered from stroke also revealed an enhanced neurogenesis in the SVZ (Macas et al., 2006). Increased neurogenesis in the SVZ and/or SGZ was also observed in many other pathological conditions such as seizures (Bengzon et al., 1997; Hellsten et al., 2004; Parent, 2003; Parent et al., 2002a, 1997; Scharfman, 2004), Huntington disease (Curtis et al., 2003, 2005) and Alzheimer disease (Jin et al., 2004a). In contrast, neurogenesis is diminished in Parkinson disease mainly because of the dopamine depletion that has been shown to play an important role in the proliferation of neuronal precursors in the SVZ (Hoglinger et al., 2004; Winner et al., 2006).

The adult brain reacts to different pathological conditions not only by enhancing the neurogenesis, but also by promoting migration of neuronal precursors to the sites of injury. In some pathological conditions, including physical injuries and neurodegenerative diseases, neuronal precursors cells are found at the site of damage in the brain (Goings et al., 2004; Gotts and Chesselet, 2005a; Nakatomi et al., 2002; Ohab and Carmichael, 2008; Picard-Riera et al., 2002). Following strokes, neuronal precursors are found in ischemic areas in the rodent striatum (Arvidsson et al., 2002; Jin et al., 2001; Parent et al., 2002b) and cortex (Jin et al., 2001, 2003; Ohab et al., 2006). Likewise, in patients with stroke, neuronal precursors are also found in the ischemic penumbra (Jin et al., 2006). Thus, after ischemic insult, migration is reduced in the SVZ–RMS–OB pathway (Ohab et al., 2006) and neuroblasts are derouted to the site of injury. Migration of endogenous neuronal precursors from the SVZ to the damaged brain regions have been demonstrated using bromodeoxyuridine (BrdU) labeling (Arvidsson et al., 2002; Parent et al., 2002b; Zhang et al., 2004a), DiI labeling (Jin et al., 2003), Cre-loxP reporter system (Yamashita et al., 2006), grafted cells in the SVZ (Zhang et al., 2003) and *ex vivo* imaging technique in the striatum of Dcx-eGFP mice (Zhang et al., 2009).

In the MCAO model, depending on the severity of the stroke, the damages are restricted either to the striatum or also reach the cortex (Thored et al., 2006). With the stroke damages being adjacent to the SVZ, the migration occurs within the region of ischemia (Carmichael, 2005; Jin et al., 2001; Ohab and Carmichael, 2008). In a model of focal cortical stroke, where ischemic cellular damage is localized in the somatosensory and motor cortex, more than 1 mm away from the SVZ (Ohab et al., 2006), the immature neurons navigate through undamaged regions of white matter before reaching the damaged cortex (Tsai et al., 2006).

Not only endogenous neuronal precursors are able to travel in the complex mature brain environment for long distance, but they also retain this migratory capacity for several months. In rats, the migration in post-stroke striatum occurs without decline for at least for 4 months (Thored et al., 2006). During this period neuroblasts that reach sites of injury either differentiate into mature neurons or undergo apoptosis through caspase-dependent mechanisms (Arvidsson et al., 2002; Parent et al., 2002b; Thored et al., 2006; Yamashita et al., 2006). The differentiated neuronal precursors express the phenotype of striatal projection neurons, the medium spiny neurons, which are the most affected cell type by the ischemic lesion (Arvidsson et al., 2002; Parent et al., 2002b). Electron microscopy studies revealed that these cells possess long processes, presynaptic vesicles and form synapses with neighboring cells (Yamashita et al., 2006). However, only a small fraction of migrating neuroblast in the post-stroke striatum mature, integrate and survive for a substantial amount of time (Arvidsson et al., 2002; Ohab et al., 2006; Zhang et al., 2001). According to the estimation made by Arvidsson et al. (2002) these newborn neurons represent only a tiny proportion of the destroyed cells (0.02%). These observations suggest that while re-routing the migration of neuronal precursors is used by the injured/diseased brain as a repair/compensation mechanism, its efficacy is still not sufficient. One of the possibilities to improve the repair of the injured neural circuitry could be the potentiation of the mechanisms that are already used by the adult brain for the replacement of the dying cells by the newcomers. In light of this, the recently discovered role of blood vessels in the migration of neuronal precursors under normal and pathological conditions give us new and important clues to better understand the mechanisms of neuronal recruitment to injured sites.

3. Vasophilic migration and neurovascular niche in post-stroke striatum

The first strong evidence for the importance of the vasculature in the process of neurogenesis was documented about 10 years ago, with the emergence of the “neurovasculature niche” concept (Leventhal et al., 1999; Louissaint et al., 2002; Palmer et al., 2000). It then started to become clear that vascular endothelial cells play a major role in neurogenesis by releasing soluble factors (Alvarez-Buylla and Lim, 2004; Leventhal et al., 1999; Shen et al., 2004; Wurmser et al., 2004). We now know that, not only does neurogenesis occur in close association with SVZ and SGZ endothelial cells in a neurovascular niche but, also, that neuroblasts migrate on blood vessels (Bovetti et al., 2007b; Saghatelyan, 2009; Shen et al., 2008; Snapyan et al., 2009; Tavazoie et al., 2008). There are now strong evidences that neuroblasts also use blood vessels for their migration into the ischemic striatum and as in the SVZ–RMS–OB pathway they do so in a chain-like structure (Yamashita et al., 2006; Zhang et al., 2004a, 2009). Blood vessels seem to serve as a physical scaffold as well as a source of molecular cues.

3.1. Evidences for physical proximity between neuroblasts and the vasculature in the post-stroke striatum

Immunohistological analysis of fixed brain specimens revealed that SVZ-derived neuroblasts are located in close proximity to blood vessels in the post-stroke striatum (Ohab et al., 2006; Thored et al., 2007; Yamashita et al., 2006). Neuroblasts are assembled in aggregates and either can be found as spherical clusters or as elongated chain-like structures. Interestingly, spherical clusters are at some distance from the vasculature whereas all the chain-like structures are found around vascular endothelial cells (Yamashita et al., 2006). This blood vessels-associated migration is sustained up to 4 months post-injury (Thored et al., 2007). Importantly, in patients with stroke, newborn Dcx+ cells are also found in the ischemic penumbra in the vicinity of blood vessels (Jin et al., 2006).

This vasculature-associated chain migration of Dcx-eGFP+ neuroblasts has been visualized in living slices of ischemic brains using time-lapse microscopy (Zhang et al., 2009). Migrating chains from the SVZ to the ischemic striatum are very long with an average length of approximately 450 μm. Neuroblasts in the chains are highly motile and actively extend or retract their processes. Individual neuroblasts sometimes move away from the chain but usually end-up by re-joining the same or neighboring chains. In the ischemic striatum, some chains are parallel to blood vessels and

individual neuroblasts also use vessels for their migration. Neuroblasts at the end of the chains migrate out of the chain toward a blood vessel and form clusters nearby. The cells within these clusters move around the vessels and exhibit multiple branches (Zhang et al., 2009).

3.2. Causal relationships between neuroblasts migration and the vasculature after stroke

As it is stated above, angiogenesis and neurogenesis are associated in the normal (non-stroke) germinal zones of the adult brain (Alvarez-Buylla and Lim, 2004; Louissaint et al., 2002; Wurmser et al., 2004). It is therefore not surprising that following stroke angiogenesis and neurogenesis are enhanced and appear in the same spatiotemporal frame (Gotts and Chesselet, 2005b; Hellsten et al., 2004). SVZ progenitor cells up-regulate the expression of many genes associated with angiogenesis and neurogenesis following stroke when compared to non-stroke SVZ cells (Beck and Plate, 2009; Liu et al., 2007). Angiogenesis is detected during the first 2 weeks in the post-stroke striatum which also exhibit a long-lasting increase in the vascularization (Thored et al., 2007). Following stroke, neuroblasts closely associate not only with functional blood vessels but also with the remodeling vasculature that did not yet receive vascular flow (Ohab et al., 2006).

Angiogenesis occurs in the peri-infarct tissue (Beck and Plate, 2009; Hayashi et al., 2006; Ohab et al., 2006), an area that is hypoxic (Marti et al., 2000; Thored et al., 2007). *In vitro* experiments, using rat organotypic hippocampal cultures exposed to 6 h of hypoxia, showed that hypoxia activates proliferation and differentiation of neural progenitor cells (Zhou and Miller, 2006). Proliferation of neural stem cells also occurs *in vivo*, in the SVZ and DG of adult rats exposed to intermittent hypoxia (exposed to high altitude 4 h per day for 2 weeks) (Zhu et al., 2005). Following ischemia, hypoxia is believed to stimulate angiogenesis through activation of the vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), erythropoietin (EPO) and angiopoietin–tie receptor systems (Beck and Plate, 2009; Marti et al., 2000). VEGF is inducible by hypoxia (Gleadle et al., 1995; Ikeda et al., 1995; Marti and Risau, 1998; Shweiki et al., 1992) and known to be a main regulator of angiogenesis (Ferrara, 1995). VEGF is up-regulated in the brain after ischemic or physical injury (Cobbs et al., 1998; Hayashi et al., 1997; Jin et al., 2000; Kovacs et al., 1996; Lennmyr et al., 1998). In the ischemic border, there is an up-regulation of VEGF, followed by an up-regulation of both VEGF receptors (VEGFR-1 and VEGFR-2) (Beck and Plate, 2009; Marti et al., 2000). VEGFR-1 mRNA is up-regulated in peri-ischemic endothelial cells (Plate et al., 1999). Following stroke, immunostaining of VEGFR-1 is increased in endothelial cells, neurons and glial cells whereas VEGFR-2 immunoreactivity is prominent in glial cells but is also detected in endothelial cells (Lennmyr et al., 1998). A causal relationship between neurogenesis and angiogenesis and its dependence on VEGF has been also demonstrated using the co-culture system (Teng et al., 2008). When neural progenitor cells isolated from SVZ of normal adult rats were cultured with endothelial cells isolated from the stroke boundary, their proliferation and neuronal differentiation was increased. On the other hand, supernatant obtained from stroke SVZ cells which was found to contain high levels of VEGF promoted capillary tube formation of normal cerebral endothelial cells. Inhibition of VEGFR-2 completely abolished supernatant-induced angiogenesis and also suppressed the effect of stroke-activated endothelial cells on neurogenesis (Teng et al., 2008).

Hypoxia also stimulates BDNF secretion from brain endothelial cells as shown by *in vitro* studies using the mouse brain microvascular endothelial cell line (Wang et al., 2006a). Cultures of brain-derived endothelial cells produce BDNF which has a humoral neurotrophic effect on neuronal precursors (Leventhal et al., 1999). BDNF produced by cerebral endothelial cells can also protect neurons against oxygen–glucose deprivation, oxidative damage and hypoxia (Guo et al., 2008). Gain and loss of function studies showed that BDNF has mitogenic and anti-apoptotic effects on neuronal cells in the SVZ–RMS–OB system (Linnarsson et al., 2000; Pencea et al., 2001b; Young et al., 2007; Zigova et al., 1998), but see also (Galvao et al., 2008). Intriguingly, using the same approach to deliver exogenous BDNF into the lateral ventricle, Pencea et al. (2001b) have reported an increased number of BrdU+ cells in the OB, whereas Galvao et al. (2008) did not found any changes in the number of newly generated bulbar neurons. The reasons for such discrepancy are not yet clear. In the normal adult RMS, BDNF mRNA is expressed in the endothelial cells of the blood vessels where it plays a central role in the vasculature-guided migration (Snapyan et al., 2009). BDNF expression is regulated by endothelial nitric oxide synthase (eNOS) (Chen et al., 2005). This enzyme was also found to be a downstream mediator of VEGF. Therefore, eNOS phosphorylation has an impact on angiogenesis, progenitor cell proliferation, neuronal migration, neurite outgrowth and also affects functional recovery after stroke (Chen et al., 2005). Nitric oxide, produced by eNOS plays a crucial role in the regulation of systemic blood pressure, vascular tone, vascular remodeling and angiogenesis (Murohara et al., 1998; Rudic et al., 1998).

Another causal interaction between neuroblast migration and the vasculature in post-stroke striatum implies SDF-1. Following stroke, hypoxia up-regulates SDF-1 (Imitola et al., 2004; Ohab et al., 2006; Robin et al., 2006; Thored et al., 2006) and Ang1 (Ohab et al., 2006) in the endothelial cells of the blood vessels in the peri-infarct areas whereas no specific SDF-1 staining is seen in uninjured striatum (Thored et al., 2006). Many SDF-1+ cells are also GFAP+ and thought to be reactive astrocytes (Imitola et al., 2004; Thored et al., 2006). Neural precursor cells and migrating neuroblasts express SDF-1 receptor, CXCR4 (Imitola et al., 2004; Ohab et al., 2006; Robin et al., 2006; Thored et al., 2006) and Ang1 receptor, Tie2 (Ohab et al., 2006). Pharmacological blockade of CXCR4 results in the attenuation of the migration (Ohab et al., 2006; Robin et al., 2006; Thored et al., 2006). In addition, exposure of SDF-1alpha to quiescent neural stem cells enhance proliferation, promote chain migration and transmigration in a dose-dependent manner (Imitola et al., 2004; Robin et al., 2006; Thored et al., 2006). *In vivo* administration of SDF-1beta or Ang1 causes a dose-dependent increase in the recruitment of neuroblasts to the site of infarct and lead to the behavioral recovery (Ohab et al., 2006).

The extracellular matrix molecules (ECM) and matrix metalloproteinases (MMPs), that are responsible for ECM modification, might also be important players of the vasculature-guided migration of neuronal precursors to the post-stroke striatum. After stroke, migrating neuroblasts express MMP9. *In vivo*, inhibition of MMP activity reduces migration in post-stroke brain (Lee et al., 2006). *In vitro* experiment showed that endothelial cells, activated by erythropoietin (EPO) significantly increase secretion of MMP2 and MMP9 which could enhance the migration of neural progenitor cells (Wang et al., 2006b). In the normal adult rodent OB, neuroblasts associate with blood vessels trough an ECM-astrocyte end foot interaction (Bovetti et al., 2007b). Inhibition of MMPs, inhibits tangential and radial migration in the RMS and OB (Bovetti et al., 2007a). A disintegrin and metalloproteinase 21 (ADAM21) could also play a role in neurogenesis and neuroblast migration. ADAM21 is expressed in the adult rodent ependyma and SVZ cells with long basal processes. ADAM21+ processes are also present within the RMS, where they are intermingled with neuroblasts and contact the blood vessels (Yang et al., 2005).

EPO, the principal growth factor that regulates red blood cells production and its receptor EpoR are also induced in hypoxic conditions (Bernaudin et al., 1999; Marti et al., 1996). In EpoR conditional knock-down animals, SVZ cell proliferation is reduced and, in post-stroke conditions, lower number of Dcx+ cells reach the site of injury (Tsai et al., 2006). In addition, exogenous EPO have neuroprotective and neurotrophic effects in many type of brain injury models, including ischemia (Brines et al., 2000). However, endogenous levels of EPO and EpoR seem to have limited neuroprotective effects (Tsai et al., 2006). Exogenous EPO enhances angiogenesis and neurogenesis *in vivo* and *in vitro* and improves neurological outcomes following stroke (Wang et al., 2004). EPO seems to act through both BDNF and VEGF signaling pathways. Indeed, treatment with EPO *in vivo* increases brain levels of BDNF and VEGF and EPO-induced capillary-like tube formation is blocked by VEGFR-2 antagonist (Wang et al., 2004).

4. Toward efficient neuronal replacement: how to influence and improve these mechanisms?

As it is outlined above, many of the cellular and molecular factors involved in the migration of neuroblasts to ischemic sites are major constituents of the neurovasculature niche. While a substantial amount of work is still awaited to elucidate the exact molecular guidance systems mediating neuroblasts migration into post-stroke striatum, in this section we review some molecular cues that have been used or has a potential to de-route migration and/or enhance neuroblasts recruitment to lesion sites.

4.1. VEGF

In transgenic mice over-expressing VEGF, migration of neuronal precursors toward peri-infarct cortical areas is increased following MCAO. About 80% more BrdU/NeuN-positive cells were found in the stroke penumbra of transgenic mice when compared to wild-type animals 21 days post-MCAO. VEGF over-expression also enhances SVZ neurogenesis, reduces infarct volume and improves post-ischemic motor function (Wang et al., 2007). Infusion of VEGF (intracerebroventricularly for 3 days) after stroke also promotes angiogenesis, reduces the infarct volume and improves neurological function (Sun et al., 2003; Zhang et al., 2000). Timing of the administration of VEGF seems to be important since delayed, but not early, post-stroke administration of VEGF improves neurological recovery. This is likely due to VEGFs ability to enhance vascular permeability that may cause edema (Beck and Plate, 2009; Sun et al., 2003; Zhang et al., 2000).

4.2. BDNF

Intraventricular administration of BDNF in normal adult rats results in recruitment of new neurons to the striatum (Benraiss et al., 2001; Pencea et al., 2001b). Newly generated cells found in the striatum express the neuronal marker microtubule-associated protein-2 (MAP-2) or neuron-specific tubulin (TuJ1) (Pencea et al., 2001b). Neuronal recruitment to the neostriatum also occurs 18 days following injection in the lateral ventricule of an adeno-virus carrying the BDNF (AdBDNF) gene. Many of these cells also express markers of medium spiny neurons (MSNs). These newly generated neurons survive for at least 5–8 weeks after viral induction (Benraiss et al., 2001). The number of newborn cells with MSN phenotype can also be increase in the striatum of adult primates by the injection of AdBDNF (Bedard et al., 2006). Furthermore, the neuronal addition can be enhanced by adding with AdBDNF adenovirally expressed noggin (AdNoggin) that inhibits glial differentiation of the progenitor cells and boosts BDNF-mediated neuronal recruitment (Chmielnicki et al., 2004). The new MSNs extend long processes and successfully project to their target region, the globus pallidus (Chmielnicki et al., 2004).

Anterograde delivery of BDNF to striatum (by injection of a recombinant adeno-associated viral vector carrying a BDNF gene in the substantia nigra) several weeks before MCAO highly increases BDNF level and significantly augment the number of migrating cells in the lesioned striatum. However, the continuous delivery of BDNF before the infarct does not protect projection neurons from stroke-induced damage and exaggerates the loss of many interneurons. This method results in very high striatal levels of BDNF and produces motor abnormalities in rats (with and without stroke) (Gustafsson et al., 2003a). In another study BDNF was injected exogenously into the striatum of adult mice 7 days before MCAO, using an AdBDNF regulated by hypoxia responsive element (Ad5HRE:BDNF) (Shi et al., 2009). This method did result in a reduction of the infarct volume and improvement of sensorimotor scores. Intravenous administration of BDNF during the first 5 days after the stroke improved sensorimotor behavior and induces increased neurogenesis and enhanced migration of SVZ-derived progenitors to the striatum (Schabitz et al., 2007). By contrast, intrahippocampal delivery of BDNF 5 weeks before to the ischemic insult suppresses the dentate gyrus neurogenesis (Larsson et al., 2002). In line with these results, the same group has shown that intraventricular infusion of TrkB-Fc fusion protein to trap endogenous BDNF is beneficial for the stroke-induced generation of newborn neurons in the hippocampus (Gustafsson et al., 2003b). Therefore, timing and dosage seems to be important for BDNF delivery as well.

4.3. Angiopoietin 1(Ang1) and stromal-derived factor 1 (SDF-1)

As discussed earlier, administration of Ang1 and SDF-1 promote neuroblasts migration to the site of injury following stroke. Ohab et al. (2006) used a focal cerebral stroke model in mice and delivered through osmotic minipumps low and high doses of recombinant Ang1 and SDF-1. The drugs were delivered systematically for 7 days after stroke. The effect of SDF-1 was dose-specific. Thousands of additional neuroblasts reached the peri-infarct cortex specifically clustered around blood vessels. Administration of both high and low doses of Ang1 resulted in approximately 5000 more neuroblasts in peri-infarct cortex. Administration of Ang1 and SDF-1beta improves behavioral recovery after stroke (Ohab et al., 2006).

4.4. Tenascin-R

Tenascin-R (TNR) is an ECM molecule involved in cell detachment and radial migration in the OB. Grafting tenascin-R-transfected cells into the striatum of the adult mice de-routes migrating neuroblasts toward this region. While ectopic expression of TNR resulted in a 4- to 6-fold greater number of neuroblasts migrating out of the SVZ as compared with control grafted cells (Saghatelyan et al., 2004), its regulation following ischemia and implication in the stroke-induced migration of neuroblasts into the sites of injury still needs to be demonstrated.

4.5. Erythropoietin

Intraperitoneal administration of recombinant human EPO (rhEPO) to adult rats following stroke results in enhanced recruitment of neuroblasts into the ischemic boundary of the cortex and striatum. It also increases angiogenesis and improves neurological outcomes (Wang et al., 2004, 2006b). EPO appears to act directly on the stem cells, promoting the production of neuronal progenitors at

the expense of transient amplifying cell population (Shingo et al., 2001).

4.6. FGF

Adenovirally mediated transfer of the FGF-2 gene, in the ventricles of adult gerbils, promote progenitor cell proliferation. It also resulted in a mild increase in the number of BrdU+ cells in the cortex of the normal animals and in a dramatic increase in the cortex of animals that received post-stroke injection. This treatment worked more efficiently than continuous intraventricular infusion of the FGF-2 protein, for which no BrdU+ cells were found in the cerebral cortex (Matsuoka et al., 2003).

4.7. EGF

Intraventricular administration of human recombinant epidermal growth factor (EGF) after focal cerebral ischemia in adult mice enhances the neuronal recruitment process and leads to 100-fold increase in the number of new neurons expressing mature parvalbumin+ neuronal phenotype. Surprisingly, while no endogenous EGF expression is detected in the post-stroke striatum, using Western blot analysis, neuronal precursors (nestin+ cells) express EGF receptor in post-ischemic SVZ (Teramoto et al., 2003). Recently, it has been demonstrated that in a rat model of stroke, when EGF and EPO are intraventriculary infused together, but not individually, they promote substantial regeneration of the damaged cerebral cortex and reverse impairments in spontaneous and skilled motor tasks (Kolb et al., 2007). This recovery is largely due to the migration of neuronal precursors from the SVZ into the injured regions in the cerebral cortex (Kolb et al., 2007). Jin and colleagues studied the effect of another member of EGF family, the heparin-binding epidermal growth factor-like growth factor (HB-EGF) (Jin et al., 2004b). HB-EGF administration was made via the intracerebroventricular route, 1–3 days after focal cerebral ischemia in adult rats. Although they found a reduced infarct size and improved behavioral recovery when compared to control, the number of newborn neurons that migrated into the ischemic striatum was decreased (Jin et al., 2004b).

5. Concluding remarks

The possibility of manipulating the molecular and cellular mechanisms that control neuronal migration, maturation and integration in the adult brain, so as to increase the number, dispersal and survival of neurons in the diseased areas may open novel avenues for the treatment of devastating neurodegenerative diseases and brain trauma. As it is outlined above, stroke induces massive migration of endogenous neuronal precursors from their generation site (SVZ) to the damaged brain region. These observations suggest that strategy of re-routing the migration of neuronal precursors might be already used by the injured brain as a repair/compensation mechanism. If so, then it also suggests that intervening in this process could be an effective therapy to treat brain injuries. Interestingly, adult brain reacts to stroke by up-regulating the mechanisms that are already at play during constitutive neuronal replacement process in the OB and hippocampus. It is still not clear, however, to which degree the mechanisms of ***induced*** and ***constitutive*** neuronal migrations overlap. While the substantial amount of evidences suggests that the general strategy of cell navigation in the healthy uninjured brain is recapitulated after the injury, stroke also induces some cellular and molecular changes that are specific to the ischemic penumbra. It is thus conceivable that the dynamic and the mechanisms of neuronal precursors' guidance employed by the adult brain might be modulated by the microenvironment and molecular cues specific to the sites of injury. In order to get further understanding to the processes of neuronal navigation in the diseased/damaged brain areas, it would be important to perform comparative studies on the mechanisms involved in the constitutive cell migration and those employed after injury. It is conceivable that the knowledge about similarities and differences in the migration (as well as maturation and survival) pattern of newborn cells in the normal and diseased brain areas will allow to discern the general intrinsic molecular and cellular mechanisms orchestrating the cell guidance process in the adult brain as well as stroke-induced micro-environmental cues influencing it. Another important avenue in the stroke-induced neuronal replacement research would be the validation of the molecular mechanisms discovered in the rodent models, in the human and non-human primates as well as in the post-mortem tissues derived from patients who suffered stroke. Altogether, this knowledge will be important for the development and design of new strategies aiming to control not only the navigation of endogenous neuronal precursors but also the dispersal of exogenously grafted progenitors in the injured brain.

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