Review

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The role of inflammatory cytokines as key modulators of neurogenesis

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Neurogenesis is an important process in the regulation of brain function and behaviour, highly active in early development and continuing throughout life. Recent studies have shown that neurogenesis is modulated by inflammatory cytokines in response to an activated immune system. To disentangle the effects of the different cytokines on neurogenesis, here we summarise and discuss *in vitro* studies on individual cytokines. We show that inflammatory cytokines have both a positive and negative role on proliferation and neuronal differentiation. Hence, this strengthens the notion that inflammation is involved in molecular and cellular mechanisms associated with complex cognitive processes and, therefore, that alterations in brain–immune communication are relevant to the development of neuropsychiatric disorders.

Building, refining, and modulating neural circuits

Neurogenesis is as a complex neurobiological process by which new neurons are generated from neural stem cells (NSCs) [1]. The ability of stem cells to self-renew and then differentiate into specific cell subtypes has been demonstrated both *in vitro* [2] and, more recently, *in vivo* [3]. For this reason, the term 'neural progenitor cells' (NPCs) is now used to loosely define all dividing cells with some ability to generate different neural units [3]. Current data have estimated that approximately 700 new neurons are added to the adult human hippocampus daily, suggesting that adult hippocampal neurogenesis has a critical role in mediating human brain functions, such as memory formation and cognition [4,5]. In rodents, two neurogenic niches are located in specific regions of the brain: the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the dentate gyrus (DG) in the hippocampus. Neurons generated in the adult SVZ migrate through the rostral migratory stream and develop into granule neurons and periglomerular neurons in the olfactory bulb (OB). Neurons generated in hippocampal adult SGZ migrate into the DG and become dentate granule cells (Figure 1) [3]. Likewise, adult neurogenesis in humans also occurs in both the SVZ and the SGZ; however, newborn neurons in the SVZ follow a putative migration towards the striatum (STR), where they finally develop into mature neurons (Figure 2) [6]. Unfortunately, neurogenesis in the adult brain is too limited to repair central nervous system (CNS) damage [7]. However, understanding how it is regulated might suggest ways in which it can be harnessed to promote regeneration after brain insult [7]. Moreover, regulation of adult hippocampal neurogenesis is crucial to the development of depressive behaviour and the ability to cope with stress [8].

NSCs and NPCs are continuously stimulated to proliferate, migrate, differentiate, and survive. However, any pathological perturbation to the brain, including injury, insult, or infection, can threaten normal CNS stability, provoking a cascade of molecular and cellular events that occurs mostly through microglial activation and a concomitant release of various inflammatory mediators, particularly cytokines [9]. Cytokines can have a substantial role in the brain [10]: on the one hand, they can confer immune protection, clearing the system from dead and damaged neurons and, on the other hand, they can exert certain detrimental effects on NSC niches, leading to neuronal death [11].

Although several studies have focused on both pro-and anti-inflammatory cytokines, with respect to their either positive or negative effects on neurogenesis [10], there is still the need for further understanding of their contribution in modulating cell differentiation and survival. To clarify this issue, here we review *in vitro* (cellular) studies that investigate the effect of individual cytokines on cell proliferation and differentiation of NPC types from different donor tissue and species. In addition, we give an overview of the molecular mechanisms underlying the described effects.

The role of inflammatory cytokines on brain function and neurogenesis

Cytokines are low-molecular-weight regulatory proteins or glycoproteins secreted by various cells in the body, including white blood cells, in response to an inflammatory stimulus [12]. Many cytokines are referred to as interleukins (ILs), a name indicating that they are secreted by some leukocytes and act on other similar cell types

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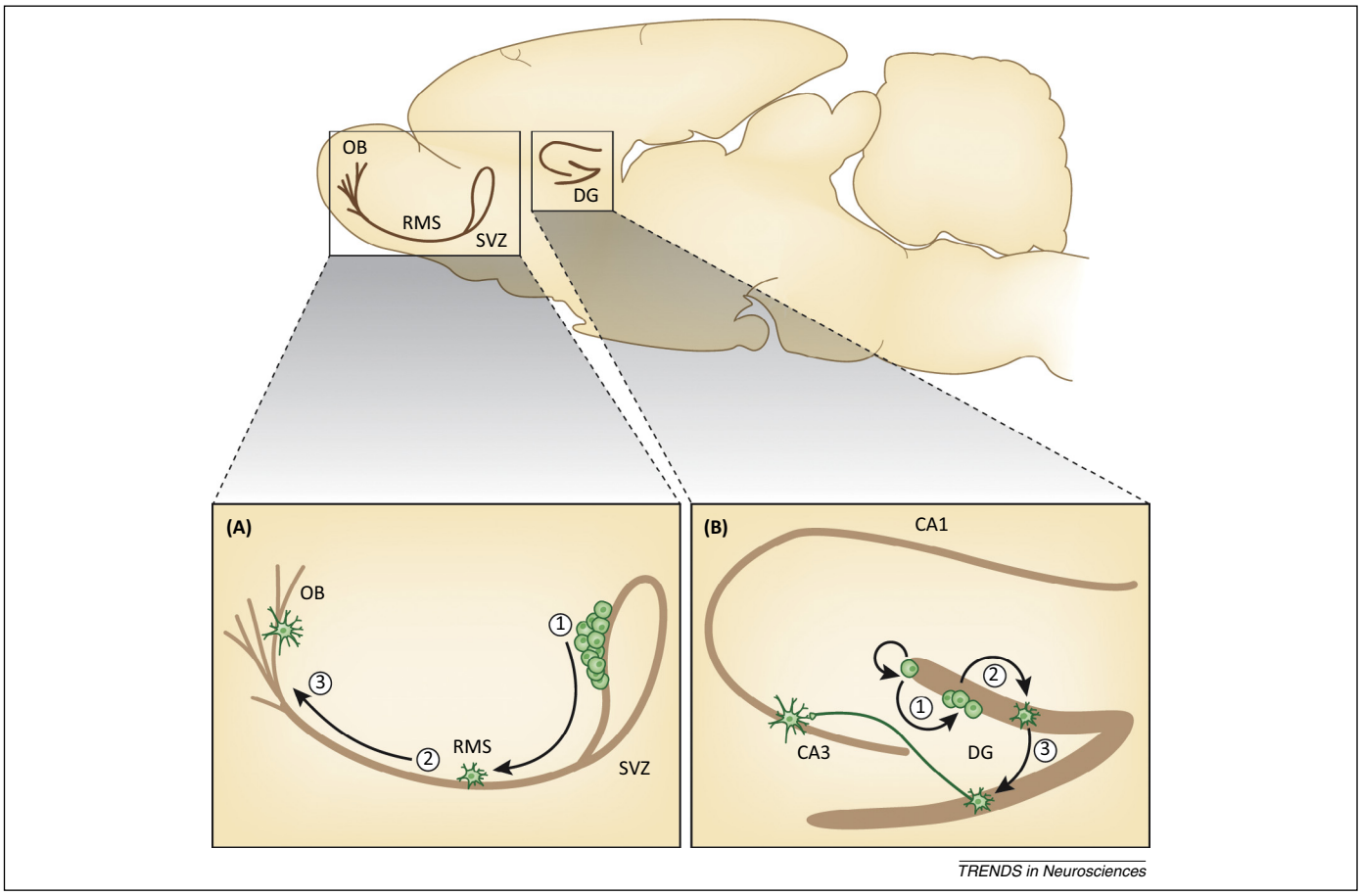

Figure 1. Illustration of the sagittal view of a rodent brain showing the two neurogenic niches: the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the dentate gyrus (DG) in the hippocampus. **(A)** Neural progenitor cells (NPCs) generated in the adult SVZ proliferate (1), migrate through the rostral migratory stream (RMS) (2) and develop into granule neurons and periglomerular neurons in the olfactory bulb (OB) (3). **(B)** NPCs generated in the adult SGZ of the DG proliferate (1), migrate into the granule cell layer (2) and mature into new granule neurons (3), extending projections into the CA3 region of the hippocampus.

[13]. Two other important types of cytokine include interferons (IFNs), which have the ability to activate immune cells such as natural killer cells and macrophages [14], and tumour necrosis factors (TNFs), which have been implicated in causing cell death [15]. In the brain, these inflammatory mediators have the important role of conferring immune protection and clearing the system from dead and damaged neurons, as well as exerting physiological and even neuroprotective functions [16]. By contrast, activation of peripheral inflammation is associated with increased expression of cytokines in the neurogenic niches [17], which directly impairs hippocampal-dependent forms of synaptic plasticity [18], potentially leading to cognitive impairment [19].

Cytokines have a central role in CNS functions [9,20]. Emerging evidence suggests that, during an inflammatory response, cytokines influence the neurogenic niche and regulate NPC proliferation and neurogenesis, particularly in the context of psychiatric and neurodegenerative conditions [21,22]. Indeed, overexpression of proinflammatory cytokines has been associated with several neuropsychiatric disorders, such as depression [23], and neurodegenerative diseases, including Alzheimer's disease (AD) and Parkinson's disease (PD) [24,25]. Patients with major depressive disorder (MDD) exhibit both increased immune activation and aberrant regulation of neuronal plasticity, including neurogenesis [26], which have been linked with abnormal cellular immunity [10]. Particularly, recent meta-analyses have reported significant upregulation of immune molecules, particularly IL-1β, IL-6, and TNF-α, in both serum and plasma of patients with depression [27]. These distinct cytokines, together with the transforming growth factor beta (TGF-β), are involved in the molecular and cellular mechanisms associated with complex cognitive processes, such as mood and learning functions [28]. Moreover, IL-1, together with IL-18 and TNF-α, contributes to inhibition of synaptic plasticity and memory consolidation [20,29], as reported in patients with MDD or in experimental models of depression [23]. Similar abnormalities have also been reported in PD and AD, which are conditions characterised by progressive neurodegeneration as well as by an abnormal immune response, due to hyperstimulation of microglia to produce inflammatory cytokines [10]. For example, in a mouse model of progressive PD, neurodegeneration was associated with an upregulation of IL-1β and TNF-α [30]. Similarly, brains of patients with AD showed increased production of IL-1 [31], together with an increased depletion of the neural progenitor pool in distinct neurogenic areas, including the SVZ [32]. Several pathways by which cytokines may cause damage to PD and AD brains have been proposed [33–35]. Overall evidence suggests that cytokines induce an