Developmental Dynamics of Neurogenesis and Gliogenesis in the Postnatal Mammalian Brain in Health and Disease: Historical and Future Perspectives

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Abstract

The mature mammalian brain has long been thought to be a structurally rigid, static organ since the era of Ramón y Cajal in the early 20th century. Evidence accumulated over the past three decades, however, has completely overturned this long-held view. We now know that new neurons and glia are continuously added to the brain at postnatal stages, even in mature adults of various mammalian species, including humans. Moreover, these newly added cells contribute to structural plasticity and play important roles in higher-order brain function, as well as repair after damage. A major source of these new neurons and glia is neural stem cells (NSCs) that persist in specialized niches in the brain throughout life. With this new view, our understanding of normal brain physiology and interventional approaches to various brain disorders has changed markedly in recent years. This article provides a brief overview on the historical changes in our understanding of the developmental dynamics of neurogenesis and gliogenesis in the postnatal and adult mammalian brain and discusses the roles of NSCs and other progenitor populations in such cellular dynamics in health and disease of the postnatal mammalian brain.

INTRODUCTION

The Spanish neuropathologist Santiago Ramón y Cajal, often called "the father of modern neuroscience," wrote in his publication in 1914, "*Once the development was ended, the founts of growth and regeneration of the axons and dendrites dried up irrevocably. In the adult centres, the nerve paths are something fixed, ended, immutable. Everything may die, nothing may be regenerated*" [1]. Although this Cajal's notion was based mainly on his

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histological observations of damaged nerve tracts, he also left a vast amount of work on the regeneration (and the lack thereof) of nerve cells (neurons and glia in contemporary terms) in injured brains of various animal species. Since then, it has long been thought that little structural changes occur in the brain in mature animals, in particular, those in mammals.

Remarkable advances of molecular and cellular neurobiology over the past three decades, however, have completely changed such a grim view. First starting from demonstrations of changes in fine subcellular structures at the level of dendrites and synapses in the 70's and 80's [2] to more recent discoveries of neural stem cells (NSCs) in the 90's [3, 4], recent new findings have let us realize that the mature mammalian brain is actually quite plastic and dynamically changes over time. In particular, the discovery of continuous neurogenesis and gliogenesis (i.e., production of new neurons and glia) in the adult brain has drawn renewed attention to the developmental dynamics of the mammalian brain at the cellular level [3, 4]. Now we know that new neurons and glia are continuously produced from various types of undifferentiated progenitors, including NSCs, beyond birth, and that such an activity persists throughout life in some areas of the adult brain [3, 4]. In this review, we summarize our current understanding of the developmental dynamics of the three major neural cell types in the mammalian brain, i.e., neurons, oligodendrocytes, and astrocytes, in the postnatal and adult brain, and discuss implications of recent findings for future development of new intervention strategies for various brain disorders.

Neurogenesis in the postnatal and adult brain

In the developing rodent (mouse and rat) telencephalon (the most anterior part of the brain), differentiation of a variety of neuronal subtypes begins at mid-gestation stages [embryonic (E) day 9 to E10 in mouse] and mostly complete before birth [5, 6] (Figure 1A–B). There are, however, two notable exceptions: One is various interneurons in the olfactory bulb (OB), and the other is granule cells in the hippocampal dentate gyrus (DG) (Figure 1C–H). The peak of the generation of these two neuronal subtypes lies at an early postnatal stage [postnatal (P) day 7 to P14], and, although gradually wearing down by P30, it continues at the adult stage and sustains even in aged animals [7–10]. It has been estimated that approximately 9,000 new neurons are added to the hippocampal DG each day, accounting for about 0.6% of the total DG granule cells in rat and monkey [11, 12]. A larger number of neurons, 10,000 to 30,000 cells per day, corresponding to 1% of the total population, are thought to be continuously supplied to the mouse OB [13, 14]. Moreover, in the OB, more than twice as many cells are initially generated, but not all these newborn cells survive to become mature neurons [14, 15]. Such production of new neurons continues even in aged animals albeit at a lower level [16]. Thus, although the daily addition of new neurons is small in number relative to the total neuronal population in the adult brain as a whole, their cumulative contribution to the respective structures over the entire life span is substantial.

This phenomenon, so-called "adult neurogenesis" in the mammalian brain, is now widely recognized and accepted [3, 4]. It is noteworthy, however, that there have been interesting twists of our view on this matter in the history of neuroscience. Although experimental evidence for adult neurogenesis was repeatedly reported by several pioneering researcher groups, including Altman and Bayer, and Hiss, such findings were largely ignored at the

time of their publications [for details, see refs. 17, 18, and references therein]. In the 80's, however, a breakthrough came from an unexpected direction. Fernando Nottebohm and his colleagues in New York reported a series of studies that investigated the neural mechanisms underlying the seasonal acquisition of new courtship/territorial songs by adult male canaries and zebra finches [19]. Surprisingly, they found that this sophisticated learning-memory function in birds involves an addition of a large number of new neurons followed by a loss of existing neurons in specific brain nuclei [19, 20]. This seminal finding has completely changed our view on neuronal cell genesis and replacement in adult animals. Although amazing functional restoration of a part of the central nervous system (CNS) after injury have long been recognized through studies on the regeneration of the eyes and spinal cord in newts and other amphibian species, a major view in the field had been that such cases are rather exceptional for so-called "lower vertebrates" and restricted merely to specialized or "peculiar pathological" conditions [21]. The new finding discovered in songbirds has dampened down such a long-held view and firmly established the case that new neurons added to pre-existing, mature neural circuitries significantly contribute to higher brain function under physiological conditions. Following these studies on songbirds, many groups have "re-discovered" sustained production of new neurons in the adult brain, now commonly called "adult neurogenesis," first in rodents, and later in many other mammalian species, including large mammals such as sheep and marmoset, as well as non-human primates in the late 90's and early 2000's [22–28]. Later, these studies were further expanded to include the human brain [29], and the occurrence of postnatal and adult neurogenesis across all mammalian species, including humans, has become a widely accepted view by the beginning of the 21st century [3, 4].

How active and widespread is adult neurogenesis?

It should be noted, however, that several important questions still remain unanswered regarding adult neurogenesis. First, to what extent neurogenesis actually occurs in the postnatal human brain is still under hot debates [30–40]. One school of investigators propose that significant neurogenesis persists even in aged human brains [30–35], whereas others argue that production of new neurons become undetectable in early postnatal life and does not sustain in adult humans [36–40]. Such discrepancies are based on different results obtained using distinct methods, and further investigations are necessary to reconcile the differences [for details, see refs. 30 and 40].

Another unsettled issue is how spatially widespread neurogenesis is in the adult mammalian CNS. Although neurogenesis in the OB and DG regions of the adult brain is commonly detected across mammalian species under physiological conditions, whether a similar cell genesis also occurs in other parts of the CNS has been highly controversial [reviewed in detail in ref. 41]. For example, a recent study has provided evidence for the production of a small but significant number of new neurons in the adult human striatum [42]. Similar neuronal addition in the adult striatum has also been reported in rodents and non-human primates [43–46]. Likewise, detection of similar low-level production of new neurons has been reported in many other parts of the adult CNS, notably the cerebral cortex [46–50] and hypothalamus [51–54]. Many other studies, however, do not support such findings [55, 56].

Thus, how widespread neurogenesis is in the intact postnatal mammalian CNS is still an unsolved issue [for more details, see ref. 41].

Physiological roles of adult neurogenesis in brain function

Another unanswered important issue is that despite extensive studies over the past three decades, what roles new neurons actually play in the adult mammalian brain is still unclear. In an analogy with the case of adult neurogenesis in songbirds, it is widely thought that newly produced neurons in the mammalian brain play important roles in the plasticity of brain function through the modulation of the activity of the existing neural circuitry in certain ways, and results reported in many published studies support this idea in one way or another [reviewed extensively in refs. 57–59]. In fact, one notable feature common to the two neural circuitries to which new neurons are constantly added, i.e., the hippocampal and olfactory circuitries, is that they both exhibit high functional plasticity and play important roles in learning and memory [57]. Moreover, it has been shown that the level of the production of new neurons in these two regions significantly changes in response to a variety of environmental stimuli such as exposure to new odors and spatial/acoustic cues, exercise, stress, and fear [57]. Various neurological and psychiatric disease conditions are also known to alter the level of neurogenesis in these regions, and in certain cases, including epilepsy and depression, such changes are implicated in disease pathogenesis [58, 59]. Yet, conclusions drawn in different studies are surprisingly different from each other on the actual role of new neurons in these brain functions [reviewed in detail in refs. 3 and 4]. Thus, a better understanding of how adult neurogenesis contributes to the plasticity of higher-order brain function is an outstanding important issue in future studies.

NSCs as the source of new neurons in the postnatal and adult brain

These new findings also raise the issue of the cell of origin of new neurons in the adult mammalian brain. In the early 90's, around the same time when adult neurogenesis was re-discovered, another breakthrough occurred and quickly answered this question. Two groups of researchers, Sally Temple and her colleagues in New York and Samuel Weiss and his group in Calgary, have independently developed new cell culture methods that allow researchers to examine the properties of each individual neuronal progenitor cell in the embryonic and adult brains at the single cell level [60, 61]. Studies using these new techniques have demonstrated the occurrence of specialized progenitor cells that retain the capacity of both self-renewal and multi-lineage-differentiation, first in the embryonic and later in the adult mouse brain. These progenitors are now collectively called NSCs given their similarities with so-called "tissue-specific" or "adult" stem cells in other organs and tissues [3, 4].

Subsequent studies have identified specialized regions where these NSCs reside in the adult rodent brain (Figure 1C–H). In the hippocampal DG, the subgranular zone (SGZ), a narrow layer of cells beneath the granule cell layer, is the area where NSCs and their early progeny reside, and new neurons produced by them migrate in a short distance to the overlaying granule cell layer [3] (Figure 2G–H). In contrast, new neurons in the OB originate from NSCs that reside in the so-called ventricular-subventricular zone (VZ-SVZ) or ependymal-subependymal layer, a thin strip of tissue lining the lateral ventricle (LV) of the

telencephalon (for reasoning of the nomenclature of this structure, see below) [66, 67] (Figure 2C–D). New OB neurons are first produced by NSCs within this VZ-SVZ region, and subsequently migrate anteriorly through a specialized narrow path called the rostral migratory stream (RMS) that physically connects the VZ-SVZ and the OB [4] (Figure 2F). These two stem cell residences, i.e., the SGZ and VZ-SVZ, are collective called 'neurogenic' or "stem cell" niches in the adult mammalian brain and are distinguished from the remaining 'non-neurogenic' brain parenchyma [41]. Histological evidence has also shown the presence of similar neurogenic/stem cell niches in the brain of humans and non-human primates [30–40].

Similarities and differences between neurogenesis and NSCs in two neurogenic regions in the postnatal brain

There are a number of interesting similarities and differences between these two adult neurogenic/stem cell niches. First, NSCs are preserved throughout life mostly as quiescent, non-dividing cells (qNSCs) in both regions (Figure 2). When these qNSCs are activated and begin to proliferate (aNSCs), they produce transient amplifying progenitors (TAPs), which in turn undergo rapid cell divisions a few times and subsequently differentiate into immature neurons called neuroblasts (NBs) (Figure 2). Thus, the capacity of stem cells to self-renew, either through symmetric or asymmetric divisions, and rapid and transient amplification of TAPs and NBs are key mechanisms to maintain a relatively small number of NSCs locally while generating a much larger number of new neurons continuously over a prolonged period of time [62, 63].

These NSCs also share some morphological and molecular features with specialized glial cells such as radial glial cells (RGCs) in embryos and astrocytes in the adult brain [63, 64] (see Figure 4). One notable example is that all these cells commonly express glial fibrillary acidic protein (Gfap) and the glial high affinity glutamate transporter (Slc1a3 or Glast) [67, 68]. Second, recent studies have revealed many common molecular players and mechanisms that control the maintenance and differentiation of NSCs in both regions [see refs. 62, 62, and references therein]. For example, in both the VZ-SVZ and SGZ, the Sox family of high-mobility-group-containing TFs Sox2 and Sox9, as well as the orphan nuclear receptor Tlx (Nr2e1) have been shown to be crucial for the long-term maintenance of adult NSCs, whereas the basic helix-loop-helix transcription factor (TF) Ascl1, the homeodomain factor Prox1, and Sox family factors Sox4 and Sox11 commonly play important roles in the neuronal differentiation of NSCs (Figure 2) [62, 63, 68–72].

Yet, some important differences also exist between NSCs in the VZ-SVZ and SGZ. Granule cells produced in the adult DG are glutamatergic projection neurons, whereas newly generated OB neurons are interneurons that use γ-aminobutyric acid (GABA) or dopamine as neurotransmitters [4]. Moreover, newly produced DG granule cells are generally thought to be homogeneous and belong to a single neuronal subtype, and no subtype heterogeneity has so far been identified among them [4]. By contrast, OB interneurons produced in the adult SVZ include diverse neuronal subtypes that settle and integrate into different laminae of the mature OB [73]. Recent studies have demonstrated that these diverse subtypes of neurons are generated by NSCs that reside in distinct subdomains within the VZ-SVZ and

retain different molecular identities [74–77]. Such heterogeneity has not yet been identified in NSCs in the DG. Reflecting these differences, distinct sets of TFs, including Gsx1, Gsx2, Nkx2.1, Zic1, Pax6, Arx, and Dlx2 in the VZ-SVZ] and Tbr2 and Neurod1 in the SGZ, have been shown to play important roles in the neuronal differentiation of NSCs in respective regions (Figure 2) [refs. 62, 63, and references therein.

The developmental time course of neurogenesis is also different between the two regions. The production of OB interneurons in mice begins very early (as early as E10) in embryos and continues throughout the rest of the embryonic and postnatal development [7, 8]. Yet, distinct interneuron subtypes have different peak stages for their production, and some are mostly generated before birth, whereas others are most actively produced in the first and second postnatal weeks [7, 8]. Subsequently, the overall level of OB neurogenesis gradually declines and reaches a steady-state level by P30 and sustains for the rest of life. Such differential kinetics among distinct neuronal subtypes are explained by the idea that NSCs residing in distinct embryonic primordia produce different neuronal subtypes at different stages, and that these distinct NSC populations gradually mature and settle in distinct subdomains of the adult VZ-SVZ niche with different time courses [74–77]. In this scenario, the OB neurogenesis can be seen as a life-long activity of diverse NSC populations that sustain from early embryogenesis to the end of life. By contrast, the production of DG granule cells is mostly a postnatal event, and the formation of the mature form of the DG completes by P30 in mice [9, 10]. Interestingly, a recent study has proposed that progenitors that are responsible for the generation of the major part of the DG in the first three postnatal weeks and those that become NSCs in the SGZ and continuously supply new granule cells at the adult stage have topologically distinct embryonic origins [78]. This new scenario suggests that the initial development of the DG and its subsequent modulations by new neurons supplied by adult NSCs are separable developmental events. The significance of this finding remains to be further investigated.

Finally, extensive studies over the past three decades have identified a variety of extracellular signaling mechanisms that regulate the behavior of NSCs in the VZ-SVZ and DG either commonly or differentially [for details, see refs. 3, 4, 41]. An important concept drawn from these studies is that NSCs in the postnatal brain act as sensitive responders to various physiological stimuli. This property of NSCs also plays an important role in regenerative and restorative responses after injury (see below).

Prolonged development of oligodendrocytes

Oligodendrocytes are myelin-forming glia in the mammalian CNS. In the rodent brain, myelinated axons are scarce at birth, and the full complement of myelination in the whole brain does not occur until the fourth week of postnatal development [79, 80]. Full myelination in the human brain is further delayed to an age of 10 to 12 years in some cortical regions responsible for higher cognitive function such as the prefrontal cortex, and such a delay is considered to be a notable example of the so-called neoteny feature of the human development [81]. Therefore, oligodendrocytes have long been thought to be the last cell types to be generated during development among the three major cell types in the mammalian CNS.

Studies over the past three decades, however, have totally changed this view. It has turned out that the delayed appearance of oligodendrocytes examined in old studies was simply because the cells had been detected based on either the formation of myelin sheets in electron microscopic (EM) studies or the expression of major myelin proteins such as myelin basic protein (MBP) and myelin glycoprotein (MAG) in conventional histology. Since the early 90's, many studies have identified a variety of molecular markers for progenitor/precursor cells that stay undifferentiated for a long period of time during embryonic and early postnatal stages and eventually become myelin-expressing mature oligodendrocytes at later stages [82, 83]. For instance, platelet-derived growth factor receptor α (PDGFRα) and chondroitin sulfate proteoglycan 4 (Cspg4) (also known as NG2) are selectively expressed in early-stage proliferative cells called oligodendrocyte progenitor cells (OPCs) [82, 83] (Figure 3B). These OPCs also express the basic helix-loop-helix TFs Olig1, Olig2, and Ascl1, as well as the Sox family of high-mobility-group-containing TFs Sox8, Sox9, and Sox10 [82, 83]. These OPCs cease cell divisions and begin to differentiate first into pre-myelinating immature oligodendrocytes (Pre-OL) at early postnatal stages, and subsequently gradually undergo maturation as myelin-expressing oligodendrocytes (OLs) (Figure 3B). The stage of pre-OLs is defined by the expression of the homeodomain TFs NKx2–2 and Nkx6–2, and various zinc-finger TFs such as Myt1 (Nzf2), Zfp24 (ZFP191), and Zfp488 [83]. In myelinating OLs, the TF MYRF (Gm98) directly regulates the expression of various myelin proteins including MBP and MAG. Studies on the expression and function of these stage-specific regulatory genes have now revealed details of the developmental time course of oligodendrogenesis. In mouse embryonic telencephalon, cells in the oligodendrocyte lineage begin to emerge as early as E11.5, and these OPCs are continuously produced throughout the rest of embryogenesis and increase their number while migrating toward various brain regions, thereby becoming abundant and widespread already at birth [83, 84] (Figure 3A). Generation of new OPCs further continue during early postnatal stages, but begin to cease cell divisions from the second postnatal week, and eventually differentiate into Pre-OLs and OLs by the end of the first postnatal month [84–90]. In general, the transition from OPCs to Pre-OLs and OLs proceeds in a ventro-caudal to dorso-rostral gradient in the mouse telencephalon, but the precise mechanisms that control the timing of their transitions in different regions of the brain remain largely unknown.

Importantly, similarly to neurogenesis of OB interneurons, there is evidence that production of new OPCs in the VZ-SVZ sustains albeit at a low level in the fully matured adult brain under both physiological and pathological conditions [91–99]. Moreover, a significant number of OPCs generated during embryonic and early postnatal periods remain undifferentiated and sustain in the widespread regions of the mature brain parenchyma throughout life [79, 80]. A small fraction of these pre-existing and newly generated OPCs in the adult brain become mature oligodendrocytes and replace existing OLs that are lost physiologically or after injury in both rodents [84–98] and humans [99]. Thus, the development of oligodendrocytes from their generation to maturation proceeds on an extremely protracted schedule in the mammalian CNS.

Interestingly, recent lineage-tracing studies have shown that the generation of OPCs from NSCs in the telencephalon occurs in spatially distinct progenitor domains at different stages. Early born OCPs start to emerge E12.5 onward from ventral progenitor domains such as the

preoptic area (POA) and median ganglionic eminence (MGE), and their generation subsequently spreads to a more dorsal domain called the lateral ganglionic eminence (LGE) at later embryonic stages (by E15.5) [84, 85] (Figure 3A). In addition to these ventral domains, progenitors in the pallium (dorsal telencephalon) become a major source of OPCs at late embryonic (E18.5 onward) and early postnatal stages [86–90]. OPCs derived from ventral progenitor domains mainly populate the ventral aspect of the telencephalon, while those from both ventral and dorsal domains contribute to oligodendrocytes that later myelinate axons in the dorsal telencephalon such as the neocortex and corpus callosum [84–90]. Thus, the origin of oligodendrocytes is diverse both spatially and temporary. It is currently unknown, however, whether oligodendrocytes originating from distinct domains at different stages exhibit any functional differences.

Development of astrocytes

Astrocytes are among the most abundant and widely distributed cell types in the mammalian CNS and exert multiple important functions [100, 101]. Nevertheless, our current understanding of the development of astrocytes remains surprisingly sketchy. As in the case of oligodendrocytes, the lack of appropriate molecular markers had long hampered detailed analysis of astrocyte development until the late 80's [101]. By then, studies on the ontogeny of astrocytes heavily relied on the detection of so-called glial filaments, which are composed of unique intermediate filament proteins such as glial fibrillary acidic protein (GFAP) and vimentin (Vim), by either EM or conventional histology. Like myelin proteins in oligodendrocytes, the expression of GFAP and Vim is a relatively late event in the developing brain so that earlier-stage precursors of astrocytes were difficult to identify [101]. More recent studies have begun to identify several molecular regulators of early-stage astrocyte development such as the TFs Sox2, Sox9, Nf1a, and Zbtb20 [102–108] (Figure 4B). These TFs, however, are also expressed in NSCs and other progenitors in the germinal zones of both embryonic and postnatal brains [102–108]. In fact, when the *in vivo* identity of NSCs in the adult mouse brain was first identified, a surprising finding was that astrocytes and adult NSCs share many features [64, 65]. For example, not only GFAP and Vim, but also the glutamate transporter Glast (Slc1a3) and the water-selective channel aquaporin 4 (Aqp4) are all important regulators of certain aspects of astrocyte functions, but they are also expressed in adult NSCs [68, 69]. Likewise, the TFs Sox2, Sox9, and Nfia have been shown to play crucial roles in both differentiation of astrocytes in embryos and maintenance of NSCs in adults [102–107]. Thus, adult NSCs and astrocytes share many common gene expression profiles and regulatory mechanisms. Nevertheless, only NSCs, but not astrocytes, retain *bona fide* capacities as stem cells, and we do not fully understand yet what molecular programs actually distinguish these two cell types in the adult brain. This similarity between astrocytes and NSCs also makes studies on astrocyte development even more difficult than that of oligodendrocytes.

Thus, based mostly on indirect morphological and marker analysis, two ontogenic pathways to generate astrocytes have been speculated: One is that germinal zone immature progenitors such as NSCs produce precursors committed to an astrocyte lineage, and these precursors migrate to the brain parenchyma and differentiate into mature astrocytes later in development [109] (Figure 4A, left). This mode of astrocyte generation is in an analogy with

the specification of oligodendrocytes and consistent with the observation that some scattered cells expressing Sox2, Sox9, Nfia, and/or Zbtb20 begin to emerge outside the germinal zone in the late embryonic and early postnatal brain [102–108]. Another possible pathway is transformation of so-called radial glial cells (RGCs) into astrocytes. In mid-gestation embryos, RCGs, which are thought to serve as the origin of both neurons and glia, exhibit elongated morphology, and their radial process spans across the entire apico-basal axis of the developing brain [65] (Figure 4A, right). At late embryonic stages, however, their apical and basal processes gradually retract, and they appear to transform into cells that populate widespread regions of the brain parenchyma in a scattered manner. Based on their morphology and marker expression, these cells are thought to become astrocytes during the postnatal period [65]. This second scenario supports the idea that both postnatal NSCs and astrocytes are descents of embryonic RGCs, and, thus, share common features [64, 65]. Recent studies using various transgenic mice, in which RGCs and their progeny can be genetically labeled and their fates can be tracked, have provide evidence that supports both of these two scenarios, but do not necessarily proves one idea over the other [48, 109–111]. Thus, it remains unknown whether either pathway is correct, or both pathways co-exist in astrocyte development. In the mature adult brain, there is evidence that a small number of new astrocytes are generated by NSCs in the hippocampal DG, although their number appears to be quite small [114–116]. NSCs in the adult VZ-SVZ region have also been demonstrated to generate new astrocytes in the corpus callosum and RMS [117], although whether such NSCs are the same as those for new neurons and oligodendrocytes at the clonal level remain uncertain [118, 119].

Relationship between neurogenesis and gliogenesis in the postnatal brain

It is noteworthy here that the spatiotemporal dynamics of the development of OB interneurons and oligodendrocytes look very similar. In fact, both cell types are continuously generated from multiple progenitor domains from early embryonic to postnatal stages in the mouse telencephalon. This raises the question of whether or not these two cell types originate from common progenitors. In particular, the dorsal progenitor domain that covers the roof region of the LV in the postnatal and adult brain has been identified as the source of both OB interneurons and oligodendrocytes in different studies [91–98]. A cell culture experiment has provided evidence that NSCs in this region differentiate into oligodendrocytes only but not neurons, whereas those derived from more ventral regions preferentially generate neurons only [93]. Other studies, however, have reported that the same region contains NSCs that produce new OB neurons *in vivo* and *in vitro* [74, 77]. Thus, it is currently unknown whether the same pool of NSCs produces both cell types simultaneously, or separate pools of NSCs co-exist in the same region. This question is related to a more general issue regarding the distinction between the *in vivo* fate and capacity of NSCs in the postnatal and adult NSCs. Lineage-tracing studies have demonstrated that NSCs in the adult DG generate both neurons and astrocytes [115, 116]. Moreover, a recent clonal level analysis of the fate of single NSCs has shown that some NSCs produce both neurons and astrocytes, while other cells produce only one of these two cell types over a period of one year [114]. The same study, however, did not detect any NSCs that produced oligodendrocytes in the same period. It remains unknown whether these neuron-astrocyte bi-potent NSCs and those that are mono-potent and produce neurons or

astrocytes only have intrinsically different capacities, or they all are multipotent but choose particular fates stochastically. Likewise, although NSCs derived from various VZ-SVZ subdomains in the adult brain often behave as multipotent progenitors that produce all three neural lineages when cultured *in vitro*, whether each individual cell indeed produces both neurons and glia *in vivo* has not been experimentally determined.

Another important point is the ontogenic relationship between oligodendrocytes and astrocytes. When OPCs were first identified in the 80's, cell culture experiments demonstrated that they behave as bi-potent progenitors that can differentiate into both oligodendrocytes and astrocytes *in vitro* [120]. Subsequent *in vivo* studies, however, have demonstrated that the same cells become almost exclusively oligodendrocytes only, but not astrocytes [82, 83]. Thus, a current consensus view is that the so-called OPCs are progenitors committed to an oligodendrocyte lineage. Yet, some recent studies using genetic lineage-tracing methods have provided evidence that a fraction of PDGFRα/NG2-expressing OPCs differentiate not only into oligodendrocytes, but also into astrocytes and/or neurons in certain regions of the brain *in vivo*, although such cells seems to be relatively rare [121– 124]. Other studies, however, argues that OPCs are committed exclusively to an oligodendrocyte lineage [125, 126]. Thus, the actual potency and fate of OPCs *in vivo* still needs to be further investigated.

Impacts of non-neuronal/glial cell types on postnatal brain development

There are several structurally and functionally important non-neuronal/glial cell types in the postnatal mammalian brain. Ependymal cells form a single-cell layer epithelium that separates the brain parenchyma from the LV and other ventricular systems [127]. Although ependymal cells lining the LV have long been thought to develop postnatally, recent studies have demonstrated that they start to emerge as early as E13 in mice near the posterior edge of the LV and progressively spread over the entire LV during late embryonic and early postnatal stages [128, 129]. Importantly, while embryonic RGCs in the germinal zone transform into postnatal NSCs in the VZ-SVZ region, they also generate ependymal cells in the same region [130]. Thus, postnatal NSCs are intercalated with ependymal cells within the ependymal layer, and they together confer unique pinwheel architecture to the ventricular surface of the LV [131]. Such a pinwheel structure is not evident in non-neurogenic parts of the ependymal layer such as those in the fourth ventricle of the hindbrain or the central canal of the spinal cord.

Because of this unique microarchitecture, there have been intense debates over the identity of adult NSCs within the VZ-SVZ region over the past two decades [132]. When the cellular identity of NSCs in the adult mouse brain was first reported, one group proposed that a pool of NSCs reside in the ependymal layer, whereas another group argued that NSCs are strictly confined to the subependymal region [66, 67]. Since then, there have been a number of studies that support both ideas [131, 134–136]. At the end, it has turned out that the soma and/or apical processes of NSCs actually reside in both the ependymal and subependymal regions, and, thus, cells with a capacity as NSCs and typical ependymal cells with motile multi cilia co-exist in the ependymal layer [124–131]. Yet, there have been revived conflicting views in recent years regarding the exact identity and functional properties of

individual cells that exist in the ependymal layer of the LV [134–136]. This issue is related to the question of why NSCs that actively produce new neurons are detected only in the telencephalon, but not in other parts of the CNS, although the so-called ependymal cells are ubiquitous all along the ventricular system. Importantly, a number of *in vitro* culture studies have identified the occurrence of cells with properties similar to NSCs in widespread regions of the adult mammalian CNS [for details, see ref. 41, 132]. Therefore, the issues of the exact identity of NSCs and the reason why active neurogenesis is confined to specialized regions in the adult mammalian CNS remain to be further investigated. It also remains unknown whether any functional crosstalk between NSCs and ependymal cells exits within the ependymal layer.

The choroid plexus is a single-cell layer epithelial structure that protrudes from the ependymal layer into the lateral, third, and fourth ventricles [136]. Together with some underlying mesenchymal components, it is thought to be responsible for the production and absorption of the CSF [136]. The epithelial cells in the choroid plexus are morphologically similar to ependymal cells, and both cell types are thought to differentiate from embryonic RGCs in a similar way. However, ependymal cells are ubiquitously present throughout the ventricular system of the CNS, whereas choroid plexus cells develop only in a few restricted regions [137]. The mechanisms underlying such region-selective generation of the choroid plexus remains largely unknown [137]. Importantly, recent studies have demonstrated that certain secreted signaling molecules from choroid plexus cells regulate proliferation of NSCs in the adult VZ-SVZ [138]. It has also been shown that the flow of the CSF generated by the choroid plexus and ependymal cells regulates both proliferation NSCs and directional migration of their neuronal progeny in the VZ-SVZ niche [139, 140]. Meningeal fibroblastic cells, which cover the entire outer surface of the CNS, are also an important part of the CNS ventricular system. They are thought to be mainly involved in the production and absorption of the CSF, but a recent study has revealed their surprising function in development. Evidence has demonstrated that meningeal cells overlaying the dorsal aspects of the embryonic telencephalon produce retinoic acid, which in turn controls the elongation of the RGCs along the apico-basal axis and subsequent temporary regulated production of cortical pyramidal neurons with specific laminar phenotypes [141]. Whether the meninge in other parts of the CNS has similar function is currently unknown.

The blood vessels are also an important cellular component in the CNS. In particular, pericytes are a unique cell type that participates into the formation and maintenance of the BBB, together with vascular endothelial cells and astrocytes, at the border between the brain parenchyma and a dense network of microvasculature within the brain [142]. Recent studies have proposed that a subset of pericytes derive from peripheral macrophages migrating into the brain [142, 143]. Yet, given the recent discovery of the molecular heterogeneity of pericytes, the origin of pericytes in various brain regions need to be further investigated. Importantly, recent studies have demonstrated intricate communications between the brain vasculature and various neural cell types, including NSCs [144]. For example, it has been shown that angiogenesis in the mouse embryonic telencephalon progresses in a ventral-to-dorsal gradient, apparently coinciding with the progression of neurogenesis, and that such temporal gradient is regulated by various homeodomain TFs that are expressed commonly in both embryonic NSCs and vascular endothelial cells in a region-specific manner [145].

Moreover, blood vessels actively participate in controlling various aspects of the development of neurons and glia [144]. A notable example is crosstalk between NSCs and blood vessels in the postnatal and adult VZ-SVZ, in which NSCs and their progeny physically interact with specialized blood vessels called the SVZ vasculature that forms a dense and widespread vascular network just beneath the ependymal layer of the LV [146, 147]. Through this interaction, blood vessels are thought to send various signals to postnatal NSCs that control their proliferation and differentiation.

Microglia are another cell type that comes into the postnatal CNS from the periphery [148]. As major immune-competent cells in the brain, microglia exert multiple functions under various physiological and pathological conditions [148]. Notably, recent studies have demonstrated that microglia regulate proliferation and differentiation of NSCs and OPCs either positively or negatively depending on conditions, thereby affecting the cellular dynamics of the postnatal brain in both the VZ-SVZ and DG [150–153]. Yet, what impact microglia have on normal brain development remains to be further investigated. Taken together, it is important to note that these vascular-NSC and microglia-NSC interactions serve as important mechanisms by which various systemic and local environmental signals regulate the behavior of NSCs and other CNS cell types, thereby affecting the cellular dynamics of the postnatal and adult brain under various physiological and pathological conditions.

Neurogenesis and gliogenesis in the injured brain

As described above, many lines of recent studies have collectively established that production of new neurons and glia is active beyond embryogenesis, and continues, albeit at a lower level, even at the fully mature stage in the mammalian brain under physiological conditions [3, 4]. Importantly, numerous studies in the past two decades have further demonstrated that such cell genesis occurs at an elevated level under various pathological conditions [41, 154]. For example, acute brain injury such as ischemia, trauma, and epilepsy stimulates the net production of new neurons in both the VZ-SVZ and hippocampal DG [41, 154] (Figure 5). Chronic neurodegenerative conditions such as Alzheimer's and Parkinson's diseases also lead to a sustained high level of neurogenesis in these regions [41]. Although most of these studies used rodent models, several studies have demonstrated evidence for similar enhancement of endogenous neurogenesis in the injured brain of adult humans and non-human primates [for example, see refs. 155–160].

It is important to note, however, that such increased production of neurons in these so-called neurogenic regions do not necessary lead to a replacement of neurons lost to insult in damaged areas. It appears that most of the newly produced neurons after injury stay within the normally neurogenic areas and are considered as a part of compensatory responses to injury [41]. In certain cases, however, there is clear evidence that neurons newly produced after injury migrate toward lesion and replace lost cells. For example, new neurons that resemble striatal and cortical projection neurons have been detected in the adult brain after ischemic and hemorrhagic injury in rodents, humans, and non-human primates [155–164] (Figure 5A). Replacement of hippocampal CA1 pyramidal neurons after ischemic injury has also been reported in rats [165] (Figure 5B). These studies have, thus, demonstrated that

neuronal regeneration indeed occurs under certain pathological conditions in the mammalian brain. Given that the production of these types of projection neurons is normally undetectable or negligible in the adult brain under physiological conditions, it is speculated that NSCs that normally produce OB interneurons in the VZ-SVZ region under physiological conditions change their properties after injury to produce these neuronal subtypes, or, alternatively, normally dormant NSCs are activated by injury to give rise to new neurons [discussed in detail in ref. 41]. In fact, recent single-cell transcriptome analysis of NSCs have demonstrated injury-induced changes in the properties of otherwise dormant NSCs in normally non-neurogenic regions of the adult CNS [134, 166].

Studies using different injury models have shown that such increased neurogenesis after injury occurs through multiple different mechanisms such as recruitment of more NSCs into cell divisions, stimulation of proliferation of intermediate progenitors, and/or survival and maturation of new neurons depending on injury types [for details, see ref. 41]. Recent studies have also begun to reveal the molecular mechanisms underlying these regulations. For example, it has been shown that the TFs Gsx2 and Ascl1, which are essential for neurogenesis in the intact brain, also play crucial roles in injury-induced neurogenesis [70, 75]. In addition, a variety of exogenous manipulations, including systemic and local administration of growth factors, cytokines, and hormones, have been shown to augment the extent of such injury-induced neurogenesis [for details see ref. 41]. By contrast, both acute and chronic inflammation and treatment with corticosteroids significantly attenuate injury-induced neurogenesis [167–171]. An important unsolved issue is how much contribution these newly generated neurons have to the restoration of function lost to insult. Some studies present evidence that new neurons are integrated into existing circuitry and exhibit properties similar to lost cells, thereby contributing to functional repair [154, 165]. Other studies, however, argue that new neurons detected in damaged areas do not show region-appropriate phenotypes and have little functional impact [171]. Further studies are necessary to address this issue in order to harness the endogenous regenerative capacity for brain repair.

The production of glial cells is also stimulated after injury. As mentioned above, a low level of oligodendrogenesis continues in the postnatal brain [91–95]. A number of recent studies have shown that its level is significantly increased in response to injury [96–98]. In particular, in the early postnatal brain, in which production of new oligodendrocytes is very active, demyelinating injury of the white matter markedly stimulates the production of OPCs in the VZ-SVZ region, and these new OPCs are recruited to demyelinated lesion and enhance re-myelination [96–98]. Whether similar re-myelination also occurs in the damaged gray matter remains to be investigated. Studies using various animal models of ischemic and traumatic injury have also shown that new astrocytes are produced following insult [110, 111]. These studies have demonstrated that reactive astrocytes originate from NSCs in the VZ-SVZ and participate in the formation of so-called glial scar, which physically seals off lesion and prevents the spreading of secondary tissue damage [110, 111]. On the other hands, other studies have reported that after localized injury such as stab wound in the cerebral cortex, reactive astrocytes are generated mainly through proliferative divisions of local resident astrocytes, but not by NSCs in the VZ-SVZ [112, 113]. Thus, it could be that

new astrocytes originate from distinct cellular sources depending on the type of injury and location.

Interestingly, some recent studies suggest that reactive astrocytes in injured areas acquire certain properties of NSCs and produce new neurons locally under certain pathological conditions [112, 113, 173]. Moreover, recent studies have demonstrated that many non-neuronal cell types in the adult brain, including astrocytes, OPCs, and pericytes, can be directly converted into functional neurons *in vivo* by targeted genetic manipulations, offering a new strategy to regenerate neurons in injured brains [174]. How widespread such a phenomenon of cell type conversion or reprogramming is in injured brains, and whether converted/reprogrammed NSCs and neurons have any significant contributions to tissue repair need to be further investigated.

All together an important message drawn from these studies is that the postnatal and adult mammalian brain has a significant intrinsic capacity for tissue repair. Such a finding has raised the possibility that their endogenous capacity can be further harnessed for better regeneration and repair of the damaged brain by certain means [41]. Yet, the extent of the replacement of lost neurons and glia revealed in these studies so far is rather small with a few exceptions [41]. Therefore, further studies are necessary to develop more effective strategies to augment the endogenous regenerative capacity to achieve functionally meaningful repair after injury.

CONCLUSION AND FUTURE PERSPECTIVES

As described in detail above, studies in recent years have revealed that dynamic changes in the cellular composition continues beyond birth, and even sustains to some extent throughout life in the mammalian CNS. This is a significant departure from the long-held static view on the postnatal brain since the era of Ramón y Cajal and has led us to understand the overall picture of the development of the mammalian brain very differently. Such a new view also lets us take new approaches to understand the pathophysiology of various neurological and psychiatric disorders such as autism spectrum disorders and developmental disabilities that affect the postnatal brain of humans, and to develop new interventional strategies to treat these diseases.

Many important basic developmental biology questions, however, remain unanswered. For instance, although a number of important regulators of postnatal and adult NSCs have so far been identified, our current understanding of how their long-term maintenance and commitment to particular lineages are controlled is still sketchy [62, 63]. In addition, although generation of new neurons and glia continues from embryonic to postnatal periods, the mode of cell genesis markedly changes over time. Little has so far been known about details of such temporal changes and underlying control mechanisms. We need to better understand the similarities and differences between NSCs in embryonic, early postnatal, and adult brains at the molecular level to better understand postnatal brain development [62].

These issues are also important for future advancement of restorative neurology aiming at regeneration and repair of damaged/diseased brains. Although active neurogenesis and

gliogenesis is confined to a few restricted regions in the adult mammalian brain under physiological conditions, injury not only accelerates such ongoing cell production, but also induces new neurons and glia in more widespread regions, and, importantly, some of these new cells exhibit properties not seen in the intact brain. Whether the same NSC pool is responsible for such new cell genesis under physiological and pathological conditions is currently unknown. It could be that new neurons and glia produced in injured brain originate from a unique NSC pool that normally remains dormant in the intact brain but is activated by injury. In fact, some recent studies have provided evidence for the occurrence of such dormant NSCs outside the normally neurogenic regions [113, 133, 134, 173]. Alternatively, injury may alter the properties of existing NSCs and change the fate of their progeny. In order to harness the intrinsic regenerative capacity of NSCs for better functional restoration after injury and disease, we need to understand what stimuli regulate their proliferation and differentiation *in vivo*, and how we can manipulate their responses for better repair. Obviously, such mechanisms and effective interventional manipulations could be significantly different between early postnatal and adult stages, as well as under various pathological conditions.

One thing that has become clear over the past three decades, however, is that unlike in Cajal's and subsequent eras when people considered the postnatal mammalian brain as a static, rigid structure, we now know that it is actually quite a dynamic and plastic organ. In this regard, it is noteworthy that Cajal himself wrote, after the famous quote, "*It is for the science of the future to change, if possible, this harsh decree. Inspired with high ideas, it must work to impede or moderate the gradual decay of the neurons, ….. We must recognize that, in the matter of neurogenesis and nerve regeneration, we are still in the phase of collection of materials*" [1]. We are indeed still in the phase of collection of materials, but with much better tools and methods in our hands now compared with Cajal's era. Further advances in molecular and cellular neurobiology will certainly lead us to better understand the development of the mammalian brain and to develop effective strategies for regeneration and repair of the damaged brain in the future.

ACKNOWLEDGEMENTS

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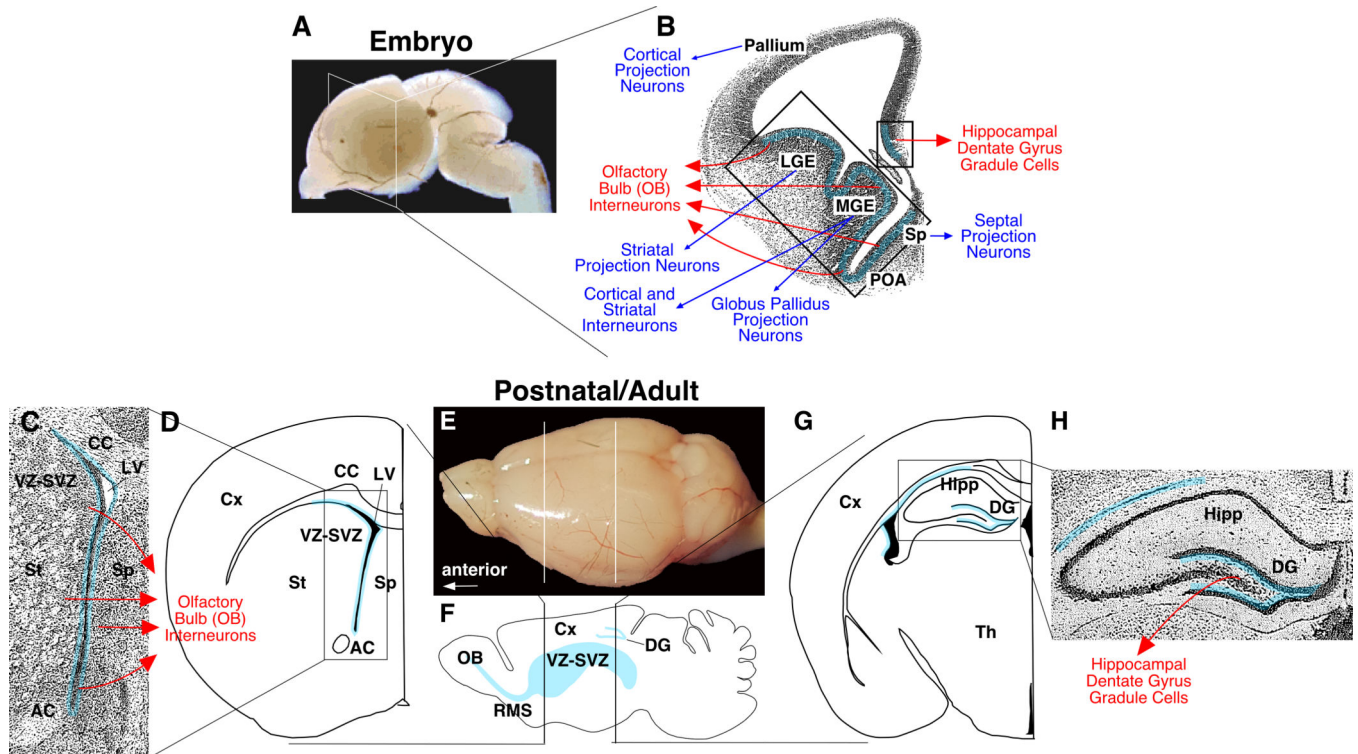
Figure 1.

Continuous production of new neurons from embryonic to adult stages in the mammalian brain. **(A, B)** Production of different subtypes of neurons in distinct progenitor domains of the embryonic mouse telencephalon. Panel A shows a representative lateral view of the embryonic brain, and panel B shows its view at a coronal plane (indicated by a while square in A). The light blue line in B indicates the areas where progenitors of new neurons reside. The embryonic primordia of the pallium, lateral ganglionic eminence (LGE), medial ganglionic eminence (MGE), and septum produce region-specific projection neurons (blue arrows). The MGE also serves as the source of pallial (cortical) and striatal interneurons. The generation of these projection neurons and interneurons ceases by the end of embryogenesis. By contrast, the production of olfactory bulb (OB) interneurons and hippocampal dentate gyrus (DG) granule cells (red arrows) begins at embryonic stages and continues beyond birth in the postnatal and adult brain in rodents. Importantly, progenitor domains that produce OB interneurons partially overlap with those for region-specific projection neurons. **(C-H)** Neurogenic/stem cell niches in the postnatal and adult mouse brain. Panel E shows a dorsolateral view of the adult mouse brain (anterior to the left). Panel F shows the locations of two neurogenic/stem cell niches, the VZ-SVZ and hippocampal DG (areas indicated by light blue shades), in a parasagittal view. Panels C and D schematically show the anatomical relationships of the VZ-SVZ with other brain structures in a coronal plane indicated by the left horizontal lines in E and F. Panels G and H show the location of the hippocampal DG in a coronal plane indicated by the right horizontal lines in E and F. Panels C and H are magnified photographic views of the boxed areas in D and G, respectively. In all panels, areas shaded with light blue are where NSCs reside and produce new OB interneurons and DG granule cells (red arrows in C and H, respectively).
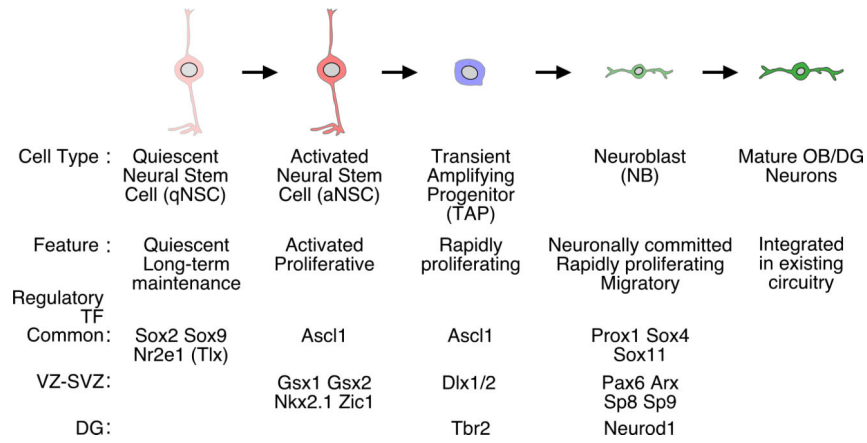
Abbreviations: AC, anterior commissure; CC, corpus callosum; DG, dentate gyrus; LV, lateral ventricle; LGE, lateral ganglionic eminence; Hipp, hippocampus; MGE, medial ganglionic eminence; OB, olfactory bulb; POA, preoptic area; RMS, rostral migratory stream; Sp, septum; St, striatum; Th, thalamus; VZ-SVZ, ventricular-subventricular zone.

| Cell Type :	Quiescent Neural Stem Cell (qNSC)	Activated Neural Stem Cell (aNSC)	Transient Amplifying Progenitor (TAP)	Neuroblast (NB)	Mature OB/DG Neurons
Feature :	Quiescent Long-term maintenance	Activated Proliferative	Rapidly proliferating	Neuronally committed Rapidly proliferating Migratory	Integrated in existing circuitry
Regulatory TF Common:	Sox2 Sox9 Nr2e1 (Tlx)	Ascl1	Ascl1	Prox1 Sox4 Sox11	
VZ-SVZ:		Gsx1 Gsx2 Nkx2.1 Zic1	Dlx1/2	Pax6 Arx Sp8 Sp9	
DG:			Tbr2	Neurod1	

Figure 2.
Stepwise differentiation of NSCs into new neurons through intermediate cell types in the postnatal and adult brain. Intermediate progenitor cell types, and their features and representative regulatory transcription factor (TF) genes are schematically shown. Note that some TFs regulate NSCs in both the VZ-SVZ and DG, whereas others operate in one stem niche but not in the other. For details, see text. Abbreviations: aNSCs, activated neural stem cells; NB, neuroblast; qNSCs, quiescent neural stem cells; TAP, transient amplifying progenitor. Others are the same as Figure 1.
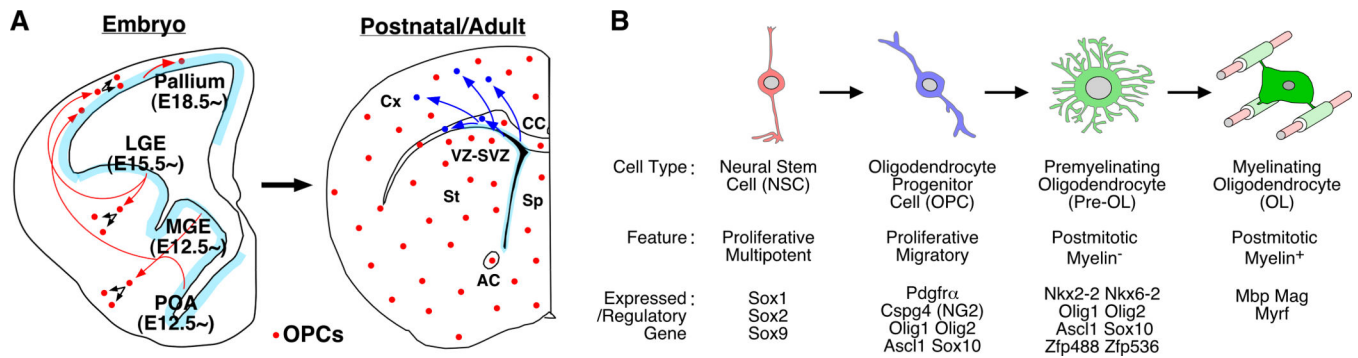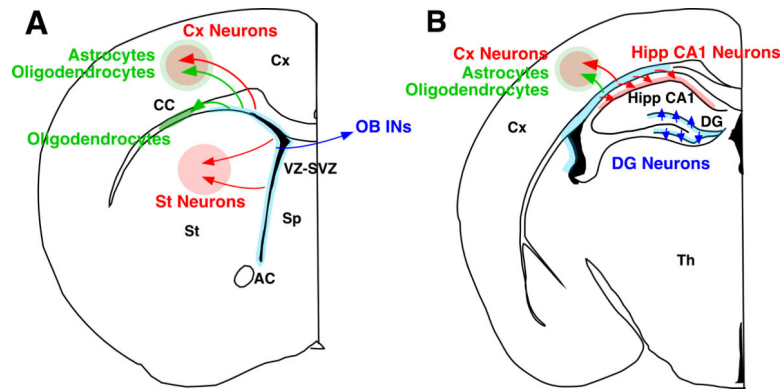
Figure 3.
Continuous production of oligodendrocytes from embryonic to adult stages in the
mammalian brain. (**A**) The left panel schematically shows that multiple progenitor domains
(POA, MGE, LGE, and pallium) generate oligodendrocyte progenitor cells (OPCs) (red
circles) at distinct embryonic stages in the developing mouse telencephalon. Red arrows
indicate their migratory routes. The right panel schematically shows the sustained
production of new OPCs (blue circles) in the VZ-SVZ in the postnatal and adult brain,
which exist as a population separate from embryonically produced OPCs. Note that OPCs
continue cell divisions and increase in number while migrating toward widespread regions of
the brain parenchyma (black arrows). (**B**) Stepwise differentiation of oligodendrocytes from
NSCs. Intermediate progenitor cell types in the oligodendrocyte lineage, and their features
and representative expressed/regulatory genes are schematically shown. For details, see text.
Abbreviations: NSC, neural stem cell; OL, oligodendrocyte; OPC, oligodendrocyte
progenitor cell; Pre-OL, pre-myelinating oligodendrocyte. Others are same as in Figure 1.
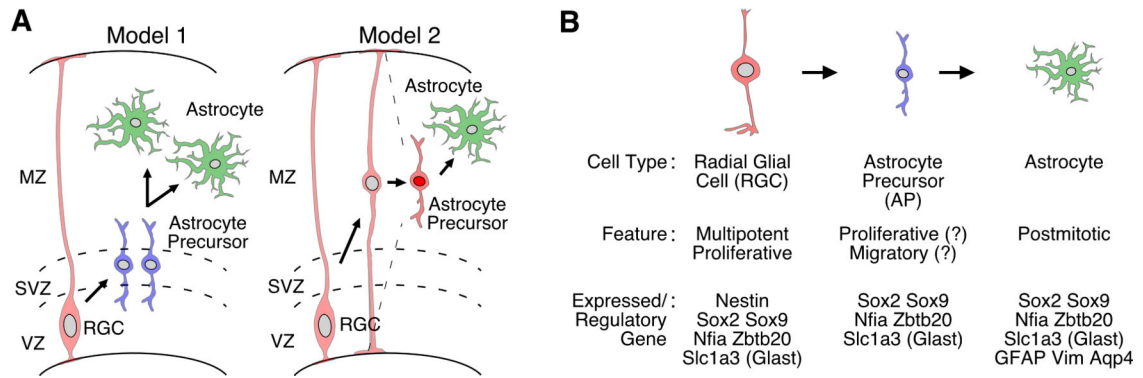
Figure 4.

Production of astrocytes in the mammalian brain. (**A**) Two proposed models for the generation of astrocytes from radial glial progenitors (RGCs) in the developing cerebral cortex (boxed area). (**B**) Proposed stepwise differentiation of astrocytes from NSCs. The features and representative expressed/regulatory genes of RGCs, astrocyte precursors (APs), and astrocytes are schematically shown. Like NBs and OPCs in the neuronal and oligodendrocyte lineages, the occurrence of an intermediate proliferative precursor cell type [astrocyte precursor (AP)] is speculated in the astrocyte lineage, but their exact identity is currently unknown. For details, see text. Abbreviations: MZ, mantle zone. Others are same as in Figure 1.

Figure 5.
Injury-induced neurogenesis and gliogenesis in the postnatal and adult mammalian brain. In the intact brain, NSCs in the VZ-SVZ and DG selectively produce OB interneurons (A) or DG granule cells (B), respectively (blue arrows). In response to various insults, however, those in the VZ-SVZ are thought to produce new neurons and glia (astrocytes and/or oligodendrocytes) that migrate to damaged areas such as the corpus callosum (CC), cerebral cortex (Cx), striatum (St), and hippocampal CA1 region (highlighted in red and green shades), and replace cells lost to insult (red arrows). The exact identity and functional properties of these cells, however, remain poorly understood. Abbreviations are the same as in Figure 1.