DOI:
10.1016/j.tins.2014.12.006

Document Version
Peer reviewed version

Review

CellPress

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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Keywords: inflammation; immune activation; neurogenesis; cell differentiation; cytokines; interleukins.

0166-2236/
 http://dx.doi.org/10.1016/j.tins.2014.12.006

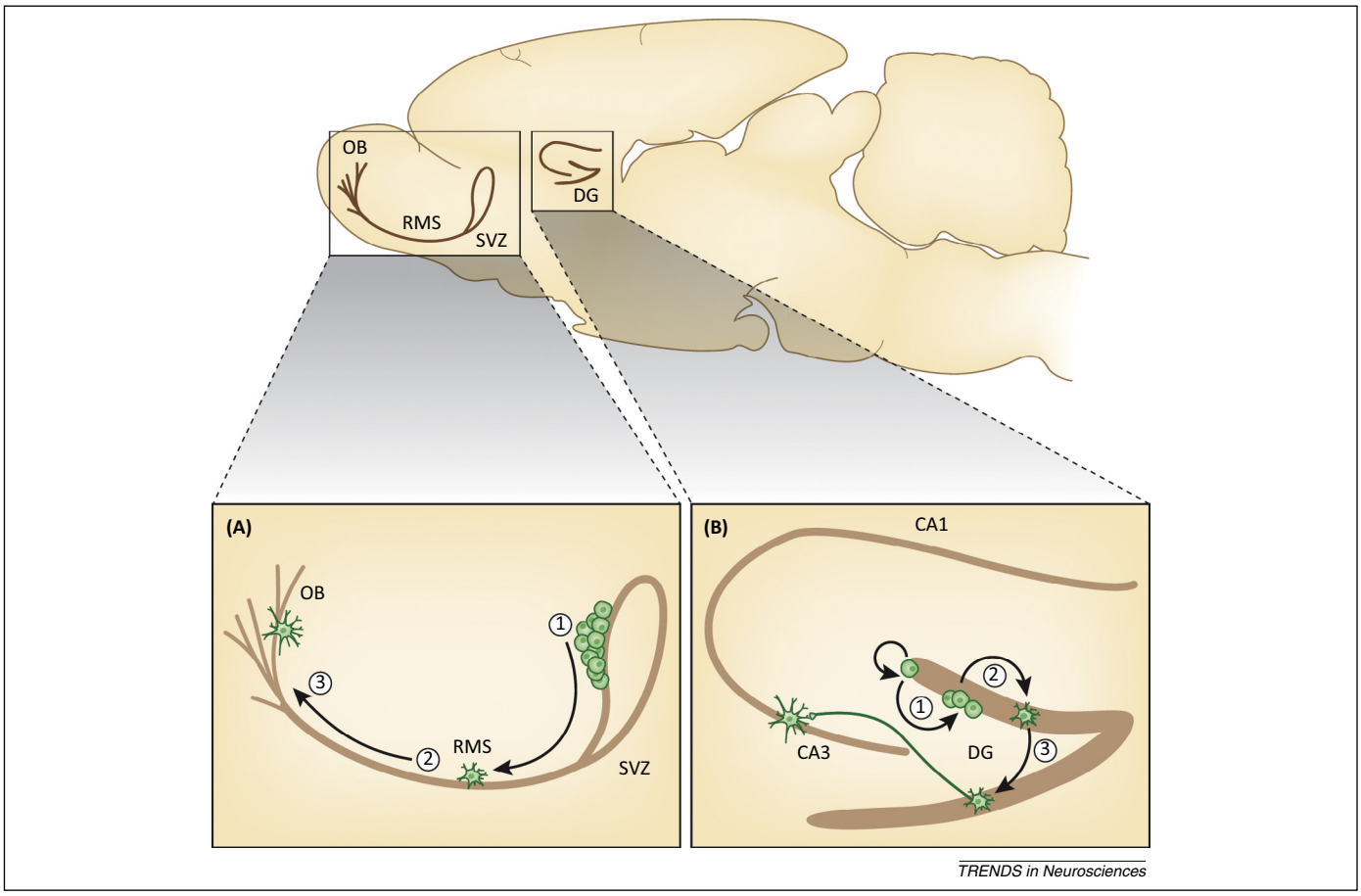

Figure 1. Illustration of the sagittal view of a rodent brain showing the two neurogenic niches: the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the dentate gyrus (DG) in the hippocampus. **(A)** Neural progenitor cells (NPCs) generated in the adult SVZ proliferate (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

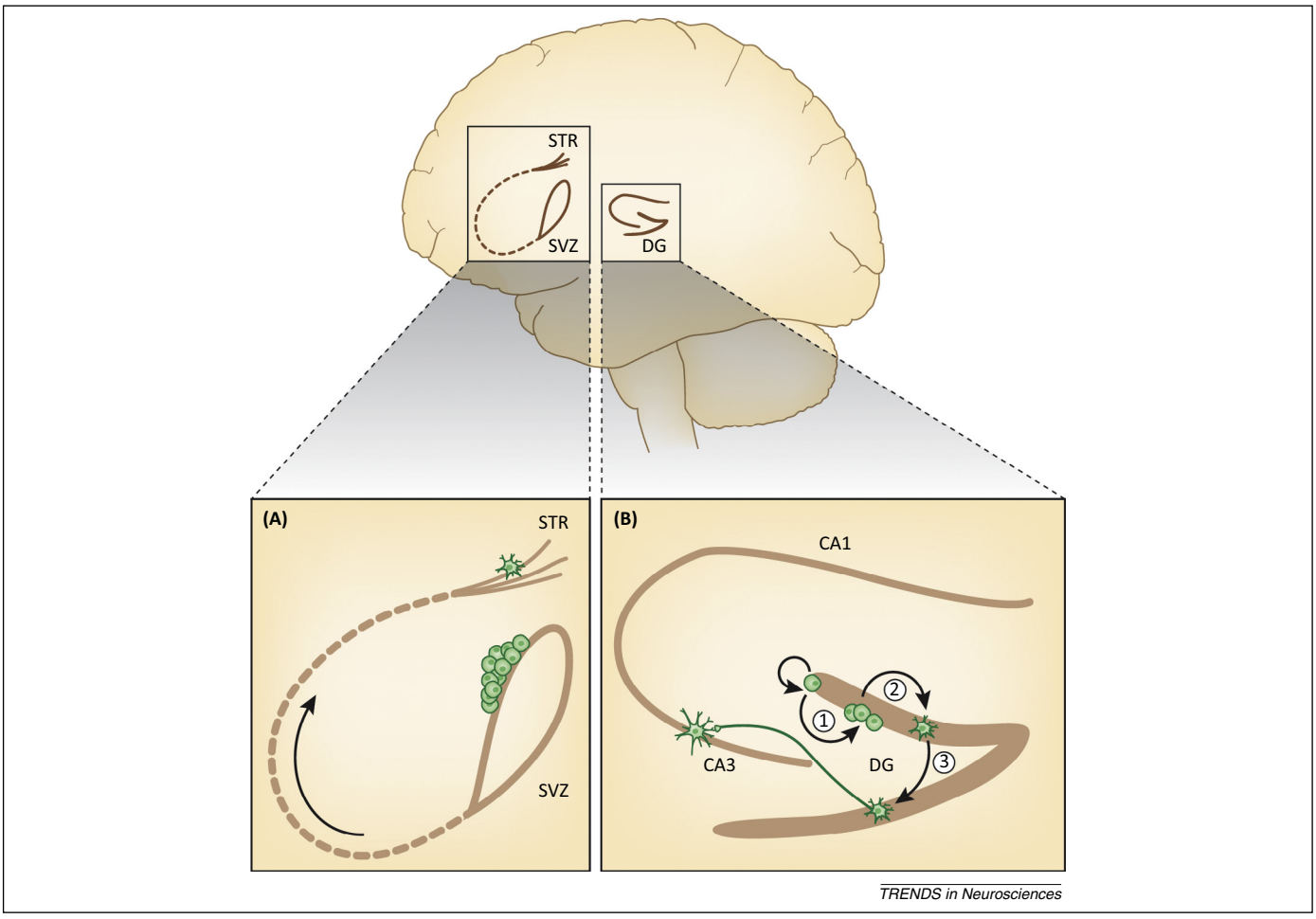

Figure 2. Illustration of the sagittal view of a human brain showing the two neurogenic niches: the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the dentate gyrus (DG) in the hippocampus. **(A)** Neural progenitor cells (NPCs) generated in the adult SVZ proliferate and follow a putative migration towards the striatum where they develop into mature neurons. **(B)** NPCs generated in the adult SGZ of the DG proliferate and reside into the granule cell layer where they mature into new granule neurons, extending projections into the CA3 region of the hippocampus.

inflammatory response mainly via glial activation, which subsequently leads to cell neurodegeneration [29]. These results support the hypothesis that neuroinflammatory changes are key pathological components of MDD as well as PD and AD, and highlight the potential clinical importance of the effects of cytokines on neurogenesis.

The effects of cytokines on neurogenesis

This section of the review is organised into six subsections, each one describing the effect of specific cytokines on cell generation: ILs (Table 1A–C), IFNs (Table 1D), and TNFs (Table 1E). In each subsection, we first describe the studies that assessed adult neurogenesis, using either human cells (from the DG) or rodent cells (from the DG or SVZ). Second, we report those studies that investigated fetal developmental neurogenesis, using either human or rodent cells taken from other brain regions. In addition, if available, we discuss the molecular mechanisms underlying the described effects. Given that we reviewed articles using different NPC types from different donor tissue and species, in Table 1 we have also highlighted the different neurogenesis markers used within each study, and Box 1 provides further insight into the role of markers for the detection of NPCs during the phase of proliferation and differentiation. Table 2 gives an overview of the findings, and Box 2 discusses their relevance for *in vivo* brain function.

IL-1α and IL-1β

IL-1α increases neurogenesis *in vitro* whereas, in most studies, IL-1β reduces NPC proliferation and neuronal differentiation, and enhances gliogenesis (Table 1A). This is different from *in vivo* studies, where evidence suggests that both IL-1α and IL-1β have inhibitory influence on hippocampal neurogenesis upon treatment [36]. However, this discrepancy between *in vitro* and *in vivo* studies may be partly explained by the different brain cells used *in vitro*, because IL-1α has a stimulatory effect in mesencephalic cells (in the only *in vitro* study) [37], while IL-1β has stimulatory effects in mesencephalic cells [37] but inhibitory effects in hippocampal cells [38,39].

IL-1β decreased proliferation and neurogenesis in rat adult DG NPCs, whereas co-treatment with IL-1 receptor antagonist (ra) prevented the negative effect of IL-1β on cell proliferation [40]. Likewise, IL-1β reduced proliferation and differentiation of rat neonatal DG NPCs into serotonergic (5-hydroxytryptamine; 5-HT) neurons. Accordingly, treatment with IL-1ra blocked the inhibiting effect of IL-1β on

Table 1. Studies examining the effect of inflammatory cytokines on cell proliferation, gliogenesis, neurogenesis, cell migration, and apoptosis[a,b]

Inflammatory challenge	Cell type	Markers for:					Findings					Refs
		Proliferation	Gliogenesis	Neurogenesis	Cell migration	Apoptosis	Proliferation	Gliogenesis	Neurogenesis	Cell migration	Apoptosis	
A. IL-1α and IL-1β												
IL-1β	Human fetal HNPCs		GFAP	β-III-tubulin				↑	↓			[43]
	Human fetal HNPCs	BrdU, Ki-67		MAP-2, DCX			↑		↓			[38]
	Rat fetal HNPCs	Measurement of neurosphere diameter and volume	GFAP	β-III-tubulin		CASP-3	↓	↑	↓		=	[39]
IL-1α	Rat fetal mesencephalic NPCs			TH					↑*			[37]
IL-1β				TH					↑*			
IL-1β	Rat fetal HNPCs	[^{3}H] thymidine				FITC-labeled annexin V	↓				↓	[50]
IL-1βra		[^{3}H] thymidine				FITC-labeled annexin V	↑				↑	
IL-1β	Rat fetal HNPCs	BrdU					↓					[49]
IL-1β	Rat neonatal DG NPCs	BrdU		MAP-2, 5-HT			↓		↓**			[41]
IL-1ra				MAP-2, 5-HT					↑**			
IL-1β	Rat adult DG NPCs	BrdU				TUNEL	↓				=	[40]
IL-1ra	Rat adult DG NPCs	BrdU		DCX			↓		↓			[42]
Co-treatment with IL-1ra		BrdU					↑					
LPS-MDM-derived IL-1β***	Human fetal cortical NPCs	[^{3}H] thymidine	GFAP	β-III-tubulin			↑	↑	↓			[51]
Pretreatment with IL-1ra***		[^{3}H] thymidine					=					
B. IL-6												
Human-IL-6	Human fetal STR NPCs, human fetal HNPCs		GFAP, GalC	β-III-tubulin				=	↑			[59]
Rat IL-6			GFAP, GalC	β-III-tubulin				=	=			
Neutralisation of IL-6	Human fetal cortical NPCs		GFAP					↑				[60]
Neutralisation of LIF			GFAP					↓				
LIF	Rat fetal mesencephalic NPCs			TH					↑*			[37]
IL-6	Rat adult DG NPCs	BrdU	GFAP, NG-2	β-III-tubulin, DCX		TUNEL	=	=	↓		↑	[56]
Neutralisation of IL-6				β-III-tubulin					↑			
IL-6	Rat adult DG NPCs		GFAP	β-III-tubulin				=	↑			[55]
H-IL-6	Mouse fetal SVZ NPCs	BrdU	GFAP, MBP	β-III-tubulin			↓	↑	↑			[53]
IL-6	Mouse adult DG NPCs		GFAP	β-III-tubulin				↑	↓			[54]

Microglial-derived IL-6 and LIF***	Rat fetal SVZ NPCs		GFAP					↑				[61]
Microglial-derived CNTF***			GFAP					=				
C. IL-4, IL-10, and IL-11												
IL-11	Rat fetal mesencephalic NPCs			TH					↑*			[37]
IL-10	Mice adult SVZ NPCs	Ki-67	NG-2	β-III-tubulin			=	=	↓			[65]
IL-4-TM****	Mouse fetal cortical NPCs	BrdU	GFAP	MAP-2			↓	↑	↑		↓	[63]
IL-10-TM****		BrdU	GFAP	MAP-2			↑	=	=		↓	
IL-4-TM****	Mouse adult SVZ NPCs		NG-2	DCX				↑	↑			[67]
D. IFN-α and IFN-γ												
Human-IFN-γ, rats-IFN-γ	Human fetal STR NPCs		GFAP, GalC	β-III-tubulin				=	↑			[59]
Human-IFN γ, rats-IFN-γ	Human fetal HNPCs		GFAP, GalC	β-III-tubulin				↑	=			
IFN-γ	Rat fetal HYNPCs		GFAP	β-III-tubulin				↑	↑			[77]
IFN-γ	Rat fetal STR NPCs	BrdU				TUNEL	↓				↑	[75]
IFN-α	Mouse adult DG NPCs	Total number of neurospheres					↓					[71]
IFN-α	$Cr2^{-/-}$ mice DG NPCs	Total number of neurospheres					=					
IFN-γ	Mouse fetal HYNPCs	BrdU	GFAP	β-III-tubulin			↓	↑	↑			[76]
IFN-γ+TNF-α	Mouse neonatal SVZ NPCs		GFAP	NeuN	EGFP expressed under XYZ protein	TUNEL		↑	=	↑	↑	[72]
IFN-γ –TM****	Mouse adult SVZ NPCs		NG-2	DCX				↑	↑			[67]
E. TNF-α												
TNF-α	Human fetal HNPCs		GFAP	β-III-tubulin				↑	↓			[38]
Human-TNF-α, rats-TNF-α	Human fetal STR NPCs, fetal HNPCs		GFAP, GalC	β-III-tubulin		CASP-3		↑	↓		↑	[59]
TNF-α	Human fetal cortical NPCs		GFAP	β-III-tubulin				↑	↓			[51]
	Rat adult SVZ NPCs	BrdU	GFAP	β-III-tubulin		TUNEL	↑	=	=		↑	[80]
			GFAP	β-III-tubulin				↑	↓			[60]
	Rat adult DG NPCs			β-III-tubulin, DCX					↓			[56]
	Mouse neonatal SVZ NPCs			β-III-tubulin					↑			[79]
TNF-α + INF-ϒ	Mouse neonatal SVZ NPCs		GFAP	NeuN	EGFP	TUNEL		↑	=	↑	↑	[72]
TNF-α (1 ng/ml mouse or human recombinant)	Mouse neonatal SVZ NPCs	BrdU		NeuN			↑		↑			
TNF-α (10 and 100 ng/ml mouse or human recombinant)						TUNEL					↑	[81]

Table 1 (*Continued*)

Inflammatory challenge	Cell type	Markers for:			Findings				Refs
		Proliferation	Gliogenesis	Neurogenesis	Cell migration	Apoptosis	Proliferation	Gliogenesis	Neurogenesis	Cell migration	Apoptosis	
MDM-derived TNF-α***	Human fetal cortical NPCs	[^{3}H] thymidine	GFAP	β-III-tubulin			↑	↑	↓			[51]
Pretreatment with TNF-αR1, TNF-αR2***		[^{3}H] thymidine					↓					

[a] Abbreviations: β-III-tubulin, class III β-tubulin; BrdU, bromodeoxyuridine; CASP-3, caspase-3; DCX, doublecortin; EGFP, enhanced GFP; FITC, fluorescein isothiocyanate; GalC, galactocerebroside; GFAP, glial fibrillary acidic protein; 5-HT, 5-hydroxytryptamine; MAP-2, microtubule-associated protein-2; MBP, myelin basic protein; NeuN, neuronal nuclei; NG-2, new glue-2; TH, tyrosine hydroxylase; TM, treated microglia; TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labelling.

Legend: [b] ↑ increase; ↓ decrease; = no difference; * dopaminergic (DA) neurons; ** serotonergic (5-HT) neurons; *** conditionated media experiments; **** co-culture, empty cell denotes no data.

Box 1. Molecular markers for cell proliferation and differentiation

Distinct molecular markers have been used *in vitro* to detect NPCs during the phase of proliferation or differentiation into neurons, oligodendrocytes, and astrocytes [106]. Most of the current markers used for *in vitro* NSCs and/or NPCs and derived differentiated cells have been drawn from *in vivo* data. Namely, during development progenitors have been labelled with SRY-related HMG box-2 transcription factor (SOX-2) and nestin [107,108]. In particular, SOX-2 is a member of the SOX family of transcription factors [108], whereas nestin is a type VI intermediate filament protein [107]. Both markers detect Type 1 (quiescent radial NSCs, GFAP+ SOX-2+) hippocampal cells [3]. As the CNS develops, these markers become increasingly restricted until adulthood, where they are only expressed in adult NSCs [109]. In the DG, certain subtypes of adult NPC also express the GFAP, specifically Type 1 (quiescent radial NSCs, GFAP+ SOX-2+) hippocampal cells and Type B (quiescent radial adult NSCs, GFAP+) SVZ cells [3]. However, such markers cannot be used solely because SOX-2 can label both subtypes of stem cell and glial cell (astrocytes) [110], suggesting the need to use a combination of positive markers. Given that NPCs can self-renew, another useful marker is the synthetic nucleoside BrdU, because it indicates cell proliferation. Specifically, BrdU is a synthetic nucleoside that can be easily incorporated into the newly synthesized DNA of replicating cells [111]. Furthermore, because BrdU labelling is an indication that a cell has recently been dividing, when colabelled with a mature marker of a specific CNS cell type, it will reveal the fate of the newborn cells (namely neurogenesis when double labelled with a neuronal marker) [100]. Finally, upon differentiation, specific markers for neurogenesis and gliogenesis are expressed. In particular, the neuronal migration protein DCX is detected in immature neurons, and is a marker for the early stages of neurogenesis [98]. Contrarily, GFAP is expressed in mature astrocytes and has become a prototypical marker for astrogliogenesis [112].

differentiation [41]. IL-1β reduced proliferation as well as cell apoptosis also in rat adult DG NPCs [42]. Interestingly, co-incubation with an inhibitor of nuclear factor (NF)-kB blocked the antiproliferative effect of IL-1β [42].

Recombinant IL-1β decreased neurogenesis, but enhanced astrogliogenesis in human fetal hippocampal (H) NPCs [38,43] and in rat fetal HNPCs, without affecting cell apoptosis [39]. Conversely, IL-1α and IL-1β enhanced differentiation of rat fetal mesencephalic NPCs into dopaminergic (DA) neurons [37]. These apparent contrasting findings are partially supported by results *in vivo*. Evidence shows that IL-1 (α + β) promotes re-innervation and differentiation of DA neurons in the STR and mesencephalon [44,45], whereas both IL-1α and IL-1β inhibit neurogenesis in the hippocampus [36].

Finally, despite decreasing neuronal differentiation, IL-1β promoted cell proliferation in human fetal HNPCs [43]. Previous findings have reported different effects on proliferation upon IL-1β treatment. For example, repeated but not single intrahippocampal injection with IL-1β enhanced proliferation, whereas there were no changes if systemically administered [46]. Another study showed an increase in proliferation in young but not older mice upon IL-1α treatment, which acts through the same IL-1r as IL-1β [47]. However, other pharmacological compounds have also been shown to have differential effects on proliferation versus differentiation, for example when cells are treated with antidepressants [48].

The inhibitory effects of IL-1β on neurogenesis in human fetal HNPCs are mediated, at least in part, by activation of

Table 2. Summary of the main results on the effect of different cytokines on characterisation of progenitors and newborn cells by assay and expression of specific markers for cell proliferation, neurogenesis, and gliogenesis[a,b]

Cytokine	Marker expression										
				Immature neurons		Mature neurons		Mature oligodendrocytes		Immature oligodendrocytes	Mature astrocytes
	BrdU	Ki-67	[3H] thymidine	β-III-tubulin	DCX	MAP-2	NeuN	NG-2	GalC	MBP	GFAP
	Proliferation			Neurogenesis				Gliogenesis			
IL-1α	*			↑				*			
IL-1β	↓			↓				↑			
IL-4	↓			↑				↑			
IL-6	↓=			↑				=			
IL-10	↑=			↓=				=			
IL-11	*			↑				*			
INF-α	↓			*				*			
INF-γ	↓			↑				↑			
TNF-α	↑			↓				↑			

[a] Abbreviations: GalC, galactocerebroside; MAP-2, microtubule-associated protein-2; MBP, myelin basic protein; NeuN, neuronal nuclei; NG-2, new glue-2; BrdU, bromodeoxyuridine; β-III-tubulin, class III β-tubulin; DCX, doublecortin; GFAP, glial fibrillary acidic protein.
Legend: [b] ↑ increase; ↓ decrease; = no difference; * no studies.

Box 2. The relevance of inflammation for neurogenesis: the translational link between *in vitro* and *in vivo* data

The inflammatory process in the neurogenic regions of the brain significantly alters the microenvironment of the NPCs and consequently influences the fate of these cells [9]. *In vitro* evidence suggests that hyperactivation of the immune response impairs progenitor survival and differentiation. However, some of the inflammatory products, including cytokines, are proneurogenic and, therefore, promote recovery [10]. Due to the complex mechanisms by which the immune system differently determines the final developmental fate of the NPCs, further *in vivo* evidence is needed to better clarify *in vitro* data. Particular attention should be given to the dialogue between innate immunity (i.e., natural killer cells and macrophages) and adaptive immunity (i.e., cytokines and lymphocytes), and the way they differently interact and/or stimulate one another in the context of acute or chronic neurodegeneration [113]. This might provide further insight into how the two types of immunity contribute to the severity of these conditions. Moreover, different brain insults, including stressors, diversely activate the immune system, leading to either a potentiation or a reduction in neurogenesis [58]. Therefore, understanding the inflammatory pathways by which different challenges modulate neurogenesis will contribute to the development of novel therapeutic targets specific for the type of insult [10]. While *in vitro* findings help to identify the molecular and cellular mechanisms underlying the effects of inflammation on neurogenesis, clinical studies provide further insight into the role of inflammation in the behavioural and cognitive impairments seen in patients with depression and/or neurodegenerative conditions. Therefore, future research should focus on immune products, such as cytokines, especially on those for which sufficient evidence has been accumulated on their molecular and cellular effects on mood and cognitive functions, ultimately allowing the possible translational link between *in vitro* data and clinical applications to be determined [18]. Understanding the mechanisms underlying the association between inflammation and neurogenesis will have profound implications for the pathogenesis and treatment of neurodegenerative and neuropsychiatric disorders.

the kynurenine pathways and the production of neurotoxic tryptophan metabolites [43]. In rat fetal mesencephalic NPCs, activation of phospho-p38 mitogen-activated protein kinases (MAPK) reversed the negative effect of IL-1β on cell proliferation [39]. In rat fetal HNPCs, IL-1β reduced proliferation and apoptosis via phosphorylation of the stress-activated protein kinase (SAPK)/c-Jun N-terminal kinase (JNK). Indeed, SAPK/JNK inhibitor or IL-1ra reversed the inhibition of cell proliferation and apoptosis [49]. IL-1β-induced impaired proliferation in rat fetal HNPCs was partly mediated by activation of the enzyme glycogen synthase kinase-3β (GSK-3β) and subsequent reduction of the protein orphan nuclear receptor tailless homolog (TLX) expression [50]. In fact, GSK-3β inhibition ameliorated the effects of IL-1β on TLX expression in both proliferating and differentiating cells [50]. In human fetal HNPCs, the inhibitory effects of IL-1β on neurogenesis were mediated, at least in part, by activation of signal transducer and activator of transcription 3 (STAT3) pathway [38].

IL-1β induced by lipopolysaccharide-activated human monocyte-derived macrophages. To our knowledge, one study examined the role of IL-1β induced by lipopolysaccharide (LPS)-activated human monocyte-derived macrophages (MDM) using conditioned media (CM) experiments. IL-1β from LPS-MCM stimulated human fetal cortical NPCs proliferation, although pretreatment with

IL-1ra did not block this effect. The culture also decreased neurogenesis but enhanced astrogliogenesis [51]. Results suggest a direct involvement of MCM, but not of IL-1β, in cell proliferation. In fact, it is possible that MCM alone induced the production of other factors, such as cyclin-dependent kinases (CDKs) [51], which are well known to regulate the NPC cycle and positively influence cell proliferation [52].

IL-6

In most studies, IL-6 reduces (or does not affect) proliferation and gliogenesis, while increases neuronal differentiation (Table 1B), although some of the molecular mechanisms activated by IL-6 in the brain depend on the type of brain cells and on cell age [53,54].

IL-6 promoted neurogenesis in rat adult DG NPCs but did not cause any considerable modifications in astrogliogenesis [55]. By contrast, IL-6 decreased neurogenesis and increased apoptosis in rat adult DG NPCs, without affecting proliferation and gliogenesis, and a blocking antibody to IL-6 restored neurogenesis [56]. Indeed, IL-6 may inhibit neurogenesis by reducing soluble factors, such as the protein sonic hedgehog (SHH), which is known to promote neuronal differentiation [57,58]. Finally, IL-6 inhibited neurogenesis also in mice adult DG NPCs; however, it enhanced astrogliogenesis in this experimental setting [54]; the different types of cell culture, particularly if from rat or mouse, could account for these discrepant results on astrogliogenesis [59].

In contrast to rat-IL-6, human-IL-6 increased neurogenesis but not gliogenesis in either human fetal STR NPCs or in human fetal HNPCs [59]. Similarly, hyper-IL-6 (H-IL-6; a fusion of IL-6 and the soluble IL-6-receptor, sIL-6R) decreased cell proliferation and increased neurogenesis, but did not have any effect on gliogenesis in mouse fetal SVZ NSCs [53]. In addition, neutralising antibody for the leukaemia inhibitory factor (LIF), one of the IL-6 family cytokines, but not for IL-6, reduced astrogliogenesis in human fetal cortical NPCs [60]. LIF also induced differentiation of rat fetal mesencephalic NPCs into DA neurons [37].

In terms of mechanisms, in mouse adult DG NPCs, IL-6 decreased neurogenesis via activation of cyclin-dependent kinase inhibitor 1A (p21) [54], whereas H-IL-6 increased neurogenesis in mouse fetal SVZ NSCs via activation of the MAPK/cAMP response element-binding protein (CREB) cascade [53].

Microglial-derived IL-6-family cytokines. To our knowledge, one study examined the role of microglial-derived IL-6, LIF, and the ciliary neurotrophic factor (CNTF) on cell proliferation and differentiation, using CM experiments. Microglial-derived IL-6 CM and LIF CM, but not CNTF CM, promoted astrogliogenesis in rat fetal SVZ NPCs [61]. Previous *in vivo* evidence suggests that both IL-6 and LIF induce gliogenesis via inhibition of neuronal differentiation. Indeed, IL-6 and LIF receptor complex are involved in the activation of the transcription factor hairy-enhancer-of-split 1 (HES-1), which in turns negatively regulates neurogenesis and induces gliogenesis [62]. However, this hypothesis cannot be confirmed here because the authors did not investigate the neuronal fate of the NPCs.

IL-4, IL-10, and IL-11

There are fewer studies on IL-4, IL-10, and IL-11, and not all aspects of the neurogenic process have been examined with all of them. However, some main findings have been replicated in most studies: IL-4 reduces proliferation and increases both neuronal and glial differentiation; IL-10 has opposite effects, that is, increases (or does not affect) proliferation and reduces (or does not affect) both neuronal and glial differentiation; and IL-11 increases neuronal differentiation (Table 1C). The different results reported for IL-4 and IL-10 might depend on the different modalities of cell treatment: cytokine-treated NPCs (with IL-10) or cytokine-treated microglia (TM) (with IL-4 and Il-10), co-incubated with NPCs [63]. However, in one study, IL-4-and IL-10-TM had different effects on both proliferation and differentiation [63], suggesting that not only the presence of microglia *per se*, but also the type of microglia activator (IL-4 or IL-10) influence cell fate in different ways [64].

IL-10 had no effect on both proliferation and oligodendrogenesis [65]. However, treatment with IL-10 in mouse adult SVZ NPCs impaired neurogenesis [65]. In fact, absence of IL-10 *in vivo* induced neuronal differentiation of SVZ NPCs and increased incorporation of new neurons in the adult OB [65].

IL-11 promoted differentiation of rat fetal mesencephalic NPCs into DA neurons [37]; however, there are no studies using animal models, which prevents the complete understanding of the role of this cytokine for neurogenesis [66].

IL-4-and IL-10-TM. To our knowledge, two studies examined the role of IL-4-and IL-10-TM on cell generation. Indeed, co-culture of mice adult SVZ NPCs with IL-4-TM, but not with LPS-TM, induced neurogenesis and oligodendrogenesis [67]. These results suggest that specific stimuli (IL-4 or LPS) produce different types of activated microglia, ultimately determining different cell fates. In fact, here it is possible that quiescent microglia, residing in the vicinity of the proliferating NPCs, become activated by IL-4, but not by LPS to support neurogenesis, via putative production of neurotrophic factors [68,69].

Co-culture of mouse fetal cortical NPCs with IL-4-or IL-10-TM reduced or enhanced proliferation, respectively. Furthermore, in contrast to IL-10-, IL-4-TM increased neurogenesis and astrogliogenesis [63]. This again stresses the importance of the type of inflammatory challenge (IL-4 or IL-10) in influencing microglia activation [64]. Most importantly, co-culture with microglia only showed an antiapoptotic effect, which was strengthened mainly by IL-4-TM [63]. Therefore, it is possible that (IL-4-treated) microglia were either antiapoptotic or prophagocytic, which might in part explain the proneurogenic output [70].

IFN-α and IFN-γ

In most studies, both IFN-α and IFN-γ reduce proliferation, and IFN-γ increases both neuronal and glial differentiation (Table 1D). These results are relatively consistent among the studies reviewed; however, in one case, contradictory findings might be due to the use of cell

cultures from specific brain regions, with distinct proliferating and differentiating properties [59].

IFN-α, a ligand of the complement receptor 2 (CR2), impaired proliferation in mice adult DG NPCs. Accordingly, IFN-α treatment on mice lacking Cr2 ($Cr2^{-/-}$) did not affect proliferation [71]. In addition, combination treatment with IFN-γ +TNF-α caused no changes in neurogenesis in mice neonatal SVZ NPCs [72], suggesting that, although IFN-γ primarily shows proneurogenic properties, TNF-α counterbalanced the effects of IFN-γ by inhibiting neurogenesis [73]. However, IFN-γ+TNF-α enhanced astrogliogenesis, cell migration, and apoptosis [72].

Human IFN-γ or rat IFN-γ enhanced neurogenesis, but not gliogenesis in human fetal STR NPCs. By contrast, when conducting the same experiment in human fetal HNPCs, both treatments increased gliogenesis, but did not alter neurogenesis [59]. These differences can partially be explained by region-specific characteristics. In fact, the hippocampus expresses higher levels of cytokines receptors compared with the STR [74]. Here, human HNPCs had a threefold higher level of IFN-γ-r compared with human STR NPCs [59], suggesting that the diverse receptor levels affected the results. IFN-γ also reduced proliferation and enhanced apoptosis in rat fetal STR NPCs [75]. Likewise, IFN-γ impaired mouse fetal hypothalamic (HY) NPCs proliferation, while it increased neurogenesis and astrogliogenesis. Of note, in one study, numerous cells co-expressed beta-III tubulin (β-III-tubulin) and the glial fibrillary acid protein (GFAP), but electrophysiological results showed that cells were functionally distinct from mature neurons as well as astrocytes, suggesting IFN-γ as a promoter of the dysregulated NPC-derived cellular phenotype [76]. Results were replicated, confirming a phenotypic dysregulation (β-III-tubulin-GFAP co-expression) induced by IFN-γ in rat fetal HYNPCs [77].

In the aforementioned studies examining phenotypic dysregulation, genes, such as *STAT1* and proteins, including SHH, were upregulated by IFN-γ [76,77]. Likewise, previous experiments revealed that STAT1 and STAT2 signals are the major pathways for IFN-γ-mediated functions *in vivo* [78].

IFN-γ-TM. To our knowledge, one study examined the effect of IFN-γ-TM on cell differentiation. Co-culture of 20 ng/ml IFN-γ-TM with mouse adult SVZ NPCs induced both neuronal and glia differentiation [67]. Indeed, previous data demonstrated that the effect of IFN-γ in conferring a neuroprotective phenotype on microglia is mainly restricted to a low range of concentrations (1–50 ng/ml) [68], which in part explains the positive results found here upon IFN-γ treatment [67].

TNF-α

In most studies, TNF-α increases proliferation and gliogenesis, but reduces neurogenesis (Table 1E). Few studies reported contradictory results, which might be due to the use of diverse types of cell culture, particularly mouse [79] or rat samples [80].

Treatment with TNF-α+INF-γ had no effect on neurogenesis; however, it increased astrogliogenesis, cell migration, and apoptosis in mouse neonatal SVZ NPCs (see IFN-γ subsection) [72]. Conversely, TNF-α reduced neurogenesis in rat adult DG NPCs [56] and promoted apoptosis in rat adult SVZ NPCs [80]. TNF-α increased also proliferation, but it did not affect neurogenesis and astrogliogenesis [80]. By contrast, TNF-α increased neuronal differentiation in mouse neonatal SVZ NPCs [79]. Likewise, a low dosage of TNF-α (1 ng/ml mouse or human recombinant) increased proliferation and neurogenesis in mouse neonatal SVZ NPCs, whereas a higher dosage (10 and 100 ng/ml mouse or human recombinant) induced apoptosis [81]. In addition to dosage-related difference, the effects of TNF-α on neurogenesis also have species differences. Indeed, although TNF-α exerts neuroprotective properties in rat hippocampal neurons [82], it is toxic to mouse-derived neurospheres, because it interferes with their formation [83].

Human TNF-α or rat TNF-α impaired neurogenesis in both human fetal STR NPCs and HNPCs, whereas they promoted gliogenesis and apoptosis [59]. Likewise, TNF-α decreased neurogenesis but enhanced astrogliogenesis in human fetal HNPCs [38] and in rat adult SVZ NPCs [60]. TNF-α increased astrogliogenesis, but inhibited neurogenesis also in human fetal cortical NPCs [51].

In mouse neonatal SVZ NPCs, activation of NF-kB signalling increased TNF-α-induced neuronal differentiation; in fact, treatment with an NF-kB-specific inhibitor IkB kinase (IKKβ)-V prevented this effect [79]. Conversely, TNF-α reduced neurogenesis in human fetal HNPCs via activation of STAT-3 pathway [38].

TNF-α induced by LPS-MDM. To our knowledge, one study has examined the role of TNF-α induced by LPS-MDM on cell generation, using CM experiments. The culture enhanced cell proliferation and astrogliogenesis, but decreased neurogenesis in human fetal cortical NPCs [51]. Accordingly, pretreatment with TNF-α receptors R1 and R2 (TNF-R1R2) reduced the effect of TNF-α on proliferation [51]. Although TNF-α involvement in modulating cell proliferation was further confirmed by a dose-dependent increase in S-phase (via Cyclin D1 detection) [51], MCM may have also had a role in determining cell fate. In fact, here TNF-α in MCM upregulated the transcription factor HES-1, previously known for its antineurogenic properties [62], suggesting that TNF-α in MCM directly contributed to the impaired neuronal differentiation.

Factors regulating the effects of cytokines on neurogenesis

This review highlights the important role of cytokines as major regulators of cell proliferation and differentiation. In summary: IL-1α promotes neurogenesis, whereas IL-1β decreases proliferation and neurogenesis, and increases gliogenesis; IL-4 decreases cell proliferation, while IL-10 has stimulating or no effects; IL-4 and IL-11 enhance neurogenesis and/or gliogenesis, whereas IL-10 decreases (or has no effect) on cell differentiation; IL-6, IFN-α, and IFN-γ all reduce (or have no effect) on proliferation, whereas only IL-6 and IFN-γ increase (or have no effect) on both neuronal differentiation and gliogenesis; and, finally, TNF-α increases proliferation and gliogenesis, but inhibits neurogenesis. Overall, the evidence indicates that inflammatory cytokines have both positive and negative regulatory

roles in all processes integral to neurogenesis, including NSC proliferation, fate specification, young neuron migration, and neuronal maturation. However, although we have attempted to draw common conclusions from the different studies, there are inevitably several methodological issues that might have contributed to the many contrasting results.

First and foremost, the use of different types of cell culture, particularly human or animal cells, is an important aspect to be taken into consideration. Studies reviewed here provided evidence for divergent responses between human and animal cells after exposure to specific cytokines, including IL-1β [37,39–42,49,50], IFN-γ [67,76,77], and TNF-α [72,79–81]. In fact, while these modulators induce a striking dysregulation in neuronal formation in animals, they have diverse effects in human NSCs [78,84]. One possible explanation might be due to a qualitatively different activation of molecular downstream signals in rat versus human cells [85–87]. For example, IL-1β has an important role in activating TGF β, which has been considered one of the main mediators of NPC proliferation [88]. In human cells, IL-1β stimulates the production of TGF-β mainly in astrocytes [89], whereas in rats, IL-1β enhances TGF-β formation mainly in oligodendrocytes [89], suggesting specific molecular effects of IL-1β on different cell types [90]. Likewise, treatment with IFN-γ of murine NSCs, but not of human NSCs, significantly upregulates SHH, which in turn has an important role in influencing the pattern of the CNS during embryonic growth, via expression of a unique combination of transcription factors that leads to neuronal cell fate differentiation [91]. TNF-α also has species-dependent effects. Using a rat stroke model with TNF-α antibody, one study reported a decrease in striatal and hippocampal neurons via TNF-R1, proposing TNF-α as a promoter for survival of newly generated neurons [92]; however, other evidence demonstrates the involvement of TNF-α in the activation of inflammatory mediators in human NPCs that are known to contribute to the development of neurodegenerative disorders, including chemokine C-X-C motif ligand 2 (CXCL2), CXCL10, and CXCL12 [93,94]. Hence, cytokine-induced specific signalling pathways, differently activated between human and rodent models, may lead to qualitative differences in the development of cellular phenotypes [90]. Future research is needed to clarify whether and how effects of cytokines on neurogenesis are different in humans and rodents, and whether this is due to the activation of diverse molecular downstream signals. Indeed, new *in vivo* data, comparing animal and human samples, will allow for a better understanding and a more accurate interpretation of the *in vitro* findings (Box 2).

Contradictory results might also be due to the use of cell cultures derived from diverse brain regions, with specific proliferating and differentiating properties [95]. Studies reviewed here showed divergent reactions in distinct brain cells after exposure to the same cytokines, regardless of whether they assessed adult or fetal developmental neurogenesis. For example, there is evidence that IL-1β induces a reduction in cell proliferation and neurogenesis in the SGZ [87], causing a shift in cell lineage from neuronal to astroglial [96]; and that it has the same effect on proliferating cells in the SVZ, but in this case it prevents lineage progression, leaving NSCs undifferentiated [96]. Treatment of cultured astrocytes with H-IL-6 induces region-specific morphological changes of astrocytes from typical stellate-to fibrous-like cells only in cortex-and hippocampus-derived astroglia, while astrocytes derived from other brain regions, such as STR or cerebellum, fail to respond to H-IL-6 [97]. TNF-α has pro- and antiproliferative and neurogenic properties in SVZ cells and meningeal cells, respectively [73]. Again, future studies should clarify the influence of distinct cytokines on specific cell types, derived from diverse brain regions, and the molecular mechanisms underlying these specific responses.

Finally, contrasting findings might also be attributed to the variability in the expression of distinct molecular markers in different experimental settings. While most studies labelled proliferating cells using bromodeoxyuridine (BrdU) [98], this simple procedure has several disadvantages. For example, high or nonsaturating doses of BrdU might be toxic, and can cause inconsistent or partial labelling of proliferating cells [99]. Furthermore, specific treatments, for example with glucocorticoids, might also influence the bioavailability of BrdU [100]. Doublecortin (DCX) is a reliable marker to identify neuronal differentiation [98], because it does not require *in vivo* labelling of proliferating cells [100]. DCX is widely expressed in brain cells, including in morphologically differentiated neurons, such as the neurons in the cortex, STR, and corpus callosum [101]. However, DCX also has disadvantages because it cannot provide accurate information about long-term survival of newly generated neurons (i.e., beyond 30 days) [102]. DCX is highly expressed during the initial phase of cell differentiation (when neuroblasts are formed), reaches its peak during the second week, and starts to downregulate before neuronal maturation [98]. In fact, there is evidence that cells in adult neurogenic regions lose their ability to express DCX, and instead markers for mature glia (GFAP) and neurons (β-III-tubulin) are detected [100]. Indeed, GFAP is used for labelling mature astrocytes [100], and is expressed in distinct subpopulation of cells that have similar multipotent properties as those found in NSCs [103]. However, GFAP is sometimes associated with unusual β-III-tubulin co-expression, even if cells are functionally different from astrocytes as well as neurons, raising concerns about its validity and reliability as the main marker of gliogenesis [104]. There are also still many uncertainties on the role of β-III-tubulin as an effective marker for neurogenesis [104]: although detection of β-III-tubulin in differentiated NSCs is usually interpreted as enhanced neurogenesis [105], sometimes neurons expressing this marker appear to be dysregulated in terms of functional and molecular properties [104]. Hence, the debate on the validity and the efficacy of such molecular markers is still open. Future studies should identify new cell markers that could track accurately the different stages of neurogenesis, starting from the early stage of neuronal determination, and ending as differentiating neurons reach maturation [100].

Concluding remarks

Despite the limitations of the available literature, to our knowledge this is the first review summarising the role of

inflammatory cytokines on cell proliferation and differentiation, discussing *in vitro* human and animal studies. Overall, our findings confirm and extend evidence for inflammatory cytokines to have both positive and negative regulatory roles in all processes integral to neurogenesis, including NSC proliferation, fate specification, young neuron migration, and neuronal maturation, and thus in monitoring the normal functioning of the brain. Hence, this strengthens the notion that inflammation, particularly neuroinflammation, is relevant for the pathogenesis of neuropsychiatric and behavioural disorders, including neurodegenerative diseases and depression. We would further argue that the molecular mechanisms by which cytokines affect neurogenesis should be considered as therapeutic targets for these disorders. However, these molecular mechanisms are likely to be species specific and even brain area specific and, therefore, dissecting such mechanisms remains an important and clinically significant challenge.

Financial disclosures

The authors have obtained research funding from companies interested in the role of inflammation in neuropsychiatric disorders, such as Janssen, but the results described in this paper are unrelated to this funding.

Acknowledgements

The authors have received research funding from: the National Institute for Health Research Mental Health Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London (C.M.P. and P.A.Z.); Janssen Pharmaceutical NV/Janssen Pharmaceutical Companies of Jonhson&Jonhson (A.B., P.A.Z., S.T., and C.M.P.); the Medical Research Council (UK) MR/J002739/1 (A.B., P.A.Z., and C.M.P.); the Psychiatry Research Trust, UK, The Welton Foundation, The Alzheimer's Society, and the MRC (S.T.).

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