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Neurogenesis, Inflammation and Mental Health

Alessandra Borsini

Kristi M. Sawyer

Patricia A. Zunszain

Carmine M. Pariante

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Inflammation and Immunity in Depression

Introduction

Recent research into the pathology of mental health disorders has highlighted their association with altered patterns of neurogenesis in the brain. Neurogenesis is the process by which new neurons are formed from neural stem cells or progenitor cells¹. From here, it is possible for these new-born neurons to differentiate into specific cell subtypes. This process happens, for the most part, during foetal brain development, however, adult neurogenesis in humans also occurs in the hippocampus, where it is restricted to the subgranular zone (SGZ) of the dentate gyrus (DG), and in the subventricular zone (SVZ) of the lateral ventricles². Regulation of adult neurogenesis is thought to be involved in memory formation and cognition, as well as an adult's ability to cope with stressors, which is of particular relevance to the pathogenesis of depression.

Adult neurogenesis gives rise to two different types of neural stem cells: type 1 cells are radial glia-like cells, and type 2 cells are non-radial neural progenitor cells (NPCs)¹. NPCs are under constant stimulation to proliferate, migrate, differentiate and survive. However, pathological circumstances in the brain such as injury or infection can disrupt the usual pattern of proliferation, mainly through microglial activation and release of inflammatory mediators, such as cytokines, in the brain. Cytokines, as well as providing vital immune protection in the brain and clearing dead or damaged neurons, can also cause damage, ultimately leading to neuronal death².

Cytokines are low molecular weight proteins or glycoproteins which are produced by a number of different cell types, notably white blood cells, in response to an inflammatory stimulus³. There are various types of cytokines, including interleukins (ILs), so-called because they are secreted by leukocytes and act on other similar cell types. Other types of cytokines include interferons (IFNs), which act by activating natural killer cells and macrophages, and tumour necrosis factors (TNFs), which are involved in cell death. In addition, peripheral inflammation is associated with impairment of hippocampal-dependent forms of synaptic plasticity⁴, which may be relevant to cognitive impairment⁵.

Turning to neurogenesis, cytokines have recently been shown to regulate the proliferation, differentiation and neurogenesis of NPCs, with research focusing mainly on this mechanism in the context of psychiatric disorders, such as depression⁶. Indeed, recent research has shown that patients with depression show elevated levels of peripheral inflammatory markers⁷. A meta-analysis specifically showed upregulation of IL-1 β , IL-6 and TNF- α in both the serum and plasma of depressed patients⁸. These cytokines are involved in the mechanisms underlying a range of cognitive processes, such as mood and learning. For example, IL-1, in combination with TNF- α , has been associated with inhibition of the processes of memory consolidation and synaptic plasticity in the dentate gyrus of the hippocampus⁹.

To examine the effects of these cytokines further, this chapter, which comprises an update of the review published by Borsini *et al.*² will now take some cytokines individually in order to illustrate their effects in the brain. We begin, first, by describing experiments focused on adult neurogenesis, followed by those investigating neurogenesis in foetal-derived cells. In addition, where available, we provide information on downstream molecular mechanisms underlying the effects of cytokines in the brain.

IL-1 α and IL-1 β

IL-1 α and IL-1 β are part of the interleukin-1 family, which is responsible for the control of pro-inflammatory responses, triggered by tissue injury associated with pathogenic infection, or with release of danger-related molecules from damaged cells¹⁰.

Experiments *in vitro* have shown that IL-1 α increases neurogenesis¹¹, whereas in the majority of cases, IL-1 β reduces the proliferation and neurogenesis of NPCs, as well as enhancing gliogenesis^{12–14}.

The evidence for this mechanism is supported by experiments including co-treatment with an antagonist for the IL-1 receptor. One such study found that although IL-1 β reduced proliferation and neurogenesis in rat adult NPCs from the DG, co-treatment with an IL-1 receptor antagonist alleviated this negative effect¹⁵. Another study also showed that IL-1 β reduced the differentiation of rat neonatal NPCs into serotonergic neurons, and that this effect was blocked by co-treatment with an IL-1 receptor antagonist¹⁶. A similar abrogation of the inhibition by IL-1 β can be achieved by co-incubation with an inhibitor of NF- κ B¹⁷.

A similar pattern of effects has been observed in foetal NPCs. For example, treatment with recombinant IL-1 β reduces neurogenesis, but increased astroglialogenesis in both human foetal hippocampal NPCs (HNPCs)^{12,14} and rat foetal HNPCs¹³. However, another study also found that treatment with IL-1 α and IL-1 β promotes differentiation of rat foetal mesencephalic NPCs into dopaminergic (DAergic) neurons¹¹. These findings may be explained by *in vivo* evidence, which indicates that treatment with both can promote re-innervation and differentiation of DAergic neurons in the striatum (STR) and mesencephalon^{18,19}, but inhibit hippocampal neurogenesis²⁰.

Although IL-1 β has been shown to reduce neurogenesis, some evidence collected by our own lab suggests that it promotes proliferation of human foetal HNPCs¹⁴. However these findings are conflicted by other studies^{13,21}. One study showed that repeated, but not single, intra-hippocampal injections of IL-1 β enhances proliferation, and that these effects did not occur if administered systemically²². A different study reported that the increase in proliferation caused by IL-1 α treatment, which exerts its effects through the same IL-1 receptor, is only shown in young mice, but not old ones²³.

Regarding the mechanisms of these effects, IL-1 β -induced suppressive effects on neurogenesis in human foetal HNPCs seem to be partially mediated by activation of the kynurenine pathway, and the accumulation of tryptophan metabolites, which have neurotoxic properties¹⁴. Furthermore, as shown in rat foetal mesencephalic NPCs, where IL-1 β treatment reduces proliferation, activation of phospho-38 mitogen-activated protein kinases (MAPK) can reverse this inhibition¹³. In addition, in rat foetal HNPCs, the reduction in proliferation seemed to occur via phosphorylation of the stress-activated protein kinase (SAPK) and c-Jun N-terminal kinase (JNK) system. In support of this finding, an inhibitor of this kinase abrogated IL-1 β 's inhibiting effect on proliferation²¹. Indeed, another study using rat foetal HNPCs also found a mediating role of the glycogen synthase kinase 3 β enzyme, as when inhibited, the effects of IL-1 β were exaggerated. Activation of this enzyme is also associated with reduction in expression of the orphan nuclear receptor tailless homologue (TLX) protein. In fact, GSK-3 β inhibition ameliorated the effects of IL-1 β on TLX expression in both proliferating and differentiating cells²⁴. In human foetal HNPCs, the inhibitory effect of IL-1 β on neurogenesis seems to be mediated by activation of the STAT3 pathway¹².

IL-1 β induced by lipopolysaccharide (LPS)-activated human monocyte-derived macrophages (MDMs)

To our knowledge, just one study to date has examined the role of IL-1 β induced by LPS-MDM, in which they conduct conditioned media experiments. This study showed that IL-1 β derived from LPS-MDMs, stimulated the proliferation of human foetal cortical NPCs, however this action was not affected by pre-treatment with an IL-1 receptor antagonist, which may suggest that it was not occurring via an IL-1-dependent mechanism. In this treated culture, they also observed a reduction in neurogenesis, but increased astrogliogenesis²⁵. It is possible that these effects are caused by the independent action of MDMs, which can also stimulate production of other molecules such as cyclin-dependent kinases, which are known to regulate the cell cycle in NPCs, and can thus affect cell proliferation²⁶.

IL-6

Interleukin-6 has recently received much research attention, due to its association in humans with depressive disorders^{27,28}. The majority of pre-clinical experiments report that IL-6 either has no effect or reduces proliferation and gliogenesis, while increasing neuronal differentiation²⁹.

For example, one study found that IL-6 promoted neurogenesis in rat adult DG NPCs but did not cause any considerable modifications in astrogliogenesis³⁰. In contrast, another reported that 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 neurogenesis³¹.

Indeed, there is some evidence that IL-6 inhibits neurogenesis by reducing the expression of soluble molecules such as the Sonic Hedgehog protein (SHH)³⁰, a known promoter of neuronal differentiation. Furthermore, in humans, the administration of a neutralisation antibody against the leukaemia inhibitory factor (LIF), a member of the IL-6 family of cytokines, but not IL-6 itself, reduced astroglialogenesis in human foetal cortical NPCs³². In rats, this also induced differentiation of foetal mesencephalic NPCs into dopaminergic neurons¹¹.

In humans, IL-6 promotes an increase in neurogenesis, but has no effect on gliogenesis in both foetal NPCs and HNPs³³.

Furthermore, in mice, a fusion of IL-6 and the soluble IL-6 receptor named 'hyper IL-6' reduced cell proliferation and increases neurogenesis, although it had no effect on gliogenesis in foetal SVZ NSCs²⁹.

On a mechanistic level, evidence from mice has shown that IL-6 decreases neurogenesis in adult DG NPCs, through activation of cyclin-dependent kinase inhibitor 1A (or p21)³⁴. In contrast, hyper IL-6, as described above, increases neurogenesis in mouse foetal SVZ NSCs via activation of the MAPK and cAMP response element binding (CREB) protein cascade²⁹.

Microglial-derived IL-6-family cytokines

To date, we are aware of one study which investigated the role that IL-6 derived from microglia, as well as LIF and the ciliary neurotrophic factor (CNTF), plays in cell proliferation and differentiation. This study used conditioned media (CM) experiments. This study found that microglial-derived IL-6 CM and LIF CM, but not CNTF CM, enhanced astroglialogenesis in rat foetal SVZ NPCs³⁵. Evidence previously reported *in vivo* indicates that IL-6 and LIF exert their positive effects on gliogenesis via inhibition of neuronal differentiation. In fact, a receptor complex for IL-6 and LIF is involved in the activation of hairy-enhancer-of-split (HES-1), a transcription factor, which negatively regulates neurogenesis and induces gliogenesis³⁶. However, as the above authors did not investigate the fate of NPCs, this possibility cannot be confirmed.

IL-4, IL-10 and IL-11

Interleukins 4, 10 and 11, similarly to IL-6, show anti-inflammatory effects³⁷. There is less evidence relating to the effect of these cytokines on neuronal proliferation, differentiation and neurogenesis. However, those findings that have been reported are relatively consistent: IL-4 reduces neuronal proliferation, but increases neuronal and glial differentiation. Whereas, IL-10 seems to show the opposite effects, where it increases or has no effect on proliferation, and reduces or has no effect on differentiation of neurons or glia. IL-11 has been shown to increase neuronal differentiation³⁸⁻⁴⁰. Differing results for IL-4 and IL-10 may be attributed to differences in modalities of cell treatment: experiments with IL-10 used cytokine-treated

NPCs, whereas cytokine-treated microglia were used with both IL-4 and IL-10, which were then co-incubated with NPCs³⁸. In addition, this study found that IL-4 and IL-10- treated microglia (TM) had different effects on both proliferation and differentiation, suggesting that along with the presence or absence of microglia, the type of microglia activator may also play a role in shaping the fate of the cell⁴¹.

Another study reported that IL-10 does not affect proliferation or oligodendrogenesis. However, it did impair neurogenesis when used to treat murine adult SVZ NPCs. Indeed, this study found that lack of IL-10 *in vivo* induced neuronal differentiation of SVZ NPCs and increased the incorporation of new neurons into the adult olfactory bulb³⁹.

In contrast, IL-11 has been shown to promote the differentiation of rat foetal mesencephalic NPCs into DAergic neurons¹¹, however studies *in vivo* need to be completed to further our understanding of this mechanism⁴².

IL-4- and IL-10-Treated Microglia

This review has identified two studies which have examined the role of IL-4-TM and IL-10-TM on cell generation. The first of these used murine adult SNZ NPCs, and found that co-culture with IL-4-TM, but not with LPS-TM, induced both neurogenesis and oligodendrogenesis⁴⁰. This finding indicates that specific stimuli are capable of producing different types of activated microglia, which will ultimately impact the fate of the cell. Indeed, quiescent microglia, which reside around the proliferating NPCs, may become activated by IL-4, but not by LPS, in order to support neurogenesis by the production of neurotrophic factors^{43,44}.

The second of these studies³⁸ used murine foetal cortical NPCs, cultured with IL-4-TM and IL-10-TM. It found that IL-4-TM reduced proliferation of these cells, yet IL-10-TM increased proliferation. In addition to this, IL-4-TM increased neurogenesis and astrogliogenesis, while IL-10-TM showed the opposite pattern of effects. This finding provides further evidence that the type of inflammatory challenge is important in shaping cell fate. Indeed, co-culture with microglia alone in this experimental condition showed an anti-apoptotic effect, which was strengthened by IL-4-TM.

IFN- α and IFN- γ

Interferons are best-known for their anti-viral activity, but they are also involved in cell growth inhibition, immunosuppression, enhancement of natural killer cells function, and cell differentiation⁴⁵. In this section, we will focus on two types: interferons alpha (IFN- α) and gamma (IFN- γ).

In terms of cell proliferation, differentiation and neurogenesis, the literature regarding these two interferons is relatively consistent. Broadly, it shows that both IFN- α and IFN- γ reduce cell proliferation⁴⁶⁻⁴⁸. In addition, there is some evidence that IFN- γ increases neuronal and

glial differentiation^{33,49}. Although relatively consistent, one study which does report differences, identifies these differences in different cell types, in particular, human foetal STR NPCs versus human foetal HNPCs³³.

In mice, IFN- α acts via the complement receptor 2 (CR2), and shows impaired proliferation of adult DG NPCs. In fact, in knockout mice for CR2 (CR2 -/-), treatment with IFN- α does not affect proliferation⁴⁶, indicating that this effect of IFN- α treatment is mediated by this receptor.

Also in mice, IFN- γ treatment combined with TNF- α , does not affect neurogenesis in neonatal SVZ NPCs⁵⁰, which may suggest that although IFN- γ has independently been shown to be pro-neurogenic⁵¹, TNF α is capable of antagonising this effect. Furthermore, the combination of these two molecules has been shown to enhance cell migration, apoptosis and astriogliogenesis⁵⁰.

Turning to foetal cells, treatment with both rat and human IFN- γ enhances neurogenesis but has no effect on gliogenesis in human foetal STR NPCs. However there is perhaps cell-type specific influences on these effects, as in human foetal HNPCs, both human and rat IFN- γ increased gliogenesis, but interestingly had no effect on neurogenesis³³. These differences could be attributed to higher levels of cytokine receptors expressed in the hippocampus, when compared with the STR⁵². Indeed, in the above study, receptor expression for IFN- γ was three-fold higher in the hippocampal cells than those from the STR³³.

In rat foetal cells, IFN- γ treatment has been shown to reduce proliferation and enhance apoptosis of STR NPCs⁴⁸. A similar effect has been observed in murine foetal hypothalamic NPCs, as well as an increase in neurogenesis and astrogliogenesis⁴⁷.

Interestingly, one of the above-mentioned studies⁴⁷ reported the presence of cells which co-expressed beta-III-tubulin a marker of mature neuron and the glial-fibrillary acid protein (GFAP) a marker for astrocytes, but electrophysiological results showed that these cells were functionally distinct from mature neurons and astrocytes. This perhaps suggests that IFN- γ may cause a dysregulated phenotype of NPC-derived cells. These authors then replicated these findings and confirmed a phenotypic dysregulation, where cells co-expressed beta-III-tubulin and GFAP, which was induced by treatment with IFN- γ in rat foetal hypothalamic NPCs⁴⁹. On a mechanistic level, IFN- γ treatment has been associated with up-regulation of the STAT-1 gene and SHH protein^{47,49}. This role for STAT1 and STAT2 signalling in the effects of IFN- γ has also been replicated *in vivo*⁵³.

IFN- γ -TM

We are aware of one study which has looked at the effect of IFN- γ -TM on cell differentiation. Co-culture of IFN- γ -TM with murine adult SVZ NPCs causes increased differentiation of

neurons and glia⁴⁰. This study used an IFN- γ -TM concentration of 20 ng/mL, which relates to previous findings by the same group, showing that low concentrations (1 to 50 ng/mL) can have a neuroprotective effect on microglia⁴⁴.

TNF- α

In the majority of studies, TNF- α has a stimulatory effect on proliferation and gliogenesis, but inhibitory effect on neurogenesis^{12,25,32,33,50,54,55}. There are few contradictions to these findings, although one finds no effect on gliogenesis⁵⁴. Where discrepancies do exist, it seems that increased neurogenesis can be seen in murine neonatal SVZ NPCs, so this may be as a result of different cell type being cultured^{55,56}.

We have already discussed the anti-neurogenic effect of TNF- α above, in the context of its co-treatment with IFN- γ . In isolation, it has been shown to cause a reduction in neurogenesis in adult rat DG NPCs³¹. As well as this, in SVZ NPCs it increased proliferation and apoptosis, but had no effect on neurogenesis or astroglialogenesis⁵⁴.

In mice, TNF- α increases neuronal differentiation in neonatal SVZ NPCs⁵⁶. Indeed, even a low dose of TNF- α (1 ng/mL or mouse or human recombinant protein) has been shown to increase neuronal proliferation and neurogenesis in neonatal SVZ NPCs, however doses from 10 to 100 ng/mL induce apoptosis⁵⁷.

These conflicting data suggest that TNF- α exhibits species differences with regards to its effect on neurogenesis. In rats, it seems to show neuroprotective properties in the hippocampus⁵⁸, however is toxic to mouse-derived neurospheres, due to its interference with their formation⁵⁹.

In human foetal STR NPCs and HNPs, treatment with human or rat TNF- α inhibits neurogenesis, but stimulates gliogenesis and apoptosis³³. A similar pattern of impaired neurogenesis but enhanced astroglialogenesis was found in human foetal HNPs¹² and human foetal cortical NPCs²⁵.

When trying to understand the underlying mechanism for these effects, it has been found that, in murine neonatal SVZ NPCs, activation of NF- κ B signalling can increase the neuronal differentiation induced by TNF- α treatment. Indeed, co-treatment with a specific inhibitor of NF- κ B blocks this effect⁵⁶. On the other hand, in human foetal HNPs, the reduction in neurogenesis caused by TNF- α seems to occur via activation of the STAT-3 pathway¹².

TNF- α induced by LPS-MDM

We are aware of one study²⁵ investigating the role of TNF- α induced by LPS-MDM, where CM experiments are used. In this case, cell proliferation and astroglialogenesis both increased, but

a reduction in neurogenesis was shown by human foetal cortical NPCs. To support these findings, the authors also found that pre-treatment with TNF- α receptors R1 and R2 partially reduced the effect of TNF- α on proliferation. The authors comment that this shows that although TNF- α is involved in the modulation of cell proliferation, MDM might have also contributed to the impaired neuronal differentiation.

Discussion and Conclusions

Taking these interleukins individually, it is clear that further experiments need to be conducted to reconcile the conflicting evidence which has emerged regarding their effects on neuronal proliferation, differentiation and neurogenesis. Some of these discrepancies can be attributed to different cell types being used in experiments, or cells derived from different species, in which it would be interesting to learn more regarding the distinct downstream molecular mechanisms in these cell types, which underpin the differences observed. In addition, it is possible that stimulation with cytokines activate different mechanistic responses in distinct brain regions .thus suggesting the need of a combination of additional *in vitro* and *in vivo* experiments in order to understand this relationship more completely.

Despite these conflicting results over the directionality of the effects, it is clear that changes in cytokine levels in the brain can have profound effects on brain functioning. This effect has been most associated with the pathogenesis of depression, as well as some neurodegenerative diseases. There is evidence suggesting that depression itself is associated with impaired functioning of hippocampal neurogenesis mechanisms, and that antidepressants and other antidepressant treatments, such as electroconvulsive therapy, can have a positive impact on the way in which, and the rate at which, neurogenesis occurs in the hippocampus⁶⁰. Further *in vivo* data is required to translate *in vitro* findings into clinical context, in order that treatments for depression can be developed with the neurogenesis theory in mind⁶¹.

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