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The Adult Neural Stem Cell Niche: Lessons for Future Neural Cell Replacement Strategies

Daniel A. Lim, MD, PhD[a,*], Yin-Cheng Huang, MD[b], Arturo Alvarez-Buylla, PhD[a]

[a]*Department of Neurological Surgery, University of California, San Francisco, 505 Parnassus Street, M779, Box 0112, San Francisco, CA 94143, USA*
[b]*Chang-Gung Memorial Hospital, Number 5, Fu-hsin, St. Kweishan, Taoyuan, Taiwan 333*

Cell replacement therapies for diseases of the adult brain have attracted considerable attention since the initial reports of successful transplantation of embryonic dopaminergic cells to patients with Parkinson's disease [1]. Although the clinical successes of these transplantation trials for Parkinson's disease have been marginal [2,3], the enthusiasm for developing cell replacement therapies continues to grow. Contributing to this enthusiasm was the relatively recent discovery that the adult human brain maintains populations of neural stem cells (NSCs) capable of producing glia and neurons, renewing hope in the possibility of brain repair. Furthermore, there has been an explosion of knowledge about embryonic stem (ES) cells, including techniques of producing NSCs from human ES cells. Regardless of the origin of the NSC population, the clinical success of cell replacement therapies depends on a more detailed knowledge of NSC biology.

Determining the factors that regulate NSC self-renewal is important for expansion of NSC populations in vitro to numbers sufficient for transplantation. Knowledge of signals controlling progenitor cell migration and differentiation may allow us to direct grafted cells to particular targets and cellular fates. In addition to transplantation strategies, a comprehensive knowledge of NSC biology may allow us to mobilize endogenous NSCs or progenitors for glial or neural repair with targeted infusion or expression of certain niche factors.

NSC self-renewal and progenitor cell differentiation are modulated by the specialized microenviroment—or "niche"—in which these cells are maintained. The concept of a stem cell niche was originally developed in hematopoietic studies, whereby it was found that stem cell fate is controlled by soluble factors as well as by membrane-bound molecules and the extracellular matrix (ECM) [4]. For stem cells in general, such soluble and nonsoluble signals may be derived from the stem cells themselves, their progenitors, and neighboring cells [5].

In the embryo, NSCs and their niches exist only for relatively brief periods as the brain develops. In contrast, in the adult brain, NSCs and their niches are maintained in restricted regions throughout life. Although there are many differences between embryonic NSCs and those of the adult brain, it is now clear that many developmental signals and morphogens are retained in the adult brain niches [6].

The adult rodent brain has NSCs concentrated in the dentate gyrus subgranular zone (SGZ) and lateral ventricle subventricular zone (SVZ) (Fig. 1A–D). Throughout life, cells born in the rodent SVZ migrate a long distance anteriorly to the olfactory bulb, wherein they differentiate into interneurons [7]. Newly born hippocampal neurons are born locally in the SGZ and migrate a short distance into the overlying dentate gyrus [8].

* Corresponding author.
E-mail address: limd@neurosurg.ucsf.edu (D.A. Lim).

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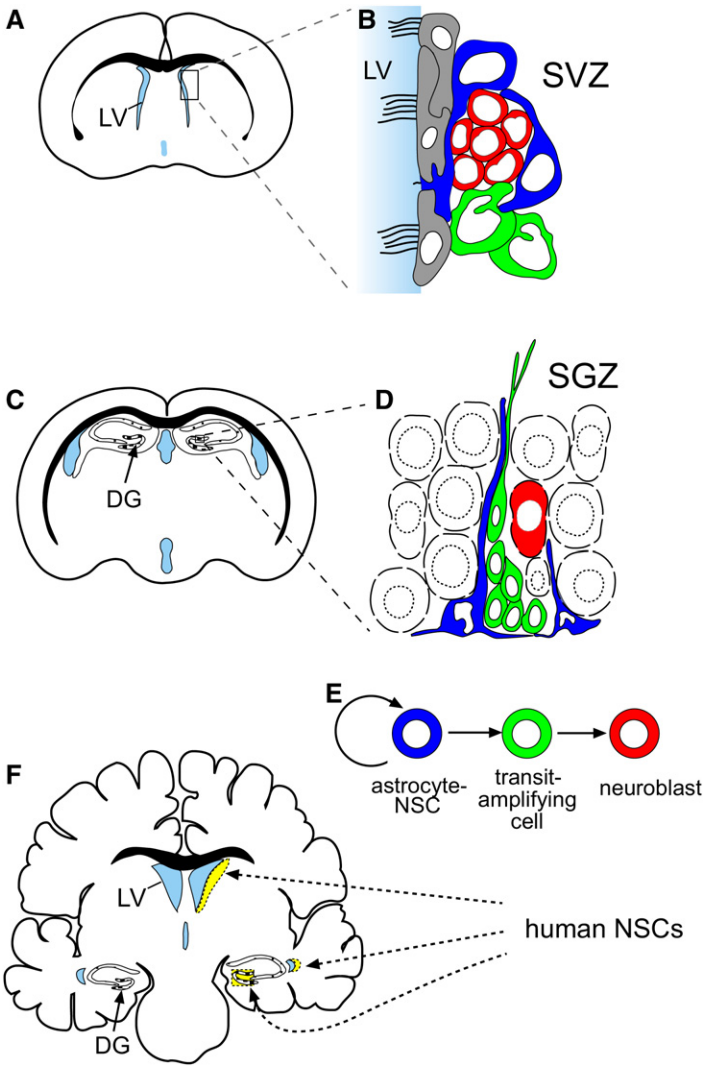

Fig. 1. Schematic of adult brain NSC niches. (*A–D*) Adult mouse brain. (*A*) Coronal slice through mouse brain shows the relation of the SVZ to the lateral ventricle (LV). Ventricles are light blue. The corpus callosum is solid black. (*B*) Enlarged view of the SVZ niche. Gray ciliated cells are the ependyma. Astrocyte-NSCs (*blue*) are glial fibrillary acidic protein-positive cells that divide and give rise to transit-amplifying cells (*green*), which then give rise to migratory neuroblasts (*red*). Neuroblasts migrate from the SVZ to the olfactory bulb. Note that astrocyte-NSCs are in close contact with all other SVZ cell types. (*C*) Coronal slice of mouse brain at the level of the hippocampus. The dentate gyrus (DG) is indicated by the arrow. (*D*) Enlarged view of the SGZ niche. In the SGZ, astrocyte-NSCs (*blue*) also give rise to an intermediate cell type (*green*), which then produces young granule neurons (*red*). Mature granule neurons are white. As in the SVZ, astrocyte-NSCs are intimately associated with all other cell types in the niche. (*E*) Schematic of general lineage of the SVZ and SGZ. Note that the mode of self-renewal (eg, asymmetric versus symmetric) is not known and that there may be other differentiation pathways not indicated by this simplified lineage. (*F*) Coronal section of adult human brain. Ventricles are light blue, and the corpus callosum is solid black. Human NSCs may be isolated from regions shown in yellow, indicated by the dotted arrow lines. Populations of neural progenitors may also be isolated from regions of subcortical white matter.

In the adult human brain, neurogenesis occurs in the dentate gyrus of the hippocampus [9,10] and from cells isolated from the lateral ventricle SVZ [11,12] and subcortical white matter (Fig. 1F) [13]. Although human NSCs can be distinguished from those of the rodent, there are many parallels in the biology (eg, human and rodent NSCs have astrocyte-like characteristics and grow in similar culture conditions). Therefore, lessons learned from the rodent SVZ and SGZ are likely to be important to the development of NSC therapies. The authors do not comprehensively cover all aspects of the adult brain germinal niche; other recent reviews can be consulted for excellent discussions of the roles that vasculogenesis [14] and the ECM [15] play in NSC biology. Instead, they focus on the dual role that astrocytes play as stem cells and niche cells and discuss some of the niche signals that may be derived from these germinal zone astrocytes.

Some astrocytes are neural stem cells

Although astrocytes have been classically thought of as simply glial "support" elements of the adult brain, in the rodent SVZ and SGZ, some astrocytes function as neurogenic stem cells [16–20]. These SVZ and SGZ astrocyte-NSCs express glial fibrillary acidic protein (GFAP) and have ultrastructural characteristics typical of astrocytes. In the human brain, there is a ribbon of GFAP-positive astrocytes that lines the ventricles; a subpopulation of these human SVZ astrocytes proliferate in vivo and behave as multipotent stem cells in vitro [12]. Astrocyte-NSCs in the rodent give rise to transit-amplifying cells, which then give rise to neuroblasts or young neurons (Fig. 1E). Under normal conditions, astrocytes outside the SVZ and SGZ do not seem to be neurogenic. Are SVZ and SGZ astrocytes intrinsically different than astrocytes found outside these germinal regions? The lineage relation and molecular characteristics of stem cell astrocytes versus non-stem cell astrocytes remain to be determined.

SVZ and SGZ neurogenesis is partially determined by signals restricted to their respective germinal niches. Mouse SVZ cells transplanted homotopically to another SVZ give rise to large numbers of olfactory bulb interneurons in the recipient animal [21]. In contrast, SVZ cells transplanted to nonneurogenic brain regions do not produce neurons [22]. Similarly, cultured SGZ progenitors produce interneurons when grafted back to the SGZ but not when transplanted to nonneurogenic brain regions [23]. Intriguingly, the SVZ niche instructs appropriate neurogenesis of grafted SGZ progenitors [23]. Likewise, normally gliogenic progenitor cells become neurogenic when transplanted to the SGZ niche [24,25]. Thus, the SVZ and SGZ germinal niches, in addition to maintaining the population of NSCs, also instruct their neuronal differentiation. Determining the molecular nature of these neurogenic signals may be important for developing NSC therapies.

Astrocytes are also niche cells

Which SVZ and SGZ cell types are critical for the niche? It seems that astrocytes are important niche cells in these germinal zones (see Fig. 1B, D). In the SVZ, astrocytes are in direct contact with all other SVZ cell types, including the rapidly dividing transit-amplifying cells as well as the committed migratory neuroblasts [7]. SVZ precursor cells cultured in serum-free medium in direct contact with monolayers of other astrocytes proliferate to form colonies of young neuroblasts [26]. Similarly, astrocyte-derived soluble and membrane-bound factors promote neurogenesis from SGZ stem cells [27]. In the SGZ, astrocyte-stem cells form basket-like structures, cradling the newly born neuroblasts [28]. It thus seems that the close proximity or contact between astrocytes and other cell types in these adult germinal zones is critical for NSC neurogenesis.

Not all astrocytes can serve as NSC niche cells. Astrocytes from the postnatal cortex and hippocampus support NSC neurogenesis in coculture, but spinal cord–derived astrocytes cannot [27]. These differences in the neurogenic niche cell capability of different populations of astrocytes may be one way in which neurogenesis is restricted to specific brain regions. Astrocytes express a variety of secreted and membrane-bound factors [29,30]. Perhaps the array of such factors varies depending on the age and location of each particular astrocyte population. It also remains to be determined whether or not SGZ and SVZ astrocytes can serve a dual role as stem cells and niche cells or whether these properties are mutually exclusive.

A brief update about epidermal growth factor and fibroblast growth factor-2 signaling

Epidermal growth factor (EGF) and fibroblast growth factor (FGF)-2 are the principal mitogens

used to propagate NSC in vitro, and they are believed to be critical for proliferation in vivo. Although it is not clear which cells in the adult brain produce these mitogens, cultured astrocytes express EGF [31] and FGF [32], and thus may provide these proliferative signals for the stem cell niche. EGF and FGF receptors (EGFR and FGFR) are expressed in the SVZ, and mice null for FGF2 [33] or the EGFR ligand transforming growth factor-α (TGFα) [34] have significantly reduced SVZ neurogenesis, supporting the notion that they are important in vivo. Although EGF and FGF are often thought of primarily as mitogens, they are also likely to have roles in determining the developmental fate of NSCs and may even cause NSC dedifferentiation [35,36].

In SGZ-derived NSC cultures, FGF2 signaling is potentiated by Cystatin C, an N-glycosylated protein that has been isolated as an autocrine or paracrine factor from the culture medium of adult SGZ and embryonic SVZ NSC cultures. It seems that this niche factor is important in vivo: in the adult SGZ and SVZ, cells undergoing division express Cystatin C and mice null for cystatin C have a 60% reduction of SGZ neurogenesis [37].

Notch signaling: regulating self-renewal and a potential feedback mechanism?

Maintenance of self-renewal and an undifferentiated state is critical for the effective in vitro amplification of NSCs for clinical application. The Notch family of transmembrane signaling molecules participates in many developmental cell fate decisions and, in some contexts, promotes an undifferentiated precursor cell state [38]. Notch1 and two cognate membrane-bound ligands, Jagged-1 and Delta-1, are expressed in the adult NSC niches [39–41]. Notch signaling may participate in suppressing neuronal differentiation and maintaining precursor cell properties. Retroviral induction of activated Notch (ActN) in the embryonic brain promotes radial glial identity and produces dense clusters of SVZ astrocytes after birth [42]. Furthermore, ActN in postnatal SVZ cells prevents migration to the olfactory bulb, suppresses neuronal differentiation, and decreases proliferation, creating a more "quiescent" cell type [43]. Recently, Nyfeler and colleagues [40] showed that Jagged1-Notch1 signaling in vivo is important for SVZ cellular proliferation; in vitro, soluble Jagged1 promotes SVZ NSC self-renewal and increases its neurogenic potential. In the adult SVZ, Jagged1 is expressed by a subset of GFAP-positive astrocytes and Notch1 is expressed by adjacent clusters of cells; SVZ astrocytes were not found to coexpress Jagged1 and Notch1. One interpretation of these findings is that the Jagged1-expressing astrocytes serve as niche cells for adjacent Notch1-expressing astrocytes.

Jagged1- and Delta1-expressing cells are also found in the migratory cells of the SVZ [39]; this expression pattern suggests a potential feedback regulation of the SVZ niche: the accumulation of newly born neuroblasts expressing Jagged1 or Delta1 upregulates Notch signaling in the NSCs, suppressing differentiation and potentiating self-renewal. Such dynamic regulation of adult NSCs remains to be demonstrated.

Wnt signaling: integrated with Notch?

The Wnt family of secreted signaling molecules has many diverse roles in neural development, including stem cell maintenance, cellular proliferation, differentiation, migration, and axon guidance [44]. In the adult brain, Lie and coworkers [45] demonstrated that overexpression of Wnt3 stimulates SGZ neurogenesis in culture and in vivo; conversely, inhibition of Wnt3 signaling greatly reduces SGZ neurogenesis in vitro and in vivo. Wnts are produced by cells adjacent to the SGZ; in vitro, Wnts are expressed by SGZ-derived astrocytes. To investigate the mechanism by which Wnts control SGZ neurogenesis further, it is important to determine which cell types express Wnts and Frizzleds (the Wnt receptors). Whether Wnts are influencing SGZ stem cell self-renewal, proliferation, or differentiation is not yet known. For SVZ-derived NSC cultures, Wnt3a or Wnt5a promotes precursor cell proliferation and differentiation into neuronal lineages [46]. Which cells in the SVZ express Wnts is not known; however, Wnt5a expression has been described in the postnatal [47] and adult olfactory bulb [48].

In hematopoiesis, there is evidence that Notch and Wnt signaling is integrated to maintain the stem cell phenotype [49]. The mechanism of this Notch-Wnt signal integration is not known, but it is intriguing to note that Jagged1 seems to be a downstream target of canonical Wnt signaling [50]; it is possible that Wnt induces Jagged1 expression, which, in turn, signals through Notch1.

Sonic hedgehog: roles in stem cell maintenance and proliferation

Sonic hedgehog (Shh) is an important morphogen in development [51], and it has been

shown to regulate stem cells and neurogenesis in the SVZ and SGZ neurogenic niches. For the hippocampus, Lai and colleagues [52] showed that Shh overexpression near the SGZ increases local cell proliferation and neurogenesis; in vitro, Shh can maintain the proliferation of SGZ-derived NSCs. Conversely, pharmacologic inhibition of Shh signaling by cyclopamine reduces SGZ neurogenesis.

Machold and coworkers [53] conditionally removed the Shh coreceptor Smo (Smoothened) from neural precursors at E12.5 by crossing floxed *Smo* (*Smo*$^{n/c}$) with Nestin-Cre (*N*^{cre}) mice; *Smo*$^{n/c}$/*N*^{cre} mice have less SVZ and SGZ cell proliferation and neurogenesis. Furthermore, fewer NSCs can be cultured from these *Smo*$^{n/c}$/*N*^{cre} animals. Despite these dramatic effects on adult neurogenesis, the mature brains of *Smo*$^{n/c}$/*N*^{cre} mice seem to be of normal size, suggesting that Shh is primarily important in ''maintaining'' the stem cell population in postnatal and adult brain germinal niches. Although the data are consistent with this role of Shh as a ''maintenance'' factor, it has also been shown that Shh acts as a mitogen for SVZ-derived NSC cultures when the EGF concentration is not saturating [54].

Although the precise cellular source of Shh for the SVZ and SGZ has not been clearly demonstrated, Shh signaling can be inferred to be active in cells expressing the Gli1 transcription factor [55]. Gli1+ cells are found in SVZ and SGZ [53], including SVZ astrocytes and transit-amplifying cells, specifically [54]. Recently, Ahn and Joyner [56] showed that Gli1+ cells in the SVZ and SGZ behave as NSCs in vivo. These investigators engineered mice to express a Cre–estrogen receptor (ER) fusion gene under the control of the Gli1 promoter, restricting Cre-ER expression to cells with Shh signaling. Cre-ER can only cross into the nucleus in the presence of tamoxifen, thus providing temporal control to Cre-mediated recombination. Gli1–Cre-ER mice crossed to a Cre-reporter line (R26R) thus have LacZ reporter gene expression in a cohort of cells that is responding to Shh signaling during tamoxifen administration. Ahn and Joyner [56] treated Gli1–Cre-ER R26R mice with tamoxifen, eliminated rapidly dividing cells with administration of an antimitotic, and then followed the fate of LacZ+ cells. Initially, the number of LacZ+ cells in the niches increases, possibly representing the expansion of transit-amplifying cells. Over the next year, LacZ+ cells continue to be generated from the SVZ and SGZ niches for their respective neurogenic targets. Thus, Shh signaling is active in SVZ and SGZ stem cells, which are relatively quiescent, and these Gli1+ cells can respond to antimitotic insult by increasing proliferation.

Bone morphogenetic proteins and their antagonists: choice between glia and neuron fates

Another family of neural morphogens, the bone morphogenetic proteins (BMPs), also regulates adult brain germinal niches. BMP signaling promotes astrocyte differentiation of embryonic SVZ-derived precursors at the expense of oligodendrogliogenesis and neurogenesis [57]. Adult SVZ cells produce BMPs and their receptors [58,59]. Noggin, a secreted BMP antagonist, is also locally expressed, most strongly in the ependymal cells [58,60]. This locally derived BMP antagonist may contribute to the neurogenic niche for SVZ stem cells because it promotes neurogenesis in vitro and in ectopic locations in vivo [58]. Overexpression of BMP7 in the SVZ suppresses neurogenesis [58], and overexpression of Noggin from the ependyma suppresses gliogenesis [61]. Hence, a ''balance'' between BMPs and their antagonists may control the levels of neurogenesis and gliogenesis from NSCs in adult brain niches.

There is evidence for a similar mechanism in the hippocampus. In the SGZ, BMP signaling may be inhibited by neurogenesin-1 (Ng1). Ng1 is expressed in astrocytes in the SGZ and SVZ; in vitro, Ng1 antagonizes BMPs, thereby promoting neuronal fate by blocking glial differentiation [62]. Noggin is also expressed in the dentate gyrus [63], and infusion of Noggin antisense oligonucleotides into the brain ventricles for 3 days decreases SGZ proliferation by 40% when compared with sense oligonucleotide and saline controls [64]. Although these data are somewhat preliminary, rats treated with antisense Noggin oligonucleotides have impaired learning and memory, as assessed by Morris water maze testing [63]. In vivo, overexpression of BMP from a neuron-specific promoter results in cell cycle exit and reduced expression of progenitor cell markers (eg, Sox1, vimentin) in the SGZ astrocytes; conversely, overexpression of Noggin from the same promoter leads to increased proliferation and progenitor cell marker expression in the GFAP-positive SGZ cells [65]. If BMP overexpression reduces progenitor marker expression, one may wonder if BMP-induced astrocytes lose stem cell competence.

Leukemia inhibitory factor and bone morphogenetic protein induction of glial fibrillary acidic protein expression: are these astrocytes the same?

Are astrocyte-niche cells and astrocyte-stem cells molecularly distinct? Although BMPs and leukemia inhibitory factor (LIF) induce GFAP-positive astrocyte differentiation from NSCs, Bonaguidi and coworkers [65] recently demonstrated that BMP- and LIF-induced astrocytes from embryonic SVZ-derived NSCs are morphologically and molecularly distinct. BMP-induced GFAP-positive cells exit the cell cycle, take on a stellate morphology, and have limited NSC potential. In contrast, LIF treatment generates GFAP-positive cells that have a bipolar or tripolar morphology, remain in the cell cycle, express progenitor cell markers, and behave as NSCs in culture. In addition, LIF-treated NSCs have a greater neuronal differentiation potential. In ES cells, BMPs act in concert with LIF to sustain self-renewal and suppress differentiation [66]. It would be interesting to know what the effect of simultaneous BMP and LIF signaling has on adult NSCs. It is possible that the ratio of BMP/LIF signaling in the adult GFAP-positive SVZ or SGZ cell determines which is to serve as the niche cell and which is to be the stem cell. Reduction of BMP signaling by Noggin, Ng1, or other BMP antagonists may increase the LIF/BMP signaling ratio, increasing the likelihood that the GFAP-positive cell remains a NSC.

Integration of niche signals with cell-intrinsic factors

In addition to a set of niche factors, certain cell intrinsic factors are likely required for proper interpretation of the extracellular signals by NSCs. For instance, Bmi-1 [67] and TLX [68], both nuclear transcriptional regulators, are critical for adult NSC maintenance. Another example can be found in the studies of BMP signaling. Although BMPs induce gliogenesis of adult NSCs (as discussed previously) and E17-18 neural precursors [57], BMP signaling promotes neuronal rather than glial differentiation of neural precursors from the E13-14 embryo [69,70]; this may be related to the expression of high levels of the neurogenin1 (Ngn1) transcription factor by E13-14 neural precursors. Ngn1 not only activates genes for neuronal differentiation but also sequesters the BMP downstream signaling factor SMAD1 from astrocyte differentiation genes; interestingly, overexpression of Ngn1 can convert BMP into a neuronal differentiation signal from a gliogenic signal [71]. Along a similar line, in the adult SVZ cellular lineage, BMPs induce astrocyte differentiation in the early precursors [58] while inducing cell-cycle exit and enhanced survival of late lineage neuroblasts [72]; this difference in BMP activity may be related to differential expression of BMP receptor subtypes [58,73]. This is a reminder that cell intrinsic factors, such as transcription factors and specific signaling molecule receptor subtypes, are likely to be as important as niche factors for the control of NSCs and their daughter cells.

Developing a catalog of niche and neural stem cell intrinsic factors

To generate a more extensive catalog of genes important for SVZ and SGZ biology, several groups have used microarrays to analyze the gene expression of these brain regions or cells derived from these germinal zones (Table 1) [48,74–81]. Many niche and NSC intrinsic factors may have been identified in these transcriptional profile analyses, but it is sometimes difficult to know which genes are the most important to study. It is notable that certain genes are identified in several of the studies. Perhaps the genes that are consistently discovered by different investigators using dissimilar techniques are the highest yield candidates. A consolidated analysis of the data sets from these many studies might therefore be useful.

Potential clinical utility of lessons from the subventricular zone and subgranular zone niches

Improving the ability to culture human neural stem cells

The success of direct fetal cell transplantation for Parkinson's disease has been constrained by the limited availability (ethical and otherwise) of fetal tissue, limited migration of grafted cells, and poor differentiation and survival of grafted neurons [82]. Many of these issues can be better addressed by working toward an in vitro culture system capable of greatly expanding the number of human NSCs. Larger numbers of cells available for grafting are likely to improve the success of such therapies; in addition, an unlimited supply

Table 1
Transcriptional profile analyses of adult neurogenesis: working toward a catalog of neural stem cell niche and intrinsic factors

Authors/ Reference	Year	RNA derivation		Species	Cell origin	Age	Analysis platform	Special conditions
		Cultures	In vivo					
Lim, et al [48]	2006		+	Mouse	SVZ, Ob	Adult	Affymetrix, Mu11K, Santa Clara, CA	FACS and SVZ regeneration
Aiba, et al [74]	2006	+		Mouse	SVZ	Adult	Agilent Dev 2 chip, Palo Alto, CA	
Pennartz, et al [79]	2004		+	Mouse	SVZ	Adult	SAGE	FACS of PSA-NCAM+ cells
Gurok, et al [77]	2004	+		Mouse	SVZ	Postnatal	cDNA microarray	
Lein, et al [78]	2004		+	Mouse	Dentate gyrus[a]	Adult	Affymetrix, Mu11K, Santa Clara, CA	
Yoshiya, et al [80]	2003		+	Mouse	SVZ	Adult	InCyte, LifeArray, Palo Alto, CA	Head injury model
Easterday, et al [75]	2003	+		Mouse	Striatum[b]	Postnatal	UCLA microarray	
Elliott, et al [76]	2003		+	Rat	Dentate gyrus	Adult	Affymetrix, rat U34A, Santa Clara, CA	Seizure model
Zhao, et al [81]	2001		+	Mouse	Dentate gyrus[a]	Adult	Affymetrix, Mu11K, Santa Clara, CA	

Abbreviations: FACS, fluorescent activated cell sorting; Ob, olfactory bulb; PSA-NCAM, polysialyated neural cell adhesion molecule; SAGE, serial analysis of gene expression; SVZ, subventricular zone; +, positive.

[a] Other hippocampal regions were analyzed in addition.

[b] Striatum includes SVZ.

of NSCs should make their study much more approachable.

Where can one obtain human NSCs for culture? Populations of NSCs can be obtained from human ES cell cultures [83,84]. ES cells are an extremely promising source of cells for transplantation in general, and one can expect the ability to manipulate ES cells to continue to grow. Although ES cells are totipotent and adult brain-derived NSCs are restricted in their differentiation potential, there does seem to be at least some commonalities to their gene expression patterns [85,86]; this might suggest that signals used in the adult brain niches may have important and similar roles for ES cells. In support of this notion, it has been found that Noggin [87], Cystatin C [88], and Notch [89] can induce neural precursors from ES cell cultures. The development of chemically defined culture conditions for ES cell cultures is required to overcome some of the regulatory restrictions surrounding the clinical use of human ES cells, and the SVZ and SGZ niches may continue to provide clues to the induction of NSCs and maintenance of NSC self-renewal.

Cells from human fetal brain can be expanded in vitro; however, such cell cultures tend to undergo senescence under conditions commonly used. Similarly, neural precursor cells grown from adult brain also cease proliferating at approximately 20 doublings [90]. This limitation may be partially attributable to telomere loss, because increasing telomerase activity by addition of LIF [91] or direct transduction of telomerase reverse transcriptase (hTERT) [92] delays culture senescence. It is also possible that certain adult stem cell niche factors yet to be applied to the human culture conditions may promote self-renewal. Future investigations may demonstrate improved human NSC culture expansion with modulation

of Notch-Jagged, Shh, Wnt, LIF, and Noggin-BMP signaling (Fig. 2).

Possibility of inducing neurogenesis from endogenous precursors

SVZ and SGZ studies should continue to advance the understanding of the molecular determinants not only of NSC self-renewal but of those signals important for progenitor cell migration, differentiation, and survival. Such knowledge should contribute to the possibility that endogenous NSCs in the SVZ and SGZ can be mobilized to repair areas of diseased brain (see Fig. 2 for schematic) [93]. Early studies demonstrated that infusions of niche factors can modulate the NSC population in vivo: osmotic pump administration of EGF or FGF2 into mouse brain ventricles greatly expands the population of SVZ cells [94,95]. Although under normal conditions, the SVZ only generates neurons for the olfactory bulb, overexpression of Noggin and brain-derived neurotrophic factor (BDNF) from the ventricle wall induces SVZ neurogenesis for the adjacent striatum [61].

More intriguing are studies demonstrating functional recovery in rodent models of neurologic disease after induction of neurogenesis from endogenous NSCs. In a rodent model of Parkinson's disease, Fallon and colleagues [96] showed that infusion of TGFα induces proliferation and migration of cells from the SVZ into the striatum; new dopaminergic neurons appear in the striatum, correlating with functional recovery. Nakatomi and coworkers [97] showed that EGF and FGF2 infusions into the rat lateral ventricle induce the birth of new hippocampal pyramidal neurons from the caudal SVZ after ischemic injury; this treatment results in behavioral recovery, and the pyramidal cells survive at least 6 months after the injury. Although these two studies are compelling, future studies need to confirm that the neurogenesis itself is directly responsible for the behavioral recovery; the infused growth factors may have had neurotrophic effects on injured neurons (eg, enhancing survival of injured neurons, potentiating synaptic plasticity).

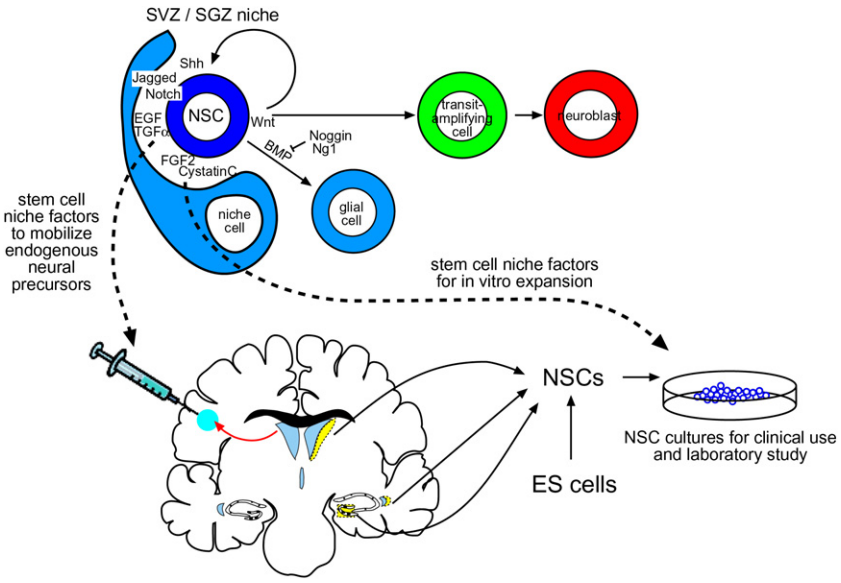

Fig. 2. Lessons from the SVZ and SGZ niches. Jagged-Notch and Shh signaling may help to maintain the stem cell state. FGF2 with Cystatin C and EGF/TGFα promote self-renewal and proliferation. Wnts promote cell proliferation and neurogenesis. BMP antagonists (Noggin, Ng1) inhibit BMP-directed glial differentiation, promoting neurogenesis; BMP antagonism may also help to maintain the NSC undifferentiated state. All these extracellular signals may prove to have multiple distinct roles in the niche, depending on integration by cell intrinsic factors (see text for details). Niche factors identified in the SVZ and SGZ may be used in vitro to expand populations of human NSCs obtained from the adult human brain or ES cells. Brain infusions of certain niche factors may also mobilize endogenous precursors to generate new neurons for brain repair (eg, TGFα for Parkinson's disease [96] and EGF/FGF2 [97] for ischemic injury; see text for details).

Summary

Success in treating neurologic disorders with NSCs depends not only on a detailed understanding of the cellular and molecular biology of NSCs but on insight into pathologic processes of the diseases being treated. Diseases in which only one or a few cell types are lost may be more amenable to cell replacement strategies. Although the authors have mentioned Parkinson's disease in this review and have focused the discussion on neurogenesis, cell replacement for demyelinating disorders (eg, multiple sclerosis) may be more approachable in that glial cell replacement does not necessarily require synaptic integration of the grafted cell into complex neuronal circuits. Adult and ES cell–derived NSCs can be induced to generate oligodendrocyte precursors [98,99], and the SVZ gives rise to oligodendrocytes in vivo [100,101]; thus, the study of the SVZ niche is also likely to advance the development of remyelination therapies. The potential of glial-restricted progenitors is nicely reviewed elsewhere [102] (and by Keyoung and his colleagues in this issue).

The adult SVZ and SGZ have many more lessons for us in the pursuit of neuronal or glial cell replacement therapies. Although there are many parallels between adult brain germinal zones and embryonic brain development, certain gene functions may be unique to adult NSCs and their niches. For instance, as compared with NSCs in development, adult brain NSCs face the additional challenge of requiring prolonged (up to years) self-renewal. Thus, the molecular "secrets" of a durable self-renewal NSC mechanism may only be learned from the adult brain, and harnessing the molecular determinants of such long-lasting self-renewal should aid in the development of NSC-based cell replacement strategies.

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