Neurosci Bull August 1, 2014, 30(4): 542–556. http://www.neurosci.cn
DOI: 10.1007/s12264-014-1453-5

·Review·

Activity-dependent signaling mechanisms regulating adult hippocampal neural stem cells and their progeny

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Adult neural stem cells (NSCs) reside in a restricted microenvironment, where their development is controlled by subtle and presently underexplored cues. This raises a significant question: what instructions must be provided by this supporting niche to regulate NSC development and functions? Signaling from the niche is proposed to control many aspects of NSC behavior, including balancing the quiescence and proliferation of NSCs, determining the cell division mode (symmetric *versus* asymmetric), and preventing premature depletion of stem cells to maintain neurogenesis throughout life. Interactions between neurogenic niches and NSCs also govern the homeostatic regulation of adult neurogenesis under diverse physiological, environmental, and pathological conditions. An important implication from revisiting many previously-identified regulatory factors is that most of them (e.g., the antidepressant fluoxetine and exercise) affect gross neurogenesis by acting downstream of NSCs at the level of intermediate progenitors and neuroblasts, while leaving the NSC pool unaffected. Therefore, it is critically important to address how various niche components, signaling pathways, and environmental stimuli differentially regulate distinct stages of adult neurogenesis.

Keywords: neural stem cell; neuronal development; neuronal plasticity

Introduction

Neurogenesis occurs throughout life in discrete regions of the mammalian brain and substantial evidence supports critical roles of adult-born neurons for specific brain functions, such as learning, memory, and olfactory processing[1-3]. It is widely accepted that there are two primary neurogenic regions in the adult brain: the olfactory bulb where newborn neurons arise from the subventricular zone (SVZ) of the lateral ventricles, and the dentate granule cell layer of the hippocampus where newborn neurons are generated locally within the subgranular zone (SGZ). The origin of the new neurons is from a resident population of adult neural stem cells (NSCs)[4-7]. Although NSCs are also known to arise from other adult brain regions under pathological conditions and with injuries[8], it remains controversial whether active neurogenesis normally occurs outside of the SVZ and SGZ.

The adult mammalian brain is a plastic structure, capable of dynamic cellular and molecular remodeling in response to various environmental stimuli and pathological conditions. The adult hippocampus is a primary neuronal structure involved in memory formation and synaptic plasticity. Within the hippocampus, circuit dynamics in the dentate gyrus (DG) is facilitated by continuously generating new neurons throughout life. Adult hippocampal neurogenesis has attracted much interest because newborn neurons have been suggested to adapt the brain to various behavioral tasks, including spatial learning

and retention, pattern discrimination, and the clearance of memory traces[9, 10]. An emerging concept is that the amenability of newborn neurons confers advantageous properties toward higher usage in the hippocampus. For instance, newborn neurons at specific stages of maturation are preferentially recruited into circuitry due to their unique properties, including hyper-excitability, high excitation/inhibition balance, and enhanced synaptic plasticity[11-13]. In addition, adult hippocampal neurogenesis is involved in responses to antidepressants[14], stress[15], brain injuries, and mental disorders[16-18]. A basic understanding of precursor properties and their niche interactions will illuminate how precursor cells sense and respond to changes in the external environment to promote tissue homeostasis or repair.

It is commonly believed that adult neurogenesis arises from precursors with the properties of NSCs[5], but the developmental origin of adult hippocampal NSCs remains unclear. Recently, Li *et al*. showed that NSCs initially originate from the ventral hippocampus during late gestation and then relocate to the dorsal hippocampus, suggesting that the ventral hippocampus is the primary location that contributes to the NSCs in the adult hippocampus[19]. NSCs were originally defined by their potential to both self-renew and generate neurons and glia from a single cell *in vitro*[5, 20]. However, reprogramming studies have raised the question of whether cultured lineage-restricted neural progenitors acquire increased potential not evident *in vivo*[21-23]. Therefore, investigations of NSC properties *in vivo* are critical in interpreting neurogenesis under both physiological and pathological conditions. Moreover, the cellular targets of environmental effects have been shown to influence later stages of neurogenesis[16]. Signaling from the niche is proposed to control many aspects of NSC behavior, including their mitotic state, cell fate specification, and precursor maintenance. Therefore, understanding how various niche components, signaling pathways, and environmental stimuli differentially regulate NSC behavior will reveal how they contribute to homeostasis and repair. In this review, we summarize recent progress in understanding how adult NSCs and their progeny are regulated by intrinsic and extrinsic factors in an activity-dependent manner, and how they are affected by various environmental stimuli and pathological conditions.

Adult Neurogenesis Exhibits Distinct Developmental Stages

Significant progress has been made in identifying the major milestones and processes underlying adult neurogenesis[16]. In the adult mouse DG, lineage-tracing studies have shown that nestin$^+$MCM2$^-$ quiescent radial and non-radial NSCs give rise to highly proliferative Tbr2$^+$MCM2$^+$ intermediate progenitors, which in turn generate mitotic DCX$^+$MCM2$^+$ neuroblasts to become DCX$^+$MCM2$^-$ immature post-mitotic neurons and finally DCX$^-$NeuN$^+$ mature dentate granule neurons (GCs) (Fig. 1).

Neural Stem Cells

Radial glia-like cells have been classified as Type-1 cells, which are infrequently labeled by retroviruses and thymidine analogs, such as BrdU or EdU, indicative of a low proliferative capacity. Morphologically, their cell bodies reside in the SGZ region, and possess an apical process that extends into the inner molecular layer. These cells express glial fibrillary acidic protein (GFAP), intermediate filament protein (nestin), brain lipid-binding protein, and Sry-related HMG-box transcription factor (Sox2). Despite some overlap with the expression of astrocytic markers, Type-1 cells are morphologically and functionally different from mature astrocytes. Recent fate mapping studies using inducible Cre recombinase driven by various promoters or enhancers, including Gli, GFAP, nestin, and glutamate aspartate transporter, have shown radial glia-like cells to be the primary NSCs in the adult brain[24]. In another model, it has been shown that a single Sox2$^+$ cell can self-renew, or give rise to a neuron or an astrocyte *in vivo*, suggesting that non-radial/horizontal neural progenitor cells possess stem-cell properties[7]. While still under vigorous debate, these models may represent the coexistence of multiple NSC types in the adult brain[25] (Fig. 2).

Activation and maintenance of radial NSCs In the adult mammalian brain, adult NSCs are currently thought to be a slowly-dividing, relatively quiescent population with radial morphology. The function of quiescence may serve as a protective mechanism that counteracts stem-cell exhaustion similar to that of somatic stem cells[26, 27]. Thus, the activation and maintenance of NSCs are inseparable processes in which a change of one would correspondingly alter the other. The balance of NSC maintenance and

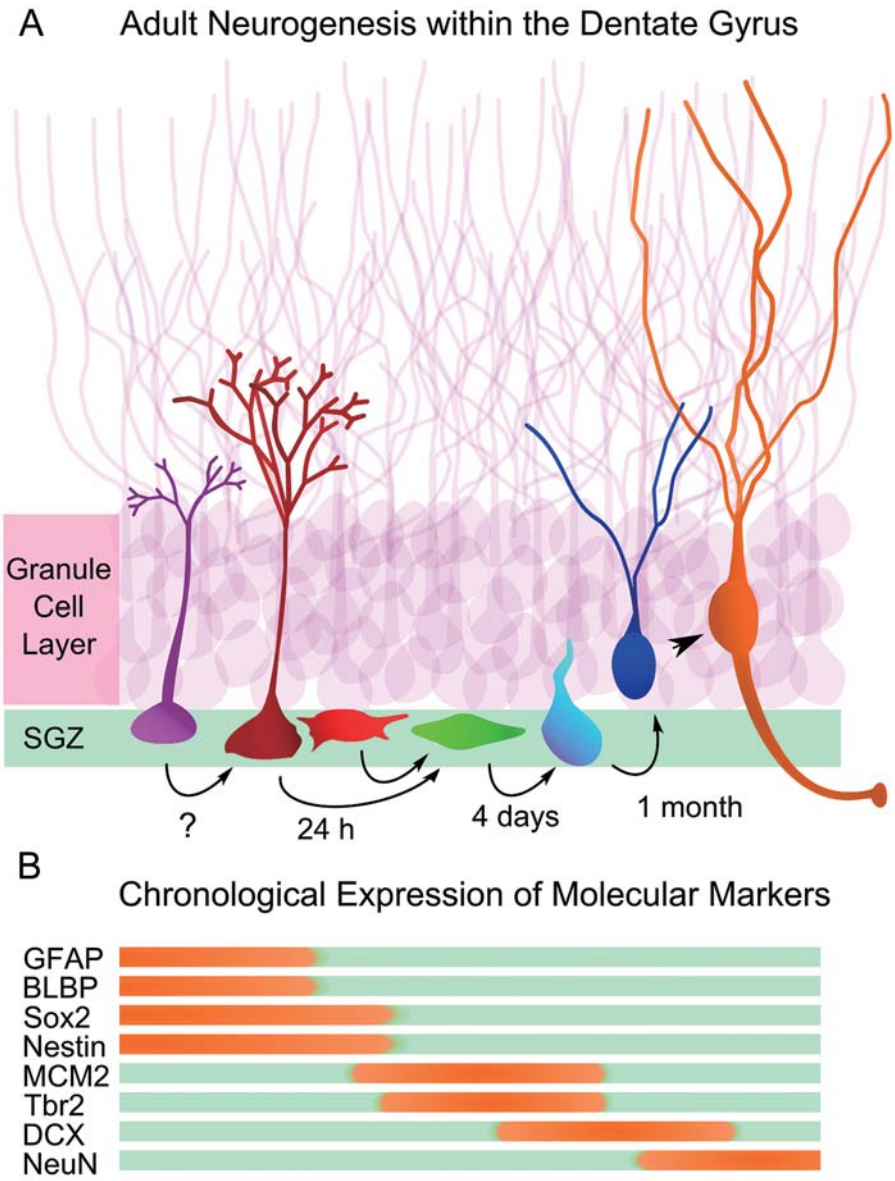

Fig. 1. Adult neurogenesis in the dentate gyrus of the hippocampus. A. Schematic summary of the development of newborn cells as characterized by the estimated timeline for each developmental stage. B. Expression of specific molecular markers at each stage.

neurogenesis is essential for ensuring the continuous generation of new hippocampal neurons throughout life without depleting the NSC pool. Incomplete maintenance and premature differentiation can cause depletion of the NSC pool and subsequent loss of neurogenesis; while excessive maintenance at the expense of neuronal differentiation compromises the neurogenesis rate necessary for proper hippocampal functions.

Fate choice of NSCs Multipotency and self-renewal are hallmarks of NSCs. In the adult brain, the neuronal lineage is thought to begin with the asymmetric cell division of a radial NSC to generate a highly proliferative intermediate progenitor, then the radial NSC returns to quiescence. Radial NSCs exhibit a low frequency of symmetric self-renewal under normal conditions, suggesting a capacity of the adult brain to amplify the NSC pool. Activated

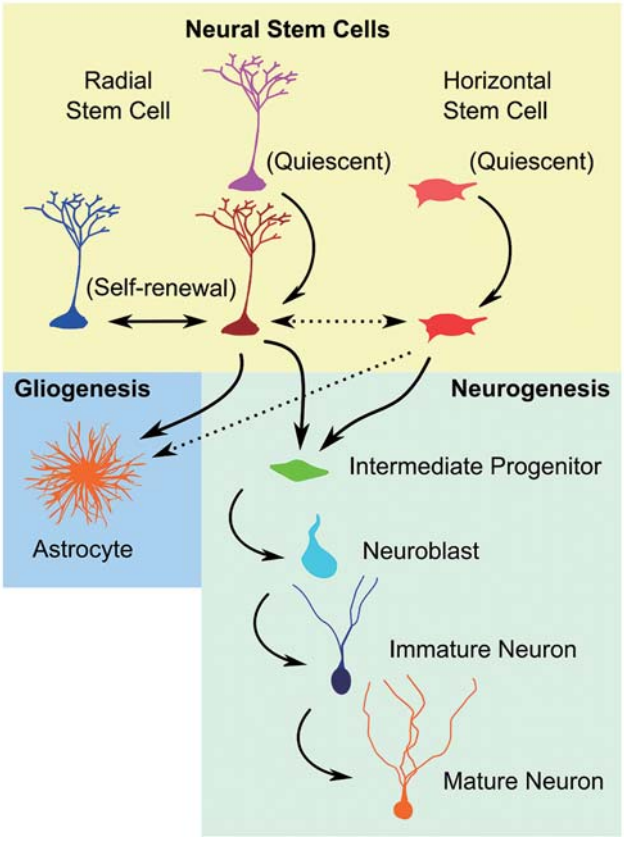

Fig. 2. Lineage of radial and horizontal NSCs and their progeny. Radial NSCs cycle between quiescent and mitotic states. Once activated, radial NSCs can divide symmetrically to generate additional radial NSCs, or asymmetrically to produce the neuronal and astroglial lineages. Though still to be further confirmed, horizontal NSCs are thought to be capable of generating neurons, astrocytes, and even radial NSCs.

NSCs have the potential to make various fate choices during multiple rounds of self-renewal, thus the total radial NSC pool reflects maintenance through quiescence or asymmetric self-renewal, reduction through terminal differentiation, and expansion through symmetric self-renewal.

The fate specification of radial NSCs is subject to dynamic regulation under diverse physiological, environmental, and pathological conditions. Furthermore, fate specification is a form of cellular plasticity which reflects brain adaptation to the environment. For example, social isolation stress promotes the expansion of radial NSCs, which in turn prepares the brain for increased neurogenic potential when more favorable conditions return[28]. The signals and molecular mechanisms dictating the fates of the NSC lineage remain to be determined. Of particular interest is to address how niche components couple the activity of neuronal circuitry to the regulation of NSCs under both physiological conditions and after specific experiences.

Interactions between NSC subtypes Recent studies have started to challenge the notion that radial NSCs are the only primitive stem cells in the adult brain, with the demonstration of the existence of a second morphologically distinct NSC population which in general is referred to as non-radial or horizontal NSCs[7, 25]. Within this pool, radial and horizontal NSCs can shuttle between mitotic activity and quiescence and respond selectively to neurogenic stimuli, pointing to the heterogeneous nature of the NSC population. The predominant evidence comes from the manipulation of Notch signaling in primitive NSCs which distinguishes two morphologically distinct populations: quiescent radial NSCs and active $Sox2^+$ horizontal NSCs. Interestingly, they respond differentially to physiological (exercise) and pathological (seizure) stimuli and aging. However, it remains unclear how these two subpopulations interact to orchestrate the precise regulation of adult neurogenesis. Accumulating evidence supports the view that radial NSCs are a reserve pool that can be recruited into the active pool to increase the neurogenic process in response to changes in conditions, while horizontal NSCs (possibly coming from the activated radial NSCs) can amplify themselves through symmetric expansion. Therefore, in these two subpopulations, “tissue-on-demand” constitutes their main mode of regulation. In future studies, it will be fundamentally important to define the relationships among distinct NSC populations (quiescent radial, active radial, quiescent horizontal, and active horizontal), how they are differentially regulated by various physiological and pathological stimuli, and the underlying molecular mechanisms of how they are influenced by neuronal activity to produce differentiated progeny.

Intermediate Neural Progenitors and Neuroblasts

In the adult SGZ, proliferating radial and non-radial NSCs give rise to intermediate progenitors (Type-2 cells), which

then become neuroblasts (Type-3 cells). Several types of highly proliferative intermediate progenitors have been identified according to their specific morphologies, electrophysiological properties, and expression of unique molecular markers[6, 29]. Type-2 cells are further divided into two subtypes: one subset maintains expression of the glial marker GFAP, but lacks radial processes (Type-2a); the other lacks GFAP and expresses the transcription factors Prox1 and NeuroD (Type-2b). Morphologically, horizontal cellular processes are still prominent in these cells[30, 31]. Type-2 cell proliferation is promoted by activity-dependent regulation through both physiological stimuli such as voluntary wheel running[32] or pharmacological stimulation such as treatment with the antidepressant fluoxetine[33]. Type-3 cells exit the cell cycle and express markers of the neuronal lineage, including DCX, PSA-NCAM, NeuroD, Prox1, and calretinin[34]. Morphologically, neuroblasts possess processes of various lengths, complexities, and orientations. Under pathological conditions, such as seizures, Type-3 cells display an aberrant state characterized by dramatically increased proliferation[35]. Many studies have revealed a substantial loss of newborn progeny during the first 4 days after they are born, when the majority of these precursors are still proliferating and express DCX[32, 36-38]. Due to the proliferative capacity of neural progenitors and neuroblasts, regulation at this stage would have a profound impact on the ultimate number of mature adult-born neurons.

Integration and Maturation of Immature Neurons

After precursor cells exit the cell cycle, most newborn neurons are eliminated within a short time. The mechanisms underlying the cell death of newborn neurons soon after birth are poorly understood. In the SGZ, the survival of newborn neurons at 1–3 weeks of age is influenced by the experiences of the animals, such as spatial learning and exposure to an enriched environment[39]. Glutamatergic signaling *via* NMDA receptors plays a cell-autonomous role in survival during the third week after birth, which coincides with the formation of dendritic spines and functional glutamatergic inputs[7, 40]. Those neurons that survive the early elimination phase are generally believed to be stably and persistently integrated into the DG neuronal networks.

The functional integration of newborn neurons *in vivo* requires the extension of dendrites and axons, and the formation of synapses with other neurons. Immature neurons send their axons to the CA3 region to form appropriate synapses within two weeks after cell-cycle exit. Dendrites of these cells reach the DG molecular layer within one week and continue to elaborate for at least 4 weeks. At 6–8 weeks of age, newborn neurons display overall morphological and functional characteristics similar to those of fully mature GCs[11, 41-43].

Regulation of Adult Neural Stem Cells and Their Progeny

The processes controlling adult neurogenesis depend on intrinsic and extrinsic variables that are responsible for NSC activation and maintenance, progenitor proliferation and differentiation, and immature neuron integration, survival, and maturation. A number of molecular players and signaling pathways have been identified, including niche factors/receptors, cytoplasmic factors, transcription factors, and epigenetic factors (Table 1). Most of the molecular players identified are involved in the later stages of adult SGZ neurogenesis. Recently, with the availability of promoter-specific transgenic mouse lines that selectively label distinct NSC and progenitor populations during adult neurogenesis, the molecular mechanisms responsible for the early events of adult neurogenesis are beginning to be elucidated.

Neurotransmitter-mediated Regulatory Mechanisms

Neurotransmitters are likely candidates to relay experiential information that influences adult neurogenesis. SGZ progenitor cells reside within a complex microenvironment and are potentially influenced by a plethora of synaptic inputs from local circuitry and distant brain areas through different neurotransmitters, including the main neurotransmitters gamma-aminobutyric acid (GABA) and glutamate, and other modulatory neurotransmitters such as acetylcholine, serotonin, and dopamine.

GABA Studies using engineered onco-retrovirus[44] and transgenic reporter mice[45, 46] have revealed that the synaptic integration of newborn neurons recapitulates embryonic neurogenesis by following a stereotypic sequence: (1) Initial GABA inputs to NSCs are non-synaptic and are mediated through GABA spillover from the mature synapses formed between presynaptic local interneuron terminals and mature GCs. (2) Then, neural progenitors begin to be innervated by local interneurons through input-

Table 1. Regulation of adult neurogenesis at distinct developmental stages

Signaling mechanism	Developmental stage							
	Neural stem cells		Neural progenitors		Neuroblasts to immature neurons		Immature to mature neurons	
	Activation	Maintenance	Proliferation	Differentiation	Dendritic development	Integration	Maturation	Cell Survival
Neurotransmitters	GABA↓, ACh↑		ACh↑, 5-HT↑	GABA↑, 5-HT↑	Glutamate↑	GABA↑, Glutamate↑		GABA↑, Glutamate↑
Morphogens	Notch1/ RBP-J↓, Wnt↓, BMP↓	Notch1/ RBP-J↑, Wnt↑, PTEN↑	Notch1/ RBP-J↓, BMP↓		Wnt↓		Wnt↓	
Transcription factors		Sox-2↑, shh↑					NeuroD↑, Prox1↑, Klf9↑	
Epigenetic regulators			Mbd1↓, Gadd45b↑	Mbd1↑	Gadd45b↑			
Environmental regulators	Exercise↑, social isolation↑, learning↑	Aging↓, social isolation↓	Exercise↑			Enrichment↑, learning↑	Learning↑	Enrichment↑, learning↑
Disease genes		FMRP		FMRP	DISC1, Mecp2	DISC1	Mecp2	
Disease effects	Seizure↑	Neurode-generation↓	Seizure↑		Seizure↑	Seizure↑, Neurode-generation↓	Seizure↑	Neurode-generation↓

specific GABAergic signaling[47, 48]. This initial synaptic transmission is slow and displays immature properties due to the relatively low concentration of GABA receptors on the newborn progeny[49]. (3) Between 2 and 3 weeks of cellular age, GABAergic inputs are converted from excitatory to inhibitory, and meanwhile, excitatory glutamatergic dendritic inputs start to form on newborn neurons. (4) Finally, inhibitory GABAergic synaptic inputs begin to appear on the cell body to form perisomatic synapses.

GABA is the major inhibitory neurotransmitter in the adult brain and acts *via* two main receptor types: ionotropic $GABA_A$ and G-protein-coupled metabotropic $GABA_B$ receptors. GABA can promote or suppress proliferation depending on the developmental stage, brain region, and the fate of distinct progenitor populations[50-52]. In the adult hippocampus, $GABA_A$ receptors have been reported to decrease the proliferation of quiescent NSCs[50, 53], promote the differentiation of neural progenitors[49], and promote the integration and survival of immature neurons[44, 54]. Recently, a study by Giachino *et al.* showed that NSCs of the SGZ also express metabotropic GABA receptors, and selective deletion of $GABA_{B1}$ receptors increases the proliferation of quiescent NSCs, supporting a role of $GABA_{B1}$ receptors in maintaining the quiescence of NSCs[55]. It remains unclear how these two types of receptors synergize with $GABA_A$ receptors to inhibit NSC activation/proliferation within the neurogenic lineage.

Though informative, previous *in vivo* studies have mostly used systemic manipulation and cell-autonomous manipulation by genetically knocking down a gene of interest through a genetic or retrovirus-mediated approach. Therefore, little is known about the source of neurotransmitters within the neurogenic niche and the underlying neuronal circuitry. One major advance in recent years has been the identification of functional inputs to newborn neurons and their synaptic partners during adult neurogenesis and the functional impact of existing neuronal circuits on the neurogenic process[2]. A recent study using

paired recording in acute slices showed that interneurons of the neurogliaform cell family provide a source of GABA for immature neurons labeled with POMC-EGFP at 11–12 days after birth[46] in the adult mouse DG[56]. Using a combination of optogenetics and lineage-tracing to target the quiescent radial glia-like NSCs, Song *et al.* showed that parvalbumin-expressing (PV^+) interneurons are a critical and unique niche component among different interneuron subtypes that couples neuronal circuit activity to regulate radial NSC activation through γ_2-containing $GABA_A$ receptors[53]. In contrast to the direct synaptic inputs onto immature neurons in POMC-EGFP mice[48], no apparent functional GABAergic synaptic responses were detected when radial NSCs were recorded in this and previous studies[57], suggesting that GABA spillover from activated PV^+ interneuron-mature GC synapses indirectly regulates nearby radial NSCs. Tonic GABA signaling spillover from presynaptic/postsynaptic neurons provides a means of acting on cells that might be located some distance from the signaling synapse. Therefore, it is an especially attractive candidate signal that reflects the overall local network activity for potential translation to local neural progenitors. Interestingly, a recent study showed that tonic and phasic GABA activation of neural progenitor cells and immature neurons is modulated by chemokine stromal cell-derived factor 1 co-released with GABA from local interneurons[58]. The mechanisms underlying such regulation remain to be determined.

In contrast to the inhibitory role in quiescent radial NSC activation, PV^+ interneuron activity positively regulates the survival of proliferating neuronal progeny[49]. Specifically, proliferating neuronal precursors in the adult mouse DG exhibit immature GABAergic synaptic inputs originating from local PV^+ interneurons. Moreover, PV^+ interneurons promote the survival of proliferative newborn progeny during the early phases of adult hippocampal neurogenesis upon optogenetic activation, whereas their suppression leads to decreased newborn progeny survival under both basal and enriched environment conditions. Taken together, these studies identify a novel niche mechanism involving PV^+ interneurons that couples local circuit activity to diametric regulation of quiescent NSC activation and survival of their proliferating neuronal progeny, two sequential phases of adult hippocampal neurogenesis. These findings provide the basic mechanisms underlying the dynamic control of adult neurogenesis during early developmental stages.

Glutamate The three pharmacologically-defined classes of ionotropic glutamate receptors in the adult brain were originally named after selective agonists — NMDA, AMPA, and kainate. The most studied subtype in adult neurogenesis is NMDA receptors. Accumulating evidence suggests that NMDA receptor-mediated glutamatergic signaling regulates distinct stages of adult neurogenesis. For example, injection of NMDA rapidly decreases cell proliferation in the adult rat DG, whereas injection of an NMDA receptor antagonist has the opposite effect[59, 60]. On the other hand, induction of long-term potentiation (LTP) at glutamatergic medial perforant path-granule cell synapses promotes the proliferation of adult neural progenitors and the survival of newborn neurons in an NMDA receptor-dependent fashion[61, 62]. 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 non-cell-autonomous effects through modulation by existing neuronal circuits. Genetic deletion of NR1, an obligatory subunit of the NMDA receptor, in proliferating adult neural progenitors reduces the survival of their neuronal progeny 2 to 3 weeks after birth[40]. Interestingly, injection of an NMDA receptor antagonist (CPP) diminishes differences in NMDA receptor signaling in all newborn neurons and promotes the survival of NR1-deficient neurons, suggesting a critical period for NMDA receptor-dependent competitive survival of newborn neurons in the adult brain[40]. This critical period coincides 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 on newborn GCs during their maturation process has identified another critical period during which newborn neurons exhibit enhanced LTP. When 4–6 weeks old, newborn neurons exhibit both a reduced induction threshold and increased LTP amplitude in response to a physiological pattern of stimulation[7]. This critical period is associated with developmentally regulated NR2B-containing NMDA receptors in newborn neurons, since pharmacological inhibition of these receptors completely abolishes LTP in these neurons, but not in mature neurons[7].

In contrast to the regulatory role of glutamate in

later stages of neurogenesis, evidence that glutamate receptors regulate adult NSCs is still lacking. Kainate-induced seizures significantly stimulate the proliferation of NSCs[63], indicating the involvement of kainate receptors in the regulation of progenitor proliferation. Recently, a study using comparative recordings from patches excised from the soma and main process of NSCs has demonstrated the presence of AMPA receptors on the radial processes[64]. The functional roles of AMPA and kainate receptors in the regulation of NSCs remain to be determined.

Acetylcholine Accumulating evidence suggests that cholinergic signaling is involved in the regulation of adult hippocampal neurogenesis. For example, selective lesioning of the medial septum system negatively affects the proliferation of neural precursor cells[65, 66] and the administration of acetylcholinesterase inhibitors promotes NSC/neuronal progenitor cell proliferation and leads to a rapid Ca^{2+} rise in NSCs[67, 68]. Newborn neurons in nicotinic receptor α_7-knockout mice show delayed dendritic development and stunted maturation[69]. These studies indicate that neural precursors and their progeny are stimulated by cholinergic activation; however, direct evidence of how cholinergic activity regulates distinct stages of adult neurogenesis is still lacking. In addition, it remains unclear how various cholinergic receptor subtypes in neural precursor cells and their progeny work together to coordinate their responses to acetylcholine release. Future studies using targeted manipulations of components of this circuit are required to elucidate the nature of cholinergic signaling in neurogenesis.

Serotonin Studies of serotonergic signaling have been limited and conflicting[70-72], probably due to the diversity and complexity of serotonin (5-HT) receptor expression in the DG. The 5-HT receptor families are extremely diverse[73], and almost all fifteen receptor subtypes are expressed in the DG[74-79]. Depending upon which subsets of the 5-HT receptors are activated, DG neurons may be either depolarized or hyperpolarized by 5-HT and therefore increase or decrease their excitability. The opposing effects of activating different subsets of 5-HT receptors may explain the conflicting results in some studies. For example, selective 5-HT depletion has been reported to have no effects on the proliferation, survival, and differentiation of SGZ neuronal progenitors in the adult hippocampus[80]. Despite various manipulations leading to inconsistent results, it has been shown that an increase in the level of 5-HT enhances neural progenitor proliferation and differentiation[81], whereas depletion of 5-HT reduces these processes[82]. Future studies targeting the serotonergic-hippocampal circuitry in combination with genetic manipulations of their targets will help to tease out the complicated mechanisms associated with serotonergic circuitry and the relevant receptor subtypes.

Dopamine It has been proposed that dopamine (DA) plays a role in regulating the proliferation of neural precursor cells in the SGZ, although conflicting results have been reported[83, 84]. Denervation of dopaminergic neurons decreases the proliferation of NSCs in the SGZ[85]. Despite emerging studies that enhance our understanding of the role of DA during adult neurogenesis, studies targeting dopaminergic regulation of distinct stages of adult neurogenesis are still largely lacking. Therefore, it remains unclear whether the effect of DA on hippocampal neurogenesis is direct or indirect. Recently, a study using patch-clamp recording suggested that DA has distinct modulatory effects on dentate GCs at different developmental stages and through different receptor subtypes. DA modulates the strength of cortical inputs that newborn neurons receive from the medial perforant path through D1-like receptors, whereas D2-like receptors mediate the modulation of medial perforant path inputs to mature adult-born neurons[86]. It remains to be determined whether DA regulates early stages of adult neurogenesis.

Non-neurotransmitter-mediated Mechanisms

Morphogens A number of morphogens serve as niche signals to regulate the maintenance, activation, and fate choice of adult hippocampal neural precursors, including Notch, Wnts, and bone morphogenetic proteins (BMPs). Conditional disruption of BMP or Notch/RBP-J signaling in NSCs results in rapid initial activation of NSCs accompanied by a transient increase in the proliferation of intermediate neural progenitors and the production of new neurons. However, the long-term consequences of excessive activation of Notch signaling are depletion of the NSC compartment and impaired maintenance of NSCs, which ultimately lead to loss of the regenerative capacity of the radial NSC population and neuronal production[87, 88]. Direct evidence is still lacking in regard to whether the failure of stem cell maintenance is

due to increased astrocytic differentiation of radial NSCs or cell death of their downstream neuronal progeny. In addition to the intrinsic factors that regulate adult NSC development, extrinsic niche factors also play an important role in the regulation of distinct stages of adult neurogenesis. Using lineage-tracing and retrovirus-mediated approaches, the naturally-secreted Wnt inhibitor sFRP3 expressed by local mature GCs has been identified as an inhibitory niche factor, capable of suppressing multiple phases of adult neurogenesis[89]. Although the sources of most niche signals remain to be fully characterized, it is clear that they play important roles in fine-tuning the number of quiescent NSCs and the level of neurogenesis in the adult brain.

Transcription factors The sequential activation of different transcription factors ensures the proper development of adult neural precursors. Sox2 is a major mediator of Notch signaling in maintaining the precursor pool in the adult SGZ[87]. 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[90]. The orphan nuclear receptor TLX is also required for self-renewal and maintenance of neural precursors in the adult brain, likely through the canonical Wnt/β-catenin pathway[91]. Inhibitor of DNA binding (Id) genes encode dominant-negative antagonists of the basic helix-loop-helix transcription factors, and Id1 is highly expressed in radial NSCs in both the adult SVZ and SGZ[92]. In contrast, the transcription factors Prox1, NeuroD, and Kruppel-like factor 9 are sequentially required for the maturation and survival of new neurons in the adult hippocampus[93-95].

Epigenetic factors 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[96]. For example, the epigenetic regulator methyl-CpG-binding domain protein 1 suppresses the expression of FGF-2 and several microRNAs controlling the balance between proliferation and differentiation during adult hippocampal neurogenesis[97]. Another epigenetic regulator, Gadd45b, is involved in maintaining the proliferation of neural precursors and the dendritic growth of newborn neurons by promoting BDNF and FGF1 expression in mature GCs in response to neuronal activation[98].

Cell-cycle regulators Cell-cycle inhibitors 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. A recent study has shown a requirement for the cyclin-dependent kinase inhibitor p57 in the maintenance of NSC quiescence; when p57 is deleted from NSCs *in vivo* a transient increase in neurogenesis through uncontrolled NSC activation is sharply followed by NSC pool exhaustion and reduced adult neurogenesis[99]. These findings fall among various other studies supporting a critical role of endogenous cyclin-dependent inhibitors and cyclin-dependent kinases in the cell-autonomous mechanics of adult neurogenesis[100]. Another recent study using an *in vivo* clonal approach clearly demonstrated that quiescent radial NSCs with PTEN deletion fail to be maintained over time due to increased astrocytic differentiation at the expense of neuronal differentiation[4]. How cell-cycle components dictate NSC fate choice is particularly important when considering the necessity of maintaining this population over a lifetime and neurogenic deficiencies that arise during aging.

Adult Neural Stem Cells in Experience-Mediated Plasticity and Disease

The generation of new neurons from adult NSCs is a dynamic and regulated process. Under physiological conditions, adult neurogenesis is regulated by controlling NSC activation, neuronal precursor proliferation/differentiation, and the survival of the newly-generated cells. Several physiological stimuli contribute to the dynamic regulation of adult neurogenesis, including physical exercise, various environmental and experiential conditions, learning, and aging. Physical activity enhances the generation of new neurons by inducing the proliferation of radial $Sox2^+$ progenitors and neuronal precursors[7]. The stress of social isolation promotes the expansion of radial NSCs, while exercise within enriched environments increases their neurogenic potential[28]. Chronic social isolation stress induces the activation and symmetric cell division of quiescent NSCs, and the long-term consequences of such an experience contribute to decreased adult neurogenesis. Aging is associated with a continuous decline in the number of new neurons, which could be due to increased quiescence of horizontal

NSCs[25] or the disappearance of radial NSCs *via* their conversion into mature hippocampal astrocytes[101]. Different neurogenic stimuli appear to affect cells at distinct stages of neurogenesis, and each of these stimuli can act at one or multiple levels of the neurogenic lineage. For example, voluntary running increases cell proliferation, while exposure to an enriched environment promotes new neuron survival. Learning modulates neurogenesis in a complex yet specific fashion, presumably by inducing the activation of NSCs and subsequently enhancing their survival and incorporation into neuronal circuits[102, 103]. Though a causal link between altered neurogenesis and animal behavior has not been established, it is likely that altered adult neurogenesis partially contributes to animals' overall behavioral outcomes.

Adult NSCs are also influenced by pathological conditions. Acute seizure activity robustly induces the production of aberrant dentate GCs at nearly every stage of adult neurogenesis. This includes increased activation of radial and horizontal NSCs[25], increased proliferation of neural progenitors and neuroblasts[35], ectopic migration, and aberrant dendritic and axonal development in immature neurons[104]. Chronic neurodegeneration impacts stem-cell maintenance, proliferation, survival, and functional integration in complex ways. For example, in mouse models of Alzheimer's disease, impaired GABA signaling leads to reduced hippocampal neurogenesis. This appears to occur, in part, through a mechanism involving a switch in NSC fate from a neurogenic to a gliagenic fate[105]. Abnormal dendritic growth and aberrant synaptic integration have also been reported[106]. In mice deficient in fragile X mental retardation protein (FMRP; a gene responsible for fragile X syndrome), both the 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[107]. Methyl-CpG-binding protein 2 (a gene mutated in Rett syndrome) regulates the maturation and spine formation of new neurons in the adult hippocampus[108]. Adult neurogenesis is also influenced by several additional pathological conditions, including inflammation induced by injury and irradiation, HIV infection, and drug addiction[3].

A number of neurological disease risk genes have been shown to regulate adult neurogenesis in a cell-autonomous fashion. 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[18]. Disrupted-in-schizophrenia 1 (a gene implicated in major mental disorders) promotes the proliferation of neural progenitors through the GSK3β/β-catenin pathway[109], while limiting dendritic growth and synapse formation of new neurons through AKT/mTOR signaling in the adult hippocampus[110, 111]. These findings raise the intriguing possibility that aberrant postnatal neurogenesis may contribute to the juvenile and adult onset of many mental disorders[17].

It is becoming increasingly clear that adult neurogenesis is a multistep process modulated at different steps by various extrinsic and intrinsic neurogenic stimuli and influenced by pathological situations. Each neurogenic modulator may act at only one or at multiple levels of the neurogenic lineage. However, it is not clear whether changes in neurogenesis are NSC responses, adaptation in proliferation and survival of other cell types, or a combination of these effects. It is also unclear whether distinct NSC populations have different requirements for their maintenance and differentiation. Furthermore, it is also unclear if the most primitive NSCs in the adult brain, a quiescent population, can directly sense neuronal network activity and change their behavior. In future studies, it will be fundamentally important to define the relationships among distinct NSC populations (quiescent radial, active radial, quiescent horizontal, and active horizontal), how they are differentially regulated by various physiological and pathological stimuli, and the underlying molecular mechanisms of how they couple with neuronal activity to produce differentiated progeny. Identification of these mechanisms is critically important for harnessing this novel plasticity of adult neurogenesis to help repair the injured, diseased, and aged brain.

Concluding Remarks

Rapid progress in the field over the past decade has led to a better understanding of the distinct developmental steps of adult neurogenesis. Efforts have been made to elucidate different aspects of the regulation of adult neurogenesis

and a plethora of intrinsic and extrinsic factors have been associated with distinct steps of adult neurogenesis. Despite the identification of a variety of molecules involved in regulating distinct stages of adult neurogenesis, it remains unclear how extrinsic niche signaling is coupled to this intrinsic regulatory machinery. Moreover, the contributions of various anatomical and functional components within the SGZ remain to be determined. Future studies are needed to identify the molecular and cellular mechanisms underlying the activity-dependent circuitry regulation at distinct developmental stages of adult neurogenesis. Moreover, the heterogeneity of NSCs also raises the question of region-specific niche organization. It is important that further studies address how different niche components and signaling pathways interact to orchestrate the precise regulation of distinct stages of adult neurogenesis. Identification of new markers that dissect 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. Understanding novel cellular and molecular mechanisms that regulate adult NSCs and the incorporation of newborn neurons into mature circuits will add greatly to our understanding of neuronal development and adult neurophysiology. This information is essential for designing strategies for the prevention and treatment of neurodevelopmental disorders, and also regeneration within the adult nervous system.

ACKNOWLEDGEMENTS

We thank Reid HJ Olsen for discussion and comments. This review was supported by startup funds from the Department of Pharmacology at the University of North Carolina (UNC), and grants from NARSAD, the Whitehall Foundation, and the American Heart Association and a UNC Biological and Biomedical Sciences Program training grant, and an NIH T32 Neurobiology Curriculum training grant.

Received date: 2014-04-06; Accepted date: 2014-07-15

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