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Understanding our own neural stem cells *in situ*: can we benefit from them?

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TABLE OF CONTENTS

1. ABSTRACT

The discovery of endogenous adult neurogenesis within the mammalian brain has unwrapped wide expectation about the potential use of this process for nervous system repair and regeneration. Neural stem cells residing in specific niches are able to proliferate and differentiate, giving rise to migrating neuroblasts, which in turn mature into functional neurons. These new neurons integrate into the existing circuits and contribute to the structural plasticity of certain brain areas. However, recent evidence suggests that the process could become more general under pathological conditions. Adult neurogenesis increases under acute and chronic brain diseases. Neuronal precursors are directed to the lesioned areas where they contribute to tissue repair. Given this intrinsic capability of the adult brain for tissue regeneration, researchers are focusing on strategies aimed at manipulating endogenous neurogenesis to optimize therapeutic benefit. These new approaches depend on a better understanding of the physiological role of stem cells *in situ*, and the elucidation of the molecular cues governing neurogenesis in normal and pathological situations. In this work, I review what is actually known about the physiology of well-described adult neural stem cell populations, and how several factors defining their niches could be used to manipulate and direct the neurogenic process towards amelioration of disease.

2. INTRODUCTION

Recent evidence has changed the way we think about the adult mammalian nervous system. Contrary to previous dogma (1), we now know that adult neurogenesis continues in two regions of the adult mammalian brain, the dentate gyrus of the hippocampal formation and the subventricular zone and its projection to the olfactory bulb. The study of these areas revealed the existence of an outstanding population of cells capable of self-renewal and differentiation into all three central nervous system (CNS) differentiated cell types: astrocytes, oligodendrocytes and neurons. The so-called adult neural stem cells are responsible for the generation of new neurons within the neurogenic zones, and hence they direct the structural plasticity of the adult CNS function (2).

The discovery and study of adult neural stem cells has raised vast expectation for the therapeutic treatment of neurological diseases. Various degenerative nervous system diseases result from the loss of neurons and their connections, impairing normal neural circuits and drastically reducing the patient's quality of life. Thus, recent biomedical research efforts, on an international scale, have been dedicated to the study of neural stem cell function, with the ultimate goal of using them as therapeutic agents. On the other hand, basic neuroscientists

are interested in adult neural stem cells to understand tissue homeostasis. They investigate the basic mechanisms by which these cells contribute to tissue plasticity, maintenance and repair. However, these two approaches to the study of adult neural stem cell function are not always compatible. While clinically oriented experiments tend to focus on the expansion of neural stem cells in culture for therapeutic use, basic neuroscientists focus on understanding the physiological role of neural stem cells *in vivo*, which is incompatible with culturing the cells, since it has been shown that stem cells can dramatically change their properties when cultured *in vitro* (3). Hence, since the behavior of neural stem cells in a culture dish can differ greatly from their behavior *in vivo*, researchers should proceed cautiously when using the cells for therapeutic purposes if they have been expanded *in vitro*. To reconcile both developmental science and clinical goals, perhaps the best approach for utilizing neural stem cells will be to take advantage of their normal physiology in order to improve the outcome of the disease. If we come to an understanding of the regulation of stem cell function *in vivo*, we should be able to use this knowledge to improve a disease outcome, by manipulating the stem cell behavior within the affected tissue. This seems a particularly interesting issue considering the limited and slow progress being made in the use of exogenously cultured neural cells for the treatment of disease (4, 5).

This review tries to put together the current knowledge on the physiological function of known adult neural stem cell populations, including the dentate gyrus stem cells, the subventricular zone stem cells, and the neural crest-derived stem cells residing within the adult enteric nervous system (6). By reviewing the regulatory mechanisms governing neurogenesis from these adult stem cells *in vivo*, we might develop new ideas on how to use their physiology for our therapeutic benefit. The actual known role of these adult neural stem cells in the pathophysiology of disease and the implications of their manipulation on clinical prognosis will also be discussed.

2. NEURAL CREST-DERIVED ENTERIC STEM CELLS PERSIST INTO ADULTHOOD BUT LITTLE IS KNOWN ABOUT THEIR PHYSIOLOGICAL ROLE

The peripheral nervous system (PNS) is formed by a population of neural stem cells that delaminate from the neuroectoderm during the closure of the neural tube (7, 8). The so-called neural crest-derived stem cells (NCSCs) migrate during embryonic development towards multiple target tissues where they differentiate into a great variety of cell types including melanocytes, neurons, glia, neurosecretory cells or even cartilage and bone cells in certain areas. NCSC self-renewal and differentiation capacities vary during their migration towards their target tissues, although it has been shown that postmigratory cells can retain *in vivo* multilineage differentiation capabilities (9).

NCSCs that give rise to the enteric nervous system have been prospectively identified and isolated by flow cytometry from mid-gestation embryos (10). These cells are able to both self-renew extensively in culture and differentiate *in vitro* into all three typical neural crest cell lineages: neurons, glial cells and myofibroblasts (10). They are also able to undergo multilineage differentiation *in vivo* after transplantation into the neural crest migration stream of developing chicken embryos (6, 10). These gut NCSCs persist into adulthood but change their basic self-renewal and differentiation properties *in vitro*, including the neuronal subtypes they give rise to (6). However, neurogenesis has not been reported within the adult enteric nervous system of the gut, raising the question about whether the gut NCSCs are able to behave as multipotent stem cells within the adult enteric tissue *in situ*.

To prove that gut neural stem cells are intrinsically neurogenic, transplantation experiments with fetal gut cells were performed to compare them with a different subpopulation of NCSCs, those isolated from the developing sciatic nerve. These peripheral nerve NCSCs also give rise to neurons, glial cells and myofibroblasts in the culture dish (10). However, they have been shown to only differentiate into Schwann cells and endoneurial fibroblasts within the developing nerve (11). They seem to have no neurogenic activity once they migrate into the nerves. Transplantation experiments of both gut and sciatic nerve fetal cells into developing chick nerves determined that, unlike the sciatic nerve cells, the gut cells were indeed able to differentiate into neurons in this environment (10). These data suggest that, rather than responding to a restrictive nerve environment, different types of NCSCs have cell-intrinsic differences in neurogenic potential. Furthermore, enteric NCSCs seem to retain their neurogenic potential in the adult (6). The fact that no neurogenesis has been described in the adult enteric nervous system could simply indicate that no appropriate stimuli have been found for that to happen.

Impairment in the normal migration of gut NCSCs along the developing intestines has been shown to cause Hirschprung disease (12), a gut motility syndrome caused by a failure to form enteric nervous system ganglia in the colon. This can lead to fatal distention of the gut (megacolon). Therapeutic treatment of this disease by the transplantation of the patient's own gut NCSCs will first require knowledge about the molecular cues that might induce these cells to undergo neurogenesis within the aganglionic segments.

Two other cell populations have been recently described as adult pluripotent NCSCs. These populations were isolated from heart tissue (13) and from the hair follicle (14). However, these cells have not been prospectively isolated, and their multipotentiality has only been tested *in vitro*. Hence, it is not clear whether they have a multipotent and therapeutically useful physiological role within their tissues *in vivo*.

3. THE CENTRAL NERVOUS SYSTEM CONTAINS TWO DISCRETE NEUROGENIC NICHES

It seems clear that most mature neurons cannot replicate themselves once they are terminally differentiated.

The complexity of both their dendritic trees and the polysynaptic axonal branching make it impossible for them to re-enter a cell cycle and divide. These facts led to the long-lasting previous dogma of no structural plasticity within the CNS. However, a couple of decades ago, two rather discrete areas of the brain were described where new neurons were generated. The important finding was that these young neurons did not result from the division of old ones, but rather were the product of differentiation from neural precursors. The so-called neural stem cells exist throughout life in the adult brain and are able to self-renew and give rise to new neurons, astrocytes and oligodendrocytes. They were first described in the subventricular zone (15, 16), and then in the dentate gyrus of the hippocampus (17, 18), the two adult brain areas where neurogenesis has been demonstrated. Although other neural cells from other regions of the brain are able to respond to growth factors and even differentiate into neurons and glia *in vitro*, it is not clear whether these cells show this multipotentiality and regenerative power *in vivo*, hence they might not behave as true neural stem cells within the brain parenchyma (19-22).

It is therefore critical to analyze the mechanisms governing the course of neurogenesis in those two adult brain regions, and learn more about the *in situ* behavior of neural stem cells, if we want to be able to control the process and direct the migration of the precursors to other injured areas.

3.1. Adult neurogenesis from hippocampal stem cells

The hippocampus is located in the temporal lobe of the brain, forms part of the limbic system, and seems to play an important role in learning and memory. The hippocampal formation consists of pyramidal neurons forming the CA regions, and an interior and curved structure called the Dentate Gyrus (DG), formed by a layer of granule cell neurons. The subgranular layer (SGL) of the DG contains a subpopulation of astrocytes able to give rise to migrating neuroblasts, which in turn differentiate into granular neurons (23, 24). This hippocampal neurogenesis was originally highlighted by the immunohistochemical detection of bromodeoxyuridine (BrdU), a synthetic thymidine analogue incorporated into DNA by S-phase cells. Proliferating BrdU positive cells and their neuronal derivatives have been observed in the DG of every mammal examined, including humans (25).

The SGL progenitor astrocytes have radial processes going through the granule cell layer, and short tangential processes extending along the border of the granular layer. Understanding what makes the SGL special in supporting the proliferation and neuronal differentiation of multipotent neural progenitors is crucial to be able to control the process and take advantage of it for therapeutic purposes. Members of the epidermal (EGF) and fibroblast (FGF) growth factor families are primary mitogens used to propagate the SGL stem cells *in vitro* and are likely to perform similar functions *in vivo* (26). Activation of the Wnt pathway due to the presence of Wnt3a has also been shown to control the self-renewal of SGL progenitors (27). Special astrocytes and endothelial cells have been postulated as the source of all this paracrine signaling, which would define a unique neurogenic niche (26, 28). Hippocampal astrocytes, for example, promote proliferation and neuronal fate specification of co-cultured adult neural progenitors (29). In contrast, astrocytes from non-neurogenic regions do not promote neuronal differentiation (29). It becomes clear that astrocytes in the adult CNS are not merely supporting cells as traditionally believed, but, just as neurons, have a broad diversity of subtypes and functions.

The vascular nature of the neural niche is an area of intense investigation. Hot spots of cell proliferation within the SGL are found to be in close proximity to capillaries (28), suggesting an intimate relationship between neurogenesis and vasculogenesis. Endothelial cells, co-cultured with neural progenitors, can stimulate self-renewal, and enhance neuron production (30). Furthermore, the addition of vascular endothelial growth factor (VEGF), a typical vasculogenic factor, to the hippocampus of adult rats, induced a two-fold increase in the number of BrdU+ young neurons within the DG (31). Colocalization of the VEGF receptor with the immature neuronal marker doublecortin (Dcx) suggested a direct action of VEGF on neuronal progenitors (32). It becomes clear that vascular cells and vasculogenesis can influence the course of neurogenesis, suggesting the interesting possibility of controlling the neurogenic process by introducing exogenous vascular-associated factors.

Extensive research is being devoted to elucidating the functional consequences of the incorporation of new granule cells to the DG. Recent evidence indicates that the new neurons are able to integrate into the preexisting neural circuits, contributing to the functional plasticity of the two processes controlled by the hippocampus -learning and memory (33, 34). The functional importance of the neurogenic process in the hippocampus is highly signified by the intimate relationship described between the local circuit activity and the proliferation and differentiation of the progenitors. Simply by exposing rodents to physical exercise, there is an increase in cell proliferation and neurogenesis in the adult DG (35). More complicated behavioral tests, such as associative learning tasks, also clearly increase the number of adult-generated neurons within the DG (36). These data indicate that at least in certain circumstances there is a need for new neurons in the hippocampus to contribute to the functional plasticity of the circuit. Numerous researchers are working on this activity-neurogenesis coupling, which will likely lead to better control of the neurogenic process and possible therapeutic applications.

Although little is known about the involvement of the hippocampal circuitry on the activity-neurogenesis coupling process, recent evidence indicates that the SGL progenitors receive active direct neural inputs (37, 38). Malenka and col. demonstrated that the proliferating precursors sense the excitation via calcium channels and NMDA receptors, which in turn will translate to inhibition of glial genes and activation of neuronal genes such as NeuroD (37). A GABAergic innervation of the progenitor

cells has also been described, which depolarizes them, initiating an intracellular calcium rise and the expression of genes involved in neuronal differentiation such as NeuroD (38). Thus, it appears that GABAergic inputs to hippocampal progenitors promote activity-dependent neurogenesis. Moreover, hippocampal ambient GABA has also been shown to regulate synapse formation and dendritic development of the newborn neurons that incorporate into the granule cell layer (39). Taken together, these data shed light on the mechanism for activity-dependent regulation of adult hippocampal neurogenesis, indicating that progenitors and newborn neurons are able to sense neuronal network activity through multiple intracellular signaling pathways.

The vascular origin of the paracrine signaling and the activity dependence of the hippocampal neural niche are all aspects that will improve our ability to generate therapeutic applications from this neurogenic process.

3.2. Molecular mechanisms governing subventricular zone neurogenesis

Along the lateral walls of the lateral ventricles lies the largest germinal zone of the adult mammalian brain, the subventricular zone (SVZ) (40). New neurons are continuously born in the SVZ to migrate anteriorly into the olfactory bulb (OB) where they differentiate into local interneurons (41-43). The SVZ neural niche contains, in addition to the ependymal cells lining the ventricle, special astrocytes that are able to self-renew and give rise to transit-amplifying progenitors, which in turn differentiate into migrating neuroblasts (44). Hence, the adult SVZ constitutes an important reservoir of neural stem cells that can be grown in culture with growth factors, but that could also be potentially manipulated *in vivo* to ameliorate the outcome of disease. The regulatory mechanisms governing SVZ neurogenesis need to be elucidated in order to be able to control the process for therapeutic purposes.

A common characteristic of the adult SVZ neural niche biology is the persistence of molecular morphogens and signals typical from the embryonic development. These molecular cues, reminiscent from the embryo, seem to control both the self-renewal and differentiation of the neural progenitors in this area (45). Bone morphogenetic proteins (BMPs), commonly studied in ontogeny, were found to inhibit adult SVZ neurogenesis by cell-autonomously blocking the production of neurons and directing glial differentiation (46). Moreover, SVZ ependymal cells express noggin, a BMP antagonist, which was found to promote neurogenesis and inhibit glial differentiation (46). Hence, noggin creates a neurogenic environment in the SVZ by blocking endogenous BMP signaling. Another example is the secreted factor Sonic hedgehog (Shh), which plays multiple roles in the formation of the CNS, including the regulation of the early ventral patterning in the neural tube (47). Recently, it has been shown that both SVZ astrocytic stem cells and transit-amplifying progenitors respond to Shh signaling. Moreover, Shh regulates the self-renewal of neurosphere-forming stem cells, and modulates the proliferation of SVZ lineages by acting as a mitogen in cooperation with epidermal growth factor (EGF) (48). These data demonstrate a critical and conserved role of Shh signaling in the regulation of stem cell lineages within the adult mammalian SVZ. Thus, major developmental signaling pathways, including Shh and BMPs, are retained in adult germinal niches such as the SVZ, where they appear to regulate important aspects of proliferation and differentiation, hence controlling the course of neurogenesis.

Similar to the SGL, the SVZ germinal area is also intimately associated to vascular tissue, and vascular cells and factors also regulate the SVZ neurogenic process (reviewed in 45, 49). Intraventricular infusion of erythropoietin (Epo), a potent vasculogenic factor, promoted neurogenesis by increasing the number of newly generated migrating neuroblasts and new OB interneurons (50). Infusion of anti-Epo antibodies had the opposite effect: a decrease in the number of newly generated cells migrating to the bulb (50). These findings suggest that Epo is a paracrine factor capable of regulating the production of neuronal progenitors by forebrain stem cells. The search for endothelium-derived factors that could have potential effects on the self-renewal and differentiation of SVZ progenitors recently led to the discovery of pigment epithelium-derived factor (PEDF) as a regulator of SVZ neurogenesis. Intraventricular PEDF infusion activated the proliferation of slowly dividing astrocytic stem cells, whereas a blockade of endogenous PEDF decreased their cycling (51). These data further indicate the close relationship between neurogenesis and vasculogenesis within the SVZ germinal niche, suggesting new approaches to control this neurogenic process in pathological situations.

Another factor that may regulate the SVZ neurogenic activity could be the actual need for new neurons in the olfactory bulb. Extensive research is being devoted to understanding the process of survival and integration of newly formed neurons in the OB (reviewed in 52), processes that could influence neurogenesis in the SVZ. Recent results show that the newly formed cells arriving to the OB become mature neurons, following a unique sequence of electrophysiological events leading to their functional integration (53). However, rodents exposed to tasks of odor discrimination learning increase the number of adult-born neurons in the OB, but through increased survival of the new cells rather than an augmentation of SVZ neurogenesis (54). These data suggest that, unlike in the case of the SGL, the activity-dependent regulation of neurogenesis might not be that relevant in the SVZ.

4. NEURAL STEM CELL BEHAVIOR IN RESPONSE TO INJURY AND DISEASE –POSSIBLE MANIPULATIONS

Pathological conditions can alter ongoing adult neurogenesis. Following ischemia or brain trauma, proliferation is increased in the SGL and SVZ neurogenic areas (55, 56). Furthermore, non-neurogenic regions, such as cortex and striatum, also respond to injury by allowing

new neurons to invade and integrate into the lesioned area (57-59). However, other pathological conditions may have negative effects on adult neurogenesis. For example, chronic inflammation, following cranial radiation therapy, impairs neurogenesis within the hippocampus, which induces a debilitating cognitive decline in affected patients (60). The data suggest that inflammatory processes may contribute to neural stem cell dysfunction (61). Thus, adult neural stem cells can respond to different types of injury either positively by proliferating and migrating to the affected areas, or negatively by becoming damaged and impairing neurogenesis.

However, even in the case of injury-induced proliferation and differentiation of progenitors, the effect of this stem cell activity might not be beneficial for the disease outcome. In a rat model of limbic epilepsy, prolonged seizures caused an increase in dentate granule cell neurogenesis. However, these developing newborn granule cells projected axons aberrantly to the CA regions and the dentate inner granule layer, giving rise to anomalous network reorganization and epileptogenesis (62). In this case, it seems more plausible to look for drugs that would inhibit stem cell function, in order to prevent their deleterious effects. Another common situation is when the new cells migrate and differentiate into the affected area, but then die soon after, due to lack of trophic support. In an experimental stroke model immature neurons migrate from the SVZ to the damaged striatal area where they start to express markers for striatal neurons. Most of these new neurons die between two and five weeks after the stroke (57). 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. Intraventricular infusion of trophic factors such as EGF or FGF-2 seemed to improve survival of the new neurons that incorporated in the hippocampus after global ischemia (63). These results denote complementary strategies to take advantage of injury-induced neurogenesis.

The study of depression as a treatable disorder has led to very significant research aimed at understanding the role of adult neural stem cells in the pathophysiology of this disease. It has been reported that stress paradigms conducting to depression, as well as some animal models of the disease, produce a decrease in hippocampal cell proliferation and neurogenesis. Conversely, treatment with different classes of antidepressant drugs increases cell proliferation and neurogenesis (64, 65). A current hypothesis is that prevention of the decrease in neurogenesis may be one way to improve the antidepressant treatments. It has been proposed that factors favoring vasculogenesis and neurogenesis in the hippocampus, such as brain-derived neurotrophic factor (BDNF), VEGF, or FGF, could be intermediaries in the effector mechanism of antidepressants (66).

Finally, even chronic degenerative neurological disorders significantly alter adult neurogenesis. Brains from both Huntington and Alzheimer patients show an increase in the expression of proliferation and immature neuronal markers within the SGL, suggesting an activation of the hippocampal progenitors (67, 68). In the case of Parkinson patients, an impairment of progenitor proliferation is observed in both SGL and SVZ areas (69), presumably as a consequence of dopaminergic denervation. Thus, emerging evidence suggests that adult neurogenesis may be an intrinsic compensatory response to repair the adult CNS, and hence, it might be possible to manipulate this process for optimal therapeutic benefit.

5. PERSPECTIVE

In the past few decades we have witnessed the decline of an old dogma and the dawn of a new and exciting field of adult neurogenesis. The actual focus of this newly formed field is to understand the regulatory mechanisms and functions of neurogenesis, elucidating the stimuli and molecular cues governing the production of new neurons, and understanding the functions of these neurons and their effects on the homeostasis of the brain. Studies are converging on the adult neural stem cells, a special population of cells residing in specific niches, whose properties of proliferation and differentiation allow them to be responsible for the production of the new neurons. Recently, several niche factors modulating stem cell behavior have been characterized, as well as other molecules regulating the survival of the new neurons. It has also been shown that neurogenesis increases in the damaged brain, not only after stroke or traumatic injury, but also under various chronic neurodegenerative pathologies. Remarkably, progenitors from the subventricular zone are incorporated to the damaged areas, where they apparently replace some of the sick neurons. Hence, the nervous system seems to have the potential capacity to repair itself. As a consequence, researchers are trying to develop strategies aimed at reinforcing neurogenesis within the diseased areas. Once we have observed evidences about the intrinsic capabilities of the adult brain for tissue repair, recent works focus on enhancing proper cell replacement by using molecular cues known to regulate the endogenous activity of the neural progenitors. Therefore, accumulating evidences allow us to be optimistic about a potential use of endogenous neurogenesis for nervous system repair and regeneration.

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7. REFERENCES

1. J. Altman. Are new neurons formed in the brains of adult mammals? *Science* 135, 1127-1128 (1962)

2. F. H. Gage. Neurogenesis in the adult brain. *J Neurosci* 22, 612-613 (2002)

3. N. M. Joseph and S. J. Morrison. Toward an understanding of the physiological function of Mammalian stem cells. *Dev Cell* 9, 173-183 (2005)

4. S. Goldman. Stem and progenitor cell-based therapy of the human central nervous system. *Nat Biotechnol* 23, 862-871 (2005)

5. G. Martino and S. Pluchino. The therapeutic potential of neural stem cells. *Nat Rev Neurosci* 7, 395-406 (2006)

6. G. M. Kruger, J. T. Mosher, S. Bixby, N. Joseph, T. Iwashita and S. J. Morrison. Neural crest stem cells persist in the adult gut but undergo changes in self-renewal, neuronal subtype potential, and factor responsiveness. *Neuron* 35, 657-669 (2002)

7. J. H. Christiansen, E. G. Coles and D. G. Wilkinson. Molecular control of neural crest formation, migration and differentiation. *Curr Opin Cell Biol* 12, 719-724 (2000)

8. N. M. Le Douarin and E. Dupin. Multipotentiality of the neural crest. *Curr Opin Genet Dev* 13, 529-536 (2003)

9. M. Bronner-Fraser and S. Fraser. Developmental potential of avian trunk neural crest cells *in situ*. *Neuron* 3, 755-766 (1989)

10. S. Bixby, G. M. Kruger, J. T. Mosher, N. M. Joseph and S. J. Morrison. Cell-intrinsic differences between stem cells from different regions of the peripheral nervous system regulate the generation of neural diversity. *Neuron* 35, 643-656 (2002)

11. N. M. Joseph, Y. S. Mukouyama, J. T. Mosher, M. Jaegle, S. A. Crone, E. L. Dormand, K. F. Lee, D. Meijer, D. J. Anderson and S. J. Morrison. Neural crest stem cells undergo multilineage differentiation in developing peripheral nerves to generate endoneurial fibroblasts in addition to Schwann cells. *Development* 131, 5599-5612 (2004)

12. T. Iwashita, G. M. Kruger, R. Pardal, M. J. Kiel and S. J. Morrison. Hirschsprung disease is linked to defects in neural crest stem cell function. *Science* 301, 972-976 (2003)

13. Y. Tomita, K. Matsumura, Y. Wakamatsu, Y. Matsuzaki, I. Shibuya, H. Kawaguchi, M. Ieda, S. Kanakubo, T. Shimazaki, S. Ogawa, N. Osumi, H. Okano and K. Fukuda. Cardiac neural crest cells contribute to the dormant multipotent stem cell in the mammalian heart. *J Cell Biol* 170, 1135-1146 (2005)

14. M. Sieber-Blum, M. Grim, Y. F. Hu and V. Szeder. Pluripotent neural crest stem cells in the adult hair follicle. *Dev Dyn* 231, 258-269 (2004)

15. B. A. Reynolds and S. Weiss. Generation of neurons and astrocytes from isolated cells of the adult mammalian central nervous system. *Science* 255, 1707-1710 (1992)

16. L. J. Richards, T. J. Kilpatrick and P. F. Bartlett. De novo generation of neuronal cells from the adult mouse brain. *Proc Natl Acad Sci U S A* 89, 8591-8595 (1992)

17. F. H. Gage, P. W. Coates, T. D. Palmer, H. G. Kuhn, L. J. Fisher, J. O. Suhonen, D. A. Peterson, S. T. Suhr and J. Ray. Survival and differentiation of adult neuronal progenitor cells transplanted to the adult brain. *Proc Natl Acad Sci U S A* 92, 11879-11883 (1995)

18. T. D. Palmer, J. Takahashi and F. H. Gage. The adult rat hippocampus contains primordial neural stem cells. *Mol Cell Neurosci* 8, 389-404 (1997)

19. T. Kondo and M. Raff. Oligodendrocyte precursor cells reprogrammed to become multipotential CNS stem cells. *Science* 289, 1754-1757 (2000)

20. T. D. Palmer, E. A. Markakis, A. R. Willhoite, F. Safar and F. H. Gage. Fibroblast growth factor-2 activates a latent neurogenic program in neural stem cells from diverse regions of the adult CNS. *J Neurosci* 19, 8487-8497 (1999)

21. T. D. Palmer, J. Ray and F. H. Gage. FGF-2-responsive neuronal progenitors reside in proliferative and quiescent regions of the adult rodent brain. *Mol Cell Neurosci* 6, 474-486 (1995)

22. L. S. Shihabuddin, P. J. Horner, J. Ray and F. H. Gage. Adult spinal cord stem cells generate neurons after transplantation in the adult dentate gyrus. *J Neurosci* 20, 8727-8735 (2000)

23. B. Seri, J. M. Garcia-Verdugo, L. Collado-Morente, B. S. McEwen and A. Alvarez-Buylla. Cell types, lineage, and architecture of the germinal zone in the adult dentate gyrus. *J Comp Neurol* 478, 359-378 (2004)

24. B. Seri, J. M. Garcia-Verdugo, B. S. McEwen and A. Alvarez-Buylla. Astrocytes give rise to new neurons in the adult mammalian hippocampus. *J Neurosci* 21, 7153-7160 (2001)

25. P. S. Eriksson, E. Perfilieva, T. Bjork-Eriksson, A. M. Alborn, C. Nordborg, D. A. Peterson and F. H. Gage. Neurogenesis in the adult human hippocampus. *Nat Med* 4, 1313-1317 (1998)

26. D. C. Lie, H. Song, S. A. Colamarino, G. L. Ming and F. H. Gage. Neurogenesis in the adult brain: new strategies for central nervous system diseases. *Annu Rev Pharmacol Toxicol* 44, 399-421 (2004)

27. D. C. Lie, S. A. Colamarino, H. J. Song, L. Desire, H. Mira, A. Consiglio, E. S. Lein, S. Jessberger, H. Lansford, A. R. Dearie and F. H. Gage. Wnt signalling regulates adult hippocampal neurogenesis. *Nature* 437, 1370-1375 (2005)

28. T. D. Palmer, A. R. Willhoite and F. H. Gage. Vascular niche for adult hippocampal neurogenesis. *J Comp Neurol* 425, 479-494 (2000)

29. H. Song, C. F. Stevens and F. H. Gage. Astroglia induce neurogenesis from adult neural stem cells. *Nature* 417, 39-44 (2002)

30. Q. Shen, S. K. Goderie, L. Jin, N. Karanth, Y. Sun, N. Abramova, P. Vincent, K. Pumiglia and S. Temple. Endothelial cells stimulate self-renewal and expand neurogenesis of neural stem cells. *Science* 304, 1338-1340 (2004)

31. L. Cao, X. Jiao, D. S. Zuzga, Y. Liu, D. M. Fong, D. Young and M. J. During. VEGF links hippocampal activity with neurogenesis, learning and memory. *Nat Genet* 36, 827-835 (2004)

32. K. Jin, Y. Zhu, Y. Sun, X. O. Mao, L. Xie and D. A. Greenberg. Vascular endothelial growth factor (VEGF) stimulates neurogenesis *in vitro* and *in vivo*. *Proc Natl Acad Sci U S A* 99, 11946-11950 (2002)

33. J. B. Aimone, J. Wiles and F. H. Gage. Potential role for adult neurogenesis in the encoding of time in new memories. *Nat Neurosci* 9, 723-727 (2006)

34. A. Tashiro, V. M. Sandler, N. Toni, C. Zhao and F. H. Gage. NMDA-receptor-mediated, cell-specific integration of new neurons in adult dentate gyrus. *Nature* 442, 929-933 (2006)

35. H. van Praag, G. Kempermann and F. H. Gage. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nat Neurosci* 2, 266-270 (1999)

36. E. Gould, A. Beylin, P. Tanapat, A. Reeves and T. J. Shors. Learning enhances adult neurogenesis in the hippocampal formation. *Nat Neurosci* 2, 260-265 (1999)

37. K. Deisseroth, S. Singla, H. Toda, M. Monje, T. D. Palmer and R. C. Malenka. Excitation-neurogenesis coupling in adult neural stem/progenitor cells. *Neuron* 42, 535-552 (2004)

38. Y. Tozuka, S. Fukuda, T. Namba, T. Seki and T. Hisatsune. GABAergic excitation promotes neuronal differentiation in adult hippocampal progenitor cells. *Neuron* 47, 803-815 (2005)

39. S. Ge, E. L. Goh, K. A. Sailor, Y. Kitabatake, G. L. Ming and H. Song. GABA regulates synaptic integration of newly generated neurons in the adult brain. *Nature* 439, 589-593 (2006)

40. F. Doetsch, J. M. Garcia-Verdugo and A. Alvarez-Buylla. Cellular composition and three-dimensional organization of the subventricular germinal zone in the adult mammalian brain. *J Neurosci* 17, 5046-5061 (1997)

41. J. Altman. 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, 433-457 (1969)

42. D. R. Kornack and P. Rakic. The generation, migration, and differentiation of olfactory neurons in the adult primate brain. *Proc Natl Acad Sci U S A* 98, 4752-4757 (2001)

43. C. Lois and A. Alvarez-Buylla. Long-distance neuronal migration in the adult mammalian brain. *Science* 264, 1145-1148 (1994)

44. F. Doetsch, I. Caille, D. A. Lim, J. M. Garcia-Verdugo and A. Alvarez-Buylla. Subventricular zone astrocytes are neural stem cells in the adult mammalian brain. *Cell* 97, 703-716 (1999)

45. A. Alvarez-Buylla and D. A. Lim. For the long run: maintaining germinal niches in the adult brain. *Neuron* 41, 683-686 (2004)

46. D. A. Lim, A. D. Tramontin, J. M. Trevejo, D. G. Herrera, J. M. Garcia-Verdugo and A. Alvarez-Buylla. Noggin antagonizes BMP signaling to create a niche for adult neurogenesis. *Neuron* 28, 713-726 (2000)

47. T. M. Jessell and J. R. Sanes. Development. The decade of the developing brain. *Curr Opin Neurobiol* 10, 599-611 (2000)

48. V. Palma, D. A. Lim, N. Dahmane, P. Sanchez, T. C. Brionne, C. D. Herzberg, Y. Gitton, A. Carleton, A. Alvarez-Buylla and A. Ruiz i Altaba. Sonic hedgehog controls stem cell behavior in the postnatal and adult brain. *Development* 132, 335-344 (2005)

49. F. Doetsch. A niche for adult neural stem cells. *Curr Opin Genet Dev* 13, 543-550 (2003)

50. T. Shingo, S. T. Sorokan, T. Shimazaki and S. Weiss. Erythropoietin regulates the *in vitro* and *in vivo* production of neuronal progenitors by mammalian forebrain neural stem cells. *J Neurosci* 21, 9733-9743 (2001)

51. C. Ramirez-Castillejo, F. Sanchez-Sanchez, C. Andreu-Agullo, S. R. Ferron, J. D. Aroca-Aguilar, P. Sanchez, H. Mira, J. Escribano and I. Farinas. Pigment epithelium-derived factor is a niche signal for neural stem cell renewal. *Nat Neurosci* 9, 331-339 (2006)

52. P. M. Lledo and A. Saghatelyan. Integrating new neurons into the adult olfactory bulb: joining the network, life-death decisions, and the effects of sensory experience. *Trends Neurosci* 28, 248-254 (2005)

53. A. Carleton, L. T. Petreanu, R. Lansford, A. Alvarez-Buylla and P. M. Lledo. Becoming a new neuron in the adult olfactory bulb. *Nat Neurosci* 6, 507-518 (2003)

54. M. Alonso, C. Viollet, M. M. Gabellec, V. Meas-Yedid, J. C. Olivo-Marin and P. M. Lledo. Olfactory discrimination learning increases the survival of adult-born neurons in the olfactory bulb. *J Neurosci* 26, 10508-10513 (2006)

55. P. K. Dash, S. A. Mach and A. N. Moore. Enhanced neurogenesis in the rodent hippocampus following traumatic brain injury. *J Neurosci Res* 63, 313-319 (2001)

56. A. C. Rice, A. Khaldi, H. B. Harvey, N. J. Salman, F. White, H. Fillmore and M. R. Bullock. Proliferation and

neuronal differentiation of mitotically active cells following traumatic brain injury. *Exp Neurol* 183, 406-417 (2003)

57. A. Arvidsson, T. Collin, D. Kirik, Z. Kokaia and O. Lindvall. Neuronal replacement from endogenous precursors in the adult brain after stroke. *Nat Med* 8, 963-970 (2002)

58. K. Jin, Y. Sun, L. Xie, A. Peel, X. O. Mao, S. Batteur and D. A. Greenberg. Directed migration of neuronal precursors into the ischemic cerebral cortex and striatum. *Mol Cell Neurosci* 24, 171-189 (2003)

59. J. M. Parent. Injury-induced neurogenesis in the adult mammalian brain. *Neuroscientist* 9, 261-272 (2003)

60. M. L. Monje, H. Toda and T. D. Palmer. Inflammatory blockade restores adult hippocampal neurogenesis. *Science* 302, 1760-1765 (2003)

61. M. L. Monje, S. Mizumatsu, J. R. Fike and T. D. Palmer. Irradiation induces neural precursor-cell dysfunction. *Nat Med* 8, 955-962 (2002)

62. J. M. Parent, T. W. Yu, R. T. Leibowitz, D. H. Geschwind, R. S. Sloviter and D. H. Lowenstein. Dentate granule cell neurogenesis is increased by seizures and contributes to aberrant network reorganization in the adult rat hippocampus. *J Neurosci* 17, 3727-3738 (1997)

63. H. Nakatomi, T. Kuriu, S. Okabe, S. Yamamoto, O. Hatano, N. Kawahara, A. Tamura, T. Kirino and M. Nakafuku. Regeneration of hippocampal pyramidal neurons after ischemic brain injury by recruitment of endogenous neural progenitors. *Cell* 110, 429-441 (2002)

64. J. Benninghoff, A. Schmitt, R. Mossner and K. P. Lesch. When cells become depressed: focus on neural stem cells in novel treatment strategies against depression. *J Neural Transm* 109, 947-962 (2002)

65. J. E. Malberg. Implications of adult hippocampal neurogenesis in antidepressant action. *J Psychiatry Neurosci* 29, 196-205 (2004)

66. S. S. Newton and R. S. Duman. Regulation of neurogenesis and angiogenesis in depression. *Curr Neurovasc Res* 1, 261-267 (2004)

67. M. A. Curtis, E. B. Penney, A. G. Pearson, W. M. van Roon-Mom, N. J. Butterworth, M. Dragunow, B. Connor and R. L. Faull. Increased cell proliferation and neurogenesis in the adult human Huntington's disease brain. *Proc Natl Acad Sci U S A* 100, 9023-9027 (2003)

68. K. Jin, A. L. Peel, X. O. Mao, L. Xie, B. A. Cottrell, D. C. Henshall and D. A. Greenberg. Increased hippocampal neurogenesis in Alzheimer's disease. *Proc Natl Acad Sci U S A* 101, 343-347 (2004)

69. G. U. Hoglinger, P. Rizk, M. P. Muriel, C. Duyckaerts, W. H. Oertel, I. Caille and E. C. Hirsch. Dopamine depletion impairs precursor cell proliferation in Parkinson disease. *Nat Neurosci* 7, 726-735 (2004)

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