Opinion TRENDS in Molecular Medicine Vol.12 No.9

New regulators in adult neurogenesis and their potential role for repair

Ravi Jagasia[1], Hongjun Song[2], Fred H. Gage[3] and D. Chichung Lie[1]

[1] Institute of Developmental Genetics, GSF-National Research Center for Environment and Health, 85764 Munich Neuherberg, Germany
[2] Institute for Cell Engineering, Departments of Neurology and Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA
[3] Laboratory of Genetics, The Salk Institute, La Jolla, CA 92037, USA

Adult neural stem cells hold great promise for repair because of their unique location within the central nervous system, their potential to proliferate and to differentiate into all major neural lineages, and their ability to incorporate functionally into the existing neuronal circuitry. However, recruitment of these cells for repair is hampered by the lack of knowledge about the signals that control the generation of a functional neuron from adult neural stem cells. Here, we discuss recent findings on the regulatory mechanisms that underlie neurogenesis from neural stem cells in the adult hippocampus and the implications of these findings for future stem-cell-based repair strategies.

Endogenous neural stem cells and repair of the adult central nervous system

Tissue-specific stem cells ensure proper function of many different organs by replacing cells that are lost to physiological wear and tear, injury and disease. Lack of such tissue-specific stem cells has long been considered a major reason for the limited regeneration in the adult mammalian CNS. During the past decade, however, several studies have consistently shown that cells with neural stem-cell-like properties seem to reside throughout the adult mammalian CNS [1,2]. These endogenous cells, which we will call neural stem cells (NSCs) throughout this discussion, hold great promise for repair because of their extensive proliferation potential and their ability to generate all neural lineages, including neurons. Multiple studies have repeatedly shown that new neurons are generated from NSCs in the subventricular zone–olfactory bulb system and the hippocampal dentate gyrus throughout life, which demonstrates that endogenous NSCs can, in principle, generate new neurons *in vivo* [3].

The first evidence that endogenous neural stem cells can replace neurons in adult CNS regions outside those neurogenic regions was provided by Magavi *et al.* [4]. In their landmark study, corticothalamical projecting neurons in the neocortex of adult mice were selectively ablated. Using fate-mapping studies and retrograde-tracing analysis, these authors demonstrated that new neurons were formed from endogenous NSCs in the areas undergoing neuronal cell death and that these neurons sent appropriate axonal projections, suggesting that the new neurons might become functionally integrated [4]. Using a similar lesion paradigm, Macklis and colleagues [5] more recently have provided evidence that dying cortical motoneurons can be regenerated from NSCs and that the newborn motoneurons can extend appropriate long-distance connections to the spinal cord, suggesting that regeneration of neurons from endogenous NSCs might not be restricted to a small pool of neuronal subtypes. This study is also of great clinical interest because cortical motoneurons are severely affected by amyotrophic lateral sclerosis.

These two studies provided an important proof of principle for the ability of endogenous stem cells to replace dying neurons in different regions of the central nervous system. In addition, they suggest that, following neuronal cell death, developmental programs might be reactivated that promote the generation of new functional neurons. Clinical and experimental experience, however, indicate that regenerative programs are either not sufficiently activated in the diseased brain or that inhibitory programs might be at work. Acute neurological insults such as stroke and trauma are accompanied by severe destruction of surrounding tissue, whereas neurons in neurodegenerative diseases such as Parkinson's and Alzheimer's disease degenerate over decades. These features are absent in the selective lesion paradigm applied in the studies described above [4,5]. Work in animal models suggests that the program that recruits endogenous NSCs for neurogenesis might be partially activated in stroke, ischemia and neurodegenerative diseases. Cell death in stroke strongly stimulates the proliferation of endogenous NSCs and can also promote the migration of newborn cells to the site of damage [6–8]. The fate of the cells that are generated in response to ischemia seems to be region dependent: in some areas such as the striatum newborn cells adopt an immature neuronal phenotype [9,10], whereas newborn cells in the lesioned cortex fail to differentiate into neurons [9]. Thus, neuronal fate determination is, at least in a subset of CNS regions, a major limitation for endogenous NSC-based regeneration. Moreover, of the immature neurons that are generated in response to ischemia, only few survive for long and mature into potentially functional neurons [9]. Thus, survival and integration place additional restrictions on the replacement of degenerating neurons from endogenous NSCs.

Corresponding author: Lie, D.C. (chichung.lie@gsf.de).
Available online 4 August 2006.

 1471-4914/$ – see front matter doi:10.1016/j.molmed.2006.07.006

Adult hippocampal neurogenesis: a model for neurogenesis from endogenous stem cells

Embryonic stem cell research illustrates that the understanding of the principles of development provides powerful strategies to harness stem cells for tissue repair. With regard to adult NSCs and their recruitment for neuronal replacement therapy, it is indispensable to understand the mechanisms that control NSC behaviour in the adult brain. The characterization of the mechanisms *in situ* is particularly important because new neurons interact with mature neural cells and have to integrate into existing neuronal networks.

The dentate gyrus of the adult hippocampus represents an *in vivo* model system to characterize the molecular and cellular mechanisms that underlie neurogenesis from NSCs in the adult CNS. Except for the subventricular zone–olfactory bulb system, the dentate gyrus is the only adult brain region where NSCs generate new functional neurons throughout adulthood [3]. Conceptually, this process can be divided into four steps: (i) proliferation of NSCs; (ii) neuronal fate determination of NSC; (iii) survival and maturation of new neurons; and (iv) functional integration of new neurons into the hippocampal neuronal network.

Environmental control of adult hippocampal neurogenesis

Transplantation studies provided direct evidence for the regulation of fate determination by extrinsic signals that are derived from the neurogenic microenvironment [11]. Cells with NSC properties that were isolated from neurogenic and various non-neurogenic regions of the adult CNS, such as the substantia nigra and the spinal cord, differentiate into neurons when transplanted into the dentate gyrus or the subventricular zone–olfactory bulb system, but fail to generate neurons when transplanted into non-neurogenic regions [12–14]. In addition, NSCs that have been transplanted into neurogenic regions will adopt a neuronal subtype that is appropriate for the neurogenic region that they have been grafted to [14]. These observations demonstrate that neuronal fate determination and subtype specification is controlled by signals provided by the neurogenic microenvironment.

Cellular components of the hippocampal neurogenic niche

Endothelial cells, astrocytes and neurons in the dentate gyrus form a unique cellular environment that controls hippocampal neurogenesis. NSCs in the dentate gyrus proliferate and differentiate in close proximity to blood vessels [15]. Interaction with endothelial cells seems to participate in the regulation of NSC proliferation [16]. NSCs might give rise to new endothelial cells in the dentate gyrus, thereby creating their own proliferative environment and potential cellular feedback mechanisms [17].

Astrocytes interact with NSCs and their early neuronal progeny [18,19]. This interaction is crucial for neurogenesis. Hippocampal astrocytes produce signals that promote proliferation and neuronal fate determination of NSCs. In addition, astrocyte-derived factors might stimulate synaptogenesis of newborn neurons [19,20]. Diffusible and membrane-bound factors produced by hippocampal astrocytes are involved in the control of neuronal fate determination. Importantly, astrocytes from non-neurogenic regions do not promote neurogenesis, indicating that hippocampal astrocytes are specialized and generate a unique set of signals that is crucial for maintaining neurogenesis throughout adulthood.

Role of Wnt-signalling in the hippocampal neurogenic niche

Recently, we have made progress on the identification of neurogenic signals [21,22]. Wnt proteins regulate various processes during embryonic development including proliferation, differentiation and maturation of stem cells and their progeny [23]. We and others have shown that several Wnt-family members are present in the dentate gyrus [22,24]; at least one family member (i.e. Wnt3) is expressed by hippocampal astrocytes [22]. In addition, we have found evidence that hippocampal astrocyte-derived Wnts stimulate Wnt–β-catenin signalling in NSCs and that Wnt signalling promotes the generation of neurons from NSCs *in vitro*. The *in vitro* neurogenic effects of Wnt signalling are the result of increased neuronal fate commitment and proliferation of neuroblasts. Consistent with these *in vitro* observations, enhanced Wnt signalling promotes the generation of immature neurons in the adult dentate gyrus. By contrast, overexpression of a dominant-negative Wnt mutant that inhibits all Wnt-signalling pathways, suppresses neurogenesis in the adult hippocampus almost completely [22] (Figure 1). Taken together, these results identify Wnt as a signalling pathway through which hippocampal astrocytes regulate adult neurogenesis. Moreover, these findings demonstrate that Wnts are key regulators of adult neurogenesis *in vivo* and suggest that Wnt signalling might be a central pathway for neuronal fate determination of endogenous NSCs [22].

Role of GABA neurotransmission in hippocampal neurogenesis

Several studies have demonstrated that electrical activity modulates broad functions in the development of the CNS, including proliferation [25], survival [26], neuronal subtype specification and connectivity [27–29]. The putative stem cell in the adult subgranular zone (SGZ) has an apical process that spans the granule-cell layer into the inner molecular layer [18,30] through which it might interact with the local neuronal population. The observation that various behavioural changes such as environmental enrichment, running and learning modulate neurogenesis provided an early hint at the possibility that neuronal activity might influence NSC behaviour [31–33]. A strong indication that neuronal activity participates in the regulation of NSCs comes from analysis of animal models for epilepsy. Many studies have shown that epileptic activity increases proliferation of NSCs [10,34] and accelerate synaptic integration of newborn granule neurons [35]. In addition, pharmacological inhibition of *N*-methyl-D-aspartic acid (NMDA) receptors in the adult dentate gyrus modulates the proliferative rate of hippocampal NSCs [36].

Recently, we and others have succeeded to characterize some of the neuronal input and the neurophysiological

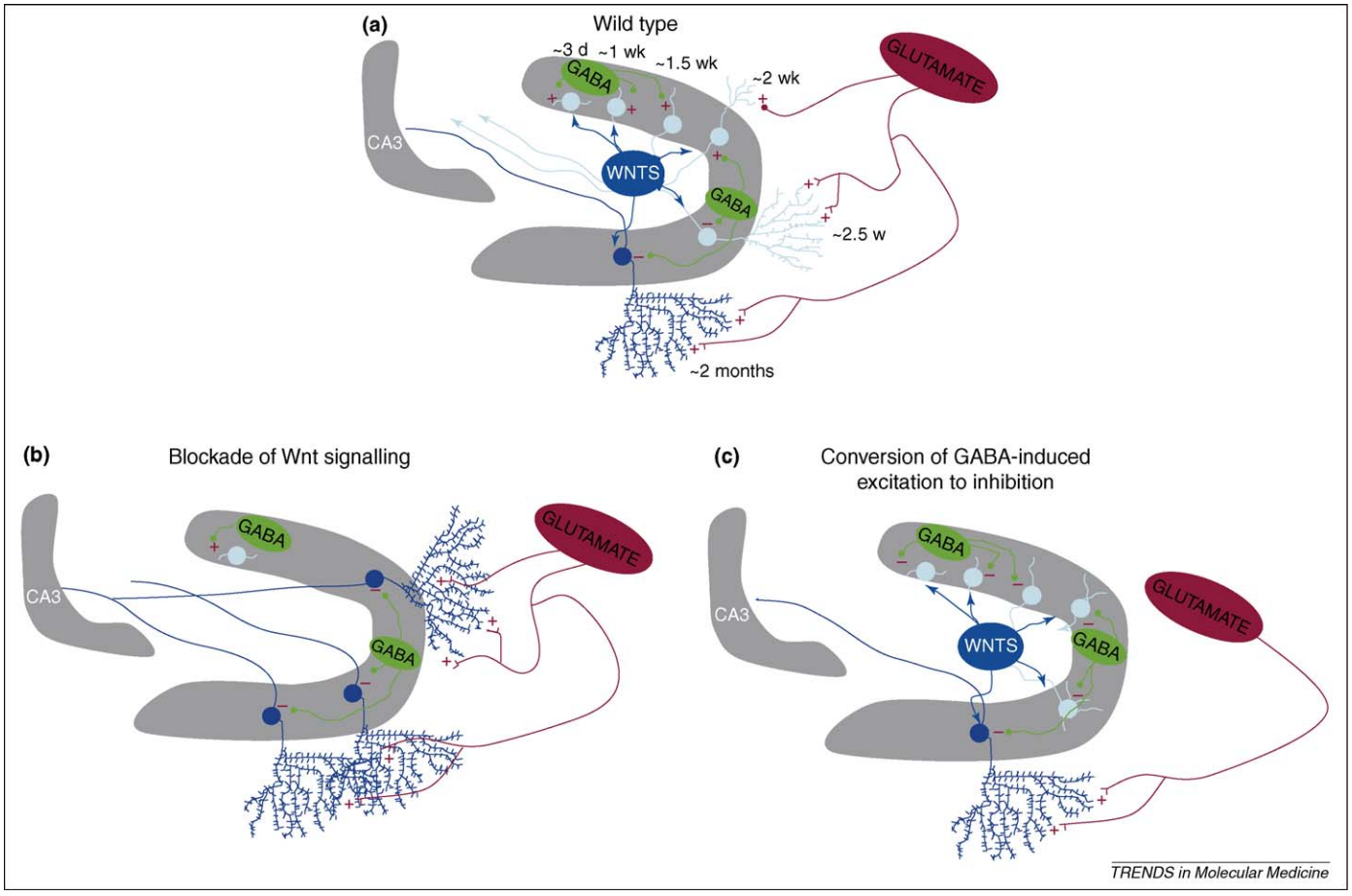

Figure 1. Role of Wnt and GABA signalling in the development of new functional dentate granule neurons in the adult hippocampus. **(a)** Newborn granule neurons proceed through distinct stages en route to maturing into a functional granule neuron (~2 months, dark blue cell). These developmental stages include polarization, axonal and dendritic growth, axon reaching the CA3 region, dendritic arborization, increased dendritic complexity accompanied by spine formation and changes in the GABA and glutamate inputs. These processes might be cooperatively regulated by Wnt and GABA signalling. Immature newborn neurons are shown in light blue. An approximate timeline based on retroviral-labelling studies [38,44] is indicated. **(b)** Inhibition of Wnt signalling abolishes neurogenesis almost completely because of its role in neuronal fate determination and expansion of the neuroblast pool [22]. The role of Wnt signalling in later stages of neurogenesis remains to be explored. **(c)** When GABA-induced depolarization (excitation) is converted into hyperpolarization (inhibition), synapse formation and dendritic development of newborn granule neurons is impaired. Thus, GABA-induced excitation is crucial for synaptic integration and maturity of newly generated neurons in the adult hippocampus [38].

properties of NSCs and their progeny in the adult dentate gyrus during the first four weeks after their generation [37–43]. These studies indicate that neuronal inputs on NSCs, their neuronal progeny and neurophysiological development follow a stereotypical pattern. Electrophysiological analysis shows that, at early stages, precursor cells are activated by ambient γ-amino butyric acid (GABA) through non-synaptic mechanisms before showing any spontaneous or evoked postsynaptic currents [38]. Furthermore, stimulation of local interneurons cells enhances the tonic GABA current, implying that changes in the local GABA concentration are sensed by precursors [38]. During their maturation into granule neurons, newborn cells subsequently receive GABA synaptic inputs, followed by glutamate inputs, which appear with a delay of approximately one week after the synaptic GABA inputs. Curiously, axonal outgrowth of newborn granule neurons into the hippocampal CA3 region parallels these changes in synaptic input [44]. In light of previous studies that reported that electrical activity modulates the growth and guidance of the developing axon [29], it will be interesting to examine whether these changes in synaptic input are involved in the control of axonal growth of the newborn granule neuron.

Newborn granule cells initially express high levels of the Na^+–K^+–$2Cl^-$ (NKCC1) chloride importer and have a high intracellular Cl^- content. This results in a reversal potential for GABA-induced currents that is higher than the resting membrane potential during the first 2–3 weeks after the birth of the new neuron. Thus, GABA initially depolarizes newborn immature neurons in the adult dentate gyrus.

The Song laboratory has recently examined the role of GABA-induced depolarization in hippocampal neurogenesis using short-hairpin RNA (shRNA)-mediated knockdown of NKCC1 in newborn neurons [38]. In the absence of NKCC1, GABA hyperpolarizes newborn neurons. Importantly, loss of GABA-induced depolarization results in defects in the formation of GABA- and glutamate-mediated synapses and impaired dendritic development of newborn neurons in the adult brain, indicating that GABA-induced depolarization is crucial for the maturation and functional integration of new dentate granule neurons [38] (Figure 1).

Taken together, these data illustrate that multiple cell types regulate hippocampal neurogenesis through developmental morphogens, neurotransmitters and electrical activity.

Is there an interaction between Wnt and GABA signalling?

How do these different signals coordinate the behaviour of NSCs in the adult hippocampus? Based on our studies, it is possible that Wnts instruct NSCs to adopt a neuronal phenotype and that GABA-induced depolarization promotes the maturation and integration of neuronally committed precursors. However, studies indicate that signalling molecules and electrical activity might synergistically regulate the development of the nervous system [45]. Moreover, there is a substantial body of evidence that electrical activity can regulate the expression of morphogens [46] and growth factors [47], and that growth factors can induce depolarization of neurons [48].

Indeed, there are several hints that Wnt signalling and GABA-induced electrical activity might synergistically regulate hippocampal neurogenesis. Deisseroth *et al.* [49] found that depolarization and the resulting increase in intracellular Ca^{2+} enhance the expression of the pro-neuronal basic helix–loop–helix (bHLH) transcription factor NeuroD and of neuronal markers in NSCs, and suggested that depolarization controls the neuronal fate commitment of NSCs through the regulation of NeuroD. The effect of depolarization on NSCs was observed in the presence of hippocampal astrocytes, which control neuronal fate determination of NSCs at least in part through Wnt signalling [22,49]. Interestingly, it has been demonstrated that Wnts control the expression of pro-neuronal bHLH transcription factors in neural progenitor cells during cortical development [50], raising the possibility that electrical activity and Wnt signalling converge onto pro-neuronal bHLH factors to control neuronal fate commitment in hippocampal neurogenesis. Current *in vivo* data also support the hypothesis that Wnt signalling and electrical activity synergistically regulate neuronal fate commitment of NSCs in the adult hippocampus. As described above, increased Wnt signalling strongly stimulates neurogenesis in the adult hippocampal dentate gyrus [22]. Wang *et al.* [43] and Tozuka *et al.* [41] reported that GABAergic synapses are formed on neural precursors. Tozuka *et al.* [41] further showed that GABA-induced excitation increases the expression of NeuroD in this cell population in a slice culture preparation. Moreover, they showed that systemic administration of a $GABA_A$-receptor agonist leads to increased generation of new dentate granule neurons. Although it is not clear whether this effect can be attributed to a direct effect of $GABA_A$-receptor activation on NSCs, this study provides *in vivo* evidence that GABA can modulate neuronal fate commitment of NSCs in the adult hippocampus. How electrical activity and potentially increased intracellular Ca^{2+} regulate the expression of NeuroD remains to be determined. In addition, it has to be considered that electrical activity and Ca^{2+} can also lead to post-translational modification of NeuroD, thereby controlling the function of this transcription factor [51].

There are also circumstantial observations that raise the possibility that members of the Wnt-protein family might participate in later steps of hippocampal neurogenesis such as the maturation and integration of newborn dentate granule neurons. Analysis of the Wnt–β-catenin reporter mice BATGAL showed that this pathway is active not only in proliferating precursors and early neuroblasts of the SGZ of the dentate gyrus but might also be active in more-mature neurons of the granule-cell layer [22,52]. In addition to Wnt3, Wnt5a, Wnt7a and Wnt8b are expressed in the SGZ or the granule-cell layer of the adult dentate gyrus [24]. Some of these Wnt proteins regulate axonal and dendritic morphology and promote synaptogenesis during development not only through the Wnt–β-catenin pathway but also through non-canonical Wnt-signalling pathways [53]. The expression of several Wnt-family members and their participation in maturation processes during embryonic development raise the possibility that non-canonical Wnt signalling is involved in the control of maturation and integration of adult-born hippocampal neurons. The non-canonical Wnt signalling pathways are interesting candidates because they can increase Ca^{2+} [54] and cAMP [55] levels in some tissues. These second messengers are also used in activity-dependent processes in the nervous system and might be a molecular interface for crosstalk between electrical activity and Wnt signalling in the regulation of adult neurogenesis.

Implications for repair

Recent data indicate that various signals, including developmental morphogens and electrical activity, synergistically regulate the generation and integration of new functional neurons in the adult hippocampus [3]. We expect that the interplay between signalling molecules and electrical activity will be crucial for successful recruitment of endogenous NSCs for repair in the adult brain. Several studies have shown a promising effect of developmental signalling molecules on the recruitment of neurons for repair [56–58]. It will be interesting to investigate whether the efficiency of this process can be further enhanced by, for example, GABA signals, electrical activity and stimulation of Wnt signalling. Such combined treatment might induce a greater number of NSCs to commit to a neuronal fate, to integrate and, importantly, to survive long-term as a functional neuron. It will also be important to identify the intracellular regulators that mediate the potential interaction between Wnt signalling and electrical activity in the control of neurogenesis. Such molecular integrators might be promising targets for intervention to promote regeneration from endogenous NSCs.

One problem is how to promote Wnt signalling and electrical activity in the lesion context. Virus-mediated expression of Wnt molecules might be one approach to increase Wnt signalling in the diseased CNS. Yet, this strategy might pose additional challenges such as the control of expression levels, the temporal control of Wnt expression and the need for stereotactic surgery. Chemical biology and combinatorial chemistry, however, might provide an alternative solution in the future through the generation of small molecules that can selectively stimulate Wnt signalling and can be non-invasively delivered.

How can the activation of neural stem cells and their progeny through neurotransmitters and neuronal activity be increased? Several drugs that affect neurotransmission are currently in use for the treatment of neurological and psychiatric diseases. It will be important to test the potential of these drugs to promote neuronal replacement from

endogenous stem cells in animal models for neurological diseases. Protection of compromised neurons in the disease location not only will reduce the number of neurons that need to be regenerated but might also result in enhanced neurotransmitter input and electrical stimulation of local NSCs and their progeny. Clinical studies have provided convincing evidence for the beneficial impact of rehabilitation on functional recovery in neurological diseases. It has been suggested that plasticity induced by neuronal activity is a crucial contributor to this recovery process. Given the fact that complex behaviour has major impact on adult neurogenesis [31–33], it is tempting to speculate that stimulation of Wnt signalling in combination with behavioural modifications might synergistically promote neuronal replacement from endogenous stem cells.

Morphogens, electrical activity and neurotransmitter input will have to be fine-tuned. Animal models for epilepsy have revealed that dysregulated electrical activity can lead to the generation of new neurons with altered electrophysiological properties [59]. In addition, developmental studies indicate that precise electrical activity is important for the proper targeting of dendrites and axons, synaptogenesis and the acquisition of the proper neurotransmitter phenotype [60].

Nevertheless, by increasing the knowledge about the complex regulatory mechanisms in adult neurogenesis, the ultimate goal to harness successfully endogenous NSCs for repair of the CNS will get closer.

Acknowledgement

R. J. is supported by a fellowship of the Alexander von Humboldt Foundation. D.C.L. is supported by the Deutsche Forschungsgemeinschaft. H.J.S. is supported by grants from the NINDS, NIA, McKnight Scholar Award and Packard Center for ALS. F.H.G. is supported by grants from the NINDS/NIA, the Max Planck Research Award Program funded by the German Ministry for Education, Science, Research and Technology, the Lookout Fund, the Christopher Reeves Paralysis Foundation and Project ALS.

References

1 Arlotta, P. *et al.* (2003) Induction of adult neurogenesis: molecular manipulation of neural precursors *in situ*. *Ann. N. Y. Acad. Sci.* 991, 229–236
2 Lie, D.C. *et al.* (2004) Neurogenesis in the adult brain: new strategies for central nervous system diseases. *Annu. Rev. Pharmacol. Toxicol.* 44, 399–421
3 Ming, G.L. and Song, H. (2005) Adult neurogenesis in the mammalian central nervous system. *Annu. Rev. Neurosci.* 28, 223–250
4 Magavi, S.S. *et al.* (2000) Induction of neurogenesis in the neocortex of adult mice. *Nature* 405, 951–955
5 Chen, J. *et al.* (2004) Neurogenesis of corticospinal motor neurons extending spinal projections in adult mice. *Proc. Natl. Acad. Sci. U. S. A.* 101, 16357–16362
6 Liu, J. *et al.* (1998) Increased neurogenesis in the dentate gyrus after transient global ischemia in gerbils. *J. Neurosci.* 18, 7768–7778
7 Parent, J.M. *et al.* (2002) Rat forebrain neurogenesis and striatal neuron replacement after focal stroke. *Ann. Neurol.* 52, 802–813
8 Sharp, F.R. *et al.* (2002) Neurogenesis following brain ischemia. *Brain Res. Dev. Brain Res.* 134, 23–30
9 Arvidsson, A. *et al.* (2002) Neuronal replacement from endogenous precursors in the adult brain after stroke. *Nat. Med.* 8, 963–970
10 Parent, J.M. *et al.* (2002) Prolonged seizures increase proliferating neuroblasts in the adult rat subventricular zone-olfactory bulb pathway. *J. Neurosci.* 22, 3174–3188
11 Alvarez-Buylla, A. and Lim, D.A. (2004) For the long run: maintaining germinal niches in the adult brain. *Neuron* 41, 683–686
12 Lie, D.C. *et al.* (2002) The adult substantia nigra contains progenitor cells with neurogenic potential. *J. Neurosci.* 22, 6639–6649
13 Shihabuddin, L.S. *et al.* (2000) Adult spinal cord stem cells generate neurons after transplantation in the adult dentate gyrus. *J. Neurosci.* 20, 8727–8735
14 Suhonen, J.O. *et al.* (1996) Differentiation of adult hippocampus-derived progenitors into olfactory neurons *in vivo*. *Nature* 383, 624–627
15 Palmer, T.D. *et al.* (2000) Vascular niche for adult hippocampal neurogenesis. *J. Comp. Neurol.* 425, 479–494
16 Shen, Q. *et al.* (2004) Endothelial cells stimulate self-renewal and expand neurogenesis of neural stem cells. *Science* 304, 1338–1340
17 Wurmser, A.E. *et al.* (2004) Cell fusion-independent differentiation of neural stem cells to the endothelial lineage. *Nature* 430, 350–356
18 Seri, B. *et al.* (2004) Cell types, lineage, and architecture of the germinal zone in the adult dentate gyrus. *J. Comp. Neurol.* 478, 359–378
19 Song, H. *et al.* (2002) Astroglia induce neurogenesis from adult neural stem cells. *Nature* 417, 39–44
20 Song, H.J. *et al.* (2002) Neural stem cells from adult hippocampus develop essential properties of functional CNS neurons. *Nat. Neurosci.* 5, 438–445
21 Barkho, B. *et al.* (2006) Identification of astrocytes-expressed factors that modulate neural stem/progenitor cell differentiation. *Stem Cells and Development* 15, 407–421
22 Lie, D.C. *et al.* (2005) Wnt signalling regulates adult hippocampal neurogenesis. *Nature* 437, 1370–1375
23 Kleber, M. and Sommer, L. (2004) Wnt signaling and the regulation of stem cell function. *Curr. Opin. Cell Biol.* 16, 681–687
24 Shimogori, T. *et al.* (2004) Members of the Wnt, Fz, and Frp gene families expressed in postnatal mouse cerebral cortex. *J. Comp. Neurol.* 473, 496–510
25 Barres, B.A. and Raff, M.C. (1993) Proliferation of oligodendrocyte precursor cells depends on electrical activity in axons. *Nature* 361, 258–260
26 West, A.E. *et al.* (2001) Calcium regulation of neuronal gene expression. *Proc. Natl. Acad. Sci. U. S. A.* 98, 11024–11031
27 Borodinsky, L.N. *et al.* (2004) Activity-dependent homeostatic specification of transmitter expression in embryonic neurons. *Nature* 429, 523–530
28 Ince-Dunn, G. *et al.* (2006) Regulation of thalamocortical patterning and synaptic maturation by NeuroD2. *Neuron* 49, 683–695
29 Ming, G. *et al.* (2001) Electrical activity modulates growth cone guidance by diffusible factors. *Neuron* 29, 441–452
30 Seri, B. *et al.* (2001) Astrocytes give rise to new neurons in the adult mammalian hippocampus. *J. Neurosci.* 21, 7153–7160
31 Gould, E. *et al.* (1999) Learning enhances adult neurogenesis in the hippocampal formation. *Nat. Neurosci.* 2, 260–265
32 Kempermann, G. *et al.* (1997) More hippocampal neurons in adult mice living in an enriched environment. *Nature* 386, 493–495
33 van Praag, H. *et al.* (1999) Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nat. Neurosci.* 2, 266–270
34 Jessberger, S. *et al.* (2005) Seizures induce proliferation and dispersion of doublecortin-positive hippocampal progenitor cells. *Exp. Neurol.* 196, 342–351
35 Overstreet-Wadiche, L.S. *et al.* (2006) Seizures accelerate functional integration of adult-generated granule cells. *J. Neurosci.* 26, 4095–4103
36 Cameron, H.A. *et al.* (1998) Adrenal steroids and N-methyl-D-aspartate receptor activation regulate neurogenesis in the dentate gyrus of adult rats through a common pathway. *Neuroscience* 82, 349–354
37 Esposito, M.S. *et al.* (2005) Neuronal differentiation in the adult hippocampus recapitulates embryonic development. *J. Neurosci.* 25, 10074–10086
38 Ge, S. *et al.* (2006) GABA regulates synaptic integration of newly generated neurons in the adult brain. *Nature* 439, 589–593
39 Overstreet-Wadiche, L.S. *et al.* (2006) Delayed development of adult-generated granule cells in dentate gyrus. *J. Neurosci.* 26, 2326–2334
40 Schmidt-Hieber, C. *et al.* (2004) Enhanced synaptic plasticity in newly generated granule cells of the adult hippocampus. *Nature* 429, 184–187
41 Tozuka, Y. *et al.* (2005) GABAergic excitation promotes neuronal differentiation in adult hippocampal progenitor cells. *Neuron* 47, 803–815

42 van Praag, H. *et al.* (2002) Functional neurogenesis in the adult hippocampus. *Nature* 415, 1030–1034
43 Wang, L.P. *et al.* (2005) A subpopulation of precursor cells in the mouse dentate gyrus receives synaptic GABAergic input. *Mol. Cell. Neurosci.* 29, 181–189
44 Zhao, C. *et al.* (2006) Distinct morphological stages of dentate granule neuron maturation in the adult mouse hippocampus. *J. Neurosci.* 26, 3–11
45 Dijkhuizen, P.A. and Ghosh, A. (2005) Regulation of dendritic growth by calcium and neurotrophin signaling. *Prog. Brain Res.* 147, 17–27
46 Chen, J. *et al.* (2006) Activity-dependent synaptic WNT release regulates hippocampal long-term potentiation. *J. Biol. Chem.* 281, 11910–11916
47 Lu, B. (2003) BDNF and activity-dependent synaptic modulation. *Learn. Mem.* 10, 86–98
48 Kafitz, K.W. *et al.* (2000) Neurotrophin-evoked rapid excitation of central neurons. *Prog. Brain Res.* 128, 243–249
49 Deisseroth, K. *et al.* (2004) Excitation-neurogenesis coupling in adult neural stem/progenitor cells. *Neuron* 42, 535–552
50 Hirabayashi, Y. *et al.* (2004) The Wnt/beta-catenin pathway directs neuronal differentiation of cortical neural precursor cells. *Development* 131, 2791–2801
51 Gaudilliere, B. *et al.* (2004) A CaMKII–NeuroD signaling pathway specifies dendritic morphogenesis. *Neuron* 41, 229–241
52 Maretto, S. *et al.* (2003) Mapping Wnt/beta-catenin signaling during mouse development and in colorectal tumors. *Proc. Natl. Acad. Sci. U. S. A.* 100, 3299–3304
53 Fradkin, L.G. *et al.* (2005) Wnt signaling in neural circuit development. *J. Neurosci.* 25, 10376–10378
54 Kuhl, M. (2004) The WNT/calcium pathway: biochemical mediators, tools and future requirements. *Front. Biosci.* 9, 967–974
55 Chen, A.E. *et al.* (2005) Protein kinase A signalling via CREB controls myogenesis induced by Wnt proteins. *Nature* 433, 317–322
56 Chmielnicki, E. *et al.* (2004) Adenovirally expressed noggin and brain-derived neurotrophic factor cooperate to induce new medium spiny neurons from resident progenitor cells in the adult striatal ventricular zone. *J. Neurosci.* 24, 2133–2142
57 Nakatomi, H. *et al.* (2002) Regeneration of hippocampal pyramidal neurons after ischemic brain injury by recruitment of endogenous neural progenitors. *Cell* 110, 429–441
58 Androutsellis-Theotokis, A. *et al.* (2006) Notch signalling regulates stem cell numbers *in vitro* and *in vivo*. *Nature*
59 Scharfman, H.E. *et 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, 6144–6158
60 Spitzer, N.C. *et al.* (2004) Orchestrating neuronal differentiation: patterns of Ca^{2+} spikes specify transmitter choice. *Trends Neurosci.* 27, 415–421