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Forebrain Neurogenesis after Focal Ischemic and Traumatic Brain Injury

Steven G. Kernie[1] and **Jack M. Parent**[2]

[1] Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX

[2] Department of Neurolgogy, University of Michigan Medical Center, Ann Arbor, MI

Abstract

Neural stem cells persist in the adult mammalian forebrain and are a potential source of neurons for repair after brain injury. The two main areas of persistent neurogenesis, the subventricular zone (SVZ)-olfactory bulb pathway and hippocampal dentate gyrus, are stimulated by brain insults such as stroke or trauma. Here we focus on the effects of focal cerebral ischemia on SVZ neural progenitor cells in experimental stroke, and the influence of mechanical injury on adult hippocampal neurogenesis in models of traumatic brain injury (TBI). Stroke potently stimulates forebrain SVZ cell proliferation and neurogenesis. SVZ neuroblasts are induced to migrate to the injured striatum, and to a lesser extent to the peri-infarct cortex. Controversy exists as to the types of neurons that are generated in the injured striatum, and whether adult-born neurons contribute to functional restoration remains uncertain. Advances in understanding the regulation of SVZ neurogenesis in general, and stroke-induced neurogenesis in particular, may lead to improved integration and survival of adult-born neurons at sites of injury. Dentate gyrus cell proliferation and neurogenesis similarly increase after experimental TBI. However, pre-existing neuroblasts in the dentate gyrus are vulnerable to traumatic insults, which appear to stimulate neural stem cells in the SGZ to proliferate and replace them, leading to increased numbers of new granule cells. Interventions that stimulate hippocampal neurogenesis appear to improve cognitive recovery after experimental TBI. Transgenic methods to conditionally label or ablate neural stem cells are beginning to further address critical questions regarding underlying mechanisms and function significance of neurogenesis after stroke or TBI. Future therapies should be aimed at directing appropriate neuronal replacement after ischemic or traumatic injury while suppressing aberrant integration that may contribute to co-morbidities such as epilepsy or cognitive impairment.

First proposed nearly a century ago (Allen, 1912), the persistence of neural stem cells and neurogenesis in the adult mammalian central nervous system (CNS) is now accepted. This change in dogma is based largely upon evidence accumulated over the past four decades indicating that neural stem cells populate two main areas, the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the hippocampal dentate gyrus, where they give rise to neurons throughout adulthood. Adult neurogenesis is found in these forebrain regions in all mammalian species examined, including humans (Curtis et al., 2007; Eriksson et al., 1998a), and may serve to replace cells damaged by brain insults. Whether they do replace dying or diseased cells, and if so to what extent, are among the questions upon which current research is intensely focused. In this review, we will briefly describe the normal pathways of adult forebrain neurogenesis and then discuss how neurogenesis is altered in models of

Please send correspondence to either author: Steven Kernie: Tel: 214-648-4183; Fax: 214-648-1960, Steven.Kernie@UTSouthwestern.edu, Address: Department of Pediatrics, University of Texas Southwestern Medical Center, 6000 Harry Hines Blvd. ND5.124A, Dallas, TX 75390-9133. Jack Parent: Tel: 734-936-1988; Fax: 734-763-7686, parent@umich.edu, Address: Department of Neurology, University of Michigan Medical Center, 5021 BSRB, 109 Zina Pitcher Place, Ann Arbor, MI 48109-2200.

ischemic stroke and traumatic brain injury (TBI). For the former, we focus on studies of the SVZ, and for the latter on the hippocampal dentate gyrus.

The SVZ neural stem cell is a nestin- and glial fibrillary acidic protein (GFAP)-immunoreactive radial glia-like cell that probably arises from embryonic radial glia (Merkle et al., 2004). SVZ neural stem cells give rise to neuroblasts that migrate in chains to the olfactory bulb through the rostral migratory stream (Fig 1A; (Corotto et al., 1993; Lois and Alvarez-Buylla, 1994; Lois et al., 1996). Once they reach the bulb, the migrating neuroblasts detach from the chains, disperse and differentiate into granule and periglomerular neurons (Altman, 1969; Corotto et al., 1993; Lois and Alvarez-Buylla, 1994). A portion of adult-born granular and periglomerular interneurons survive long-term (Winner et al., 2002) and appear to integrate into bulb circuitry (Carlen et al., 2002; Carleton et al., 2003; Livneh et al., 2009). Studies using conditional transgenic reporter mice and ablation strategies show that olfactory granule and periglomerular cells are continuously added to the bulb to both increase total cell numbers over time in these layers as well as replace pre-existing cells (Imayoshi et al., 2008; Lagace et al., 2007). The function of persistent olfactory bulb neurogenesis is largely unknown. Increasing evidence supports a role for the new neurons in olfactory memory and odor discrimination (Gheusi et al., 2000; Petreanu and Alvarez-Buylla, 2002; Rochefort et al., 2002); however, the use of transgenic ablation strategies has failed to yield deficits in some of these measures (Imayoshi et al., 2008).

The SGZ of the dentate gyrus is the other anatomically discrete location where neural precursors persist throughout life. The rodent dentate gyrus develops mostly during the postnatal period and the reservoir of SGZ progenitors persists well into adulthood (Pozniak and Pleasure, 2006). As in the SVZ, the primary progenitor or neural stem-like cell in the SGZ is a nestin- and GFAP-expressing, radial glia-like astrocyte (Fig. 1B; (Seri et al., 2001)). These progenitors give rise almost exclusively to granular neurons within the most basal layers of the dentate gyrus (Duan et al., 2008). The dentate gyrus receives input from the cortex and other brain areas where it is integrated and transmitted to the rest of the hippocampus. Its precursors, which integrate throughout the lifespan, generate neurons that make and receive functional synapses (Eriksson et al., 1998b; Faulkner et al., 2008; Palmer et al., 2000; Song et al., 2002; Toni et al., 2008; van Praag et al., 2002). Enhanced neurogenesis that occurs in the hippocampus is also known to facilitate long-term potentiation and stimulate learning and memory (Farmer et al., 2004; Imayoshi et al., 2008; van Praag et al., 1999; Wang et al., 2005). Ablation of adult-born dentate granule cells impairs certain forms of hippocampus-dependent learning (Clelland et al., 2009; Dupret et al., 2008; Imayoshi et al., 2008), further suggesting that these cells play a role in this function. In addition, adult-born dentate granule cells may be involved in regulating anxiety-associated behavior (Revest et al., 2009).

Despite the tremendous interest in neural stem cell biology, there is little mechanistic insight into stem cell survival following common conditions induced by trauma or other brain insults. Recently, many paradigms of brain injury, including TBI, seizures, stroke, hypoxia-ischemia, and neurodegenerative diseases, implicate neural stem cells in the remodeling that occurs following such injuries (Arvidsson et al., 2002; Jin et al., 2001; Kernie et al., 2001a; Miles and Kernie, 2008; Parent et al., 2002; Parent et al., 1997; Zhang et al., 2001). The physiologic relevance of this proliferation remains unknown, but it may in part explain some of the spontaneous recovery that occurs in all of these disease states. Alternatively, aberrant neurogenesis after injury could contribute to ongoing morbidity that impairs functional recovery. In the following sections, we describe the current knowledge and outstanding research questions in the field of injury-induced neurogenesis. We first focus on experimental stroke and the SVZ, and then shift to TBI models and dentate granule cell neurogenesis.

Stroke-induced neurogenesis

Stroke is a leading cause of morbidity and mortality, yet no regenerative therapies currently exist. Focal ischemic stroke is the most common form and involves a discrete area of necrotic brain tissue surrounded by hypoperfused tissue at risk known as the ischemic penumbra. Treatments aimed at salvaging the penumbra using neuroprotective strategies have received considerable attention without substantial success, but the idea of improving functional recovery by replacing lost neurons remains relatively unexplored. The persistence of neural stem cells in the adult brain, as well as advances in stem cell biology, raise the possibility of using endogenous or transplantable neural stem cells to replace neurons lost after ischemic insults as regenerative therapies. Here we focus on endogenous SVZ neural progenitors and stroke, and describe current knowledge of how stroke influences neurogenesis, the potential underlying mechanisms, and current challenges for the field.

Studies of experimental stroke in rodents over the past decade indicate that focal ischemia potently stimulates forebrain SVZ cell proliferation and neurogenesis (Arvidsson et al., 2002; Jin et al., 2001; Parent et al., 2002; Zhang et al., 2001). The striatal SVZ expands and contains increased numbers of neuroblasts identified by immunolabeling for doublecortin (Fig. 2A, B), neuron-specific β-tubulin or polysialylated neural cell adhesion molecule. Most of these studies involve the classic transient middle cerebral artery occlusion (tMCAO) stroke model. Although initial studies suggested that the increase in SVZ neurogenesis after stroke is transient (Arvidsson et al., 2002; Parent et al., 2002), more recent work indicates that it persists for at least four months after ischemia (Thored et al., 2006).

Potential mediators of stroke-induced cell proliferation and neurogenesis are beginning to be identified. Several groups have found that Notch signaling, particularly through Notch1, stimulates SVZ cell proliferation and neurogenesis after stroke (Androutsellis-Theotokis et al., 2006; Wang et al., 2009), although conflicting results have been found (Carlen et al., 2009). Infusion of various growth factors or reagents that stimulate growth factor expression also increases stroke-induced SVZ neurogenesis (Chen et al., 2004; Jin et al., 2002a; Jin et al., 2002b; Kolb et al., 2007; Leker et al., 2007; Sun et al., 2003; Teramoto et al., 2003; Wang et al., 2004). Conversely, decreased growth factor expression via inhibitors or in knockout mice impairs SVZ neurogenesis after stroke (Chen et al., 2005; Tsai et al., 2006; Yan et al., 2006). Other signaling pathways that appear important for stroke-induced SVZ neurogenesis include retinoid (Plane et al., 2008), bone morphogenetic protein (Chou et al., 2006), tumor necrosis factor-alpha (TNF-α) (Iosif et al., 2008) and sonic hedgehog (Sims et al., 2009) pathways.

The SVZ neuroblasts are normally destined to migrate to the olfactory bulb via chain-like formations in the rostral migratory stream. After focal ischemia, however, many of them migrate in chains toward the ischemic striatum (Arvidsson et al., 2002; Jin et al., 2003; Ohab et al., 2006; Parent et al., 2002; Yamashita et al., 2006). This redirected migration occurs at the expense of olfactory bulb migration as fewer neuroblasts reach the ipsilateral bulb (Fig. 2C–F). Several molecular factors that direct this ectopic migration to peri-infarct regions have been identified. These include matrix metalloproteases (Lee et al., 2006; Liu et al., 2009b) and chemokine/chemokine receptor interactions (Ohab et al., 2006; Robin et al., 2006; Thored et al., 2006; Yan et al., 2007). In addition, the vasculature appears to play an important role in the migration of neuroblasts to regions of ischemic damage. Many neuroblasts are found in close proximity to blood vessels in the ischemic striatum (Ohab et al., 2006; Thored et al., 2007; Yamashita et al., 2006), and infusion of pro- or anti-angiogenic factors stimulate and inhibit neuroblast migration to peri-infarct regions, respectively (Ohab et al., 2006). Interestingly, a population of neural progenitor cells that inhabit more caudal aspects of the SVZ underlying the corpus callosum appears to generate neuroblasts that migrate to the injured hippocampus after more global ischemic insults that damage the hippocampal pyramidal cell

layer (Nakatomi et al., 2002). Thus, the population of SVZ progenitors that may potentially serve as a source of cells for neuronal replacement after injury is likely dispersed throughout the forebrain periventricular regions.

What is the fate of neuroblasts that migrate to the injured striatum after focal ischemia? Although a large number of neuroblasts reach regions of striatal damage after stroke, few of them differentiate into mature neurons. Most adult-born neurons appear to die (Arvidsson et al., 2002; Parent et al., 2002), perhaps from a failure to integrate or due to the inflammatory milieu. In support of the latter idea, treatment with the anti-inflammatory agent indomethacin to suppress inflammation and microglial activation stimulates the accumulation of newborn cells in the injured striatum following 2-hour MCAO in adult rats (Hoehn et al., 2005). Furthermore, signaling through the TNF-α receptor-1 suppresses stroke-induced SVZ neurogenesis (Iosif et al., 2008). Although inhibiting inflammation and microglia might prove useful, this approach may be complicated by recent findings of positive chronic effects of microglia on stroke-induced neurogenesis (Thored et al., 2009). Importantly, the migration of SVZ neuroblasts to the injured striatum persists for up to a year after ischemia (Thored et al., 2007), suggesting that the SVZ may serve as a constant reservoir of new neurons that offers a long time window for therapeutic manipulations.

In most stroke models, many of the surviving cells differentiate into neurons, but the precise nature of the neurons that persist long-term (at least months) in the striatum is controversial. Two groups first reported that most neurons expressed markers of striatal medium spiny neurons, including DARPP-32 and calbindin, after tMCAO in adult rats (Arvidsson et al., 2002; Parent et al., 2002). Subsequently, another group using tMCAO in adult mice along with epidermal growth factor infusions found mostly parvalbumin-expressing interneurons were generated after stroke (Teramoto et al., 2003). All of these studies used bromodeoxyuridine (BrdU) administration to label progenitors at early time points after ischemia and determine their phenotypes after varying survival durations. More recently, Liu and colleagues used retroviral reporters to label SVZ progenitors prior to inducing stroke in adult rats and found that the adult-born neurons exclusively differentiated into calretinin-expressing interneurons (Liu et al., 2009a). The reasons for these disparate findings are not entirely clear. Additional studies using retroviral reporter injections or transgenic approaches to permanently label adult-born neurons are therefore necessary to resolve this issue.

A critical question revolves around the functional significance of stroke-induced neurogenesis. At present, it is not clear whether the limited numbers of surviving adult-born neurons replace lost cells by integrating appropriately, and whether this improves recovery. Some evidence supports the integration of a small portion of adult-born neurons that migrate to the injured striatum after stroke (Yamashita et al., 2006), but whether these cells make appropriate connections remains uncertain. Several approaches should help to answer these questions in the near future. First, the use of newer retroviral reporter constructs (e.g., using synapse-specific promoters) should allow a more in depth analysis of the integration of adult-born neurons that survive after stroke. This analysis should include combinations of electron microscopy and slice electrophysiology to assess both the structural and functional integration of the maturing neurons. Manipulations that are directed at increasing neurogenesis have been shown to improve functional outcome (e.g., (Leker et al., 2007; Ohab et al., 2006; Wang et al., 2004)), but interventions that are more specific to neurogenesis, particularly the survival of adult-born neurons after stroke, are needed to more convincingly link improved behavioral recovery with increased neurogenesis. Finally, more specific means to ablate adult-born neurons have been developed recently (Garcia et al., 2004; Imayoshi et al., 2008; Revest et al., 2009; Singer et al., 2009; Yu et al., 2008a). These methods should allow a determination of whether the absence of neurogenesis after stroke impairs recovery. If stroke-induced neurogenesis indeed

contributes to stroke recovery, then focused efforts are needed to direct and augment this process for the development of regenerative therapies for cerebral ischemia.

Neurogenesis following traumatic brain injury

Significant self-recovery occurs following all but the most severe episodes of TBI (Anderson et al., 2000; Demeurisse, 2000; Ewing-Cobbs et al., 2003). The mechanisms underlying this remain unclear, though injury-induced neurogenesis is one compelling potential contributor to post-injury recovery (Chen et al., 2003; Chirumamilla et al., 2002; Eriksson et al., 1998a; Richardson et al., 2007). As described above, the two most well studied and validated reservoirs for neural stem and progenitor cells in mammals are the SVZ of the lateral ventricles and the SGZ of the dentate gyrus (Alvarez-Buylla et al., 2001; Seaberg and van der Kooy, 2002). Normally, the postnatal SVZ contributes progenitors to the rostral migratory stream to support ongoing olfactory neurogenesis, while the SGZ of the dentate gyrus provides new granular neurons throughout life (Alvarez-Buylla et al., 2001; Temple and Qian, 1995). Following TBI, progenitor cells in each of these areas become activated, though it is still unclear whether this activation results in stable and productive neurogenesis (Richardson et al., 2007). Since the dentate gyrus is a key component to the hippocampus, where the basis for much of learning and memory reside, it is a particularly compelling target for studying the potential implications of injury-induced neurogenesis and is the focus of this part of the review.

Evidence for long-lasting hippocampal neurogenesis after traumatic cortical injury has been accumulating since first described in 2001 (Dash et al., 2001; Kernie et al., 2001b). The dentate gyrus itself develops mostly during the postnatal period and the reservoir of subgranular zone progenitors persists well into adulthood (Pozniak and Pleasure, 2006). These progenitors develop almost exclusively into granular neurons within the most basal layers of the dentate gyrus and their functions remain largely unknown (Duan et al., 2008). After injury, however, even in adult animals, it is clear that progenitors are activated and increased neurogenesis follows whereby new neurons are found in the outer layers of the dentate gyrus, where normally this would occur only during early development (Chen et al., 2003; Chirumamilla et al., 2002; Dash et al., 2001; Ramaswamy et al., 2005; Richardson et al., 2007; Urrea et al., 2007; Yu et al., 2008b). Most of the evidence to support these findings is based on BrdU (5-bromo-2-deoxyuridine) incorporation into dividing cells that when followed over time express markers suggesting mature and stable neurogenesis. There are a variety of problems with using cell cycle markers such as BrdU to quantify this effect (Gould and Gross, 2002). For example, since BrdU is a thymidine analogue that incorporates into dividing cells, it may be a marker of cells undergoing DNA repair or alternatively may mark dying cells attempting to repair themselves. In addition, BrdU only labels cells dividing at the time that BrdU or other thymidine analogues are administered and therefore only provides a temporally limited glimpse at the full contributions of the progenitor population to injury-induced neurogenesis.

There are two major reasons why the extent and relevance of injury-induced neurogenesis in the hippocampus has not become more clearly delineated. One is that tracing of dentate gyrus progenitors has been limited to labeling with thymidine analogues such as BrdU. The second is that many of the genetic and histologic markers that these progenitors express are also found in reactive astrocytes (Eng and Ghirnikar, 1994; Myer et al., 2006; Ridet et al., 1997). Since reactive astrocytosis is a hallmark of TBI, it becomes difficult to differentiate between stem/progenitor cells within the dentate gyrus and astrocytes that have become activated and express some of the same markers. Thus, expression of nestin, Sox 2, vimentin, and glial fibrillary associated protein (GFAP) are not specific for neural stem and progenitor cells but may also be expressed in astrocytes following injury (Ridet et al., 1997; Yu et al., 2008b).

Recently, genetic tools have become available that, at least in part, attenuate some of these limitations. By directing expression of a variety of transgenes specifically in neural stem and progenitors in mice, more clearly defining the implications of injury-induced neurogenesis is more straightforward. One of the most commonly used markers for stem and progenitor cells is expression of the intermediate filament protein nestin. However, nestin expression is not limited to neural stem and progenitor cells, but is also found in developing muscle, endothelial cells, and reactive astrocytes (Lendahl et al., 1990; Lin et al., 1995). The genetic enhancer elements that regulate this expression have been defined in mice, and the second intron of the nestin gene directs expression exclusively in neural stem and progenitor cells (Figure 1B, C) (Zimmerman et al., 1994). Many investigators have taken advantage of this specificity to make transgenic mice that express a variety of genes exclusively in the progenitor population (Kawaguchi et al., 2001; Mignone et al., 2004; Yu et al., 2005). It has also been recently demonstrated that reporter transgenes under the control of the nestin promoter are not expressed in reactive astrocytes after injury, making it a compelling model for the study of injury-induced neurogenesis (Miles and Kernie, 2008; Shi et al., 2007; Yu et al., 2008b).

Using this kind of transgenic approach, a few issues have emerged regarding TBI-induced hippocampal neurogenesis. First, it is the early, nestin-expressing progenitors that are activated by the injury, whereas the later doublecortin-expressing committed neuroblasts appear especially vulnerable (Miles and Kernie, 2008; Yu et al., 2008b). Later, the doublecortin-expressing cells within the dentate reemerge and are the likely contributors to stable neurogeneis (Yu et al., 2008b). Finally, tamoxifen-inducible systems allow for the ultimate fate labeling of these activated progenitors, and it does appear that stable neurogenesis persists over time (Figure 3) (Lagace et al., 2007; Li et al., 2008).

Since it is reasonably well established that hippocampal progenitors are activated by injury and result in increased numbers of new neurons within the dentate gyrus, ongoing studies can now be directed at relevance and mechanism. First, it needs to be established whether injury-induced neurogenesis is an adaptive response. There are three possibilities for its ultimate relevance. First, the generation of new neurons might be beneficial and contribute to recovery of learning and memory and possibly other functions impaired by brain injury. Second, neurogenesis may contribute to TBI-related morbidity such as temporal lobe epilepsy, which occurs relatively commonly following moderate and severe TBI. Finally, this reservoir of progenitors may be nothing more than a developmental remnant that is incapable of providing functionally relevant neurons into the sophisticated hippocampal circuitry.

In order to test these various possibilities, a number of strategies have emerged. One is to ablate neurogenesis at the time of injury to determine whether this then impairs recovery. Strategies to do this include systemic or local administration of anti-mitotic agents such as Ara-C that are known to affect dividing neural progenitors (Doetsch et al., 1999; Lau et al., 2009). Another is to perform cranial irradiation directed to neurogenic zones such as the SVZ and dentate gyrus in order to more selectively impair neurogenesis (Hellstrom et al., 2008; Naylor et al., 2008). Problems with these approaches include both their lack of specificity and potentially toxic side effects that lead to unwanted immune activation that may affect other mediators of recovery or damage not related to neurogenesis.

Recently, genetically engineered mice have become available that can regulate neurogenesis in a more direct and temporally controlled manner. One strategy is to inducibly express diptheria toxin or its receptor in progenitor cells that can be ablated in a temporally controlled manner (Durieux et al., 2009; Luquet et al., 2005). One confounder with this approach is that all progenitors are ablated and not just dividing ones and therefore the pool becomes depleted and cannot be reactivated. An alternative approach that has been used in traumatic brain injury is a transgenic mouse that expresses the herpes simplex virus thymidine kinase (HSV-TK)

under the control of the GFAP promoter. This allows for the inducible ablation of dividing cells that express GFAP, which includes early type 1 hippocampal progenitor cells as well as dividing reactive astrocytes (Morshead et al., 2003; Saxe et al., 2006; Sofroniew et al., 1999). Recently, a more specific modified version of HSV-TK has been shown in nestin-expressing progenitor cells to inducibly ablate early progenitors after TBI. These inducible approaches show promise as to determining the relevance of endogenous progenitor activation following injury (Yu et al., 2008b).

Whether endogenous TBI-induced neurogenesis proves to be adaptive or not, it also needs to be determined whether enhancing this process can improve outcome. Several studies have shown that a variety of pharmacologic agents associated with increasing neurogenesis lead to improved outcomes following TBI. These include exogenously administered or endogenously produced molecules such as estrogen, erythropoietin, and basic fibroblast growth factor (bFGF), as well as administration of drugs developed for other purposes such as statins and antidepressants (Encinas et al., 2006; Garcia-Segura et al., 2001; Lu et al., 2007; Sun et al., 2009; Wu et al., 2008; Xiong et al., 2008; Yoshimura et al., 2001). All of these molecules and drugs have effects on the brain that are independent of their promotion of hippocampal neurogenesis and it therefore becomes difficult to attribute improvements in behavior to their effects on neurogenesis in the dentate gyrus.

In order to demonstrate that functional recovery requires progenitor cell activation, more cell-specific genetic assays need to be used. These can include but are not limited to either selectively ablating tumor suppressor genes known to play roles in neurogenesis such as PTEN (phosphatase and tensin homolog deleted on chromosome 10) in the progenitor population at the time of injury, or activating known regulators of growth such as inducible overexpression of activated forms of the epidermal growth factor receptor (Gregorian et al., 2009; Holland et al., 1998). Although, these genetic models may not provide direct therapeutic targets, they will be able to answer the critical question of whether it is hippocampal neurogenesis itself that leads to improved outcomes.

Finally, although injury-induced neurogenesis occurs both in response to injury and selectively to cells that are adjacent to a more vulnerable population, the mechanisms underlying these observations need more mechanistic investigation. The injured brain releases numerous extracellular proteins and ions that may play roles in regulating neurogenesis. Two of the best studied of these, KCl and glutamate, have both been implicated in enhancement of proliferation in immature cells while at the same time directing toxicity in more mature cell types (Mattson, 2008; Shi et al., 2007). In addition, the injured brain activates both astroctyes and microglia, which are both known to secrete a variety of growth factors as well as immune modulators that may effect progenitor proliferation and survival (Bessis et al., 2007; Myer et al., 2006). Also, the progenitor cells themselves make physical contact with the vasculature so circulating factors such as cytokines and growth factors that increase after injury may also direct some of these effects (Mignone et al., 2004). Thus, the mechanisms underlying TBI-induced neurogenesis are likely not straightforward nor easily worked out, and therefore remain compelling targets to study.

Amid all the optimism surrounding the potential of injury-induced neurogenesis, there remain a variety of significant concerns. Post-traumatic epilepsy is a fairly common morbidity associated with both stroke and TBI (Diaz-Arrastia et al., 2009). One postulated mechanism for this is that aberrant neurogenesis serves as the epileptic focus (Parent and Murphy, 2008). Clearly, any strategy aimed at enhancing neurogenesis might result in this and other unwanted side effects. In addition, since all strategies aimed towards enhancing neurogenesis would increase cell growth, it remains a possibility that increasing proliferation could result in potentially unwanted tumor development. Therefore, although enhancing neurogenesis

following stroke or TBI remains a compelling and potentially field-changing strategy towards improving recovery, many issues regarding specificity, mechanism, and potential toxicity need to be more thoroughly investigated before meaningful clinical interventions can occur.

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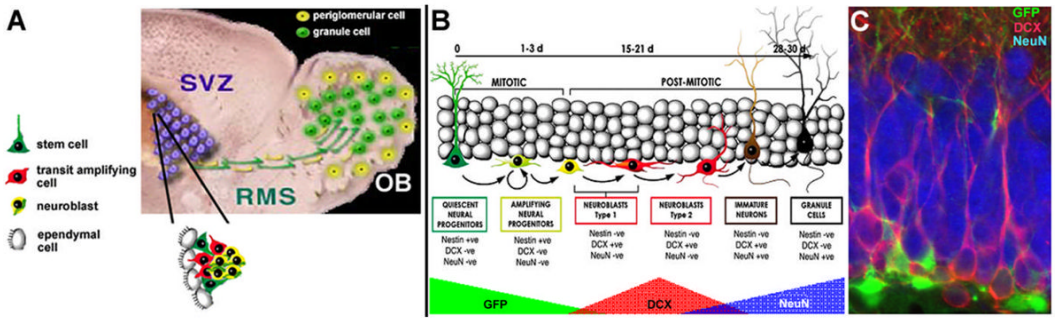

Figure 1.

Regions of persistent neurogenesis in the adult. A, The subventricular zone (SVZ)-olfactory bulb (OB) pathway. Radial glia-like neural stem cells in the SVZ give rise to rapidly dividing transit amplifying cells and then neuroblasts. All these cells are closely apposed in the SVZ niche that includes ependymal cells and endothelial cells (not shown). The SVZ-derived neuroblasts migrate tangentially to the bulb in neuronophilic chains via the rostral migratory stream (RMS). B, Stages of neurogenesis in the dentate subgranular zone (SGZ). GFP refers to reporter expression in a nestin-GFP mouse line. C, Section through the dentate granule cell layer of an adult nestin-GFP mouse showing GFP-expressing progenitors (green), doublecortin immunolabeled neuroblasts (DCX, red) and NeuN immunoreactive mature dentate granule cells (blue). The dentate hilus is at the very bottom of the image.

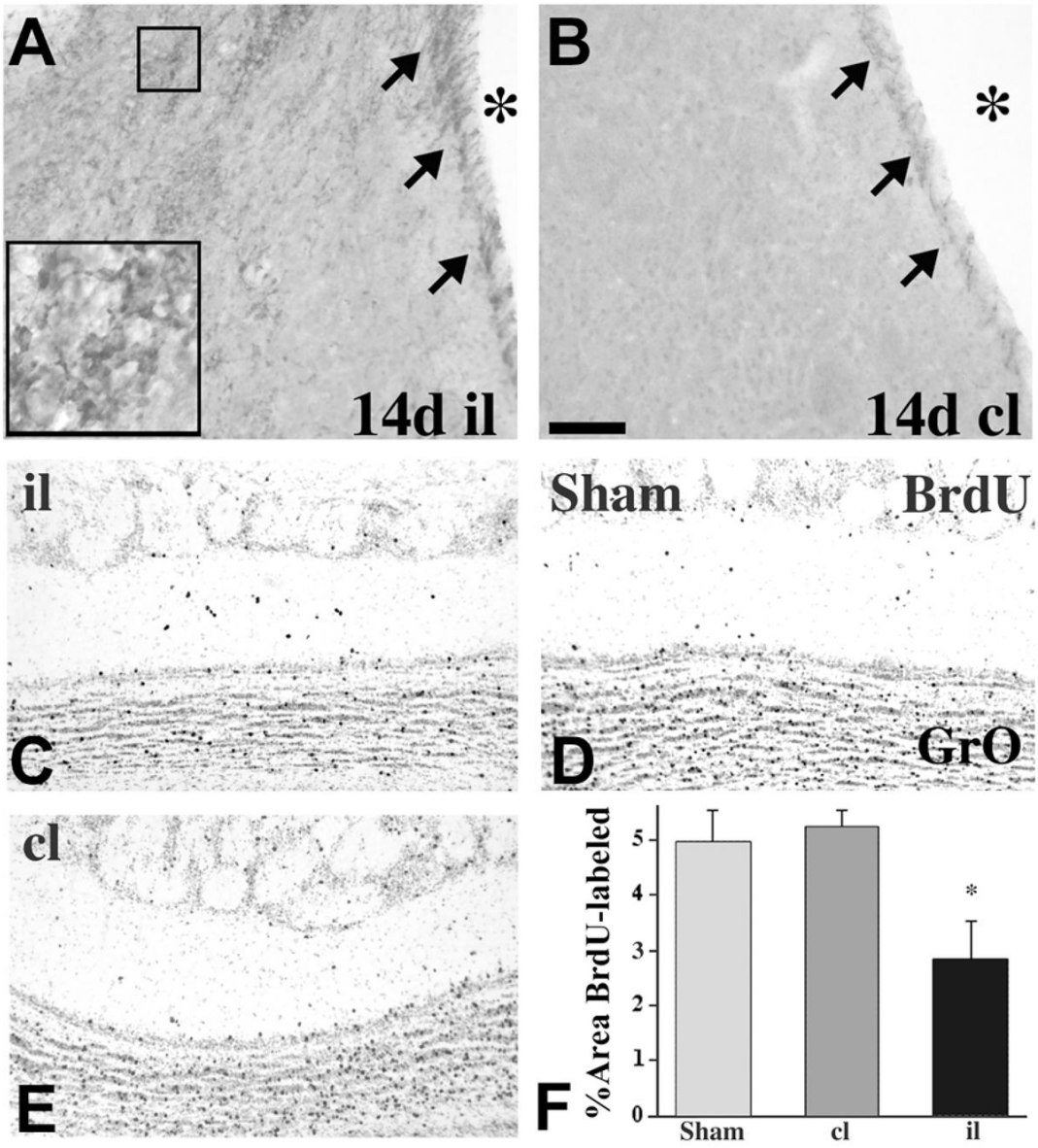

Figure 2.

Stroke-induced neurogenesis. A, B, Doublecortin immunostaining at 14 days after tMCAO shows increased SVZ and striatal neurogenesis of the ipsilateral (il) hemisphere compared to contralateral (cl). The asterisks denote the lateral ventricle. C–E, Coronal sections of BrdU-immunoreactive olfactory neurons in the granular layer (GrO) of rats after tMCAO either ipsilateral (il, C) or contralateral (cl, D) to the infarct, or from a sham-operated control (E) at 28 days after surgery. (D) Quantification of GrO BrdU labeling shows significantly decreased BrdU-immunoreactivity il to the stroke after 28 days. *, $p < 0.05$ vs. cl and sham control. Scale bar, 50 μm for A and B; 150 μm for C–E.

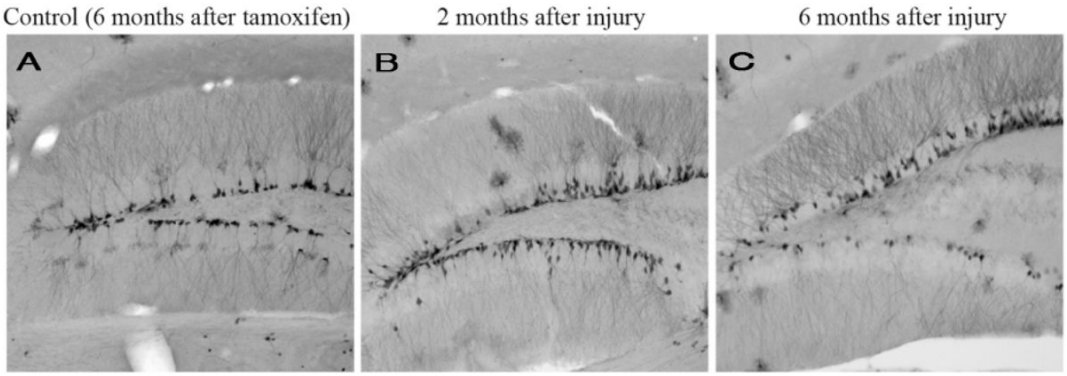

Figure 3.
YFP-expressing cells in the dentate gyrus following tamoxifen-mediated cre recombination in controls and after injury. In control animals, YFP-expressing progenitors and neurons remain confined to the most basal layers of the dentate gyrus (A). In the injured dentate gyrus both 2 and 6 months after tamoxifen injection followed by injury, there are stably incorporated neurons throughout the granular layer that exhibit extensive dendritic arborizations (B, C).