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Review

Adult neurogenesis, neuroinflammation and therapeutic potential of adult neural stem cells

Philippe Taupin [1, 2]

1. Fighting Blindness Vision Research Institute, National Institute for Cellular Biotechnology, Glasnevin. Dublin 9, Ireland.
2. Dublin City University, Dublin 9, Ireland.

Correspondence to: Philippe Taupin, Fighting Blindness Vision Research Institute. National Institute for Cellular Biotechnology. Dublin City University. Glasnevin. Dublin 9, Ireland. Email: philippe.taupin@dcu.ie

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The pathogenesis of neurological diseases and disorders remains mostly unknown. Neuroinflammation has been proposed as a causative factor for neurological diseases. The confirmation that neurogenesis occurs in the adult brain and neural stem cells (NSCs) reside in the adult central nervous system (CNS) of mammals has tremendous implications for our understanding of the physio- and pathology of the nervous system. The generation of newborn neuronal cells in the adult brain is modulated in neurological diseases and during inflammation. This suggests that adult neurogenesis is involved in the pathogenesis of neurological diseases and disorders, particularly during neuroinflammation. In this manuscript, we will review the modulation of adult neurogenesis in neurological diseases and during neuroinflammation. We will discuss the role and contribution of neuroinflammation and adult neurogenesis to neurological diseases and disorders, and for the therapeutic potential of adult NSCs.

Key words: neurogenesis, neuroinflammation, neural stem cells

Introduction

Neuroinflammation is a process in which the brain responds to infections, diseases and injuries [1, 2]. Neuroinflammation involve two types of immune cells: lymphocytes, monocytes and macrophages of the hematopoietic system, and microglial cells of the CNS [3, 4]. Neuroinflammation disrupts the blood-brain barrier (BBB), allowing cells from the hematopoietic system to leave the blood stream and come in contact to the injury site [5]. The immune cells respond to injuries by eliminating debris and, synthesizing and releasing a host of powerful regulatory substances, like the complements, cytokines, chemokines, glutamate, interleukins, nitric oxide, reactive oxygen species and transforming growth factors [6-10]. The substances have both beneficial and harmful effects on the cellular environment, creating further damages [11] (fig. 1). Mature astrocytes are also activated following injury to the CNS [12, 13]. Astrocytic activation is believed to be necessary for containing the immune response, repairing the BBB and attenuating further neuronal death [5, 14].

Contrary to a long-held dogma, neurogenesis occurs in the brain and NSCs reside in the CNS of adult mammals, in various species including human [15, 16]. NSCs are the self-renewing multipotent cells that generate the main phenotypes of the nervous system. Neurogenesis is modulated in the brain of patients and in animal models of neurological diseases and disorders, like Alzheimer's disease (AD), epilepsy and Huntington's disease (HD) [17]. This suggests that the adult brain may be amenable to repair and that adult neurogenesis may contribute to the functioning, and phyio- and pathology of the CNS, particularly to the etiology of neurological diseases and disorders.

Neuroinflammation in neurological diseases and injuries

Inflammation is a process in which the body's white blood cells and chemicals protect us, from infections, foreign substances and injuries. In the CNS, neuroinflammation occurs following traumatic brain injuries, spinal cord injuries and cerebral strokes. It involves immune cells from the hematopoietic and nervous system [1, 2, 6, 18]. It is now well documented that neuroinflammation is actively involved in neurological diseases and disorders, like AD, amyotrophic lateral sclerosis, depression, epilepsy, HD, multiple sclerosis and Parkinson's disease (PD) [19-22]. Particularly, in AD, there is a correlation between local inflammation, and presence of amyloid plaques and neurofibrillary tangles [23].

It is proposed that chronic inflammation is a causative factor to the pathogenesis of neurological diseases and disorders [20, 24] (fig. 1). The immune

cells and pro-inflammatory chemicals involved in neuroinflammation would underlie the mechanisms of diseases and neurodegeneration. The activation, or over activation, of immune cells involved in neuroinflammation and release of pro-inflammatory substances would result in reduced neuroprotection and neuronal repair, and increased neurodegeneration, leading to neurodegenerative diseases [10, 25, 26]. Depression is a common antecedent to many neurological diseases, particularly neurodegenerative diseases like AD and PD [27, 28]. Chronic inflammation during depressive episodes could predispose depressive patients to neurodegenerative diseases, later in life [29].

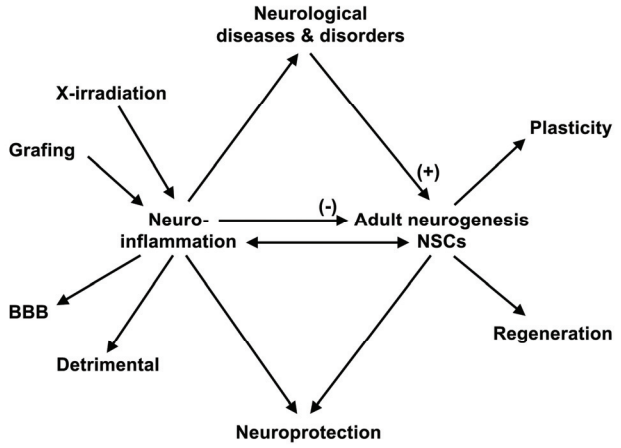

Figure 1. Adult neurogenesis and neuroinflammation. Neuroinflammation has been proposed as a causative factor for neurological diseases and disorders. It has both beneficial and harmful effects on the cellular environment. Neuroinflammation disrupts the BBB. Adult neurogenesis in modulated in a broad range of neurological diseases and disorders; it is decreased during inflammation. Adult neurogenesis may be involved in regenerative attempts and the plasticity of the nervous system. Adult-derived neural progenitor and stem cells grafted in the brain promote neuroprotection, by an immunomodulatory mechanism. Grafted neural progenitor and stem cells interact with the host immune system to promote functional recovery, an interaction that may provide clinical benefit for NSC-based therapy.

Adult neurogenesis, neural stem cells and cellular therapy

In the adult mammalian brain, including in humans, neurogenesis occurs primarily in two regions, the dentate gyrus (DG) of the hippocampus and subventricular zone (SVZ) [30, 31]. Neurogenesis involves a relatively small number of cells, particularly in the DG, and is modulated by environmental stimuli, trophic factors/cytokines, drug treatments, and in various physio- and pathological conditions, like neurological diseases and disorders [32]. Newborn neuronal cells, in the adult brain, establish functional connections, survive for extended period of time, at least 2 years in human, and reproduce processes similar to development, to integrate the mature network [30, 33, 34]. Adult neural progenitor and stem cells have been isolated and characterized in vitro, from various species [16], including from human biopsies and post-mortem tissues [35]. It is hypothesized that newborn neuronal cells in the adult brain originate from residual stem cells. The existence of stem cells in the adult brain suggests that it has the potential for self-repair and that newborn neuronal cells may contribute to the functioning, and physio- and pathology of the CNS [36]. However, adult NSCs remain elusive cells and to be unequivocally identified and characterized in vitro and in vivo [37, 38].

Two strategies are being considered for adult NSC-based therapy in the CNS, the stimulation of endogenous neural progenitor or stem cells and the transplantation of adult-derived neural progenitor and stem cells [39]. Self-renewing multipotent neural progenitor and stem cells have been isolated and characterized in vitro, from various regions of the adult mammalian CNS, including the spinal cord [16]. This suggests that neural progenitor and stem cells reside throughout the adult CNS, in mammals. The stimulation of endogenous neural progenitor or stem cells locally would represent a strategy to promote regeneration of the diseased and injured nervous system. Alternatively, new neuronal cells are generated at sites of degeneration in the diseased brain and after CNS injuries, like in HD and in experimental models of cerebral strokes 40, 41]. These cells originate from the SVZ and migrate partially through the rostro-migratory stream to the sites of degeneration. This suggests that strategies to promote regeneration and repair may focus on stimulating SVZ neurogenesis. Adult derived-neural progenitor and stem cells may be transplanted locally [42] or administered intravenously to promote regeneration and repair [43]. Systemic injection provides a model of choice for delivering adult derived-neural progenitor and stem cells for the treatment of neurological diseases and injuries, where the degeneration is widespread, like AD and HD.

Adult neurogenesis in neurological diseases and disorders

Adult neurogenesis is modulated in the brains of patients and in animal models of neurological diseases and disorders, like AD, depression, epilepsy, Huntington's and Parkinson's diseases [17]. Neurogenesis is increased in the hippocampus of

brains of patients with AD, as revealed after autopsies by an increase in the expression of markers for immature neuronal cells, like doublecortin and polysialylated nerve cell adhesion molecule, in hippocampal regions [44]. In animal models of AD, neurogenesis is increased in the DG of transgenic mice expressing the Swedish and Indiana amyloid protein precursor (APP) mutations, a mutant form of human APP, [45] and decreased in the DG and SVZ of knock-out mice for presenilin 1 and APP [46, 47]. This shows that adult neurogenesis is enhanced in AD brains. The discrepancies observed on adult neurogenesis in brain autopsies of patients with AD and animal models of AD may originate from the limitations of animal models, particularly transgenic mice, as representative models of complex diseases, particularly AD [48] and to study adult phenotypes, like adult neurogenesis. Result from autopsies reveals that neurogenesis is not altered in the brains of depressive patients [49]. Neurogenesis is enhanced in the DG and SVZ of animal models of epilepsy, like after pilocarpine treatment [50]. After pilocarpine treatment, ectopic granule-like cells in the hilus are labeled for bromodeoxyuridine (BrdU). BrdU is a thymidine analog that incorporates DNA of dividing cells during the S-phase of the cell cycle and is used for birthdating and monitoring cell proliferation [51]. MF-like processes immunostained for TOAD-64, a marker for newly generated neuronal cells, are also detected in the granule cell layer of the *stratum oriens* of CA3 and the inner molecular layer of the DG, in rodents [50]. Low-dose, whole-brain, X-ray irradiation in adult rats, after pilocarpine treatment, inhibits neurogenesis, but does not prevent seizure-induced ectopic granule-like cells and MF sprouting [52]. Hence, neurogenesis is enhanced in the DG and SVZ in animal models of epilepsy and seizure-induced ectopic granule-like cells and MF sprouting arises not only from newborn neuronal cells, but also from mature dentate granule cells. Immunohistochemistry and confocal microscopy analysis of autopsies for markers of the cell cycle and neuronal differentiation, like proliferating cell nuclear antigen and β-tubulin, show that cell proliferation and neurogenesis are increased in the SVZ of brains of patients with HD [41]. In adult R6/1 transgenic mouse model of HD, neurogenesis decreases in the DG [53]. After quinolinic acid striatal lesioning of adult brain, neurogenesis is increased in the SVZ [54], as observed in brains of HD patients [41]. These data provide evidences that adult neurogenesis is increased in the SVZ of brains with HD. Data from R6/1 transgenic mouse model of HD are difficult to interpret in the context of adult neurogenesis in HD, as mutated forms of huntingtin affect brain development [55]. This could underlie the decrease of neurogenesis reported in adult transgenic mice R6/1. In PD, one study reports that the rate of neurogenesis, measured by BrdU labeling, is stimulated in the substantia nigra (SN), following lesion induced by a systemic dose of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) [56]. Another study reports no evidence of new dopaminergic neurons in the SN of 6-hydroxydopamine-lesioned hemi-Parkinsonian rodents [57]. Hence, neurogenesis in the SN is the source of debates and controversies, and remains to be further evaluated.

In all, adult neurogenesis in modulated in a broad range of neurological diseases and disorders (fig. 1). The contribution and significance of this modulation to the etiology and pathogenesis of neurological diseases and disorders remain mostly unknown. In epilepsy, low-dose, whole-brain, X-ray irradiation in adult rats, after pilocarpine treatment, inhibits neurogenesis, but does not prevent the induction of recurrent seizures [52]. These data provide a strong argument against a critical role of adult neurogenesis in epileptogenesis. However, although increased hippocampal neurogenesis may not be critical to epileptogenesis, it could be a contributing factor to limbic seizures when present. In depression, chronic administration of antidepressants, like the selective serotonin reuptake inhibitors fluoxetine, increases neurogenesis in the DG, but not the SVZ in adult rats, suggesting that adult neurogenesis is involved in the activity of antidepressants [58, 59]. X-irradiation of the hippocampal region, but not other brain regions, like the SVZ or the cerebellar region, inhibits neurogenesis and prevents the behavioral effect of the antidepressants, like fluoxetine, in adult mice [60]. Hence, it is proposed that adult neurogenesis mediate the activities of antidepressants, particularly selective serotonin reuptake inhibitors. In HD, in brains of HD patients and after quinolinic acid striatal lesioning of adult brain the enhanced neurogenesis in the SVZ leads to the migration of neuroblasts and formation of new neuronal cells in damaged areas of the striatum. This suggests that neurogenesis may be involved in regenerative attempts in HD brains [41, 54] (fig. 1).

There are however debates and controversies over the modulation of adult neurogenesis in neurological diseases and disorders, particularly for studies involving BrdU labeling for studying neurogenesis. BrdU is a thymidine analog that incorporates DNA of dividing cells during the S-phase of the cell cycle and is used for birthdating and monitoring cell proliferation [51]. There are limitations and pitfalls over the use of BrdU for studying neurogenesis. BrdU is toxic and mutagenic substances.

It triggers cell death, the formation of teratomes, alters DNA stability, lengthens the cell cycle, and has mitogenic, transcriptional and translational effects on cells that incorporate it. BrdU is not a marker for cell proliferation, but a marker for DNA synthesis [61-63]. High level, 4 to 10%, of tetraploid nerve cells have been reported in regions in which degeneration occurs in AD, like the hippocampus [64]. It is proposed that cell cycle re-entry and DNA duplication, without cell proliferation, precede neuronal death in degenerating regions of the CNS [65]. Some of the data observed by mean of immunohistochemistry for cell cycle proteins and BrdU labeling in the brains of AD patients and in animal models of the disease, may therefore not represent adult neurogenesis, but rather labeled nerve cells that may have entered the cell cycle and underwent DNA replication, but did not complete the cell cycle [62]. In addition, many physio- and pathological processes, like exercise, neurological diseases and injuries, like AD, PD and cerebral strokes and drugs treatments affect the permeability of the BBB and cerebral flow [66-68]. Some of the data observed by mean of BrdU labeling in animal models of neurological diseases and after drug treatments may reflect bio-availability of BrdU in the brain, rather than neurogenesis.

Neuroinflammation in adult neurogenesis

Neuroinflammation inhibits neurogenesis in the adult hippocampus [69, 70] (fig. 1). The mechanism, function and significance of the modulation of neurogenesis during inflammatory processes remain to be elucidated. Molecules released by the immune cells, like interleukins and nitric oxide, regulate negatively adult neurogenesis and may underlie the molecular mechanisms of inflammatory reactions on adult neurogenesis [71, 72]. Neuroinflammation is actively involved in neurological diseases and disorders, like AD, depression and PD [19-22]. It is proposed that chronic inflammation is a causative factor to the pathogenesis of these neurological diseases and disorders [20, 24]. Hence, the modulation of adult neurogenesis during the inflammatory process may contribute or cooperate with the activity of neurological diseases and disorders on adult neurogenesis. Since the function of newborn neuronal cells is still the subject of debates and remains to be elucidated, the significance of the modulation of adult neurogenesis during inflammatory processes and in neurological diseases and disorders can only be speculated. Newborn neuronal cells may represent a regenerative attempt and contribute to the plasticity of the nervous system [73] (fig. 1).

There are however debates and controversies over the modulation of adult neurogenesis during inflammatory processes, particularly for studies involving BrdU labeling for studying neurogenesis. Neuroinflammation alters the permeability of the BBB [5]. Hence, some of the data observed by mean of BrdU labeling in animal models during inflammatory processes may reflect bio-availability of BrdU in the brain, rather than neurogenesis. Investigators have used X-ray irradiation to inhibit neurogenesis and study the function of adult neurogenesis [52, 60, 74]. Brain irradiation induces inflammatory responses (fig. 1). Hence, the effects of brain irradiation on adult neurogenesis in animal models, particularly of neurological diseases and disorders, are therefore difficult to interpret in light of these data. In all, the modulation of adult neurogenesis during inflammatory processes and after X-irradiation treatments remains to be further evaluated.

Neural progenitor and stem cells express receptors, and respond to trophic factors and cytokines. Hence, the inflammation resulting from the pathological processes to be treated by the transplantation of neural progenitor and stem cells, as well as the transplantation procedure itself may have adverse effects of the success of the graft (fig. 1). The timing of transplantation in the diseased brain or after injury is therefore critical for successful transplantation of neural progenitor and stem cell therapy [75]. Studies reveal that adult-derived neural progenitor and stem cells promote neuroprotection, by an immunomodulatory mechanism [76] (fig. 1). Grafted neural progenitor and stem cells interact with the host to promote functional recovery, an interaction that may provide clinical benefit for NSC-based therapy (fig. 1). The interaction of grafted neural progenitor and stem cells with the immune system suggests that pre-clinical studies involving immuno-depressed mice may not represent an appropriate model to characterize and validate sources of human-derived neural progenitor and stem cells for therapy [77].

Conclusion and Perspectives

Neuroinflammation is involved in the pathogenesis of neurological diseases and disorders, but its contribution and involvement to these pathological processes remain to be elucidated. It may be involved in the modulation of neurogenesis in neurological diseases and disorders, but the contribution and significance of this modulation remain to be understood. Neuroinflammation has tremendous implications for cellular therapy. On the one hand, it may limit the therapeutic potential of adult NSCs in vivo and ex vivo. On the other hand, it may interact with the neurogenic niches to promote the regenerative potential in vivo, and the integration of the grated neural progenitor and stem cells ex vivo.

Hence, neuroinflammation may have both beneficial and detrimental effects on the potential of adult NSCs, to promote regeneration and repair in vivo and ex vivo. Therapeutic strategies for promoting the potential of adult NSCs in vivo and ex vivo may involve pro- and anti-inflammatory treatments. Future studies will aim at unraveling the molecular mechanisms governing the interaction between neural progenitor and stem cells and the immune system, and it implications for cellular therapy.

Conflict of interest

The author has declared that no conflict of interest exists.

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