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Ischemia-Induced Neural Stem/Progenitor Cells Within the Post-Stroke Cortex in Adult Brains

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1. Introduction

Stroke is one of the major causes of death and disability in developed countries. The central nervous system (CNS) is known for its limited reparative capacity, but several studies demonstrated that the CNS has some reparative potential and cerebral ischemia is followed by activation of endogenous neurogenesis (Nakatomi *et al.*, 2002; Taguchi *et al.*, 2004). It is well-known that new neurons are continuously generated in specific brain regions such as the subventricular zones (SVZ) (Alvarez-Buylla *et al.*, 2002) and the subgranular zone within the dentate gyrus of the hippocampus (SGZ) (Kuhn *et al.*, 1996). Although adult cerebral cortical neurogenesis remains controversial, accumulating evidence has shown that under pathological conditions, new neurons are generated in the adult mammalian cerebral cortex (Magavi *et al.*, 2000; Jiang *et al.*, 2001; Jin *et al.*, 2006; Yang *et al.*, 2007). This suggests that neural stem/progenitor cells (NSPCs) can be activated in the cortex by brain injury such as ischemic stroke. In support of this notion, we demonstrated that NSPCs develop in the post-stroke area of the cortex in the adult murine (Nakagomi *et al.*, 2009a; Nakagomi *et al.*, 2009b; Nakano-Doi *et al.*, 2010; Saino *et al.*, 2010) and human brain (Nakayama *et al.*, 2010), and we referred to these as ischemia/injury-induced NSPCs (iNSPCs). These cells express markers of NSPCs, such as nestin and Sox2. They also form neurospheres that have the capacity for self-renewal, and differentiate into electrophysiologically functional neurons, astrocytes, and myelin-producing oligodendrocytes (Nakagomi *et al.*, 2009a; Nakagomi *et al.*, 2009b; Nakano-Doi *et al.*, 2010; Clausen *et al.*, 2011). In addition, we demonstrated that iNSPCs originate, at least in part, from within the cerebral cortex, but not from SVZ cells (Nakagomi *et al.*, 2009b). However, the detailed origin and identity of the iNSPCs remains unclear. In this chapter, we introduce the characterization and possible origin of iNSPCs based on our reports and recent viewpoint, and compare them to other previously reported types of CNS stem/progenitor cells, including SVZ astrocytes (Doetsch *et al.*, 1999), ependymal cells (Moreno-Manzano *et al.*, 2009), reactive astrocytes (Shimada *et al.*, 2010), resident glia (Zawadzka *et al.*, 2010), and oligodendrocyte precursor cells (OPCs) (Kondo *et al.*, 2000). We also refer to the possible cortical neurogenesis by iNSPCs and to the therapeutic potential of iNSPC transplantation in stroke patients.

2. NSPCs in the adult cortex

In the CNS of adult mammals, it is well-known that NSPCs are present in the SVZ and SVG, and that ongoing neurogenesis is retained in these two zones. However, accumulating evidence suggests that NSPCs reside in many parts of the adult brain including the cortex (Arsenijevic *et al.*, 2001; Joh *et al.*, 2005; Kallur *et al.*, 2006; Jiao *et al.*, 2008; Willaime-Morawek *et al.*, 2008), striatum (Kallur *et al.*, 2006; Willaime-Morawek *et al.*, 2008), subcortical white matter (Nunes *et al.*, 2003), and spinal cord (Weiss *et al.*, 1996; Parr *et al.*, 2008). These observations suggest that NSPCs are widely distributed throughout the adult CNS. In this chapter, we introduce iNSPCs, which are induced within the post-stroke cortex after brain injury/ischemia in adult brains.

2.1 Cortical development in the embryonic stage: comparison to iNSPCs in the cortex

In the embryonic stage, neurogenesis was observed throughout the CNS including the cortex. Mignone and colleagues traced nestin-expressing NSPCs, and showed that green fluorescent protein (GFP) expression in developing transgenic nestin-GFP mice was evident on as early as day 7 of embryonic development (e7). At e8, a GFP signal was observed predominantly in the neural plate, and by e10 intense GFP fluorescence was observed throughout the neuroepithelium. At e10 to e12, GFP signals marked the entire thickness of the cerebral wall, but GFP expression became weaker near the pial surface and stronger in the ventricular zones starting from e12. Finally, in the adult brain, GFP was selectively expressed in the SVZ and SGZ in areas related to continuous neurogenesis (Mignone *et al.*, 2004). Thus, in the postnatal CNS, constitutive neurogenesis is known to be retained in only two regions the SVZ (Alvarez-Buylla *et al.*, 2002) and SGZ (Kuhn *et al.*, 1996). However, under pathological conditions, neurogenesis may occur again in the adult cerebral cortex (Magavi *et al.*, 2000; Jiang *et al.*, 2001; Jin *et al.*, 2006; Yang *et al.*, 2007). Supporting their observations, nestin-positive NSPCs were observed after brain injury/ischemia in nonconventional neurogenic zones, such as the cortex (Nakagomi *et al.*, 2009b; Nakayama *et al.*, 2010). Because they were rarely observed in the absence of brain injury (Nakagomi *et al.*, 2009b), cortical neurogenesis may reoccur only in the case of brain injury. These findings suggest that in adult mammalian brains, NSPC activation and neuronal homeostasis are maintained under physiological conditions, at least in part, in specific brain regions, such as the SVZ and SGZ. However, after brain injury, it appears that regional NSPCs are mobilized to accelerate tissue repair by a mechanism similar to embryonic neurogenesis. Taken together, these observations suggest that ischemia/hypoxia is essential for the induction of NSPCs in the adult cortex, although we remain unaware of the required signaling and/or factors.

2.1.1 Characteristics of iNSPCs from the post-stroke cortex

To confirm the possible adult neurogenesis induced by brain injury, we have sought to isolate NSPCs from the injured area of the post-stroke cortex. Previously, we established a highly reproducible murine model of cortical infarction using CB-17/Icr-+/+Jcl and CB-17/Icr-Scid/scid Jcl mice. The infarct area in mice of this background has been limited to the ipsilateral cerebral cortex of the territory occupied by the middle cerebral artery (MCA) (Taguchi *et al.*, 2004; Taguchi *et al.*, 2007; Nakagomi *et al.*, 2009a; Nakagomi *et al.*, 2009b;

Nakano-Doi *et al.*, 2010; Saino *et al.*, 2010; Taguchi *et al.*, 2010). Following MCA occlusion, abundant nestin-positive cells emerged within the post-stroke cortex, although they were rarely observed in the non-ischemic cortex (Nakagomi *et al.*, 2009b; Nakano-Doi *et al.*, 2010; Saino *et al.*, 2010). To examine whether these cells showed stem cell-characteristics, we cultured cells isolated from the post-stroke cortex under conditions that promoted the formation of neurospheres (Reynolds *et al.*, 1992). In brief, tissue from the ischemic core of the post-infarct cerebral cortex was obtained on day 7 after MCA occlusion. Cells were dissociated by passage through 23 and 27 gauge needles, and cell suspensions were incubated in tissue culture flasks with DMEM containing epidermal growth factor (EGF), basic fibroblast growth factor (bFGF) and N2 supplement. This procedure allowed us to obtain nestin-positive neurosphere-like cell clusters (iNSPCs) (Nakagomi *et al.*, 2009a; Nakagomi *et al.*, 2009b; Nakano-Doi *et al.*, 2010) (Fig. 1).

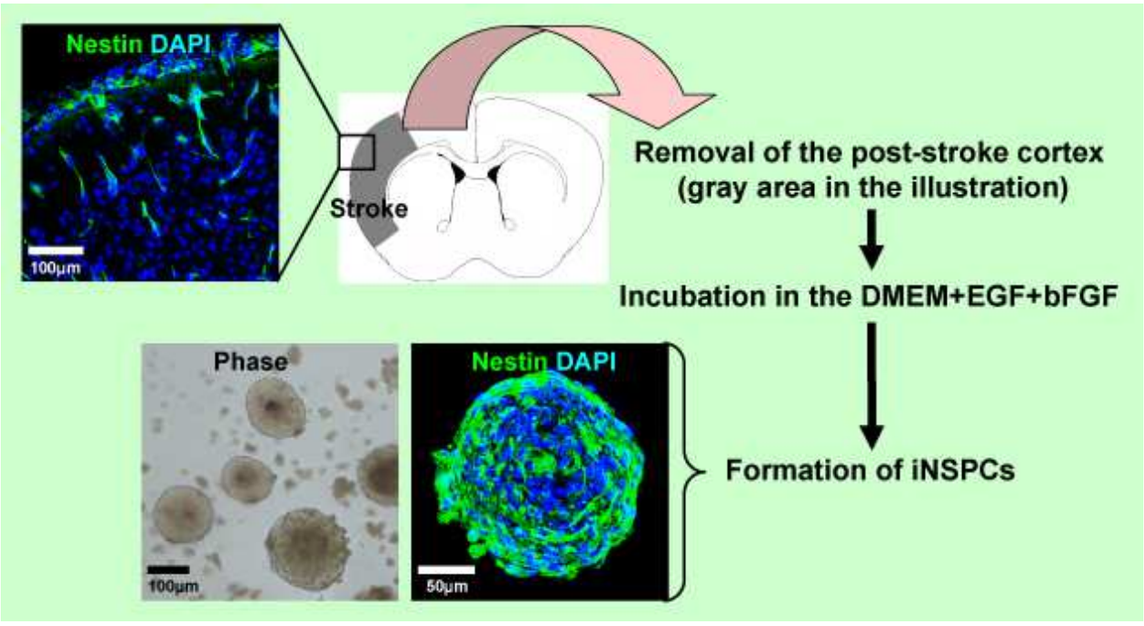


Fig. 1. Isolation of nestin-positive iNSPCs developing within the post-stroke cortex

However, iNSPCs were rarely obtained in the absence of brain injury. Notably, because we could not obtain iNSPCs from the peri-stroke cortex, it is possible that these cells are generated within the degenerating cortical tissue after ischemic stroke.

Uptake of 5-bromo-2′-deoxyuridine (BrdU) by iNSPCs was confirmed *in vivo* (Nakano-Doi *et al.*, 2010; Saino *et al.*, 2010) and *in vitro* (Nakagomi *et al.*, 2009a; Nakagomi *et al.*, 2009b), showing that they have the proliferative activity. They possessed self-renewal capacity, which was confirmed by a clonal assay. However, in contrast to the embryonic stem cells, the cluster formation in the same medium at a clonal density was limited to between three and five cell passages (Nakagomi *et al.*, 2009b; Nakano-Doi *et al.*, 2010), consistent with other adult candidates of stem cells, such as neurospheres derived from hippocampus (Bull *et al.*, 2005) and subcortical white matter (Nunes *et al.*, 2003). These observations suggest that cortex-derived iNSPCs are more likely to be neural progenitors than neural stem cells (NSCs). However, they certainly differentiated into electrophysiologically functional

neurons, astrocytes, and myelin-producing oligodendrocytes (Nakagomi *et al.*, 2009a; Nakagomi *et al.*, 2009b; Nakano-Doi *et al.*, 2010), indicating that iNSPCs have a stemness-capacity similar to other adult NSPCs. Interestingly, they predominantly differentiated into neurons (approximately 35%) and oligodendrocytes (approximately 30%) rather than astrocytes (approximately 5%) (Nakagomi *et al.*, 2009a; Nakano-Doi *et al.*, 2010; Nakagomi *et al.*, 2011) with characteristics discriminating from other adult NSPCs such as SVZ astrocytes, most of which are known to differentiate into astrocytes. These findings suggest that iNSPCs have a strong potential of contributing to cortical neurogenesis compared to NSPCs derived from other origins, especially under the conditions of brain injury.

Consistent with the SVZ-derived NSPCs (Kim *et al.*, 2009b), cortical iNSPCs expressed several pluripotent/undifferentiated cell markers, including Sox2, Klf4, c-myc and Nanog (Nakagomi *et al.*, 2009b; Nakagomi *et al.*, 2011). However, expression of various pluripotent/undifferentiated cell markers was not observed in the cortex without brain injury. These observations suggest that cell reprogramming may occur in unknown cells of the cortex in response to brain injury/ischemia, thereby promoting the induction of iNSPCs. However, further studies are needed to clarify this hypothesis.

2.1.2 Comparison to other types of reported CNS stem/progenitor cells

Accumulating evidence has shown several candidates for adult NSPCs, which can contribute to adult neurogenesis in the cerebral cortex. One of these candidates may be radial glia cells, which are derived from neuroepithelial cells and functions as NSPCs during development. The radial glia are able to develop into several types of NSPCs, such as SVZ astrocytes, ependymal cells, and OPCs in adult (Kriegstein *et al.*, 2009). However, precise cell source of cortical NSPCs remains unclear, especially in the injured brain.

Previous studies demonstrated that SVZ astrocytes have the capacity to migrate towards injured lesions, including the cerebral cortex (Goings *et al.*, 2004). However, our study using GFP-expressing vector, failed to demonstrate cell migration from the SVZ to the cortex after cerebral infarction *in vivo*, but demonstrated that iNSPCs in the post-stroke cortex originated, at least in part, from the cerebral cortex (Nakagomi *et al.*, 2009b). Consistently, subsequent studies showed that NSPCs developing within and around the post-stroke cortex are derived from locally activated stem/progenitor cells, but not from SVZ cells (Ohira *et al.*, 2010; Shimada *et al.*, 2010). To answer which cells can be activated by cerebral injury, some studies proposed the reactive astrocytes as a source of injury-induced NSPCs (Oki *et al.*, 2010; Shimada *et al.*, 2010), because NSPCs express the astrocyte marker, GFAP. However, we could not detect GFAP- (Nakagomi *et al.*, 2011) and S100β-positive astrocytes within the post-stroke cortex (Nakagomi *et al.*, 2009b). Eventually, the isolated iNSPCs from the infarct cortex rarely expressed GFAP and developed few astrocytic traits even after differentiation (Nakagomi *et al.*, 2011). In addition, although we found some nestin and GFAP double-positive reactive astrocyte-like cells in the peri-infarct area, we could not obtain neurospheres from these areas. These findings strongly suggest that the source of iNSPCs within the infarct cortex is distinct from reactive astrocytes.

Currently, it is still highly controversial whether periventricular NSPCs can be derived from SVZ astrocytes, ependymal cells, or both (Chojnacki *et al.*, 2009). Ependymal cells were originally considered to be the resident stem cell population in the wall of the lateral

ventricle, in which they locate nearby perivascular cells (Pfenninger *et al.*, 2007; Coskun *et al.*, 2008). Although it is controversial whether ependymal cells have NSPC activity or not, recent studies confirmed that ependymal cells do not play a role in adult neurogenesis under normal conditions, but do possess NSPC activity and can differentiate into neurons, astrocytes, and oligodendrocytes in response to the CNS injuries including ischemic stroke (Carlen *et al.*, 2009; Moreno-Manzano *et al.*, 2009). Furthermore, ependymal cells express PDGFRα (Danilov *et al.*, 2009) and NG2 (Moreno-Manzano *et al.*, 2009), and have the structure of lipid droplets, microvilli, and cilia (Coskun *et al.*, 2008; Danilov *et al.*, 2009). Consistent with the traits of ependymal cells, iNSPCs express PDGFRα and NG2, but do not possess microvilli-like structures (Nakagomi *et al.*, 2011). These findings indicate that iNSPCs do not have completely identical characteristics to those of ependymal cells.

Adult OPCs comprise approximately 5%–8% of the glial cell population in the CNS. Their function in the CNS remains unknown, although accumulating evidence has shown that they have NSPC activity (Kondo *et al.*, 2000; Gaughwin *et al.*, 2006), in addition to myelin-producing abilities (Sundberg *et al.*, 2010). OPCs are known to express NG2 (Ulrich *et al.*, 2008) and PDGFRα (Hall *et al.*, 1996), and OPCs expressing A2B5 have NSPC activity (Kondo *et al.*, 2000; Gaughwin *et al.*, 2006). To investigate whether iNSPCs are derived from OPCs, we analyzed OPC markers expressed by iNSPCs *in vivo* and *in vitro*. Although iNSPCs express some OPC markers such as NG2 and PDGFRα, they do not possess A2B5 or even Olig2 (another OPC marker) (Billon *et al.*, 2002). These observations indicate that iNSPCs are different from reported multipotent OPCs (Kondo *et al.*, 2000; Gaughwin *et al.*, 2006). However, when iNSPCs were incubated in OPC-promoting medium (Chen *et al.*, 2007), they began to express Olig2. In addition, almost all cells developed from iNSPCs in this medium differentiated into O4- and/or myelin-associated glycoprotein (MAG)-positive oligodendrocytes (Nakagomi *et al.*, 2011). These findings suggest that iNSPCs express some OPC markers during their development/differentiation.

It is well-known that NG2 is not only the marker of OPC, but is also the marker of resident glial cells/glial progenitors (Stallcup *et al.*, 1987). More recently, NG2-positive resident glia was reported to develop NSPC activity after brain injury (Yokoyama *et al.*, 2006; Zawadzka *et al.*, 2010). We demonstrated that cortical iNSPCs express NG2 and PDGFRα in a similar manner to resident glial/progenitor cells. However, neuronal differentiation from NG2- and/or PDGFRα-positive glial cells is rarely observed (Zawadzka *et al.*, 2010; Richardson *et al.*, 2011), suggesting that iNSPCs may be different from these glial cells or belonging to unknown cell type, which expresses some glial markers.

2.1.3 What is the origin of iNSPCs in the cortex?

So far, it seems possible that iNSPCs are different from previously proposed CNS stem/progenitor cells such as SVZ astrocytes, reactive astrocytes, ependymal cells, or OPCs. The essential difference of these cells may be their induction pattern and localization, because iNSPCs were found only after ischemic insult, and in close association with the blood vessels in the cortex. This unique localization allowed us to examine the characteristics of cells nearby blood vessels as a candidate of iNSPCs.

Our studies showed that the nestin-positive iNSPCs developed in the perivascular regions of the post-stroke cortex (Nakano-Doi *et al.*, 2010; Nakayama *et al.*, 2010), where nestin-positive

cells express NG2 and PDGFRβ (both of which are the pericyte marker), suggesting that the iNSPCs are derived from pericytes. Pericytes with multipotent progenitor activity have been indentified in various organs (Crisan *et al.*, 2009) as well as in the CNS (Dore-Duffy *et al.*, 2006). In addition, Dore-Duffy and colleagues (Dore-Duffy *et al.*, 2006) showed that pericyte-derived NSPCs can be isolated from the CNS of non-injured animals. However, we hardly obtained iNSPCs from the nonischemic cortex (Nakagomi *et al.*, 2009b), suggesting that pericytes in the cortical tissues increase their stemness activity during the progression of cerebral injury.

Increasing evidence has shown that ischemic insult promotes stem cell activity, and NSPCs (Sirko *et al.*, 2009; Xue *et al.*, 2009) and neuronal progenitors (Ohira *et al.*, 2010) are also induced in response to cortical ischemic injury. These cortical NSPCs are frequently observed at the subpial/cortical layer 1 regions, suggesting that NSPCs can be activated preferentially in the cortical surface. Independent of these studies, we found nestin/Sox2-positive iNSPCs proliferating in the pia mater, which covers the surface of the post-ischemic cortex (Nakagomi *et al.*, 2011). Pia mater is widely distributed throughout the CNS, and is closely associated with the blood vessels. It has been reported that leptomeninges (including pia mater and arachnoid membrane) regulate NSPCs (Sockanathan *et al.*, 2009) and cortical neuron generation (Siegenthaler *et al.*, 2009) in embryonic cortical formation, and function as a niche for stem/progenitor cells with neuronal differentiation potential (Bifari *et al.*, 2009). These findings suggest that pia mater contains NSPCs at embryonic stage. The pial iNSPCs, which we found in the adult brain, partially spread into the cortical parenchyma as perivascular cells/pericytes with expression of pericyte markers such as NG2 and PDGFRβ. In addition, cells isolated from the infarcted area including pia mater and cortex and sorted by magnetic cell sorting (MACS) with a pericyte marker (PDGFRβ) had NSPC activity and differentiated into neurons (Nakagomi *et al.*, 2011). These findings indicate that the microvascular pericytes that distribute from the pia mater to the cortex are a potential source of the iNSPCs (Fig. 2).

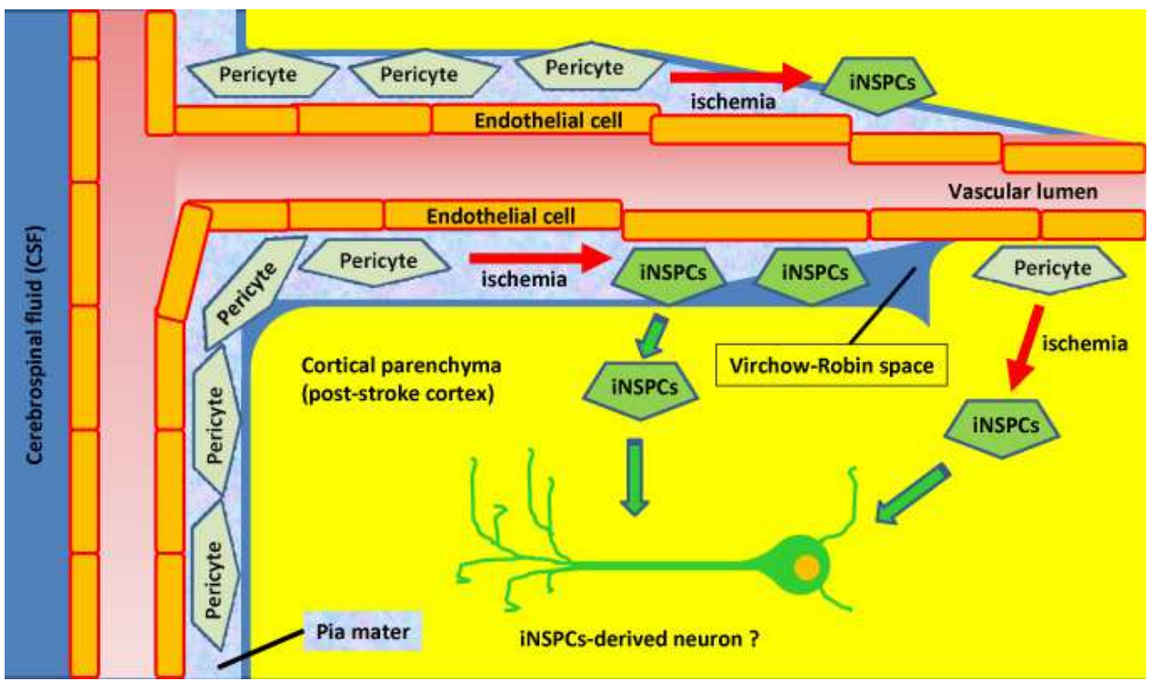


Fig. 2. Schematic representation for the fate of iNSPCs following cortical infarction

Thus, our recent study suggests that pia mater may have the potential to generate NSPCs even in the adult brain. Until now, it has been demonstrated that pia mater, as well as some CNS pericytes, originate from the neural crest (Morse *et al.*, 1984; Etchevers *et al.*, 2001). We recently demonstrated that pial iNSPCs express various neural crest markers, such as Sox9, Sox10, Snail, Slug, and Twist (Aihara *et al.*, 2010; Nakagomi *et al.*, 2011), suggesting that pial iNSPCs are neural crest derivatives. This may provide a novel concept that neural crest-derived cells play a crucial role in the CNS repair following cortical infarction by a similar mechanism to the CNS formation in development. Considering that the neural crest has stem cell potential (neural crest-derived stem cells) (Teng *et al.*, 2006) with differentiation into a variety of cell types including neurons and glia (Nagoshi *et al.*, 2009), this hypothesis would not be surprising. In addition, this might explain why Schwann cells, which have neural crest origin, are induced in the injured CNS (Zawadzka *et al.*, 2010). However, the precise source, lineage, and traits of iNSPCs warrants further investigation. This may be clarified through experiment of lineage labeling by genetic means.

2.2 Potential contribution of endogenous iNSPCs to cortical neurogenesis

Although iNSPCs are generated within the post-stroke area following cortical infarction, almost all of them can undergo apoptotic cell death (Saino *et al.*, 2010). Subsequently, appropriate support for survival of iNSPCs is essential in maintaining post-stroke neurogenesis. Because iNSPCs developed in close association with the blood vessels from the pia mater to the cortex, they must be influenced by the vascular microenvironment, consisting of endothelial cells (ECs) (Palmer *et al.*, 2000; Louissaint *et al.*, 2002) and inflammatory cells infiltrated after cerebral injury (Saino *et al.*, 2010).

ECs are a component of the blood brain barrier (BBB) and also function as a vascular niche (Shen *et al.*, 2008). It has been reported that although inflammation exacerbates post-stroke neuronal damage, inflammation is a strong stimulus for activation of neurogenesis. Such inflammatory reactions may happen in perivascular (Virchow-Robin) spaces (Hutchings *et al.*, 1986), in which inflammatory cells such as macrophage and lymphocytes infiltrate and may affect angiogenesis and neurogenesis after brain injury. These factors should be considered when observing cortical neurogenesis through iNSPCs after ischemic stroke.

NSPCs reside in a vascular niche and the vasculature is regarded as a key element, especially in the adult SVZ (Tavazoie *et al.*, 2008). ECs are believed to make valuable contribution to this vascular microenvironment (Palmer *et al.*, 2000; Louissaint *et al.*, 2002). In support of this viewpoint, co-culture experiments showed that ECs increase proliferation of NSPCs derived from the adult SVZ (Shen *et al.*, 2004; Teng *et al.*, 2008). Furthermore, we demonstrated both *in vitro* and *in vivo*, that the presence of ECs enhances survival, proliferation, migration, and differentiation of iNSPCs (Nakagomi *et al.*, 2009a), indicating that augmentation of ECs (e.g., proliferation of ECs [angiogenesis]) can promote neurogenesis by enhancing the proliferation of endogenous iNSPCs.

Thus, therapeutic angiogenesis may enhance endogenous neurogenesis even after cerebral injury (Hamano *et al.*, 2000; Chen *et al.*, 2003). It has been reported that bone marrow cells (BMCs) such as bone marrow mononuclear cells (BMMCs) (Li *et al.*, 2006; Kim *et al.*, 2009a; Ribeiro-Resende *et al.*, 2009) and mesenchymal stem cells (MSCs) (Labouyrie *et al.*, 1999; Mahmood *et al.*, 2004; Kurozumi *et al.*, 2005) induce angiogenic effects by secreting multiple

growth factors including vascular endothelial growth factor (VEGF), glia-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and hepatocyte growth factor (HGF). We showed that BMMCs can contribute to the proliferation of endogenous iNSPCs through vascular niche regulation, which includes EC proliferation following cortical infarction (Nakano-Doi *et al.*, 2010).

In addition to ECs, astrocytes are also reported to be important niche cells for NSPCs in the SVZ (Song *et al.*, 2002), SGZ (Lim *et al.*, 1999) and cortex (Jiao *et al.*, 2008). Our study already showed that astrocytes, as well as ECs, promote the proliferation of iNSPCs (Nakagomi *et al.*, 2009a), suggesting that astrocytes function as a niche for cortex-derived iNSPCs. Although astrocytes were not observed within the post-stroke cortex after permanent ischemia (Nakagomi *et al.*, 2011), astrocytes are resistant to hypoxia/ischemia and they can still survive after transient ischemia (Li *et al.*, 1995). These findings might explain the reason why new-born neurons are frequently found in the post-stroke cortex after mild transient ischemia (Ohira *et al.*, 2010), but are not seen after severe permanent ischemia (Nakagomi *et al.*, 2009b).

Regulation of the immune system has also been proposed as one of the key factors in enhancing neurogenesis and functional recovery after stroke. Our studies showed that T lymphocytes, mainly CD4- but not CD8-positive T cells, induce apoptosis in iNSPCs (Saino *et al.*, 2010; Takata *et al.*, 2011). The details of the mechanism are still under investigation, but these findings suggest that the immune response and/or enhanced inflammation triggered by CD4-positive T cells, are major deteriorating modulators of post-stroke neurogenesis. These findings, at least in part, are consistent with previous results demonstrating that transplantation of mesenchymal cells accelerates endogenous neurogenesis after stroke (Li *et al.*, 2008; Yoo *et al.*, 2008), because such treatment is known to suppress the immune response in graft-versus-host disease.

2.3 Exogenous iNSPC transplantation after cerebral infarction

Compared to the strategy focusing on enhanced endogenous neurogenesis, exogenous NSPC transplantation may have some advantages in treating stroke patients; this therapy allows a longer therapeutic time window to administer larger numbers of stem cells, and to repeat the treatment. The therapeutic time window to enhance the endogenous neurogenesis may be limited, because we observed that neurogenesis peaks for several days and ends within a few weeks after stroke onset in patients (Nakayama *et al.*, 2010).

Until now, various cell sources for exogenous NSPC transplantation have been proposed; e.g., fetal brain (Ishibashi *et al.*, 2004; Kelly *et al.*, 2004; Cayre *et al.*, 2006; Darsalia *et al.*, 2007), adult brain tissue obtained from the SVZ (Cayre *et al.*, 2006; Hicks *et al.*, 2007; Kameda *et al.*, 2007), gene transfected bone marrow cells (Dezawa *et al.*, 2004), immortalized tumor cell lines (Staines *et al.*, 1994), embryonic stem (ES) cells/induced pluripotent stem cell (iPS) cells (Bjorklund *et al.*, 2002; Wei *et al.*, 2005; Buhnemann *et al.*, 2006) and *ex vivo* expanded cortex-derived iNSPCs (Nakagomi *et al.*, 2009a; Nakagomi *et al.*, 2009b; Nakano-Doi *et al.*, 2010). Transplantation of exogenous NSPCs can be performed even at the chronic stage of post-stroke. In experimental models of stroke using fetal NSPCs, transplanted cells were reported to survive within the host brain, migrate into the injured area, and maintain their multipotency (Ishibashi *et al.*, 2004; Kelly *et al.*, 2004; Darsalia *et al.*, 2007). However, there are

some issues to be solved for clinical application of exogenous NSPC transplantation in stroke patients; e.g., survival, safety and suitability of transplanted cells, and their capacity to repair injured adult brain. Indeed, the other lines of experiment using NSPCs derived from adult mammalian brains showed that only a small population of grafted cells can survive in the injured brain (Toda *et al.*, 2001; Hicks *et al.*, 2007; Kameda *et al.*, 2007; Takahashi *et al.*, 2008). Consistent with these reports, we showed that the majority of transplanted iNSPCs, which are derived from the adult cortex, cannot survive in the injured cortex (Nakagomi *et al.*, 2009a).

A higher survival rate of transplanted NSPCs carrying the property of neoplasm (such as ES/iPS-derived NSPCs) can be expected, because survival is often attributed to a lack of apoptotic signaling. However, this property may be directly linked to a high risk of tumorigenesis. Whether the transplanted fetal NSPCs will be able to contribute to reconstitution of the adult brain is also an issue to be addressed, because they are the cells destined to form the infant brain. Therefore, we must achieve significant recovery of impaired neurological functions of the adult brain to determine the suitability of transplanted cells.

Our study showed that iNSPCs from the injured cortex differentiate into functional neurons with less tumorigenesis, suggesting that these cells are one of the most suitable NSPCs for transplantation. Therefore, we may choose alternative ways to continue the survival of transplanted iNSPCs. Recently, we reported that co-transplantation of iNSPCs with ECs as a vascular niche, enhances functional recovery after cortical infarction with longer survival of transplanted cells (Nakagomi *et al.*, 2009a). This suggests that the microenvironment around the transplants has to be considered for cell therapy. From another point of view, as differentiated cells are more resistant to apoptotic cell death, enhancing differentiation of NSPCs into mature neurons may be a choice in maintaining the transplant. Recent studies showed that transplantation of NSPCs with valproic acid, which inhibits proliferation but enhances differentiation of transplanted stem cells to functional neurons, significantly improves motor function in a spinal cord injury model (Abematsu *et al.*, 2010). These results may indicate a future direction for the clinical application of exogenous NSPC transplantation for patients after cerebral infarction.

Another problem regarding cell transplantation is the difficulty in regulating the differentiation of transplanted NSPCs *in vivo*. It is well-known that a variety of chemical mediators/cytokines are produced/activated at the site of brain injury, and among these, IL-6, CNTF, and BMPs promote differentiation of NSPCs into the astrocytic phenotype (Nakashima *et al.*, 1999; Okada *et al.*, 2004). Our previous studies showed that transplanted iNSPCs largely differentiated into glial cells *in vivo*, although they predominantly differentiated into neuronal cells *in vitro* (Nakagomi *et al.*, 2009a). These results suggest that the neurogenesis-oriented regulation of transplanted iNSPCs might accomplish a real functional restoration of stroke patients in the future.

3. Conclusion

In conclusion, we demonstrated that iNSPCs, which are the potential cell sources for neocortical neurogenesis, develop in the murine post-stroke cortex (Nakagomi *et al.*, 2009a; Nakagomi *et al.*, 2009b; Nakano-Doi *et al.*, 2010; Saino *et al.*, 2010). Furthermore, we

demonstrat that iNSPCs develop within the post-stroke pia mater, suggesting that pia mater is an important target for cortical neurogenesis. In the field of cardiology, accumulating evidence has shown that cardiac stem/progenitor cells reside in epicardium, termed as "epicardial progenitor cells" (Zhou *et al.*, 2008; Smart *et al.*, 2011). These findings may raise a possibility that stem/progenitor cells are present in the surface of multiple organs as well as those observed in the brain and heart. In addition, deposition of several materials including cell sheets onto infarcted heart could improve cardiac repair and functions after myocardial infarction (Zakharova *et al.*; Miyahara *et al.*, 2006; Derval *et al.*, 2008). Thus, patches of cell sheets carrying bioactive substances on post-stroke pia mater may promote cortical repair/neurogenesis without parenchymal damage, due to the intracerebral approach of cell transplantation.

In the past, cerebral infarction was believed to be a region occupied only by necrotic tissue and inflammatory cells. However, we detected viable cells with the capacity for proliferation, differentiation, and multipotency within the post-stroke cortex and pia mater in an experimental murine model of ischemic stroke. Because similar iNSPCs were detected in the post-stroke human cortex (Nakayama *et al.*, 2010), further investigation will establish novel therapeutic neurogenesis for stroke patients by iNSPCs.

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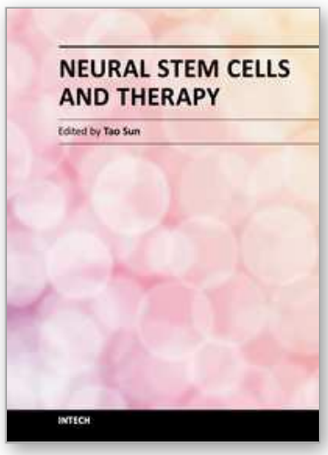
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This book is a collective work of international experts in the neural stem cell field. The book incorporates the characterization of embryonic and adult neural stem cells in both invertebrates and vertebrates. It highlights the history and the most advanced discoveries in neural stem cells, and summarizes the mechanisms of neural stem cell development. In particular, this book provides strategies and discusses the challenges of utilizing neural stem cells for therapy of neurological disorders and brain and spinal cord injuries. It is suitable for general readers, students, doctors and researchers who are interested in understanding the principles of and new discoveries in neural stem cells and therapy.

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