Activity-dependent Extrinsic Regulation of Adult Olfactory Bulb and Hippocampal Neurogenesis

Dengke K. Ma,[a,b] Woon Ryoung Kim,[b,c] Guo-li Ming,[a,b,c] and Hongjun Song[a,b,c]

[a]The Solomon Snyder Department of Neuroscience, [b]Institute for Cell Engineering, and [c]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

The adult mammalian brain continuously generates new neurons in the olfactory bulb and hippocampus throughout life. Adult neurogenesis, a highly dynamic process, has been shown to be exquisitely modulated by neuronal circuit activity at different stages, from proliferation of adult neural progenitors, to differentiation, maturation, integration, and survival of newborn neurons in the adult brain. Strategic activity-dependent addition of new neurons into the existing neuronal circuitry represents a prominent form of structural plasticity and may contribute to specific brain functions, such as learning, memory, and mood modulation. Here we review extrinsic mechanisms through which adult neurogenesis is regulated by environmental cues, physiological learning-related stimuli, and neuronal activities.

Key words: **plasticity; adult stem cells; neurotransmitter; neurogenesis; neural activity**

Introduction

Since the pioneering studies by Altman *et al.* in the early 1960s, adult neurogenesis has now been unambiguously established in discrete brain regions in most mammals.[1–7] New excitatory granule neurons and inhibitory granule and periglomerular interneurons are continuously added to existing circuits in the dentate gyrus and olfactory bulb, respectively (Fig. 1A). Such continuous adult neurogenesis represents a surprising and intriguing type of plasticity conserved in adult mammalian brains.[5–8] In contrast to the main form of neural plasticity, through synaptic-level modification, adult neurogenesis confers plasticity through the addition of populations of new neurons with functional synaptic inputs and outputs. Distinct features of these two types of plasticity may endow the brain with parallel yet complementary capacities for information processing. Common in all neural plasticity and similar to synaptic changes, adult neurogenesis is under the exquisite control of neural activity. Studies in the last few years have delineated the sequential steps of endogenous adult neurogenesis in these two brain regions, from proliferation and fate specification of adult neural progenitors to differentiation, maturation, axon and dendritic targeting, formation of functional synaptic inputs and outputs, and selective survival of newborn neurons.[9,10] Accumulating evidence has implicated adult neurogenesis in specific brain functions, such as olfactory learning, spatial memory formation, and mediation of behavioral effects of antidepressants.[11–15] Accordingly, many environmental cues, physiological learning-related stimuli, and neuronal activities

Address for correspondence: Hongjun Song, Ph.D., Institute for Cell Engineering, Departments of Neurology and Neuroscience, Johns Hopkins University School of Medicine, 733 N. Broadway, BRB731, Baltimore, MD 21205. Voice: 443-287-7499; fax: 410-614-9568. shongju1@jhmi.edu

International Symposium on Olfaction and Taste: Ann. N.Y. Acad. Sci. 1170: 664–673 (2009).
doi: 10.1111/j.1749-6632.2009.04373.x © 2009 New York Academy of Sciences.

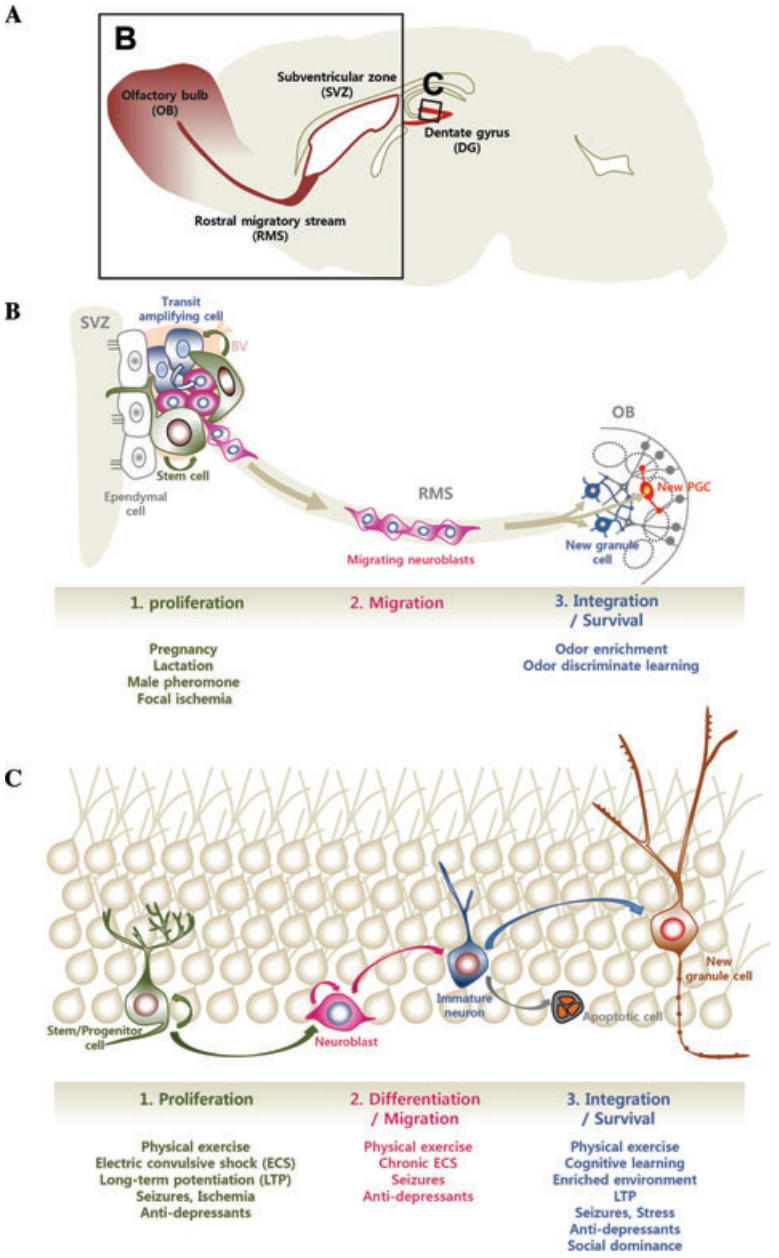

Figure 1. Regulation of adult neurogenesis by various types of neural activity. (**A**) Schematic representation of a sagittal view of the adult mouse brain. New neurons are generated continuously throughout life in the SVZ–olfactory bulb (OB) system and the dentate gyrus (DG) of the hippocampus. (**B**) Activity-dependent neurogenesis in the adult OB. Transient amplifying cells give rise to neuroblasts, migrating toward the OB through the rostral migratory stream (RMS). Within the OB, these neuroblasts differentiate into two types of interneurons as the granule cell and periglomerular cell (PGC). Integration into the preexisting circuits by newly entered neurons and their survival are predominantly influenced by odor experiences, such as enriched odor exposure or odor discriminate learning. (**C**) Activity-dependent neurogenesis in the dentate gyrus. Neural progenitors in the SGZ proliferate and differentiate into neuroblasts that migrate a short distance into the inner granular cell layer, processes that are modulated by various types of neural activity. The survival and integration of new neurons is also regulated in an activity-dependent manner. (In color in *Annals* online.)

dynamically influence different stages of adult neurogenesis.[16–18] The underlying molecular and cellular mechanisms through which diverse types of activity selectively regulate different stages of adult neurogenesis are only beginning to be unraveled.

Activity-dependent Regulation of Adult Olfactory Bulb Neurogenesis

New neurons generated in the adult olfactory bulb originate from progenitors in the subventricular zone (SVZ) of the lateral ventricle of the forebrain.[19] The physical distance between the place of their birth and place of final destination naturally creates two distinct compartments for potential extrinsic regulation. In the SVZ, adult progenitor cells are located in a developmental "vestige" where embryonic counterparts generate the majority of neurons, and not surprisingly their maintenance, proliferation, and fate specification are subject to numerous developmental signaling controls in a largely activity-independent manner.[19,20] Highly specialized niche structures, such as a "glial tunnel,"[21] may also function to segregate the earlier stages of neurogenesis from influences of circuit neuronal activity. After neuroblasts migrate through the rostral migratory stream and reach the bulb, where olfactory information processing takes place, the newly generated neurons switch to radial migration to their final positions and start to receive synaptic inputs and are subject to activity-dependent survival and final integration into the preexisting circuitry.

Olfactory bulbs process odorant information from the nose to the brain; thus, the main type of activity results from sensory stimuli of odorant exposure. Using a technique of reversible olfactory deprivation, Cummings *et al.* showed that unilateral olfactory deprivation during the first postnatal month in rodents led to a dramatic reduction in the size of the olfactory bulb on the experimental side.[22] Surprisingly, the bulb size had mostly recovered within 40 days after normal stimulation was restored. Thymidine analog labeling revealed that the recovery was accompanied by the addition of a large population of new neurons. Other similar experiments have shown that the increased number of neurons after deprivation is due to rescued survival from the "default" apoptosis program.[23–25] Thus, neuronal survival in the olfactory bulb can be profoundly influenced by afferent activities.

Several recent studies have directly examined whether physiological exposure to an odor-enriched environment or learning tasks affect neurogenesis in the adult olfactory bulb.[26] Using bromodeoxyuridine (BrdU) to birth date progenitors from SVZ and their progeny, Rochefort *et al.*[27] found that long-term exposure to an odor-enriched environment dramatically increased the number of surviving new neurons at 3 weeks after BrdU injection. The number of BrdU-labeled progenitors was not altered 4 h after a single BrdU injection, suggesting a lack of effects on cell proliferation. Interestingly, this effect appears to temporally transient, because the number of newborn neurons returned to control levels 30 days after experiencing the odor-enriched environment.[27] Furthermore, odor discrimination learning for an extended period, not just exposure to a single odor, is also able to significantly increase the survival of newborn neurons in the olfactory bulb.[28] The effects are region specific, because enriched odor exposure does not influence hippocampal neurogenesis. Although it remains under debate,[29,30] olfactory bulb neurogenesis might be associated with specific olfactory functions, such as olfactory discrimination and olfactory memory. For example, olfactory enrichment induces not only an increase in the number of surviving newborn neurons but also enhancement of short-term olfactory memory.[6,26,27] Conversely, mutant mice deficient in a neural cell adhesion molecule with reduced olfactory neurogenesis exhibit reduced olfactory sensitivity and olfactory memory.[11] Studies have also indicated a correlation between the age-dependent decline of olfactory

bulb neurogenesis and fine odorant discrimination ability.[31] These functional correlations suggest that the activities from odorant-related environmental stimuli may not only increase the number of surviving neurons but also enhance their integration into the circuitry to participate in information processing. Using immediate-early gene activation to monitor the integration of new neurons, Magavi *et al.* showed that odor familiarization specifically increases the response of adult-born neurons but depresses the response of the overall population of granule neurons.[32]

In addition to odorants and olfactory learning, other physiological conditions have also been shown to modulate olfactory bulb neurogenesis in rodents. Compared to subordinate male mice, pheromones from dominant males stimulate neuronal production in the olfactory bulb of female mice by increasing cell proliferation in the SVZ (Fig. 1B).[33] In a similar vein, pregnancy of female mice promotes both SVZ proliferation and the production of new interneurons in the olfactory bulb through prolactin (Fig. 1B).[34] Although the SVZ progenitors express receptors for these gender-specific cues, it remains unclear to what extend neuronal activity is directly involved in mediating the actions of these cues and the long-term outcome.

Activity-dependent Regulation of Adult Neurogenesis in the Hippocampus

Neurogenesis in the adult hippocampus occurs in the granule cell layer of the dentate gyrus. New neurons are born in the subgranular zone (SGZ) and then migrate a short distance before maturing into excitatory dentate granule cells in the inner granule cell layer (Fig. 1C). The entire neurogenesis process, including progenitor proliferation, fate specification, migration, and neuronal differentiation, is spatially restricted compared to the extensive spreading of neurogenesis from the SVZ to the olfactory bulb. The dentate gyrus receives inputs from numerous regions of the brain.[35] Particularly, the SGZ is known to be enriched in exuberant neuronal communications between mature granule neurons and local interneurons.[36] The spatial proximity to high neuronal network circuit activity may place adult hippocampal neurogenesis under more elaborate, activity-dependent control than in the SVZ.

The hippocampus is a brain region crucial for acquisition of new episodic memory and the dentate gyrus plays a role in "pattern separation,"[37] distinguishing similarly encoded contextual information. This functional requirement may engender the dentate gyrus to be superiorly sensitive to the surrounding environment and ongoing cortical activity. Consistent with this notion, the dentate hilus region is one of the major loci responsible for temporal lobe epilepsy.[38] As part of the limbic system, another established role of the dentate gyrus is its modulation of emotions, such as stress and depression.[39] As reviewed below, major types of activity in the dentate gyrus, including those induced of an enriched environment, voluntary exercises, and cognitive and emotional processes, modulate different aspects of adult hippocampal neurogenesis.

Exposure to an enriched environment is known to produce structural and functional alterations in the brain; its specific effects on adult hippocampal neurogenesis were examined by Kempermman *et al*.[40] Compared with littermates housed in standard cages, significantly more new neurons were found in the dentate gyrus of mice exposed to an enriched environment. Surprisingly, van Praag *et al.* further showed that voluntary exercise alone, without other components of an enriched environment, was sufficient to enhance neurogenesis.[41] This effect could be observed as early as day 1 after the start of exercise, but the most profound effect was detected after 3 days of exercise, manifested by the enhanced proliferation of early neural progenitors. Continued exercise elicits a predominantly enhanced survival of

newborn neurons and results in a net increased number of integrated neurons in the adult brain.

Cognitive activity, mainly from hippocampus-dependent learning, also modulates adult hippocampal neurogenesis. Training on associative learning tasks that require the hippocampus, such as trace eye blink conditioning and Morris water maze learning, significantly increases the number of newly generated neurons in the adult dentate gyrus, whereas tasks that do not require the hippocampus do not change the numbers of new neurons.[42] Analysis using BrdU-based birth dating further suggests that the learning behavior specifically promotes the survival of new neurons between 1 and 3 weeks after they are generated in the adult brain.[42] Interestingly, the survival of earlier, 3-day-old newborn neurons is actually inhibited by the similar Morris water maze learning paradigm, suggesting a stage-dependent effect and a finely sculpted developmental selection of newborn neurons for strategic addition.[43] The learning process involves precisely timed and highly patterned neuronal activity; excessive or abnormal patterns of activity, such as those occurring during temporal lobe epileptic seizures, dramatically impact neurogenesis, including progenitor proliferation and dendritic development, synapse formation, and survival of new neurons as documented in numerous clinical and experimental settings.[44] On the other hand, negative emotional activity, including stress and depression, has been shown to be a potent inhibitor of adult hippocampal neurogenesis.[39] The major effect of stress on neurogenesis appears to be decreased cell proliferation, while reduced cell survival of newborn neurons has also been reported. The discrepancy may be due to the different stress paradigms used in the different studies.[39] Stressful events are known to induce depression; interestingly, a variety of antidepressant treatments elevate hippocampal neurogenesis. The most effective antidepressant used in clinics, electroconvulsive treatment, promotes the entire adult neurogenic process, including progenitor proliferation, survival, and dendritic development of newborn neurons.[44,45]

Cellular and Molecular Mechanisms

The activity-dependent regulation of adult neurogenesis in both the olfactory bulb and the dentate gyrus of the hippocampus has now been widely observed and extensively studied. The specific molecular and cellular mechanisms through which activity regulates different stages of adult neurogenesis, however, are only beginning to be explored. Particularly, the extrinsic mechanisms of how diverse types of activities are translated into actions on sequential processes of adult neurogenesis remain unclear. Although various cell types in the brain, such as microglia, endothelial cells, and T cells, have been shown to play interesting roles,[46–48] mature neurons are likely the major cellular players in extrinsic regulation of neurogenesis by mediating effects of neural activity. Here we focus our discussion on two major types of molecular mediators for activity-dependent adult neurogenesis: neurotransmitters and membrane-associated and diffusible factors from neurons.

GABA is the major neurotransmitter used by mature interneurons in the brain and has emerged as a key regulator for adult neurogenesis.[18] GABA, activating both synaptic and extrasynaptic GABA-A receptors, causes hyperpolarization of mature neurons while it depolarizes neural progenitors and immature neurons in the adult brain.[10,49] Electrophysiological analysis revealed that neural progenitors are initially activated by ambient GABA, followed by sequential GABAergic and glutamatergic inputs.[18] In the SVZ, GABA released from migrating neuroblasts regulates proliferation, which is probably not directly connected to circuit activity-dependent modification.[50] In the SGZ, GABA is released from local interneurons and tonically activating progenitors and immature neurons. Importantly, both tonic and phasic GABA activation is essential for the

maturation, dendritic development, and synaptic integration of newborn granule cells.[51,52] Given extensive recurrent connections between granule cells and interneurons in the adult dentate gyrus,[36] the ambient GABA levels might reflect general local circuit activity and translate neuronal stimuli into actions on neural progenitors, while phasic GABA activation may serve as an input-specific modulator for immature new neurons. Interestingly, recent studies have shown that both tonic and phasic GABA activation of neural progenitors and immature newborn neurons in the dentate gyrus is modulated by chemokine stromal cell-derived factor 1 coreleased from local interneurons.[53,54] Current evidence suggests that regulation by GABA from interneurons creates a favorable condition to orchestrate the integration of new neurons into a mature neuronal environment in the SGZ. It would be interesting to examine whether activity-dependent maturation, integration, and survival of new neurons also recruits GABA-mediated regulation in the olfactory bulb.

Glutamate is the major neurotransmitter used by excitatory principal neurons in the brain and has long been implicated in regulating adult hippocampus neurogenesis through *N*-methyl-D-aspartate receptors (NMDARs). Direct injection of *N*-methyl-D-aspartate negatively regulates cell proliferation in the adult rat dentate gyrus,[55,56] while induction of long-term potentiation at the glutamatergic perforant path to dentate granule cells promotes the proliferation of adult neural progenitors and survival of newborn neurons in an NMDAR-dependent fashion.[57,58] These results suggest that glutamate has both cell autonomous effects in immature neurons and non-cell autonomous effects through modulation of existing neuronal circuits. Although local mature neurons have predominantly heightened NMDAR signaling, ionotropic glutamate receptors are present in immature neurons and early progenitors. Interestingly, direct NMDAR signaling has been shown to regulate newborn neurons during two critical periods.[10] In the first phase, NMDAR activation of new neurons promotes competitive survival of these new neurons during the 1–3 weeks after their birth.[59] In the second phase, NR2B-dependent activation of NMDARs is required for the enhanced synaptic plasticity of glutamatergic inputs to new neurons during the 4–6 weeks after their birth, potentially serving as a substrate for learning from new experience.[60,61] Parallel to such a direct impact of glutamate on newborn neurons, NMDAR activation in mature neurons is known to lead to a gene expression program that produces diffusible factors profoundly influencing adult neurogenesis.

Cells membrane-associated or diffusible factors serve as major mediators for short-range cell–cell communication. Given that adult neural progenitors and their progeny are extensively regulated by a plethora of growth factors, neurotrophins, and developmental cues,[20,62] nearby mature neurons are suited to contribute, producing these diffusible niche factors or their antagonists in response to neuronal activity. Brain-derived neurotrophin factor is one prime example. As a classic activity-dependent neurotrophin,[62] its expression is bidirectionally sensitive to activity in dentate granule neurons and can exert pleiotropic yet strong influences on adult hippocampal neurogenesis.[63,64] In the olfactory bulb, the extracellular matrix glycoprotein tenascin-R regulates the initiation of the detachment of neuroblasts from the migrating chain as well as their radial migration.[65] Interestingly, tenascin-R is expressed from adult olfactory bulb neurons in an activity-dependent manner, as it is markedly reduced by odor deprivation. Similarly, other extrinsic factors, including Wnts and their antagonists, fibroblast growth factors, vascular endothelial growth factors, and neuropeptide VGF, may be regulated by various neuronal stimuli in the dentate gyrus and perhaps also in the olfactory bulb to modulate activity-dependent neurogenesis.[62] Ample evidence suggests that the genetic program driving activity-dependent gene expression of diffusible factors in mature granule neurons requires NMDAR signaling, which

is critically important for synaptic plasticity and information storage of neurons per se.[66,67] This may provide a mechanism by which encoded information from patterned neuronal stimuli is specifically and precisely translated into local neurogenic responses for strategic neuronal addition to the circuitry.

Functional Implications

The scope and modes of activity-dependent regulation of adult neurogenesis discussed above have interesting implications for functional contributions of newborn neurons. During adult neurogenesis, nearly half of the precociously generated neurons are destined to die,[5,28,59] and this specific stage of life-or-death decision has predominantly been used to serve as the substrate of activity-dependent modification in both the olfactory bulb and hippocampus. Importantly, the survival of individual neurons is competitive, so that only new neurons activated by information-relevant activity are selectively preserved and integrated into the circuitry. One intriguing idea is that the newly integrated neurons (4–6 weeks) with enhanced plasticity may encode information that is specific to what that particular neuron has encountered during its history of activity-dependent regulation, such as competitive survival (1–3 weeks), thus representing a trace of memory.[59,60,68] The same GABA-, glutamate-, or diffusible factor-based mechanisms may have been used during the earlier period (1–3 weeks) and later encoding of the memory trace (4–6 weeks) perpetuates the time-specific network activity or input-specific information.

Conclusions and Future Directions

Activity-dependent addition of new neurons to the existing circuitry represents a prominent form of structural plasticity and may contribute to specific brain functions in the adult brain. Research over the past decade has established an intimate relationship between adult neurogenesis and neuronal activity resulting from various environmental cues, physiological learning-related stimuli, and internal cognitive, emotional activities. The remarkable scope and modes of activity-dependent regulation of adult neurogenesis suggest that the adult brain has evolved mechanisms to exquisitely tailor neuronal addition into its information processing capacity, to which in turn the new population of neurons contributes.

Neuron-derived GABA, glutamate signaling, and diffusible factors have emerged as major molecular mediators for activity-dependent modification of adult neurogenesis. The molecular mechanisms underlying activity-dependent survival and integration remain to be further studied. Many other neurotransmitter systems are known to innervate the SVZ, olfactory bulb, and SGZ, and their specific roles in regulating different phases of adult neurogenesis are being characterized. Finally, exploring the mutual relationship between activity and neurogenesis in the context of neural circuit dynamics to infer the exact functional role of adult neurogenesis remains a great and challenging yet rewarding goal.

Acknowledgments

This work was supported by grants from the NIH, McKnight Scholar, NARSAD, Rett Syndrome Research Foundation, the Muscular Dystrophy Association, and the Packard Center for ALS Research at Johns Hopkins (to H.S.) and from the NIH, Sloan, March of Dimes, and Adelson Medical Research Foundation (to G.-L.M.).

Conflicts of Interest

The authors declare no conflicts of interest.

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