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Review

Adult Neurogenesis in the Mammalian Brain: Significant Answers and Significant Questions

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Adult neurogenesis, a process of generating functional neurons from adult neural precursors, occurs throughout life in restricted brain regions in mammals. The past decade has witnessed tremendous progress in addressing questions related to almost every aspect of adult neurogenesis in the mammalian brain. Here we review major advances in our understanding of adult mammalian neurogenesis in the dentate gyrus of the hippocampus and from the subventricular zone of the lateral ventricle, the rostral migratory stream to the olfactory bulb. We highlight emerging principles that have significant implications for stem cell biology, developmental neurobiology, neural plasticity, and disease mechanisms. We also discuss remaining questions related to adult neural stem cells and their niches, underlying regulatory mechanisms, and potential functions of newborn neurons in the adult brain. Building upon the recent progress and aided by new technologies, the adult neurogenesis field is poised to leap forward in the next decade.

Introduction

Neurogenesis, defined here as a process of generating functional neurons from precursors, was traditionally viewed to occur only during embryonic and perinatal stages in mammals (Ming and Song, 2005). Altman's pioneering studies decades ago provided the first anatomical evidence for the presence of newly generated dentate granule cells in the postnatal rat hippocampus (Altman and Das, 1965). Functional integration of new neurons in the adult central nervous system (CNS) was first shown in songbirds (Paton and Nottebohm, 1984). Multipotent neural stem cells were later derived from the adult mammalian brain (Reynolds and Weiss, 1992; Richards et al., 1992). The field of adult neurogenesis took off after the introduction of bromodeoxyuridine (BrdU), a nucleotide analog, as a lineage tracer (Kuhn et al., 1996), and demonstrations of life-long continuous neurogenesis in almost all mammals examined, including humans (Eriksson et al., 1998).

Propelled by a general interest and aided by methodological advancements, significant progress has been made over the past decade in the study of almost every aspect of adult neurogenesis in the mammalian CNS. Active adult neurogenesis is spatially restricted under normal conditions to two specific "neurogenic" brain regions, the subgranular zone (SGZ) in the dentate gyrus of the hippocampus, where new dentate granule cells are generated; and the subventricular zone (SVZ) of the lateral ventricles, where new neurons are generated and then migrate through the rostral migratory stream (RMS) to the olfactory bulb to become interneurons (Figure 1A) (Gage, 2000). Adult neurogenesis is a dynamic, finely tuned process and subject to modulation by various physiological, pathological, and pharmacological stimuli. Neurogenesis in other adult CNS regions is generally believed to be very limited under normal physiological conditions but could be induced after injury (Gould, 2007). Much has been learned about identities and properties of neural precursor subtypes in the adult CNS, the supporting local environment, and sequential steps of adult neurogenesis, ranging from neural precursor proliferation to synaptic integration of newborn neurons (Alvarez-Buylla and Lim, 2004; Duan et al., 2008; Lledo et al., 2006). Studies have also started to illustrate the functional impact of new neurons on the existing neural circuitry and their contributions to brain functions under both normal and disease states (Deng et al., 2010). These areas of research have been very rewarding as they have not only provided significant answers to many fundamental questions about adult neurogenesis but also made a broad impact on general principles of stem cell regulation, neuronal development, structural plasticity, and disease mechanisms. These studies have also led to a number of controversies, intense debates, and conflicting conclusions and models that need to be independently validated. Here we review recent progress on understanding various aspects of adult neurogenesis in the mammalian SGZ/hippocampus and SVZ/olfactory bulb in vivo. Our goal is to provide a global view of the field with a focus on emerging principles and remaining important questions. We will direct readers interested in specific aspects of adult neurogenesis to recent and in-depth reviews.

Neural Stem Cells in the Adult Mammalian Brain

Stem cells exhibit two defining characteristics, the capacity for self-renewal through cell division and the capacity for generating specialized cell type(s) through differentiation (reviewed by Gage, 2000). The current concept of self-renewing and multipotent neural stem cells in the adult mammalian brain has been largely based on retrospective in vitro studies. Cells capable of long-term expansion and differentiation into neurons and glia have been derived from adult rodent brains (Palmer et al.,

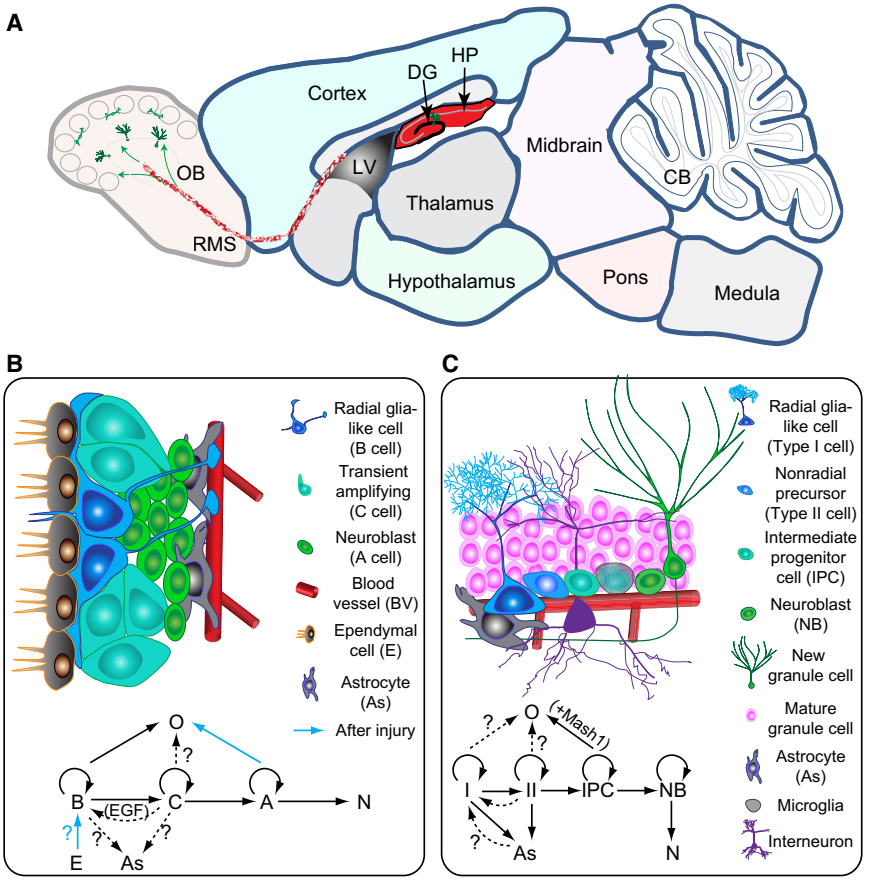

Figure 1. Models of Neural Stem Cells and Lineage Relationship in the Adult Dentate Gyrus and Subventricular Zone

(A) A sagittal section view of an adult rodent brain highlighting the two restricted regions that exhibit active adult neurogenesis: dentate gyrus (DG) in the hippocampal formation (HP), and the lateral ventricle (LV) to the rostral migratory stream (RMS) to the olfactory bulb (OB).

(B) A schematic illustration of the neural stem cell niche in the subventricular zone (SVZ) and a model of potential lineage relationship under basal (solid arrows) and injury conditions (blue arrows). N: immature neurons.

(C) A schematic illustration of the neural stem cell niche in the subgranular zone (SGZ) in the dentate gyrus and a model of potential lineage relationship.

(D) Three lineage models of neural precursors in the adult mammalian brain. In the first model (left), adult neural stem cells ($S_{1,2,3...}$) generated from primitive neural stem cells (S) are intrinsically diverse, exhibiting vastly different developmental potential depending on their regions of distribution and developmental origins. In the second model (middle), adult neural stem cells (S) are relatively homogenous and give rise to a heterogeneous population of lineage-restricted progenitors ($P_{1,2,3...}$). In the third model (right), only lineage-restricted neural progenitors ($P_{1,2,3...}$) are present in the adult brain; self-renewal and multilineage differentiation represent a collective property of a mixture of different lineage-restricted neural progenitors. N: neurons; O: oligodendrocytes; As: astrocytes.

1999; Reynolds and Weiss, 1992; Richards et al., 1992) and humans (Kukekov et al., 1999; Palmer et al., 1995; Roy et al., 2000). The derivation process generally requires long-term culture, which may reprogram and expand the capacity of endogenous cells. Indeed, lineage-restricted neural progenitors, after exposure to growth factors, can acquire properties that are not evident in vivo (Gabay et al., 2003; Kondo and Raff, 2000; Palmer et al., 1999).

Different models have been put forward on the identity and lineage-relationship of putative neural stem cells in the adult mammalian brain (Figures 1B and 1C). In one model (reviewed by Alvarez-Buylla and Lim, 2004), glial fibrillary acidic protein (GFAP)-expressing radial glia-like cells represent quiescent neural stem cells that give rise to neurons in the olfactory bulb and oligodendrocytes in the nearby corpus callosum (Figure 1B). GFAP-expressing radial glia-like cells also generate dentate granule neurons in the adult hippocampus (Figure 1C). The initial support for this model came from evidence of new neuron generation from retrovirus-based lineage tracing under basal conditions and after antimitotic treatment to eliminate rapidly proliferating neural precursors and neuroblasts (Doetsch et al., 1999; Seri et al., 2001). Recent fate-mapping studies in mice using inducible Cre recombinase driven by promoters and enhancers at genomic loci of Gli, GFAP, GLAST (glutamate aspartate transporter), and nestin have provided additional supporting evidence for the concept of radial glia-like cells as the primary precursor to new neurons in the adult brain (reviewed by Dhaliwal and Lagace, 2011). In another model, sex-determining region Y-box 2 (Sox2)-expressing nonradial cells with basal processes are active neural stem cells that give rise to new neurons and glia in the adult SGZ (Figure 1C) (Suh et al., 2007). Lineage tracing of a small number of $Sox2^+$ neural precursors in the adult SGZ for a duration of three weeks has revealed that the majority of labeled cell clusters appears as individual cells and some cell pairs consisting of a $Sox2^+$ precursor and either a neuron or an astrocyte, indicative of limited self-renewal and unipotent differentiation. It is possible that long-term lineage tracing is required to reveal self-renewal and multilineage differentiation by neural precursors in the adult brain. While still under intense debate,

these models are not mutually exclusive and may represent the coexistence of multiple neural stem cell types in the adult brain (Lugert et al., 2010).

A number of significant questions remain regarding neural precursors in the adult mammalian brain. First, almost all studies so far have performed at the population level; thus it remains unknown whether there exist bona fide individual neural stem cells that display the capacity for both self-renewal and multipotential differentiation in the adult mammalian brain. Alternatively, multilineage differentiation and self-renewal may represent a collective property derived from a mixed population of unipotent neural progenitors that are either neurogenic or gliogenic under physiological conditions (Figure 1D). Second, a related question concerns the heterogeneity of adult neural precursor properties (Figure 1D). Do neural precursors in the adult SVZ and SGZ exhibit similar intrinsic properties, despite the fact that SGZ and SVZ neurogenesis produce different neuronal subtypes? Studies of different somatic stem cells have shown significant heterogeneity, even among precursors residing in the same tissue (reviewed by Li and Clevers, 2010). For example, SVZ radial glia-like cells give rise to different interneuron subtypes in the adult olfactory bulb depending on their rostrocaudal location (Merkle et al., 2007). Notably, proliferating neural precursors are present in other CNS regions where they give rise to oligodendrocytes and astrocytes (Barnabé-Heider et al., 2010; Lie et al., 2002; Palmer et al., 1999). There remains significant controversy about whether these precursors generate significant numbers of neurons under physiological conditions in the adult CNS (reviewed by Breunig et al., 2007; Gould, 2007). Do these precursors represent lineage-restricted progenitors or, alternatively, an additional pool of multipotent neural stem cells with their fate dictated by the local environment? The third question is about the lineage relationship among different subtypes of adult neural precursors. When are neuronal and glial fate choices made: at the stage of neural precursors or intermediate progenitors? Are lineage-restricted progenitors, such as $NG2^+$ oligodendrocyte progenitors, related to putative multipotent adult neural stem cells? In the adult olfactory neuroepithelium, horizontal basal cells function as a reservoir to resident neural stem cells and fully reconstitute the neuroepithelium after depletion of resident neuronal precursors by extensive injury (Leung et al., 2007). Is there a similar reserved pool of neural stem cells in the adult CNS? Do they transit through a resident neural precursor stage to give rise to neurons and glia? While still under debate, the ependymal cells lining the ventricles have been proposed as a reservoir of neural stem cells that are recruited after injury (Carlén et al., 2009; Coskun et al., 2008; Mirzadeh et al., 2008). The fourth question regards the origin(s) of different neural precursors in the adult brain. Do adult precursors arise from neural precursors that are also responsible for embryonic neurogenesis? Alternatively, they may be quiescent and set aside as a reserved pool during embryonic neurogenesis.

The major roadblock to answering these questions is the limitation of our current tool box. Cumulative evidence based on marker expression and antimitotic agent treatment suggests that putative adult neural stem cells are mostly quiescent (Doetsch et al., 1999; Morshead et al., 1994; Seri et al., 2001); thus classic lineage-tracing tools, such as BrdU and retroviruses, which require cell division, are not effective for labeling this population. Unlike invertebrate model systems where stem cells can be identified by their position for clonal analysis (reviewed by Li and Xie, 2005), somatic stem cells in mammals are distributed across a large volume of tissue. Despite the significant technical challenges, lineage tracing of precursors at the clonal level in intact animals will provide the temporal and spatial resolution needed to address these fundamental questions (reviewed by Snippert and Clevers, 2011). The effort will be facilitated by new mouse lines in which inducible Cre recombinase is expressed in specific subtypes of neural precursors (reviewed by Dhaliwal and Lagace, 2011), coupled with more versatile reporters, such as the Mosaic Analysis with Double Markers (MADM) (Zong et al., 2005), Confetti (Snippert et al., 2010), and Brainbow systems (Livet et al., 2007). In addition, time-lapse imaging has been very useful for analyses of neural precursors in slices from embryonic rodent and human cortex (Hansen et al., 2010; Noctor et al., 2001). Similar imaging approaches to track individual adult neural precursors in slice cultures, or even in vivo after implantation of a miniature lens (Barretto et al., 2011), will be powerful.

An area of both basic and clinical significance concerns neural stem cells and neurogenesis in adult humans. Despite several innovative approaches, such as BrdU-labeled samples from cancer patients (Eriksson et al., 1998) and ^{14}C labeling from nuclear weapon testing (Spalding et al., 2005), we still know very little about adult human neurogenesis. Because of limitations of tools that can be applied to humans, there is still ongoing debate about the existence of adult SVZ neurogenesis and a prominent RMS of new neurons in humans (Curtis et al., 2007; Sanai et al., 2004; Wang et al., 2011). One direction is to develop better and more reliable endogenous markers for characterization of neural precursors and neurogenesis in postmortem human tissues (Knoth et al., 2010; Wang et al., 2011). Another is to develop new imaging methods for high-resolution, longitudinal analysis of neurogenesis in humans. One study using magnetic resonance imaging appears to be able to identify neural precursors in rodent and human hippocampus through a complex signal-processing method (Manganas et al., 2007), but this approach awaits independent confirmation.

Development of Neural Stem Cells in the Adult Brain

Adult neurogenesis recapitulates the complete process of neuronal development in embryonic stages and we now know a great deal about each of developmental milestones (reviewed by Duan et al., 2008). The rapid progress can be largely attributed to introducing BrdU (Kuhn et al., 1996) and retroviral (van Praag et al., 2002) methods for birth-dating, genetic marking, and phenotypic characterization by immunohistology, confocal and electron microscopy, and electrophysiology.

In the adult SVZ, proliferating radial glia-like cells give rise to transient amplifying cells, which in turn generate neuroblasts (Figure 2). In the RMS, neuroblasts form a chain and migrate toward the olfactory bulb through a tube formed by astrocytes (Lois et al., 1996). Once reaching the core of the olfactory bulb, immature neurons detach from the RMS and migrate radially toward glomeruli where they differentiate into different subtypes of interneurons (reviewed by Lledo et al., 2006). The majority

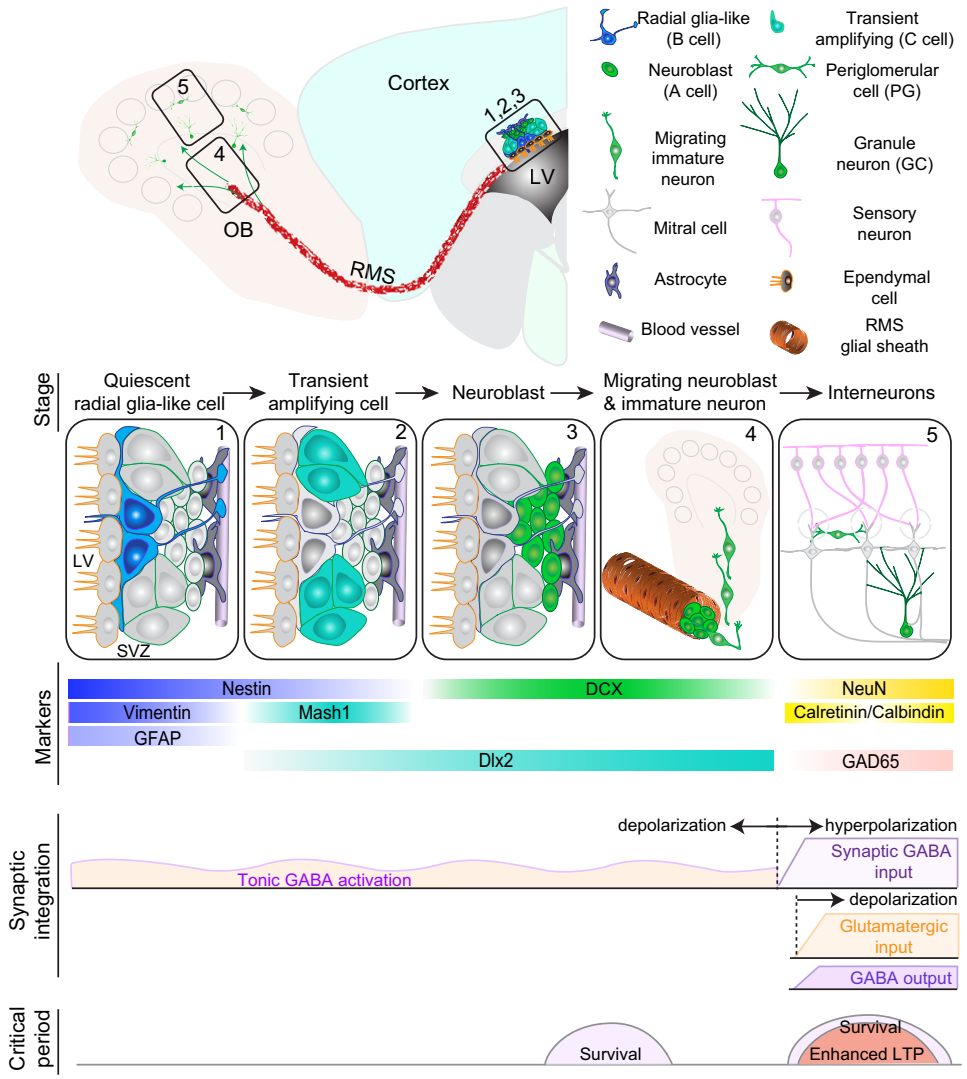

Figure 2. Adult Neurogenesis in the Subventricular Zone of the Lateral Ventricle and Olfactory Bulb

Summary of five developmental stages during adult SVZ neurogenesis: (1) activation of radial glia-like cells in the subventricular zone in the lateral ventricle (LV); (2) proliferation of transient amplifying cells; (3) generation of neuroblasts; (4) chain migration of neuroblasts within the rostral migratory stream (RMS) and radial migration of immature neurons in the olfactory bulb (OB); and (5) synaptic integration and maturation of granule cells (GC) and periglomerular neurons (PG) in the olfactory bulb. Also shown are expression of stage-specific markers, sequential process of synaptic integration, and critical periods regulating survival and plasticity of newborn neurons. GFAP: glial fibrillary acidic protein; DCX: doublecortin; NeuN: neuronal nuclei; LTP: long-term potentiation.

become GABAergic granule neurons, which lack axons and form dendro-dendritic synapses with mitral and tufted cells. A minority become GABAergic periglomerular neurons, a small percentage of which are also dopaminergic. One study suggests that a very small percentage of new neurons develop into glutamatergic juxtaglomerular neurons (Brill et al., 2009). Analysis of labeled precursors and newborn neurons by electrophysiology and confocal imaging, including live imaging in vivo, have revealed physiological properties and sequential stages of neuronal development and synaptic integration (Figure 2) (reviewed by Lledo et al., 2006).

In the adult SGZ, proliferating radial and nonradial precursors give rise to intermediate progenitors, which in turn generate neuroblasts (Figure 3). Immature neurons migrate into the inner granule cell layer and differentiate into dentate granule cells in the hippocampus. Within days, newborn neurons extend dendrites toward the molecular layer and project axons through the hilus toward the CA3 (Zhao et al., 2006). New neurons follow a stereotypic process for synaptic integration into the existing circuitry (Figure 3) (reviewed by Ge et al., 2008). They are initially tonically activated by ambient GABA released from local interneurons (Bhattacharyya et al., 2008; Ge et al., 2006), followed by GABAergic synaptic inputs, and finally glutamatergic synaptic inputs (Espósito et al., 2005; Ge et al., 2006; Overstreet-Wadiche et al., 2006b) and mossy fiber synaptic outputs to hilar and CA3 neurons (Faulkner et al., 2008; Toni et al., 2008). Compared to mature granule cells, newborn neurons exhibit hyperexcitability and enhanced synaptic plasticity during

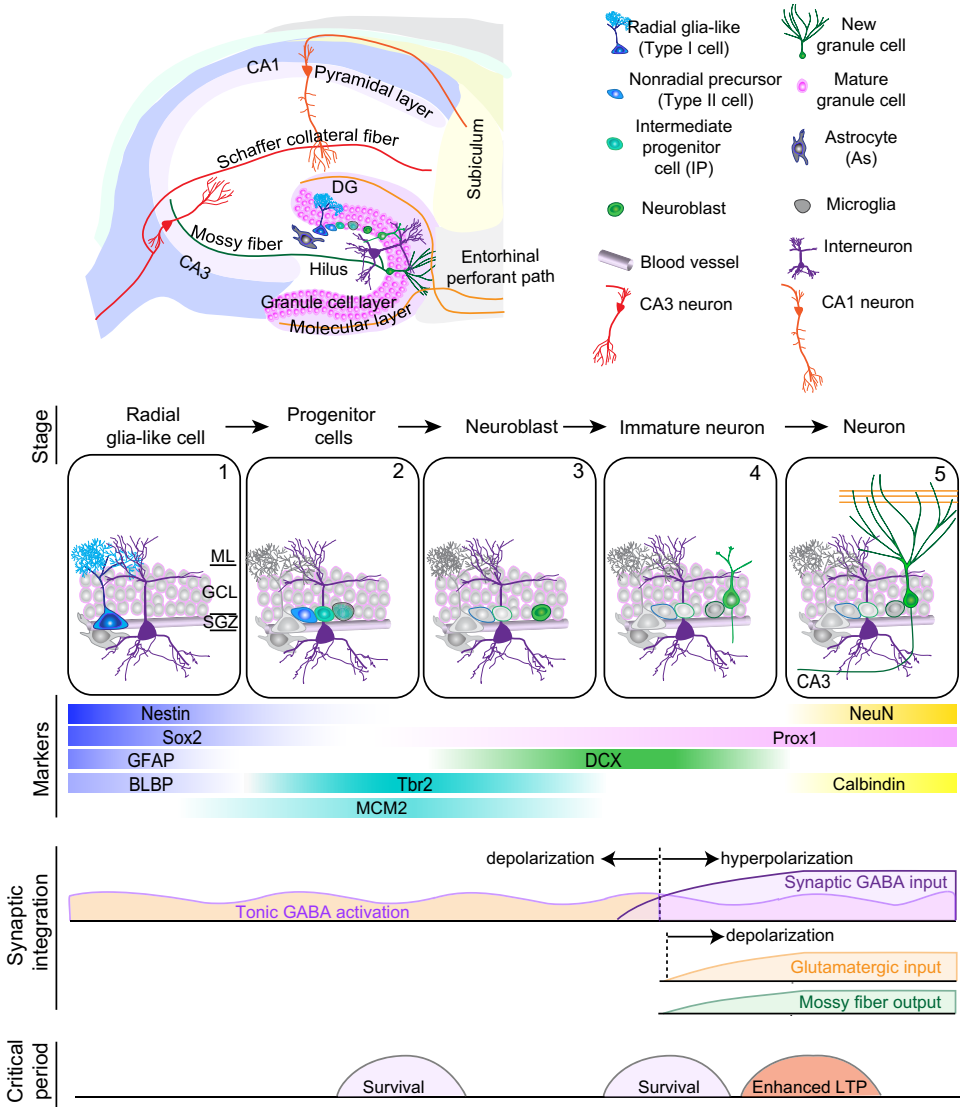

Figure 3. Adult Neurogenesis in the Dentate Gyrus of the Hippocampus

Summary of five developmental stages during adult hippocampal neurogenesis: (1) activation of quiescent radial glia-like cell in the subgranular zone (SGZ); (2) proliferation of non radial precursor and intermediate progenitors; (3) generation of neuroblasts; (4) integration of immature neurons; and (5) maturation of adult-born dentate granule cells. Also shown are expression of stage-specific markers, sequential process of synaptic integration, and critical periods regulating survival and plasticity. ML: molecular layer; GCL: granule cell layer; SGZ: subgranular zone; GFAP: glial fibrillary acidic protein; BLBP: brain lipid-binding protein; DCX: doublecortin; NeuN: neuronal nuclei; LTP: long-term potentiation.

specific developmental stages (Ge et al., 2008; Schmidt-Hieber et al., 2004). After a prolonged maturation phase, adult-born neurons exhibit similar basic electrophysiological properties as mature neurons, such as firing behavior and the amplitude and kinetics of GABAergic and glutamatergic inputs (reviewed by Mongiat and Schinder, 2011), although other properties could still be different.

Several principles have emerged from basic characterizations of the adult neurogenesis process. First, major milestones of neuronal development are highly conserved among embryonic, early postnatal, and adult neurogenesis. As in embryonic development, immature neurons receive GABAergic synaptic inputs before the formation of glutamatergic inputs and are depolarized by GABA due to high expression levels of the chloride importer NKCC1 (Ge et al., 2008). One notable difference is a significantly slower tempo of neuronal maturation in adult compared to embryonic development (Overstreet-Wadiche et al., 2006a; Zhao et al., 2006). The physiological significance of this prolonged development remains unknown, yet acceleration of the maturation tempo sometimes leads to aberrant integration of newborn neurons in the adult hippocampus (Duan et al., 2007; Overstreet-Wadiche et al., 2006b; Parent et al., 1997). Second, precursor subtypes display significant plasticity in their lineage choice (Figures 1B and 1C). DCX^+ neuroblasts in the adult SVZ can be converted to an oligodendrocyte fate upon demyelination of the corpus callosum (Jablonska et al., 2010), whereas

retroviral-mediated Mash1/Ascl1 expression redirects neurogenic intermediate progenitors to an exclusive oligodendocyte lineage in the adult SGZ (Jessberger et al., 2008). Third, there are similar critical periods for specific aspects of adult neurogenesis in both SGZ and SVZ (Figure 2 and Figure 3). Neural progeny survival exhibits two critical periods (Figure 3), one at the intermediate progenitor and neuroblast stage (Platel et al., 2010; Sierra et al., 2010) and one at the immature neuron integration stage (Mouret et al., 2008; Tashiro et al., 2006). Newborn neurons also exhibit enhanced synaptic plasticity of their glutamatergic inputs within a critical period (Ge et al., 2007; Nissant et al., 2009; Schmidt-Hieber et al., 2004). There are two potential physiological consequences of this time-dependent facilitation for associative plasticity of adult-born neurons, which are not mutually exclusive. Such enhanced plasticity may give adult-born neurons an advantage in the competition with mature neurons for selective formation and stabilization of afferent and efferent synaptic connections (Tashiro et al., 2006; Toni et al., 2007). Such properties may also allow integrated adult-born neurons to make a unique contribution to information processing during this period.

There are significant questions remaining. First, when does the neuronal versus glial fate become fixed and how is it determined? Second, given the drastic changes in the local environment, are there any differences between embryonic and adult neurogenesis beyond the maturation tempo? Furthermore, are there any intrinsic differences between neural precursors or newborn neurons during development and in the adult? Do putative adult neural stem cells display a temporally segregated sequence of symmetric self-renewal, neurogenesis, and gliogenesis as occurs during embryonic cortical development (reviewed by Okano and Temple, 2009)? Third, we have limited knowledge about synaptic partners of newborn neurons and potentially dynamic nature of these synaptic interactions. Do embryonic-born and adult-born neurons have different synaptic partners? New technologies, such as optogenetics (reviewed by Zhang et al., 2010), transneuronal tracers (reviewed by Callaway, 2008), and in vivo imaging, will help to address these questions. Fourth, there are significant regional differences in properties of neuronal precursor subtypes along dorso-ventral/rostro-caudal axes in the adult SGZ and SVZ (Merkle et al., 2007; Snyder et al., 2009). How are development and properties of new neurons differentially regulated?

Neurogenic Niche in the Adult Mammalian Brain

First suggested from transplantation studies of hematopoietic progenitors (Schofield, 1978), niches are defined as microenvironments that anatomically house stem cells and functionally control their development in vivo. In the past decades, significant progress has been made in describing stem cell niches at cellular, molecular, and functional levels in several model systems, including *Drosophila* germ line, mammalian skin, intestines, and bone marrow (reviewed by Li and Xie, 2005; Morrison and Spradling, 2008). In the adult brain, the unique niche structure seems to restrict active neurogenesis to two discrete regions and much has been learned about cellular elements that form these neurogenic niches (reviewed by Riquelme et al., 2008; Ihrie and Álvarez-Buylla, 2011 this issue).

Endothelial cells, astrocytes, ependymal cells, microglia, mature neurons, and progeny of adult neural precursors are among major cellular components of the adult neurogenic niche (Figures 1B and 1C). Vascular cells play a prominent role in regulating proliferation of adult neural precursors. The initial suggestive evidence came from observations of increased neuronal differentiation of adult rat SVZ explants in coculture with endothelial cells (Leventhal et al., 1999). In the adult SGZ, dense clusters of dividing cells were found to be anatomically close to the vasculature, especially capillaries (Palmer et al., 2000). In the adult SVZ, the vasculature comprises an extensive network of planar interconnected blood vessels (Shen et al., 2008; Tavazoie et al., 2008). Contacts between adult SVZ precursors and blood vessels are unusually permeable and frequently devoid of astrocyte and pericyte interferences, suggesting that blood-derived cues are gaining direct access to adult neural precursors and their progeny. The vasculature also provides the substrate for new neuron migration after injury in the adult striatum (Kojima et al., 2010). With endfeet surrounding blood vessels, astrocytes form gap junctions and are closely associated with the vasculature and its basal lamina in the adult SVZ and SGZ. They may serve as an interface to modulate influences of endothelial and circulation-derived factors as well as the availability of cytokines and growth factors in the basal lamina. In addition, astrocytes derived from neurogenic hippocampus and SVZ, but not from nonneurogenic spinal cord, promote proliferation and neuronal fate commitment of multipotent adult neural stem cells in culture (Lim and Alvarez-Buylla, 1999; Song et al., 2002). Astrocytes express a number of secreted and membrane-attached factors both in vitro and in vivo that are known to regulate proliferation and fate specification of adult neural precursors as well as neuronal migration, maturation, and synapse formation (Barkho et al., 2006). In the adult SVZ, astrocytes express Robo receptors and regulate the rapid migration of Slit1-expressing neuroblasts through the RMS (Kaneko et al., 2010). Adult SVZ astrocytes also appear to release glutamate to regulate the survival of neuroblasts (Platel et al., 2010). Unique to the adult SVZ, ependymal cells lining the ventricular wall are in close association with neural precursors and their progeny, acting like a shield to protect the neurogenic niche. Ependymal cells actively regulate neuronal fate specification of adult neural precursors through release of Noggin (Lim et al., 2000). Beating of the cilia of ependymal cells appears to set up concentration gradients of guidance molecules to direct migration of neuroblasts (Sawamoto et al., 2006). Microglia also actively regulate adult neurogenesis. Under basal conditions, apoptotic corpses of newly generated neurons are rapidly phagocytosed from the niche by unactivated microglia in the adult SGZ (Sierra et al., 2010). Under inflammatory conditions, reactivated microglia can have both beneficial and detrimental effects on different aspects of adult neurogenesis, depending on the balance between secreted molecules with pro- and anti-inflammatory action (reviewed by Ekdahl et al., 2009). In one study, the activation of microglia and recruitment of T cells were suggested to be required for enriched environment-induced SGZ neurogenesis (Ziv et al., 2006).

Recent studies have begun to reveal the dynamic and plastic nature of the adult neurogenic niche. Via feedback, newborn progeny can regulate the behavior of neural precursors. In both

adult SVZ and SGZ, quiescent radial glia-like cells are rapidly activated to support continuous neurogenesis after eliminating rapidly proliferating progeny with AraC treatment (Doetsch et al., 1999; Seri et al., 2001). In the adult SVZ, neuroblasts release GABA, leading to tonic $GABA_AR$ activation of neural precursors and a decrease in proliferation (Liu et al., 2005). Mature neurons also serve as a niche component critical for activity-dependent regulation of adult neurogenesis through different neurotransmitter systems. In the adult SGZ, local interneurons release GABA, which in turn regulates cell proliferation as well as maturation, dendritic development, and synaptic integration of newborn neurons (Ge et al., 2006; Tozuka et al., 2005). On the other hand, glutamate regulates survival of newborn neurons in the adult SGZ through an NMDAR-dependent mechanism (Tashiro et al., 2006). The adult neurogenic niche also appears to exhibit significant cellular plasticity to maintain integrity under adverse conditions. For example, after severe damage to the ependymal ventricular wall with postnatal Numb/numb-like deletion residual neural progenitors appear to contribute to the repair and remodeling of the SVZ niche (Kuo et al., 2006).

While neurogenic niches for hippocampal and olfactory bulb neurogenesis exhibit many similarities, there are clearly differences. The whole process of hippocampal neurogenesis is physically localized to dentate gyrus. In addition, the SGZ is enriched with different nerve terminals and subjected to dynamic circuit activity-dependent regulation through different neurotransmitters. In contrast, the SVZ does not reside within a dense neuronal network and is physically segregated from the olfactory bulb where integration of new neurons occurs. Future studies are needed to identify cellular and molecular mechanisms by which individual niche components control developmental decisions made at distinct stages of adult neurogenesis. Adult neural precursors also appear to be arranged in a highly organized fashion across the tissue, such as the pinwheel architecture in the adult SVZ (Mirzadeh et al., 2008). How are the "unitary" niche structure and arrangement of each unit established during development? Do different "units" interact with each other for homeostatic tuning of adult neurogenesis? The heterogeneity of adult neurogenesis in subdomains of the SVZ, and potentially also in the SGZ, also raises the question of region-specific organization of the niche. As the niche is a highly dynamic center for complex biochemical signaling and cellular interaction, future studies are needed to address how different niche components and signaling mechanisms interact to orchestrate the complex and precise development of adult neural precursors under different conditions. A comparative analysis of niches in development and in both neurogenic and nonneurogenic adult CNS regions will be fruitful.

Molecular Mechanisms Regulating Adult Neurogenesis

Both intrinsic and extrinsic mechanisms regulate different aspects of adult neurogenesis. Many molecular players and signaling pathways have been identified, including niche factors/receptors, cytoplasmic factors, transcriptional factors, and epigenetic regulators (reviewed by Ma et al., 2010; Mu et al., 2010; Ninkovic and Götz, 2007; Sun et al., 2011). Given the significant similarity between embryonic and adult neurogenesis, it is not surprising that many intrinsic signaling pathways are conserved, although the origin and nature of extrinsic signals could be different.

Extracellular Players

A number of morphogens serve as niche signals to regulate maintenance, activation, and fate choice of adult neural precursors, including Notch, Shh, Wnts, and BMPs. In the adult SVZ, nestin-$CreER^{T2}$-mediated deletion of RBPj, a downstream mediator of all Notch receptors, activates radial glia-like cells to differentiate into transient amplifying cells, resulting in depletion of quiescent neural precursors and loss of continuous neurogenesis (Imayoshi et al., 2010). Similar effects were found in the adult SGZ after deletion of Notch1 or RBPj in neural precursors (reviewed by Pierfelice et al., 2011). Interestingly, Notch signaling also appears to regulate niche components through EphB2 to keep ependymal cells from differentiating into niche astrocytes in the adult SVZ (Nomura et al., 2010). Notably, many Ephrins and Eph receptors regulate cell proliferation in the adult SVZ (Genander and Frisén, 2010). Shh signaling is also activated in radial glia-like cells (Ahn and Joyner, 2005) and required for their establishment and maintenance in the adult SVZ and SGZ (Balordi and Fishell, 2007; Han et al., 2008). On the other hand, Wnt3 promotes proliferation and neuronal fate commitment of neural precursors in the adult SGZ (Lie et al., 2005) and possibly arises from niche astrocytes (Song et al., 2002). In contrast, BMPs promote glia differentiation and inhibit neural differentiation in the adult brain (Bonaguidi et al., 2005; Lim et al., 2000). The BMP action can be antagonized by noggin and neurogenesin-1, which are expressed by SVZ ependymal cells (Lim et al., 2000) and by SGZ astrocytes and granule cells (Ueki et al., 2003), respectively. Blockade of BMP signaling in adult SGZ neural precursors initially leads to their activation and an increase in neurogenesis but subsequently results in depletion of precursors and loss of neurogenesis (Mira et al., 2010). Although the source of most niche signals remains to be fully characterized, it is clear that multiple morphogens are concurrently acting on adult neural precursors to fine tune the number of quiescent precursors and the amount of new neurons and astrocytes in the adult brain. The system may be adapted to ensure sustained neurogenesis over the life span while maintaining exquisite sensitivity to diverse stimuli.

Growth factors, neurotrophins, cytokines, and hormones are also major regulators of adult neurogenesis (reviewed by Zhao et al., 2008). Different phases of adult neurogenesis are subject to regulation by pharmacological manipulations, mostly through various neurotransmitter systems (reviewed by Jang et al., 2008). Both the dentate gyrus and olfactory bulb are enriched with inputs from many brain regions that release different neurotransmitters and neuropeptides. Among classic neurotransmitters, glutamate, GABA, and probably acetylcholine directly regulate migration, maturation, integration, and survival of newborn neurons. In most of other cases, it is not always clear whether pharmacological manipulations act by directly affecting neural precursors and newborn neurons or through indirect modulation of the niche. Interestingly, antidepressants used in clinics, through changes in serotonin and nonrepinephrine levels, increase neural progenitor proliferation, accelerate dendritic development, and enhance survival of newborn neurons in the adult hippocampus (reviewed by Sahay and Hen, 2007; Warner-Schmidt and Duman, 2006).

Our understanding of extracellular cues that regulate targeted neuronal migration, axon/dendritic development, and synapse formation during adult neurogenesis is limited. A number of adhesion molecules (e.g., β1-integrin, PSA-NCAM, Tenascin-R) and extracellular cues (e.g., GABA, NRGs and Slits) are known to regulate the stability, motility, or directionality of neuronal migration during adult SVZ neurogenesis (reviewed by Lledo et al., 2006; Ming and Song, 2005). In the dentate gyrus, reelin signaling prevents new neurons from migrating into the hilus region; loss of reelin expression from local interneurons after pilocarpine-induced seizures may explain the ectopic hilar localization of new granule cells (Gong et al., 2007).

Intracellular Players

Cell-cycle regulators, transcription factors, and epigenetic factors are major intracellular regulators of adult neurogenesis (Zhao et al., 2008). Cell-cycle inhibitors, including p16, p21, and p53, play major roles in maintaining the quiescence of adult neural precursors; deletion of these factors leads to transient activation and subsequent depletion of the precursor pool. Sequential activation of different transcription factors ensures proper development of adult neural precursors. Sox2 is a major mediator of Notch signaling in maintaining the precursor pool in the adult SGZ (Ehm et al., 2010). Shh appears to be a direct target of Sox2 in neural precursors and deletion of Sox2 in adult mice results in a loss of hippocampal neurogenesis (Favaro et al., 2009). Orphan nuclear receptor TLX is also required for self-renewal and maintenance of neural precursors in the adult brain, probably through a canonical Wnt/β-catenin pathway (Qu et al., 2010). Inhibitor of DNA binding (Id) genes encode dominant-negative antagonists of the basic helix-loop-helix transcription factors and Id1 has been shown to be highly expressed in radial glia-like cells in both adult SVZ and SGZ (Nam and Benezra, 2009). FoxOs regulate multiple intracellular signaling pathways and are also required for long-term maintenance of adult neural precursors (Paik et al., 2009; Renault et al., 2009). In contrast, Prox1 (Lavado et al., 2010), NeuroD (Gao et al., 2009; Kuwabara et al., 2009), and Krüppel-like factor 9 (Scobie et al., 2009) are sequentially required for maturation and survival of new neurons in the adult hippocampus. In the adult SVZ, Olig2 specifies transient amplifying cell fate whereas Pax6 and Dlx-2 direct neuronal fate (Doetsch et al., 2002) and promote a dopaminergic periglomerular phenotype in adult mice (Brill et al., 2008; Hack et al., 2005).

Various epigenetic mechanisms play important roles in fine tuning and coordinating gene expression during adult neurogenesis, including DNA methylation, histone modifications, and non-coding RNAs (reviewed by Sun et al., 2011). For example, Methyl-CpG-binding domain protein 1 (Mbd1) suppresses the expression of FGF-2 and several miRNAs to control the balance between proliferation and differentiation during adult hippocampal neurogenesis (Liu et al., 2010). Among many histone modifiers, Mll1 (mixed-lineage leukemia 1), a TrxG member that encodes an H3K4 methyltransferase, is specifically required for neuronal differentiation in the adult SVZ, at least partially through its direct target Dlx2 (Lim et al., 2009). Bmi-1, a member of the PcG complex, is required for neural precursor maintenance in the adult SVZ through the cell-cycle inhibitor p16 (Molofsky et al., 2003). Through silencing Sox2 expression, HDAC2 is required for maturation and survival of newborn neurons in the adult brain, but not embryonic neurogenesis (Jawerka et al., 2010). In addition, several micoRNAs (miR124, 137, and 184) have been shown to fine tune the amount and timing of adult neurogenesis (reviewed by Sun et al., 2011).

Players Associated with Neurological Disorders

A number of neurological disease risk genes have been shown to regulate adult neurogenesis. In the adult SGZ, expression of human presenillin (PS) variants linked to early-onset familial Alzheimer's disease in microglia impairs proliferation and neuronal fate commitment (Choi et al., 2008), whereas deletion of PS1 in forebrain excitatory neurons affects enrichment-induced hippocampal neurogenesis (Feng et al., 2001). PS1 mutants also exhibit impaired self-renewal and differentiation of adult SVZ precursors involving notch signaling (Veeraraghavalu et al., 2010). Deletion of doublecortin (DCX; a gene mutated in most cases of double cortex syndrome) in newborn neurons causes severe morphologic defects and delayed migration along the RMS (Koizumi et al., 2006). In mice deficient in fragile X mental retardation protein (Fmrp; a gene responsible for fragile X syndrome), both proliferation and glial fate commitment of neural precursors are increased in the adult SGZ, through regulation of the Wnt/GSK3β/β-catenin/neurogenin1 signaling cascade (Luo et al., 2010), whereas newborn granule cells in the adult olfactory bulb display increased spine density and length (Scotto-Lomassese et al., 2011). Methyl-CpG-binding protein 2 (Mecp2; a gene mutated in the Rett Syndrome) regulates maturation and spine formation of new neurons in the adult hippocampus (Smrt et al., 2007). Disrupted-in-schizophrenia 1 (DISC1; a gene implicated in major mental disorders) promotes proliferation of neural progenitors through the GSK3β/β-catenin pathway (Mao et al., 2009) while limiting dendritic growth and synapse formation of new neurons through AKT/mTOR signaling in the adult hippocampus (Duan et al., 2007; Faulkner et al., 2008; Kim et al., 2009). These findings raise the intriguing possibility that aberrant postnatal neurogenesis may contribute to the juvenile and adult onset of many mental disorders (reviewed by Christian et al., 2010). Indeed, ablation of Fmrp in adult nestin-expressing precursors disrupts hippocampus-dependent learning and restoration of Fmrp expression specifically in adult nestin-expressing precursors rescues these learning deficits in Fmrp-deficient mice (Guo et al., 2011b).

Players Involved in Activity-Dependent Regulation

The molecular mechanisms underlying activity-dependent adult neurogenesis are starting to be delineated, including the involvement of neurotransmitters, neurotrophins, growth factors, and epigenetic regulators. In the adult SVZ, GABA released from neuroblasts promotes their migration while inhibiting precursor proliferation (Liu et al., 2005). In the adult SGZ, GABA promotes dendritic growth, synapse formation, and survival of newborn neurons through CREB signaling (Jagasia et al., 2009). NMDAR signaling regulates survival of neuroblasts in the adult SVZ (Platel et al., 2010) and immature neurons in the adult SGZ (Tashiro et al., 2006). Furthermore, NR2B is specially required for enhanced synaptic plasticity of newborn dentate granule cells during the critical period (Figure 3B) (Ge et al., 2007; Snyder et al., 2001). Gadd45b and TET1, two epigenetic regulators of active DNA demethylation, promote BDNF and FGF1 expression

in mature dentate granule cells in response to neuronal activation and deletion of Gadd45b reduces activity-induced proliferation of neural precursors and dendritic growth of newborn neurons in the adult hippocampus (Guo et al., 2011a; Ma et al., 2009).

While much has been learned about molecular regulators for different aspects of adult neurogenesis, several areas remain largely unexplored. For example, what regulates symmetric verse asymmetric cell division of adult neural precursors? What controls axon/dendritic guidance and synapse specificity during adult neurogenesis? The combinatorial logic of intrinsic regulators and the hierarchical order have to be established in the near future. Moreover, we need to decipher how extrinsic niche signaling is coupled to the intrinsic machinery. A better understanding of molecular mechanisms regulating adult neurogenesis will require systematic analysis of putative adult neural stem cells and their progeny at different developmental stages, including transcriptome, proteome, epigenetic status, and metabolic states. Recent development of new tools, such as TRAP (Heiman et al., 2008) and Split-Cre (Beckervordersandforth et al., 2010), and advances in the technology of next-generation sequencing and metabolomics will greatly facilitate the effort. A comparative approach between SVZ and SGZ neurogenesis will be particularly instrumental to understand general mechanisms regulating adult neural precursors, neuronal fate commitment, subtype differentiation, development, and integration in the adult brain.

Environmental Regulation of Adult Neurogenesis

One hallmark of adult neurogenesis is its sensitivity to physiological and pathological stimuli at almost every stage, from proliferation of neural precursors to development, maturation, integration, and survival of newborn neurons (Zhao et al., 2008). A large body of literature has accumulated over the past decade demonstrating the impact of these factors (reviewed in Table 1 in Ming and Song, 2005, Table S4 in Zhao et al., 2008, and references therein).

Adult neurogenesis is dynamically regulated by many physiological stimuli. For example, in the adult SGZ, physical exercise increases cell proliferation (van Praag et al., 1999), while an enriched environment promotes new neuron survival (Kempermann et al., 1997). In contrast, aging leads to a significant reduction in cell proliferation in both adult SGZ and SVZ (reviewed by Rossi et al., 2008). Learning modulates adult neurogenesis in a complex, yet specific fashion (reviewed by Zhao et al., 2008). For example, adult SGZ neurogenesis is only influenced by learning tasks that depend on the hippocampus. Subjecting animals to specific learning paradigms mostly regulates the survival of new neurons, and effects depend on the timing of cell birth and learning phases, which can be either positive or negative (Drapeau et al., 2007; Mouret et al., 2008).

Adult neurogenesis is also influenced bidirectionally by pathological states. Seizures increase cell proliferation in both SGZ and SVZ (reviewed by Jessberger and Parent, 2007). In the adult SGZ, seizures also lead to mis-migration of newborn neurons to the hilus, aberrant dendritic growth, mossy fiber recurrent connections (Kron et al., 2010; Parent et al., 1997), and altered electrophysiological properties of GABAergic and glutamatergic synaptic inputs for newborn granule cells (Jakubs et al., 2006). Strikingly, even a transient seizure, induced by pilocarpine (hours) (Parent et al., 1997) or electroconvulsion (minutes) (Ma et al., 2009), leads to sustained increases in precursor proliferation for days and weeks, indicating a form of memory in regulation of neurogenesis by neuronal activity. Another potent inducer of adult neurogenesis is focal or global ischemia (reviewed by Lindvall and Kokaia, 2007). Stroke induces cell proliferation and migration of newborn neurons to infarct sites, the vast majority of which fail to survive over the long term, presumably due to a lack of functional connections and trophic support (Arvidsson et al., 2002). On the other hand, various paradigms of chronic stress lead to decreased cell proliferation in the adult SGZ, whereas the effect of acute stress on cell proliferation and new neuron survival depends on paradigms and species/sex of animals (reviewed by Mirescu and Gould, 2006). The effect of neurodegeneration on adult neurogenesis is also very complex (reviewed by Winner et al., 2011). During neurodegeneration, activation of resident microglia, astrocytes, and infiltrating peripheral macrophages release a plethora of cytokines, chemokines, neurotransmitters, and reactive oxygen species, which in turn affect various aspects of adult neurogenesis. For example, in animal models of Alzheimer's disease, aberrant GABA signaling affects fate specification of neural progenitors and dendritic growth of newborn neurons in the aged SGZ (Li et al., 2009; Sun et al., 2009). In both insulin-deficient rats and insulin-resistant mice, diabetes impairs cell proliferation in the adult SGZ through a glucocorticoid-mediated mechanism (Stranahan et al., 2008). Another major negative regulator of adult neurogenesis is inflammation, induced by injuries, degenerative neurological diseases, and irradiation (reviewed by Carpentier and Palmer, 2009). Inflammation induced by irradiation not only diminishes the proliferative capacity and neuronal fate commitment of neural progenitors in the adult SGZ but also disrupts the local niche with aberrant angiogenesis and increasing number of reactivated microglia cells, resulting in sustained inhibition of neurogenesis from both endogenous and transplanted neural progenitors (Monje et al., 2003).

It is clear that every single phase of adult neurogenesis can be regulated by different stimuli and each stimulus can have multiple targets. Furthermore, different stimuli interact with each other and impact the final outcome of adult neurogenesis. In general, regulation of adult neurogenesis by external stimuli is complex and the effect depends on timing, dose/duration, specific paradigms, animal models (age, sex, genetic background), and methods of analysis. The major challenge is to identify cellular and molecular mechanisms underlying different means of adult neurogenesis regulation. What are targets of a particular stimulation-quiescent putative stem cells, their specific progeny (cell-autonomous effect), or mature cell types from the niche (non-cell-autonomous effect)? Are subregions of SGZ and SVZ/olfactory bulb differentially regulated by the same stimuli? Identification of new markers that divide the neurogenic process into multiple stages and the availability of genetically modified mice for cell type-specific gain- and loss-of-function analysis will significantly accelerate these efforts (Figure 2 and Figure 3). These mechanistic studies may ultimately lead to new therapeutic strategies to enhance functional neurogenesis for regenerative medicine.

Potential Functions of Adult Neurogenesis

In the adult brain, the dorsal and ventral hippocampus has been implicated in learning/memory and affective behaviors, respectively, whereas the olfactory bulb is involved in olfaction. Immediately after the initial discovery of neurogenesis in the postnatal rat hippocampus, Altman suggested that new neurons are critical for learning and memory (Altman, 1967). While still under intensive debate, analyses at the cellular, circuitry, system, and behavioral levels over the past few years have generated mounting evidence supporting critical contributions of adult-born neurons to hippocampal and olfactory bulb functions (reviewed by Deng et al., 2010; Lazarini and Lledo, 2011; see also Aimone et al., 2011 and Sahay et al., 2011 in this issue).

At the cellular level, newborn neurons display special properties that are distinct from mature counterparts. Synaptically connected newborn neurons exhibit hyperexcitability and enhanced synaptic plasticity of their glutamatergic inputs during a critical period of maturation in both hippocampus and olfactory bulb (Figure 2 and Figure 3), which may allow newly integrated adult-born neurons to make unique contribution to information processing. At the circuitry level, adult-born neurons are responsible for certain special properties of the local circuitry. Slice electrophysiology has shown that long-term potentiation (LTP) of evoked field potentials induced by tetanic stimulation of the afferent medial perforant pathway is abolished by radiation to abrogate adult neurogenesis (Snyder et al., 2001). One potential mechanism is a much-reduced sensitivity of newborn neurons to powerful perisomatic GABAergic inhibition from basket interneurons during the critical period (Ge et al., 2008). In vivo recording from the dentate gyrus in anesthetized mice has shown that elimination of adult neurogenesis leads to decreased amplitude in perforant-path evoked responses and a marked increase in both the amplitude of spontaneous γ-frequency bursts in the dentate gyrus and the synchronization of dentate neuron firing to these bursts (Lacefield et al., 2010). At the system level, a number of computational models of adult neurogenesis have provided clues on how the addition of new neurons may alter neural network properties and have suggested distinct roles for adult-born neurons at different stages of neuronal maturation (reviewed by Aimone and Gage, 2011). More importantly, these computational approaches can guide future experiments to specifically test new predictions.

At the behavioral level, the field has gone through the initial stage of correlative studies with manipulations that lack specificity and general behavioral tests, to a stage combining more targeted behavioral tests and sophisticated genetic approaches with enhanced temporal and spatial specificity. While many studies have shown positive correlation between the amount of neurogenesis with performance in specific behavioral tasks, the first causative evidence came from the effect of antimitotic agent MAM to block hippocampal neurogenesis and disrupt trace eye-blink conditioning and trace fear conditioning, but not contextual fear conditioning and spatial memory, all of which are considered hippocampus-dependent forms of memory (Shors et al., 2001). Later studies using irradiation in rodents and more recently using genetically modified mice to inducibly eliminate adult neurogenesis have provided substantial evidence that newborn neurons in the adult brain are required for some, but not all, hippocampus or olfactory bulb-dependent tasks (reviewed by Deng et al., 2010; Lazarini and Lledo, 2011). Because of differences in many parameters, such as the timing, duration and cell types of ablation, paradigms of training and behavioral tests, and animals used (age, sex, and genetic background), it is not surprising to find apparent discrepancies in the literature. Collectively, these studies have suggested significant contribution of adult hippocampal neurogenesis to spatial-navigation learning and long-term spatial memory retention, spatial pattern discrimination, trace conditioning and contextual fear conditioning, clearance of hippocampal memory traces, and reorganization of memory to extrahippocampal substrates (reviewed by Deng et al., 2010; Aimone et al., 2011 in this issue). Adult hippocampal neurogenesis has also been suggested to be required for certain, but not all, antidepressant-induced behavioral responses in specific strains of mice (reviewed by Sahay and Hen, 2007; Sahay et al., 2011 in this issue). The potential role of adult hippocampal neurogenesis in affective behaviors is still under debate. Cumulative evidence has implicated adult olfactory bulb neurogenesis in maintaining long-term structural integrity of the olfactory bulb, short-term olfactory memory, olfactory fear conditioning, and long-term associative olfactory memory involving active learning (reviewed by Lazarini and Lledo, 2011). In addition, olfactory bulb neurogenesis may regulate pheromone-related behaviors, such as mating and social recognition (Feierstein et al., 2010). On the other hand, aberrant adult neurogenesis contributes to pathophysiological states. For example, seizure-induced SGZ neurogenesis may contribute to epileptogenesis and long-term cognitive impairment (Jessberger et al., 2007; Kron et al., 2010).

One fundamental question is how a small number of newborn neurons can affect global brain function. The answer may reside in the capacity of adult-born neurons both as encoding units and as active modifiers of mature neuron firing, synchronization, and network oscillations (Figure 4). First, adult-born neurons are preferentially activated by specific inputs as indicated by immediate early gene expression in both hippocampus (Kee et al., 2007; Ramirez-Amaya et al., 2006) and olfactory bulb (Belnoue et al., 2011). Second, adult-born neurons actively inhibit local circuitry output. In the olfactory bulb, granule neurons and periglomerular neurons inhibit many principal mitral and tufted cells (Figure 4A). In the hippocampus, adult-born dentate granule cells, while making a small number of extremely potent, large mossy fiber connections with target CA3 pyramidal neurons, innervate tens of hilar basket interneurons, each of which in turn inhibits hundreds of mature granule cells in the dentate gyrus (Figure 4B) (Freund and Buzsáki, 1996). Third, adult-born neurons also modify the local circuitry through selective activation of modulatory pathways. One recent study using an optogenetic approach has suggested that newborn neurons contact several distinct subtypes of local interneurons (Bardy et al., 2010), thus introducing dis-inhibition. In the dentate gyrus, granule cells are known to innverate hilar mossy cells, which in turn activate many mature dentate granule cells contralaterally (Figure 4B). Future studies will address this unified hypothesis with a better characterization of anatomical and functional connectivity of adult-born neurons and electrophysiological analysis of both adult-born neurons and network properties in

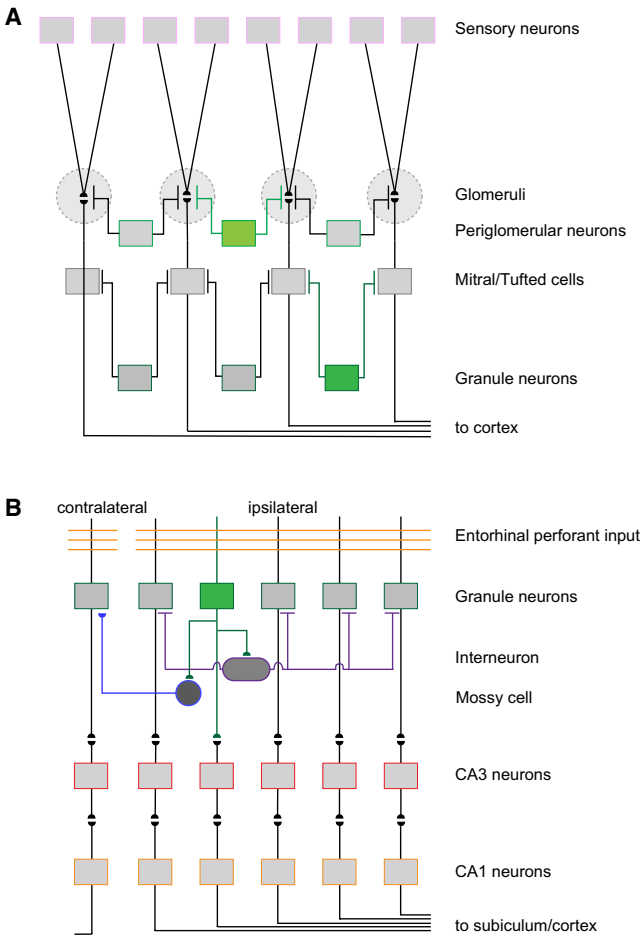

Figure 4. Basic Circuit Architecture of the Olfactory Bulb and Hippocampal Dentate Gyrus and a Unified Model on How New Neurons Impact the Local Circuitry

(A) In the olfactory bulb, primary sensory neurons project to glomeruli where they synapse onto mitral and tufted cells, which in turn relay information to the olfactory cortex. Periglomerular neurons provide lateral inhibition between individual glomeruli, whereas granule cells provide lateral inhibition between mitral and tufted cells. Adult-born interneurons (green), although in small numbers, can have powerful inhibition of the local circuitry in the olfactory bulb. (B) In the hippocampus, layer II entorhinal cortical inputs innervate dentate granule cells, whereas dentate granule cells innervate CA3 neurons, which in turn innervate CA1 neurons. In addition, granule cells synapses onto hilar basket interneurons, each of which inhibit hundreds of mature dentate granule cells. Granule cells also synapse onto hilar mossy cells, which also innervate many mature dentate granule cells on the contralateral dentate gyrus. Adult-born dentate granule cells (green), although in small numbers, can have powerful influence in the local circuitry through basket interneurons and mossy cells.

behaving animals. We also need to understand the contribution of potential modulatory inputs to adult-born neurons from other brain regions, such as centrifugal inputs to the olfactory bulb and dopaminergic inputs to the dentate gyrus (Mu et al., 2011).

The field is poised to make major breakthroughs in understanding functions of adult neurogenesis in animal models, given the recent technical advances. A number of sophisticated genetic models allow targeting of specific subtypes of neural progenitors or newborn neurons at specific maturation stages. Optogenetic approaches permit manipulating the activity of adult-born neurons with exquisite spatial and temporal precision and without the complication of injury responses and homeostatic compensation associated with the physical elimination of adult neurogenesis. With a combinatorial approach for analyses at cellular, circuitry, system, and behavior levels, future studies will clarify how adult neurogenesis may contribute to olfaction, learning, memory, and mood regulation. Furthermore, these studies may identify new functions of adult neurogenesis under physiological states and how aberrant neurogenesis may contribute to mental disorders, degenerative neurological disorders, and injury repair.

Concluding Remarks

The discovery of continuous neurogenesis in the adult mammalian brain has overturned a century old dogma and provided a new perspective on the plasticity of the mature nervous system. In the past decade, the field of adult neurogenesis has turned its focus from documenting and characterizing the phenomenon and its regulation to delineating underlying molecular mechanisms, stem cell regulation, neuronal development, and functional contributions. Many significant questions have been addressed and some basic principles have emerged. There are striking overall similarities between active adult neurogenesis in the two neurogenic regions, including niche composition, signaling pathways maintaining precursor pools, temporal sequence of new neuron integration, critical periods of survival and enhanced plasticity, and contributions to learning and memory. There are also differences between SVZ and SGZ neurogenesis in specific aspects, mainly in the niche organization, neuronal subtype differentiation, and migration of newborn neurons. Adult neurogenesis recapitulates many features of embryonic neurogenesis. Indeed, the adult neurogenesis field has benefit tremendously from our knowledge of embryonic neurogenesis, such as the role of classic morphogens and transcription factors. Genetic analysis of adult neurogenesis is generally challenging and requires inducible and conditional approaches to ensure normal embryonic and early postnatal development. On the other hand, because of its relative simplicity, adult neurogenesis may provide an optimal system to investigate underlying molecular mechanisms and explore functions of susceptibility genes for mental disorders in neuronal development (reviewed by Christian et al., 2010). Indeed, some novel pathways were first identified in adult neurogenesis and later shown to be conserved in embryonic development (Cancedda et al., 2007; Ge et al., 2006). Future comparative studies of embryonic and adult neurogenesis will remain to be fruitful. Significant questions still remain to be addressed regarding clonal properties of adult neural precursor subtypes, organization of the niche, cellular and molecular mechanisms regulating different aspects of neurogenesis under basal and stimulated conditions, contributions of new neurons to normal and aberrant brain functions, and properties and functions of human adult neurogenesis. We also need to have a better understanding whether there are causal relationships between adult neurogenesis and animal behavior and between defects in adult neurogenesis and symptoms of degenerative neurological disorders.

The presence of functional adult neurogenesis throughout life demonstrates the strikingly plastic nature of the adult mammalian brain. While we focused our discussion on newborn neurons, it is important to appreciate that the adult CNS environment is also permissive for continuous structural rearrangement and development of adult-born neurons and that mature neurons can be extremely plastic as they constantly form new functional synaptic connections with adult-born neurons. Given the lack of effective regeneration after injury for neurons in the adult mammalian CNS (reviewed by Kim et al., 2006), more effort needs to be devoted to investigate the plastic nature of the adult CNS in general. Building upon the exciting recent progress and development of new tools, the adult neurogenesis field is poised to make another giant leap forward. These adventures will not only address major questions related to adult neurogenesis, but will also reveal general principles of stem cell biology, neuronal development, and plasticity, as well as novel insights into functions of the hippocampal and olfactory circuitry and new strategies for treatment of neurological and psychiatric disorders.

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