Vertebrate Neural Stem Cells: Development, Plasticity, and Regeneration

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Natural recovery from disease and damage in the adult mammalian central nervous system (CNS) is limited compared with that in lower vertebrate species, including fish and salamanders. Species-specific differences in the plasticity of the CNS reflect these differences in regenerative capacity. Despite numerous extensive studies in the field of CNS regeneration, our understanding of the molecular mechanisms determining the regenerative capacity of the CNS is still relatively poor. The discovery of adult neural stem cells (aNSCs) in mammals, including humans, in the early 1990s has opened up new possibilities for the treatment of CNS disorders via self-regeneration through the mobilization of these cells. However, we now know that aNSCs in mammals are not plastic enough to induce significant regeneration. In contrast, aNSCs in some regenerative species have been found to be as highly plastic as early embryonic neural stem cells (NSCs). We must expand our knowledge of NSCs and of regenerative processes in lower vertebrates in an effort to develop effective regenerative treatments for damaged CNS in humans. (doi: 10.2302/kjm.2015-0005-IR)  

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Introduction

In vertebrate CNS development, NSCs generate various types of neurons and glia in spatially and temporally regulated patterns to form complex networks that control complex behavioral patterns. Moreover, NSCs exist in the ventricular neuroaxis throughout the life of vertebrates and continue to generate new neurons constitutively in particular CNS regions.1–3 Adult neurogenesis is involved in continuous brain growth or neuronal turnover in different functional contexts in various species.4 Adult NSCs, including latent NSCs in non-neurogenic regions, can also be mobilized for regeneration in response to CNS damage.4,5 In particular, many non-mammalian vertebrates are able to effectively regenerate damaged CNS via mobilization of NSCs and progenitors.4 In contrast, adult mammals have limited regenerative capacity, although some NSCs and progenitors are mobilized in response to several types of damage.5 The species-specific differences in regenerative ability and broadening of neurogenic regions within vertebrates appear to correlate with phylogenetic interrelations.3 These differences partly may be caused by differences in the developmental potential of adult NSCs. In mammals, the developmental potential of NSCs is likely to be temporally and spatially restricted during development.6,7 For instance, many projection neurons, such as motor neurons (MNs) and dopaminergic (DA) neurons (DANs), which are generated in the early embryonic stage, are hardly generated at all by adult NSCs located in the corresponding ventricular neuroaxis where these neurons were born. In contrast, motor neuron and DA neuron regeneration can be induced in teleost fish SC and newt midbrain, respectively, after specific lesions.8,9

In humans, restoration of CNS functions that are lost in neurological disorders and injuries is very hard to achieve.
because of poor plasticity of the mature CNS. The identification of embryonic and adult NSCs in mammals, including humans, has elicited high expectations for their clinical application, especially in cell replacement therapies, to treat many types of CNS disorders. Indeed, a number of studies in animal models of various neurological disorders have investigated the transplantation of in vitro-expanded neural progenitor cells (NPCs), including NSCs and their differentiated progenies, and the mobilization of latent NPCs in vivo.10 Some enhancement of functional recovery was observed in many of these studies. The creation of induced pluripotent stem cells11,12 and the direct reprogramming of non-neural somatic cells into NPCs and neurons13 appear to have resolved many of the divisive ethical issues associated with the sourcing of highly plastic NSCs. Before these new techniques were introduced, NSCs in the early developmental state and early-born neurons such as MNs and DANs were obtainable only from embryos and embryonic stem cells (ESCs). However, there are still potential problems with the quality of neural cells derived via reprogramming, which often induce aberrant epigenomic reprogramming even in the absence of genomic integration of reprogramming factors, raising safety issues in their clinical use.14 Furthermore, transplantation of large numbers of specific types of neurons into specific brain regions may result in unusual structural changes, thereby causing unexpected side effects. Indeed, some Parkinson's disease patients who underwent transplantation into striatum of DANs derived from the human embryonic midbrain developed involuntary movements called dyskinesias as a side effect.15 Thus, ideal and ultimate cures for damaged CNS should be based on self-regeneration of lost neurons and glia via mobilization of endogenous NPCs and rewiring of functional neural circuits, processes that are often observed in certain lower vertebrates.

In this review, I discuss the ways in which mammalian NSCs develop and lose plasticity and summarize evolutionary differences in the regenerative capacity of adult CNS and the plasticity of adult NSCs. Progress in these fields is requisite for the development of an ultimate cure for damaged CNS via self-regeneration.

Temporal Specification of NSCs

During vertebrate ontogeny, the first irreversible specification of NSCs is regional specification, which is regulated by various inductive signals emanating from certain places in the embryo with the right timing to generate regionally specific neuronal subtypes16 (Fig. 1). NSCs can first be detected during the period of neural plate formation17 and are at this stage already partially regionalized along the anterior–posterior (A–P) axis that is defined until the end of gastrulation16 (Fig. 1A). At this time, NSCs can give rise to both the neural crest lineage and the CNS lineage, depending on the concentration of neural crest inductive signals, including bone morphogenic proteins (BMPs), Wnt family proteins, and fibroblast growth factors (FGFs). The neural plate with proliferating cells then invaginates and detaches from the epidermis to form the neural tube. During this period, the regional identity of NSCs can be determined more precisely by their position along the dorsal–ventral (D–V) and A–P axes (Fig. 1B–D).

After neural tube closure, NSCs as neuroepithelial cells in the ventricular zone initially symmetrically divide to expand the NSC pool and transform into radial glia (RG); they then start asymmetric division to generate neurons. In the developing mammalian cortex, neurons generated by RG in the VZ and subventricular zone (SVZ) migrate radially to the cortical plate to form six distinct layers containing specific types of excitatory neurons in each layer (Fig. 2A). The layer-specific neurons are sequentially generated by RG, and later-born neurons migrate past the earlier-born neurons to their final laminar location in an “inside-out” fashion based on their birth order. Clonal lineage analyses in vitro and in vivo have indicated that the sequential generation of preplate (ppl), deeplayer (DL), and upper-layer (UL) neurons and then glia is encoded, at least in part, within individual RG18–20 (Fig. 2A). In contrast, Franco et al. provided evidence that supports a model in which multiple types of progenitors differentiate into the layer-specific neurons at different times under control of intrinsic programs and/or extrinsic signals21 (Fig. 2B). By lineage tracing analyses using cutlike homeobox 2 (Cux2)-Cre and -CreERT2 driver mouse lines, they found that Cux2-expressing VZ progenitors that exist during the period of DL neuron production are already fate-restricted to give rise to UL neurons. However, using the same driver and reporter lines, Guo et al. later demonstrated that Cux2+ RG generate both DL and UL neurons.19 There is no clear explanation for this discrepancy.

In recent years, many factors involved in the specification of laminar fates have been identified18,22–24 (Fig. 3). However, how temporal identity of the developing NSCs is determined is poorly understood. Forebrain embryonic zinc finger protein 2 (Fezf2), which is transiently expressed in early cortical RG and is maintained in early-born DL V–VI neurons, has been shown to promote the specification of DL projection neurons.24 Fezf2 represses the expression of chromatin-remodeling protein special AT-rich sequence-binding protein 2 (Satb2), which promotes UL callosal-projection neuron identity by repressing expression of COUP transcription factor (TF)-interacting protein 2 (Ctip2).24 However, it is not clear whether Fezf2 expression in RG is essential for the specification of DL neurons. Both Satb2 and Ctip2 act in postmitotic neurons to promote UL- and DL-specific phenotypes, respectively,24 suggesting that Fezf2 plays a critical role in postmitotic neurons, rather than in progenitors, in terms of the acquisition of DL neuron identities. Indeed, forced expression of Fezf2 in postmitotic UL neurons convert
their identities to that of DL neurons. Foxg1 is a member of the forkhead box family of TF that is highly expressed in early cortical progenitors, DL neurons, and UL neurons but not in ppl Cajal-Retzius (CR) cells. Foxg1 is required for the transition from the production of the earliest CR cells to DL neurons. This transition requires, at least in part, the repression of T-box brain 1 (Tbr1) TF which represses Fezf2 expression by Foxg1, which represses Fezf2 expression. Since Tbr1 is detectable only in postmitotic neurons, Foxg1 may also act in postmitotic neurons. COUP-TF1 and COUP-TFII nuclear receptors are also essential for the switch from early-born to late-born neurons not only in the cerebral cortex but also in the basal ganglia. However, it is also unclear whether these factors act in NSCs or in committed neuronal lineages. In contrast, Ikaros, a mammalian homolog of Drosophila

Fig. 1 Regional specification in the developing CNS. (A) Neuroectoderm is partially regionalized along the A-P axis by gradients of various inductive signals including Wnt, FGFs, and retinoic acid secreted from the node and Wnt inhibitors/antagonists and nodal antagonists secreted from the anterior visceral endoderm at the neural plate stage. (B, C) Regionalization of neuroepithelium occurs along the D-V axis as a result of gradients of Shh from the NC and FP and gradients of BMPs and Wnts from the roof plate (RP) during neural tube closure. Neural crest cells arise and delaminate from the RP of the neural tube shortly after closure and migrate through the periphery. (D) The regional specification of NSCs regulated by various inductive signals during development is summarized. A, anterior; P, posterior; D, dorsal; V, ventral; TEL, telencephalon; DI, diencephalon; ME, mesencephalon; RH, rhombomere; ZLI, zona limitans intrathalamica; IS, isthmus.

Fig. 2 Temporal regulation of cortical cytogenesis and layer formation in mammals. (A) The schematic shows a competence model for the temporally regulated generation of various types of neurons for formation of the six layers of the cerebral cortex and glia. Several in vivo and in vitro clonal analyses have indicated that individual progenitors, including stem cells, are temporally specified to sequentially produce different types of neurons that migrate along RG processes to the superficial layers in an “inside-out” fashion. RG in the VZ start production of neurons after transformation from neuroepithelial cells. They first produce ppl neurons, including CR cells, which primarily migrate into layer I, and subplate neurons, followed by DL and UL neurons. Intermediate progenitors and basal RG (bRG) in the SVZ are born from RG to increase neuronal production. RG and bRG acquire gliogenic competence to respond to gliogenic signals during midgestation and finally differentiate into glia after neurogenesis is complete. (B) A lineage model for the temporally regulated generation of DL and UL neurons. Two types of progenitors, Cux2+/Fezf2+ progenitors and Cux2+/Fezf2− or − progenitors are born from Cux2+/Fezf2+ progenitors at the same time but differentiate into DL (TBR1+ and Ctip2+/Fezf2+) neurons and UL (Cux2+/Satb2+) neurons, respectively, at different time points.
hunchback (Hb, a temporal identity factor specifying the first-born fate in the neuroblasts that sequentially generate several types of neurons in the Drosophila embryonic CNS), may also act as a temporal identity factor for NSCs in the developing mammalian cortex. In the developing mouse cortex, Ikaros is specifically expressed in progenitors, and its expression level dramatically decreases with development. Forced and sustained expression of Ikaros, specifically in cortical progenitors from an early stage, prolonged production of DL neurons, whereas overexpression of Ikaros at a later stage after the natural decrease of Ikaros did not rejuvenate progenitors producing UL neurons back to DL neuron production mode. Because COUP-TFI/II are mammalian homologs of Drosophila Seven-up, which is transiently expressed in neuroblasts to regulate the timing of expressions of temporal identity factors including Hb, it would be intriguing to investigate the genetic interaction between COUP-TFI/II and Ikaros in the regulation of laminar fate determination.

In addition to that in the cerebral cortex, the regulation of sequential generation of distinct types of neurons by TFs has also been found in the developing midbrain and hindbrain. In the ventral midbrain, the sequential generation of ocular MNs and red nucleus neurons from progenitors located lateral to the DA neuron progenitor domain is controlled by the LIM homeodomain TF Lmx1b and the homeodomain TF Phox2a. In the ventral hindbrain, a complex network formed by several TF, including Nkx2.2, Foxa2, and Phox2b, is likely to control the sequential generation of MNs, serotonergic neurons, and oligodendrocyte progenitors (OLPs). To elucidate the regulatory mechanisms of temporal specification of NSCs for the sequential generation of distinct types of neurons during development, future studies should address specific functions and regulations of expression of known factors involved in this process in NSCs, in addition to the identification of additional temporal identity factors. Finally, it will be essential to understand how these factors are integrated into the transcription network in NSCs and their progenies for the regulation of temporal specification.

In the developing vertebrate CNS, the first gliogenesis (which is actually oligodendrogliaogenesis) starts in the ventral regions after or during neurogenesis, depending on the A-P neuroaxis. Despite extensive studies by numerous investigators, the mechanism of oligodendrocytic differentiation of NSCs is still enigmatic. It is even unclear whether oligodendrocytes or OLPs can be generated stochastically from NSCs (stochastic model), or are generated deterministically through the differentiation of NSCs into bipotent glial-restricted progenitors (GRPs) (deterministic model), or both. The lack of definitive NSC markers to distinguish stem cells from committed intermediate progenitor cells makes it difficult to visualize how NSCs differentiate into neurons or glia. In particular, there is no reliable method to distinguish GRPs and astrocyte precursors from stem cells prospectively, whereas neuron-restricted progenitors can be identified by prominent expressions of several markers, including the basic helix-loop-helix TF Neurogs and Tbr2 in the developing cortex. The first acquisition of OLPs in the embryonic SC requires sonic hedgehog (Shh), which is initially secreted from the floor plate (FP) and notochord (NC) for D-V patterning of the progenitor domain; this induces pMN domain generating MNs, which later become a site of OLP origin. However, the detailed molecular mechanisms by which Shh actions are transduced remain to be determined. Progenitors in the pMN domain do not generate OLPs during motor neuron generation, despite the existence of the Shh signal. Moreover, the existence of a Shh-independent pathway for OLP specification has been demonstrated. Consequently, it is not clear how NSCs differentiate into OLPs. Nonetheless, factors that are required for the acquisition of OLPs have been identified. Deletion of Sox9, a member of the SOX family of high mobility group TF, resulted in a prolonged period of motoneurogenesis in the developing spinal cord (SC), coupled with a delay in the onset of
oligodendrogliogenesis. The knockdown of COUP-TFI/II also resulted in prolonged neurogenesis and inhibition of OLP acquisition in the developing mouse ventral forebrain, as well as in cultured NPCs derived from mouse ESCs. The important thing is that these factors are essential also for the initiation of astrogliogenesis.

The initiation of astrogliogenesis by NSCs requires two steps: the acquisition of gliogenic competence and the increase of inductive gliogenic signals such as ciliary neurotrophic factor-1 (CT-1), with development. (Fig. 4C). The most important known gliogenic signaling pathways that promote astrocyte-specific differentiation [defined by expression of astrocyte-specific proteins such as glial fibrillary acid protein (GFAP) and S100β] are the interleukin-6 (IL-6)/Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway, the BMP2/4/mothers against decapentaplegic homolog (SMAD) pathway, and the Notch signaling pathway. IL-6 family cytokines [e.g., ciliary neurotrophic factor (CNTF)], leukemia inhibitory factor, and CT-1 bind to receptors that share a common co-receptor (glycoprotein 130: gp130), thereby triggering activation of the JAK family of non-receptor tyrosine kinases, which in turn activate STAT1 and STAT3. BMP2/4 bind to a tetrameric complex of type I and type II serine/threonine kinase receptors that phosphorylate and activate SMAD TFs. In canonical Notch signaling, Notch ligands such as Delta and Jagged bind to Notch receptors at the cell surface, leading to nuclear translocation of the Notch intracellular domain (NICD) after proteolytic cleavage of Notch. NICD subsequently
forms a transcriptional complex with the coactivator Mastermind and the DNA-binding protein recombination signal binding protein for immunoglobulin kappa J region (RBPJ)/CSL to activate target genes.\textsuperscript{44} It has been shown that BMP signals and gpl30-mediated cytokine signals synergistically facilitate astrocytic differentiation of NPCs via the cooperative activation of SMAD1 and STAT3 to induce astrocyte-specific genes.\textsuperscript{40,41} However, the responsiveness of NSCs to these signals changes with development. NSCs in the early neurogenic phase cannot differentiate into astrocytes even in the presence of BMPs and IL-6 family cytokines.\textsuperscript{29,45–48} In fact, BMPs facilitate neuronal differentiation of NSCs at this developmental phase.\textsuperscript{49,50} NSCs acquire gliogenic competence to respond to these signals at midgestation in mammals. Sox9 and COUP-TFI/II are involved in this competence change in the developing NSCs. An increase of Sox9 expression at midgestation induces expression of the TF nuclear factor I(NFI)A, which acts as a key regulator for the initiation of gliogenesis.\textsuperscript{39,51,52} Sox9 forms a complex with NFIA to induce a subset of glial-specific genes.\textsuperscript{59} Moreover, NFIA is required for Notch signaling-induced demethylation of Gfap gene promoter in NSCs.\textsuperscript{53} Developmental changes in the epigenetic status of astrocyte-specific genes critically determine the responsiveness of NSCs to gliogenic signals.\textsuperscript{47} The transient increase of COUP-TFI/II expression in NSCs at midgestation is also essential for the acquisition of gliogenic competence and alters the epigenetic status of the Gfap promoter to respond to gliogenic signals.\textsuperscript{29} Moreover, members of the microRNA-17/106 (miR-17/106) family were found to play a critical role in regulation of the neurogenesis-to-gliogenesis switch downstream of COUP-TFI/II in NSCs.\textsuperscript{54} The downregulation of miR-17/106 in NSCs during development leads to increased levels of one of their targets, mitogen-activated protein kinase 14 (MAPK14, also known as p38α), which is essential for the acquisition of gliogenic competence independent of epigenetic regulation of the Gfap gene. Intriguingly, overexpression of miR-17/106 or the loss of function of MAPK14 forced stage-progressed NSCs, which are normally highly gliogenic, to regain neurogenic competence.\textsuperscript{54} Because the epigenetic status of the promoter of neurogenic gene Neurog1 and its enhancer element (which transcribes a long non-coding RNA designated as utNgn1, which regulates Neurog1 transcription in cortical NPCs) becomes silent during the acquisition of gliogenic competence,\textsuperscript{55,56} it would be interesting to know how the miR-17/106-MAPK14 axis regulates neurogenic competence, including the epigenetic status of neurogenic genes. The extracellular signal-regulated kinase kinases (MEK)/extracellular signal-regulated kinase pathway also plays a critical role in the acquisition of gliogenic competence. Loss of MEK1 and 2 in NSCs leads to attenuated gliogenesis and prolonged neurogenesis, whereas forced expression of constitutively active MEK1 robustly enhances astrogliogenesis in the developing mouse cortex.\textsuperscript{57} More importantly, NSCs lacking MEK1/2 cannot respond to the astrogliogenic signal CNTF \textit{in vitro}. Intriguingly, the expression level of COUP-TFI1 is significantly decreased in the brains of Mek1/2-deleted mice, as is that of the transcription family member Erm, which is a downstream effector of the MEK-mediated pathway for the acquisition of gliogenic competence.\textsuperscript{57} The transforming growth factor (TGF)-β signal may be a candidate upstream factor for the activation of MEK1/2, because inhibition of MEK activity attenuates astrocytic differentiation stimulated by TGF-β \textit{in vitro}.\textsuperscript{58} MAPK14 is also activated by the TGF-β signal in other cellular contexts.\textsuperscript{59} Moreover, the TGF-β signal has been shown to control the timing of oligodendrogliogenesis in the developing hindbrain and SC.\textsuperscript{60} Therefore, the neurogenic-to-gliogenic competence transition of NSCs is probably governed by a multi-layered system composed of complex gene networks (Fig. 4D).

Despite recent advances in the identification of factors that regulate the neurogenic-to-gliogenic competence transition, as described above, it is still not clear how NSCs differentiate into glia because NSCs and GRPs are currently indistinguishable, as mentioned above. Therefore, we do not even know whether astrogliogenic signals act on NSCs, GRPs, or both to effect astrocytic differentiation. If they can induce astrocytic differentiation of NSCs directly, “gliogenic competence” must be the competence to respond to instructive gliogenic signals for a stochastic differentiation of NSCs into astrocytes (see the competence model in Fig. 4D). Otherwise, there can be no acquisition of “gliogenic competence”; instead, an increased frequency of differentiation of NSCs into the glial lineage must be initiated by an intrinsic timer mechanism that involves regulations operated by the factors described above (see the differentiation model in Fig. 4D). Work by Nagao et al. (2008) may support the latter possibility.\textsuperscript{51} They proposed a linkage between the self-renewal capacity and neurogenic competence in NSCs under control of the opposing actions of Myc TF and the tumor suppressor p19ARF-p53 TF pathway during CNS development. In their model, the Myc-dominant status resulting from low expression of p19ARF (which activates p53) links the high self-renewal capacity in NSCs with a high neurogenic propensity at early neurogenic stages. A time-dependent increase in p19ARF expression attenuates self-renewal and neurogenesis while facilitating gliogenesis via the actions of p53. In short, increased activation of p53 (which inhibits Myc functions) may increase the frequency of differentiation of NSCs into GRPs, resulting in reductions of self-renewal of NSCs and neurogenesis. In this case, astrogliogenic signals merely induce astrocytic differentiation of GRPs and/or terminal differentiation of astrocyte precursors. Intriguingly, p38 has also been shown to activate p53 directly in other cellular contexts.\textsuperscript{59} Future study should include identification of markers to
distinguish NSCs from to draw firm conclusions about what constitutes “gliogenic competence.”

**Timing of Differentiation by Environmental Factors**

The timing of terminal and phenotypic differentiation of neural cells in the developing CNS often depends on time-dependent changes in environmental signals (Fig. 4B). In the developing mouse cortex, a time-dependent increase in the local concentration of CT-1 secreted by newly born neurons is critical for the expression of GFAP and CD44, another astrocyte marker, which means that increased activation of the JAK/STAT pathway during the progression of neurogenesis is essential for the timing of astrocyte differentiation. Thus, astrocyte markers normally become detectable only after the end of neurogenesis. Similarly, the activation of Notch signaling in RG likely increases along with an increase in the number of neurons that express high levels of Notch ligands, such as Delta, the expression of which is positively regulated by the JAK/STAT pathway. Non-cell autonomous cooperation of the JAK/STAT and Notch signaling pathways may be important for the progression of astrogliogenesis.

Conversely, a signal mediated by ErbB2 and ErbB4 receptors suppresses astrogliogenesis during the neurogenic period in the developing mouse cortex. ErbB4 activation in RG by ligands such as neuregulin-1 leads to the cleavage of ErbB4 and translocation of its intracellular domain to form a complex of ErbB4/TGF-β-activated kinase-binding protein 2 (TAB2)/nuclear receptor co-repressor (N-CoR) to repress the transcription of Gfap and S100β. Because JAK/STAT signaling leads to the translocation of N-CoR to the cytoplasm, which may inhibit formation of the ErbB4 complex, a balance between the JAK/STAT pathway and ErbB4-mediated signaling may also be important for determining the timing of astrocyte differentiation.

The phenotypic specification of UL neurons in the developing mouse cortex is also likely to depend on time-dependent changes in the environment. Toma et al. demonstrated that the acquisition of UL competence in neurons or their precursor cells after DL neurogenesis requires a feedback signal from postmitotic DL neurons. Specific ablation of postmitotic DL neurons prolonged DL neurogenesis at the expense of UL neurogenesis.

**Adult Stem Cells and Regeneration**

The regenerative capacity of the CNS largely depends on the number and developmental potential of NSCs. In mammals, as the developmental potential and neurogenic competence of NSCs decrease during development in most regions of the CNS (Figs. 2–4), so also does the degree of functional and structural recovery from CNS damage (Fig. 5). Finally, in the adult CNS, although a limited number of NSCs are present throughout the ventricular neuroaxis, most are dormant; the exceptions are those NSCs localized in two regions (ventricular–subventricular zone (V-SVZ) of the lateral ventricles and sub-granular zone (SGZ) of the hippocampus) that continuously generate new neurons that functionally integrate into specific neural circuits (Fig. 6). NSCs in the V-SVZ give rise to GABAergic neurons that migrate into olfactory bulbs (OB) throughout life from midgestation. The SGZ generates granule neurons in the dentate gyrus. In the adult brain, both latent and active NPCs, including stem cells, can be mobilized to generate new neurons and glia in response to brain lesions, such as those resulting from ischemia, traumatic injury, and demyelination (Fig. 6).

Transient forebrain ischemia in the rat induces selective degeneration of hippocampal CA1 pyramidal neurons followed by their limited regeneration by mobilization of latent progenitor cells located around the posterior periventricle (pPV) adjacent to the hippocampus. A middle cerebral artery occlusion model of stroke in rodents induces enhanced neurogenesis in the V-SVZ and subsequent migration of new neurons toward the ischemic cortex and striatum. Neurogenesis in the SGZ is facilitated in several models of brain injury, including hypoxia–ischemia, stroke, and the controlled cortical impact model of traumatic brain injury. Although such injury-induced neurogenesis is insufficient to repair significant brain damage, further enhancement of neurogenesis and neuronal migration by administration of appropriate growth factors and cytokines (such as FGF2, epidermal growth factor/TGF-α, brain-derived neurotrophic factor, vascular endothelial growth factor, erythropoietin, stem cell factor, and granulocyte-colony stimulating factor) often results in substantial and functional tissue regeneration.

Factors that are known to enhance neurogenesis or neuronal migration after various brain injuries are summarized in Table 1. However, there is no clear evidence for the regeneration of early-born neurons, such as midbrain DA neurons (DANs), MNs, and forebrain cholinergic neurons (CNs), by NPCs in the adult mammalian CNS. Moreover, regeneration of cortical projection neurons has not been reported. A major cause of this limited regenerative capacity in the mammalian CNS is likely the developmental decrease in the plasticity of NSCs and/or the depletion of juvenile NPCs that can generate early-born neurons.

In contrast, some lower vertebrates, such as urodele amphibians and teleost fish, have much higher regenerative capacity in the adult CNS than mammals do. In these animals, adult neurogenesis is much more widespread, and this may be linked to the overall regenerative capacity of their CNSs (Table 2). Among all vertebrates studied, teleost fish exhibit the most active and widespread adult neurogenesis, with a remarkable regenerative capacity after severe injuries, such as ablation of a large portion of the CNS, along the whole rostro-caudal neuroaxis. In zebrafish, 16 different neurogenic niches have been...
identified along the entire neuroaxis, including the SC. In these regions, many different neuronal subtypes are constitutively generated throughout adult life. Other than those in teleost fish, neurogenic regions in the adult CNS are restricted to forebrain in most species, except for the axolotl, which has proliferating NPCs in more caudal regions, including the SC to a limited extent. Brain lesions often enhance proliferation of NPCs in these neurogenic regions. Quiescent ependymoglia are mobilized to generate DANs. (D) In the adult zebrafish, regeneration of SC neurons, including MNs, from ependymoradial glia takes place after complete spinal transection. DP, dorsal pallium; LP, lateral pallium; BNST, bed nucleus of the stria terminalis; TC, tectum; TM, midbrain tegmentum.
spinal transection.114 In axolotl, cultured NPCs derived from adult SC can reconstitute all SC cell types, including MNs, after tail amputation.115 Why can these latent progenitors in the adult CNS generate early-born projection neurons (such as DA and MNs) in urodeles and fish? Are NSCs with early developmental potential retained or are aged NSCs rejuvenated and/or respecified in response to stimulation after injury? In the case of DA neuron regeneration in the newt, increased levels of Shh, which are essential for the specification of NSCs to generate DANs in the developing midbrain, are also essential for DA neurogenesis by ependymoglia in response to DA neuron ablation.113 The inhibition of Shh signaling reduced DA neuron regeneration but not the proliferation of ependymoglia after lesions were induced, indicating that ependymoglia in the midbrain of the adult newt are at least plastic enough to respond to Shh signaling to generate DANs. Similarly, Shh signaling regulates D-V patterning of SC progenitors during regeneration in the larval axolotl.116 Although the gene expression pattern along the D-V axis in the larval SC resembles that in the embryo, the regional identity can be respecified in response to injury.117 Thus, although it is not clear whether adult NSCs in these animals are rejuvenated in response to CNS lesions, such cells are plastic enough to be respecified to generate appropriate types of neurons, including early-born neurons, for complete CNS regeneration.

Table 1 Growth factors and cytokines that facilitate CNS regeneration via mobilization of NPCs

| Factor   | Reference | Function                           |
|----------|-----------|------------------------------------|
| FGF      | 67, 71–73 | Proliferation of progenitors        |
| EGF/TGF-α| 67, 74–79 | Proliferation of progenitors        |
| BMP7     | 80        | Proliferation of progenitors        |
| Gal-1    | 81        | Proliferation of progenitors        |
| GDNF     | 82, 83    | Proliferation of progenitors        |
| SCF      | 84, 85    | Proliferation of progenitors        |
| G-CSF    | 84–88     | Proliferation of progenitors, neuronal differentiation |
| HB-EGF   | 89, 90    | Proliferation of progenitors, neuronal differentiation |
| HGF      | 91        | Proliferation of progenitors, neuronal differentiation |
| IGF1     | 82, 92–95 | Proliferation of progenitors, neuronal differentiation |
| TGF-β    | 96        | Proliferation of progenitors, neuronal differentiation |
| VEGF     | 97–99     | Proliferation of progenitors, neuronal differentiation |
| EPO      | 76, 100–103 | Proliferation of progenitors, neuronal differentiation |
| BDNF     | 104–106   | Neuronal differentiation            |
| ANG1     | 107       | Cell migration                      |
| Meteorin | 108       | Cell migration                      |
| SDF-1    | 107       | Cell migration                      |

EGF, epidermal growth factor; Gal-1, galectin-1; GDNF, glial cell line-derived neurotrophic factor; SCF, stem cell factor; G-CSF, granulocyte colony stimulating factor; HB-EGF, heparin-binding EGF; HGF, hepatocyte growth factor; IGF1, insulin-like growth factor 1; VEGF, vascular endothelial growth factor; EPO, erythropoietin; BDNF, brain-derived neurotrophic factor; ANG1, angiopoietin 1; SDF-1, stromal cell-derived factor-1.

Table 2 Neurogenic niches and regenerative capacity in the adult vertebrate CNS

| Region | Fish | Urodeles | Anurans | Reptiles | Birds | Mammals |
|--------|------|----------|---------|----------|-------|---------|
|        | N    | R        | N       | R        | N     | R       |
| FB     | +    | +        | +       | +        | +    | +/−     |
| MB     | ?    | +/−      | +       | +/−      | +    | +/−     |
| HB     | +    | +        | +/−     | +        | +    | +/−     |
| SC     | +/−  | +        | +/−     | +        | +    | +/−     |

N, neurogenesis; R, regeneration; FB, forebrain; MB, midbrain; HB, hindbrain; SC, spinal cord; ?, Lack of sufficient information; +, reported in multiple species; +/−in N, rare case; +/−in R, a limited recovery or rare case.
Conclusions

A primary objective of neural stem cell research is to answer the fundamental question “Can we regenerate our brain?” Currently, we do not have a clear answer to this question. Moreover, we do not have an efficient treatment for any neurodegenerative disease via the regenerative approach, including cell replacement therapy. Because the regenerative potential of our brain is quite limited, replacement of lost cells by transplantation to achieve functional recovery has extensively been studied. Recent developments in cell reprogramming technology, such as iPSC and direct reprogramming to induce NSCs, neurons, and glia from other somatic cells (which resolve the ethical problems associated with cell sourcing), should further facilitate the development of transplantation therapeutics. However, the induction of self-regeneration is still the ultimate goal. To achieve self-regeneration, we have to overcome several barriers. First, we have to definitively answer the question “do we have plastic populations of NSCs in our brain?” If not, then we need to find ways to rejuvenate and/or reprogram adult NSCs in vivo. To do this, it is of primary importance to elucidate the underlying mechanisms by which NSCs lose plasticity and are specified to generate specific types of neurons and glia during development. Simultaneously, we need to find ways to create a permissive environment for the differentiation of appropriate cells and the reconstruction of proper neural circuits. This is also important in transplantation therapeutics. In the mammalian brain, NPCs are difficult to differentiate into neurons outside of neurogenic regions. Although some lesions, such as ischemic lesions, may yield a permissive environment for neuronal differentiation, at least in a restricted time frame, it is not clear whether that is sufficient for the functional regeneration. Moreover, in addition to the fact that a large number of glia express several axon growth inhibitors that prevent axonal extensions and the fact that the ability of injured axons to regenerate declines with age, adult brain may not have adequate guidance cues for the projection of new neurons to their proper target sites. To help address these issues, we can learn much from comparative analyses of lower vertebrates with respect to the plasticity of NSCs and the environment in the adult CNS. We still do not know why NSCs in adult lower vertebrates are so plastic. I hope that we can make our brains more plastic in the future.

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