Modification of Hippocampal Circuitry by Adult Neurogenesis

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ABSTRACT: The adult hippocampus is one of the primary neural structures involved in memory formation. In addition to synapse-specific modifications thought to encode information at the subcellular level, changes in the intrahippocampal neuro-populational activity and dynamics at the circuit-level may contribute substantively to the functional capacity of this region. Within the hippocampus, the dentate gyrus has the potential to make a preferential contribution to neural circuit modification owing to the continuous addition of new granule cell population. The integration of newborn neurons into preexisting circuitry is hypothesized to deliver a unique processing capacity, as opposed to merely replacing dying granule cells. Recent studies have begun to assess the impact of hippocampal neurogenesis by examining the extent to which adult-born neurons participate in hippocampal networks, including when newborn neurons become engaged in ongoing network activity and how they modulate circuit dynamics via their unique intrinsic physiological properties. Understanding the contributions of adult neurogenesis to hippocampal function will provide new insight into the fundamental aspects of brain plasticity, which can be used to guide therapeutic interventions to replace neural populations damaged by disease or injury. © 2012 Wiley Periodicals, Inc. Develop Neurobiol 72: 1032–1043, 2012

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INTRODUCTION

The seminal discovery of postnatal neurogenesis by Altman and Das in the 1960s overturned a long-held dogma that the adult mammalian brain is mainly a postmitotic structure lacking the capacity to regenerate neurons. Two discrete "neurogenic" regions have since been identified in the adult rodent and primate brains using tritiated thymidine labeling of proliferating cells – namely, the subventricular zone (SVZ) of the lateral brain ventricles, and the subgranular zone (SGZ) of the dentate gyrus in the hippocampus (Lledo et al., 2006; Zhao et al., 2008). New neurons in these regions originate from a residential population of adult neural stem cells (NSCs; Gage, 2000; Alvarez-Buylla and Lim, 2004; Ma et al., 2009). Although NSCs may arise in other regions of the adult brain under pathological conditions and following injuries (Ming and Song, 2005), it remains controversial whether, and to what extent, active neurogenesis occurs outside of the SVZ and SGZ under physiological conditions. In the present review, we will focus on adult SGZ neurogenesis within the local hippocampal network.

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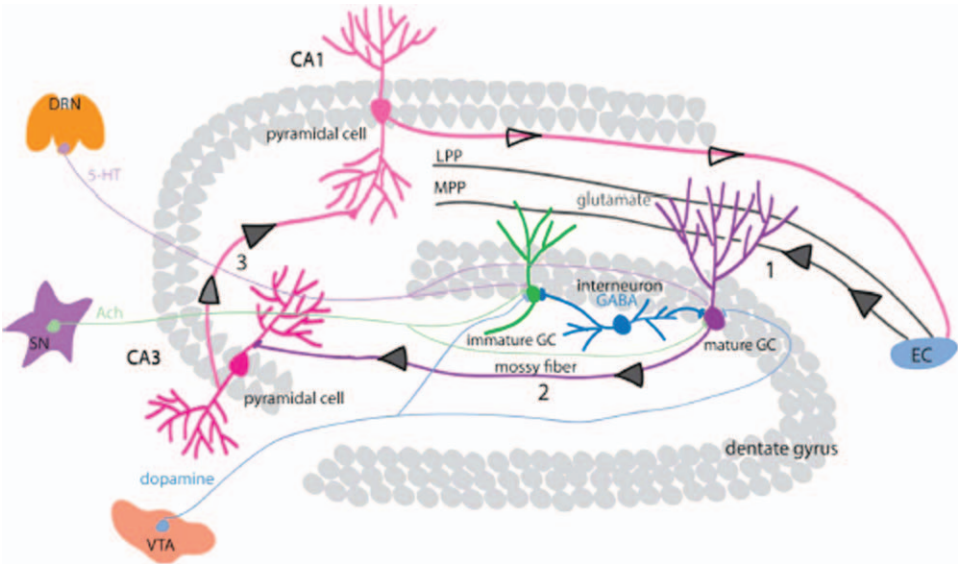

Figure 1 Trisynaptic circuits of the hippocampal network. A diagram of the transversal section of the hippocampus shows the different subregions: DG, CA3, and CA1. The principle cells located in densely packed cell layers are synaptically connected via "trisynaptic circuit". Mature and newborn granule cells receive their major synaptic input from the medial and lateral perforant path (MPP and LPP) that originates from the entorhinal cortex (EC) (1). Granule cells send their axons (mossy fibers) that terminate on the proximal dendrites of CA3 pyramidal cells (2). CA3 pyramidal cells send axons (Schafer collateral axons) to CA1 pyramidal cells (3), whose axons in turn projects back to the EC. Inhibitory interneurons (such as basket cells) provide a dense network of GABAergic synaptic boutons within the granule cell layer and SGZ, innervating both mature and newborn granule cells. Hippocampal circuitry is subject to the regulation by various synaptic inputs: glutamate from EC, GABA from local interneurons, serotonin (5-HT) from dorsal raphe nucleus (DRN), Ach (acetylcholine) from septal nucleus (SN), and dopamine from ventral tegmental area (VTA). NSC: neural stem cell; NPC: neural progenitor cell. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Adult hippocampal neurogenesis is a complex, multistep process that is highly regulated by existing neuronal network activity (Kempermann et al., 2004; Ma et al., 2009; Ming and Song, 2011). At the cellular level, the origin and development of NSCs in the adult mouse brain have been examined using a combination of immunohistological, electrophysiological, imaging and genetic approaches. Given the central role of the hippocampus in many forms of learning and memory, the potential contribution of adult neurogenesis to these processes at the system level has been a central question in the field. Specifically, how does the dynamic composition of the dentate granule cell population alter the information processing capacity of the hippocampus as a whole? Recently, much progress have been made in understanding how adult neurogenesis is regulated by mature circuitry in an activity-dependent manner, and in turn how newborn neurons affect the existing circuitry at the circuit and behavioral levels. Understanding the basic mechanism regulating adult neurogenesis and their contribution to brain functions is important for both basic biology and for clinical applications if we are to harness cell replacement potential to help repair the injured, diseased and aged central nervous system (Goh et al., 2003).

ADULT MAMMALIAN HIPPOCAMPAL CIRCUITRY

The hippocampal neural network is highly dynamic, with the capacity to modify its connectivity by changing the number and strength of synaptic contacts in an activity-dependent manner. Hippocampal principal neurons are located in three primary subregions: granule cells in the dentate gyrus (DG), and pyramidal neurons in CA1 and CA3. The principal neurons are synaptically connected to form the "trisynaptic circuit" (Fig. 1). Within this trisynaptic circuit, information flows from entorhinal cortex (EC), the afferent input to the DG through medial and lateral perforant pathways, then to CA3 pyramidal

cells via mossy fibers (axons of DG granule cells), then to CA1 pyramidal cells via Schaffer collateral projections (axons of CA3 neurons), then to the subiculum and back to the EC (Claiborne et al., 1986; Kohler, 1986). This primary hippocampal projection pattern forms a closed loop wherein sensory information from specific cortical areas converges onto the EC through excitatory pathways, processed through the hippocampal circuitry, and returns to the cortical region of origin EC (Li et al., 2009). Besides principal excitatory neurons that form the trisynaptic circuit, another major component in the hippocampus is the inhibitory interneurons that release GABA, which is important for the generation of field potential oscillations. Furthermore, adult hippocampal circuitry is under the influence of multiple modulatory neurotransmitters, such as acetylcholine from septal nucleus, serotonin from dorsal rophe nucleus, and dopamine from ventral tegmental area. In addition to activity-induced changes at the synapse, a unique feature to this circuitry is the large-scale structural modification via the addition of new granule cells arising from ongoing neurogenesis. The entire milieu must preserve the functional integrity of the existing circuitry, and at the same time, it needs to provide a niche to support the development of adult-born granule cells and allowing these cells to modify the local neuronal network.

DEVELOPMENT OF ADULT NEURAL STEM CELLS

Among hippocampal principal cells, only granule cells are continuously generated throughout adulthood in the dentate gyrus. Self-renewing and multipotent NSCs residing in the SGZ, a narrow band of tissue lying between the granule cell layer and the hilus, give rise to both neurons and astrocytes, but not oligodendrocytes (Bonaguidi et al., 2011). The development of newborn neurons in the adult hippocampus can be divided into five distinct phases: (i) Stem cell maintenance, activation and fate specification; (ii) expansion of intermediate neural progenitors; (iii) migration and initial pruning of newborn granule cells; (iv) maturation and functional integration of newborn neurons; and (v) late-phase maturation and maintenance of adult-born neurons (Fig. 2). It is estimated that the entire neurodevelopmental process takes approximately 7–8 weeks in the young adult mouse brain (Zhao et al., 2006).

Stem Cell Maintenance, Activation, and Fate Specification

Adult hippocampal neurogenesis originates from a population of NSCs in the SGZ. It appears that multiple types of NSCs, such as radial and nonradial precursors, coexist in the adult SGZ (Lugert et al., 2010). Radial glia-like cells have been traditionally classified as Type I cells, which are infrequently labeled by retroviruses or BrdU, indicative of their quiescence state. Morphologically, radial glia-like NSCs possess a long process that extends and branches into the inner molecular layer. Biochemically, these cells express glial fibrillary acidic protein (GFAP), the intermediate filament protein Nestin, a radial glia marker BLBP, and the Sry-related HMG-box transcription factor Sox2. Despite expressing several astrocytic markers, the radial glia-like NSCs are morphologically and functionally distinct from mature astrocytes. Recent fate mapping studies using inducible Cre recombinase driven by various promoters or enhancers, including Gli, GFAP, Nestin, and GLAST (glutamate aspartate transporter), have provided evidence in support of radial glia-like cells as the primary NSCs in the adult brain (Dhaliwal and Lagace,

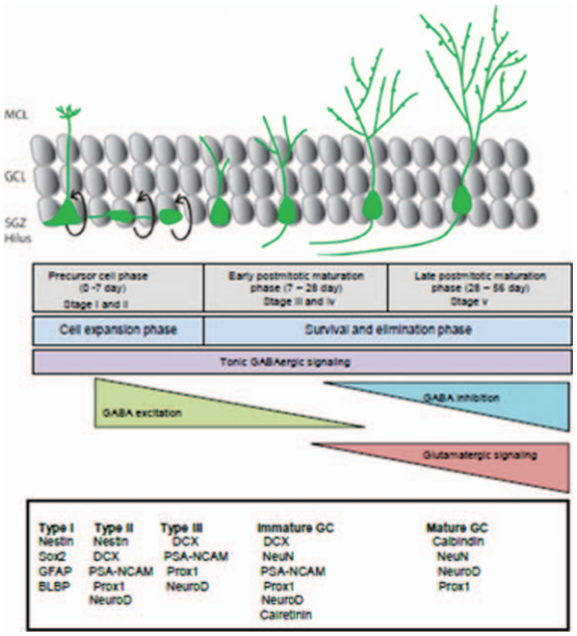

Figure 2 Adult neurogenesis in the dentate gyrus of the hippocampus. Shown is a schematic summary of the developmental stages of dentate neurogenesis as characterized by estimated timeline for each developmental stage. Physiological properties and expression of specific molecular markers at each stage are also shown. MCL, molecular cell layer; GCL, granule cell layer; SGZ, subgranular zone. GFAP, glial fibrillary acidic protein; BLBP, brain lipid-binding protein; DCX, doublecortin; NeuN, neuronal nuclei; PSA-NCAM: the polysialylated form of the neural cell adhesion molecule NCAM; GABA, γ-aminobutyric acid. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

2011). *In vivo* clonal analysis using a novel genetic labeling approach has demonstrated that radial glia-like cells are capable of both self-renewal and multipotent differentiation into neurons and astrocytes (Bonaguidi et al., 2011). Critically, the maintenance and activation of these quiescent population of cells appears to be dynamically regulated by experience and aging (Dranovsky et al., 2011; Encinas et al., 2011). The clonal properties of nonradial NSCs and how the behavior of these cells is regulated *in vivo* remain to be further characterized.

Expansion of Intermediate Neural Progenitors

In the adult SGZ, NSCs give rise to Type II intermediate progenitors, which in turn generate neuroblasts (Type III). Distinct subpopulations of actively proliferating intermediate progenitors can be identified according to their specific morphologies, electrophysiological properties, and molecular marker expression (Seri et al., 2001, 2004). Morphologically, horizontal cellular processes are prominent in these progenitor cells (Fukuda et al., 2003; Steiner et al., 2006). Interestingly, the proliferation of Type II cells is subject to activity-dependent regulation through either physiological stimuli such as voluntary wheel running (Kronenberg et al., 2003) or pharmacological stimulation, such as antidepressant treatment (Encinas et al., 2006). Type III cells express markers of neuronal lineage (DCX, PSA-NCAM, NeuroD, and Prox1), and transiently express the calcium-binding protein calretinin (Brandt et al., 2003). Morphologically, Type III cells possess processes of various lengths and complexities, and the orientation of their processes incrementally changes from horizontal to vertical. These cells are believed to have limited proliferative activity and thus considered to be a transitional cell type from proliferating neuroblasts to postmitotic immature neurons. Under pathological conditions, such as seizures, Type III cells display an aberrant state characterized by dramatically increased proliferation (Jessberger et al., 2005).

Migration and Initial Pruning of Newborn Neurons

In the dentate gyrus, newborn neurons migrate to the inner granule cell layer and elaborate axon and dendritic processes to CA3 and molecular layer, respectively. Recent studies suggest that migration of newborn granule cells is tightly regulated. For example, knockdown of Disrupted-in-Schizophrenia 1 (DISC1) in newborn granule cells leads to overextended migration to the molecular layer (Duan et al., 2007). On the other hand, loss of Reelin expression from local interneurons in an animal model of seizures results in the ectopic hilar localization of newborn granule cells (Gong et al., 2007). During this early stage of development, a significant percentage of newborn progeny is eliminated through apoptosis and microglia-mediated phagocytosis (Sierra et al., 2010). The survival of newborn neurons can also be influenced by the experience of animals, such as spatial learning and exposure to an enriched environment (Tashiro et al., 2006, 2007).

Maturation and Synaptic Integration of Newborn Neurons

Functional integration of newborn granule cells *in vivo* depends on the formation of synaptic input and output with other neurons in the hippocampal circuitry. Dendritic and axonal (mossy fiber) development initiates immediately upon exit of immature neurons from the cell cycle. It was recently demonstrated that synaptic integration with afferent projections from the entorhinal cortex depends on the emergence and assembly of primary cilia that occurs between 14 and 21 after the birth of adult born granule cells (Kumamoto et al., in press). Mossy fibers can be detected around 10 days after cell birth and gradually grow and reach CA3 region before spines are formed (Hastings and Gould, 1999; Zhao et al., 2006). Newborn neurons exhibit very similar axonal and dendritic projection patterns to the neighboring mature neurons upon maturation, as revealed by retrovirus-mediated labeling (Zhao et al., 2006). For example, at 6–8 weeks of age, newborn neurons display overall morphological and functional characteristics very similar to that of fully mature dentate granule cells (van Praag et al., 2002; Ambrogini et al., 2004; Schmidt-Hieber et al., 2004). Additionally, high-resolution morphological studies using electron tomography and serial section electron microscopy confirmed that new granule cells at 30 days of cell age receive a variety of synaptic inputs from axosomatic, axodendritic, and axospinous connections comparable to mature neurons. The functional integration of newborn granule cells into the existing hippocampal circuitry have been studied in much detail by electrophysiological recording of these cells, either labeled by engineered onco-retrovirus (Song et al., 2005; Ge et al., 2006) or marked in transgenic reporter mice (Overstreet et al., 2004; Overstreet-Wadiche et al., 2006; Markwardt and Overstreet-Wadiche, 2008; Markwardt et al., 2009). These studies have revealed that synaptic integration of newborn granule cells fol-

lows a stereotypic sequence, similar to that observed in embryonic and early postnatal development (Fig. 2): 1) Initial activation of newborn neurons is nonsynaptic, which is mediated by ambient GABA present in the local milieu; 2) Newborn neurons become activated by synaptic transmission from local interneurons through input-specific GABAergic signaling; 3) GABAergic inputs are converted from excitatory to inhibitory, and concomitantly, excitatory glutamatergic dendritic inputs begin to activate the developing neurons; 4) Finally, inhibitory GABA synaptic inputs begin to appear at perisomatic synapses to complete the mature granule cell innervation pattern.

Late-Stage Maturation and Maintenance of Adult-Born Neurons

This phase represents the fine-tuning stage of the hippocampal circuitry in response to ongoing activity. To date, little is known about the adaptive changes that occur in this late neurodevelopmental phase of adult neurogenesis. Although new granule cells undergo a switch in the expression of calcium-binding proteins from calretinin to calbindin, it takes several more weeks to become electrophysiologically indistinguishable from their mature counterparts (van Praag et al., 2002). One unique trait of new neurons at this stage is that they exhibit enhanced synaptic plasticity (Schmidt-Hieber et al., 2004; Ge et al., 2007), which may facilitate integration in order to achieve long-term changes in the network (Ramirez-Amaya et al., 2006; Wiskott et al., 2006). Such enhanced plasticity is suggested to give adult-born neurons an advantage in competing with mature neurons for selective formation and stabilization of afferent and efferent synaptic connections (Tashiro et al., 2006; Toni et al., 2008). Functionally, this unique physiological property of newborn granule cells after integration may contribute to the plasticity of the hippocampal network (Ge et al., 2008). Once mature, adult-born neurons are maintained throughout life (Kempermann et al., 2003).

ACTIVITY-DEPENDENT REGULATION OF ADULT HIPPOCAMPAL NEUROGENESIS

Adult neurogenesis is highly sensitive to neuronal activity within the hippocampal circuitry and is regulated at multiple developmental stages, including alterations in the activation of radial glia-like NSCs and in the rate of precursor cell proliferation, changes in the survival of newborn neurons, and strategic synaptic integration of newborn neurons.

Activity-dependent regulation of hippocampal neurogenesis has been examined under several physiological conditions. For instance, enriched physical environment affects neurogenesis by enhancing the survival of newborn neurons (Leuner et al., 2006; Drapeau et al., 2007; Sisti et al., 2007). On the other hand, the neurogenic effects of physical exercise, such as voluntary wheel running or forced treadmill, appear to be due to an increase in the proliferation of intermediate precursor cells (van Praag et al., 1999). Interestingly, some forms of learning and memory behavioral paradigm, such as trace eye-blink conditioning and Morris water maze, two hippocampal dependent tasks, increase the number of newly generated neurons (Leuner et al., 2006). In contrast, hippocampal-independent learning tasks, such as delay eye-blink conditioning and active shock avoidance, have little to no effect on neurogenesis (Gould et al., 1999; Leuner et al., 2006). An interesting example comes from the study of interaction of spatial learning and hippocampal neurogenesis (Dupret et al., 2007). The acquisition of spatial memory appears to have a differential effect on the survival of newborn neurons at different developmental stages. When 7-day-old newborn neurons were monitored, the water maze paradigm elicits an increase in neurogenesis. However, when 3-day-old newborn neurons were monitored, there is actually a decrease in survival due to increased apoptosis. This study demonstrates that spatial learning can selectively stabilize a population of new neurons, and this tightly regulated sculpture of hippocampal network is in turn important for memory formation. Similarly, LTP induction in the hippocampus, which is thought to be associated with the mechanism for memory formation and retention, has been shown to increase dentate progenitor proliferation and promote survival of new neurons of 1–2 weeks of cell age (Bruel-Jungerman et al., 2006).

Hippocampal neurogenesis is also affected by aging, seizures, and antidepressant treatments. For example, seizure activity induces aberrant proliferation of both intermediate neural progenitors and neuroblasts, and results in abnormal morphological development and ectopic migration of newborn granule cells (Overstreet-Wadiche et al., 2006; Parent, 2007). Furthermore, this seizure-induced production of newborn neurons can integrate into the hippocampal circuitry and contribute to seizure-associated cognitive deficits. A drastic reduction of adult hippocampal neurogenesis is known to associate with aging, resulting from the depletion of NSCs, alterations in precursor properties, and changes in the hippocampal niche (Fabel and

Kempermann, 2008). Antidepressants used in clinics have also been shown to regulate adult hippocampal neurogenesis by increasing neural progenitor proliferation, accelerating dendritic development, and enhancing survival of newborn neurons, presumably though indirect modulation of the niche (Warner-Schmidt and Duman, 2006; Sahay and Hen, 2007).

MOLECULAR MECHANISMS UNDERLYING ACTIVITY-DEPENDENT REGULATION OF ADULT HIPPOCAMPAL NEUROGENESIS

A critical question is how hippocampal network activity is translated into regulation of adult neurogenesis and which signals are responsible for driving the changes at different stages. SGZ NSCs and progenitor cells reside within a complex microenvironment and their behavior can be influenced by a plethora of modulatory factors from many brain areas through different neurotransmitters (Fig. 1) - in particular, GABA and glutamate, the major inhibitory and excitatory neurotransmitters in the adult brain, respectively. The release of neurotransmitters is a direct outcome of network activity and can affect hippocampal neurogenesis via two forms: either through synaptic transmission, sometimes called "phasic activation" or through "tonic activation" (Ge et al., 2007). Tonic activation describes a phenomenon that the activation of receptors is triggered by an ambient level of neurotransmitter due to their diffusion from the synapses within the local microenvironment. Tonic signaling has distinct attributes that make it an important regulator of neurodevelopment. First, tonic signaling transcends individual presynaptic/postsynaptic cellular pairs, thus it provides a means for a spatial regulation that can influence cells located at some distance. Second, the ambient neurotransmitter level may represent an integrated signal to translate the overall local network activity. Indeed, several studies show that GABA is released from local interneurons and tonically activate progenitors and immature neurons (Ge et al., 2006; Platel et al., 2008). Interestingly, a recent study showed that both tonic and phasic GABA activation of neural progenitors and immature neurons are modulated by the chemokine stromal cell-derived factor 1 (SDF-1), which is coreleased with GABA from local interneurons (Bhattacharyya et al., 2008; Kolodziej et al., 2008).

Glutamate signaling has long been implicated in regulating adult hippocampus neurogenesis. Injection of NMDA rapidly decreases cell proliferation in the adult rat DG, whereas injection of an NMDAR antagonist exhibits the opposite effect (Cameron et al., 1995; Nacher et al., 2001). On the other hand, induction of LTP at the glutamatergic medial perforant path-granule cell synapses promotes the proliferation of adult neural progenitors and survival of newborn neurons in a NMDAR-dependent fashion (Bruel-Jungerman et al., 2006; Chun et al., 2006). These findings highlight the complexity of glutamate signaling in regulating adult neurogenesis, which is likely to involve both cell autonomous effects in immature neurons and noncell autonomous effects through existing neural circuits. Genetic deletion of NR1 in proliferating adult neural progenitors reduces the survival of their neuronal progeny 2–3 weeks after they are born (Tashiro et al., 2006). Interestingly, injection of an NMDAR antagonist diminishes differences in NMDA receptor signaling in all new neurons and promotes the survival of these NR1 knockdown neurons, suggesting a critical period for NMDAR-dependent competitive survival of newborn neurons in the adult brain. Of note, this critical period coincide with a transition from excitatory to inhibitory GABA signaling. Whether GABA cooperates with glutamate signaling in regulating the survival of new neurons during this critical period remains to be determined. Analysis of the plasticity of glutamatergic synaptic inputs onto newborn granule cells during their maturation process has identified another critical period during which recently born neurons exhibit enhanced LTP. New neurons within 4–6 weeks of birth exhibit both a reduced induction threshold and increased LTP amplitude in response to a physiological pattern of stimulation (Ge et al., 2007). Interestingly, this critical period is associated with developmentally regulated NR2B-containing NMDARs in adult-born neurons, because pharmacological inhibition of these receptors completely abolished LTP in these young neurons, but not in mature neurons.

Other neurotransmitters such as serotonin and dopamine also exert regulatory effects on adult SGZ neurogenesis (Fig. 1). Serotonergic neurons originating from the dorsal raphe nuclei (DGN) send projections to the dentate gyrus and serotonergic signaling has been implicated in mood regulation (Jacobs et al., 2000; Suh et al., 2009). Increased serotonin transmission is positively linked to hippocampal neurogenesis, as evidenced by enhanced neurogenesis following antidepressant treatments that act on serotonin transporters (Malberg et al., 2000; Santarelli et al., 2003). Similar to serotonergic effects, denervation of dopaminergic neurons decreases proliferation of NSCs in the SGZ (Hoglinger et al., 2004). A recent study showed that dopamine is particularly effective in modulating the activities of hyperexcitable young neurons (but not mature neurons) by decreasing their

capacity to express LTP, suggesting that dopamine may play a role in gating afferent information to the hippocampus (Mu et al., 2011).

Diffusible molecules produced by local cells can also influence hippocampal neurogenesis. Growth factors, including neurotrophins and developmental cues, play critical roles in regulating NSCs and their progeny (Ma et al., 2005; Schmidt and Duman, 2007). Given the possibility that systemic diffusible factors might be involved in the activity-dependent control of adult neurogenesis, early efforts have been made to identify circulating factors that mediate enhanced neurogenesis by exercise. Two factors identified from these studies are insulin-like growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF), both of which were shown to be necessary in mediating the exercise-induced increase of neurogenesis (Trejo et al., 2001; Fabel et al., 2003). Blocking either factor prevented the exercise-induced increase in SGZ neurogenesis. In addition, growth factors such as epidermal growth factor (EGF) and fibroblast growth factor 2 (FGF2) are critical for the maintenance of adult NSCs *in vitro*. Although infusion of FGF2 does not affect SGZ proliferation in young mice, deletion of *fgfr1* (FGF receptor 1) in the CNS decreases SGZ neurogenesis, indicative of a permissive role of FGF2 signaling in SGZ proliferation (Zhao et al., 2007). Furthermore, conditional ablation of TrkB, the high-affinity receptor for BDNF, in both embryonic and adult-born NSCs led to an impairment of hippocampal neurogenesis and prevented behavioral improvements induced by chronic antidepressant administration or wheel-running (Rossi et al., 2006; Babu et al., 2009). In contrast, deleting *TrkB* in differentiated neurons of the same brain regions does not affect neurogenesis or the behavioral responses to antidepressants, supporting the notion that dentate NSCs are a required component in the amelioration of depression (Li et al., 2008). Other extrinsic factors, such as Wnts and their antagonists, VEGF, and the neuropeptide VGF, are likely to be regulated by various neuronal stimuli in the dentate to modulate activity-dependent neurogenesis (Schmidt and Duman, 2007).

REGULATION OF THE HIPPOCAMPAL CIRCUITRY BY NEWBORN NEURONS

One fundamental question in adult neurogenesis is how addition of a small number of newborn neurons can affect global network activity and specific brain functions. Accumulating evidence supports the notion that newborn neurons do not merely replace lost neurons in the adult hippocampus; but are rather part of a continuously ongoing process that sculpt the existing neuronal circuitry of the adult brain as it responds to experiences encountered throughout life (Ge et al., 2008). Adult-born neurons exhibit a number of unique transient properties that are distinct from their neighboring mature neurons (Schmidt-Hieber et al., 2004; Ge et al., 2007). For instance, they display high-input resistance and activation of low threshold T-type Ca^{2+}-channels, which lead to enhanced excitability and generation of action potentials in response to weak excitatory inputs. A recent study using calcium imaging and electrophysiology demonstrated that immature neurons respond at higher rates to a given stimulus at both the single cell and population levels (Marin-Burgin et al., in press). This increased intrinsic excitability of immature granule cells is coupled with a resistance to GABA-mediated inhibition to result in a lower activation threshold and the potential of this population to serve as an integrator of weak afferent signals. Furthermore, associative LTP can be induced more easily in young neurons than in mature neurons under identical conditions. The enhanced synaptic plasticity with increased LTP amplitude and decreased LTP induction threshold is present only within a fairly narrow time window, between 4 and 6 weeks of cell age. These unique properties may allow newborn neurons to function differently from their mature neighbors, thus bringing special properties to the local microcircuits, with or without changing the characteristics of their mature afferent and efferent neuronal targets. In addition to serve as an independent encoding unit, adult-born neurons may play an important role in modulate activity at the circuitry level. For example, adult-born dentate granule cells innervate tens of basket interneuron; each basket cell in turn inhibits hundreds of mature granule cells (Fig. 3; Freund and Buzsaki, 1996). Dentate granule neurons are also known to innervate hilar mossy cells, which in turn activate many mature granule cells contralaterally (Fig. 3). *In vivo* recording from the adult mouse dentate gyrus showed that elimination of newborn neurons leads to a marked increase in the spontaneous gamma-frequency burst amplitude in the dentate gyrus and hilus, supporting a role of adult-born neurons in inhibiting recurrent network activity in the dentate gyrus, likely through regulation of interneurons (Lacefield et al., 2012).

In supporting a functional role of adult-born neurons in hippocampal circuitry, numerous studies have shown a correlation between changes in hippocampal neurogenesis and effects on learning and memory. Early studies utilized two major approaches to reduce the number of adult-generated neurons: antimitotic drugs, such as methylazoxy - methonol (MAM), and

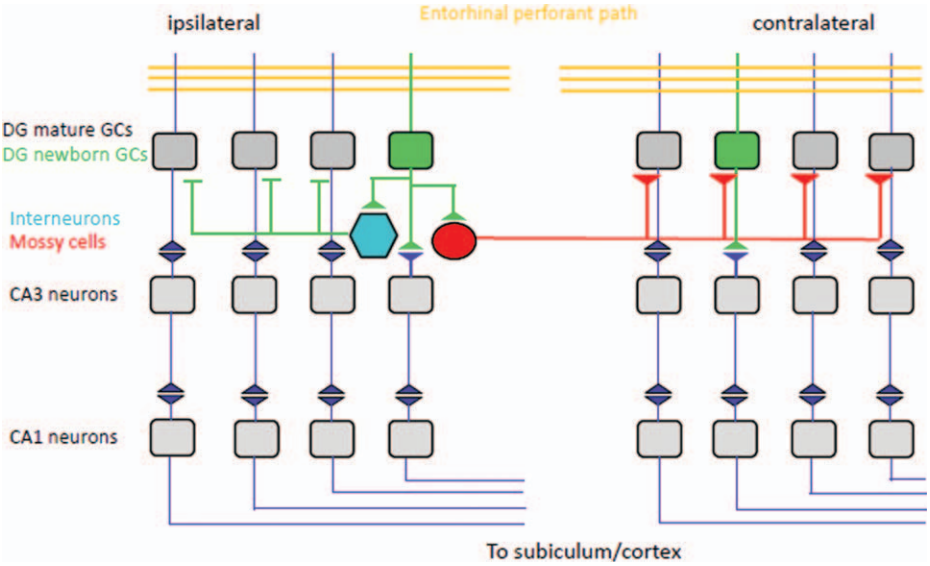

Figure 3 Basic circuit architecture of adult hippocampus and a model on how new neurons impact the local circuitry. Entorhinal cortical inputs innervate dentate gyrus granule cells, and dentate granule cells innervate CA3 neurons, which in turn innervate CA1 neurons. New granule cells innervate hilar interneurons, each of which inhibit hundreds of mature dentate granule cells. New granule cells also innervate hilar mossy cells, which activate many granule cells on the contralateral dentate gyrus. Through innervations of local interneurons and mossy cells, a single adult-born granule cell has the capacity to modulate the network activity at the circuitry level. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

X-irradiation (Shors et al., 2001; Snyder et al., 2005). Mice treated with MAM displayed obvious deficits in some but not all hippocampus-dependent tasks, such as trace eye-blink conditioning and trace fear conditioning, but not contextual fear conditioning (Shors et al., 2001). MAM treatment also prevents the long-term memory improvement normally induced by environmental enrichment (Bruel-Jungerman et al., 2005). Similarly, mice treated with cranial ionic irradiation reveal significant impairments in the acquisition of several hippocampus-dependent tasks, such as T-maze place recognition, spatial learning in Barnes maze, contextual fear conditioning, and nonmatching-to-sample (NMTS) tasks, whereas water maze spatial learning, and hippocampus-independent tasks were largely unaffected (Raber et al., 2004; Snyder et al., 2005; Saxe et al., 2006; Winocur et al., 2006). Though several learning deficits were identified in these studies, these acute manipulations are not anatomically restricted to the hippocampus and therefore nonspecific effects may account for some of the observed impairments. To eliminate the side effects associated with antimitotic drugs and irradiation, genetic approaches have been employed to manipulate adult neurogenesis. By exploiting transient expression of markers in developing adult-born neurons, it is possible to selectively ablate adult-born populations of cells in an inducible manner. Introducing herpes virus thymidine kinase (TK) under either the GFAP or nestin promoters, followed by treatment with the antiviral pro-drug, ganciclovir, results in a 50–75% reduction in neurogenesis and impairments in long-term spatial memory and contextual fear memory acquisition and extinction (Saxe et al., 2006; Deng et al., 2009). Using a similar approach to induce expression of the pro-apoptotic gene, Bax, under the nestin promoter resulted in a deficit in the acquisition of spatial relational memory, which was associated with a $\sim$ 60% reduction in proliferating cells (Dupret et al., 2008). Interestingly, manipulating this system in the other direction, through suppression of endogenous Bax under the nestin promoter resulted in an expansion of the adult-born neuronal population and an enhancement in pattern separation in a contextual discrimination task (Sahay et al., 2011). Cumulative evidence thus suggests that adult hippocampal neurogenesis contributes significantly to long-term spatial memory retention, spatial pattern separation, trace conditioning and contextual fear conditioning, clearance of hippocampal memory traces, reorganization of memory to extrahippocampal substrates, and certain antidepressant-induced behavioral responses in

specific mouse strains (Sahay and Hen, 2007; Deng et al., 2010; Aimone et al., 2011; Sahay et al., 2011). Collectively, these studies provide substantial evidence to support a functional role of adult hippocampal neurogenesis in learning and memory. In parallel with experimental evidence, a number of computational models of adult neurogenesis have provided further clues on how addition of new neurons may alter the global neural network properties and have suggested distinct roles of adult-born neurons in mediating information processing in the hippocampus (Aimone et al., 2011), which can guide the future experimental design for validation.

Adult neurogenesis has also been suggested to play a critical role in mood regulation, another hippocampal-associated higher brain function (Santarelli et al., 2003; Sahay and Hen, 2007). The potential impact of adult neurogenesis in pharmacological treatment of mood disorders was first demonstrated in a study showing that ablated SGZ neurogenesis by x-irradiation prevents the ameliorative behavioral effects of antidepressants fluoxetine and imipramine (Santarelli et al., 2003). However, the dependence of behavioral effects of antidepressants on neurogenesis is complicated by variability in factors such as species, genetic background, nature of antidepressants, and behavioral protocols (Duman et al., 2001; Sahay and Hen, 2007; Surget et al., 2011). Therefore, it remains to be tested whether impaired hippocampal neurogenesis is an etiological factor for depression. Further studies are needed to test whether and to what extent the reduction in neurogenesis contributes to hippocampal pathology associated with depressed patients.

CONCLUDING REMARKS

Rapid progress in the field over the past decade has led to a better understanding of the distinct developmental milestones of adult neurogenesis. Mounting evidence clearly demonstrate that adult-born hippocampal neurons possess unique electrophysiological features, making synaptic contacts with presynaptic and postsynaptic partners, responding to tonic and synaptic stimulation, and most importantly, integrating into the existing hippocampal network in an activity-dependent fashion. However, the physiological significance of these unique properties at the circuit level is much less clear. The exact manner by which adult NSCs and their progeny interact with and exert impact on the existing network in the adult brain remains poorly understood. To address these issues, future research targeting the specific contribution of newborn neurons at different developmental stages to the circuit and behavior will be of great importance. To dissect the functional contributions of newborn neurons to different brain functions, such as memory formation, consolidation, and retrieval, more refined behavioral paradigms with higher sensitivity and consistency are required. Future studies, using *in vitro* and *in vivo* electrophysiology and light-based network stimulation, will help interpreting the network properties associated with adult-born neurons. Finally, a better understanding of endogenous neurogenesis under physiological and pathological conditions may lead to the therapeutic interventions for various neurological diseases associated with neurodegeneration, aging, and depression.

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