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Adult neural stem cells in the mammalian central nervous system

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Abstract

Neural stem cells (NSCs) are present not only during the embryonic development but also in the adult brain of all mammalian species, including humans. Stem cell niche architecture *in vivo* enables adult NSCs to continuously generate functional neurons in specific brain regions throughout life. The adult neurogenesis process is subject to dynamic regulation by various physiological, pathological and pharmacological stimuli. Multipotent adult NSCs also appear to be intrinsically plastic, amenable to genetic programming during normal differentiation, and to epigenetic reprogramming during de-differentiation into pluripotency. Increasing evidence suggests that adult NSCs significantly contribute to specialized neural functions under physiological and pathological conditions. Fully understanding the biology of adult NSCs will provide crucial insights into both the etiology and potential therapeutic interventions of major brain disorders. Here we review recent progress on adult NSCs of the mammalian central nervous system, including topics on their identity, niche, function, plasticity, and emerging roles in cancer and regenerative medicine.

Keywords

Adult neurogenesis; neural stem cells; stem cell niche; plasticity; regeneration; reprogramming; cancer stem cells; hippocampus; olfactory bulb

Introduction

The discovery of adult mammalian neural stem cells (NSCs) marks a milestone in the odyssey of our contemporary understanding of adult brain plasticity. Early in the twentieth century, influential histological and anatomic studies of Koelliker, His, Bizzozero and Cajal had established that the adult mammalian brain remained structurally constant after birth and no new neurons could be conceivably generated in adulthood [1–3]. In his masterpiece [1], Cajal commented "*Once the development was ended, the founts of growth and regeneration of the axons and dendrites dried up irrevocably. In the adult centers, the nerve paths are something fixed, ended, and immutable. Everything may die, nothing may be regenerated. It is for the science of the future to change, if possible, this harsh decree.*" The stability of neural circuits was also thought to be essential for higher brain functions, such as storing long-term memory [4,5]. Over the second half of the twentieth century, the notion of activity-dependent neuronal

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synaptic modification had gained steam and significantly enriched our understanding of the plastic nature of the mammalian brain [6,7]. Structural plasticity at the cell population level, however, remained less apparent. Scattered evidence suggested the presence of dividing cells in the postnatal and adult brain [8–10], yet little attention was given to those studies since the neuronal fate of those cells and the extent of such phenomena were not immediately clear. Within the past two decades, technical advances, particularly the fate mapping method using 5-bromo-2-deoxyuridine (BrdU) in animals, have allowed researchers to demonstrate that a large number of newly generated cells in the adult brain were indeed neurons [11,12]. Meanwhile, the identification of trophic and mitogenic actions of growth factors, including fibroblast growth factors (FGF) and epidermal growth factor (EGF) family proteins, paved the way to culture and maintain a variety of neural cells *in vitro* [13,14]. In early 1990s, it was demonstrated that neural cells derived from the adult rodent brain were capable of self-replicating and giving rise to both neurons and glia in culture [15,16]. Adult NSCs with similar properties were subsequently found to be present in many other brain regions of mammals [17–21].

Rapid progress in the field has since led to the general acceptance that adult NSCs are present specifically in the subventricular zone (SVZ) of the lateral ventricle wall and the subgranular zone (SGZ) of the hippocampal dentate gyrus [21–27]. It is believed that the unique niche architectures present in these regions permit functional neurogenesis from NSCs *in vivo* [22, 23,28]. Interestingly, NSCs have also been derived from a variety of adult brain regions [18–20,29], yet it remains controversial whether those regions harbor similar NSCs and enable neurogenesis under physiological conditions *in vivo*. Once isolated and grown in culture, adult NSCs are better defined in terms of the capacity to self-renew and generate multiple neural lineages, including neurons, astrocytes and oligodendrocytes. Intrinsically, adult NSCs appear to be plastic in their fate programming and reprogramming in certain conditions, giving rise to a variety of lineages not expected from their *in vivo* counterparts. Perhaps in part due to the plastic nature of adult NSCs, it is becoming increasingly appreciated that many forms of neoplastic conditions in brain cancers might result from dysregulation of adult NSCs *in vivo*. Advances in derivation and culture of multipotent adult NSCs *in vitro* also fuel the hope for therapeutic intervention in combating a cohort of neurodegenerative diseases that elicit irreversible loss of neurons and glia. Here we discuss a range of topics related to adult NSCs in the mammalian central nervous system (CNS), including their identity, niche, function, plasticity, application and emerging relevance to brain cancer and neural degenerative diseases.

Adult neural stem cells: identity and properties

NSCs are self-renewing, multipotent progenitors residing in the nervous system. In the adult brain, NSCs are primarily located in the SVZ of the lateral ventricle and the SGZ of the hippocampal dentate gyrus (Figure 1A)[22, 23]. In the currently prevalent view, primary adult SVZ NSCs *in vivo* are slowly dividing, long-term BrdU-retaining progenitors that exhibit several common features of subventricular radial glia-like astrocytes and ventricular ependymal cells, including morphological characteristics and expression of the glial fibrillary acidic protein (GFAP) and the glycoprotein CD133. A double nucleotide thymidine analogue-labeling paradigm has been used to identify adult NSCs, based on their ability to re-enter cell cycle after long-term retention of thymidine analogues. Anatomical features and a comprehensive panel of immunohistochemical markers also help ascertain their identity. In the adult SVZ, the quiescent adult NSC population is believed to locate underneath the ependymal layer but contact the ventricle through their apical surfaces (Figure 1B). A subset of these cells is characterized as positive for LeX, CD133, GFAP, and Nestin while negative for differentiated cell markers CD24, O4, NeuN and S100β. Adult SVZ NSCs give rise to $Dlx2^+Mash1^+$ transient amplifying progenitors. The majority of these intermediate progenitor cells, in turn, give rise to PSA-$NCAM^+$ $doublecortin^+$ (DCX^+) neuroblasts that migrate towards

the olfactory bulb (OB) through the rostral migratory stream (RMS) in rodents; recently this has also been proposed to occur in humans through an anatomically distinct migratory stream [30, 31]. In the SGZ of the dentate gyrus, a similar subset of $GFAP^+$, $S100\beta^-$, $Sox2^+$, $Nestin^+$ radial cells corresponds to quiescent or dormant NSCs (Figure 1C). These NSCs may co-exist with the actively self-renewing population of $GFAP^-$, $S100\beta^-$, $Sox2^+$, $Nestin^+$ adult NSCs that generate $GFAP^+$, $S100\beta^+$ mature astrocytes and DCX^+ neuroblasts. Unlike the interneuron lineage differentiation in the OB, adult NSCs in the SGZ of the hippocampus predominantly give rise to local glutamatergic excitatory dentate granule cells. The $Sox2^+$ SGZ cells have recently been proposed to possess self-renewal capacity and multipotentiality [32], while these properties have not been strictly tested *in vivo* for SVZ NSCs under physiological conditions. Nonetheless, it remains unclear whether a single adult NSC undergoes extensive self-renew and generates progeny of multiple neural lineages *in vivo*.

Despite general acceptance of their existence, the exact identity and location of adult NSCs *in vivo* have long been controversial [33]. In the lateral ventricle, extensive early efforts had shown that the adult NSCs are mainly located in the SVZ sub-ependymal layers [19,34]. The findings are particularly intriguing since during development, the SVZ is occupied by intermediate progenitors while embryonic NSCs, radial glia, are located in the ventricular zone. A subsequent study, nevertheless, suggested that *bona fide* adult NSCs could be identified from the ventricular zone ependymal layer [35]. These controversies have prompted further examination of the exact location of adult NSCs, yet follow-up studies in different labs did not reach consensus [36–38]. The most recent results may provide a unifying hypothesis on this issue: the cell bodies of adult NSCs are located in the SVZ while they contact the ventricles through ependymal cell-like apical surfaces [39]. In the SGZ of the dentate gyrus, two populations of adult NSCs likely co-exist as discussed above, yet their lineage relationship, respective self-renewal properties, and developmental potentials are to be further examined in the future. Rigorous future study of adult NSCs *in vivo* will require both structural and functional characterization using multiple complementary approaches.

During CNS ontogenesis, adult NSCs appear to descend from their region-specific embryonic counterpart, radial glia [40]. Radial glia of different regions, when labeled during the neonatal period, produced different types of neurons in adulthood, suggesting that postnatal NSCs may be regionally specified according to their locations [41]. Although this study suggested interesting similarity between embryonic and postnatal NSCs, the true diversity of adult NSCs was not directly addressed. It also remains an intriguing possibility that adult NSCs may give rise to a diverse type of lineage-restricted progenitors and neuroblasts that are heterogeneous and regionally specified (Figure 2A, B). In support of this notion, dopaminergic periglomerular neurons, but not granule neurons, in the OB originate mainly from the RMS [42]. In addition, proliferating adult SVZ NSCs express the transcription factor Pax6, but only a small subset of neuroblasts and new OB interneurons derived from these progenitors retains Pax6 expression [43]. In the SGZ, while genetic evidence suggests that radial $GFAP^+$ NSCs correspond to the ancestor population of the majority of new neurons [44], non-radial $Sox2^+$ NSCs may also self-renew and give rise to neurons and astrocytes [32]. Collectively, these findings indicate that adult NSCs and their progeny may exhibit a significant degree of functional diversity resulting from their regional distribution and developmental origins. It will be interesting to investigate how such functional diversity of adult NSCs and their progeny may contribute to, and can be manipulated for specific benefits of brain plasticity under physiological and pathological settings.

Given better-defined culture conditions, adult NSCs have been widely studied *in vitro*. Both the SVZ and SGZ-derived NSCs can be expanded continually as free-floating cell cluster, termed “neurosphere”, exhibiting self-renewal and multi-lineage neural potentiality, defining hallmarks of NSCs [19,45]. Intriguingly, such adult NSCs *in vitro* seem to regain some glial

characteristics when cultured as neurospheres [46], and may similarly exhibit certain diversity as *in vivo* [47]. Distinct from lineage-restricted progenitors, adult NSCs are capable of serial neurosphere formation while maintaining multipotentiality at the clonal level [48]. The adult SGZ-derived NSCs can also be expanded as monolayer for a prolonged period of time [17]. In the presence of FGF-2, they can be clonally derived, proliferate while maintaining an undifferentiated state, and capable of differentiating into neurons and glia both *in vitro* and after transplantation back into the CNS [17,18,49–51]. Adult NSCs grown in culture thus provide an advantageous system to study their cellular properties, including self-renewal and multipotency, and may also serve as a valuable model and substrate for developing therapeutic strategies.

Adult neural stem cell niche: architecture and signals that regulate adult neurogenesis

The “niche” is defined as the microenvironment that intimately supports and tightly regulates stem cell behaviors, including their maintenance, self-renewal, fate specification and development [52,53]. While dormant NSCs might be present and can be derived from multiple regions of the adult brain, unique local niche structure seems to restrict active neurogenesis from adult NSCs to two discrete regions: SVZ and SGZ [22,23]. The overall structure of SVZ and SGZ niches has been extensively characterized [23,54,55]. In the SVZ, the NSC niche spreads extensively from the lateral ventricle along the RMS to the OB to accommodate local generation of new neurons in the OB [31]. In the adult SGZ, the niche is less structurally apparent and largely confined within the SGZ hilus region [55]. These distinguishing features of each niche structure may thus allow regulation of adult SVZ or SGZ NSCs in a region-specific manner, exemplified by a varying degree of modulation by external cues through neuronal activity [56–58]. Though the specific niche architecture in the SVZ and SGZ is distinct, there are common features, including their cellular niche components and extra-cellular niche signals that regulate behavior of adult NSCs and their development.

Astroglia, ependymal cells, vascular cells, NSC progeny and mature neurons are among major cellular components of the neurogenic niche. Ample *in vitro* and *in vivo* evidence suggests pivotal roles of astroglia in regulating almost every developmental process of adult neurogenesis, including self-renewal, fate specification of adult NSCs, migration, differentiation and final synaptic integration of new neurons [22,50,59,60]. Mature ependymal cells seem to mainly regulate the quiescence and self-renewal of adult NSCs in the SVZ by direct cell-cell contact and diffusible signals including the pigment epithelium-derived factor [61]. Through oriented cilia beating and formation of gradient guidance cues, ependymal cells also promote neuroblasts migration along the RMS [62]. On the other hand, SGZ neurogenesis is known to be particularly sensitive to the surrounding neuronal activity. Thus, mature neurons near the neurogenic site are suited to function as niche cells, providing spatiotemporal regulation of adult neurogenesis in response to neuronal activity [56,58,63]. Accumulating evidence also points to prominent roles of vascular cells in regulating the proliferation of adult NSCs, with early studies focused on particularly the SGZ [64]. Recent three-dimensional imaging techniques have revealed that the SVZ vasculature comprises an extensive network of planar interconnected blood vessels [65,66]. The contacts between adult SVZ NSCs and vessels are unusually permeable and frequently devoid of astrocytic and pericyte interferences, suggesting that blood-derived cues are gaining access to regulate adult NSCs. Though these individual cellular niche components have been well described so far, their exact modes of regulation, relative importance in different developmental processes of the adult NSCs, and their mutual cross-talk and coordination remain under intensive investigation.

Recent advances have led to the identification of major molecular niche signals for adult NSCs [67]. A plethora of developmental cues and physiological humoral factors have been shown to

promote progenitor proliferation and maintenance, including Wnt [68], Sonic Hedgehog (Shh) [69], Bone Morphogenic Protein (BMP) antagonists [45], membrane-associated Notch signaling [70], leukemia inhibitory factor (LIF) [71], transforming growth factor-alpha (TGF-a) [72] and cytokines [73,74]. Growth factors, including FGFs and neurotrophins such as brain-derived neurotrophic factor (BDNF), also significantly contribute to proliferation, survival and dendritic development of newborn neurons in the adult brain [75–78]. The extracellular matrix (ECM) provides a platform for presentation of molecular cues and cellular interaction within neurogenic niches [79]. Most of these factors exert specific effects on both SVZ and SGZ NSCs in the adult brain, reminiscent of their roles in regulating NSCs in the developing nervous system. The cellular environments of NSCs in the adult versus developing nervous system, however, are strikingly different. The regulated production of diffusible factors from niche cells, therefore, may serve to translate a myriad of physiological milieu into precise regulation of adult NSCs and strategic addition of new neurons into the existing neuronal circuitry.

Functions of adult neural stem cells

Most types of adult stem cells outside of the nervous system, especially those from epithelial origins, function to maintain tissue homeostasis by providing a continual replacement for lost cells during physiological cell turnover or upon injury [52]. This general “cell replacement” view of adult stem cells is also part of the initial skepticism of the functional relevance of adult NSCs and new neurons for any significant higher brain functions. Accumulating evidence has clearly shown that a large number of newborn neurons can be generated from adult NSCs, and integrate into pre-existing neural circuits [80]. Adult neurogenesis in either the SVZ or the SGZ is also highly sensitive to environmental cues, physiological stimuli and neuronal activity [24,56,81,82], suggesting that the tailored addition of new neurons might serve specific neuronal functions. Direct functional evidence for adult NSCs and newly generated neurons, however, has not been obtained until recently.

Early efforts attempted to use anti-mitotic drugs or X-irradiation to assess the contribution of adult NSCs to animal behavior [83,84]. Though certain learning deficits have been shown in early studies, the specificity of manipulation was called into question because other proliferating precursor cells and mature cell types were affected. Using elegant mouse genetic approaches, Zhang et al. demonstrated that removal of a crucial regulator of adult NSC proliferation, the transcription factor TLX [85], specifically from the adult NSCs resulted in marked deficits in spatial learning [86]. In contrast, suppressed adult neurogenesis does not affect contextual fear conditioning, locomotion or diurnal rhythmic activities, indicating a selective contribution of adult NSCs to specific cognitive functions. More recent results based on cell type-specific and temporally controlled genetic ablation of adult NSCs or neurogenesis seem to suggest distinct modes for adult SVZ and SGZ contribution to brain functions [87]. While the SVZ NSCs and neurogenesis are essential for the maintenance of the olfactory bulb, the hippocampal SGZ NSCs and neurogenesis provide a substrate for additional brain plasticity and are crucial for spatial learning and memory [87]. By maintaining the high rate of cellular turnover in the OB from the SVZ NSCs, a complement of new young neurons may confer on the sensory organ with a privilege in behavior adaptation, such as olfactory learning of novel odorants. Supporting this notion, OB neurogenesis is functionally correlated with olfactory discrimination learning, and new OB neurons are preferentially recruited during olfactory behavior [88,89]. Unlike other adult somatic tissues, the dentate gyrus appears to increase its volume over the lifetime of an animal through continued addition of new neurons. Ablation of adult $Nestin^+$ progenitors blocked the increase of its volume over time and resulted in behavior deficits in spatial learning and memory [87]. At the circuitry level, new neurons from adult SGZ NSCs possess unique physiological properties with enhanced plasticity during specific time windows and are preferentially recruited for information processing in hippocampus-dependent learning behaviors [90–92]. Thus, adult SGZ NSCs are essential for neuronal

addition and hippocampal growth, potentially contributing to new memory formation and an extra cellular level of neural plasticity throughout life.

In addition to expanding plasticity for the hippocampus, adult NSCs from the SGZ have also been suggested to play a significant role in mood regulation [93,94]. On one hand, stress and various antidepressant treatments can profoundly affect adult hippocampal neurogenesis [93, 95]. On the other hand, disrupting antidepressant-induced adult SGZ neurogenesis blocks behavioral responses to antidepressants [94]. Furthermore, “learned safety”, a physiological paradigm mimicking anti-depressant treatment, promotes the survival of new neurons from adult SGZ NSCs and its antidepressant effects are abolished in mice with ablated adult hippocampal NSCs and neurogenesis [96]. Such mood regulation appears to be uniquely attributed to the SGZ NSCs, and might be explained by the convergent role of adult SGZ NSCs in expanding plasticity for the hippocampus: new neurons generated from the SGZ NSCs may gate contextually appropriate new memory formation to prefrontal cortical–striatal circuits in alleviating depression. The exact manner by which adult SGZ NSCs and their progeny participate in alleviating depression or learning and memory remains a fascinating issue to be explored.

Cellular plasticity of adult neural stem cells

Under physiological conditions, adult NSCs follow a highly stereotypic differentiation path to generate predominantly inhibitory granule/periglomerular interneurons in the OB and excitatory granule neurons in the dentate gyrus. While the local niches significantly shape such stereotyped neuronal differentiation, multipotent adult NSCs appear to be intrinsically plastic in their neural fate programming *in vivo*. In the adult SVZ, transient amplifying progenitors may revert to an adult NSC-like state when situated in certain conditions, such as heightened EGF receptor signaling [97]. Over-expression of the transcription factor Olig2 diverts the neuronal fate of transient progenitors from adult NSCs towards oligodendrocytes that migrate away from the SVZ to the corpus callosum [42]. Similarly, the neuronal subtype differentiation in the OB is not completely fixed since high Pax6 maintenance leads to almost complete conversion of all precursors in the RMS towards a periglomerular neuron fate [42]. In the SGZ, retrovirus-mediated over-expression of the transcription factor Ascl1 redirected the fate of the adult NSCs predominately to oligodendrocytes [98]. Such role of Ascl1 is region-specific since no fate switch and oligodendrocyte differentiation of SVZ progenitors occurred. In certain pathological conditions, such as brain injury, new neurons appear to be also generated in local non-neurogenic sites, including the cortex [60,99]. For example, non-neurogenic, ventricular ependymal cells can be activated during stroke and surprisingly generate both neuroblasts and glia [100]. In the SGZ, loss of Disrupted-In-Schizophrenia 1 (DISC1) during NSC differentiation causes accelerated neuronal integration and mis-positioning of new neurons in a cell-autonomous fashion [101]. These findings indicate that adult NSCs might be highly plastic in nature and are subject to a combination of extrinsic and intrinsic instructions during neural differentiation.

Consistent with their plastic nature *in vivo*, adult NSCs are also amenable to epigenetic reprogramming *in vitro* [102]. Adult NSCs co-cultured with endothelial cells were converted to cells that stably express endothelial markers and form capillary networks, independent of cell fusion [103]. This is particularly surprising because NSCs and endothelial cells are believed to be descendants of the ectoderm and mesoderm, respectively. Adult NSCs may even contribute to the formation of tissues from all three germ layers when injected into early mouse embryo [104], although the possibility of cell fusion events to host cells was not thoroughly examined. Nevertheless, it is an intriguing possibility that specific culture conditions to expand adult NSCs *in vitro* may reprogram their epigenetic status and partially contribute to expanded capacity of their developmental potential [46,105–107]. Directed reprogramming of adult

NSCs to generate pluripotent embryonic stem cell (ESC)-like cells further demonstrates the striking plasticity of adult NSCs (Figure 2C). Somatic cell nuclear transfer or cell fusion with pluripotent ESCs can reprogram most types of adult somatic cells into pluripotency, yet reprogramming of NSCs using these methods appear to be particularly efficient [108]. In accordance with the epigenetic nature of reprogramming, altering the epigenetic status through DNA or histone modification of adult NSCs can dramatically affect the efficiency of reprogramming [109]. For genetic factor-induced reprogramming of somatic cells [110,111], only one factor Oct4 is sufficient to reprogram adult NSCs into induced pluripotent stem (iPS) cells whereas most other cell types require three or four factors [111–114]. The reduced requirement for reprogramming of adult NSCs may be due to their close resemblance to ESCs, including unlimited self-renewal and expression of key transcription factors, such as Sox2 and c-myc [115]. These exciting findings suggest that adult NSCs may possess unusually plastic epigenomes that can be manipulated for reprogramming, thus providing an important experimental model for understanding reprogramming mechanisms and for therapeutic applications.

Adult NSCs in brain disorders and therapeutic application

Dysregulation or disruption of endogenous adult NSCs has been implicated in brain disorders. In the SGZ, ectopic integration of the progeny of adult NSCs into epileptogenic networks may directly contribute to mossy fiber sprouting and increased seizure susceptibility [116]. Aberrant regulation of adult NSCs *per se* has been increasingly studied in the context of brain tumors that are hypothesized to result from subversion of intrinsic properties of adult NSCs [117] (Figure 2C). As functional roles of adult neurogenesis become more defined, adult NSCs may well contribute to the capacity of the brain to maintain physiological tissue homeostasis and to protect the animal against anxiety, depression, learning and memory deterioration.

One major implication of adult NSC study is pertinent to understanding brain tumor formation. Brain tumors are essentially a diverse group of neoplasm conditions that closely resemble most tissue organs in their cellular and functional hierarchy, as the homeostasis is governed by a distinct sub-population of stem-like cells in both situations. There is now increasing evidence that the tumor-initiating cells might arise from endogenous stem cells through accumulated multiple genetic and epigenetic alterations [117]. Cancer stem cells (CSCs) have been isolated from major malignant brain tumors, including medulloblastomas, glioblastoma, and ependymomas, and they share several key properties of adult NSC, such as long-term self-renewal [118–121]. These $CD133^+$ brain CSCs form self-renewing neurosphere-like colonies *in vitro*, and can differentiate into one or more neural lineages. Unlike adult NSCs, however, CSCs are genetically or epigenetically aberrant with growth factor-independent proliferation and differentiation [122]. Certain CSCs also seem to further acquire the ability to take advantage of the vascular niche structure of normal adult NSCs in order to gain uncontrolled growth in metastatic tissue loci [123]. Importantly, multiple studies have shown that the purified population of $CD133^+$ sphere-forming CSCs expedites tumor formation following transplantation into the immunodeficient mice [119,121,124]. It remains to be further investigated whether most brain tumors originate from endogenous adult NSCs. Though endogenous adult NSCs are attractive candidates due to their long-term self-renewal capacity in accumulating mutations, direct evidence is lacking on whether cancer-initiating events occur in NSCs, progenitors or differentiated cells. Clinically, many types of human brain tumors are known to frequently arise deep in the brain near the SVZ region [125]. In animal models, introducing the oncogene constitutively active EGFR and deleting the tumor suppressor gene Ink4a/Arf in NSCs lead to high-grade glioma [126], while mutant mice deficient in p53 and with conditional null allele NF1 or PTEN in a $GFAP^+$ population developed glioblastoma at very high penetrance [127,128]. In the future, more sophisticated genetic models may clarify

the issue of the origin(s) of different types of tumors, and pinpoint novel targets for potential therapeutic interventions against malignant brain cancer.

Discovery of endogenous adult NSCs with unique capacity to expand in culture and diverse developmental potential for neuronal and glial differentiation also opens doors for therapeutic application of these cells. Adult NSCs provide tools for understanding disease mechanisms and for drug screening using differentiated neural cells from these adult NSCs *in vitro* [26, 129]. Common neurological disorders and neurodegenerative diseases, including Parkinson's disease, Alzheimer's disease, spinal cord injury, epileptic seizure, demyelinating diseases, stroke and multiple sclerosis, among others, are caused by, or accompanied with a major irreversible loss of neurons and glial cells [130,131]. The application of adult NSCs has been quite successful in several animal models and has yielded important insights for potential stem cell-based human trials [130,132,133]. Substantial challenges remain before translating animal studies into clinically meaningful human therapy, such as efficient isolation and expansion of human NSCs; tumorigenicity of cells after transplantation; delivery methods for transplantation of cells; full maturation and functional integration of transplanted cells. Ultimately, any effective cell replacement therapy would require disease-specific application of stem cells, and equally important, the basic understanding of mechanisms regulating their *in vitro* proliferation, differentiation, *in vivo* integration, and optimization of functional recovery in disease-specific animal models. In addition to directly replacing lost cells in diseases, accumulating evidence suggests that transplanted NSCs may also ameliorate neuronal dysfunction through various other mechanisms, including serving as pumps of neuroprotective agents [134], restoring homeostasis to the surrounding tissue [135], and acting in synergy with other established therapies [136].

Endogenous adult NSCs seem to be involved in tissue repair during pathological conditions, such as brain injury, and thus may be therapeutically useful for self-repair if properly mobilized [137]. For example, induced apoptotic degeneration of corticothalamic neurons in anterior cortex of adult mice was shown to stimulate proliferation of local progenitors, and the generation of new pyramidal neurons that appeared to eventually integrate into the corticothalamic circuit [99]. In a brain ischemic model, endogenous adult NSCs were found to proliferate in response to ischemic stroke, and migrate to the hippocampal area regenerating local pyramidal neurons. This process is inherently limited but greatly enhanced by infusion of mitogens including FGF-2 [138]. Compared with transplantation of adult NSCs, mobilization of endogenous adult NSCs for self-repair has advantages, including reduced immune rejection, better location-specific recruitment, enhanced maturation and functional integration of generated progeny. To realize the clinical potential of such endogenous adult NSCs, however, it is essential to understand modes and mechanisms of adult NSC mobilization, as well as novel means to maximize the extent of such mobilization for self-repair in a highly controlled manner.

Conclusions

After a century-long conceptual assumption on the fixed regenerative capacity of the adult mammalian brain, the surprising discovery of adult mammalian NSCs and continued neurogenesis throughout life heralds a new era for deeper understanding of brain plasticity. Adult NSCs not only contribute to the maintenance of neural tissue, but also offer expanded plasticity to key brain structures that are critical for learning and memory. Isolation and culture of adult NSCs provide an advantageous model for understanding the basic biology regulating self-renewal, developmental potential and reprogramming of stem cells, in addition to serving as a valuable source for cell replacement-based therapy in treating neurological disorders. Knowledge of adult NSCs both *in vitro* and *in vivo* also proves to be directly pertinent toward

understanding the capacity of the brain for self-repair, as well as yielding novel insights into brain cancer research and treatment.

Rapid and exciting progress in the field has shed light on the biology and clinical potential of adult NSCs. Still more unknowns and uncharted territories awaits further exploration. At the systems level, the exact manner by which adult NSCs and their progeny interact with and exert impact on the host tissue in the adult brain still remains poorly understood. Evolutionarily, the functional significance of adult NSCs extant in mammals remains an open and intriguing question. The clinical promise of adult NSCs is yet to be realized, which requires a comprehensive understanding of the mechanisms of their properties, regulation, and application through long-term collaborative efforts of both basic and translational research. There is no doubt that science of today is "*changing the harsh decree of adult (brain) centers*" viewed by Cajal a century ago.

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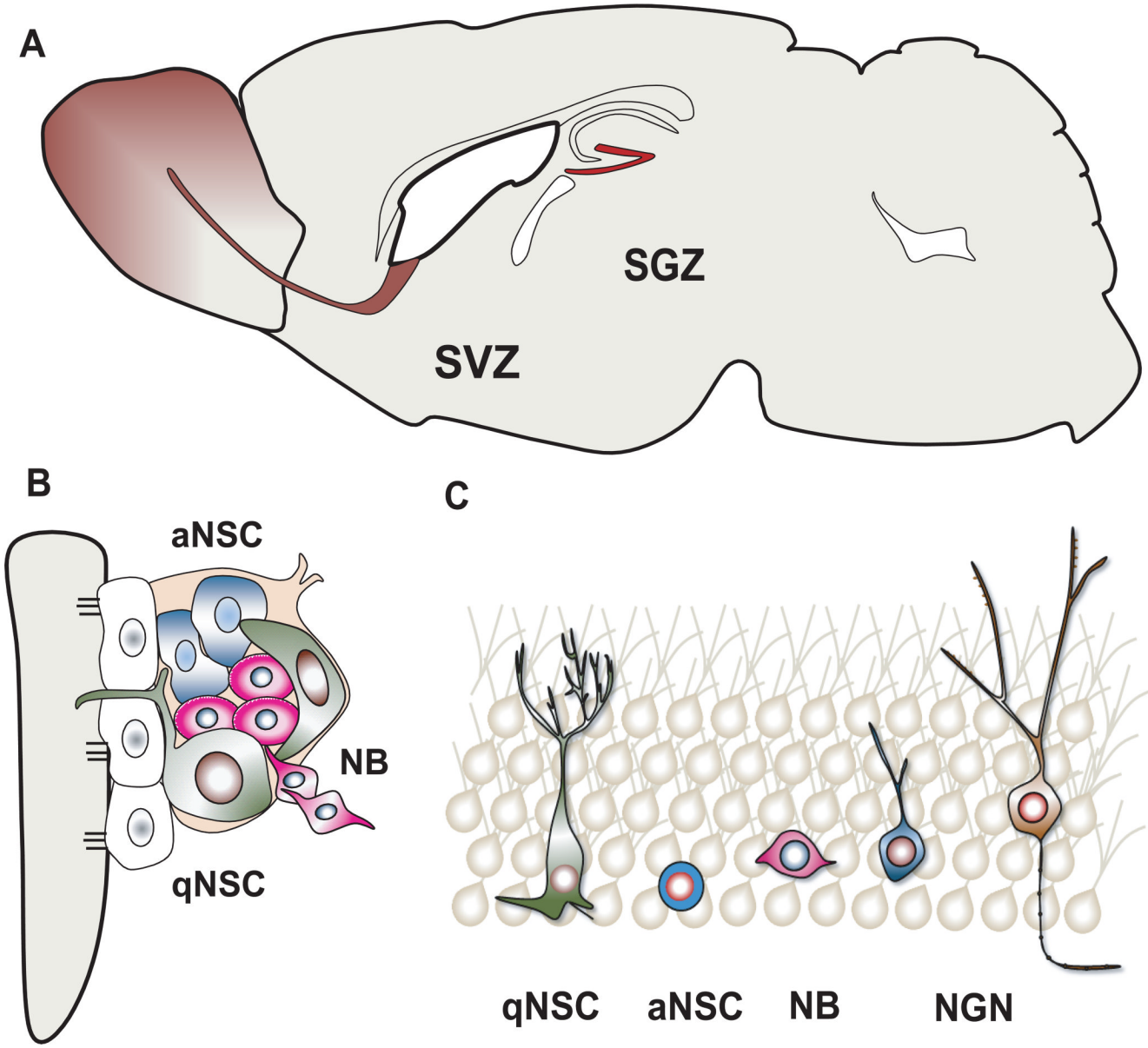

Figure 1.

Adult NSCs in the SVZ and SGZ of the mammalian brain. (**A)** A schematic illustration of the adult mammalian brain in mice. Adult NSCs are primarily present in two germinal regions: the subventricular zone (SVZ) of the lateral ventricle wall and the subgranular zone (SGZ) of the hippocampal dentate gyrus. **(B)**. Adult NSCs in the SVZ. Quiescent or dormant adult SVZ NSCs (dNSC) correspond to a unique type of cell population with cell bodies in the SVZ while contacting the ventricle through apical surfaces. They also share several common features of $GFAP^+$ astrocytes and $CD133^+$ ependymal cells. Actively self-renewing adult SVZ NSCs (sNSC) are located in the SVZ and give rise to neuroblasts that migrate toward the olfactory bulb. (**C**) Adult NSCs in the SGZ. Quiescent or dormant adult SGZ NSCs correspond to radial glia-like cells, some of which might transit to actively self-renewing adult SGZ NSCs and give rise to neuroblasts (NB) and newly generated neurons (NGN).

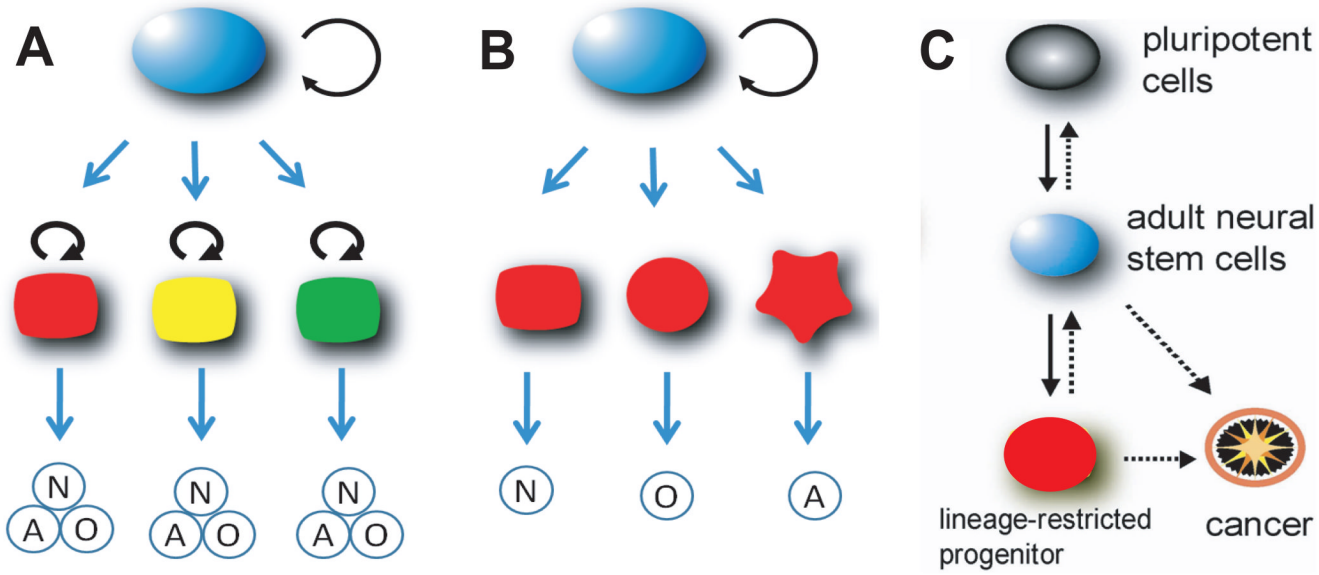

Figure 2.

The lineage model of adult NSCs in the mammalian brain. **(A)**. In one lineage model, adult NSCs (red, green, yellow) generated from primitive NSCs (blue) are intrinsically diverse, exhibiting vastly different developmental potential depending on their regions of distribution and developmental origins. (**B**). In an alternative model, adult NSCs are relatively homogenous (blue) and give rise to a heterogeneous population of lineage-restricted progenitors. (**C**). Under normal conditions, adult NSCs differentiate into lineage-restricted progenitors and mature neurons and glia. Lineage-restricted progenitor may revert to adult NSCs, which can be further reprogrammed into a pluripotent state under epigenetically altered conditions. Pathologically, adult NSCs or lineage-restricted progenitors may undergo genetic and epigenetic changes, transforming into tumorigenic cancer stem cells.