PHILIPPE TAUPIN

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Stem Cells

Cellular and Drug Therapies

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Stem Cells - Laboratory and Clinical Research

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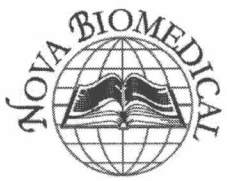
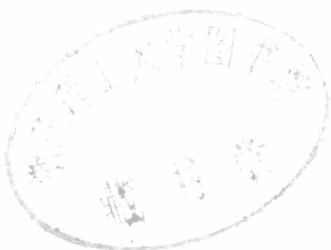
STEM CELLS: CELLULAR AND DRUG THERAPIES

(VOLUME 1)

PHILIPPE TAUPIN





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Preface

Stem Cells: Cellular and Drug Therapies aims at providing an overview and in depth analysis of recent developments in stem cell research and therapy. It is composed of recently published review articles that went through peer-review process.

Stem cells are the building blocks of the body. They can develop into any of the cells that make up our bodies. Stem cells carry a lot of hope for the treatment of a broad range of diseases and injuries, spanning from cancers, diabetes, genetic diseases, graft-versus-host disease, eye, heart and liver diseases, inflammatory and autoimmune disorders, to neurological diseases and injuries, particularly neurodegenerative diseases, like Alzheimer's and Parkinson's diseases, cerebral strokes, and traumatic brain and spinal cord injuries. Stem cell research is therefore as important for our understanding the physio- and pathology of the body, as for development and therapy, including for the nervous system.

Introduction

Adult Neural Stem Cells from Promise to Treatment: the Road Ahead

The confirmation that neurogenesis occurs in the adult brain and neural stem cells (NSCs) reside in the adult central nervous system (CNS) opens new opportunities to treat neurological diseases and injuries. To this aim, adult NSCs provide a promising model for cellular therapy. However, much remains to be done before NSC research be brought to therapy.

Stem cells are self-renewing cells that generate the various cell types of the body. In adult tissues, they contribute to homeostasis of the tissues and regeneration after injury [1]. Contrary to other adult tissues, the adult brain does not regenerate and repair itself, after injuries or diseases. It was believed that the adult CNS was composed of post-mitotic and differentiated nerve cells, born during development [2]. An underlying of this belief was that, contrary to other adult tissues, the adult brain was devoid of stem cells, hence of capacity of regeneration.

Seminal studies in the 1960s reported that neurogenesis occurs in discrete regions of the adult brain, in rodents [3, 4]. It was not until the late 80s and afterwards that it was confirmed that neurogenesis occurs in the adult brain and NSCs reside in the adult CNS in mammals, contrary to a long-held dogma [5]. Neurogenesis occurs primarily in two regions of the adult brain, the dentate gyrus of the hippocampus and the subventricular zone, along the ventricles, in various species including humans [6]. It is hypothesized that newborn neuronal cells in the adult brain originate from stem cells. NSCs are the self-renewing multipotent cells that generate neurons, astrocytes and oligodendrocytes in the nervous system. Because of their potential to generate the main phenotypes of the nervous system, they hold the potential to cure a broad range of neurological diseases and injuries.

The confirmation that neurogenesis occurs in the adult brain and NSCs reside in the adult CNS has tremendous implications for therapy. The adult CNS may be amenable to repair. To this aim, two strategies are being considered: the stimulation of endogenous neural progenitor or stem cells of the adult brain, and the transplantation of adult-derived neural progenitor and stem cells, to repair the degenerated or injured pathways.

Experimental studies reveal that new neuronal cells are generated in the diseased brain and at sites of lesions, after cerebral stokes, where they replaced some of the lost nerve cells

[7-9]. Neural progenitor and stem cells have been isolated and characterized *in vitro* from the adult CNS, including from human biopsies and *post-mortem* tissues, providing a source of tissue for cellular therapy [10]. However, protocols currently devised to isolate and culture neural progenitor and stem cells yield to heterogeneous population of neural progenitor and stem cells, limiting their therapeutic potential [11]. Studies from fetal- and adult-derived neural progenitor and stem cells show that grafted cells differentiate and integrate the host tissues [12, 13]. Although cell death is still occurring and full functional recovery is not achieved, these studies reveal an attempt by the CNS to repair itself, and validate the use of adult-derived neural progenitor and stem cells for therapy.

The generation of new nerve cells at sites of degeneration or injuries, from endogenous or transplanted cells, may be insufficient to promote functional recovery. This may originate from either a low number of stimulated or grafted stem cells, or a lack of integration and differentiation, into functional cells. Stem cells reside in specialized microenvironments or "niches" that regulate their self-renewal and differentiation activities, particularly in the adult brain [14]. Hence, the microenvironment plays a key role in the therapeutic potential of adult stem cells, whether endogenous or transplanted [15]. For example, gial scar tissue at sites of degenerations and injuries is a hallmark of CNS diseases and injuries [16]. This tissue is reported to limit the regenerative potential of the CNS [17].

Hence, although adult NSCs hold the promise to treat a broad range of neurological diseases and injuries, their potential for cellular therapy may be limited by both intrinsic and extrinsic cues. Future directions will aim at unraveling the cellular and molecular mechanisms underlying the neurogenic niches, in the diseased and injured brain, and to establish homogenous population of neural progenitor or stem cells, for therapy.

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References

[1] Potten CS, Loeffler M: Stem cells: attributes, cycles, spirals, pitfalls and uncertainties. Lessons for and from the crypt. *Development* 1990; 110(4): 1001-1020.

[2] Santiago Ramon y Cajal: Degeneration and Regeneration of the Nervous System. New York: Hafner (1928).

[3] Altman J, Das GD: Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats. *J. Comp. Neurol.* 1965; 124(3): 319-336.

[4] Altman J: 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.* 1969; 137(4): 433-457.

[5] Gross CG: Neurogenesis in the adult brain: death of a dogma. *Nat. Rev. Neurosci.* 2000; 1(1): 67-73.

[6] Taupin P, Gage FH: Adult neurogenesis and neural stem cells of the central nervous system in mammals. J. Neurosci. Res. *2002*; 69(6): 745-749.

[7] Arvidsson A, Collin T, Kirik D et al: Neuronal replacement from endogenous precursors in the adult brain after stroke. *Nat. Med.* 2002; 8(9): 963-970.

[8] Curtis MA, Penney EB, Pearson AG et al: Increased cell proliferation and neurogenesis in the adult human Huntington's disease brain. *Proc. Natl. Acad. Sci. U S A.* 2003; 100(15): 9023-9027.

[9] Jin K, Sun Y, Xie L et al: Directed migration of neuronal precursors into the ischemic cerebral cortex and striatum. *Mol. Cell Neurosci.* 2003; 24(1): 171-189.

[10] Palmer TD, Schwartz PH, Taupin P et al: Cell culture. Progenitor cells from human brain after death. *Nature* 2001; 411(6833): 42-43.

[11] Chin VI, Taupin P, Sanga S et al: Microfabricated platform for studying stem cell fates. *Biotechnol. Bioeng.* 2004; 88(3): 399-415.

[12] Pluchino S, Quattrini A, Brambilla E et al: Injection of adult neurospheres induces recovery in a chronic model of multiple sclerosis. *Nature* 2003; 422(6933): 688-694.

[13] Cummings BJ, Uchida N, Tamaki SJ et al: Human neural stem cells differentiate and promote locomotor recovery in spinal cord-injured mice. *Proc. Natl. Acad. Sci. U S A* 2005; 102(39): 14069-14074.

[14] Moore KA, Lemischka IR: Stem cells and their niches. *Science* 2006; 311(5769): 1880-1885.

[15] Taupin P: Adult neural stem cells, neurogenic niches and cellular therapy. *Stem Cell Reviews* 2006; 2(3): 213-220.

[16] McGraw J, Hiebert GW, Steeves JD: Modulating astrogliosis after neurotrauma. *J. Neurosci. Res.* 2001; 63(2): 109-115.

[17] Ribotta MG, Menet V, Privat A: Glial scar and axonal regeneration in the CNS: lessons from GFAP and vimentin transgenic mice. *Acta Neurochir. Suppl.* 2004; 89: 87-92.

Contents

Chapter I

Adult Neurogenesis in Mammals

Abstract

With the recent confirmation that neurogenesis occurs in the adult brain, and that neural stem cells reside in the adult central nervous system (CNS), the function of newly generated neuronal cells in the adult brain is the source of intense research and debate. Neurogenesis is modulated by a wide variety of physiopathological conditions and environmental stimuli, offering the possibility that newly generated neuronal cells might be functionally associated with the response to these processes. Newly generated neuronal cells in the hippocampus have also been implicated in mechanisms of learning, memory and depression. However, a number of studies have challenged some of these findings, and the roles of newly generated neuronal cells in the functioning of the CNS remain to be fully understood. Neurogenesis has been shown to increase bilaterally in the adult brain and new neuronal cells are generated at sites of degeneration in the brain during disease and after injuries. Taken together, these findings suggest that new neuronal cells may be involved in processes such as homeostasis of brain tissue, regeneration, plasticity, and neuroadaptation.

1. Introduction

Contrary to a long-held dogma, neurogenesis occurs in the adult brain. It is postulated that newly generated neuronal cells of the adult brain originate from residual stem cells, the identification of which remains the source of debate and controversy [1, 2]. In adults, stem cells participate in tissue homeostasis and regeneration after injuries. As the central nervous system (CNS) elicits limited capacity for regeneration and most nerve cells are post-mitotic, determining the role and contribution of neural stem cells (NSCs) in the functioning of the adult brain remains the focus of intense research.

This review highlights recent developments in the protocols used to study neurogenesis, and in the modulation of neurogenesis by various environmental and physiopathological conditions. The functions of newly generated neuronal cells and their contributions to the physiopathology of the CNS are also discussed.

2. Labeling Newly Generated Neuronal Cells in the Adult Brain

The first line of evidence that neurogenesis occurs in the adult brain were reported more than 40 years ago using [^{3}H]thymidine autoradiography labeling [3, 4]. With the advent of new methods for labeling dividing cells, such as the use of 5-bromo-2'-deoxyuridine (BrdU) and retroviruses, investigators have since reassessed the findings of these original studies and confirmed that neurogenesis does occur in the adult brain and that NSCs reside in the adult CNS [1, 2].

2.1. Birth Dating Cells and Monitoring Cell Proliferation

[^{3}H]Thymidine is a radiolabeled thymidine component of DNA biosynthesis that is used for birth dating cells and monitoring cell proliferation [5]. Autoradiographic labeling with [^{3}H]thymidine reveals the presence of cells that have incorporated the radiolabeled substrate underneath the autoradiographic grains. Because the staining does not directly label cells that have incorporated the thymidine, an alternative labeling technique, using BrdU, is currently preferred and widely used for studying adult neurogenesis. BrdU is a thymidine analog that can be administered intraperitoneally in animals and is detected by immunohistochemistry [6]. Because BrdU incorporates into the DNA during the S-phase of the cell cycle, it is used to visualize cell proliferation, including in the CNS [7]. With the advance of confocal microscopy, multiple labeling can be performed with BrdU and other markers, including those with neuronal specificity, allowing for the identification of the phenotype of BrdU-incorporated cells, as well as for stereological quantification studies.

2.2. Cell Kinetics and Fate Mapping

Investigators have developed protocols for simultaneously detecting two different thymidine analogs *in situ* with the hope of studying cell kinetics and fate mapping of neuronal cells created at different times. The combination of [^{3}H]thymidine autoradiography and BrdU immunohistochemistry has proved to be a powerful method for determining the cell-cycle kinetics of progenitor cells [8, 9]. However, technical limitations in [^{3}H]thymidine autoradiography, particularly the requirement of lengthy exposure times, have led to the development of alternative protocols, such as the double labeling of dividing cells with BrdU and 5-iododeoxyuridine (IdU) or IdU and 5-chlorodeoxyuridine (CldU) [10, 11]. This procedure was originally limited by the simultaneous use of two mouse antibodies to detect the thymidine analogs, as each may require complicated histological procedures to ensure the specificity of staining or the use of a high-salt buffer to remove antibody binding from a single substrate. A double-labeling method was recently reported to distinguish BrdU and IdU using a pair of mouse and rat monoclonal antibodies [12•], thereby circumventing previous limitations in the use of two halogenated thymidines for double immunohistochemistry [10, 11]. Further, multiple labeling of halogenated nucleosides can be performed with phenotypic

markers, allowing for the characterization of relationships between cell proliferative history and fate mapping [13•].

3. Modulation of Adult Neurogenesis

Neurogenesis occurs constitutively throughout adulthood, yet the rate of neurogenesis in the dentate gyrus (DG) and the subventricular zone (SVZ) is modulated by environmental enrichment [14] and during certain physiopathological conditions [15]. For example, neurogenesis decreases with age [16], whereas environmental enrichment and physical activity promote hippocampal neurogenesis in rodents [17-19]. Stress and experimentally induced diabetes both decrease hippocampal neurogenesis [20-22]. Neurogenesis is increased in the DG and SVZ during certain neurological diseases and injury, such as epilepsy [23], Huntington's disease (HD) [24], Alzheimer's disease (AD) [25], stroke [26], and traumatic brain injuries [27]. The modulation of neurogenesis in response to environmental stimuli and during physiopathological conditions is transient and bilateral, affecting the DG and/or SVZ [28-30]. These studies suggest the involvement of adult neurogenesis in a broad range of physiopathological conditions, and in response to environmental stimuli. However, this conclusion has been challenged by a recent study demonstrating that neurogenesis does not mediate the behavioral effects of environmental enrichment [31]. The roles of adult neurogenesis in response to environmental enrichment and in various physiopathological conditions remain to be further determined.

In the diseased or injured brain, such as in HD and after stroke, new neuronal cells are generated at the sites of degeneration, where they replace some of the lost nerve cells. Time-course studies have revealed that these new neuronal cells originate in the SVZ, from where they migrated out of the rostro-migratory stream (RMS) toward the site of lesions [32, 33, 34•]. Following a stroke, in the areas of the brain showing neurodegeneration, most of the newly generated neuronal cells do not penetrate the core of the infarct where cell loss has occurred, but remain in the penumbra surrounding the lesion. It is estimated that a mere 0.2% of the degenerated nerve cells are replaced in the striatum after middle cerebral artery occlusion, a model of focal ischemia [34•]. This low percentage of newly generated neuronal cells at the sites of injury may account for the lack of functional recovery after injury. Recently, Danilov et al reported the generation of new neuronal cells in an animal model of multiple sclerosis, providing evidence that initiation of neurogenesis may also occur in neuroinflammatory lesions of the adult spinal cord [35].

4. Function of Adult Neurogenesis

The function(s) of newly generated neuronal cells in the adult brain remains the focus of intense research and debate. Various recent lines of evidence suggest that hippocampal neurogenesis is involved in processes such as learning and memory, and depression, as discussed in the following sections.

4.1. Learning and Memory

Hippocampal neurogenesis is stimulated in response to training on associative learning tasks that require the hippocampus, such as the Morris water maze task, for which the neurogenesis has been correlated with improved performance [18, 36]. Hippocampal neurogenesis is also involved with other aspects of memory, such as the formation of hippocampal-dependent trace memories [37], but is not associated with all types of hippocampal-dependent learning processes (such as spatial navigation learning and fear responses to context) [38]. Further support for the involvement of adult hippocampal neurogenesis in learning and memory comes from studies in which adult rats were subjected to brain irradiation. Hippocampal brain irradiation blocked the formation of new neurons in the DG; 3 weeks after irradiation the animals performed worse than controls in a short-term memory hippocampal-dependent test (a place-recognition task), but not in a hippocampus-independent test (an object-recognition task) [39].

These studies indicate that hippocampal neurogenesis is involved in learning and memory. However, the involvement of adult neurogenesis in learning and memory has been challenged by other studies. In mice that were selectively bred for high levels of wheel running, increased hippocampal neurogenesis has been observed without an associated improvement of learning and memory performances during the Morris water maze test [40]. The cellular contribution of adult neurogenesis during the formation of trace memory remains for months, beyond the time required for the retention of trace memories [41]. Therefore, although there is compelling evidence of the involvement of adult neurogenesis in learning and memory, the involvement of hippocampal neurogenesis in these processes remains to be elucidated.

4.2. Depression

Depletion of serotonin decreases neurogenesis in the DG and SVZ of adult rats [42], and various chronic antidepressant treatments have been shown increase adult hippocampal neurogenesis [22, 43]. These data suggest that neurogenesis plays an important role in the biology of depression. A recent study showing that inhibition of hippocampal neurogenesis by irradiation inhibits the behavioural effects of antidepressants such as fluoxetine, further confirms the involvement of adult neurogenesis in depression [44••]. It is hypothesized that the waning and waxing of neurogenesis in the hippocampus are important factors in the precipitation of, and recovery from, episodes of clinical depression, respectively, and may be mediated through alterations in brain serotonin levels [45].

Taken together, these data suggest that newly generated neuronal cells in the adult brain are involved in processes such as learning and memory, and depression. However, the contribution of adult neurogenesis toward the mechanisms of these processes needs to be further determined. With regard to the involvement of adult neurogenesis in depression, it would be mediated through serotonin receptor subtypes in the DG [46].

5. Contribution of Adult Neurogenesis to CNS Physiopathology

5.1. Homeostasis of CNS Tissue

Stem cells are present all over the body where they ensure tissue homeostasis, contributing to the replacement of cells lost from normal turnover, so that the tissues remain functional and constant in size and structure over time. In the adult brain, the total number of neurons does not dramatically increase, and cell death is an established process. Neurogenesis occurs primarily in two areas of the adult brain, the DG and SVZ, with the SVZ harboring a larger pool of dividing neuronal progenitor cells than the DG. Neurogenesis may also occur in other areas of the brain, at low levels [1, 2]. Adult neurogenesis might, therefore, participate in the homeostasis of the adult CNS tissue. Notwithstanding the need for further investigation, this hypothesis suggests that a disturbance in the rate of adult neurogenesis could contribute to pathological processes in the CNS, such as neurological and neurodegenerative diseases.

Several studies have attempted to determine the involvement of adult neurogenesis in the pathology of CNS diseases. Neurogenesis is increased in the DG following evoked seizures in animal models, and newly generated neuronal cells elicit the two main features of epilepsy – formation of aberrant axonal projections (mossy fiber sprouting) and migration to ectopic locations [47] – suggesting that neurogenesis contributes to the pathology of epilepsy. However, low-dose radiation treatment reduces dentate granule cell neurogenesis, but has no effect on seizure-induced mossy fiber sprouting and does not prevent seizures [48]. Mossy fiber reorganization after pilocarpine-induced status epilepticus occurs even in the absence of dentate granule cell neurogenesis, suggesting that the sprouting arises from mature granule cells and not primarily from newly generated neuronal cells as previously suggested [47]. Therefore the contribution of adult neurogenesis to the pathology of epilepsy remains to be determined.

In a recent study reporting the generation of new dopaminergic neuronal cells in the adult rat substantia nigra (SN) [49], the generation of new dopaminergic neuronal cells was investigated following lesion of the SN. The SN resides in the ventral midbrain and contains dopaminergic neurons that send their axons to the striatum. It is believed that a gradual decline in the number of nigral dopaminergic neurons occurs with normal aging in humans, and that Parkinson's disease (PD) is caused by an abnormally rapid rate of cell death of these neurons. The rate of neurogenesis in a mouse model, as measured by BrdU labeling, was reported to be increased by 2-fold 3 weeks following a PD-like lesion induced by a systemic dose of 1-methyl-4phenyl-1,2,3,6-tetrahydropyridine. If such turnover of dopaminergic neuronal cells is confirmed, the progression of PD would then be determined not only by the rate of degeneration of SN neurons, but also by the efficacy in the formation of new dopamine neurons. Thus, disturbance of the equilibrium between cell genesis and cell death might result in neurodegenerative disorders. Accordingly, neurogenesis in PD might not only be necessary for functional recovery, but it may also play a key role in the pathology of the disease. However, the generation of new dopaminergic neurons in the adult SN remains the source of controversy, as previous studies have failed to detect neurogenesis in the SN [50].

Frielingsdorf et al. did not report any evidence for new dopaminergic neurons in the SN of 6-hydroxydopaminelesioned hemi-Parkinsonian rodents [51]. The administration of platelet-derived growth factor and brain-derived neurotrophic factor induces striatal neurogenesis in adult rats with 6-hydroxydopamine lesions, without any indication of newly created cells differentiating into dopaminergic neurons [52]. The administration of glial-derived neurotrophic factor (GDNF) significantly increases cell proliferation in the SN, with new cells displaying glial features and none of the BrdU-positive cells co-labeling for the dopaminergic neuronal marker tyrosine hydroxylase [53]. Rather, GDNF upregulated tyrosine hydroxylase in existing neurons, consistent with the restorative actions of this trophic factor [53, 54]. Therefore, the generation of new dopaminergic neurons in the adult SN and following lesion of the SN remains the source of dispute, as does its involvement in the pathology of PD.

Although adult neurogenesis may participate in homeostasis of the brain tissue, its involvement in the processes of neurological and neurodegenerative disease remains to be demonstrated. The question arises as to why homeostasis would be limited to discrete areas of the adult CNS? At the cellular and molecular level, the existence of neurogenic niches may hold clues to the physiological significance of such a phenomenon [55, 56••, 57], which remains an unresolved question.

5.2. CNS Regeneration

Neurodegenerative diseases, cerebral strokes, and traumatic injuries to the CNS produce neurological deficits that result from neuronal loss, and often lead to lifetime disabilities. After injury to the CNS, such as through stroke, neuronal cells are generated at the sites of lesion, where they replace some of the lost nerve cells. It is estimated that 0.2% of the degenerated nerve cells are replaced in the striatum after middle cerebral artery occlusion [34•, 58•]. The generation of new neuronal cells at the site of injury could represent an attempt by the CNS to regenerate itself following injury. The toxicity of the microenvironment at sites of injury, as well as the glial scar, may limit this regenerative process [59, 60]. Interestingly, the SVZ origin of these newly generated neuronal cells could signify that conditions known to enhance SVZ neurogenesis could promote these regenerative attempts, and, therefore, functional recovery, following injury.

5.3. Neuroplasticity

After cerebral strokes and traumatic brain injuries, there is a striking amount of neurological recovery in the following months or years, despite what is often permanent structural damage [61, 62]. It is commonly accepted that the most rapid recovery occurs within 6 months of injury, and continues to occur for as long as ten years after the injury. It has been postulated that the plasticity of the CNS may underlie this recovery after injury. Neuroplasticity allows the nerve cells in the brain to compensate for injuries and disease by reorganizing the pre-existing network, and by 'axonal sprouting', in which undamaged axons grow new nerve endings to reconnect neurons, the links of which were injured or severed, thereby forming new neural pathways to accomplish a needed function. Particularly,

reorganization of the contralateral hemisphere has been involved in plasticity after brain injury; if one hemisphere of the brain is damaged, the intact hemisphere may take over some of its functions [62, 63].

Neurogenesis is increased bilaterally in the DG and the SVZ after cerebral strokes, global and focal ischemia, and traumatic brain injuries. The bilateral increase in neurogenesis after global ischemia is unsurprising, as global ischemia affects both hemispheres. In contrast, it is more surprising following focal ischemia, traumatic brain injuries, and other models, such as those for epilepsy, where only one hemisphere is affected. Because reorganization of the contralateral hemisphere has been implicated in plasticity after brain injury, the bilateral increase in neurogenesis could be a factor contributing to this plasticity-related recovery in the CNS. This process may be the case particularly after injury to the CNS, which would promote the transient synthesis and release of trophic factors that would consequently reach the neurogenic areas of both hemispheres via the cerebrospinal fluid (CSF), ultimately stimulating neurogenesis in the hippocampus and SVZ. In support of this argument, factors known to promote neurogenesis, such as cystatin C [64], are found in the CSF, where their levels are elevated in the diseased or injured brain [65]. These factors may therefore represent a molecular basis for the bilateral increase in neurogenesis, and thus its associated plasticity, in the diseased or injured brain.

5.4. Neuroadaptation

Patients with neurological diseases, such as epilepsy, AD, HD and PD, and also patients recovering from stroke and brain injuries, are at greater risk of depression and present learning and memory impairments [66-69]. Because learning, memory and depression are associated with hippocampal neurogenesis [37, 44••], the depressive episode and learning impairments may contribute to the increase in neurogenesis observed in experimental models of neurological diseases or disorders. It is arguable that neurogenesis might therefore play a neuroadaptive role. In support of this contention, stress is a known component of many pathologies, such as stroke and traumatic brain injuries, is an important causal factor in precipitating episodes of depression, and potently suppresses adult neurogenesis [22]. As mentioned previously, it is hypothesized that the waning and waxing of neurogenesis in hippocampus is a causal factor in the precipitation of, and recovery from, episodes of clinical depression, and could be triggered by a stress-induced decrease in neurogenesis [45] – could be triggered by the stress-induced decrease in neurogenesis. Recently, Grote et al demonstrated that the cognitive disorders and neurogenesis deficits observed in HD mice are rescued by the antidepressant fluoxetine, supporting a neuroadaptive role of neurogenesis in the diseased or injured brains of patients [70•].

6. Neurogenesis in the Adult Human Brain: Particularities and Implications

Adult neurogenesis occurs throughout adulthood primarily in two areas of the brain: the DG of the hippocampus and the SVZ. In rodents and non-human primates, it has been well

documented that newly generated neuronal cells in the subgranular zone of the DG migrate to the granular layer, where they differentiate into mature neuronal cells and extend axonal projections to the CA3 area of the hippocampus. In the SVZ, cells are generated in the anterior part of the SVZ and migrate to the olfactory bulb (OB), through the RMS, where they differentiate into interneurons of the OB [1, 2, 71]. It has recently been demonstrated that neuroblast migration parallels CSF flow, and requires the beatingof ependymal cilia, principally for guidance of newly generated neuronal cells [72••]. In the adult human brain, neurogenesis has been reported to occur in the hippocampus [73•]. In the SVZ, Sanai et al have reported the existence of a ribbon of astrocytes lining the lateral ventricles of the adult human brain, which proliferate *in vivo* and behave as multipotent progenitor cells *in vitro* [74••]. Sanai and colleagues further reported no evidence of chains of migrating neuroblasts in the SVZ or in the pathway to the OB. This astrocytic ribbon has not been observed in other vertebrates, identifying SVZ astrocytes as NSCs in a niche of unique organization in the adult human brain. These findings raise the unexpected possibility that migration from the SVZ to the OB does not take place in adult humans or, if it does, precursors migrate as individual cells. Alternatively, migration from the SVZ to the OB may occur through a different path, yet to be identified [74••].

Such discordance between species would have tremendous implications with regard to translating the data generated from adult rodent and non-human primates to humans, and on the modulation and role of neurogenesis in the adult human brain. Notably, data from rodent studies show that in models of diseased or injured brains, new neuronal cells are generated at the sites of degeneration, where they replace some of the lost nerve cells; time-course studies have revealed that these new neuronal cells originate in the SVZ, from where they migrated out of the RMS toward the site of lesions. Therefore, as there is no evidence in humans of migrating chains of neuroblasts in the SVZ or in the pathway to the OB, would neurogenesis be modulated in the diseased or injured human brain, and would these new neuronal cells have the ability to migrate toward the site of injury? Studies using confocal immunofluorescence microscopy to detect molecular markers (such as the cell-cycle marker proliferating cell nuclear antigen, the neuronal marker ß-tubulin, and the glial cell marker glial fibrillary acidic protein) in the SVZ adjacent to the caudate nucleus of adult human post-mortem samples, show that progenitor cell proliferation and neurogenesis are increased in the SVZ of HD brains [24, 75]. These findings suggest that neurogenesis may indeed be modulated in the adult human brain. The previously mentioned data reported by Sanai et al. highlight the importance of studying neurogenesis and NSCs in the human brain, together with the importance of understanding the significance of possible distinctions between neurogenesis in the adult brains of human and other mammals [74••].

Conclusion

Neurogenesis is involved in learning, memory, and depression, and is modulated by a wide range of physiopathological conditions and environmental stimuli. We propose that newly generated neuronal cells in the adult brain are involved in homeostasis of the CNS tissue, regeneration, plasticity and neuroadaptation. Although the contribution of adult neurogenesis to these processes remains to be determined, it will eventually lead to a