Injury-Induced Neurogenesis in the Adult Mammalian Brain

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The persistence of neurogenesis in the adult mammalian forebrain suggests that endogenous precursors may be a potential source for neuronal replacement after injury or neurodegeneration. Limited knowledge exists, however, regarding the normal function of neurogenesis in the adult and its alteration by brain injury. Neural precursors generate neurons throughout life in the mammalian forebrain subventricular zone (SVZ)–olfactory bulb pathway and hippocampal dentate gyrus. Accumulating evidence indicates that various brain insults increase neurogenesis in these persistent germinative zones. Two brain injury models in particular, experimental epilepsy and stroke in the adult rodent, have provided significant insight into the consequences of injury-induced neurogenesis. Studies of dentate gyrus neurogenesis in adult rodent epilepsy models suggest that seizure-induced neurogenesis involves aberrant neuroblast migration and integration that may contribute to persistent hippocampal hyperexcitability. In contrast, adult rat forebrain SVZ neurogenesis induced by stroke may have reparative effects. SVZ neural precursors migrate to regions of focal or global ischemic injury and appear to form appropriate neuronal subtypes to replace damaged neurons. These findings underscore the need for a better understanding of injury-induced neurogenesis in the adult and suggest that the manipulation of endogenous neural precursors is a potential strategy for brain reparative therapies. NEUROSCIENTIST 9(4):261–272, 2003. DOI: 10.1177/1073858403252680

KEY WORDS *Stem cell, Neural regeneration, Neurogenesis, Epilepsy, Stroke*

Evidence accumulated over the past 4 decades has dispelled the long-held dogma that the adult mammalian brain cannot generate new neurons. The persistence of mitotically active cells in the adult rodent forebrain subventricular zone (SVZ) has been recognized for nearly 90 years (Allen 1912). Four decades ago, Altman and colleagues used tritiated thymidine mitotic labeling to show that proliferating precursor cells generate neurons in the adult rodent hippocampal dentate gyrus and olfactory bulb (Altman and Das 1965; Altman 1969). These findings were confirmed by electron microscopy a decade later (Kaplan and Hinds 1977). Forebrain neurogenesis in adulthood has been identified in every mammalian species examined to date, including human (for the dentate gyrus) and nonhuman primates (Eriksson and others 1998; Gould and others 1998, 1999; Pencea and others 2000; Kornack and Rakic 2001).

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This work was supported by funding from the National Institute for Neurological Disorders and Stroke, and Parents Against Childhood Epilepsy, Inc. I thank Dr. Roger Albin for helpful comments on the manuscript, Dr. Daniel Lowenstein for his outstanding mentoring and collaboration with our epilepsy studies, Drs. Donna Ferriero and Zena Vexler for their collaboration with the stroke work, Dr. Masato Nakafuku for providing Figure 6, and Denice Bliesath for her help in preparing the manuscript.

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Important work in the early 1990s first led to the notion that the adult rodent striatal SVZ maintains a population of neural stem-like cells (Reynolds and Weiss 1992). When cultured with specific growth factors, these cells self-renew and give rise to neurons, astrocytes, and oligodendrocytes in vitro. Forebrain neural stem cells also have been found in vivo, although their precise identity remains controversial (Doetsch and others 1999; Johansson and others 1999). Technical advances in recent years, including the use of bromodeoxyuridine (BrdU) and retroviral reporter mitotic labeling, have firmly established the migration patterns, phenotypes, and integration of adult-generated neurons in the hippocampal dentate gyrus and forebrain SVZ germinative regions (Fig. 1) (Cameron and others 1993; Lois and Alvarez-Buylla 1994; Lois and others 1996; van Praag and others 2002). One study also suggests that the capacity for neuronal renewal may not be limited solely to these phylogenetically older forebrain regions. Although yet to be replicated, Gould and colleagues (1999) provided evidence that the forebrain SVZ of the adult monkey is a proliferative region that generates precursor cells capable of migrating through the mature white matter to differentiate into neurons in multiple neocortical regions.

Another important feature of adult-generated neurons is their capacity for integrating into existing networks. Several groups have shown that newborn neurons in the adult rodent hippocampal dentate gyrus send and receive anatomically appropriate synaptic connections (Stanfield and Trice 1988; Markakis and Gage 1999), and more recent work has shown definitively that adult-

ISSN 1073-8584

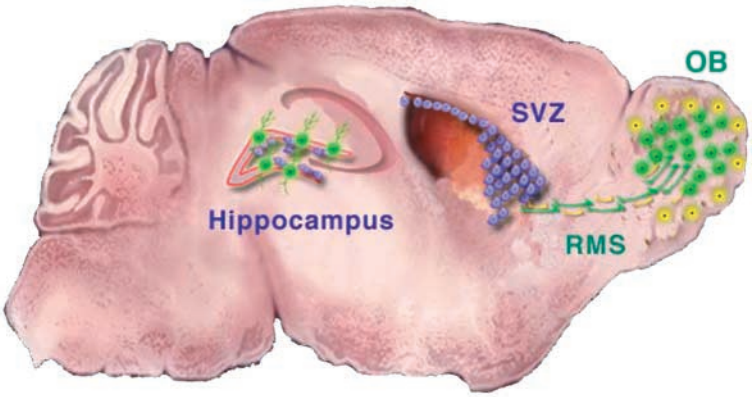

Fig. 1. Schematic sagittal view of the adult rat brain showing the two regions of persistent neurogenesis. Neural precursor cells in the subventricular zone (SVZ; purple) undergo a long-distance, tangential migration in the rostral migratory stream (RMS) to reach the olfactory bulb (OB), where they differentiate into granule (green) and periglomerular (yellow) neurons. Precursors (purple) in the hippocampal dentate gyrus migrate a short distance into the dentate granule cell layer (outlined in red) and give rise to dentate granule neurons (green).

generated neurons integrate and are electrophysiologically functional (van Praag and others 2002). These data suggest that neuronal birth is an integral part of ongoing plasticity in the adult mammalian brain and that a cellular reserve exists that potentially could be manipulated for therapeutic purposes. The persistence of neural stem cells in the adult mammalian brain therefore presents exciting prospects for potential cell-based therapies to replace neurons lost to injury or degeneration (Lowenstein and Parent 1999).

Adult Mammalian Forebrain Neurogenesis: The Dentate Gyrus and SVZ

The hippocampal dentate gyrus is one of two persistent neurogenic regions in the adult mammalian forebrain. Neuronal precursor cells in the adult rodent dentate gyrus proliferate in clusters in the subgranular zone, located at the border of the dentate granule cell (DGC) layer and hilus (Fig. 2*A*) (Kaplan and Hinds 1977; Cameron and others 1993; Kuhn and others 1996). Their progeny disperse and migrate a short distance into the DGC layer where they differentiate into mature granule neurons (Fig. 2*B*) (Cameron and others 1993; Kuhn and others 1996). A smaller number of progeny probably also differentiate into astrocytes or radial glia-like cells (Cameron and others 1993). Although the majority of DGCs in the rat are produced near the end of the first postnatal week, new DGCs continue to be generated at a lower rate throughout adulthood and into senescence (Kuhn and others 1996). This is also true of the human dentate gyrus, which generates neurons into the seventh decade of life and beyond (Eriksson and others 1998). As mentioned above, combined retrograde tracer and mitotic labeling studies in the adult rodent have shown that mossy fibers of newly born DGCs project to appropriate targets in hippocampal area CA3 (Stanfield and Trice 1988; Markakis and Gage 1999), and expriments using retroviral reporters have shown that adult-generated DGCs integrate into the hippocampal circuitry and are electrophysiologically active (van Pragg and others 2002). Although the precise function of the adult-generated DGCs is unknown, existing evidence supports a role in hippocampal-dependent learning and memory (Shors and others 2001).

The forebrain SVZ is the other germinative zone that persists into adulthood. Neuronal precursors in the adult rodent SVZ migrate to the olfactory bulb (Fig. 1) and differentiate into olfactory bulb granule and periglomerular neurons (Altman 1969; Lois and Alvarez-Buylla 1994; Lois and others 1996). To reach the olfactory bulb, SVZ neuroblasts undergo a long-distance, tangential rostral migration (Lois and Alvarez-Buylla 1994; Lois and others 1996) in a restricted pathway known as the rostral migratory stream (RMS). The neuroblasts form chain-like structures as they migrate within the RMS, and the chains are surrounded by astrocytic "tubes" (Lois and others 1996; Peretto and others 1997). Immature neurons in the SVZ and RMS express characteristic markers, such as the polysialylated form of neural cell adhesion molecule (PSA-NCAM) and doublecortin (DCx), as they proliferate and migrate (Bonfanti and Theodosis 1994; Doetsch and Alvarez-Buylla 1996; Gleeson and others 1999). Analogous neurogenic pathways may also persist in adult primates (Pencea and others 2000; Kornack and Rakic 2001). As with adult-generated DGCs, the function of persistent olfactory bulb neurogenesis is largely unknown but may involve olfactory learning or discrimination functions (Gheusi and others 2000).

Regulation of Neurogenesis in the Adult Mammalian Forebrain

Recent work is beginning to shed light on mechanisms that regulate neurogenesis in the adult mammalian forebrain. The process of neurogenesis is itself complicated as it involves multiple steps by which stem cells generate specific types of neurons or glia. This pathway includes precursor proliferation, migration, differentation, integration, and survival (Fig. 3). DGC neurogenesis during early postnatal and adult life appears to be influenced, at least in part, by factors such as aging, environmental stimulation, exercise, genetic background, stress, and afferent input to the DGC layer (Table 1; reviewed in Gage and others 1998). Several molecules that may modulate neurogenesis in the adult rodent dentate gyrus or SVZ have been described recently, and these can be classified by the stage of neurogenesis at which they act. One category involves agents with mitogenic effects on neuronal precursors in the adult.

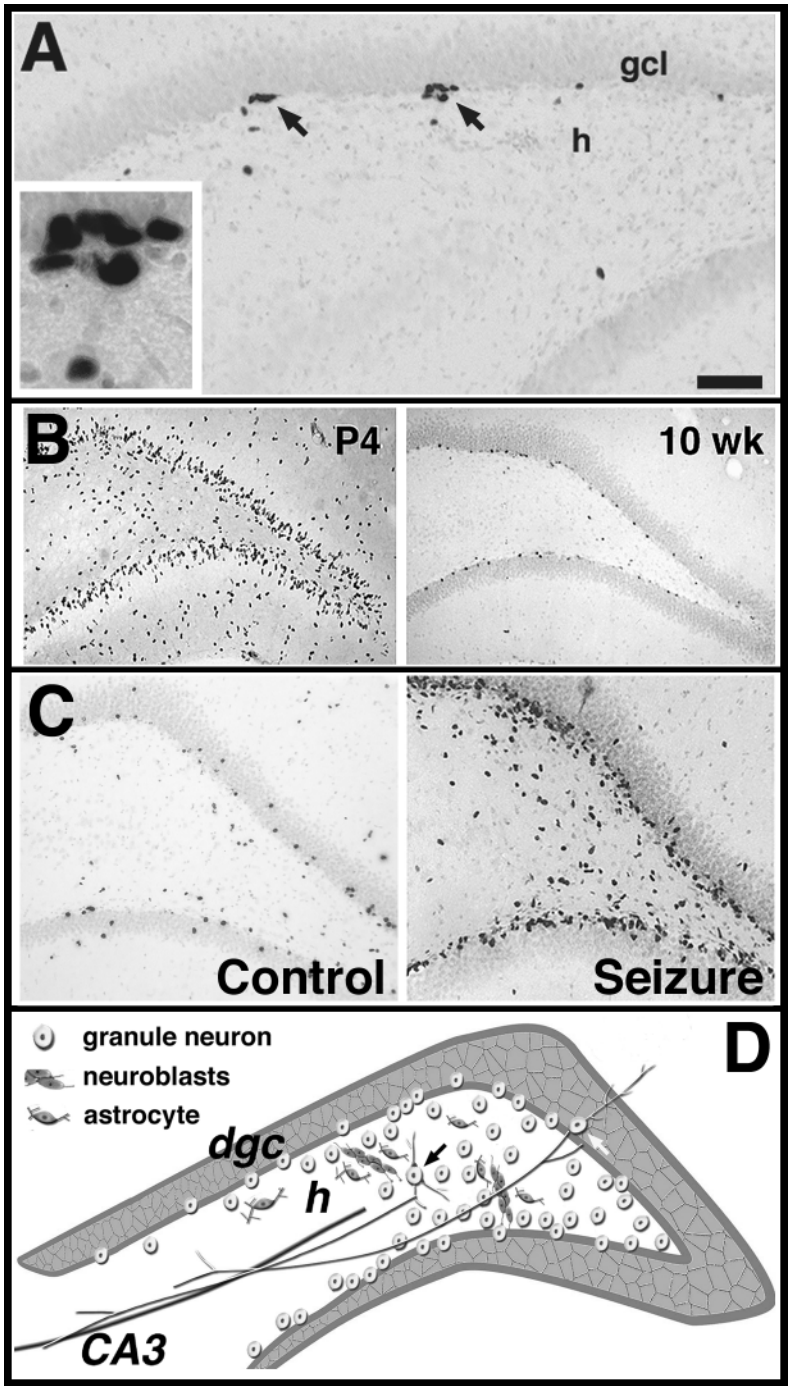

Fig. 2. Dentate granule cell (DGC) neurogenesis in the normal and injured adult rat hippocampal formation. *A*, Dentate granule cell precursors proliferate in clusters (arrows) in the subgranular zone between the granule cell layer (gcl) and hilus (h). The inset shows a higher magnification view of the cluster on the *right*. Proliferating cells were labeled by injection of a retrovirus carrying a nuclear localization signal-β-galactosidase reporter 2 days earlier. *B*, BrdU labeling of dentate granule cells in a neonatal (10-day-old; *left* panel) and young adult (10-week-old; *right* panel) rat. BrdU was given at postnatal day (P) 4 near the peak of dentate granule cell neurogenesis (*left*) or at 9 weeks of age (*right*), when neurogenesis persists but at a much lower level. *C*, BrdU immunostaining of adult rat dentate gyrus 35 d after pilocarpine-induced status epilepticus (*right*) or saline treatment in a control (*left*). BrdU labeling increased markedly in the inner granule cell layer and hilus after 2 h of continuous seizure activity (*right*). BrdU was given on days 7-21 after pilocarpine or saline treatment. *D*, Schematic diagram showing the ectopic migration of DGC precursors into the dentate hilus after seizure-induced injury. Newly generated granule neurons in the adult rodent normally take up residence in the inner aspect of the dentate granule cell layer (dgc; white arrow; see *right* panel in *B*). After seizure-induced injury, the granule neuron precursors (neuroblasts) migrate abnormally into the hilus (h) in chains adjacent to astrocytes, where they differentiate into granule neurons despite their ectopic location. Many of the ectopic granule neurons maintain immature features such as persistent basal dendrites (black arrow). Scale bar (in *A*), 75 μm for *A*; 15 μm for inset in *A*; 200 μm for *B*; and 100 μm for *C*.

Evidence from in vivo studies suggests that specific growth or neurotrophic factors influence neural precursor proliferation in the adult rodent dentate gyrus and SVZ. These factors include basic fibroblast growth factor (bFGF), insulin-like growth factor-1 (IGF-1), epidermal growth factor (EGF), and brain-derived neurotrophic factor (BDNF) (Kuhn and others 1997; Wagner and others 1999; Åberg and others 2000; Benraiss and others 2001; Pencea and others 2001). Exogenous administration of BDNF also promotes adult neurogenesis in otherwise dormant forebrain regions (Benraiss and others 2001; Pencea and others 2001). Other classes of molecules shown to influence DGC precursor proliferation include neurotransmitters, hormones, and psychotropic agents (Table 1).

A second category concerns the molecular control of neuroblast migration. Evidence for migratory cues primarily arises from investigations of forebrain SVZ precursors in the adult rodent, because the long-distance migration of SVZ neuroblasts is more amenable to study. Existing data implicate both diffusable and contact-mediated cues in guiding the neuroblast migration from

Table 1. In Vivo Modulators of Adult Rodent Dentate Granule Cell Neurogenesis

Factor	Effect	Mechanism
Aging	decrease	? increased corticosteroids
Stress	decrease	increased corticosteroids
Exercise	increase	increased proliferative rate
Environmental enrichment	increase	increased survival
Adrenalectomy	increase	decreased corticosteroids
Deafferentation	increase	? decreased glutamatergic neurotransmission
Dietary restriction	increase	? BDNF
Genetic	varies by mouse strain	unknown
Growth factors	increase	unknown
IGF-1		
FGF-2		
VEGF		
? BDNF		
MK-801	increase	decreased NMDA receptor activation
Estrogen	increase (transient)	? serotonin
Corticosterone	decrease	? NMDA receptor activity
Serotonin	increase	5-Hydroxytryptamine-1A receptor activation
Norepinephrine	increase	increased proliferative rate
Antidepressants	increase	? cyclic AMP
Opiates	decrease	unknown
Injury	increase	unknown
Seizure		
Global cerebral ischemia		
Focal cerebral ischemia		
Mechanical injury		

NMDA = N-methyl-D-aspartate; IGF-1 = insulin-like growth factor-1; FGF-2 = fibroblast growth factor-2; BDNF = brain-derived neurotrophic factor.

the SVZ to the olfactory bulb. These cues include PSA-NCAM, attractive and repulsive chemotropic factors, integrin subunits, ephrins, and reelin (Cremer and others 1994; Ono and others 1994; Jacques and others 1998; Wu and others 1999; Conover and others 2000; Hack and others 2002; Murase and Horwitz 2002). Some of these agents may also have proliferative effects (Jacques and others 1998; Conover and others 2000). Least understood is the molecular regulation of precursor differentiation, integration, and survival. Recent evidence supports a role for the BMP pathway in regulating SVZ precursor differentiation (Lim and others 2000), but much progress remains to be made in terms of understanding the full spectrum of cues that direct the differentiation and survival of adult-generated neurons.

Interestingly, several lines of evidence suggest that astrocyte-derived cues act at all of these developmental steps to influence adult SVZ and dentate gyrus neurogenesis. These data arise from structural and functional studies of neural stem cells and neurogenesis during embryonic, neonatal, and adult life. The RMS structural arrangement of neuroblast chain migration through astrocytic tubes in the adult supports a role for astrocytes in directing SVZ–olfactory bulb migration (Lois and others 1996; Peretto and others 1997). Studies of neurogenesis in the embryonic ventricular zone, adult SVZ, and adult dentate gyrus also suggest that radial glial cells or radial glia-like astrocytes are the neural stem cells from which neuroblasts derive (Doetsch and others 1999; Noctor and others 2001; Seri and others 2001). A third line of evidence relates to in vitro experiments directly assessing the effects of astrocytes on postnatal forebrain neurogenesis. Mason and colleagues (2001) found that astrocyte-conditioned media markedly increased SVZ neuroblast migration in neonatal rat olfactory bulb explants. Several dozen growth factors or guidance cues tested in their assay failed to exhibit similar effects. In the adult, astrocytes stimulate neurogenesis from striatal SVZ or hippocampal dentate gyrus neural stem cells cultured in vitro (Lim and Alvarez-Buylla 1999; Song and others 2002). Astrocytes appear to promote both neuroblast proliferation and neuronal differentiation in the stem cell cultures. Taken together, these findings indicate that astrocytes are important regulators of neural precursor cell proliferation, migration, and differentiation. The molecular mechanisms underlying the pro-neurogenic and migratory effects of astrocytes remain unknown. Because astrocytes are activated by most brain insults, they are also likely to be involved in injury-induced neurogenesis.

Effects of Brain Injury on Adult Neurogenesis

The potential of neural stem cells that persist in the adult mammalian forebrain to serve as a source of neuronal

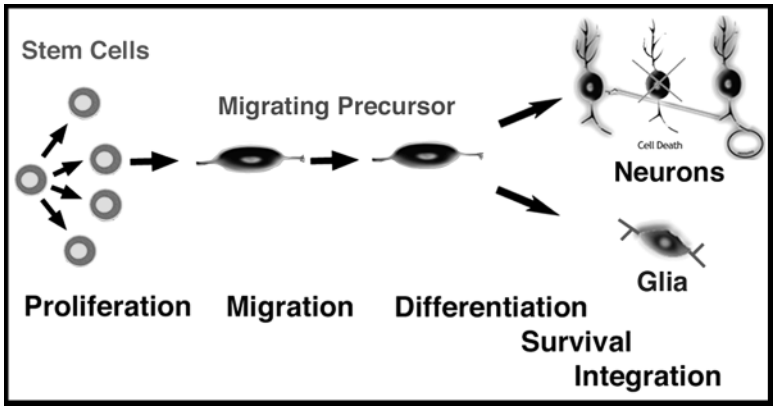

Fig. 3. Neurogenesis and gliogenesis involve multiple steps. Neural stem or precursor cells proliferate, migrate to the appropriate destinations, differentiate into specific cell types, survive (many also undergo programmed cell death), and integrate.

renewal in the setting of brain injury or degeneration raises the question of how endogenous neural precursors respond to brain insults. A rapidly increasing number of studies are beginning to address this question. Several important findings have thus far arisen consistently across different injury models and between regions of persistent cell proliferation. One of these findings is that different types of injury have remarkably similar effects on a given neural precursor population. Using mitotic labeling or morphological techniques to study the influence of injury on forebrain SVZ precursors, several groups have shown increases in the number of proliferating cells in the striatal SVZ after injury due to cortical aspiration (Szele and Chesselet 1996), cortical transection (Willis and others 1976), or inflammatory demyelination (Calzà and others 1998). The forebrain SVZ also concomitantly increases its metabolic activity after cortical injury (Valla and others 1999). Damage induced by mechanical lesions, prolonged seizures, or stroke increases dentate gyrus cell proliferation after a latent period, and a similar majority of the newly generated cells differentiate into granule neurons (Gould and Tanapat 1997; Parent and others 1997; Liu and others 1998).

Recent investigations have begun to explore the phenotypic potential of adult rodent SVZ precursors following injury. SVZ progenitors migrate out of the RMS toward sites of injury produced by focal chemical demyelination or mechanical percussion, and the cells differentiate into oligodendrocytes or astrocytes (Holmin and others 1997; Nait-Oumesmar and others 1999). Surgical cuts made through the RMS induce neural precursors to migrate out of the pathway caudal to the lesion, perhaps directed by factors associated with the glial scar, and differentiate into γ-aminobutyric acid-(GABA) and calretinin-expressing neurons in the forebrain (Alonso and others 1999). Using the 6-hydroxydopamine lesion model of Parkinson's disease, Fallon and colleagues (2000) also have found that cell proliferation and neurogenesis increase in the striatal SVZ ipsilateral to injury. The neuroblasts migrate into the striatum and form neurons, but only in lesioned animals that also receive striatal infusion of transforming growth factor-α (TGF-α). These results indicate that forebrain injury stimulates SVZ precursor proliferation and directs migration out of the normal pathway to sites of injury. Furthermore, the neural progeny appear capable of differentiating into neurons or glia, perhaps dependent upon local environmental cues induced by the specific forms of injury.

A second consistent finding is that a given injury mechanism appears to have similar effects on neural precursors in both the striatal SVZ and hippocampal dentate gyrus. As described in detail below, seizure- or cerebral ischemia–induced injury increases neurogenesis in both the adult rodent dentate gyrus and SVZ-olfactory bulb pathway. Mechanical brain insults also increase cell proliferation in these areas (Willis and others 1976; Szele and Chesselet 1996; Gould and Tanapat 1997). Precursor proliferation accelerates after a latent period in both neurogenic regions, and the progeny can give rise to neurons and glia. Importantly, neurons newly generated after injury are capable of integrating in the mature brain. Magavi and others used a photolytic apoptosis method to induce degeneration of layer VI pyramidal neurons in the adult mouse neocortex, and found that apoptotic cell death leads to the induction of neurogenesis in the damaged cortical layer (Magavi and others 2000). Remarkably, the newborn, BrdU-labeled cells exhibit the morphology of pyramidal neurons and a portion form long-distance corticothalamic connections as shown by retrograde labeling. Although the authors suspect that these newly generated neurons derive from forebrain SVZ precursors, their origin is yet to be determined. Thus, neural precursors not only give rise to new neurons in persistent germinative zones and dormant regions of the adult rodent brain after certain forms of injury, but at least a portion of the newly born neurons *integrates* into existing networks, even in the *neocortex*. Although these data raise optimism for prospects of enhancing endogenous brain repair, the actual functional consequences of neurogenesis after injury are poorly understood. As discussed below, injury-induced neurogenesis may have beneficial or adverse consequences depending upon the region of injury and cell types involved.

Seizure-Induced Neurogenesis

Studies of adult rodent models of limbic epileptogenesis or acute seizures indicate that seizures or seizure-induced injury stimulates DGC neurogenesis (Bengzon

and others 1997; Parent and others 1997, 1998; Gray and Sundstrom 1998; Scott and others 1998). In the adult rodent kainate and pilocarpine models of temporal lobe epilepsy, chemoconvulsant-induced status epilepticus (SE) increases dentate gyrus cell proliferation approximately five- to tenfold after a latent period of at least several days (Fig. 2*C*) (Parent and others 1997; Gray and Sundstrom 1998). The newly born cells disperse into the granule cell layer, and 80% to 90% differentiate into DGCs. Studies of electrical kindling models of epileptogenesis, including amygdala (Parent and others 1998; Scott and others 1998), hippocampal (Bengzon and others 1997), and perforant path (Nakagawa and others 2000) kindling, show that repeated kindled seizures also stimulate DGC neurogenesis. Similar neurogenic effects occur after acute seizures induced by intermittent perforant path or hippocampal stimulation in adult rats (Bengzon and others 1997; Parent and others 1997). Even single seizure-like afterdischarges produced by electrical stimulation appear to increase the number of newly differentiated DGCs (Bengson and others 1997).

The effect of seizures on the other persistent germinative zone in the adult, the rostral forebrain SVZ, has been relatively unexplored. Using the pilocarpine model of limbic epileptogenesis, we recently found that 2 h of SE markedly increases BrdU labeling and expression of an endogenous cell cycle marker in the adult rat forebrain SVZ and RMS within 1 to 2 weeks after seizures (Parent, Valentin, and Lowenstein 2002). Immunostaining for immature neuronal markers revealed that the seizure-induced stimulation of cell proliferation resulted in increased neurogenesis in these same brain regions. Most of the neuroblasts generated after SE migrated through the normal RMS pathway to appropriate targets in the olfactory bulb. Pulse-chase BrdU labeling and focal retroviral reporter injection into the rostral SVZ showed that the neural precursors reached the olfactory bulb more rapidly and in greater numbers after pilocarpine treatment. Moreover, a significant proportion of the neuroblasts arising from the SVZ after SE appeared to exit the RMS prematurely and migrate into injured forebrain regions.

We have also identified a third constitutively proliferating precursor population that expands after pilocarpine-induced SE. These neural precursors arise from the caudal SVZ, or posterior periventricular region, at the level of the dorsal hippocampus. Proliferating cells in the adult rat caudal SVZ labeled with BrdU 1 to 2 days before SE generate increased numbers of progeny within 10 to 14 days compared with controls. An increase in immature cells has been confirmed by immunostaining for the differentiating precursor markers PSA-NCAM, doublecortin, and collapsing response mediator protein-4. After seizure-induced injury, the neural precursors are present in the caudal SVZ, infracallosal region, and areas CA1 and CA3 of the hippocampus, and they display migratory cell morphologies. Retroviral reporters stereotaxically injected into the caudal SVZ prior to seizures provide further evidence of migration as labeled cells are found in hippocampal CA1 and CA3 regions 2 to 3 weeks later. The retroviral reporter–labeled cells exhibit glial morphologies and do not co-express neuronal markers. In controls, retroviral reporter–labeled cells with oligodendrocytic morphology appear only in the caudal SVZ and corpus callosum after posterior periventricle injections. These results indicate that prolonged seizures accelerate the proliferation of glial lineage-restricted precursors in the caudal SVZ and that the migration of newly generated glioblasts is redirected to the injured hippocampus.

The mechanisms by which seizure activity stimulates neurogenesis or gliogenesis are unknown. Experiments in which proliferating cells were labeled with BrdU prior to seizure induction have shown that epileptic activity stimulates dentate gyrus and caudal SVZ precursors that were proliferating prior to injury (Parent and others 1999). Seizures may act to increase neurogenesis indirectly through injury of mature DGCs, thereby leading to cell turnover in the dentate gyrus. Cell death is associated with subsequent cell birth in a number of postnatal neurogenic systems, including the dentate gyrus and olfactory bulb of adult rodents (Gould and McEwen 1993; Biebl and others 2000). Seizures also increase the expression of molecules with the potential to increase neurogenesis or gliogenesis such as growth factors (Humpel and others 1993) and neurotrophins (Isackson and others 1991). Specific neurotransmitters or neuromodulatory systems that normally influence DGC neurogenesis (see Table 1) may also be altered by seizure activity.

Neurogenesis after Ischemic Brain Injury

Accumulating evidence suggests that ischemic injury potently stimulates neurogenesis in proliferative regions of the adult rodent brain. This effect was initially shown in the dentate gyrus after transient focal or global ischemia in the adult rodent (Liu and others 1998; Jin and others 2001). As with seizure-induced injury, accelerated precursor proliferation occurs after a latent period, and most of the precursor progeny differentiate into DGCs in the granule cell layer. More recent work by several groups provides evidence that focal ischemic injury also increases forebrain SVZ cell proliferation and neurogenesis. Zhang and colleagues (2001b) showed increased SVZ BrdU labeling and neurogenesis that peaked 7 days after injury in an embolic rat adult stroke model, although persistent neurogenesis in peri-infarct regions was not identified. Focal ischemia-induced, short-lived SVZ neurogenesis in the adult rat has also been reported after tMCAO (Jin and others 2001).

Three recent studies provide important evidence that endogenous precursors can generate neurons after stroke in otherwise dormant regions of the adult rat forebrain. Two of the reports involve findings of neostriatal neurogenesis after stroke. Data from our laboratory and that of Arvidsson and others indicate that forebrain SVZ neurogenesis increases ipsilateral to the infarct after adult rat tMCAO (Fig. 4) (Arvidsson and others 2002; Parent, Vexler, and others 2002). The neuroblasts generated after

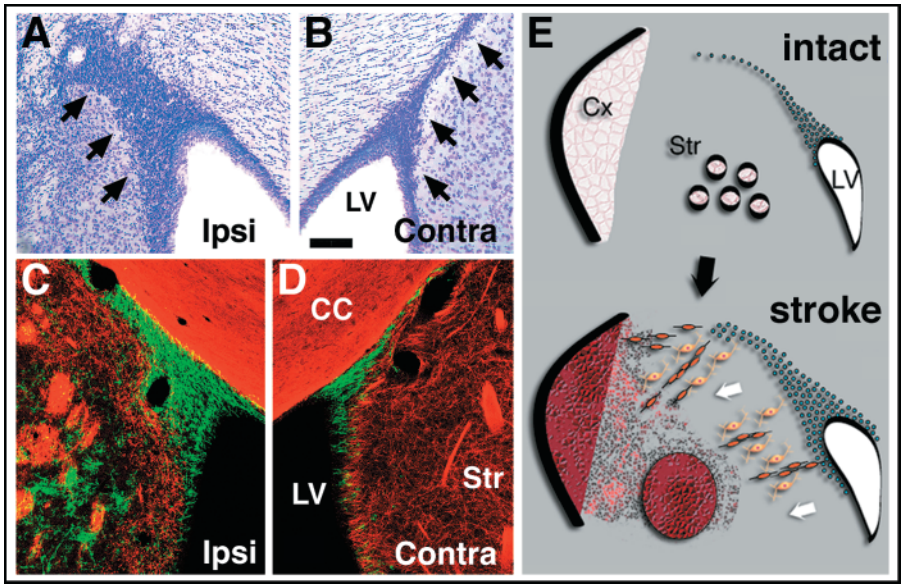

Fig. 4. Stroke-induced subventricular zone (SVZ) neurogenesis. *A*, *B*, Nissl-stained coronal brain sections from an adult rat 35 d after tMCAO show expansion of the SVZ (arrows) ipsilateral (ipsi) to the stroke (*A*) compared to the contralateral (contra) hemisphere (*B*). *C, D,* Confocal images of doublecortin (green) and myelin oligodendrocyte glycoprotein (red) double-label immunofluorescence from an adult rat 14 d after tMCAO. Increased numbers of doublecortin-immunoreactive neuroblasts are seen in the SVZ and striatum (Str) ipsilateral to the stroke (*C*) compared with contralateral (*D*). LV = lateral ventricle; CC = corpus callosum. *E*, Schematic diagram of coronal sections through the adult rat striatal SVZ shows changes after focal ischemic injury (red in *bottom* panel). The stroke expands the neural precursor population in the SVZ (blue circles) and induces neuroblast chain migration (orange) along astrocytes (yellow) to the infarct. The neuroblasts may be responding to diffusable cues released by the injured tissue (small particles). Scale bar (in *B*), 100 μm.

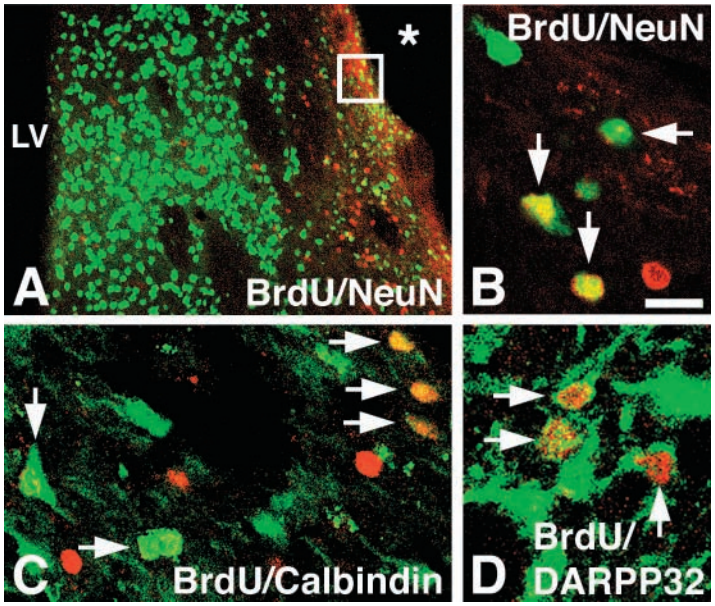

Fig. 5. Newly generated cells in the peri-infarct striatum after tMCAO express markers of medium spiny neostriatal neurons. *A-D*, Confocal images of coronal sections from an adult rat 35 d after tMCAO show BrdU-labeled cells (red) that express the neuron-specific marker NeuN (*A*, *B*) and the neostriatal neuron markers calbindin (*C*) and DARPP-32 (*D*). The panels in *B-D* are approximately from the boxed region in *A*. LV = lateral ventricle; * denotes the infarct. Scale bar (in *B*), 150 μm for *A*; 10 μm for *B-D*. Adapted with permission from Parent, Vexler, and others (2002).

stroke form chains closely apposed to astrocytes that extend from the SVZ to the injured striatum (Fig. 4*E*). This structural arrangement is remarkably similar to the chain migration of neuroblasts through astrocytic tubes characteristic of the RMS (Lois and others 1996; Peretto and others 1997) and suggests that cues induced by ischemic brain injury may redirect some of the SVZ neuroblasts to migrate into peri-infarct brain regions. Remarkably, the SVZ neuroblasts that migrate to the injured striatum differentiate into neurons that express regionally appropriate markers of medium spiny neostriatal projection neurons (Figs. 4 and 5). A portion of the newly generated neurons persists for at least 5 weeks after tMCAO, although relatively few newborn neurons are found in the damaged neostriatum at this time point compared with 2 weeks after stroke (Fig. 4*C*). It is therefore likely that many of the newborn striatal neurons do not survive. These data suggest that endogenous progenitors are capable of replacing neostriatal neurons damaged by stroke in the adult, and raise the possibility that

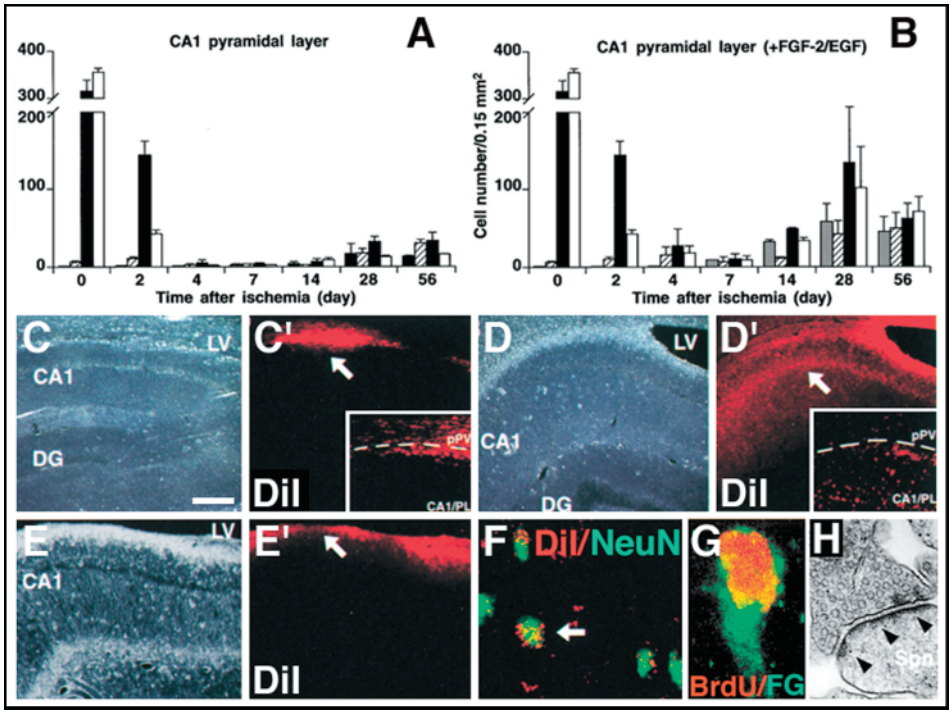

Fig. 6. Hippocampal pyramidal cell neurogenesis occurs after stroke. *A*, *B*, Counts of hippocampal CA1 pyramidal cells at different timepoints after transient global ischemia. Within 7 d, nearly all of the pyramidal cells are killed, but pyramidal cell numbers increase as new pyramidal neurons are generated at later time points after stroke, especially in animals treated with growth factors (*B*). *C-E'*, Lipophyllic tracer (DiI) labeling of cells in the posterior periventricular (pPV) region. At 4 d after stroke, labeled cells (red) remain in the periventricular region (*C'*). By day 28 (*D'*), the cells have migrated into the CA1 pyramidal cell layer (CA1/PL), suggesting that the pPV is a source of new pyramidal neurons after ischemic injury. Insets are higher magnification views showing the border of the pPV and hippocampus (dashed lines). In a control 28 d after DiI injection (*E'*), labeled cells remain in the pPV. *C*, *D*, and *E* are respective bright-field images. *F*, DiI-labeled cells express the neuronal marker NeuN. *G*, A pyramidal cell with BrdU-labeled nucleus present after stroke is co-labeled by a subicular injection of the retrograde tracer fluoro-gold (FG), showing that the newborn neurons send appropriate projections. *H*, A putatively newborn pyramidal cell 28 d after stroke receives synaptic inputs (arrowheads). Scale bar (in *C*), 250 μm for *C-E'*; 20 μm for *F*; 7.5 μm for *G*; and 0.1 μm for *H*. Adapted with permission from Nakatomi and others (2002).

treatments directed at augmenting the generation or survival of neuroblasts might improve recovery after stroke.

The third report describing neuronal replacement involves hippocampal neurogenesis after stroke. Nakatomi and others (2002) used a transient four-vessel ischemia and systemic hypotension stroke model to induce delayed hippocampal CA1 pyramidal cell death in adult rats. Despite the fact that hippocampal pyramidal cells are generated exclusively during embryonic life under normal circumstances, their data show that a modest number of pyramidal cells regenerate within 4 weeks after stroke (Fig. 6*A*). Even more remarkable is their finding that a brief intraventricular infusion of bFGF and EGF in the first week after stroke stimulates the regeneration of nearly 40% of the damaged CA1 region at 28 days (Fig. 6*B*). Using the fluorescent lipophilic carbocyanine tracer DiI (1,1'-dioctadecyl-3,3,3',3'-tetramethylindocarbocyanine perchlorate) and retroviral reporter labeling, as well as immunostaining for neural precursor cell markers, they also provided evidence that SVZ precursors are a source of the new neurons. These neural precursors arise in the posterior periventricular region and migrate ventrally to the hippocampus after injury, where they differentiate into pyramidal neurons (Fig. 6). The findings are similar to those described above after seizure-induced hippocampal injury, although after stroke the precursor progeny differentiate into neurons rather than glia. This difference in cell fate may relate to differences in the nature of CA1 pyramidal cell death induced by transient global ischemia versus prolonged seizures, or could be a consequence of the growth factor infusion. Together, the findings of neostriatal and hippocampal pyramidal cell neurogenesis after stroke provide evidence that endogenous neural stem cells contribute to self-repair in the mature brain and that pharmacological stimulation of hippocampal neurogenesis after ischemic injury can promote neuronal renewal.

Growth or neurotrophic factors are candidates for mediating ischemia-induced neurogenesis. Forebrain ischemia increases the expression of several of these factors, including bFGF and BDNF (Takami and others 1992; Kokaia and others 1995; Lin and others 1997). In some instances, increased expression is sustained for at least 10 to 14 days. This temporal pattern is consistent with that of ischemia-induced neurogenesis and neuroblast migration described above. Several of these molecules have already been shown to influence SVZ neural precursors in vivo in the intact adult rodent. For example, bFGF increases SVZ-olfactory bulb neurogenesis after intraventricular infusion in the adult rat (Kuhn and

others 1997). Delivery of BDNF by intraventricular infusion or injection of BDNF-expressing adenovirus in adult rats increases neuroblast numbers in the SVZ-olfactory bulb pathway, and also generates new neurons in ectopic sites, such as the striatum, septum, and thalamus (Benraiss and others 2001; Pencea and others 2001). TGF-α is another candidate for modulating ischemia-induced neurogenesis, as it causes SVZ precursor migration to striatum and differentiation into neurons when infused intrastriatally after 6-hydroxydopamine lesioning of adult rat (Fallon and others 2000). In addition to the stimulation of hippocampal neurogenesis by bFGF and EGF after stroke (Nakatomi and others 2002), SVZ neurogenesis ipsilateral to ischemic injury appears to be increased by nitric oxide donors and vascular endothelial growth factor (VEGF) (Zhang and others 2001a; Jin and others 2002).

Activated glia are a potential source of cues that direct stroke-induced neurogenesis. Astrocytes are implicated in the regulation of neurogenesis in the intact adult forebrain (Lim and Alvarez-Buylla 1999; Song and others 2002), and astrocyte proliferation and activation is induced by stroke. As expected, we found a marked increase in vimentin- or GFAP-expressing astrocytes in brain regions near the ischemic injury, and the chains of neuroblasts extending ectopically from the SVZ into the neostriatum after tMCAO were in close contact with astrocytes (Parent, Vexler, and others 2002; Fig. 4*E*). This structural arrangement suggests that activated astrocytes may induce or guide the aberrant migration of SVZ neuroblasts to injury and is similar to findings of astrocyte activation and altered neuronal precursor migration in the SVZ-olfactory bulb pathway after seizure-induced injury or transection lesions of the RMS (Alonso and others 1999; Parent, Valentin, and Lowenstein 2002). The inflammatory response from microglial activation could also be a source of trophic/mitogenic factors or migration-inducing cytokines that influence endogenous precursor behavior. Importantly, the modulation of SVZ neuroblast proliferation or migration by glia may explain why diverse brain insults appear to exert similar effects on SVZ and dentate gyrus neural precursor behavior.

Consequences of Injury-Induced Neurogenesis

Although many types of injury appear to increase neurogenesis in the adult mammalian forebrain, little is known regarding the effects of injury-induced neurogenesis on brain function. Existing evidence suggests that neurogenesis stimulated by brain insults may be beneficial in some contexts or maladaptive in other situations. The results appear to depend upon the affected progenitor population and the type of injury. For example, the increased neuronal birth induced by SE suggests the potential for compensatory effects after seizure-induced injury. Our findings, however, indicate that newly generated DGCs participate in aberrant network reorganization in the epileptic hippocampal formation. In the pilocarpine model of temporal lobe epilepsy, aberrant mossy fiber sprouting occurs in parallel with the generation of increased numbers of DGCs (Parent and Lowenstein 1997). To determine whether the newborn DGCs contribute to aberrant synaptic reorganization, we labeled proliferating cells in the dentate gyrus with BrdU after SE in the adult rat and examined the axonal projections of the newly generated DGCs (Parent and others 1997). We found that developing axons from these cells contributed to aberrant mossy fiber reorganization in both area CA3 and the dentate inner molecular layer. Subsequent work suggested that seizure-induced injury causes both newly generated and mature DGCs to project axons aberrantly in the epileptogenic hippocampal formation (Parent and others 1999).

A second abnormality associated with seizure-induced DGC neurogenesis concerns the ectopic location of newborn granule neurons. In human temporal lobe epilepsy, the DGC layer is often abnormal owing to dispersion and the presence of ectopic granule-like neurons in the hilus and inner molecular layer (Houser 1990). We have found that pilocarpine-induced SE in adult rats results in newly differentiating neurons with granule cell morphology in the dentate hilus and inner mole-cular layer. These cells resemble the "ectopic" granule-like neurons identified in surgical specimens from humans with temporal lobe epilepsy (Houser 1990). SE also induces a progressive increase in large BrdU-immunolabeled nuclei in the hilus over time, as well as chains of migrating neuroblasts extending from the inner DGC layer to the hilus (Fig. 2*C*,*D*). Although the precise origin of these cells is unknown, their appearance following pilocarpine treatment, but not in controls, suggests that they migrate aberrantly from the dentate subgranular zone to the hilus after prolonged seizures.

Subsequent studies have confirmed the finding of newly generated, ectopic hilar DGCs after kainic acid– or pilocarpine-induced SE (Scharfman and others 2000; Dashtipour and others 2001). Using intracellular recordings in hippocampal slices from epileptic adult rats, Scharfman and colleagues (2000) showed that the hilar ectopic granule-like cells maintain the basic electrophysiological characteristics of DGCs. Unlike mature granule neurons in the DGC layer, however, the hilar ectopic granule cells fire abnormal bursts in synchrony with CA3 pyramidal cells. In addition, many putatively newborn DGCs located in the hilus or hilar aspect of the DGC layer after seizures exhibit a much higher percentage of persistent basal dendrites than is normally found (Scharfman and others 2000; Dashtipour and others 2001). Work by Ribak and colleagues suggests that the basal dendrites of hilar ectopic DGCs receive increased excitatory input (Dashtipour and others 2001), suggesting that this structural plasticity may be a mechanism for seizure generation.

Unlike seizure-induced DGC neurogenesis, the generation of new neurons in the striatum and hippocampal CA1 region after stroke appears to have beneficial consequences. Neuroblasts attracted to the damaged neostriatum after tMCAO differentiate into neurons with an appropriate phenotype, suggesting that they may partially replace the medium spiny neurons lost after ischemic

injury (Arvidsson and others 2002; Parent, Vexler, and others 2002). Whether these new neurons integrate and result in any functional recovery after stroke remains to be determined. More convincing are the data showing CA1 pyramidal neuron replacement after transient global ischemia in the adult rat (Nakatomi and others 2002). These authors have shown that growth factor infusion after stroke in this model not only produces a partial regeneration of the hippocampal pyramidal cell, but also that the newly generated pyramidal cells integrate and are electrophysiologically functional (Fig. 6*G*,*H*; Nakatomi and others 2002). Moreover, the growth factor–induced hippocampal neuronal replacement is also associated with improvements in spatial learning deficits caused by the stroke. Neurons generated by endogenous precursors in the adult rat brain therefore appear to contribute to self-repair and recovery after ischemic injury.

Prospects for Brain Repair

The use of endogenous neural precursors to achieve repair after brain injury or neurodegeneration obviates some of the potential technical and ethical hurdles associated with neural stem cell transplantation. Our current understanding of injury-induced neurogenesis derives mainly from animal models of acute brain injury. Existing data, especially those related to seizure-induced DGC neurogenesis, suggest potential difficulties likely to arise in devising therapeutic strategies to augment endogenous neurogenesis for brain repair. The findings of ectopic hilar neurogenesis highlight this point. Although DGC precursors migrate ectopically to a region of injury (hilar cells are lost in experimental temporal lobe epilepsy), they maintain their original phenotype rather than differentiating into neuronal subtypes that could replace the injured neurons. This aberrant neurogenesis not only fails to achieve neural repair but is counterproductive in terms of its pro-epileptogenic nature. Such findings highlight the complexity of the injury environment in the mature brain and the potential for competing cues to arise, some of which may be maladaptive for promoting neuronal replacement.

Studies of endogenous neurogenesis in adult rodent models of stroke and Parkinson's disease offer more optimism for their therapeutic potential. This work shows that neurons newly generated after injury in the adult are capable of differentiating into appropriate cell types, integrating and possibly contributing to functional recovery. The finding of neocortical pyramidal neuron replacement by endogenous progenitors after focally induced apoptosis in the adult mouse indicates that integration of newly generated neurons with long-distance projections is possible after injury to the mature brain (Magavi and others 2000). A better understanding of the mechanisms that regulate endogenous neural precursors, both in the intact and injured brain, will be key to developing means of effectively modulating neurogenesis in disease states. The augmentation of endogenous neurogenesis in the adult may then offer useful therapies for brain repair after injury or neurodegeneration.

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