Published in final edited form as:
Curr Immunol Rev. 2010 August 1; 6(3): 167–173. doi:10.2174/157339510791823772.

Immune system modulates the function of adult neural stem cells

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Abstract

New neurons are continuously produced in most, if not all, mammals. This Neurogenesis occurs only in discrete regions of the adult brain: the subventricular zone (**SVZ**) and the subgranular zone (**SGZ**). In these areas, there are neural stem cells (**NSCs**), multipotent and selfrenewing, which are regulated by a number of molecules and signaling pathways that control their cell fate choices, survival and proliferation rates. It was believed that growth and morphogenic factors were the unique mediators that controlled NSCs in vivo. Recently, chemokines and cytokines have been identified as important regulators of NSCs functions. Some of the most studied immunological effectors are leukemia inhibitory factor (**LIF**), ciliary neurotrophic factor (**CNTF**), interferon-gamma (**IFN-γ**), insulin-like growth factor-1 (**IGF-1**), tumor necrosis factor alpha (**TNF-α**), and the chemokines MCP-1 and SDF-1. These substances exert a considerable regulation on proliferation, cell-fate choices, migration and survival of NSCs. Hence, the immune system is emerging as an important regulator of neurogenic niches in the adult brain, but further studies are necessary to fully establish the biological meaning of these neural effects.

Keywords

Interleukin; neural stem cells; subventricular zone; cytokine; chemokine; microglia

Introduction

Tissue-specific stem cells divide to regenerate different cell types for the purpose of tissue maintenance in the adult. For a long time, the brain was considered an exception. Although, proliferating cells were discovered in the mature brain, it was believed that cell proliferation in the brain was limited to glial cells (the supportive cells found around neurons). In the 1960s, this view began to change when new putative microneurons were first described [1]. In the 1980's neurogenesis and recruitment of new neurons into functional circuits were demonstrated to occur in the telencephalon of adult birds [2,3]. After that crucial finding, adult neurogenesis was demonstrated in several species such as, mouse, rat, rabbit, cow and primate [4–7]. To date, it is accepted that new neurons are formed and recruited into specific brain circuits probably in all adult vertebrate species, including humans [8].

In the adult brain, active neurogenesis occurs only in discrete regions of the central nervous system (**CNS**): the subventricular zone (**SVZ**) and the subgranular zone (**SGZ**). The source of new neurons in the adult brain is neural stem cells (**NSCs**). The NSCs, which are multipotent and selfrenewing, are regulated by a number of molecules and signaling pathways. Some of

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the most studied modulators are epidermal growth factor (**EGF**), basic fibroblast growth factor (**bFGF or FGF-2**), platelet derived growth factor (**PDGF**), Notch, Sonic hedgehog, gp130 and others. Recently, it has been demonstrated that immune system plays a key role in regulating NSCs population through production of chemokines and cytokines. In this review, we describe the main neural niches (the subventricular zone and the subgranular zone), the molecules involved in NSCs regulation and the evidence indicating that several immune mediators control proliferation and cell fate of neural primary progenitors. Since adult NSCs may function as a source of neural precursors for brain repair, elucidating the molecular mechanisms that control their survival, proliferation and fate is a crucial step to design effective procedures to manipulate them.

Subventricular zone (SVZ)

NSCs have been isolated from the SVZ Fig. (1), the lining of the lateral ventricles, and the SGZ of the dentate gyrus Fig. (2), within the hippocampus. The largest of these germinal regions, the SVZ, contains a population of cells that has structural and molecular characteristics of astrocytes, which function as NSCs. Astrocytic NSCs, also called Type-B1 cells, divide to give rise to actively proliferating transit amplifying progenitors (Type-C cells). Type-C cells, in turn, generate neuroblasts (Type-A cells) that migrate anteriorly through the rostral migratory stream (**RMS**) into the olfactory bulb to become interneurons Fig. (1) [9–12]. Interestingly, Type-B and Type-C cells also generate some oligodendrocytes that migrate and myelinate the neighboring corpus callosum and fimbria fornix [13,14]. The role of the SVZ-derived interneurons remains unclear but they seem to regulate the olfaction process [15].

Subgranular zone (SGZ)

The SGZ of the dentate gyrus in the hippocampus is a proliferative region that contains neuronal progenitors that give rise to granular neurons Fig. (2). The primary progenitors in this region are radial astrocytes (Type-B cells) that asymmetrically divide to give rise to Type-D cells [16]. These intermediate progenitors have at least 4 stages of maturation in (D1, D2, D2h and D3) to finally differentiate into granular neurons Fig. (2) [16,17]. These cells display multipotential characteristic *in vitro*, but so far, it has not been demonstrated their multipotential properties *in vivo*. Therefore, some authors called these SGZ precursors as neuronal progenitors instead of NSCs. The function of these newly generated neurons appears to play a fundamental role in memory process, learning and depression.

Control of cell fate and proliferation of NSCs

There is a number of trophic and morphogenic factors that regulate *in vivo* proliferation of adult NSCs in the neurogenic niches. Table 1 summarizes some of the most studied trophic factors. Members of the fibroblast and epidermal growth factor families are mitogens that expand *in vitro* and *in vivo* the adult neural progenitors. Some of these well-studied mediators are: epidermal growth factor (**EGF**) [14,18], basic fibroblast growth factor (**bFGF or FGF-2**) [19], platelet-derived growth factor (**PDGF-α**) [20], tumor-derived transforming growth factor (**TGF-α**) [21], brain-derived neurotrophic factor (**BDNF**) [22], sonic hedgehog (**Shh**) [23,24] and others.

Immunological mediators

During the last decade, increasing evidence indicates that immune system targets neurogenic niches and exerts a considerable effect on proliferation, survival, differentiation and migration of NSCs. Cytokines are immunomodulating polypeptide regulators involved extensively in cellular communication [25]. These substances are present virtually in all nucleated cells, but predominantly in macrophages, endothelium and epithelial cells [26]. The neuropoietic

cytokine family includes interleukin-6 (**IL-6**), interleukin-18 (**IL-18**), tumor necrosis factor alpha (**TNF-α**), ciliary neurotrophic factor (**CNTF**), leukemia inhibitory factor (**LIF**), interferon gamma (**IFN-γ**) and others [25,27]. Chemokines are small cytokines or proteins, which are categorized into four groups: CXC (or α-chemokines), which promote the migration of neutrophils and lymphocytes; CC chemokines (or β-chemokines), which induce the migration of monocytes, natural killers (**NK cells**) and dendritic cells; C chemokines (or γ-chemokines) that attract T cell precursors to the thymus; and CX3C chemokines (or δ-chemokines), which serve as chemoattractants and adhesion molecules [26]. Cytokines and chemokines have been shown to alter NSCs self-renewal, progenitor cell division and differentiation that is probably mediated by the Janus kinase-signal transducer and JAK/STAT, an activator of the transcription pathway [25,27].

Immunological regulation of NSCs

The brain is an immune-privileged organ because the selective permeability of the blood-brain barrier (**BBB**) only allows certain molecules and cells to enter and leave the cerebral parenchyma. Therefore, under normal physiological conditions, only macrophages, T cells and dendritic cells can go into the nervous system [26,28,29]. After damage, an inflammatory process is initiated by the activation of astrocytes and microglia. This event is followed by parenchymal infiltration of macrophages and lymphocytes. These activated and recruited cells release a number of anti- and pro-inflammatory substances, neurotransmitters, chemokines and reactive oxygen species. Then, more inflammatory factors are released, creating a positive feedback loop that results in neural damage and causes both detrimental and positive consequences to neurogenesis [25,29,30]. In particular, cytokines/chemokines seem to significantly modify the functions of adult NSCs. Table 2 summarize some of these immunological effectors, but many of them have not been fully characterized.

Acute or chronic exposure to LIF or CNTF differentially affects development and growth of NSCs derived from the adult SVZ [27]. Acute LIF or CNTF exposure stimulates the amplification and self-renewal of NSCs [31–33]. In contrasts, chronic exposure to LIF or CNTF alters the formation of NSC progenies and promotes NSC self-renewal [27]. Intracellular phosphorylation of STAT3 is essential for the effects of LIF in maintaining NSC phenotype [34]. However, leptin, which activates STAT3 after binding to the leptin receptor, inhibits differentiation of multipotent cells [27,35].

NSCs do not express a functional IL-6R, thus they do not properly respond to IL-6. However, the stimulation of NSCs with the active fusion protein of IL-6 and sIL-6R, also named as Hyper-IL-6 (**H-IL-6**), induces NSCs to differentiate into glutamate-responsive neurons and oligodendrocytes [36]. The inflammatory cytokine IFN- γ is pro-neurogenic. IFN- γ promotes neural differentiation and neurite outgrowth of murine adult NSCs [37,38] and the human neuroblastoma cells [39]. Neuronal differentiation induced by IFN-γ appears to be mediated by the c-Jun N-terminal kinase (**JNK**) pathways [40]. JNK pathway is also required for neural differentiation of embryonal carcinoma cells, embryonic stem cells and PC12 cells [41–44]. However, IFN-γ has shown a dual effect on neurogenesis, because not only stimulates neuronal differentiation [38,39] and NPC migration, but also inhibits NSCs proliferation and reduces NSCs survival [45]. The manipulation of NSCs with immune mediators may useful to repair brain injuries, as shown by Yang et al. who engineered NSCs to express IL-10, which enhanced their ability to induce immune suppression, remyelination, and neuronal repair [46].

Under pathological conditions, activated microglia produces insulin-like growth factor-1 (**IGF-1**), which activates the extracellular signal-regulated kinase (**ERK**)/mitogen-activated protein kinase (**MAPK**) pathway, increasing neurogenesis in the SGZ [47]. Microglia activated by IL-4 induces a bias towards oligodendrogenesis whereas the IFN-γ-activated microglia

induces a bias towards neurogenesis [48]. In contrast, decreased neurogenesis has been observed by effect of the pro-inflammatory cytokine TNF-α [29]. TNF-α increases the expression of MCP-1, a chemokine that induces NSCs migration mediated through the MCP-1 receptor CCR2 [49,50]. MCP-1 appears to protect neurons against NMDA-mediated excitotoxicity [51]. SDF-1 chemokyne also induces migration of NPCs and increases survival of NSCS [49,52,53], but contrasting reports demonstrated that SDF-1 promotes quiescence [54] or proliferation of neural progenitors [55]. In contrast, the CCL2 chemokine does not affect neural progenitor cell proliferation and cell survival, but promotes neuronal differentiation of SVZ progenitors [56]. Some of these intricate relationships are depicted in Fig. (3).

Hematopoietic growth factors have also been involved in the regulation of adult NSCs, Fig. (3). Granulocyte-macrophage colony stimulating factor (**GM-CSF**) stimulates neuronal differentiation of adult NSCs [57]. Granulocyte-colony stimulating factor (**G-CSF**) stimulates neuronal differentiation of NSCs in vitro [58] and enhances neurogenesis and functional recovery. Erythropoietin (**EPO**) drives neuronal differentiation of NSCs in vitro [59,60]. Interestingly, EPO-receptor deficient mice display reduced neurogenesis [59,60].

In summary, immune system is an important regulator of proliferation, migration and survival of NSCs. Yet, as findings in this field are relatively recent, there exist a number of cytokines and chemokines to be investigated. Moreover, signaling pathways involved in all these processes are to be elucidated.

Acknowledgments

O.G-P was supported by CONACyT's grant (CB-2008-101476) and in part by NIH/NINDS's grant (1K08NS055851). F.J-H was supported by CONACyT's posdoctoral fellowship (62022) and A.Y.G-C was supported by CONACyT's fellowship (214282).

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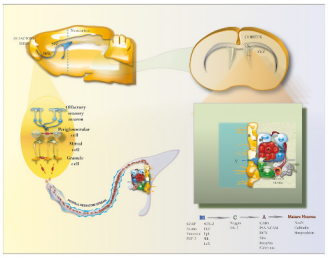

Fig. 1. The adult subventricular zone

Schematic drawing that shows the cellular organization of the adult SVZ, RMS and the olfactory bulb. New neurons born in the SVZ migrate to the olfactory bulb via the RMS. Once SVZ neuroblasts reach the olfactory bulb differentiate into granular and periglomerular GABAergic interneurons. B1: Type-B1 cell; C: Type-C cell; A: Type-A cell; V: Ventricle; CC: Corpus callosum; RMS: Rostral migratory stream; SVZ: Subventricular zone

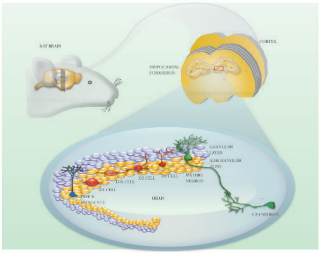

Fig. 2. The subgranular zone

Schematic drawing that shows the cellular organization of the adult subgranular zone. Radial astrocytes (Type-B cells) give rise to intermediate neuronal progenitors (also known as Type-D cells) that, in turn, differentiate into granular neurons in the dentate gyrus. Mature granular cells synapse to neuronal projections from CA3 and entorhinal cortex. Type-D cells have 4 stages: D1, D2 (radial progenitors), D2h (horizontal progenitors) and D3.

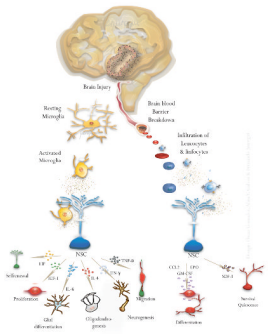

Fig. 3. Effects of cell effectors on NSCs

After a brain injury, immune cells such as lymphocytes, leucocytes and microglia can induce a number of effects on adult NSCs by releasing a number of cytokines/chemokines in the neurogenic niches.

Table 1

Effects of trophic and morphogenic factors on adult NSCs.

Factor	Proliferation	Predominant cell fate	Reference
EGF	++++	Astrocytes and oligodendrocytes	[1]
PDGF-α	+++	Astrocytes and oligodendrocytes	[2]
bFGF	+++	Neurons	[1,3]
TGF-α	+++	Immature SVZ progenitors	[4,5]
TGF-β	++	Astrocytes and neurons	[6,7]
Noggin	++	Neurons	[8]
GM-CSF	++	Neurons	[9]
G-CSF	++	Neurons	[10]
EPO	++	Neurons	[11,12]
Shh	++	Neurons	[13,14]
VEGF	+	Neurons	[15]
BMP	+	Astroglia	[16]
BDNF	+	None (in the SVZ). Neurons (in the SGZ)	[3,17]

Cell proliferation: Limited or none (+), mild (++), moderate (+++), and high (++++).

Table 2

Effects of chemokines and cytokines on adult NSCs.

Chemokine / Cytokine	Effect on neural precursor cells	Reference
IFN- γ	Reduction of proliferation and survival of NSCs. Promotion of differentiation and neurite outgrowth.	[37,38,45]
IGF-1	Increasing of neurogenesis in dentate gyrus	[47]
IL-4	Increasing of oligodendrocyte precursors	[48]
TNF- α	Decreasing of neurogenesis	[29]
Leptin	Inhibition of differentiation of neural progenitors	[27,35]
IL-6	Differentiation into glutamatergic neurons and oligodendrocytes	[36]
MCP-1	Chemotactic factor of neural precursor	[49,50]
SDF-1	Chemotactic factor that also promotes survival and proliferation of adult NSCs	[49,52,53,55]
CCL2	Neuronal differentiation of SVZ neural progenitors	[56]
LIF and CNTF	Neurogenesis promotions and stem cell self-renewal	[27,31,32,69]