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Adult Neurogenesis in the Mammalian Central Nervous System

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Key Words

neural stem cell, progenitor, development, regeneration, plasticity

Abstract

Forty years since the initial discovery of neurogenesis in the postnatal rat hippocampus, investigators have now firmly established that active neurogenesis from neural progenitors continues throughout life in discrete regions of the central nervous systems (CNS) of all mammals, including humans. Significant progress has been made over the past few years in understanding the developmental process and regulation of adult neurogenesis, including proliferation, fate specification, neuronal maturation, targeting, and synaptic integration of the newborn neurons. The function of this evolutionarily conserved phenomenon, however, remains elusive in mammals. Adult neurogenesis represents a striking example of structural plasticity in the mature CNS environment. Advances in our understanding of adult neurogenesis will not only shed light on the basic principles of adult plasticity, but also may lead to strategies for cell replacement therapy after injury or degenerative neurological diseases.

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Adult neural stem cells: a type of unspecified precursor cells that has the capacity to proliferate in generating more of itself and to make new neurons, astrocytes, and oligodendrocytes

INTRODUCTION

Neurogenesis, a process of generating functionally integrated neurons from progenitor cells, was traditionally believed to occur only during embryonic stages in the mammalian CNS (Ramon y Cajal 1913). Only recently has it become generally accepted that new neurons are indeed added in discrete regions of the adult mammalian CNS (Gross 2000, Kempermann & Gage 1999, Lie et al. 2004). In most mammals, active neurogenesis occurs throughout life in the subventricular zone (SVZ) of the lateral ventricle and in the subgranular zone (SGZ) of the dentate gyrus in the hippocampus. Neurogenesis outside these two regions appears to be extremely limited, or nonexistent, in the intact adult mammalian CNS. After pathological stimulation, such as brain insults, adult neurogenesis appears to occur in regions otherwise considered to be nonneurogenic. Our understanding of adult neurogenesis in mammals has progressed significantly over the past decade, and we now know a great deal more about the biology of this biological phenomenon, from the identity and location of adult neural stem cells, and proliferation and fate specification of neural progenitors, to migration, nerve guidance, neuronal maturation, and synaptic integration of newborn neurons in the adult CNS environment (Alvarez-Buylla & Lim 2004, Gage 2000, Goh et al. 2003, Kempermann & Gage 1999, Lie et al. 2004). We have also gained significant knowledge of how adult neurogenesis is regulated in the normal and abnormal CNS (Duman et al. 2001, Fuchs & Gould 2000, Kempermann 2002). Advances in our understanding of adult neurogenesis have been facilitated by the isolation and in vitro analysis of multipotent neural progenitors derived from the adult CNS (Gottlieb 2002). The demonstration of active adult neurogenesis also opens possibilities to repair the adult CNS after injury or degenerative neurological diseases using cell replacement therapy in the near future (Lindvall et al. 2004, Rossi & Cattaneo 2002). In this review on adult neurogenesis in the mammalian CNS systems, we start with milestone discoveries and methodologies in the field of adult neurogenesis. We then summarize the current understanding of adult neurogenesis and finish with a discussion of potential functions of mammalian adult neurogenesis. Interested readers may consult several recent comprehensive reviews on this topic (Alvarez-Buylla & Lim 2004, Goh et al. 2003, Kempermann

& Gage 1999, Lie et al. 2004, Lindvall et al. 2004, Parent 2003, Rossi & Cattaneo 2002).

The predominant repair mechanisms in the adult CNS were traditionally thought to be very limited and restricted to a postmitotic state, such as sprouting of axon terminals and synaptic reorganization. The recent demonstration of functional neurogenesis and isolation of multipotent neural stem cells from the adult mammalian CNS, including that of humans, has important implications for the development of new strategies for the treatment of injury and neurodegenerative diseases in the adult CNS. First, stem cells with the potential to give rise to new neurons appear to reside in many different regions of the adult CNS. These findings raise the possibility that endogenous neural stem cells can be mobilized for the replacement of dying neurons in neurodegenerative diseases. Indeed, recent reports have provided evidence that in some injury models limited neuronal replacement occurs in the CNS. Second, the complete process of neuronal development can be recapitulated in certain areas of the adult CNS, resulting in integration of functional new neurons into the existing circuits. Exploration of the underlying mechanisms of adult neurogenesis may lead to strategies to support functional neuronal replacements in other areas with either endogenous progenitors or neuronal progeny of stem cells from other sources, such as embryonic stem cells.

HISTORIC OVERVIEW

In addition to proving the neuron doctrine using the Golgi technique, Santiago Ramon y Cajal (1913) also concluded that neurons are generated exclusively during the prenatal phase of development. Although suggestions regarding the existence of dividing cells in the postnatal CNS were raised (Allen 1912, Hamilton 1901), it was impossible, using methods of the time, to trace the fate of those rare dividing cells and to prove that the newborn cells were in fact neurons rather than glia (Ramon y Cajal 1913). Since then, "no new neurons after birth" became a central dogma in neuroscience for almost a century (Gross 2000). In the late 1950s, a new method was developed to label dividing cells with [H^3]-thymidine, which incorporates into the replicating DNA during the S-phase of the cell cycle and can be detected with autoradiography (Sidman et al. 1959). The generation of new neurons was first reported using this technique in three-day old mouse brains (Smart 1961). Soon after, Altman and colleagues published a series of papers reporting [H^3]-thymidine evidence for new neurons in various regions of adult rats, including the dentate gyrus of the hippocampus (Altman & Das 1965), neocortex (Altman 1966) and olfactory bulb (Altman 1969). However, little attention was given to these studies, perhaps because they were considered to lack functional relevance. The issue of adult neurogenesis was revisited in the late 1970s when Kaplan & Hinds (1977) demonstrated that newborn neurons in the hippocampus survived for a long period of time. These new neurons also appeared to receive synaptic inputs (Kaplan & Bell 1983) and extend axon projections to their target area (Stanfield & Trice 1988). Meanwhile, a series of studies of adult neurogenesis in songbirds started to provide evidence for functional roles of postnatal neurogenesis in seasonal song learning (Nottebohm 2004). Adult neural stem cells, the sources of new neurons, were first isolated from the adult CNS of rodents (Reynolds & Weiss 1992) and later from humans (Kukekov et al. 1999). The field was revolutionized by the introduction of bromodeoxyuridine (BrdU), a synthetic thymidine analogue, as another S-phase marker of the cell cycle (Gratzner 1982). Because BrdU can be detected by immunocytochemistry for phenotypic analysis and stereological quantification, this approach remains the most commonly used technique in the field. Before the end of the twentieth century, adult neurogenesis was observed with BrdU incorporation in all mammals examined, including samples from human patients (Eriksson et al. 1998). Combined retroviral-based lineage tracing (Price et al. 1987, Sanes et al. 1986) and electrophysiological studies provided the most convincing evidence so far that newborn neurons in the adult mammalian CNS are

Neurogenesis: a process of generating functional neurons from progenitor cells, including proliferation and neuronal fate specification of neural progenitors, and maturation and functional integration of neuronal progeny into neuronal circuits

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indeed functional and synaptically integrated (Belluzzi et al. 2003, Carleton et al. 2003, van Praag et al. 2002). A central question in the field of adult neurogenesis remains to be answered for years to come: What is the functional significance of this biological phenomenon in mammals?

METHODOLOGIES FOR INVESTIGATION OF ADULT NEUROGENESIS

Analysis of Endogenous Adult Neurogenesis In Vivo

The field of adult neurogenesis has been propelled by technical advances to facilitate identification of newborn neurons among the billions of existing neurons in the adult CNS. Three approaches have been explored so far (**Figure 1**).

Analysis based on the incorporation of nucleotide analogs during cell division. During DNA replication in the S-phase of the cell cycle, exogenous nucleotides such as [H^3]-thymidine or BrdU are incorporated into newly synthesized DNA and then passed on to cell progeny (**Figure 1*A***). Two different analogs can be used sequentially to measure the cell-cycle length (Cameron & McKay 2001, Hayes & Nowakowski 2002). By varying the pulsing paradigm and the examination time points after pulsing, this simple technique allows quantitative analysis of proliferation, differentiation, and survival of newborn cells (Kempermann et al. 1997, Miller & Nowakowski 1988). [H^3]-thymidine requires autoradiographic detection and has good stoichiometry if consistent exposure times and development procedures are used (Rogers 1973). BrdU, on the other hand, can be detected with immunohistochemistry (not stoichiometric) and allows both phenotypic analysis and stereological quantification of new cells. There are several limitations to this approach. First, it requires tissue fixation and DNA denaturing and therefore is not suitable for analyzing live cells. Second, labeling is restricted to the nucleus and requires careful confocal microscopy to confirm colocalization with cell-type-specific markers (Rakic 2002). Third, the amount of analogs incorporated from a single injection is diluted to undetectable levels after several rounds of cell division (Hayes & Nowakowski 2002). In addition to these technical limitations, we must also pay attention to additional caveats of this approach. BrdU or [H^3]-thymidine incorporation is an indication of DNA synthesis only, not cell division. Nucleotide analogs are also incorporated into nicked, damaged DNA undergoing repair, albeit on a smaller scale than during DNA replication (Selden et al. 1993). Thus, the dose and duration of BrdU pulsing, as well as the detection of BrdU, need to be appropriately controlled to avoid misidentification of repairing/dying cells as newborn cells. Furthermore, the possibility of cell cycle reentry by postmitotic neurons as a prelude to apoptosis after brain injury (Kuan et al. 2004) needs to excluded. Demonstrating neurogenesis after brain injury requires not only BrdU uptake and mature neuronal markers but also evidence showing the absence of apoptotic markers. In addition, we need to be cautious when interpreting results from experimental manipulations that can potentially change the accessibility, stability, or diffusion of the analogs, which might affect their incorporation, instead of directly affecting cell proliferation.

Analysis based on genetic marking with retroviruses. The expression of transgenes from retroviruses requires viral integration into the host genome (Lewis & Emerman 1994). For retroviruses that lack nuclear import mechanisms, such as the Muloney murine leukemia virus, viral integration occurs only when the nuclear membrane breaks down during mitosis (Lewis & Emerman 1994), thus making it a good indicator of cell division (**Figure 1*B***). Expression of a live reporter, such as green fluorescent protein (GFP), allows direct visualization and analysis

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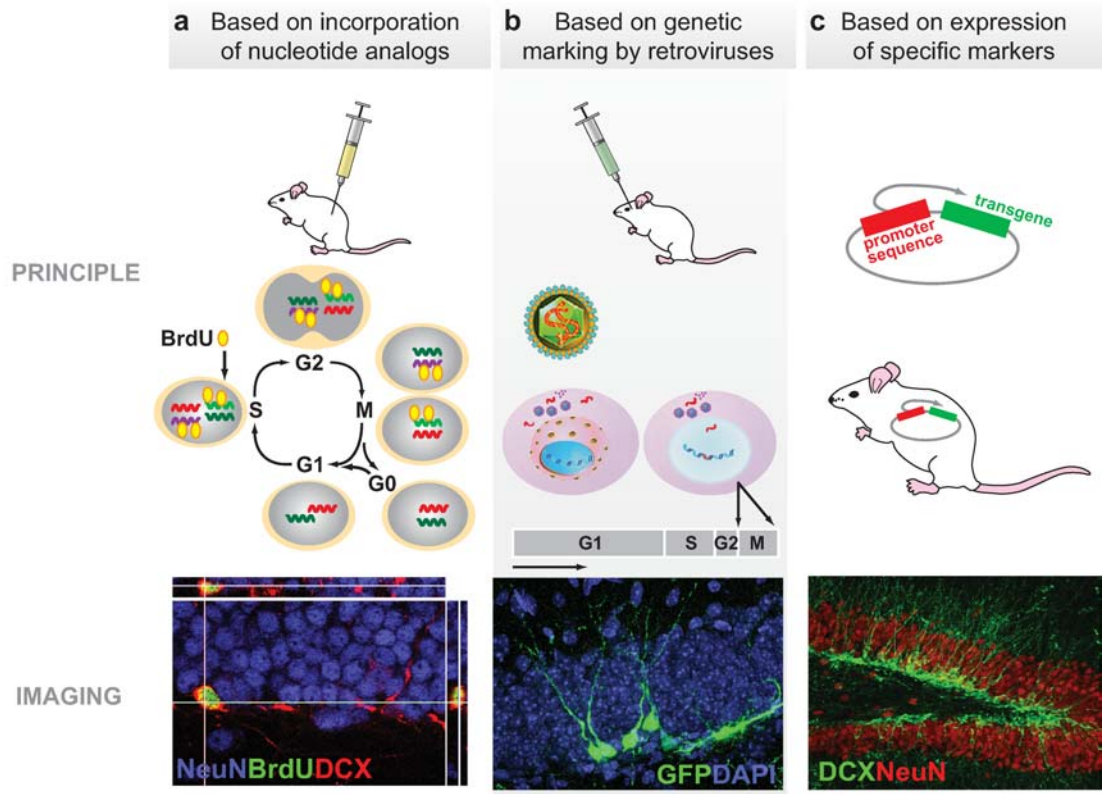

	a	b	c
Birth dating	good	good	poor
Tracing	permanent	permanent	transient / permanent
Cell Population	whole population	limited cells	whole population
Visualization	fixation / processing	direct	processing / direct
Morphology	nuclear	whole cell	cellular / whole cell
Concerns	DNA repair	invasive	specificity

Figure 1

Methodologies for analysis of adult neurogenesis in vivo. Three different approaches to identify newborn neurons of the adult CNS in vivo are illustrated. (*A*) Analysis based on the incorporation of nucleotide analogs during DNA replication in the S-phase of the cell cycle. A sample picture shows confocal analysis to confirm the colocalization of bromodeoxyuridine (BrdU) and cell-type-specific markers. (*B*) Analysis based on retroviral genetic marking. The expression of transgenes from some retroviruses requires integration of the retroviral genome into the host genome, which occurs only during mitosis (M) when the nuclear membrane breaks down. A sample picture shows the expression of green fluorescent protein (GFP) in newborn cells two weeks after stereotaxic injection of the retrovirus into the hilus region of the adult mouse hippocampus. This approach allows direct visualization of the morphology of newborn cells. (*C*) Analysis based on the expression of specific markers for immature neurons. Transgenic mice can also be made to express reporters under specific promoters. A sample picture shows the expression of markers for immature neurons (DCX) and mature neurons (NeuN) in the adult mouse dentate gyrus of the hippocampus. Some of the advantages and disadvantages of these three approaches are listed.

of living newborn cells. This approach, however, requires invasive stereotaxic injection into specific brain regions. Future combination with site-specific recombinase and siRNA systems will make this "single-cell genetic" approach very powerful to investigate mechanisms underlying adult neurogenesis.

Analysis based on expression of specific markers. Developing neurons express distinct markers during their maturation process (Kempermann et al. 2004a). Common markers used for immature neurons include PSA-NCAM (poly-sialylated-neural cell-adhesion molecule), Tuj1 (β-tubulin isoform III), CRMP (collaspin response-mediated protein 4, also known as TOAD4), and DCX (doublecortin). Among the markers used for mature neurons are MAP-2ab (microtubule-associated protein-2 a and b isoforms) and NeuN (neuronal nuclei). Newborn neurons can be identified by the presence of immature markers and absence of mature markers of neurons. This approach can be used when birth dating with nucleotide analogs or retroviruses is impractical, such as for human tissue studies. The caveat for this approach relates to the specificity of the markers used for immature neurons. Some antibodies to these immature markers (e.g., Tuj1) also stain nonneuronal cells (Katsetos et al. 2001), and some markers (e.g., PSA-NCAM) are reexpressed in preexisting neurons (Charles et al. 2002) under certain conditions.

One exciting development in the field of adult neurogenesis is the generation of animal models that allow visualization and specific manipulation of newborn neurons in the adult CNS (**Figure 1*C***). Several transgenic mice have been generated to express specific genes of interest under a desired promoter (Overstreet et al. 2004, Yamaguchi et al. 2000). For example, adult mice expressing GFP under the control of the regulatory regions of the nestin gene reveal both neural progenitors and some immature neurons (Yamaguchi et al. 2000). In the transgenic mice expressing GFP under the transcriptional control of the proopiomelanocortin (POMC) genomic sequences, a population of newly born granule cells of the dentate gyrus is selectively labeled (Overstreet et al. 2004). Because the expression of the reporter in these mice is transient (Overstreet et al. 2004, Yamaguchi et al. 2000), it is not possible to track the same population of cells along their maturation process. The next generation of animal models should take advantage of the available inducible systems in mice, such as inducible Cre recombinase (e.g., Cre-ER) and tetracycline-regulated systems (Branda & Dymecki 2004). These approaches may allow manipulation of a specific population of adult-generated neurons in a temporally and spatially precise manner for mechanistic and functional analysis of adult neurogenesis in vivo.

The phenotypic analysis of newborn cells requires examination of the colocalization of the cell-type specific markers and the lineage tracer. Because cells are tightly associated with each other in the adult CNS, the current standard is to perform three-dimensional reconstruction with confocal microscopy (**Figure 1*A***). Electron microscopy has also been used to reveal the ultrastructure of newborn cells. In addition, unbiased stereological techniques are used for quantification of the newborn cells and their phenotypes (Kempermann et al. 1997). Generally, the development of newborn cells is followed by expression of different cell-type-specific markers. Using these immature neuronal markers in conjunction with lineage tracers helps to avoid mis-identifying dying/repaired neurons as newborn neurons (Magavi et al. 2000).

The functional analysis of adult neurogenesis has been carried out at three different levels: individual synapses and cells, neuronal circuits, and whole animals. For example, individual newborn neurons have been analyzed using electrophysiology in acute slice preparations (Overstreet et al. 2004, van Praag et al. 2002). Functional integration of new neurons also has been examined using virus-based

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transsynaptic neuronal tracing and analysis of c-Fos expression induced by neuronal activity (Carlen et al. 2002). At the neuronal-circuit and whole-animal levels, consequences of manipulating the extent (increase or decrease) of adult neurogenesis have been examined with electrophysiology and behavior analysis. Unfortunately, all current manipulations also affect other physiological processes in addition to neurogenesis. Therefore, functions of adult neurogenesis remain elusive.

In the near future, we will see sophisticated animal models that allow specific genetic marking or silencing (through expression of toxic proteins) of newborn neurons in a temporally and spatially controlled manner. Rapid technical advances in multiphoton confocal microscopy for in vivo imaging of adult CNS neurons over periods of milliseconds to months will allow direct visualization and analysis of adult neurogenesis in greater detail (Mizrahi et al. 2004, Mizrahi & Katz 2003). Our efforts in understanding adult neurogenesis will also be facilitated by neural modeling approaches (Cecchi et al. 2001, Chambers et al. 2004, Deisseroth et al. 2004).

Analysis of Adult Neurogenesis In Vitro and Ex Vivo

Multipotent neural progenitors have been isolated from various regions of the adult mammalian CNS, including human CNS regions (Gottlieb 2002). These cells can be expanded and genetically modified and still maintain their multipotentiality over many passages. Because of easy access and defined culture conditions, manipulation of adult neural progenitors in monolayer (Deisseroth et al. 2004, Song et al. 2002a) or slice cultures (Bolteus & Bordey 2004, Raineteau et al. 2004) allows precise analysis of the intrinsic and extrinsic mechanisms that control the various steps of neurogenesis, including proliferation, survival, fate specification, neuronal migration, maturation, and synapse formation.

Cultures of neural progenitors from the adult CNS are largely established on the basis of their preferential growth over other cell types when grown in defined media with specific growth factors (Gottlieb 2002) (**Figure 2**). Cells dissociated from specific tissues are plated either directly (Reynolds & Weiss 1992) or after partial purification steps to remove major contaminants (Palmer et al. 1999). Prospective isolation methods using fluorescence-activated cell sorting (FACS) have recently been developed on the basis of cell properties and/or cell-surface antigens (Rietze et al. 2001, Temple 2001, Uchida et al. 2000) or the expression of reporters under specific promoters (Roy et al. 2000). Two types of progenitor cultures are commonly used (Gottlieb 2002). In the neurosphere culture, individual neural progenitors proliferate on a nonadhesive substrate and generate suspended clusters of cells (Reynolds & Weiss 1992). In the adhesive culture, neural progenitors grow as a monolayer on coated substrates, such as laminin (Ray et al. 1993). The most commonly used growth factors to maintain self-renewal of cultured adult neural progenitors are epidermal growth factor (EGF) and basic fibroblast growth factor (FGF-2). Other growth factors also appear to be effective, such as Sonic hedgehog (Shh) (Lai et al. 2003) and amphiregulin (Falk & Frisen 2002). It remains to be examined whether neurogenesis from neural progenitors expanded under different conditions will have the same properties.

Neurogenesis from these neural progenitors can be examined in culture or after transplantation using immunocytochemistry, calcium and FM-imaging, electron microscopy, and electrophysiological techniques (**Figure 2**). Whereas factors that promote neuronal differentiation of multipotent neural progenitors are largely unknown, coculture of adult neural stem cells with hippocampal or SVZ astrocytes has been shown to promote neuronal differentiation (Lim & Alvarez-Buylla 1999, Song et al. 2002a). Neural progenitors also have been transplanted into early embryos and the fetal and adult CNS to examine their development (**Figure 2**).

Self-renewal: a process of cell division to generate more cells of the same type. It is a hallmark property of stem cells.

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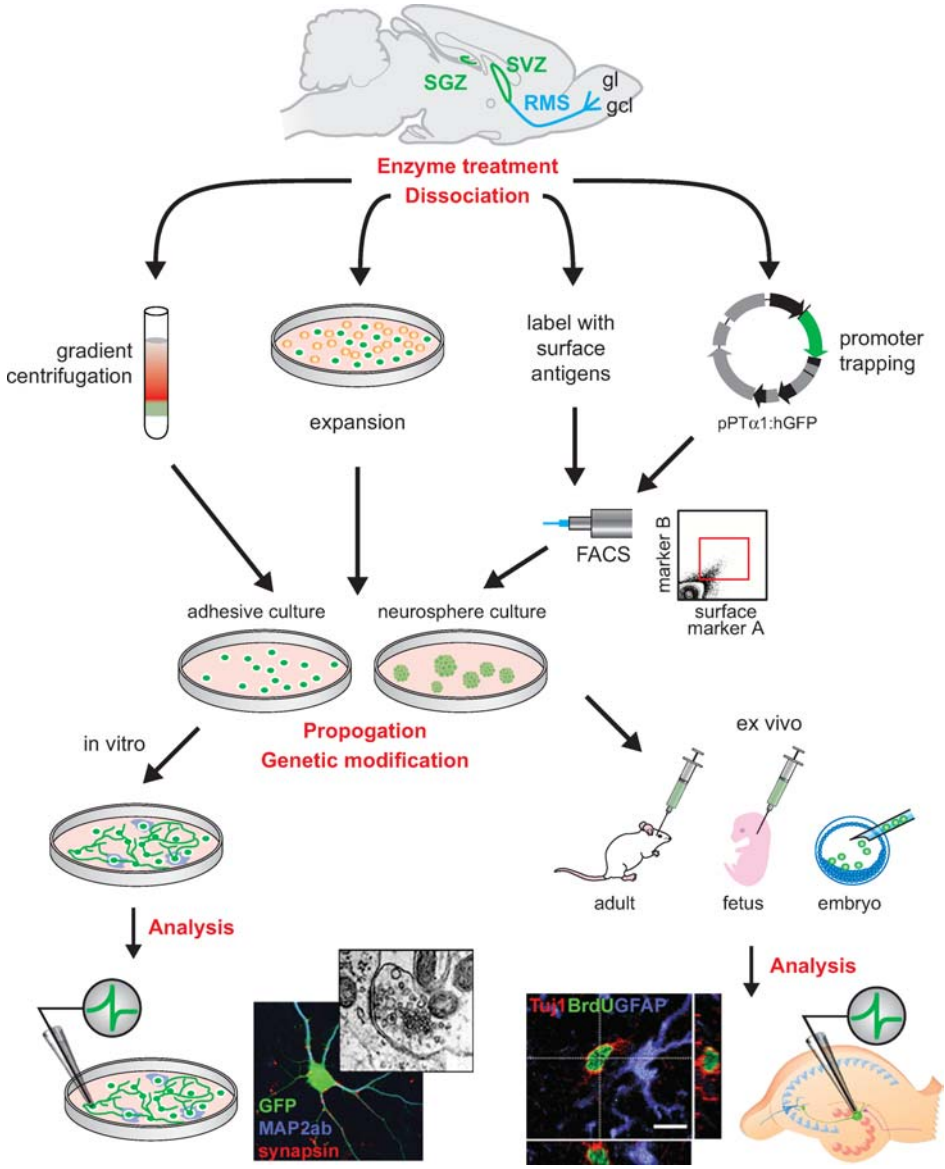

Figure 2

Methodology for analysis of adult neurogenesis in vitro and ex vivo. Multipotent neural progenitors have been cultured from various regions of the adult CNS. Here we illustrate several approaches that have been used to derive neural progenitors from the adult CNS and to analyze neurogenesis from these multipotent progenitors both in vitro and ex vivo. FACS, fluorescence-activated cell sorting.

During the past few years, many reports of isolation of adult cells with neurogenic potentials in vivo and in vitro have appeared, surprisingly, with some from nonneural tissues (Raff 2003). In many cases, single or multiple antibody markers were used as the only criteria to determine if the differentiated cells were neurons (e.g., Tuj1 or NeuN). Numerous studies have shown that morphological and immunochemical appearances are not necessarily predictive of physiological properties, thus functional analysis using electrophysiology to determine the neuronal properties is indispensable (Song et al. 2002b). In addition, cell fusion between progenitors and mature cell types occurs both in vitro and in vivo (Raff 2003). Therefore, it is also essential to distinguish between neuronal differentiation and cell-fusion events.

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NEUROGENESIS IN THE INTACT ADULT MAMMALIAN CNS

Active neurogenesis occurs only in discrete regions of the intact adult CNS (Alvarez-Buylla & Lim 2004, Lie et al. 2004). From rodents to primates, neurons are generated continuously in the SVZ and migrate anteriorly through the rostral migratory stream (RMS) into the olfactory bulb to become interneurons (**Figure 3**). In the dentate gyrus of the hippocampus, new granule neurons are continuously born locally in all mammals examined, including humans (**Figure 4**).

The Adult Neural Stem Cell, Its Proliferation, and Neuronal Fate Specification

The identity of neural stem cells that give rise to new neurons in the adult CNS has been a subject of hot debate for the past few years. Several cell types have been proposed as the resident adult neural stem cell, including astrocytes (Doetsch et al. 1999), multiciliated ependymal cells (Johansson et al. 1999) and subependymal cells (Morshead et al. 1994). The astrocyte hypothesis is currently a prevalent view (Alvarez-Buylla & Lim 2004). In the SVZ of rodents (**Figure 3**), a subset of astrocytes ($GFAP^+$) gives rise to rapidly proliferating transient amplifying cells ($GFAP^-Dlx2^+$), which in turn generate migrating neuroblasts ($GFAP^-Dlx2^+PSA\text{-}NCAM^+$). In adult humans, some astrocytes lining the lateral ventrical divide in vivo and behave like multipotent neural progenitors in vitro (Sanai et al. 2004). It remains to be determined, however, whether these astrocytes indeed give rise to neurons in adult humans. In the SGZ (**Figure 4**), a subset of astrocytes has also been proposed as the stem cells that give rise to new granule neurons (Seri et al. 2001). These astrocytes ($GFAP^+$), with their cell bodies in the SGZ, have radial processes going through the granule cell layer and short tangential processes extending along the border of the granule cell layer and hilus (**Figure 4**). These cells divide and give rise to immature neurons ($DCX^+PSA\text{-}NCAM^+$). Investigators do not know whether these astrocytes also give rise to new neurons found in the adult human dentate gryus (Eriksson et al. 1998).

The factors that regulate in vivo proliferation of adult neural stem cells in the SVZ and the SGZ have not been fully characterized. Members of the FGF and EGF growth factor families are primary mitogens used to propagate adult neural progenitors in vitro and are likely to perform similar functions in vivo (Lie et al. 2004). The transient amplifying cells of the SVZ appear to express the EGF receptor (Doetsch et al. 2002, Morshead et al. 1994). In the SVZ, infusion of EGF or FGF-2 increases cell proliferation (Kuhn et al. 1997), whereas knockout of TGFα, a ligand for the EGF receptor, leads to a significant decrease in cell proliferation (Tropepe et al. 1997). Shh also promotes proliferation of adult neural stem cells both in vitro and in vivo (Lai et al. 2003, Machold et al. 2003). Interestingly neural progenitors and brain tumors share many common features (Oliver & Wechsler-Reya 2004). They express common sets of markers (e.g., nestin, CD133, bim-1, and sox-2) and share pathways regulating their proliferation (e.g., Shh, PTEN). Future comparative studies of neural progenitors and cancer cells will facilitate the understanding of the self-renewal of adult neural stem cells and of the origins of brain tumors.

What makes the SVZ and SGZ special in supporting the proliferation and neuronal differentiation of multipotent neural progenitors is an area of intensive investigation (Doetsch 2003, Lie et al. 2004). Investigators have postulated that endothelial cells and some special astrocytes provide a unique neurogenic niche (Doetsch 2003, Lie et al. 2004, Palmer et al. 2000). Astrocytes from the SVZ and hippocampus promote proliferation and neuronal fate specification of cocultured adult neural progenitors (Lim & Alvarez-Buylla 1999, Song et al. 2002a). In contrast, astrocytes from the adult spinal cord,

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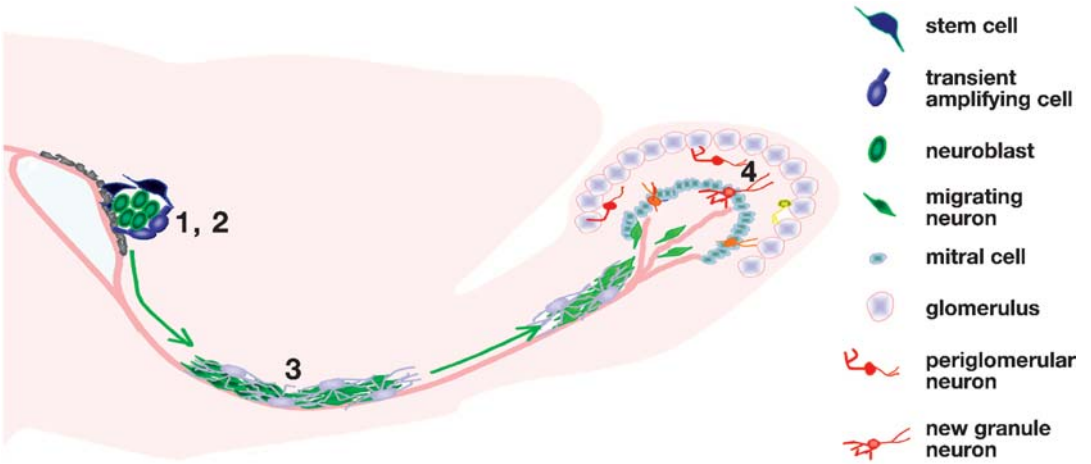

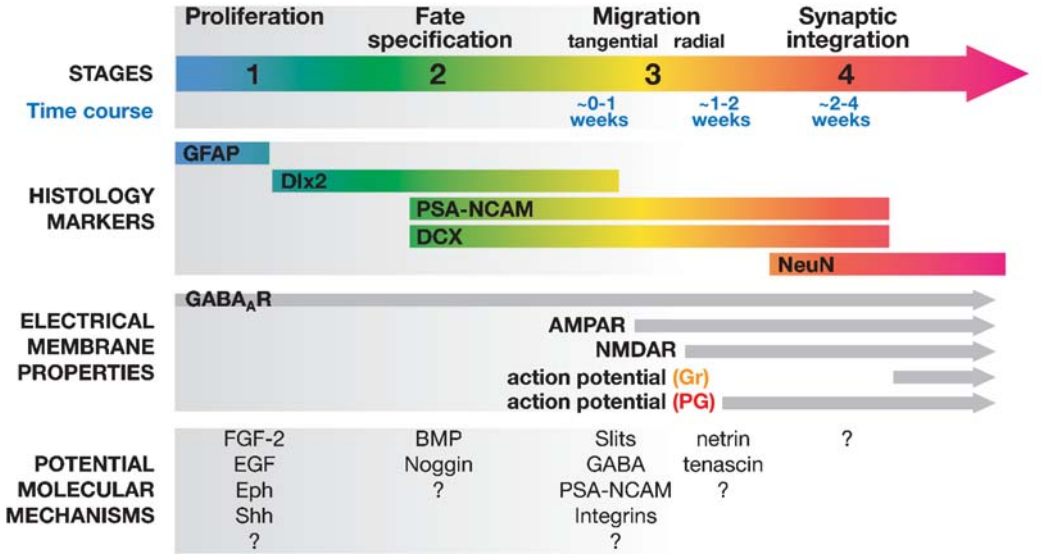

Figure 3

Generation of new interneurons in the olfactory bulb from neural stem cells in the subventricular zone (SVZ). Adult neurogenesis in the SVZ/olfactory systems undergoes four developmental stages. Stage 1. Proliferation: stem cells (*blue*) in the SVZ of the lateral ventricles give rise to transient amplifying cells (*light blue*). Stage 2. Fate specification: transient amplifying cells differentiate into immature neurons (*green*). Adjacent ependymal cells (*gray*) of the lateral ventricle are essential for neuronal fate specification by providing inhibitors of gliogenesis. Stage 3. Migration: Immature neurons (*green*) migrate with each other in chains through the rostral migratory stream (RMS) to the olfactory bulb. The migrating neurons are ensheathed by astrocytes. Once reaching the bulb, new neurons then migrate radially to the outer cell layers. Stage 4. Synaptic integration: Immature neurons differentiate into either granule neurons (Gr, *orange*) or periglomerular neurons (PG, *red*). These unusual interneurons lack an axon and instead release their neurotransmitter from the dendritic spines at specialized reciprocal synapses to dendrites of mitral or tufted cells. The specific properties of each stage are summarized below, mainly on the basis of studies in adult mice.

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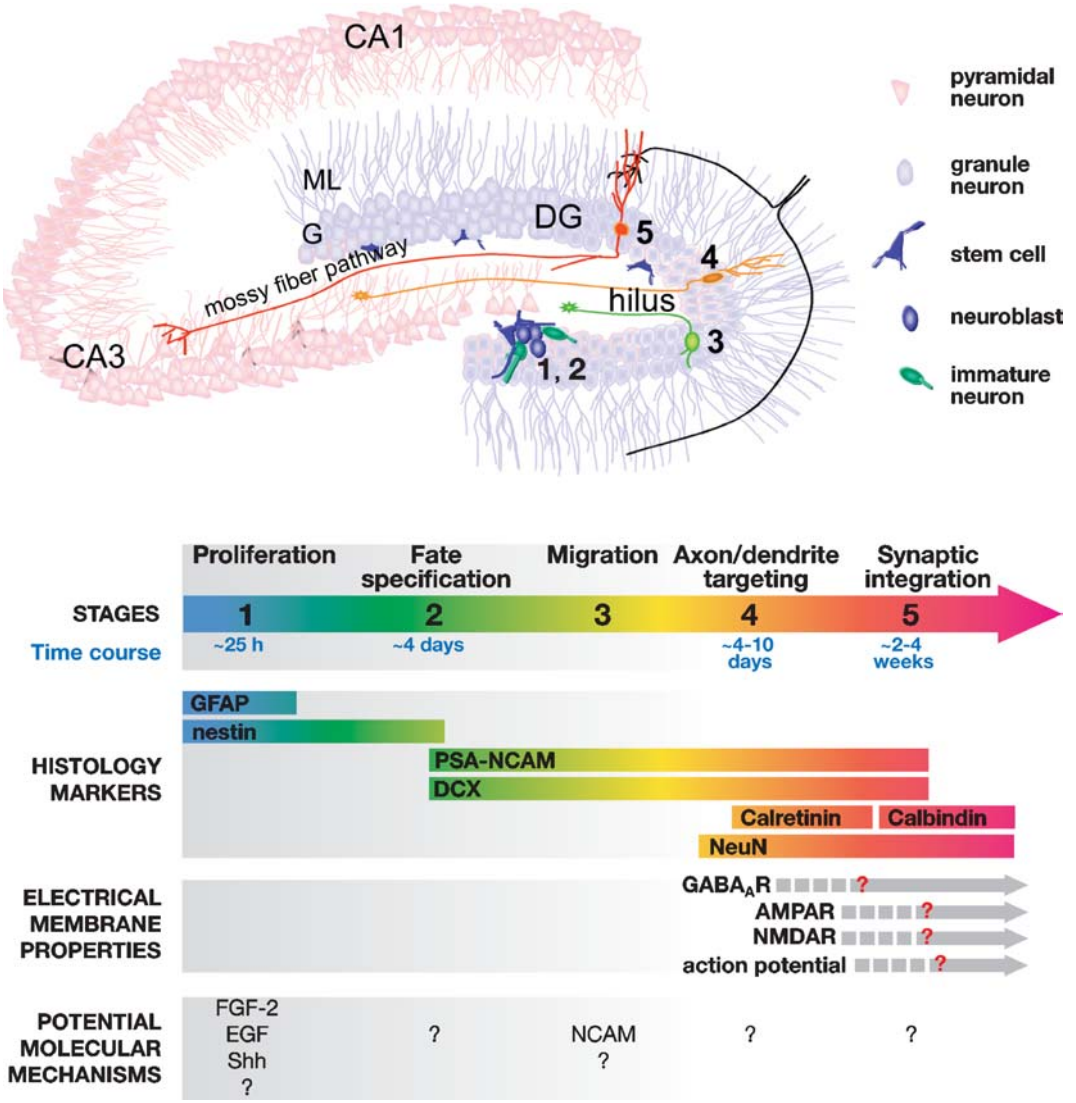

Figure 4

Generation of new granular neurons in the dentate gyrus of the hippocampus from neural stem cells in the subgranular zone (SGZ). Adult neurogenesis in the dentate gyrus of the hippocampus undergoes five developmental stages. Stage 1. Proliferation: Stem cells (*blue*) with their cell bodies located within the subgranular zone in the dentate gyrus have radial processes that project through the granular cell layer and short tangential processes that extend along the border of the granule cell layer and hilus. These stem cells give rise to transient amplifying cells (*light blue*). Stage 2. Differentiation: transient amplifying cells differentiate into immature neurons (*green*). Proliferating progenitors in the SGZ are tightly associated with astrocytes and vascular structures. Stage 3. Migration: Immature neurons (*light green*) migrate a short distance into the granule cell layer. Stage 4. Axon/dendrite targeting: Immature neurons (*orange*) extend their axonal projections along mossy fiber pathways to the CA3 pyramidal cell layer. They send their dendrites in the opposite direction toward the molecular layer. Stage 5. Synaptic integration: New granule neurons (*red*) receive inputs from the entorhinal cortex and send outputs to the CA3 and hilus regions. The specific properties of each stage are summarized below, mainly on the basis of studies in adult mice. DG, dentate gyrus region; ML, molecular cell layer; GL, granular cell layer.

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a nonneurogenic region, do not promote neuronal differentiation (Song et al. 2002a). In vivo hot spots of cell proliferation in the SGZ are found to be in close proximity to capillaries (Palmer et al. 2000) and astrocytes (Seri et al. 2004, Song et al. 2002a). During fetal development, astrocytes, however, are born after most neurons and are thus unable to provide neurogenic signals for multipotent stem cells (Temple 2001). It becomes clear that astrocytes in the adult CNS are not merely supporting cells as traditionally believed. Just like neurons, astrocytes have a broad diversity of subtypes and functions; some behave like stem cells (Doetsch et al. 1999, Seri et al. 2001), some provide neurogenic signals (Lim & Alvarez-Buylla 1999, Song et al. 2002a), and some provide synaptogenic factors (Song et al. 2002b, Ullian et al. 2004).

The molecular mechanisms underlying neuronal fate specification during adult neurogenesis are just beginning to be elucidated. The fate choice is influenced by a cohort of proliferating, gliogenic, and neurogenic signals within the niche. Bone morphogenic protein (BMP) signaling has been shown to instruct adult neural progenitors to adopt a glial fate (Lim et al. 2000). Neuronal differentiation from adult neural progenitors in the neurogenic niche proceeds partially because of the local presence of BMP antagonists. Ependymal cells in the SVZ secrete Noggin (Lim et al. 2000), and astrocytes in the SGZ secrete neurogenesin-1 (Ueki et al. 2003), to serve as the BMP antagonist, respectively. We have recently identified Wnt-signaling as one of the candidate pathways that regulate neurogenic differentiation of adult neural stem cells both in vitro and in vivo (D.C. Lie, S.A. Colamarino, H. Song, L. Desire & F.H. Gage, unpublished observations). These extracellular signaling mechanisms act in part by interacting with cellular epigenetic mechanisms (Hsieh & Gage 2004), including interaction of chromatin remodeling enzymes with neurogenic factors, maintaining genomic stability (Zhao et al. 2003b), and regulating the fate choice of adult neural progenitors by noncoding RNA (Kuwabara et al. 2004).

Neuronal Migration and Nerve Guidance

In the olfactory system, newborn neurons go through extensive migration, first migrating tangentially along the wall of the lateral ventricle, then traveling anterior along the RMS to the olfactory bulb in close association with each other, and finally dispersing radially as individual cells into the outer cell layers in the bulb (**Figure 3**). This extensive migration occurs in species from rodents to primates but not in humans (Sanai et al. 2004). The migration along the RMS is a very unique process called chain migration in which neuroblasts migrate closely associated with each other in a tube-like structure formed by glial cells (Lois et al. 1996). Six days after injection of a retrovirus-expressing GFP into the SVZ of adult mice, GFP^+ neuroblasts were observed in the core of the olfactory bulb (Carleton et al. 2003). By 14 days after viral injection GFP^+ neurons with well-developed dendritic arbors and spines were observed. Studies over the past few years have started to unravel the mechanisms that support and direct the migration of newborn neurons from the SVZ to the olfactory bulb. The motility of chain migration is regulated by a cohort of factors, including PSA-NCAM (Hu et al. 1996), EphB2/ephrin-B2 (Conover et al. 2000), netrin/DCC (Murase & Horwitz 2002), $GABA_A$ receptor activation (Bolteus & Bordey 2004), and some integrins (Murase & Horwitz 2002). The directionality of chain migration is influenced by netrin/DCC (Murase & Horwitz 2002) and Slits/Robos signaling (Nguyen-Ba-Charvet et al. 2004, Wu et al. 1999). Once migrating neuroblasts reach the olfactory bulb, reelin acts as a detachment signal (Hack et al. 2002) and tenascin-R then initiates the detachment of the neuroblasts from the chains and directs radial migration to their target

areas (Saghatelyan et al. 2004). Two types of interneurons are continuously generated in the olfactory bulb: granule neurons and periglomerular neurons. These unusual interneurons lack an axon and instead have reciprocal dendro-dendritic synapses with mitral or tufted cells (Shepherd et al. 2004).

In the dentate gyrus, newly generated neurons migrate only a short distance to the inner granule cell layer to become granule neurons (**Figure 4**). These newborn neurons rapidly extend long axonal projects along the mossy fiber pathway and reach their target CA3 pyramidal cell layer within 4 to 10 days after division (Hastings & Gould 1999). The dendrites of these neurons grow in the opposite direction of the axons, reaching the molecular layer within two weeks and maintaining growth to increase in complexity over months (van Praag et al. 2002). The molecular mechanisms underlying nerve growth and axon/dendrite guidance of adult-generated granular neurons are largely unknown. These newborn neurons may not express receptors for factors that normally inhibit axon regeneration (He & Koprivica 2004). Alternatively, they may have different internal states, such as high cytoplasmic levels of cAMP/cGMP, thus rendering them inert to inhibitory cues (Song & Poo 1999, 2001). Many developmental guidance cues, such as semaphorins, retain their expression in adulthood (Huber et al. 2003). It would be interesting to investigate whether these cues also guide newborn neurons in the adult CNS.

The existence of extensive neuronal migration, nerve growth, and axon/dendritic targeting in the adult CNS environment that otherwise is inhibitory for mature neurons (He & Koprivica 2004) provides a unique model system to investigate basic principles and mechanisms of neuronal navigation in adulthood. Advances in this field may also lead to novel strategies for repairing the adult CNS after injury or degenerative neurological diseases.

Neuronal Maturation, Synapse Formation, and Plasticity

Plasticity: the ability of the brain to reorganize neural pathways on the basis of new experiences. It can be reflected by changes in the efficacy of synaptic communication as well as by morphological changes

Many aspects of the maturation process of adult-generated neurons are surprisingly different from what occurs during fetal development. In the olfactory system, tangentially migrating neuroblasts express extrasynaptic $GABA_A$ receptors first and then AMPA receptors; NMDA receptors are expressed last in the radially migrating neurons (Bolteus & Bordey 2004, Carleton et al. 2003). In contrast, NMDA receptors are often detected before AMPA receptors in developing neonate brains (Durand et al. 1996). Shortly after the completion of radial migration, maturing new neurons start to receive synaptic inputs with GABAergic inputs ahead of glutamatergic ones (Belluzzi et al. 2003, Carleton et al. 2003). Surprisingly, new granule neurons, but not new periglomerular neurons (Belluzzi et al. 2003), appear to acquire the ability to fire action potentials after synaptic inputs are made (Carleton et al. 2003), which is also different from what occurs in developing brains. This unique developmental sequence may allow them to integrate readily into a mature brain without altering existing cognitive processes.

In the dentate gyrus, the sequential events that occur during neuronal maturation and synapse formation have not yet been fully characterized using electrophysiology. Newborn granule neurons in the dentate gyrus appear to first receive GABAergic synaptic inputs around one week after birth and then glutamatergic inputs by two weeks (S. Ge, G. Ming & H. Song, unpublished observations). The synaptogenesis process appears to be quite prolonged. During development, the dendritic spines, the major sites of excitatory synaptic transmission, reach a plateau in their density around one month at 2–4/μm dendritic length (Nimchinsky et al. 2002). Adult-generated granule neurons have a mean spine density of 0.8/μm dendritic length at one month after birth and continue to grow, reaching 1.2/μm at six months (van Praag

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Long-term potentiation: long-lasting, activity-dependent changes in the efficacy of synaptic communication. Investigators believe that LTP provides an important key to understanding the cellular and molecular mechanisms by which memories are formed and stored.

et al. 2002). Young granule neurons also differ substantially from neighboring mature granule cells in both their active and passive membrane properties (Schmidt-Hieber et al. 2004, Wang et al. 2000). Neurons appear to have a high input resistance and a subthreshold Ca^{2+}-conductance, which finally enable action potential firing with very small excitatory currents (Schmidt-Hieber et al. 2004). The enhanced excitability might be important for the young neurons when only a few excitatory contacts have been formed. Furthermore, newborn neurons exhibit special properties in synaptic plasticity, such as having a lower threshold for the induction of long-term potentiation (LTP) (Schmidt-Hieber et al. 2004, Wang et al. 2000) and long-term-depression (LTD) (J. Bischofberger, personal communication) than do mature neurons. This enhanced synaptic plasticity appears to be present at least during the time period (Schmidt-Hieber et al. 2004) when the newly generated neurons express PSA-NCAM after mitosis (**Figure 4**). However, it is unclear whether these neurons exhibit such properties beyond this time window and whether other parameters change during their developmental course. Answers to these questions will define when and how new neurons contribute to the plasticity of the local circuitry and ultimately how this affects the animal behaviors.

The outputs of newborn neurons have rarely been examined by electrophysiological studies owing to the technical difficulties in finding pairs of connected neurons in vivo. New granule neurons in the dentate gyrus are likely to release glutamate as do mature granule neurons. Early studies have suggested that a small population of granule neurons in the dentate gyrus can also release GABA, and this GABAergic signaling is upregulated after seizures (Walker et al. 2001). It would be interesting to examine how much adult-generated neurons contribute to this GABAergic signaling during their development. In one report, some GABAergic basket cells in the dentate gyrus were found to incorporate BrdU and form inhibitory synapses with the granule cells (Liu et al. 2003). Other studies, however, did not observe incorporation of either BrdU or [^{3}H]-thymidine into basket cells (Seri et al. 2004). In the olfactory bulb, granule neurons release GABA, whereas periglomerular cells release GABA and sometimes also dopamine (Shepherd et al. 2004). Whether newborn interneurons in the olfactory bulb release the same types of neurotransmitters remains to be examined with electrophysiological studies.

The cellular and molecular mechanisms that regulate the integration of newly born neurons into existing neuronal circuits in the adult CNS are unknown. Will many identified developmental mechanisms also operate for these newborn neurons? Understanding these extreme examples of structural plasticity not only will shed light on the basic mechanisms of adult plasticity in the CNS, but also may provide strategies to integrate transplanted neuronal cell types for cell replacement therapy after injury or degenerative neurological diseases.

MODULATION OF ENDOGENOUS ADULT NEUROGENESIS

Adult neurogenesis in the hippocampus and the olfactory bulb is an extremely dynamic process (Duman et al. 2001, Fuchs & Gould 2000, Kempermann 2002). Extensive studies have shown that both intrinsic and extrinsic factors regulate adult neurogenesis at different stages, including proliferation, fate specification, migration, integration, and survival (**Table 1**).

The intrinsic genetic background influences SGZ neurogenesis in adult mice, and significant differences were found in the proliferation, survival, and differentiation of neural progenitors between several wild-derived and inbred laboratory mice (Kempermann & Gage 2002). Adult neurogenesis in both the SGZ (Kuhn et al. 1996) and SVZ (Enwere et al. 2004, Jin et al. 2003) is also reduced during aging (**Table 1**). Adrenal steroids may contribute to the aging-associated decline of

TABLE 1 Regulation of adult neurogenesis in the subgranular zone (SGZ) and subventricular zone (SVZ)*

Regulatory factors	Proliferation		Survival		Neuronal differentiation		Potential mechanisms
	SVZ	SGZ	SVZ	SGZ	SVZ	SGZ	
Mice strain		+/−		+/−		+/−	
Gender	n.c.	+/−	n.c.	n.c.	n.c.	n.c.	
Aging	−	−		n.c.		−	EGFR signaling − Corticosteroids levels +
Hormones							
Corticosterone		−					
Estrogen	n.c.	+		n.c.		n.c.	
Oestrogen		+					Serotonin?
Pregnancy	+	n.c.					Prolactin
Afferents, neurotransmitters							
Dopamine	−	−					D2L receptors
Serotonin	+	+					
Acetylcholine		−	−	−			
Glutamate		−		n.c.			mGluR, NMDAR
Norepinephrine	n.c.	+		n.c.		n.c.	PAC1 and PKC
PACAP	+	+					
Nitric oxide	−	n.c./−	n.c.		+/n.c.	n.c.	
Growth factors							
FGF-2	+	n.c.					
EGF	+	n.c.				−	
IGF-1		+		+		+	
Behavior							
Enriched environment	n.c.	+/n.c.	n.c.	+/n.c.	n.c.	n.c./+	VEGF
Enriched odor exposure	n.c.	n.c.	+	n.c.			
Physical activity	n.c.	+	n.c.	+			VEGF
Learning							
Water maze		n.c.		+/n.c.		n.c.	
Blink reflex		n.c.		+			
Dietary restriction		n.c.		+			BDNF, NT-3
Stress		−		n.c.			Glucocorticoids +
Drugs							
Antidepressants		+					Serotonin
Opiates		−					
Methamphetamine		−					
Lithium		+				n.c.	
Pathological stimulations							
Ischemia	+	+/−		+	+	+	NMDAR, CREB
Seizures	+	+/−		+/n.c.		+/n.c.	
Inflammation	+/−	−		−		−	IL-6, TNFα

(*Continued*)

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TABLE 1 (*Continued*)

Regulatory factors	Proliferation		Survival		Neuronal differentiation		Potential mechanisms
	SVZ	SGZ	SVZ	SGZ	SVZ	SGZ	
Degenerative diseases							
AD/HD/PD	+	+					
Diabetes		−					

*The table is based on results from peer-reviewed publications on adult neurogenesis. It is intended to give a general overview of the diverse regulation of adult neurogenesis. We provide partial lists of examples under each category. Owing to space limitations, please see the supplementary material (follow the Supplemental Material link from the Annual Reviews home page at **http://www.annualreviews.org**) for references related to this table. It should be noted that the listed effects may not be direct. "+": increase; "−" decrease; "n.c.": no change. Unmarked indicates "not examined." Interested readers can consult several recent comprehensive reviews on this topic (Duman et al. 2001, Fuchs & Gould 2000, Kempermann 2002). AD, Alzheimer's disease; HD, Huntington's disease; PD, Parkinson's disease.

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neurogenesis in the SGZ (Cameron & Gould 1994). Reducing corticosteroid levels in aged rats can restore the rate of cell proliferation, which suggests that aged neural progenitors retain their proliferation capacity as in younger adult animals (Cameron & McKay 1999). Other hormones, including estrogen and prolactin, also regulate adult neurogenesis (**Table 1**).

Electrical activity can serve as a common link between the internal and external stimuli by regulating, either directly or indirectly, different aspects of adult neurogenesis. For example, excitatory stimuli can be sensed by proliferating SVZ neural progenitors via L-type Ca^{2+} channels and NMDA receptors to inhibit glial fate specification and promote neuronal differentiation (Deisseroth et al. 2004). Activity also regulates the expression of tenascin-R, which guides the radial migration of newborn olfactory neurons (Saghatelyan et al. 2004). Many afferent inputs and various neurotransmitters, including classic (e.g., dopamine, serotonin, acetylcholine, and glutamate), peptide (e.g., PACAP), and gaseous (e.g., nitric oxide) neurotransmitters, have been implicated in regulating adult neurogenesis (Kempermann 2002) (**Table 1**).

Environmental stimuli can greatly affect the proliferation and survival of newborn neurons in the adult CNS (**Table 1**). Exposure of rodents to an enriched environment increases the survival of newborn neurons in the SGZ without affecting SVZ neurogenesis (Brown et al. 2003, Kempermann et al. 1997, Nilsson et al. 1999). Physical exercise, such as running, promotes SGZ neurogenesis by increasing cell proliferation and survival of the new granule neurons (van Praag et al. 1999a, van Praag et al. 1999b). Vascular endothelial growth factor (VEGF) signaling may be responsible for the increased neurogenesis by both enriched environment and running (Cao et al. 2004, Fabel et al. 2003). Hippocampus-dependent learning, such as blink reflex or water maze learning, appears to increase the survival of new granule neurons that have been generated only at a particular time window before the training (Gould et al. 1999a, Leuner et al. 2004, van Praag et al. 1999a). Similarly, enriched odor exposure increases the SVZ cell proliferation but not the SGZ neurogenesis (Rochefort et al. 2002).

Both physical and psychosocial stress paradigms, as well as some animal models of depression, lead to a decrease in cell proliferation in the SGZ (Duman et al. 2001, Fuchs & Gould 2000). This decrease results from the activation of the hypothalamic-pituitary-adrenal axis, which is known to inhibit adult neurogenesis (Cameron & Gould 1994). Interestingly, adult neurogenesis is also regulated by psychotropic drugs (Duman et al. 2001, Fuchs & Gould 2000). Long-term

administration of different classes of antidepressants, including serotonin and norepinephrine-selective reuptake inhibitors, increases cell proliferation and adult SGZ neurogenesis. In contrast, several drugs of abuse decrease cell proliferation and neurogenesis in the SGZ (Eisch et al. 2000). Alcohol intoxication also decreases SGZ neurogenesis by inhibiting both proliferation and newborn cell survival (Crews et al. 2003).

The dynamic and selective regulation of neurogenesis in the hippocampus and olfactory bulb by a variety of stimulations points to the functional significance of this biological phenomenon. Understanding the mechanisms underlying these regulations will not only significantly enrich our general knowledge of adult neurogenesis, but also may shed light on the etiology and pathophysiology of some mental illness, such as depression (Kempermann 2002).

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ADULT NEUROGENESIS UNDER PATHOLOGICAL STIMULATIONS

Injury and pathological stimulations not only affect different aspects of adult neurogenesis in neurogenic regions, but also have an impact in otherwise non-neurogenic regions (Arlotta et al. 2003, Parent 2003) (**Table 1**). Most brain injuries lead to increased proliferation of progenitors in the SGZ and the SVZ after a latent period and sometimes cause migration of newborn neurons to injury sites. Specific types of injury also appear to lead to neurogenesis from endogenous neural progenitors in regions where adult neurogenesis is extremely limited or nonexisting (Magavi et al. 2000). Whether these new neurons become functionally integrated remains to be determined.

Ischemic Brain Injury

Ischemic brain insults potently stimulate progenitor proliferation in both the SGZ and SVZ of adult rodents as shown by BrdU incorporation (Kokaia & Lindvall 2003, Parent 2003). In an experimental stroke model immature neurons also migrate from the SVZ to the damaged striatal area where they start to express markers for striatal medium-sized spiny neurons, the phenotype of most of the dead neurons (Arvidsson et al. 2002, Parent et al. 2002b). Most of these new neurons died between two and five weeks after the stroke (Arvidsson et al. 2002). These studies suggest that the local environment, although providing cues for attracting immature neurons and inducing neuronal subtype differentiation, is not adequate for long-term survival of the new neurons. In another study, intraventricular infusion of EGF and FGF-2 after global ischemia led to increased proliferation and neuronal differentiation of progenitors located in the caudal extension of the SVZ adjacent to the hippocampus (Nakatomi et al. 2002). These new neurons then migrated and integrated into the CA1 region of the hippocampus, apparently receiving synaptic input and sending outputs. Importantly, these animals also exhibited partial recovery of their synaptic responses and better performance in water maze tests.

Seizures

Studies of adult rodent models of limbic epileptogenesis or acute seizures showed that seizure or seizure-induced injury stimulates neurogenesis in both the SGZ and SVZ (Parent 2003). In the dentate gyrus, epilepsy increases the proliferation of progenitors five- to tenfold after a latent period (Parent et al. 1997). Most of these newborn cells differentiate into granule neurons, some of which mislocate in the hilus region. These ectopic granule-like cells maintain the basic electrophysiological characteristics of dentate granule neurons but fire abnormal bursts in synchrony with the CA3 pyramidal cells (Scharfman et al. 2000). Newborn neurons also participate in aberrant network reorganization in the epileptic hippocampus, with aberrant mossy fiber recurrent connections

and persistent basal dendrites (Parent et al. 1997). In the SVZ, proliferation is significantly increased in a pilocarpine model of limbic epileptogenesis (Parent et al. 2002a). These neuroblasts also showed more rapid migration to the olfactory bulb, and some appeared to exit the RMS prematurely and migrated into injured forebrain regions.

Radiation Injury

Studies in animal models have shown that exposure to therapeutic doses of radiation leads to ablation of adult SGZ neurogenesis but not gliogenesis (Kempermann & Neumann 2003). This dramatic reduction of adult neurogenesis results from the combined effects of acute cell death, decreased proliferation, and neuronal differentiation of the neural progenitors. A striking feature of radiation exposure is a massive migroglial inflammatory response in the dentate gyrus, which by itself inhibits neurogenesis (Ekdahl et al. 2003, Monje et al. 2003). Recent studies showed that pharmacological blocking of inflammation elicited by irradiation, injection of bacterial lipopolysaccharide (Monje et al. 2003), or experimentally induced seizures (Ekdahl et al. 2003) can restore hippocampal neurogenesis. Proinflammatory mediators released by microglia, such as interleukin-6 (IL-6), seem to be important contributors to the inhibition of SGZ neurogenesis (Monje et al. 2003, Vallieres et al. 2002). Microglia also release trophic factors (Batchelor et al. 1999), such as brain-derived neurotrophic factor (BDNF), that promote neurogenesis (Benraiss et al. 2001). Thus, microglia may have both positive and negative effects on adult neurogenesis depending on the context.

Degenerative Neurological Diseases

Adult neurogenesis is significantly altered in chronic degenerative neurological diseases. Brains of Huntington's disease patients showed a significant increase in cell proliferation in the subependymal layer, revealed by the cell-cycle marker proliferating cell nuclear antigen (PCNA) (Curtis et al. 2003). Some of these PCNA$^+$ cells were also Tuj1$^+$, suggesting the existence of dividing new neurons in the diseased brain. In a lesion rat model of HD, BrdU incorporation in the SVZ significantly increased, and some BrdU$^+$ neurons migrated to the lesioned stratum (Tattersfield et al. 2004). Brains of Alzheimer's disease patients also showed increased expression of immature neuronal markers, such as DCX and PSA-NCAM, in the SGZ and the CA1 region of Ammon's horn (Jin et al. 2004b). In a transgenic mouse model of Alzheimer's disease, there was an approximately twofold increase in BrdU incorporation and expression of immature neuronal markers in the SGZ and SVZ even before the neuronal loss and deposition of amyloid (Jin et al. 2004a). In the case of Parkinson's disease patients, the proliferation of progenitors in the SGZ and SVZ is impaired, presumably as a consequence of dopaminergic denervation (Hoglinger et al. 2004). Experimental depletion of dopamine decreases the proliferation of progenitors in both SVZ and SGZ in rodents (Baker et al. 2004, Hoglinger et al. 2004). In the 6-hydroxydopamine mice model of Parkinson's disease, proliferation in the SVZ was reduced by ~40% (Baker et al. 2004). The same lesion model also leads to the generation of a few new neurons in the substantia nigra where neurogenesis is extremely limited (Zhao et al. 2003a) or nonexistent under normal conditions (Lie et al. 2002).

Emerging evidence suggests that adult neurogenesis may be an intrinsic compensatory response to self-repair the adult CNS. Adult neurogenesis is also a very dynamic process under the regulation of both positive and negative influences that change rapidly over time after injury or during the progress of chronic diseases. The cellular and molecular mechanisms underlying injury-induced cell proliferation, differentiation, and migration are largely unknown. Several factors—including FGF-2, BDNF, and erythropoietin (Kokaia & Lindvall 2003)—have been

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implicated in modulating neurogenesis after insults. Many pressing questions remain before we can take advantage of this limited neurogenesis after injury to functionally repair the nervous system.

POTENTIAL FUNCTIONS OF ADULT NEUROGENESIS

Despite decades of intensive research, we still search for definitive evidence for the functions of adult neurogenesis in mammals (Fuchs & Gould 2000, Kempermann et al. 2004b). After the initial discovery of neurogenesis in the postnatal rat hippocampus, Altman (1967) suggested that new neurons are crucial in learning and memory. Since then much of what we have learned about the functional importance of neurogenesis in the adult brain comes first from studies of songbirds (Nottebohm 2004). For example, the first evidence that neurons generated in the adult brain can be recruited into functional circuits came from electrophysiological studies of new neurons in adult songbird in response to sound stimulation (Paton & Nottebohm 1984). During the past decade, rapidly accumulating correlative evidence supports the notion that adult neurogenesis and specific behaviors are affected in a reciprocal fashion both in songbirds and in mammals (Gould et al. 1999b). In the dentate gyrus, for example, running-induced increase of SGZ neurogenesis in rodents is associated with enhanced spatial learning in the Morris water maze task and with enhanced LTP in the dentate gyrus either in acute slices or in vivo (Farmer et al. 2004, van Praag et al. 1999a). By comparison, decreased SGZ neurogenesis by pharmacological manipulations or radiation led to defects in specific behavior tests and a reduction of LTP in the dentate gyrus (Shors et al. 2001, 2002; Snyder et al. 2001). Genetic and radiological approaches to disrupt antidepressant-induced neurogenesis also blocked behavioral responses to antidepressants (Santarelli et al. 2003). In the olfactory bulb, an odor-enriched environment enhances neurogenesis and improves olfactory memory without upregulating hippocampal neurogenesis (Rochefort et al. 2002). Conversely, reduced olfactory neurogenesis in genetically modified mice showed an impairment of discrimination between odors (Enwere et al. 2004, Gheusi et al. 2000). Unfortunately, all of the current approaches also affect other physiological processes besides neurogenesis.

An attractive and testable hypothesis is that newly generated neurons in the adult CNS exhibit unique physiological properties at specific stages during their maturation process that allow them to serve as major mediators for structural plasticity. In turn, this active structural plasticity is important for associative learning and memory, and possibly mood (depression). Recent studies already showed that new neurons exhibit different passive and active properties as compared with mature neurons. New neurons also exhibit the striking ability to migrate and extend axons and dendrites in a hostile environment largely inhibitory for mature neurons. Of particular interest is the finding that new neurons exhibit a lower threshold for the induction of LTP/LTD and have larger amplitudes of LTP (Schmidt-Hieber et al. 2004, Wang et al. 2000). The keys to elucidating the function(s) of adult neurogenesis may then rely on our future comparative studies between newborn neurons of known ages and existing mature neurons at the cellular physiology level.

Many tasks remain before we can better understand the fundamental biological significance of adult neurogenesis. First, we have to know more about the physiological properties of the newborn neurons, especially those involved in synaptic plasticity. This will require more rigorous electrophysiological analysis of the development profiles of these new neurons. When will these neurons contribute to the plasticity of the circuits? Do adult-generated neurons exhibit special properties during a limited time window or permanently? Second, we need to know how extensively these neurons are involved in the

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BMP: bone morphogenic protein

BrdU: bromodeoxyuridine

DCX: doublecortin

EGF: epidermal growth factor

FGF-2: basic fibroblast growth factor

GFAP: glial fibrillary acidic protein

GFP: green fluorescent protein

LTP: long-term potentiation

LTD: long-term depression

MAP2ab: microtubule-associated protein 2 isoform a and b

PACAP: pituitary adenylate cyclase-activating polypeptide

PSA-NCAM: polysialylated-neural cell-adhesion molecule

RMS: rostral migratory stream

SGZ: subgranular zone

SVZ: subventricular zone

Tuj1: β-tublin isoform III

VEGF: vascular endothelial growth factor

existing neuronal circuits. This will require systematic anatomical analysis. What are the sources of the inputs these new neurons receive? Do adult-generated neurons form circuits different from those produced during development? Third, to get a clean analysis of behavioral relevance of adult neurogenesis we will need to develop animal models that can silence identified populations of adult-generated neurons in a temporally and spatially precise manner. Fourth, we need to explore which aspects of behaviors are affected by, or are affecting, adult neurogenesis. We need diverse behavior analysis. Because adult neurogenesis is evolutionarily conserved (Zupanc 2001), it should be beneficial to compare the functions of adult neurogenesis in different species. Our studies can also be guided by neural modeling. For example, theoretical modeling predicts significant advantages of new neurons over mature neurons for both temporary storage and clearance of memories (Cecchi et al. 2001).

PERSPECTIVE

The past decade has witnessed the falling of a century-old dogma and the introduction of the new field of adult neurogenesis. Now the focus of the newly formed field has shifted from documentation of the existence of adult neurogenesis to understanding its regulatory mechanisms and functions. One of the most exciting and unique features of adult neurogenesis is that the complete process of neuronal development is recapitulated in the mature CNS, an environment quite different from the embryonic CNS, where neural development has been traditionally investigated (Temple 2001). Many basic mechanisms regulating adult neurogenesis are still unknown. Much less is known about those mechanisms under pathological conditions. Intensive studies in the past decade have revealed an array of factors and signaling mechanisms regulating neuronal fate specification, migration, nerve growth, guidance, and synaptogenesis during fetal CNS development (Anderson 2001, Huber et al. 2003, Temple 2001). These studies have also identified inhibitory mechanisms underlying the extremely limited regeneration of adult CNS neurons (David & Lacroix 2003, Filbin 2003, Grandpre & Strittmatter 2001, He & Koprivica 2004, Schwab 2004). The task now is to investigate whether similar mechanisms will also govern neurogenesis in a mature CNS environment. Because in nonmammalian vertebrates new neurons are generated continuously in many regions of the adult CNS (Zupanc 2001), comparisons of adult neurogenesis between a broad range of species is likely to yield new insights into the evolution and functions of this phenomenon.

The demonstration of active neurogenesis in adult humans not only shows the unforeseen regenerative capacity of the mature CNS, but also raises hopes for repairing the damaged adult CNS after injury or degenerative neurological diseases. Understanding the basic mechanisms regulating adult neurogenesis under normal and abnormal conditions will provide the foundation for cell replacement therapy, using either endogenous adult neural stem cells or transplanted cells from different sources. As history shows, the field of adult neurogenesis is propelled by technical advances. Aided by novel technologies in live imaging, single-cell genetics with retroviruses, new animal models, and neural modeling, the best is yet to come.

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LITERATURE CITED

Allen E. 1912. The cessation of mitosis in the central nervous system of albino rat. *J. Comp. Neurol.* 19:547–68

Altman J. 1966. Autoradiographic and histological studies of postnatal neurogenesis. II. A longitudinal investigation of the kinetics, migration and transformation of cells incorporating tritiated thymidine in infant rats, with special reference to postnatal neurogenesis in some brain regions. *J. Comp. Neurol.* 1966:431–74

Altman J. 1967. In *The Neurosciences*, *Second Study Program*, ed. GC Quarton, T Melnechuck, FO Schmitt, pp. 723–43. New York: Rockefeller Univ. Press

Altman J. 1969. Autoradiographic and histological studies of postnatal neurogenesis. IV. Cell proliferation and migration in the anterior forebrain, with special reference to persisting neurogenesis in the olfactory bulb. *J. Comp. Neurol.* 137:433–57

Altman J, Das GD. 1965. Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats. *J. Comp. Neurol.* 124:319–35

Alvarez-Buylla A, Lim DA. 2004. For the long run: maintaining germinal niches in the adult brain. *Neuron* 41:683–86

Anderson DJ. 2001. Stem cells and pattern formation in the nervous system: the possible versus the actual. *Neuron* 30:19–35

Arlotta P, Magavi SS, Macklis JD. 2003. Induction of adult neurogenesis: molecular manipulation of neural precursors in situ. *Ann. N.Y. Acad. Sci.* 991:229–36

Arvidsson A, Collin T, Kirik D, Kokaia Z, Lindvall O. 2002. Neuronal replacement from endogenous precursors in the adult brain after stroke. *Nat. Med.* 8:963–70

Baker SA, Baker KA, Hagg T. 2004. Dopaminergic nigrostriatal projections regulate neural precursor proliferation in the adult mouse subventricular zone. *Eur. J. Neurosci.* 20:575–79

Batchelor PE, Liberatore GT, Wong JY, Porritt MJ, Frerichs F, et al. 1999. Activated macrophages and microglia induce dopaminergic sprouting in the injured striatum and express brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor. *J. Neurosci.* 19:1708–16

Belluzzi O, Benedusi M, Ackman J, LoTurco JJ. 2003. Electrophysiological differentiation of new neurons in the olfactory bulb. *J. Neurosci.* 23:10411–18

Benraiss A, Chmielnicki E, Lerner K, Roh D, Goldman SA. 2001. Adenoviral brain-derived neurotrophic factor induces both neostriatal and olfactory neuronal recruitment from endogenous progenitor cells in the adult forebrain. *J. Neurosci.* 21:6718–31

Bolteus AJ, Bordey A. 2004. GABA release and uptake regulate neuronal precursor migration in the postnatal subventricular zone. *J. Neurosci.* 24:7623–31

Branda CS, Dymecki SM. 2004. Talking about a revolution: the impact of site-specific recombinases on genetic analyses in mice. *Dev. Cell.* 6:7–28

Brown J, Cooper-Kuhn CM, Kempermann G, Van Praag H, Winkler J, et al. 2003. Enriched environment and physical activity stimulate hippocampal but not olfactory bulb neurogenesis. *Eur. J. Neurosci.* 17:2042–46

Cameron HA, Gould E. 1994. Adult neurogenesis is regulated by adrenal steroids in the dentate gyrus. *Neuroscience* 61:203–9

Annu. Rev. Neurosci. 2005.28:223-250. Downloaded from arjournals.annualreviews.org
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Cameron HA, McKay RD. 1999. Restoring production of hippocampal neurons in old age. *Nat. Neurosci.* 2:894–97

Cameron HA, McKay RD. 2001. Adult neurogenesis produces a large pool of new granule cells in the dentate gyrus. *J. Comp. Neurol.* 435:406–17

Cao L, Jiao X, Zuzga DS, Liu Y, Fong DM, et al. 2004. VEGF links hippocampal activity with neurogenesis, learning and memory. *Nat. Genet.* 36:827–35

Carlen M, Cassidy RM, Brismar H, Smith GA, Enquist LW, Frisen J. 2002. Functional integration of adult-born neurons. *Curr. Biol.* 12:606–8

Carleton A, Petreanu LT, Lansford R, Alvarez-Buylla A, Lledo PM. 2003. Becoming a new neuron in the adult olfactory bulb. *Nat. Neurosci.* 6:507–18

Cecchi GA, Petreanu LT, Alvarez-Buylla A, Magnasco MO. 2001. Unsupervised learning and adaptation in a model of adult neurogenesis. *J. Comput. Neurosci.* 11:175–82

Chambers RA, Potenza MN, Hoffman RE, Miranker W. 2004. Simulated apoptosis/neurogenesis regulates learning and memory capabilities of adaptive neural networks. *Neuropsychopharmacology* 29:747–58

Charles P, Reynolds R, Seilhean D, Rougon G, Aigrot MS, et al. 2002. Re-expression of PSA-NCAM by demyelinated axons: an inhibitor of remyelination in multiple sclerosis? *Brain* 125:1972–79

Conover JC, Doetsch F, Garcia-Verdugo JM, Gale NW, Yancopoulos GD, Alvarez-Buylla A. 2000. Disruption of Eph/ephrin signaling affects migration and proliferation in the adult subventricular zone. *Nat. Neurosci.* 3:1091–97

Crews FT, Miller MW, Ma W, Nixon K, Zawada WM, Zakhari S. 2003. Neural stem cells and alcohol. *Alcohol. Clin. Exp. Res.* 27:324–35

Curtis MA, Penney EB, Pearson AG, van Roon-Mom WM, Butterworth NJ, et al. 2003. Increased cell proliferation and neurogenesis in the adult human Huntington's disease brain. *Proc. Natl. Acad. Sci. USA* 100:9023–27

David S, Lacroix S. 2003. Molecular approaches to spinal cord repair. *Annu. Rev. Neurosci.* 26:411–40

Deisseroth K, Singla S, Toda H, Monje M, Palmer TD, Malenka RC. 2004. Excitation-neurogenesis coupling in adult neural stem/progenitor cells. *Neuron* 42:535–52

Doetsch F. 2003. A niche for adult neural stem cells. *Curr. Opin. Genet. Dev.* 13:543–50

Doetsch F, Caille I, Lim DA, Garcia-Verdugo JM, Alvarez-Buylla A. 1999. Subventricular zone astrocytes are neural stem cells in the adult mammalian brain. *Cell* 97:703–16

Doetsch F, Petreanu L, Caille I, Garcia-Verdugo JM, Alvarez-Buylla A. 2002. EGF converts transit-amplifying neurogenic precursors in the adult brain into multipotent stem cells. *Neuron* 36:1021–34

Duman RS, Malberg J, Nakagawa S. 2001. Regulation of adult neurogenesis by psychotropic drugs and stress. *J. Pharmacol. Exp. Ther.* 299:401–7

Durand GM, Kovalchuk Y, Konnerth A. 1996. Long-term potentiation and functional synapse induction in developing hippocampus. *Nature* 381:71–75

Eisch AJ, Barrot M, Schad CA, Self DW, Nestler EJ. 2000. Opiates inhibit neurogenesis in the adult rat hippocampus. *Proc. Natl. Acad. Sci. USA* 97:7579–84

Ekdahl CT, Claasen JH, Bonde S, Kokaia Z, Lindvall O. 2003. Inflammation is detrimental for neurogenesis in adult brain. *Proc. Natl. Acad. Sci. USA* 100:13632–37

Enwere E, Shingo T, Gregg C, Fujikawa H, Ohta S, Weiss S. 2004. Aging results in reduced epidermal growth factor receptor signaling, diminished olfactory neurogenesis, and deficits in fine olfactory discrimination. *J. Neurosci.* 24:8354–65

Eriksson PS, Perfilieva E, Bjork-Eriksson T, Alborn AM, Nordborg C, et al. 1998. Neurogenesis in the adult human hippocampus. *Nat. Med.* 4:1313–17

Annu. Rev. Neurosci. 2005.28:223-250. Downloaded from arjournals.annualreviews.org
by University of Medicine and Dentistry of New Jersey on 01/03/06. For personal use only.

Fabel K, Tam B, Kaufer D, Baiker A, Simmons N, et al. 2003. VEGF is necessary for exercise-induced adult hippocampal neurogenesis. *Eur. J. Neurosci.* 18:2803–12

Falk A, Frisen J. 2002. Amphiregulin is a mitogen for adult neural stem cells. *J. Neurosci. Res.* 69:757–62

Farmer J, Zhao X, van Praag H, Wodtke K, Gage FH, Christie BR. 2004. Effects of voluntary exercise on synaptic plasticity and gene expression in the dentate gyrus of adult male Sprague-Dawley rats in vivo. *Neuroscience* 124:71–79

Filbin MT. 2003. Myelin-associated inhibitors of axonal regeneration in the adult mammalian CNS. *Nat. Rev. Neurosci.* 4:703–13

Fuchs E, Gould E. 2000. Mini-review: In vivo neurogenesis in the adult brain: regulation and functional implications. *Eur. J. Neurosci.* 12:2211–14

Gheusi G, Cremer H, McLean H, Chazal G, Vincent JD, Lledo PM. 2000. Importance of newly generated neurons in the adult olfactory bulb for odor discrimination. *Proc. Natl. Acad. Sci. USA* 97:1823–28

Goh EL, Ma D, Ming GL, Song H. 2003. Adult neural stem cells and repair of the adult central nervous system. *J. Hematother. Stem. Cell Res.* 12:671–79

Gottlieb DI. 2002. Large-scale sources of neural stem cells. *Annu. Rev. Neurosci.* 25:381–407

Gould E, Beylin A, Tanapat P, Reeves A, Shors TJ. 1999a. Learning enhances adult neurogenesis in the hippocampal formation. *Nat. Neurosci.* 2:260–65

Gould E, Tanapat P, Hastings NB, Shors TJ. 1999b. Neurogenesis in adulthood: a possible role in learning. *Trends Cogn. Sci.* 3:186–92

Grandpre T, Strittmatter SM. 2001. Nogo: a molecular determinant of axonal growth and regeneration. *Neuroscientist* 7:377–86

Gratzner HG. 1982. Monoclonal antibody to 5-bromo- and 5-iododeoxyuridine: a new reagent for detection of DNA replication. *Science* 218:474–75

Gross CG. 2000. Neurogenesis in the adult brain: death of a dogma. *Nat. Rev. Neurosci.* 1:67–73

Hack I, Bancila M, Loulier K, Carroll P, Cremer H. 2002. Reelin is a detachment signal in tangential chain-migration during postnatal neurogenesis. *Nat. Neurosci.* 5:939–45

Hamilton A. 1901. The division of differentiated cells in the central nervous system of the white rat. *J. Comp. Neurol.* 11:297–320

Hastings NB, Gould E. 1999. Rapid extension of axons into the CA3 region by adult-generated granule cells. *J. Comp. Neurol.* 413:146–54

Hayes NL, Nowakowski RS. 2002. Dynamics of cell proliferation in the adult dentate gyrus of two inbred strains of mice. *Brain Res. Dev. Brain Res.* 134:77–85

He Z, Koprivica V. 2004. The Nogo signaling pathway for regeneration block. *Annu. Rev. Neurosci.* 27:341–68

Hoglinger GU, Rizk P, Muriel MP, Duyckaerts C, Oertel WH, et al. 2004. Dopamine depletion impairs precursor cell proliferation in Parkinson disease. *Nat. Neurosci.* 7:726–35

Hsieh J, Gage FH. 2004. Epigenetic control of neural stem cell fate. *Curr. Opin. Genet. Dev.* 14:461–69

Hu H, Tomasiewicz H, Magnuson T, Rutishauser U. 1996. The role of polysialic acid in migration of olfactory bulb interneuron precursors in the subventricular zone. *Neuron* 16:735–43

Huber AB, Kolodkin AL, Ginty DD, Cloutier JF. 2003. Signaling at the growth cone: ligand-receptor complexes and the control of axon growth and guidance. *Annu. Rev. Neurosci.* 26:509–63

Jin K, Galvan V, Xie L, Mao XO, Gorostiza OF, et al. 2004a. Enhanced neurogenesis in Alzheimer's disease transgenic (PDGF-APPSw,Ind) mice. *Proc. Natl. Acad. Sci. USA* 101:13363–67

Annu. Rev. Neurosci. 2005.28:223-250. Downloaded from arjournals.annualreviews.org
by University of Medicine and Dentistry of New Jersey on 01/03/06. For personal use only.

Jin K, Peel AL, Mao XO, Xie L, Cottrell BA, et al. 2004b. Increased hippocampal neurogenesis in Alzheimer's disease. *Proc. Natl. Acad. Sci. USA* 101:343–47

Jin K, Sun Y, Xie L, Batteur S, Mao XO, et al. 2003. Neurogenesis and aging: FGF-2 and HB-EGF restore neurogenesis in hippocampus and subventricular zone of aged mice. *Aging Cell* 2:175–83

Johansson CB, Svensson M, Wallstedt L, Janson AM, Frisen J. 1999. Neural stem cells in the adult human brain. *Exp. Cell Res.* 253:733–36

Kaplan MS, Bell DH. 1983. Neuronal proliferation in the 9-month-old rodent-radioautographic study of granule cells in the hippocampus. *Exp. Brain Res.* 52:1–5

Kaplan MS, Hinds JW. 1977. Neurogenesis in the adult rat: electron microscopic analysis of light radioautographs. *Science* 197:1092–94

Katsetos CD, Del Valle L, Geddes JF, Assimakopoulou M, Legido A, et al. 2001. Aberrant localization of the neuronal class III beta-tubulin in astrocytomas. *Arch. Pathol. Lab Med.* 125:613–24

Kempermann G. 2002. Regulation of adult hippocampal neurogenesis—implications for novel theories of major depression. *Bipolar Disord.* 4:17–33

Kempermann G, Gage FH. 1999. New nerve cells for the adult brain. *Sci. Am.* 280:48–53

Kempermann G, Gage FH. 2002. Genetic influence on phenotypic differentiation in adult hippocampal neurogenesis. *Brain Res. Dev. Brain Res.* 134:1–12

Kempermann G, Jessberger S, Steiner B, Kronenberg G. 2004a. Milestones of neuronal development in the adult hippocampus. *Trends Neurosci.* 27:447–52

Kempermann G, Kuhn HG, Gage FH. 1997. More hippocampal neurons in adult mice living in an enriched environment. *Nature* 386:493–95

Kempermann G, Neumann H. 2003. Neuroscience. Microglia: the enemy within? *Science* 302:1689–90

Kempermann G, Wiskott L, Gage FH. 2004b. Functional significance of adult neurogenesis. *Curr. Opin. Neurobiol.* 14:186–91

Kokaia Z, Lindvall O. 2003. Neurogenesis after ischaemic brain insults. *Curr. Opin. Neurobiol.* 13:127–32

Kuan CY, Schloemer AJ, Lu A, Burns KA, Weng WL, et al. 2004. Hypoxia-ischemia induces DNA synthesis without cell proliferation in dying neurons in adult rodent brain. *J. Neurosci.* 24:10763–72

Kuhn HG, Dickinson-Anson H, Gage FH. 1996. Neurogenesis in the dentate gyrus of the adult rat: age-related decrease of neuronal progenitor proliferation. *J. Neurosci.* 16:2027–33

Kuhn HG, Winkler J, Kempermann G, Thal LJ, Gage FH. 1997. Epidermal growth factor and fibroblast growth factor-2 have different effects on neural progenitors in the adult rat brain. *J. Neurosci.* 17:5820–29

Kukekov VG, Laywell ED, Suslov O, Davies K, Scheffler B, et al. 1999. Multipotent stem/progenitor cells with similar properties arise from two neurogenic regions of adult human brain. *Exp. Neurol.* 156:333–44

Kuwabara T, Hsieh J, Nakashima K, Taira K, Gage FH. 2004. A small modulatory dsRNA specifies the fate of adult neural stem cells. *Cell* 116:779–93

Lai K, Kaspar BK, Gage FH, Schaffer DV. 2003. Sonic hedgehog regulates adult neural progenitor proliferation in vitro and in vivo. *Nat. Neurosci.* 6:21–27

Leuner B, Mendolia-Loffredo S, Kozorovitskiy Y, Samburg D, Gould E, Shors TJ. 2004. Learning enhances the survival of new neurons beyond the time when the hippocampus is required for memory. *J. Neurosci.* 24:7477–81

Lewis PF, Emerman M. 1994. Passage through mitosis is required for oncoretroviruses but not for the human immunodeficiency virus. *J. Virol.* 68:510–16

Annu. Rev. Neurosci. 2005.28:223-250. Downloaded from arjournals.annualreviews.org
by University of Medicine and Dentistry of New Jersey on 01/03/06. For personal use only.

Lie DC, Dziewczapolski G, Willhoite AR, Kaspar BK, Shults CW, Gage FH. 2002. The adult substantia nigra contains progenitor cells with neurogenic potential. *J. Neurosci.* 22:6639–49

Lie DC, Song H, Colamarino SA, Ming GL, Gage FH. 2004. Neurogenesis in the adult brain: new strategies for central nervous system diseases. *Annu. Rev. Pharmacol. Toxicol.* 44:399–421

Lim DA, Alvarez-Buylla A. 1999. Interaction between astrocytes and adult subventricular zone precursors stimulates neurogenesis. *Proc. Natl. Acad. Sci. USA* 96:7526–31

Lim DA, Tramontin AD, Trevejo JM, Herrera DG, Garcia-Verdugo JM, Alvarez-Buylla A. 2000. Noggin antagonizes BMP signaling to create a niche for adult neurogenesis. *Neuron* 28:713–26

Lindvall O, Kokaia Z, Martinez-Serrano A. 2004. Stem cell therapy for human neurodegenerative disorders-how to make it work. *Nat. Med.* 10(Suppl.):S42–50

Liu S, Wang J, Zhu D, Fu Y, Lukowiak K, Lu YM. 2003. Generation of functional inhibitory neurons in the adult rat hippocampus. *J. Neurosci.* 23:732–36

Lois C, Garcia-Verdugo JM, Alvarez-Buylla A. 1996. Chain migration of neuronal precursors. *Science* 271:978–81

Machold R, Hayashi S, Rutlin M, Muzumdar MD, Nery S, et al. 2003. Sonic hedgehog is required for progenitor cell maintenance in telencephalic stem cell niches. *Neuron* 39:937–50

Magavi SS, Leavitt BR, Macklis JD. 2000. Induction of neurogenesis in the neocortex of adult mice. *Nature* 405:951–55

Miller MW, Nowakowski RS. 1988. Use of bromodeoxyuridine-immunohistochemistry to examine the proliferation, migration and time of origin of cells in the central nervous system. *Brain Res.* 457:44–52

Mizrahi A, Crowley JC, Shtoyerman E, Katz LC. 2004. High-resolution in vivo imaging of hippocampal dendrites and spines. *J. Neurosci.* 24:3147–51

Mizrahi A, Katz LC. 2003. Dendritic stability in the adult olfactory bulb. *Nat. Neurosci.* 6:1201–7

Monje ML, Toda H, Palmer TD. 2003. Inflammatory blockade restores adult hippocampal neurogenesis. *Science* 302:1760–65

Morshead CM, Reynolds BA, Craig CG, McBurney MW, Staines WA, et al. 1994. Neural stem cells in the adult mammalian forebrain: a relatively quiescent subpopulation of subependymal cells. *Neuron* 13:1071–82

Murase S, Horwitz AF. 2002. Deleted in colorectal carcinoma and differentially expressed integrins mediate the directional migration of neural precursors in the rostral migratory stream. *J. Neurosci.* 22:3568–79

Nakatomi H, Kuriu T, Okabe S, Yamamoto S, Hatano O, et al. 2002. Regeneration of hippocampal pyramidal neurons after ischemic brain injury by recruitment of endogenous neural progenitors. *Cell* 110:429–41

Nguyen-Ba-Charvet KT, Picard-Riera N, Tessier-Lavigne M, Baron-Van Evercooren A, Sotelo C, Chedotal A. 2004. Multiple roles for slits in the control of cell migration in the rostral migratory stream. *J. Neurosci.* 24:1497–506

Nilsson M, Perfilieva E, Johansson U, Orwar O, Eriksson PS. 1999. Enriched environment increases neurogenesis in the adult rat dentate gyrus and improves spatial memory. *J. Neurobiol.* 39:569–78

Nimchinsky EA, Sabatini BL, Svoboda K. 2002. Structure and function of dendritic spines. *Annu. Rev. Physiol.* 64:313–53

Annu. Rev. Neurosci. 2005.28:223-250. Downloaded from arjournals.annualreviews.org
by University of Medicine and Dentistry of New Jersey on 01/03/06. For personal use only.

Nottebohm F. 2004. The road we travelled: discovery, choreography, and significance of brain replaceable neurons. *Ann. N.Y. Acad. Sci.* 1016:628–58

Oliver TG, Wechsler-Reya RJ. 2004. Getting at the root and stem of brain tumors. *Neuron* 42:885–88

Overstreet LS, Hentges ST, Bumaschny VF, de Souza FS, Smart JL, et al. 2004. A transgenic marker for newly born granule cells in dentate gyrus. *J. Neurosci.* 24:3251–59

Palmer TD, Markakis EA, Willhoite AR, Safar F, Gage FH. 1999. Fibroblast growth factor-2 activates a latent neurogenic program in neural stem cells from diverse regions of the adult CNS. *J. Neurosci.* 19:8487–97

Palmer TD, Willhoite AR, Gage FH. 2000. Vascular niche for adult hippocampal neurogenesis. *J. Comp. Neurol.* 425:479–94

Parent JM. 2003. Injury-induced neurogenesis in the adult mammalian brain. *Neuroscientist* 9:261–72

Parent JM, Valentin VV, Lowenstein DH. 2002a. Prolonged seizures increase proliferating neuroblasts in the adult rat subventricular zone-olfactory bulb pathway. *J. Neurosci.* 22:3174–88

Parent JM, Vexler ZS, Gong C, Derugin N, Ferriero DM. 2002b. Rat forebrain neurogenesis and striatal neuron replacement after focal stroke. *Ann. Neurol.* 52:802–13

Parent JM, Yu TW, Leibowitz RT, Geschwind DH, Sloviter RS, Lowenstein DH. 1997. Dentate granule cell neurogenesis is increased by seizures and contributes to aberrant network reorganization in the adult rat hippocampus. *J. Neurosci.* 17:3727–38

Paton JA, Nottebohm FN. 1984. Neurons generated in the adult brain are recruited into functional circuits. *Science* 225:1046–48

Price J, Turner D, Cepko C. 1987. Lineage analysis in the vertebrate nervous system by retrovirus-mediated gene transfer. *Proc. Natl. Acad. Sci. USA* 84:156–60

Raff M. 2003. Adult stem cell plasticity: fact or artifact? *Annu. Rev. Cell Dev. Biol.* 19:1–22

Raineteau O, Rietschin L, Gradwohl G, Guillemot F, Gahwiler BH. 2004. Neurogenesis in hippocampal slice cultures. *Mol. Cell Neurosci.* 26:241–50

Rakic P. 2002. Neurogenesis in adult primate neocortex: an evaluation of the evidence. *Nat. Rev. Neurosci.* 3:65–71

Ramon y Cajal S. 1913. *Degeneration and Regeneration of the Nervous System*. London: Oxford Univ. Press

Ray J, Peterson DA, Schinstine M, Gage FH. 1993. Proliferation, differentiation, and long-term culture of primary hippocampal neurons. *Proc. Natl. Acad. Sci. USA* 90:3602–6

Reynolds BA, Weiss S. 1992. Generation of neurons and astrocytes from isolated cells of the adult mammalian central nervous system. *Science* 255:1707–10

Rietze RL, Valcanis H, Brooker GF, Thomas T, Voss AK, Bartlett PF. 2001. Purification of a pluripotent neural stem cell from the adult mouse brain. *Nature* 412:736–39

Rochefort C, Gheusi G, Vincent JD, Lledo PM. 2002. Enriched odor exposure increases the number of newborn neurons in the adult olfactory bulb and improves odor memory. *J. Neurosci.* 22:2679–89

Rogers AW. 1973. *Techniques of Autoradiography*. New York: Elsevier Sci.

Rossi F, Cattaneo E. 2002. Opinion: Neural stem cell therapy for neurological diseases: dreams and reality. *Nat. Rev. Neurosci.* 3:401–9

Roy NS, Benraiss A, Wang S, Fraser RA, Goodman R, et al. 2000. Promoter-targeted selection and isolation of neural progenitor cells from the adult human ventricular zone. *J. Neurosci. Res.* 59:321–31

Annu. Rev. Neurosci. 2005.28:223-250. Downloaded from arjournals.annualreviews.org
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Saghatelyan A, de Chevigny A, Schachner M, Lledo PM. 2004. Tenascin-R mediates activity-dependent recruitment of neuroblasts in the adult mouse forebrain. *Nat. Neurosci.* 7:347–56

Sanai N, Tramontin AD, Quinones-Hinojosa A, Barbaro NM, Gupta N, et al. 2004. Unique astrocyte ribbon in adult human brain contains neural stem cells but lacks chain migration. *Nature* 427:740–44

Sanes JR, Rubenstein JL, Nicolas JF. 1986. Use of a recombinant retrovirus to study post-implantation cell lineage in mouse embryos. *EMBO J.* 5:3133–42

Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, et al. 2003. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science* 301:805–9

Scharfman HE, Goodman JH, Sollas AL. 2000. Granule-like neurons at the hilar/CA3 border after status epilepticus and their synchrony with area CA3 pyramidal cells: functional implications of seizure-induced neurogenesis. *J. Neurosci.* 20:6144–58

Schmidt-Hieber C, Jonas P, Bischofberger J. 2004. Enhanced synaptic plasticity in newly generated granule cells of the adult hippocampus. *Nature* 429:184–87

Schwab ME. 2004. Nogo and axon regeneration. *Curr. Opin. Neurobiol.* 14:118–24

Selden JR, Dolbeare F, Clair JH, Nichols WW, Miller JE, et al. 1993. Statistical confirmation that immunofluorescent detection of DNA repair in human fibroblasts by measurement of bromodeoxyuridine incorporation is stoichiometric and sensitive. *Cytometry* 14:154–67

Seri B, Garcia-Verdugo JM, Collado-Morente L, McEwen BS, Alvarez-Buylla A. 2004. Cell types, lineage, and architecture of the germinal zone in the adult dentate gyrus. *J. Comp. Neurol.* 478:359–78

Seri B, Garcia-Verdugo JM, McEwen BS, Alvarez-Buylla A. 2001. Astrocytes give rise to new neurons in the adult mammalian hippocampus. *J. Neurosci.* 21:7153–60

Shepherd GM, Chen WR, Greer CA. 2004. Olfactory bulb. In *The Synaptic Organization of the Brain*, ed. GM Shepherd, pp. 165–216. New York: Oxford Univ. Press

Shors TJ, Miesegaes G, Beylin A, Zhao M, Rydel T, Gould E. 2001. Neurogenesis in the adult is involved in the formation of trace memories. *Nature* 410:372–76

Shors TJ, Townsend DA, Zhao M, Kozorovitskiy Y, Gould E. 2002. Neurogenesis may relate to some but not all types of hippocampal-dependent learning. *Hippocampus* 12:578–84

Sidman RL, Miale IL, Feder N. 1959. Cell proliferation and migration in the primitive ependymal zone: an autoradiographic study of histogenesis in the nervous system. *Exp. Neurol.* 1:322–33

Smart I. 1961. The subependymal layer of the mouse brain and its cell production as shown by autography after [H^3]-thymidine injection. *J. Comp. Neurol.* 116:325–27

Snyder JS, Kee N, Wojtowicz JM. 2001. Effects of adult neurogenesis on synaptic plasticity in the rat dentate gyrus. *J. Neurophysiol.* 85:2423–31

Song H, Poo M. 2001. The cell biology of neuronal navigation. *Nat. Cell Biol.* 3:E81–88

Song HJ, Poo MM. 1999. Signal transduction underlying growth cone guidance by diffusible factors. *Curr. Opin. Neurobiol.* 9:355–63

Song H, Stevens CF, Gage FH. 2002a. Astroglia induce neurogenesis from adult neural stem cells. *Nature* 417:39–44

Song HJ, Stevens CF, Gage FH. 2002b. Neural stem cells from adult hippocampus develop essential properties of functional CNS neurons. *Nat. Neurosci.* 5:438–45

Stanfield BB, Trice JE. 1988. Evidence that granule cells generated in the dentate gyrus of adult rats extend axonal projections. *Exp. Brain Res.* 72:399–406

Tattersfield AS, Croon RJ, Liu YW, Kells AP, Faull RL, Connor B. 2004. Neurogenesis in the striatum of the quinolinic acid lesion model of Huntington's disease. *Neuroscience* 127:319–32

Annu. Rev. Neurosci. 2005.28:223-250. Downloaded from arjournals.annualreviews.org
by University of Medicine and Dentistry of New Jersey on 01/03/06. For personal use only.

Temple S. 2001. The development of neural stem cells. *Nature* 414:112–17

Tropepe V, Craig CG, Morshead CM, van der Kooy D. 1997. Transforming growth factor-alpha null and senescent mice show decreased neural progenitor cell proliferation in the forebrain subependyma. *J. Neurosci.* 17:7850–59

Uchida N, Buck DW, He D, Reitsma MJ, Masek M, et al. 2000. Direct isolation of human central nervous system stem cells. *Proc. Natl. Acad. Sci. USA* 97:14720–25

Ueki T, Tanaka M, Yamashita K, Mikawa S, Qiu Z, et al. 2003. A novel secretory factor, Neurogenesin-1, provides neurogenic environmental cues for neural stem cells in the adult hippocampus. *J. Neurosci.* 23:11732–40

Ullian EM, Christopherson KS, Barres BA. 2004. Role for glia in synaptogenesis. *Glia* 47:209–16

Vallieres L, Campbell IL, Gage FH, Sawchenko PE. 2002. Reduced hippocampal neurogenesis in adult transgenic mice with chronic astrocytic production of interleukin-6. *J. Neurosci.* 22:486–92

van Praag H, Christie BR, Sejnowski TJ, Gage FH. 1999a. Running enhances neurogenesis, learning, and long-term potentiation in mice. *Proc. Natl. Acad. Sci. USA* 96:13427–31

van Praag H, Kempermann G, Gage FH. 1999b. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nat. Neurosci.* 2:266–70

van Praag H, Schinder AF, Christie BR, Toni N, Palmer TD, Gage FH. 2002. Functional neurogenesis in the adult hippocampus. *Nature* 415:1030–34

Walker MC, Ruiz A, Kullmann DM. 2001. Monosynaptic GABAergic signaling from dentate to CA3 with a pharmacological and physiological profile typical of mossy fiber synapses. *Neuron* 29:703–15

Wang S, Scott BW, Wojtowicz JM. 2000. Heterogenous properties of dentate granule neurons in the adult rat. *J. Neurobiol.* 42:248–57

Wu W, Wong K, Chen J, Jiang Z, Dupuis S, et al. 1999. Directional guidance of neuronal migration in the olfactory system by the protein Slit. *Nature* 400:331–36

Yamaguchi M, Saito H, Suzuki M, Mori K. 2000. Visualization of neurogenesis in the central nervous system using nestin promoter-GFP transgenic mice. *Neuroreport* 11:1991–96

Zhao M, Momma S, Delfani K, Carlen M, Cassidy RM, et al. 2003a. Evidence for neurogenesis in the adult mammalian substantia nigra. *Proc. Natl. Acad. Sci. USA* 100:7925–30

Zhao X, Ueba T, Christie BR, Barkho B, McConnell MJ, et al. 2003b. Mice lacking methyl-CpG binding protein 1 have deficits in adult neurogenesis and hippocampal function. *Proc. Natl. Acad. Sci. USA* 100:6777–82

Zupanc GK. 2001. A comparative approach towards the understanding of adult neurogenesis. *Brain Behav. Evol.* 58:246–49

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