Progress in Neurobiology 156 (2017) 149–163

Contents lists available at ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio

Review article

Brain interference: Revisiting the role of IFNγ in the central nervous system

S. Monteiro[a,b], S. Roque[a,b], F. Marques[a,b], M. Correia-Neves[a,b,1], J.J. Cerqueira[a,b,1,*]

[a] Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Campus Gualtar, 4710-057 Braga, Portugal
[b] ICVS/3B's – PT Government Associate Laboratory, Braga/Guimarães, Portugal

ARTICLE INFO

Article history:
Received 4 August 2016
Received in revised form 15 May 2017
Accepted 17 May 2017
Available online 18 May 2017

Keywords:
IFNγ
Neuroimmunology
Neuroinflammation
Central nervous system
Cytokine

ABSTRACT

Interferon gamma (IFNγ) is a pro-inflammatory cytokine, first described as a secreted molecule capable of interfering with viral replication. Since then, numerous other important actions in the context of the immune response to invading pathogens (including those invading the brain) have been ascribed to this pleiotropic cytokine. Nevertheless, the precise role of IFNγ in neuropsychiatric and neurodegenerative disorders, and its possible contribution to the regulation of normal brain function, remains enigmatic.

This review integrates and considers current knowledge about IFNγ actions with accumulating evidence of its importance on neurocytogenesis, synaptic plasticity and neurodegeneration within the framework of brain health and disease.

Contents

Abbreviations: AMPA, amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; APC, antigen-presenting cell; APP, amyloid processing protein; Aβ, amyloid-β; BBB, blood–brain barrier; BCG, bacillus Calmette-Guérin; BCSFB, blood-cerebrospinal fluid barrier; BDNF, brain-derived neurotrophic factor; BrdU, bromodeoxyuridine; CCL21, (C-C) chemokine ligand 21; CCL6, (C-C) motif ligand 6; CCR7, (C-C) chemokine receptor 7; CNS, central nervous system; CP, choroid plexus; CSF, cerebrospinal fluid; CXCL10, (C-X-C) motif chemokine ligand 10; dCLN, deep cervical lymph nodes; EGL, external granule cell layer; GABA, γ-aminobutyric acid; GAS, gamma-interferon activation site; GFAP, glial fibrillary acidic protein; GluR1, glutamate receptor 1; GNP, granule neuron precursor cell; ICAM-1, intercellular adhesion molecule-1; IDO, indoleamine 2,3-dioxigenase; IFN, interferon; IFNγR, interferon γ receptor; IL, interleukin; ISF, interstitial fluid; JAK, janus kinase; KO, knock-out; LPS, lipopolysaccharide; LTP, long-term potentiation; MBP, myelin basic protein; MHC, major histocompatibility complex; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; mRNA, messenger ribonucleic acid; MSC, mesenchymal stem cell; NK, natural killer; NMDA, N-methyl-D-aspartate; NPC, neural progenitor cell; NSC, neural stem cell; O-2A/OPCs, oligodendrocyte-type 2 astrocyte progenitor cells; $p27^{Kip1}$, cyclin-dependent kinase inhibitor 1B; PDGFR, platelet-derived growth factor receptor; PI3K, phosphatidylinositol 3-kinase; PS, presenilin; PTZ, pentylenetetrazol; Rb, retinoblastoma protein; Rit, Ras-like protein; SGZ, subgranular zone; SHH, sonic hedgehog; STAT, signal transducer and activator of transcription; SVZ, subventricular zone; Th, T helper; TNF, tumour necrosis factor; TREK-1, tandem of P domains in a weak inward rectifying K^+ channel-related potassium channel-1; WT, wild-type.

* Corresponding author at: Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Campus de Gualtar, 4710-057 Braga, Portugal.
E-mail address: jcerqueira@med.uminho.pt (J.J. Cerqueira).

[1] These authors share senior authorship.

http://dx.doi.org/10.1016/j.pneurobio.2017.05.003
0301-0082/

1. Introduction

In any history of the cytokines, the 1957 discovery by Alik Isaacs and Jean Lindenman would be a major chapter. These virologists first described "interferon" (IFN) – a released substance that can interfere with subsequent viral infections to promote survival of the invaded cell (Isaacs and Lindenmann, 1957). Just a few years later IFN was purified and shown to exist in three isoforms: IFNα, IFNβ (the type I IFNs) and IFN γ (type II IFN); the last was identified by Wheelock (Wheelock, 1965).

IFNγ is a pro-inflammatory cytokine; it is produced by a restricted set of peripheral cells, such as T lymphocytes, natural killer (NK) and NKT cells (Kasahara et al., 1983; Ye et al., 1995), but also by central nervous system (CNS) cells in response to specific stimuli (as discussed in a following section dedicated to IFNγ-producing cells).

Since its initial description as a viral replication inhibitor, IFNγ has been associated with a variety of functions related to the immune response to infection (especially to intracellular pathogens) as well as to anti-tumoural defence. The cytokine has since been recognized to be important for both, the innate and adaptive components of the immune system. It is implicated in an array of immune responses, among others, macrophage activation (Mosser, 2003), up-regulation of expression of the major histocompatibility complex (MHC) (Giroux et al., 2003), and modulation of the type of T helper (Th) response (Bradley et al., 1996; Smeltz et al., 2002).

Since T, NK and NKT cells are scarce in healthy brain parenchyma, IFNγ is thought to only play a role in brain function under pathological conditions such as CNS infections, inflammatory diseases (Olsson et al., 1990; Panitch et al., 1987; Traugott and Lebon, 1988), trauma (Lau and Yu, 2001) and stroke (Seifert et al., 2014; Yilmaz et al., 2006). More recently, IFNγ has been implicated in several neuropsychiatric and neurodegenerative disorders in which inflammation is thought to be an important component. In addition, IFNγ has been shown to influence the mechanisms of neural cell genesis and synaptic plasticity that are fundamental for normal brain physiology, suggesting that its biological functions extend beyond the boundaries of the immune response.

These newly-ascribed functions of IFNγ justify a revisitation to the original concepts that restricted neuroscientific interest in this cytokine for more than 50 years. This review intends to integrate knowledge of the established biology of IFNγ with emerging concepts about its role in maintaining constant dialogue between the nervous and immune systems under physiological and pathological conditions.

2. Revisiting IFNγ

2.1. IFNγ cell signalling

IFNγ classically acts by binding to its receptor (IFNγR) – a multimeric complex composed of two chains, the cell-surface α-chain and a transmembrane β-chain. The α-chain of IFNγR binds IFNγ with high affinity, triggering its dimerization with the β-chain of IFNγR, and induction of a signalling cascade that involves activation of Janus kinase (JAK)-signal transducer and activator of transcription (JAK-STAT) pathway. JAK-1 associates with the IFNγR α-chain while JAK-2 associates with β-chain. Activation of both JAK 1 and 2 leads to the phosphorylation of (STAT)-1α which, in turn, binds to the γ-interferon activation site (GAS), a specific DNA response element present in more than 200 IFNγ-responsive genes (Popko et al., 1997). In addition, IFNγ can activate other signalling pathways such as CRK – a nuclear adaptor protein for STAT5 and phosphatidylinositol 3-kinase (PI3K), which are important for the regulation of the cell cycle and differentiation.

The multi-functionality of IFNγ can be partially attributed to the large number of IFNγ-responsive genes and signalling cascades. This multiplicity of downstream effectors may be similarly responsible for the large number of outcomes ("interferences") with respect to brain function, as will be discussed in Section 3.

2.2. IFNγ-producing cells

The classical sources of IFNγ are T, NK and NKT cells. However, as mentioned before, specific stimuli can induce IFNγ production by other cells types. For example, macrophages, which crucially depend on IFNγ for their activation, are now known to respond to interleukin (IL)-12 and/or IL-18 stimulation with increased IFNγ production (Fig. 1); while IL-12 and IL-18 stimulate IFNγ on their own, their simultaneous presence has an amplified effect (Munder et al., 1998). Moreover, macrophage-derived IFNγ positively drives IFNγ production by macrophages through an autocrine mechanism (Munder et al., 1998).

Evidence that IFNγ can activate microglia, the brain's resident macrophages, prompted the question of whether microglia might also produce IFNγ. The ability of microglia to produce IFNγ in response to *Toxoplasma gondii* infection was confirmed by the demonstration that the infection was accompanied by intracellular staining of IFNγ in, and secretion from, $CD11b^{+}CD45^{low}$ microglial cells from infected brains; secretion was observed *in vitro* in the absence of further stimulation (Fig. 1) (Suzuki et al., 2005; Wang and Suzuki, 2007). Subsequent studies detected IFNγ in the culture medium bathing microglia exposed to lipopolysaccharide (LPS), a component of the Gram-negative bacteria cell wall (Fig. 1) (Makela et al., 2010). Later work showed that microglial production of IFNγ does not only depend on being triggered by an immune insult since stimulation by IL-12 and IL-18 or IL-12 alone, leads to IFNγ production by microglial cells (Fig. 1) (Kawanokuchi et al., 2006).

Curiously, IL-12 and IL-18 also stimulate IFNγ production by B cells *in vitro* and *in vivo* (Harris et al., 2005; Yoshimoto et al., 1997). Further, Bao et al. (2014) showed that several immune challenges (*e.g. Listeria monocytogenes*, *Escherichia coli*, vesicular stomatitis virus and Toll-like receptor ligands) allow B cells to mount an immune response by producing IFNγ to activate macrophages.

Besides microglia, other cells of the nervous system can also produce IFNγ (Fig. 1). For example, sensory neurons in cultured dorsal root ganglion cultures express IFNγ, detectable by immunocytochemistry. These cells not only express IFNγ but also its cognate receptor, suggesting the potential for autocrine regulation of IFNγ expression (Neumann et al., 1997b). Other studies showed that tumour necrosis factor (TNF)α (Xiao and Link, 1998) and traumatic and metabolic injury (Lau and Yu, 2001) cause expression of IFNγ by brain astrocytes (Fig. 1). Interestingly, Wei et al. demonstrated that IFNγ expression in the aged brain is

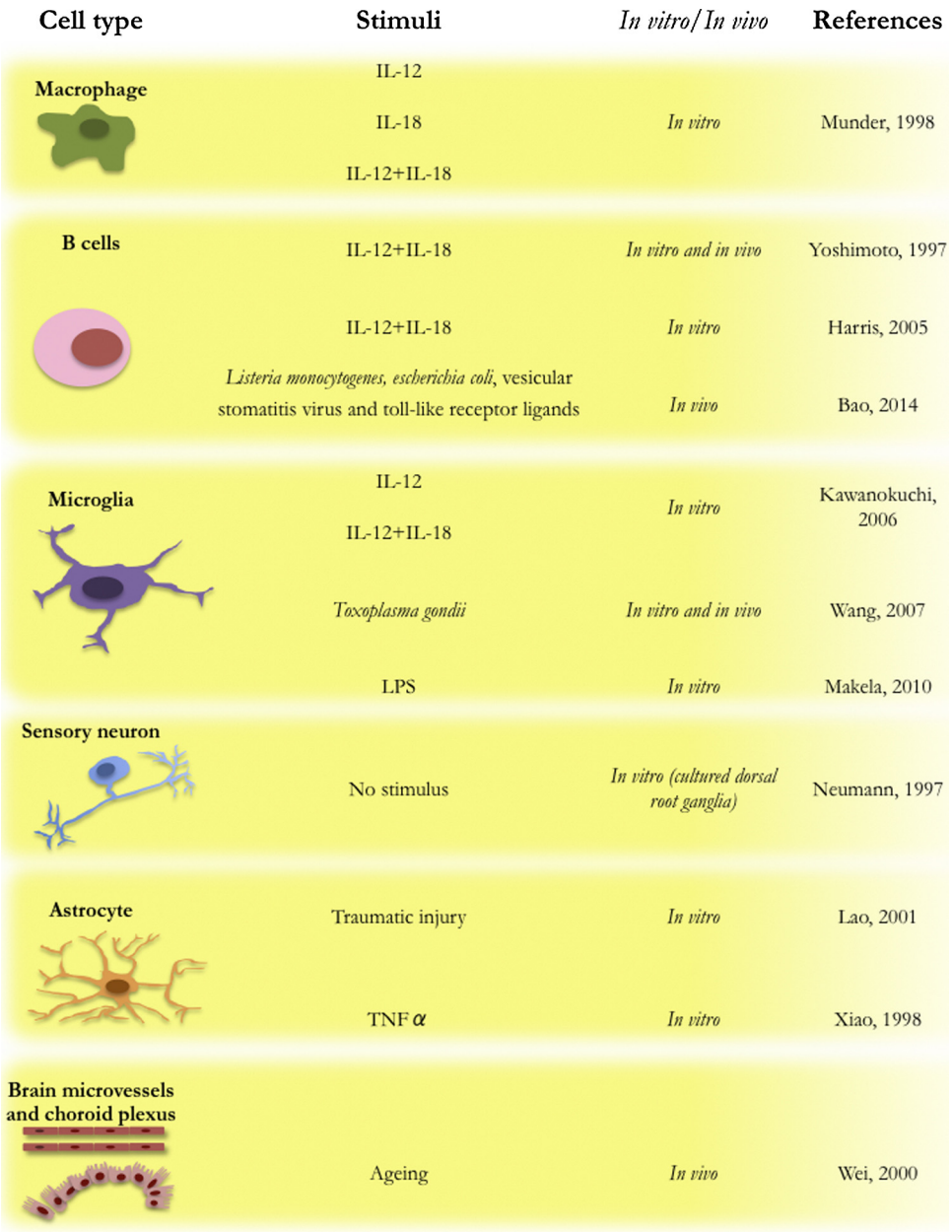

Fig. 1. Cell sources of IFNγ in addition to T, NK and NKT cells. Studies demonstrate that, in response to specific stimulus, macrophages and B cells can produce its own IFNγ. In the nervous system, microglia, sensory neurons, astrocytes, endothelial cells from microvessels and epithelial cells from the choroid plexus (CP) have been reported to have the ability to produce IFNγ in response to specific stimulus.

mainly found in the epithelial cells of the choroid plexus (CP) and endothelial cells of microvessels (Fig. 1) (Wei et al., 2000); these cells provide an important interface between the brain parenchyma and peripheral signals. However, further research will be needed to clarify the extent to which positive IFNγ immunolabelling in the CP associates with IFNγ-producing T cells that reside in the CP stromal space (Kunis et al., 2013).

An important unresolved question regarding IFNγ-producing cells concerns the comparability of IFNγ production between CNS resident cells (neurons and glia) and peripheral immune cells. To our knowledge, the only study addressing this issue reported that, while both microglia and macrophages express IFNγ in response to Toxoplasma infection, the magnitude of response in macrophages is greater than that in microglia (Suzuki et al., 2005).

While the available evidence indicates that IFNγ production by CNS cells depends on specific stimuli that most likely are related to danger signals, IFNγ receptors (IFNγR) are expressed by a far greater diversity of cell types (de Weerd and Nguyen, 2012). This raises the possibility that signalling initiated by IFNγ in the periphery might impact on brain function, a particularly attractive hypothesis in light of the fact that such signalling may be triggered in the absence of an obvious immune insult, a scenario in which the brain-barrier would be conserved.

2.3. The concept of "immune privilege"

The concept of "immune privilege" with respect to the brain was initially based on the presence of specialized barriers, such as the blood-brain barrier (BBB) and the blood-cerebrospinal fluid barrier (BCSFB), which "protect" the brain from peripheral molecules that could represent insults; at that time, infiltration of peripheral immune cells into the CNS was considered solely as a pathological hallmark. Over the last 20 years, however, this simplistic view has been challenged; the current consensus is that

while classical immune activation in the parenchyma tends to be limited, specific immune cells normally populate the surrounding areas of the brain parenchyma such as the CP, the cerebrospinal fluid (CSF) and meninges (Carrithers et al., 2002) where they support classical brain functions and play a crucial role in immune surveillance (Louveau et al., 2015a; Schwartz, 2015).

The CSF, produced by the CP, has a cellular composition that differs significantly from that of blood; it is predominantly (70%) populated by $CD4^+$ T cells (T helpers) and, unlike blood, has very few granulocytes, dendritic cells and B cells (de Graaf et al., 2011; Kivisakk et al., 2003). Memory T cells, which make up more than 90% of the $CD4^+$ T population in CSF (de Graaf et al., 2011), are cells that have previously encountered a cognate antigen and mount a fast and strong immune response upon re-encountering that antigen. Accordingly, memory T cells in the CNS are particularly important for immune surveillance, a concept extensively described by Ransohoff and Engelhardt (2012). Briefly, memory T cells actively patrol the CNS by circulating in the CSF through the subarachnoid spaces where they can be re-activated by antigens presented by meningeal myeloid cells. This active immune surveillance is rapidly translatable into an efficient immune response when pathogens or tissue damage are sensed (Hussain et al., 2014; Ransohoff and Engelhardt, 2012). The stroma of the CP also has a resident population of T cells but these differ from those found in the CSF. These so-called effector memory T cells represent more than 90% of the $CD4^+$ T cells in the CP stroma, and express mainly IL-4 or IFNγ at levels that exceed those found in the general circulation and lymphoid organs (Baruch and Schwartz, 2013; Kunis et al., 2013) (Fig. 2).

Given their abundance in different compartments surrounding the brain, it is not surprising that several recent studies indicate a role for T cells in normal brain functions. Ablation or reduction of T cells in mice using pharmacological or molecular genetic approaches has been associated with cognitive impairment, an effect that was reversible by T cell replenishment (Brynskikh et al., 2008; Derecki et al., 2010; Kipnis et al., 2004; Wolf et al., 2009; Ziv et al., 2006). In fact, the $CD4^+$ subset of T cells seems to be particularly important for cognitive tasks, since specific deletion of just this population (and not $CD8^+$ T or B cells) resulted in severely impaired performance in the Morris water maze test that correlated with reduced neurogenesis (Wolf et al., 2009; Ziv et al., 2006). The importance of T cells for cognitive processing was further suggested by the observation that training in a cognitive task results in an accumulation of T cells in the meninges (Derecki et al., 2011); production of IL-4 by these cells suggested behaviour-induced skewing of meningeal myeloid cells to an M2 phenotype (Derecki et al., 2011). Conversely, mice in which IL-4 was deleted (IL-4 knock-out (KO)) present a pro-inflammatory meningeal milieu that correlates with poor cognitive performance (Derecki et al., 2011). Consistent with these findings, deletion of IFNγ (IFNγ KO mice) was recently reported to improve cognitive abilities with concomitant increases in hippocampal plasticity (Monteiro et al., 2016). Together, these studies highlight the fact cognitive performance is determined by the state of T state activation (and consequently the cytokines they produce), rather than the presence or absence of T cells (Fig. 2). Importantly, the animal data pointing to the importance of T-cells and their cytokine products in cognitive function were recently shown to apply to humans. Using a cohort of aged individuals Serre-Miranda and colleagues reported that the number of $CD4^+$ effector T cells (the subset of T cells more likely to produce cytokines) predicts both general and executive function and memory (Serre-Miranda et al., 2015).

The fact that the vast majority of T cells in the CNS are pre-activated raises the important question as to how and where they are activated. Classical T cell activation involves antigen priming: antigens presented by specialized antigen-presenting cells (APCs) are recognized by specific receptors on the surface of T cells. Since transgenic mice engineered to express T cells that only recognize

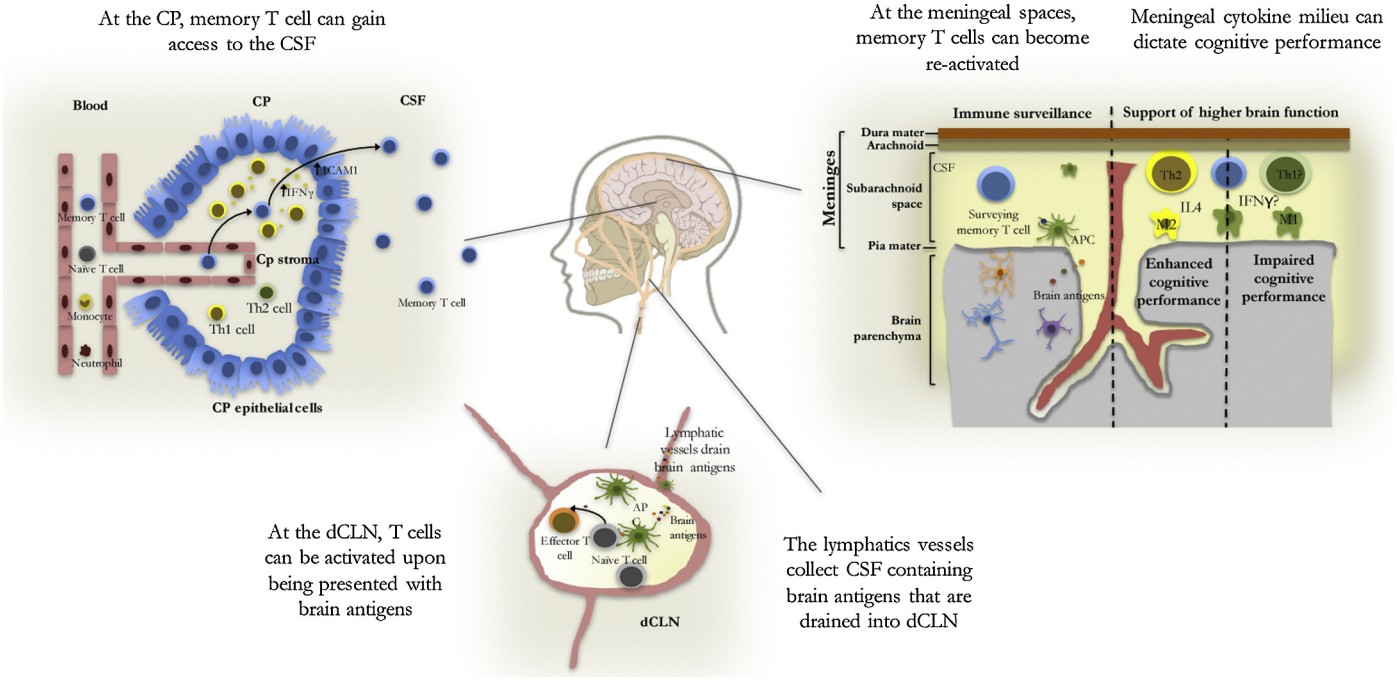

Fig. 2. Neuroimmune modulation of the CNS. Brain lymphatic vessels transport cerebrospinal fluid (CSF) containing immune cells and also brain antigens draining it to the deep cervical lymph nodes (dCLN). Brain antigens can be presented to naïve T cells at the dCLN, that upon activation can mobilize towards the CNS. Depending on the levels of IFNγ in the choroid plexus (CP), transmigration of memory T cells from the blood into the CSF can occur in a multi-step mechanism. The CSF is rich in memory T cells that patrol the CNS by actively sensing the environment. At the meningeal spaces, they can encounter pathogens or danger signals presented by local myeloid cells and become rapidly re-activated. In addition, meningeal T cells are essential for higher brain function being the flow of T cells into the meninges but also their state of activation determinants of cognitive performance.

ovalbumin present cognitive deficits (Radjavi et al., 2014b) supports the view that T cells that recognize CNS-specific antigens may be relevant for cognitive function. Interestingly, the cognitive deficits presented by mice with this limited T cell repertoire were reduced by adoptive transfer of $CD4^+$ T cells that specifically recognized a peptide normally found in the CNS (Radjavi et al., 2014b). It is important to note, however, that T and specialized APCs are relatively scarce in the healthy brain, making antigen presentation an unlikely event. In fact, the low level of antigen presentation in the brain, discovered in experiments that showed that tissue grafts in the brain survived for prolonged periods without eliciting an immune response (Medawar, 1948) was one of the key principles upon which the immune privileged status of the CNS. On the other hand, while APCs are found in the meninges and CP, active drainage of CNS antigens into the deep cervical lymph nodes (dCLN) and the consequent development of antigen-specific immune responses, has also been demonstrated (Walter et al., 2006). These findings indicate that the dCLN are a likely site at which T cells of the CNS are activated (Fig. 2). Supporting this view, surgical removal of dCLN has been shown to interrupt the flow of $CD4^+$ T cells into the meninges with the concomitant occurrence of cognitive impairments (Radjavi et al., 2014a). Nevertheless, the question of how and where these surveying and supportive immune cells enter and leave the CNS remains open.

Three potential entry routes for peripheral T cells from the blood to the CNS were discussed in an excellent review by Ransohoff et al. (2003): (1) from blood to the parenchymal perivascular space (Hickey, 1999; Piccio et al., 2002), (2) from the blood to the subarachnoid space (Hickey, 1999; Hickey and Kimura, 1988; Lassmann et al., 1993) and (3) through the CP to the CSF (Carrithers et al., 2002). The last of these, thought to occur most frequently under physiological conditions, is characterized by a multi-step mechanism in which T cells travel from the blood to the CP stroma through the fenestrated endothelium of the CP vessels, mobilize from the stroma to the basolateral surface of CP epithelial cells, finally reaching the CSF and the subarachnoid space in a process involving adhesion molecules, chemokines and cytokines (Ransohoff et al., 2003) (Fig. 2). Within the framework of this review, it is important to note that of all the cytokines found in the CP, IFNγ proved to be a key regulator of peripheral T cells entry into the CSF by upregulating CP epithelial cell expression of the adhesion molecule ICAM-1 and the immune cell chemoattractants CXCL10 and CCL6 which, together, allow the transmigration of T cells (Chang et al., 2002) (Fig. 2). Consistent with this schema, mice lacking IFNγR display reduced expression of molecules that regulate immune cell trafficking to the CP and therefore display lower infiltration of $CD4^+$ T cells into the CSF (Kunis et al., 2013). A study showing that danger signals originating in the brain parenchyma promotes leucocyte recruitment across the CP (Baruch et al., 2015) supports the notion that the CP is crucial for optimal immune surveillance in the CNS. Interestingly, decreased IFNγ signalling (decreased mRNA expression of IFNγ-dependent genes) in the CP is a common feature of ageing (Baruch et al., 2014) as well as neurodegenerative disorders such as Alzheimer's disease (Mesquita et al., 2015) and amyotrophic lateral sclerosis (Kunis et al., 2015), underlining the importance of appropriate immune surveillance for healthy brain functioning.

Other sites for leucocyte entry to the CNS, which may be regulated by a similar mechanism to the one triggered by IFNγ at the CP, are also conceivable. This view receives support from the report that co-treatment of mouse and human endothelial and BBB cells with IFNγ and TNFα, promotes leucocyte transmigration through a mechanism that involves downregulation of a tandem pore domain potassium channel (TREK-1) (Bittner et al., 2013). However, it remains unclear as to whether this type of T cell transmigration across the BBB truly represents an alternative entry route for surveying/supportive T cells, or whether it more broadly reflects pathophysiological inflammation-mediated breakdown of the BBB.

Finally, the recent anatomical discovery of a brain lymphatic system (Aspelund et al., 2015; Louveau et al., 2015b) deserves mention because it calls for a reappraisal of the relationship between immune cells and their associated molecular pathways in the brain. In particular, this discovery leads to the questions of how surveying immune cells leave the CNS and of how CSF and brain antigens reach the dCLN. Louveau et al. and Aspelund et al. independently demonstrated that meningeal lymphatic vessels run along the sagittal venous sinus draining immune cells, carrying small molecules and excess CSF from the CNS to the dCLN (Fig. 2) (Aspelund et al., 2015; Louveau et al., 2015b). This represents a second stage of the CNS clearance pathway that is at first performed by the glymphatic system. The glymphatic system carries CSF into the brain parenchyma along a para-arterial route in which solutes are exchanged with brain interstitial fluid (ISF), mediated by astrocytic aquaporin 4 water channels (Iliff et al., 2012). The CSF carrying cleared soluble proteins, waste products and excess ISF is then drained into the lymphatic system. The lymphatic vessels leave the CNS through the foramina at the base of the skull, alongside arteries, veins and cranial nerves, into the dCLN (Aspelund et al., 2015; Louveau et al., 2015b) (Fig. 2). As in other tissues, these meningeal lymphatic vessels express specific lymphatic vessel markers such as CCL21, a chemoattractant that binds to CCR7, which is typically expressed in memory T cells.

The discovery of the brain lymphatic system is exciting, not only because it represents a route for specialized immune cells to transport brain antigens into the dCLN (the classical form for CNS T cell activation), but also because malfunction of this system can result in the accumulation of waste products in the brain, a feature common to many neurodegenerative diseases.

Notwithstanding the fact that the brain is immune privileged, it is now generally recognized that healthy brain function nevertheless depends on neuroimmune interactions. Like other mediators, IFNγ has been demonstrated to be a key molecule in neuroimmune communication, including the entry of T cells through the CP and the selection/activation of distinct T cell-sub-types that impact on cognitive function (Fig. 2).

3. Impact of IFNγ in the nervous system

3.1. Influence on cell genesis

Viral replication, an important target of interferons, has similarities with cell proliferation since it also engages the DNA replication machinery (Tsurimoto and Stillman, 1990). Thus, it is not altogether surprising that IFNγ also modulates physiological cell genesis (summarized in Table 1) (Fig. 3).

Mesenchymal stem cells (MSC) are adult multipotent cells that can give rise to a variety of cell types, including neural cells (Brazelton et al., 2000; Cogle et al., 2004). Both, mouse and human MSC proliferation can be inhibited by IFNγ, but given the scope of this review, it is perhaps interesting to note that IFNγ, by activating indoleamine 2,3-dioxigenase (IDO) and consequently, the kynurenine pathway, contributes to the differentiation of human MSC along the neural cell lineage (Croitoru-Lamoury et al., 2011).

Neural stem cells (NSC) are self-renewing cells that can give rise to neurons, astrocytes and oligodendrocytes in response to specific environmental stimuli. They are particularly important for neurodevelopment but also exist in the adult rodent brain, primarily in the subventricular zone (SVZ) and the subgranular zone (SGZ) of the hippocampal dentate gyrus. Control of NSC self-renewal, proliferation and differentiation has been attributed to several different cytokines, including IFNγ.

Table 1
Summary of the studies describing the effect of IFNγ on cell genesis.

Measure	Experiment	Model	Outcome	Reference(s)
Proliferation	*In vitro*	Mesenchymal stem cells (MSC)	Inhibited	Croitoru-Lamoury et al. (2011)
		Oligodendrocyte-type 2 astrocyte progenitor cells (O-2A/OPCs)	Inhibited	Tanner et al. (2011)
		Embryonic neurospheres	Enhanced	Li et al. (2010)
		Granule neuron precursor (GNP)	Enhanced	Sun et al. (2010)
	In vivo	Neural stem cells (NSC) from the subventricular zone (SVZ)	Decreased	Pereira et al. (2015)
		Mice with pre-natal inducible-brain expression of IFNγ	Increased but dysfunctional cerebellar proliferation	Wang et al. (2004)
		Mice with inducible IFNγ expression in astrocytes	Cerebellar dysplasia; hypomyelination; severe ataxia; death before puberty	Corbin et al. (1996) and LaFerla et al. (2000)
Neurosphere formation	*In vitro*	NSC	Inhibited	Li et al. (2010) and Makela et al. (2010)
		NSC from IFNγ KO	Enhanced	Li et al. (2010)
Differentiation	*In vitro*	MSC	Enhanced	Croitoru-Lamoury et al. (2011)
		NSC	Enhanced	Kim et al. (2007)
		NSC	Increased but dysfunctional	Walter et al. (2011)
	In vivo	SVZ	Increased	Pereira et al. (2015)
Neurogenesis	*In vivo*	IFNγ KO mice	Increased	Li et al. (2010) and Monteiro et al. (2016)
		Alzheimer's disease model producing limiting amounts of IFNγ	Increased	Baron et al. (2008) and Mastrangelo et al. (2009)

Both proliferating and differentiated NSC express IFNγR (Makela et al., 2010; Walter et al., 2011) and *in vitro* stimulation with IFNγ was shown to directly inhibit neurosphere formation from NSC isolated from either the neonatal or adult SVZ without the involvement of other cell types (Li et al., 2010; Makela et al., 2010); the effects of IFNγ were shown to be mediated by cyclin-dependent kinase inhibitor p21 (Makela et al., 2010). In line with these studies demonstrating the inhibitory actions of IFNγ on neurosphere formation, SVZ cells from IFNγ KO mice were observed to display increased self-renewal capacity and to produce more and larger neurospheres than wild-type (WT) mice (Li et al., 2010).

Anti-proliferative effects of IFNγ were also demonstrated in oligodendrocyte-type 2 astrocyte progenitor cells (O-2A/OPCs) in CNS (which give rise to oligodendrocytes and astrocytes). This could be attributed to the cytokine's ability to suppress the expression of platelet-derived growth factor receptor (PDGFR)-α and Ki-67, two important proliferative factors, and to induce cell cycle by upregulating cyclin-dependent kinase inhibitor 1B ($p27^{Kip1}$) and retinoblastoma protein (Rb) (Tanner et al., 2011).

One interesting possibility that could explain the IFNγ-induced reduction of neural progenitor cells (NPCs) proliferation would be that IFNγ promotes differentiation of NPC into neurons. Kim et al. provided evidence for this hypothesis by demonstrating that IFNγ induces neuronal differentiation (increased expression levels of the neuronal marker βIII-tubulin) through the mediation of c-Jun N-terminal Kinases (Kim et al., 2007). Moreover, a recent *in vivo* study demonstrated that IFNγ decreases proliferation of $Nestin^{+}$ progenitor cells in the SVZ, while enhancing that of neuroblasts through the mediation of STAT1 (Pereira et al., 2015) (neuroblasts in the SVZ eventually develop into neurons as they migrate along the rostral migratory stream into the olfactory bulb).

It has also been reported that IFNγ treatment increases neuronal differentiation in parallel with a reduction of NPC proliferation (Walter et al., 2011). On the other hand, the differentiation observed was dysfunctional insofar that the mature cells aberrantly expressed both neuronal (βIII-tubulin) and glial markers (glial fibrillary acidic protein (GFAP)) (Walter et al., 2011). For example, IFNγ treatment was associated with dysregulated downstream signalling, including an upregulation of the sonic hedgehog (SHH) pathway and a downregulation of pro-neurogenic factors (Pax6, Math1, Mash1 and Neurogenin1) expression (Walter et al., 2011).

Interestingly, IFNγ elicits differential responses in embryonic neurospheres vs. postnatal or adult neurospheres; the embryonic neurospheres proliferate in response to activation of the SHH pathway (Li et al., 2010). Thus, *in vitro* treatment of granule neuron precursor (GNP) cells with IFNγ increases SHH protein expression and an augmentation of proliferation following binding of STAT1 to the SHH promoter; consistent with this, inhibition of SHH signalling blunts the proliferative action of IFNγ on GNP expansion (Sun et al., 2010). Notably, inducible expression of IFNγ in the prenatal mouse brain resulted in cerebellar dysplasia characterized by persistent and abnormal proliferation of granule neurons in the external granule cell layer (EGL) of the cerebellum due to SHH-mediated disrupted granular cell migration from the EGL through the molecular layer into the internal granule cell layer (Wang et al., 2004). Cerebellar dysplasia, together with high hypomyelination in the cerebellum and hippocampus, was also observed in transgenic mice expressing IFNγ in the CNS or specifically in astrocytes, respectively controlled by the myelin basic protein (MBP) (Corbin et al., 1996) or GFAP (LaFerla et al., 2000) gene promoters. These animals displayed severe ataxia and died before reaching sexual maturity (Corbin et al., 1996; LaFerla et al., 2000). On the other hand, deletion of IFNγ stimulates cytogenesis (bromodeoxyuridine (BrdU)-positive cells) and neuronal proliferation in the olfactory bulb (Li et al., 2010) and in the dentate gyrus (Monteiro et al., 2016), suggesting that IFNγ normally acts to inhibit neurogenesis in this brain area.

Interestingly, in animal models of Alzheimer's disease (AD), the production of low amounts of IFNγ appears to actually support neurogenesis (Baron et al., 2008; Mastrangelo et al., 2009), possibly by interacting with other modulators found in AD. Another puzzling observation is that IFNγ differentially affects the fate of NSC. As opposed to its effects on neurons and oligodendrocytes, IFNγ promotes the differentiation of astrocytes (Li et al., 2010; Tanner et al., 2011) and, conversely, isolated neurospheres from IFNγ KO mice differentiate more readily into neurons and

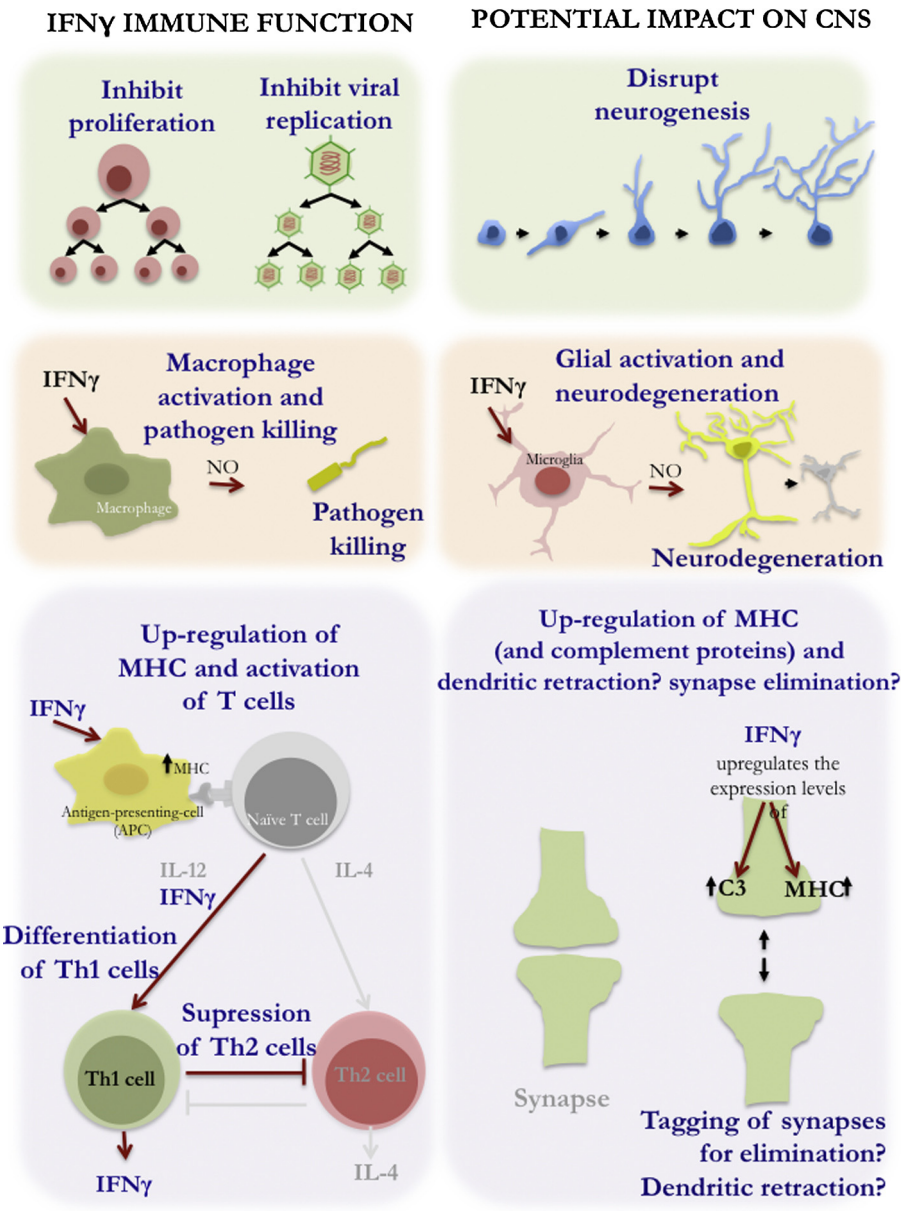

Fig. 3. IFNγ immune functions and their potential impact on CNS. The IFNγ impact in the CNS can be related to its immune function. IFNγ has an anti-proliferative function, which in the CNS may translate in the disruption of neurogenesis. IFNγ activates macrophages inducing the production of nitric oxide (NO), and similarly in the CNS it may activate microglia to produce NO leading to neurodegeneration. The IFNγ ability to induce the expression of major histocompatibility complex (MHC) I class molecules in the CNS was long though to enable communication between brain cells and immune cells during neuroinflammation, however MHC I class molecules induction may as well be involved in synaptic elimination. IFNγ is known to increase the expression levels of several complement proteins, namely of C3, that was associated with tagging of synapses for elimination.

oligodendrocytes than to astrocytes (Li et al., 2010). These findings make it plausible that IFNγ-induced astrocyte differentiation may be related to the role of IFNγ in the immune response since several studies have demonstrated that IFNγ confer astrocytes with the ability to act as non-professional antigen-presenting cells through an upregulation of MHC expression (Jarosinski and Massa, 2002; Vardjan et al., 2012); however, this issue requires further investigation.

As reviewed above, the ability of IFNγ to influence cell proliferation, differentiation and survival was demonstrated for many neural cell types; however, the divergent cell-specific outcomes highlight the necessity for future studies to elucidate the conditions under which this cytokine acts to promote or inhibit the different stages of cell genesis.

3.2. Influence on synaptic plasticity

The brain is a highly dynamic structure; it can reorganize its neural circuits to form new connections between neurons (synapses) and/or to break others during the course of learning a new task, in response to environmental stimuli, or as part of its recovery from damage. Depending on their activity, synapses can be strengthened or weakened over time, phenomena that require both, neurotransmission and dendritic remodelling.

3.2.1. Dendritic remodelling

Dendrites are neuronal projections that receive synaptic inputs and are critical for transmitting information. Each dendritic tree can combine information from multiple synapses emerging from

different axons. The dendritic tree is highly plastic and shows rapid morphological reconfiguration in response to received stimuli.

IFNγ was shown to influence synaptic connectivity in the brain by triggering the selective retraction of dendrites. For example, exposure of cultured sympathetic and hippocampal neurons to IFNγ was found to lead to an 88% reduction in the length of the dendritic tree and to inhibit synapse formation without affecting axonal outgrowth or cell survival. These changes were ascribed to mediation by STAT1 since cell transfection with a dominant-negative STAT1 mutant, which cannot be phosphorylated on Tyrosine 701, abrogated the effects of IFNγ. Furthermore, exposure of just the axonal part of these neurons to IFNγ was sufficient to elicit STAT1-mediated dendritic retraction and synaptic loss (Kim et al., 2002). Other studies suggested involvement of the *Ras*-like protein in tissue (Rit)-p38 pathway in IFNγ-induced dendritic retraction since IFNγ rapidly activated Rit in cultured rat sympathetic and hippocampal neurons, while expression of a dominant negative Rit mutant inhibited the dendritic retraction observed after IFNγ exposure (Andres et al., 2008).

Data showing that DG granule neurons in IFNγ KO mice have longer dendritic lengths and that their CA1 pyramidal neurons present more complex dendritic trees is in line with previous experiments showing that IFNγ induces dendritic retraction (Monteiro et al., 2016). Moreover, Filiano et al., using analysis of resting-state blood-oxygen-level dependent (BOLD) signals, further demonstrated hyperconnectivity between frontal to insular regions in IFNγ KO mice (Filiano et al., 2016).

Here, it is of interest to mention studies showing a crucial role for immune molecules such as MHC I and complement proteins in synapse pruning, a phenomenon that is essential for the refinement of neuronal circuits during neurodevelopment (Lee et al., 2014; Schafer et al., 2012). Similar mechanisms have been reported for synapse elimination in several diseases of the adult brain, including Alzheimer's (Hong et al., 2016), multiple sclerosis (Michailidou et al., 2015) and in West Nile virus infection, a disease associated with memory loss (Vasek et al., 2016). Since IFNγ levels are altered in these disorders and because IFNγ is known to induce the expression of MHC I in neurons (Neumann et al., 1997a) and to up-regulate the expression of complement protein 3 (C3) in human astroglioma cells (Barnum et al., 1992), it seems plausible that MHC1 and C3 may mediate the effects of IFNγ on dendritic retraction and synapse elimination (Fig. 3), although further studies are needed to prove this causality.

3.2.2. Glutamatergic transmission

Glutamate is the most abundant neurotransmitter in the brain; it is an important excitatory molecule involved in synaptic plasticity and is considered central for learning and memory processes. Imbalances in glutamatergic transmission can lead to the generation of seizures and/or to excitotoxicity that is characterized by the high influx of calcium ions, which triggers an enzymatic cascade that culminates in neuronal damage by overexcitation. Excitoxicity is a common underlying mechanism of neurodegenerative diseases such Alzheimer's (Guivernau et al., 2016; Scimemi et al., 2013), Parkinson's (Armentero et al., 2006; Hoekstra et al., 2015; Van Laar et al., 2015) and Multiple Sclerosis (Pitt et al., 2000), among others.

The first reports showing the association between IFNγ and excitatory activity came from *in vitro* experiments in which treatment of either cultured hippocampal slices or dissociated neurons with IFNγ resulted in spontaneous excitatory activity that eventually led to epileptic bursting (Muller et al., 1993; Vikman et al., 2001). Curiously, the increase in excitatory activity was found to occur slowly, being first registered minutes (Muller et al., 1993) or days (Vikman et al., 2001) after addition of IFNγ to the culture media, suggesting intermediation by other molecules. Reactive oxygen species, derived from IFNγ-stimulated microglia have been suggested to be, at least partially, responsible for eliciting excitation, since the addition of reactive oxygen species scavengers significantly blunted the effects of IFNγ (Muller et al., 1993). Abnormally high levels of IFNγ in the brain, such as those observed in CNS viral infections, have been associated with the development of seizures – the clinical manifestation of a dysfunctional glutamatergic transmission and hyperexcitability (Getts et al., 2007). Further, unlike their WT counterparts, West Nile virus-infected IFNγ KO mice do not develop seizures even though both genotypes present similar levels of the virus, TNFα and IL6 in the brain (Getts et al., 2007); the latter two cytokines have been implicated in synaptic plasticity (Balschun et al., 2004; Stellwagen and Malenka, 2006). Further, the administration of convulsive agents to mice showed that IFNγ-induced seizures are most likely mediated through amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) or kainate receptors (Getts et al., 2007). Importantly, administration of the γ-aminobutyric acid (GABA) antagonist, Pentylenetetrazol (PTZ), induced seizures in both WT and IFNγ mice, indicating that GABA receptors are not involved in the IFNγ-induced seizures. Although slower in onset, the seizures induced by N-methyl-D-aspartate (NMDA) were found to be of equal magnitude in WT and IFNγ KO. Strikingly, kainic acid-induced seizures were completely abolished in IFNγ KO mice, pointing to the involvement of either kainate receptors or AMPA receptors (kainate binds to both, kainite and AMPA receptors) in IFNγ-induced seizures (Getts et al., 2007). In a different study, AMPA receptors were shown to be crucial for IFNγ-induced excitotoxicity and neurodegeneration. Importantly, it was shown that activated IFNγR can form a unique complex with the AMPA receptor subunit GluR1, the phosphorylation of which (at serine 845) triggers the JAK1,2/Stat1 pathway and culminates in an influx of calcium ions, production of nitric oxide and formation of dendritic beads, a common feature of excitotoxic damage (Mizuno et al., 2008). Pharmacological analysis suggested that the formation of dendritic beads was mediated by activation of both, the IFNγ and AMPA/kainate (Mizuno et al., 2008).

In contrast to the upregulation of AMPA receptors observed after acute IFNγ treatment, chronic IFNγ was found to reduce AMPA receptor expression on the dendrites of hippocampal neurons (Vikman et al., 2001); this response, which most likely represents a defence mechanism that controls excitotoxic damage, was reported to increase spontaneous spiking frequency and alter gene expression in the hypothalamic suprachiasmatic nucleus which serves to synchronize daily physiological rhythms and which is implicated in neurodegenerative diseases (Kwak et al., 2008). In line with other findings described above, this IFNγ-induced decrease in synaptic plasticity does not depend on GABAergic inputs (addition of the $GABA_A$ receptor antagonist bicuculline failed to reduce spontaneous spiking frequency elicited by IFNγ treatment).

Long-term potentiation (LTP), which occurs at excitatory synapses, is a form of long-term plasticity that may occur over minutes or hours; LTP underlies learning and memory acquisition. Studies on the impact of neuroinflammation on the decline of LTP during ageing in M.A. Lynch's laboratory first showed that age-related decreases in LTP are accompanied by increases in the hippocampal levels of IL-1, IL-18 and IFNγ (Griffin et al., 2006). The same laboratory subsequently demonstrated that intracerebroventricular administration of IFNγ abrogates LTP with concomitant increases in hippocampal IL-1 levels (Maher et al., 2006). Consistent with these data, we recently showed similar LTP response in WT and IFNγ KO mice, confirming that IFNγ is not essentially linked to initiation of LTP (Monteiro et al., 2016).

3.2.3. GABAergic transmission

GABA represents the main inhibitory neurotransmitter in the CNS. Recent studies have shown that IFNγ can induce

hyperexcitability by decreasing GABAergic synaptic transmission. For example, genetic or pharmacological suppression of the protein kinase RNA-activated (PKR), a sensor of double-stranded RNA viruses that regulates IFNγ expression (Cohen-Chalamish et al., 2009), is accompanied by an increase on IFNγ, which in turn, induces hippocampal and cortical hyperexcitability by reducing inhibitory GABAergic activity and enhances long-term memory (Zhu et al., 2011). Interestingly, agonists of the benzodiazepine receptor (an allosteric modulatory site on the GABA receptor) inhibit IFNγ production, an effect that suggests a role for IFNγ in anxiety (Wei et al., 2010). Reduced GABAergic activity has also been observed after application of IFNγ in the spinal cord dorsal horn (Vikman et al., 2007), suggesting that IFNγ may contribute to central sensitization and persistent pain.

3.2.4. Serotonergic signalling

The monoamine neurotransmitter serotonin, synthesized from tryptophan, is important for the regulation of mood, appetite and sleep. The implication of IFNγ in depression is based on the ability of this cytokine to induce IDO, a rate-limiting enzyme involved in tryptophan catabolism; modulation of IDO shifts the availability of tryptophan away from serotonin production into the kynurenine pathway, resulting in the generation of the neurotoxic metabolites quinolic acid and 3-hydroxy-kinurenine. Indeed, IDO is suggested to contribute to impaired mood and recognition memory (Heisler and O'Connor, 2015; H. Kim et al., 2012; O'Connor et al., 2009b). In summary, IFNγ-induced depletion of serotonin, through induction of the kynurenine pathway, is a likely mechanism that explains the pathophysiology of ageing-related neuropsychiatric disorders and depression (Myint et al., 2013; Oxenkrug, 2011).

3.3. Involvement in neuropsychiatric and neurodegenerative diseases

3.3.1. Neuropsychiatric alterations

Recognition that almost all neuropsychiatric disorders have an inflammatory component has spurred interest in the role of immune molecules in the pathophysiology of brain diseases. Accordingly, the potential neuropathological contributions of IFNγ have not escaped attention. Polymorphisms in the IFNγ gene and its receptor were recently associated with the development of schizophrenia (Jemli et al., 2016; H.J. Kim et al., 2012; Paul-Samojedny et al., 2011) and acute manifestations of the disease have been correlated with decreased levels of IFNγ (Arolt et al., 2000). Importantly, results of a clinical trial showed that, as compared to placebo, inclusion of an immunomodulatory drug that increases endogenous IFNγ-production as part of a complex therapy for schizophrenia reduces clinical symptoms (Vetlugina et al., 2016). Furthermore, a case-report study described clinical improvements in two antipsychotic-resistant schizophrenic patients after addition of IFN-γ-1b (a biological manufactured protein similar to the IFNγ produced by immune cells) to their antipsychotic therapy for 4 weeks (Gruber et al., 2014).

Evidence for a role of IFNγ in the pathophysiology of depression includes the finding that serum levels of the cytokine are increased in depressed patients (Maes et al., 1994; Schmidt et al., 2014). Further, anti-depressants reduce serum IFNγ levels and increase those of the anti-inflammatory peptide interleukin IL-10 (Maes et al., 1999). Exposure to stressors, which increases susceptibility to develop neuropsychiatric alterations including depression, is associated with elevated IFNγ levels in the serum. For example, medical students with greater perception of stress (when subjected to pre-exam stress) display increased blood concentrations of pro-inflammatory cytokines, including IFNγ, while having lower levels of the anti-inflammatory cytokines IL-10 and IL-4 (Maes et al., 1998). In line with these observations in humans, exposure of IFNγ KO mice to chronic mild stress is not followed by increased blood levels of the pro-inflammatory cytokines TNFα and IL-2 and does not show elevated levels of corticosterone, a hallmark of the stress response (Litteljohn et al., 2010). Additionally, chronically stressed IFNγ KO mice display improved cognitive performance when compared to WT mice (Litteljohn et al., 2014), suggesting that IFNγ may be causally involved in stress-related cognitive deficits.

Several studies have reported high blood levels of IFNγ in patients with autism spectrum disorder (El-Ansary and Al-Ayadhi, 2014; Li et al., 2009; Tostes et al., 2012). It was recently found that, besides elevated levels of IFNγ, such patients also showed increased levels of gamma-interferon-inducible protein 16 (Ifi16) and reduced levels of TNFα and IL-6 (El-Ansary and Al-Ayadhi, 2014). Interestingly, multiple regression linear analyses identified associations between an imbalance in GABAergic and glutamatergic synapses and IFNγ and Ifi16 levels (El-Ansary and Al-Ayadhi, 2014), suggesting that neuroinflammation related to IFNγ may contribute to synaptic dysfunction in autism spectrum disorder.

Neuropsychiatric alterations have also been associated with certain infectious diseases characterized by an immune response mediated by IFNγ. For instance, IFNγ mRNA levels in the hippocampus were increased in piglets infected with a porcine reproductive and respiratory syndrome virus; these piglets also showed decreased performance in cognitive tasks (Elmore et al., 2014). Another example that illustrates the link between infection, IFNγ and behavioural alterations is that infection of mice with *Mycobacterium bovis* Bacillus Calmette-Guérin (BCG) induces changes in mood-like behaviour that are dependent on IFNγ (O'Connor et al., 2009a).

Data from humans, as well as animal models of various neuropsychiatric disorders, consistently show altered levels of IFNγ. While it is not clear as to whether IFNγ is beneficial or detrimental since either low or high levels are associated with different conditions, it seems likely that at least some of the neuropsychiatric states arise from interactions between IFNγ and specific mechanisms of each disease rather than from a primary effect of this cytokine. Animal models in which the *IFNγ* gene has been deleted will prove important research tools for dissecting the impact of IFNγ in the different dimensions of behaviour that are altered in neuropsychiatric disorders. For instance, studies with IFNγ KO mice have already shown that IFNγ is important for emotional (Campos et al., 2014; Kustova et al., 1998; Litteljohn et al., 2010) and cognitive (Litteljohn et al., 2014; Monteiro et al., 2016) behaviours. While the enhancement of hippocampus-dependent cognitive behaviour in the absence of IFNγ expression was previously referred to, Monteiro and colleagues provided data describing the structural, cellular and electrophysiological correlates of the hippocampal plasticity likely to underpin the altered behaviour (Monteiro et al., 2016).

Social deficits were recently observed in mice lacking IFNγ and, conversely, transcriptomic analysis showed that IFNγ-regulated genes are enriched in mice exposed to social aggregation (or to psychostimulants) (Filiano et al., 2016). The same authors reported that IFNγ KO mice display aberrant hyper-connectivity between different brain regions that could underpin their impaired social behaviour (Filiano et al., 2016). On the other hand, it is important to note that whereas deletion IFNγ produces deficits in social behaviour (Filiano et al., 2016), the absence of IFNγ associates with improved cognitive skills (Monteiro et al., 2016). Interestingly, brain hyper-connectivity is a feature of children with autism spectrum disorders (Nelson and Valakh, 2015; Supekar et al., 2013) who besides displaying altered social behaviour also show differences (positive and negative) in cognitive function (Pellicano, 2010). At the same time, while IFNγ KO mice reproduce some of the clinical features found in patients with autism spectrum

disorders, reports that IFNγ levels are elevated in such patients (El-Ansary and Al-Ayadhi, 2014; Li et al., 2009; Tostes et al., 2012) points to the need for future studies which address these apparent discrepancies.

Although it is becoming evident that IFNγ has a multiplicity of effects in the brain, particularly on social, emotional and cognitive domains, remains much to be understood regarding the mechanisms through which IFNγ impacts on neuropsychiatric health and in particular, how it interacts with other mediators of disease.

3.3.2. Neurodegenerative diseases

Neurodegenerative diseases are characterized by a slow and progressive dysfunction and death of neurons, a process commonly associated with immune activation and neuroinflammation.

IFNγ, which is known to activate nitric oxide production by macrophages (Chao et al., 1992; Spencer et al., 2016), is also able to activate nitric oxide production by microglial cells (Fig. 3) and a marked decrease on neuronal survival (Chao et al., 1992) (Fig. 3).

By analogy, astrocytes may be activated by IFNγ, eventually leading to neurodegeneration, as demonstrated by Lee et al. who showed that conditioned media from human astrocytes treated with IFNγ leads to reduced viability loss of a human neuroblastoma (SH-SY5Y) cell line (Lee et al., 2013). The potential role of astrocytes in neurodegeneration is known to be mediated by their secretion of IL-6, glutamate, proteases, oxygen-free radicals and prostaglandins (Lee et al., 2013). These findings complement previous work showing that activation of astrocytes by IFNγ, together with IL-1β, leads to the production of TNFα (Chung and Benveniste, 1990). Glial activation, with the resultant production of pro-inflammatory mediators is a classical component of neuroinflammation, a chronic condition that leads to neuronal damage and loss. Due to its ability to induce neuroinflammation, IFNγ has been implicated in a number of neurodegenerative diseases, as will be discussed below.

3.3.2.1. Parkinson's disease. Parkinson's disease is characterized by dopaminergic cell loss in the substantia nigra and striatum, leading primarily to motor deficits but also impacting on emotional behaviours. Reports that blood levels of IFNγ are elevated in Parkinson's patients and parkinsonian monkeys (Barcia et al., 2012; Mount et al., 2007; Reale et al., 2009) prompted research on the possible involvement of this cytokine in the pathophysiology of Parkinson's disease. Notably, Barcia et al. demonstrated that IFNγ and TNFα act synergistically to induce chronic glial activation and thus neurodegeneration typical of Parkinson's disease (Barcia et al., 2012). Conversely, Mount et al. using an *in vitro* approach showed lower microglial reactivity and reduced loss of substantia nigra and striatal cell loss induced by the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in neural cell cultures derived from IFNγ KO mice. The importance of microglia for manifestation of the deleterious effect of IFNγ was shown by the fact that IFNγ was only effective in neuronal-microglia co-cultures. Similarly, rotenone-induced death of dopaminergic neurons was only observed in the presence of microglia, an effect prevented by co-incubating with antibodies against IFNγ (Mount et al., 2007). In an *in vivo* study, Chakrabarty et al. treated postnatal day 2 mice with intra-cerebroventricular adeno-virus expressing IFNγ; as adults, the animals exhibited marked calcifications of the basal ganglia and severe nigrostriatal degeneration and a reduced number of tyrosine-hydroxylase positive neurons (Chakrabarty et al., 2011).

3.3.2.2. Alzheimer's disease. Abnormal accumulations of extracellular amyloid-β (Aβ) deposits and hyperphosphorylation of tau protein that form intracellular neurofibrillary tangles are the neuropathological hallmarks of Alzheimer's disease, the typical clinical symptoms of which include memory deficits that progress to dementia (Querfurth and LaFerla, 2010).

The view that IFNγ may be involved in this neurodegenerative disease stems from observations by Blasko et al. who showed that combined stimulation with IFNγ and TNFα triggers the production of Aβ peptides in a human neuroblastoma cell line (Blasko et al., 1999). In a subsequent report, the same authors showed that co-stimulation of primary astrocytes or astrocytoma cells with either IFNγ and TNFα or IFNγ with IL-1β (but not with TNFα or IL-1β alone) increased the generation of $A\beta_{1-40}$ and $A\beta_{1-42}$ (Blasko et al., 2000). Furthermore, Bate et al. showed that IFNγ could also sensitize cortical, cerebellar and SH-SY5Y neuroblastoma cells *in vitro* to the neurotoxic actions of $A\beta_{1-42}$ (Bate et al., 2006).

The adoptive transfer of IFNγ-producing Aβ-specific-CD4 Th1 cells (but not Th2 or Th17 cells which do not express IFNγ) into APP/PS1 mice, a model for Azheimer's disease, was shown to accelerate the appearance of disease markers, in parallel with increased microglial activation, Aβ deposition and cognitive decline (Browne et al., 2013). Consistent with these findings, transgenic mice that overexpresses amyloid precursor protein (APP) and exhibit some pathological features of Alzheimer's disease, were found to express higher levels of IFNγ and IL-12 (and decreased levels IL-4) in various areas of the cerebral cortex (Abbas et al., 2002). In contrast, deletion of IFNγR in APP transgenic mice was accompanied by reduced gliosis and Aβ plaque burden (Yamamoto et al., 2007).

Signalling through a pathway initiated by IL-12/IL23 may also underlie the ability of IFNγ to induce Alzheimer's disease pathophysiology. IL-12 and IL-23 share a common sub-unit p40 that is increased in the CSF from Alzheimer's disease patients and genetic deletion of this subunit or the administration of p40 antibodies reduces amyloid deposition and ameliorates the cognitive deficits displayed by APP 1 transgenic mice (Vom Berg et al., 2012).

Despite the evidence summarized above, the role of IFNγ in Alzheimer's disease remains far from clear. This is exemplified by the fact that IFNγ overexpression in the brain for 10 months is accompanied by increased *intra*cellular levels of Aβ, a reduction of phosphorylated tau and increased neurogenesis (Mastrangelo et al., 2009). On the other hand, using two mouse models of tauopathy (JNPL3 and rTg4510), Li et al. reported that adenoviral transduced expression of IFNγ expression increases tau phosphorylation without aggravating tau pathology (Li et al., 2015). Moreover, Baron et al. observed that small amounts of IFNγ enhanced neurogenesis in the DG and improved spatial learning and memory in aged WT mice as well as in a mouse model of Alzheimer's disease (Baron et al., 2008). In addition, expression of murine IFNγ in the brain of APP transgenic mice was found to increase glial reactivity and decrease Aβ burden (Chakrabarty et al., 2010).

Many factors may underlie the apparent discrepancies with respect to how IFNγ may influence the pathophysiology of Alzheimer's disease. Disease context, stage of pathogenesis, and cellular/cytokine milieu may play role singly or in a combinatorial manner. Since anti-inflammatory strategies, *e.g.* by administering IL-10, appear to worsen plaque burden by blocking microglial phagocytosis in mice *cf.* (Chakrabarty et al., 2015; Guillot-Sestier et al., 2015), re-establishment of a proper immune response balance, rather than straightforward anti-inflammatory therapies, may hold the key to ameliorating this and other neurodegenerative diseases.

3.3.2.3. Down syndrome. Although Down syndrome is primarily considered to be a developmental disorder characterized by, among others, disability and progressive memory loss, nearly all Down's patients exhibit a neurodegenerative process that

resembles Alzheimer's disease from about the age of 40 (Lockrow et al., 2012). The extra chromosome responsible for Down's syndrome encodes the APP gene but also encodes several IFNγ-related genes. Thus, the brains of trisomic (Ts16) mice which serve as a model of Down syndrome, display significantly higher levels of IFNγ and Fas receptor (an apoptosis marker). In addition, cortical neurons cultured from Ts16 mice express higher levels of caspase-1 and exhibit altered calcium homeostasis and pH. Addition of IFNγ to these cells leads to caspase-1 activation and neuronal apoptosis (Hallam et al., 2000). In line with these observations, treatment of cortical neurons from Ts16 mice with anti-IFNγ antibodies promotes neuronal viability (Hallam and Maroun, 1998), indicating a role for IFNγ in the neurodegenerative processes found in Down's syndrome.

4. Concluding remarks

During the last decade, the field of neuroimmunology has challenged a central dogma, namely that barriers protect the healthy brain from events in the peripheral immune system. The present consensus is that, even under physiological conditions, these barriers are selectively permeable and allow peripheral immune cells to populate brain sites to facilitate immune surveillance and, consequently, to influence higher brain function.

This review revisited key aspects of IFNγ actions in the CNS and attempted to integrate existing knowledge into the new framework of physiological neuroimmune modulation of the CNS (Fig. 2). We especially focused on the impact of IFNγ on key cellular and synaptic processes that underscore different behavioural dimensions, many of which may be attributable to the immunological properties of this cytokine within the unique milieu of the brain (Fig. 3). On the other hand, it is interesting that the anti-proliferative effects of IFNγ on immune cells are seen to extend to neurons, with consequences for cognitive processing (Fig. 3). Another similarity may be seen in terms of the ability of IFNγ to activate macrophages in the periphery and microglia in the CNS; the latter culminates in neuronal damage, a common event in the pathophysiology of neurodegenerative diseases (Fig. 3). At the same time, the impact of IFNγ on neurotransmission and dendritic morphology imply that, in addition to being a classical immune cytokine, IFNγ should also be regarded as a potent neuromodulatory molecule (Fig. 3).

Despite our efforts to compile a comprehensive and clear review of IFNγ action in the brain, the subject is still cloaked by ambiguity, especially because of the many contradictory reports. The latter may reflect differences in experimental conditions (*e.g. in vivo versus in vitro*, brain region analyzed, and the timing, mode of administration and doses of IFNγ used). The issue of IFNγ dose can be illustrated by the fact that the cytokine can induce or inhibit a neuroprotective phenotype in astrocytes, depending on the amount of cytokine administrated: while low amounts of IFNγ induce the release of substances associated with neuroprotection and enhanced glutamate clearance capacity, higher does produce the opposite effect (Garg et al., 2009).

Notably, while many studies describe a direct effect of IFNγ action in the brain parenchyma, they do not consider the complex network of neuroimmune interactions that occur in the vicinity of the brain and their potentially important implications for brain function. This is well exemplified by the crucial role of IFNγ in regulating the entry of surveying/supportive immune cells across the CP. Lastly, it would appear that properly balanced brain immunity is crucial for optimal brain function. Once the differential and multiplicity of IFNγ actions are better understood, there would be strong potential for targeting IFNγ (or its downstream mechanisms) to ameliorate a number of neuropsychiatric and neurological disorders.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

We gratefully acknowledge Professor Osborne Almeida for his valuable suggestions and language editing of the manuscript. We also acknowledge the Portuguese Science Foundation (FCT) for providing fellowships to S. Monteiro (SFRH/BD/69311/2010) and S. Roque (<GN1>SFRH/BPD/72710/201</GN0>1). Work by the authors was co-funded by Programa Operacional Regional do Norte (ON.2 – O Novo Norte), Quadro de Referência Estratégico Nacional (QREN), through the Fundo Europeu de Desenvolvimento Regional (FEDER), the "Programa Operacional Regional do Norte (ON.2 SR&TD Integrated Program – NORTE-07-0124-FEDER-000021), Quadro de Referência Estratégico Nacional (QREN), através do Fundo Europeu de Desenvolvimento Regional (FEDER)", and by national funds from the FCT (PEst-C/SAU/LA0026/2013), and "Fundo Europeu de Desenvolvimento Regional (FEDER), através do COMPETE (FCOMP-01-0124-FEDER-037298)".

References

Abbas, N., Bednar, I., Mix, E., Marie, S., Paterson, D., Ljungberg, A., Morris, C., Winblad, B., Nordberg, A., Zhu, J., 2002. Up-regulation of the inflammatory cytokines IFN-gamma and IL-12 and down-regulation of IL-4 in cerebral cortex regions of APP(SWE) transgenic mice. J. Neuroimmunol. 126 (1–2), 50–57.

Andres, D.A., Shi, G.X., Bruun, D., Barnhart, C., Lein, P.J., 2008. Rit signaling contributes to interferon-gamma-induced dendritic retraction via p38 mitogen-activated protein kinase activation. J. Neurochem. 107 (5), 1436–1447. doi:http://dx.doi.org/10.1111/j.1471-4159.2008.05708.x.

Armentero, M.T., Fancellu, R., Nappi, G., Bramanti, P., Blandini, F., 2006. Prolonged blockade of NMDA or mGluR5 glutamate receptors reduces nigrostriatal degeneration while inducing selective metabolic changes in the basal ganglia circuitry in a rodent model of Parkinson's disease. Neurobiol. Dis. 22 (1), 1–9. doi:http://dx.doi.org/10.1016/j.nbd.2005.09.010.

Arolt, V., Rothermundt, M., Wandinger, K.P., Kirchner, H., 2000. Decreased in vitro production of interferon-gamma and interleukin-2 in whole blood of patients with schizophrenia during treatment. Mol. Psychiatry 5 (2), 150–158.

Aspelund, A., Antila, S., Proulx, S.T., Karlsen, T.V., Karaman, S., Detmar, M., Wiig, H., Alitalo, K., 2015. A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules. J. Exp. Med. doi:http://dx.doi.org/10.1084/jem.20142290.

Balschun, D., Wetzel, W., Del Rey, A., Pitossi, F., Schneider, H., Zuschratter, W., Besedovsky, H.O., 2004. Interleukin-6: a cytokine to forget. FASEB J. 18 (14), 1788–1790. doi:http://dx.doi.org/10.1096/fj.04-1625fje.

Bao, Y., Liu, X., Han, C., Xu, S., Xie, B., Zhang, Q., Gu, Y., Hou, J., Qian, L., Qian, C., Han, H., Cao, X., 2014. Identification of IFN-gamma-producing innate B cells. Cell Res. 24 (2), 161–176. doi:http://dx.doi.org/10.1038/cr.2013.155.

Barcia, C., Ros, C.M., Annese, V., Gomez, A., Ros-Bernal, F., Aguado-Llera, D., Martinez-Pagan, M.E., de Pablos, V., Fernandez-Villalba, E., Herrero, M.T., 2012. IFN-gamma signaling, with the synergistic contribution of TNF-alpha, mediates cell specific microglial and astroglial activation in experimental models of Parkinson's disease. Cell Death Dis. 3, e379. doi:http://dx.doi.org/10.1038/cddis.2012.123.

Barnum, S.R., Jones, J.L., Benveniste, E.N., 1992. Interferon-gamma regulation of C3 gene expression in human astroglioma cells. J. Neuroimmunol. 38 (3), 275–282.

Baron, R., Nemirovsky, A., Harpaz, I., Cohen, H., Owens, T., Monsonego, A., 2008. IFN-gamma enhances neurogenesis in wild-type mice and in a mouse model of Alzheimer's disease. FASEB J. 22 (8), 2843–2852. doi:http://dx.doi.org/10.1096/fj.08-105866.

Baruch, K., Deczkowska, A., David, E., Castellano, J.M., Miller, O., Kertser, A., Berkutzki, T., Barnett-Itzhaki, Z., Bezalel, D., Wyss-Coray, T., Amit, I., Schwartz, M., 2014. Aging-induced type I interferon response at the choroid plexus negatively affects brain function. Science 346 (6205), 89–93. doi:http://dx.doi.org/10.1126/science.1252945.

Baruch, K., Kertser, A., Porat, Z., Schwartz, M., 2015. Cerebral nitric oxide represses choroid plexus NFkappaB-dependent gateway activity for leukocyte trafficking. EMBO J. 34 (13), 1816–1828. doi:http://dx.doi.org/10.15252/embj.201591468.

Baruch, K., Schwartz, M., 2013. CNS-specific T cells shape brain function via the choroid plexus. Brain Behav. Immun. 34, 11–16. doi:http://dx.doi.org/10.1016/j.bbi.2013.04.002.

Bate, C., Kempster, S., Last, V., Williams, A., 2006. Interferon-gamma increases neuronal death in response to amyloid-beta1-42. J. Neuroinflammation 3, 7. doi:http://dx.doi.org/10.1186/1742-2094-3-7.

Bittner, S., Ruck, T., Schuhmann, M.K., Herrmann, A.M., Moha ou Maati, H., Bobak, N., Gobel, K., Langhauser, F., Stegner, D., Ehling, P., Borsotto, M., Pape, H.C., Nieswandt, B., Kleinschnitz, C., Heurteaux, C., Galla, H.J., Budde, T., Wiendl, H.,

Meuth, S.G., 2013. Endothelial TWIK-related potassium channel-1 (TREK1) regulates immune-cell trafficking into the CNS. Nat. Med. 19 (9), 1161–1165. doi:http://dx.doi.org/10.1038/nm.3303.
Blasko, I., Marx, F., Steiner, E., Hartmann, T., Grubeck-Loebenstein, B., 1999. TNFalpha plus IFNgamma induce the production of Alzheimer beta-amyloid peptides and decrease the secretion of APPs. FASEB J. 13 (1), 63–68.
Blasko, I., Veerhuis, R., Stampfer-Kountchev, M., Saurwein-Teissl, M., Eikelenboom, P., Grubeck-Loebenstein, B., 2000. Costimulatory effects of interferon-gamma and interleukin-1beta or tumor necrosis factor alpha on the synthesis of Abeta1-40 and Abeta1-42 by human astrocytes. Neurobiol. Dis. 7 (6 Pt B), 682–689. doi:http://dx.doi.org/10.1006/nbdi.2000.0321.
Bradley, L.M., Dalton, D.K., Croft, M., 1996. A direct role for IFN-gamma in regulation of Th1 cell development. J. Immunol. 157 (4), 1350–1358.
Brazelton, T.R., Rossi, F.M., Keshet, G.I., Blau, H.M., 2000. From marrow to brain: expression of neuronal phenotypes in adult mice. Science 290 (5497), 1775–1779.
Browne, T.C., McQuillan, K., McManus, R.M., O'Reilly, J.A., Mills, K.H., Lynch, M.A., 2013. IFN-gamma Production by amyloid beta-specific Th1 cells promotes microglial activation and increases plaque burden in a mouse model of Alzheimer's disease. J. Immunol. 190 (5), 2241–2251. doi:http://dx.doi.org/10.4049/jimmunol.1200947.
Brynskikh, A., Warren, T., Zhu, J., Kipnis, J., 2008. Adaptive immunity affects learning behavior in mice. Brain Behav. Immun. 22 (6), 861–869. doi:http://dx.doi.org/10.1016/j.bbi.2007.12.008.
Campos, A.C., Vaz, G.N., Saito, V.M., Teixeira, A.L., 2014. Further evidence for the role of interferon-gamma on anxiety- and depressive-like behaviors: involvement of hippocampal neurogenesis and NGF production. Neurosci. Lett. 578, 100–105. doi:http://dx.doi.org/10.1016/j.neulet.2014.06.039.
Carrithers, M.D., Visintin, I., Viret, C., Janeway Jr., C.S., 2002. Role of genetic background in P selectin-dependent immune surveillance of the central nervous system. J. Neuroimmunol. 129 (1–2), 51–57.
Chakrabarty, P., Ceballos-Diaz, C., Beccard, A., Janus, C., Dickson, D., Golde, T.E., Das, P., 2010. IFN-gamma promotes complement expression and attenuates amyloid plaque deposition in amyloid beta precursor protein transgenic mice. J. Immunol. 184 (9), 5333–5343. doi:http://dx.doi.org/10.4049/jimmunol.0903382.
Chakrabarty, P., Ceballos-Diaz, C., Lin, W.L., Beccard, A., Jansen-West, K., McFarland, N.R., Janus, C., Dickson, D., Das, P., Golde, T.E., 2011. Interferon-gamma induces progressive nigrostriatal degeneration and basal ganglia calcification. Nat. Neurosci. 14 (6), 694–696. doi:http://dx.doi.org/10.1038/nn.2829.
Chakrabarty, P., Li, A., Ceballos-Diaz, C., Eddy, J.A., Funk, C.C., Moore, B., DiNunno, N., Rosario, A.M., Cruz, P.E., Verbeeck, C., Sacino, A., Nix, S., Janus, C., Price, N.D., Das, P., Golde, T.E., 2015. IL-10 alters immunoproteostasis in APP mice, increasing plaque burden and worsening cognitive behavior. Neuron 85 (3), 519–533. doi:http://dx.doi.org/10.1016/j.neuron.2014.11.020.
Chang, Y.J., Holtzman, M.J., Chen, C.C., 2002. Interferon-gamma-induced epithelial ICAM-1 expression and monocyte adhesion. Involvement of protein kinase C-dependent c-Src tyrosine kinase activation pathway. J. Biol. Chem. 277 (9), 7118–7126. doi:http://dx.doi.org/10.1074/jbc.M109924200.
Chao, C.C., Hu, S., Molitor, T.W., Shaskan, E.G., Peterson, P.K., 1992. Activated microglia mediate neuronal cell injury via a nitric oxide mechanism. J. Immunol. 149 (8), 2736–2741.
Chung, I.Y., Benveniste, E.N., 1990. Tumor necrosis factor-alpha production by astrocytes. Induction by lipopolysaccharide, IFN-gamma, and IL-1 beta. J. Immunol. 144 (8), 2999–3007.
Cogle, C.R., Yachnis, A.T., Laywell, E.D., Zander, D.S., Wingard, J.R., Steindler, D.A., Scott, E.W., 2004. Bone marrow transdifferentiation in brain after transplantation: a retrospective study. Lancet 363 (9419), 1432–1437. doi:http://dx.doi.org/10.1016/S0140-6736(04)16102-3.
Cohen-Chalamish, S., Hasson, A., Weinberg, D., Namer, L.S., Banai, Y., Osman, F., Kaempfer, R., 2009. Dynamic refolding of IFN-gamma mRNA enables it to function as PKR activator and translation template. Nat. Chem. Biol. 5 (12), 896–903. doi:http://dx.doi.org/10.1038/nchembio.234.
Corbin, J.G., Kelly, D., Rath, E.M., Baerwald, K.D., Suzuki, K., Popko, B., 1996. Targeted CNS expression of interferon-gamma in transgenic mice leads to hypomyelination, reactive gliosis, and abnormal cerebellar development. Mol. Cell. Neurosci. 7 (5), 354–370. doi:http://dx.doi.org/10.1006/mcne.1996.0026.
Croitoru-Lamoury, J., Lamoury, F.M., Caristo, M., Suzuki, K., Walker, D., Takikawa, O., Taylor, R., Brew, B.J., 2011. Interferon-gamma regulates the proliferation and differentiation of mesenchymal stem cells via activation of indoleamine 2,3 dioxygenase (IDO). PLoS ONE 6 (2), e14698. doi:http://dx.doi.org/10.1371/journal.pone.0014698.
de Graaf, M.T., Smitt, P.A., Luitwieler, R.L., van Velzen, C., van den Broek, P.D., Kraan, J., Gratama, J.W., 2011. Central memory CD4+ T cells dominate the normal cerebrospinal fluid. Cytometry B Clin. Cytom. 80 (1), 43–50. doi:http://dx.doi.org/10.1002/cyto.b.20542.
de Weerd, N.A., Nguyen, T., 2012. The interferons and their receptors – distribution and regulation. Immunol. Cell Biol. 90 (5), 483–491. doi:http://dx.doi.org/10.1038/icb.2012.9.
Derecki, N.C., Cardani, A.N., Yang, C.H., Quinnies, K.M., Crihfield, A., Lynch, K.R., Kipnis, J., 2010. Regulation of learning and memory by meningeal immunity: a key role for IL-4. J. Exp. Med. 207 (5), 1067–1080. doi:http://dx.doi.org/10.1084/jem.20091419.
Derecki, N.C., Quinnies, K.M., Kipnis, J., 2011. Alternatively activated myeloid (M2) cells enhance cognitive function in immune compromised mice. Brain Behav. Immun. 25 (3), 379–385. doi:http://dx.doi.org/10.1016/j.bbi.2010.11.009.
El-Ansary, A., Al-Ayadhi, L., 2014. GABAergic/glutamatergic imbalance relative to excessive neuroinflammation in autism spectrum disorders. J. Neuroinflammation 11, 189. doi:http://dx.doi.org/10.1186/s12974-014-0189-0.
Elmore, M.R., Burton, M.D., Conrad, M.S., Rytych, J.L., Van Alstine, W.G., Johnson, R.W., 2014. Respiratory viral infection in neonatal piglets causes marked microglia activation in the hippocampus and deficits in spatial learning. J. Neurosci. 34 (6), 2120–2129. doi:http://dx.doi.org/10.1523/JNEUROSCI.2180-13.2014.
Filiano, A.J., Xu, Y., Tustison, N.J., Marsh, R.L., Baker, W., Smirnov, I., Overall, C.C., Gadani, S.P., Turner, S.D., Weng, Z., Peerzade, S.N., Chen, H., Lee, K.S., Scott, M.M., Beenhakker, M.P., Litvak, V., Kipnis, J., 2016. Unexpected role of interferon-gamma in regulating neuronal connectivity and social behaviour. Nature 535 (7612), 425–429. doi:http://dx.doi.org/10.1038/nature18626.
Garg, S.K., Kipnis, J., Banerjee, R., 2009. IFN-gamma and IL-4 differentially shape metabolic responses and neuroprotective phenotype of astrocytes. J. Neurochem. 108 (5), 1155–1166. doi:http://dx.doi.org/10.1111/j.1471-4159.2009.05872.x.
Getts, D.R., Matsumoto, I., Muller, M., Getts, M.T., Radford, J., Shrestha, B., Campbell, I.L., King, N.J., 2007. Role of IFN-gamma in an experimental murine model of West Nile virus-induced seizures. J. Neurochem. 103 (3), 1019–1030. doi:http://dx.doi.org/10.1111/j.1471-4159.2007.04798.x.
Giroux, M., Schmidt, M., Descoteaux, A., 2003. IFN-gamma-induced MHC class II expression: transactivation of class II transactivator promoter IV by IFN regulatory factor-1 is regulated by protein kinase C-alpha. J. Immunol. 171 (8), 4187–4194.
Griffin, R., Nally, R., Nolan, Y., McCartney, Y., Linden, J., Lynch, M.A., 2006. The age-related attenuation in long-term potentiation is associated with microglial activation. J. Neurochem. 99 (4), 1263–1272. doi:http://dx.doi.org/10.1111/j.1471-4159.2006.04165.x.
Gruber, L., Bunse, T., Weidinger, E., Reichard, H., Muller, N., 2014. Adjunctive recombinant human interferon gamma-1b for treatment-resistant schizophrenia in 2 patients. J. Clin. Psychiatry 75 (11), 1266–1267. doi:http://dx.doi.org/10.4088/JCP.14l09005.
Guillot-Sestier, M.V., Doty, K.R., Gate, D., Rodriguez Jr., J., Leung, B.P., Rezai-Zadeh, K., Town, T., 2015. Il10 deficiency rebalances innate immunity to mitigate Alzheimer-like pathology. Neuron 85 (3), 534–548. doi:http://dx.doi.org/10.1016/j.neuron.2014.12.068.
Guivernau, B., Bonet, J., Valls-Comamala, V., Bosch-Morato, M., Godoy, J.A., Inestrosa, N.C., Peralvarez-Marin, A., Fernandez-Busquets, X., Andreu, D., Oliva, B., Munoz, F.J., 2016. Amyloid-beta peptide nitrotyrosination stabilizes oligomers and enhances NMDAR-mediated toxicity. J. Neurosci. 36 (46), 11693–11703. doi:http://dx.doi.org/10.1523/JNEUROSCI.1081-16.2016.
Hallam, D.M., Capps, N.L., Travelstead, A.L., Brewer, G.J., Maroun, L.E., 2000. Evidence for an interferon-related inflammatory reaction in the trisomy 16 mouse brain leading to caspase-1-mediated neuronal apoptosis. J. Neuroimmunol. 110 (1–2), 66–75.
Hallam, D.M., Maroun, L.E., 1998. Anti-gamma interferon can prevent the premature death of trisomy 16 mouse cortical neurons in culture. Neurosci. Lett. 252 (1), 17–20.
Harris, D.P., Goodrich, S., Gerth, A.J., Peng, S.L., Lund, F.E., 2005. Regulation of IFN-gamma production by B effector 1 cells: essential roles for T-bet and the IFN-gamma receptor. J. Immunol. 174 (11), 6781–6790.
Heisler, J.M., O'Connor, J.C., 2015. Indoleamine 2,3-dioxygenase-dependent neurotoxic kynurenine metabolism mediates inflammation-induced deficit in recognition memory. Brain Behav. Immun. doi:http://dx.doi.org/10.1016/j.bbi.2015.06.022.
Hickey, W.F., 1999. Leukocyte traffic in the central nervous system: the participants and their roles. Semin. Immunol. 11 (2), 125–137. doi:http://dx.doi.org/10.1006/smim.1999.0168.
Hickey, W.F., Kimura, H., 1988. Perivascular microglial cells of the CNS are bone marrow-derived and present antigen in vivo. Science 239 (4837), 290–292.
Hoekstra, J.G., Cook, T.J., Stewart, T., Mattison, H., Dreisbach, M.T., Hoffer, Z.S., Zhang, J., 2015. Astrocytic dynamin-like protein 1 regulates neuronal protection against excitotoxicity in Parkinson disease. Am. J. Pathol. 185 (2), 536–549. doi:http://dx.doi.org/10.1016/j.ajpath.2014.10.022.
Hong, S., Beja-Glasser, V.F., Nfonoyim, B.M., Frouin, A., Li, S., Ramakrishnan, S., Merry, K.M., Shi, Q., Rosenthal, A., Barres, B.A., Lemere, C.A., Selkoe, D.J., Stevens, B., 2016. Complement and microglia mediate early synapse loss in Alzheimer mouse models. Science doi:http://dx.doi.org/10.1126/science.aad8373.
Hussain, R.Z., Hayardeny, L., Cravens, P.C., Yarovinsky, F., Eagar, T.N., Arellano, B., Deason, K., Castro-Rojas, C., Stuve, O., 2014. Immune surveillance of the central nervous system in multiple sclerosis – relevance for therapy and experimental models. J. Neuroimmunol. 276 (1–2), 9–17. doi:http://dx.doi.org/10.1016/j.jneuroim.2014.08.622.
Iliff, J.J., Wang, M., Liao, Y., Plogg, B.A., Peng, W., Gundersen, G.A., Benveniste, H., Vates, G.E., Deane, R., Goldman, S.A., Nagelhus, E.A., Nedergaard, M., 2012. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid beta. Sci. Transl. Med. 4 (147), 147ra11. doi:http://dx.doi.org/10.1126/scitranslmed.3003748.
Isaacs, A., Lindenmann, J., 1957. Virus interference. I. The interferon. Proc. R. Soc. Lond. B: Biol. Sci. 147 (927), 258–267.
Jarosinski, K.W., Massa, P.T., 2002. Interferon regulatory factor-1 is required for interferon-gamma-induced MHC class I genes in astrocytes. J. Neuroimmunol. 122 (1–2), 74–84.
Jemli, A., Inoubli, O., Trifa, F., Mechri, A., Zaafrane, F., Gaha, L., Jrad, B.B., 2016. IFNGR2 genetic polymorphism associated with sex-specific paranoid schizophrenia

risk. Nord. J. Psychiatry 1–6. doi:http://dx.doi.org/10.1080/08039488.2016.1216595.
Kasahara, T., Hooks, J.J., Dougherty, S.F., Oppenheim, J.J., 1983. Interleukin 2-mediated immune interferon (IFN-gamma) production by human T cells and T cell subsets. J. Immunol. 130 (4), 1784–1789.
Kawanokuchi, J., Mizuno, T., Takeuchi, H., Kato, H., Wang, J., Mitsuma, N., Suzumura, A., 2006. Production of interferon-gamma by microglia. Mult. Scler. 12 (5), 558–564.
Kim, H., Chen, L., Lim, G., Sung, B., Wang, S., McCabe, M.F., Rusanescu, G., Yang, L., Tian, Y., Mao, J., 2012. Brain indoleamine 2,3-dioxygenase contributes to the comorbidity of pain and depression. J. Clin. Invest. 122 (8), 2940–2954. doi:http://dx.doi.org/10.1172/JCI61884.
Kim, H.J., Eom, C.Y., Kwon, J., Joo, J., Lee, S., Nah, S.S., Kim, I.C., Jang, I.S., Chung, Y.H., Kim, S.I., Chung, J.H., Choi, J.S., 2012. Roles of interferon-gamma and its target genes in schizophrenia: proteomics-based reverse genetics from mouse to human. Proteomics 12 (11), 1815–1829. doi:http://dx.doi.org/10.1002/pmic.201100184.
Kim, I.J., Beck, H.N., Lein, P.J., Higgins, D., 2002. Interferon gamma induces retrograde dendritic retraction and inhibits synapse formation. J. Neurosci. 22 (11), 4530–4539 doi: 20026431.
Kim, S.J., Son, T.G., Kim, K., Park, H.R., Mattson, M.P., Lee, J., 2007. Interferon-gamma promotes differentiation of neural progenitor cells via the JNK pathway. Neurochem. Res. 32 (8), 1399–1406. doi:http://dx.doi.org/10.1007/s11064-007-9323-z.
Kipnis, J., Cohen, H., Cardon, M., Ziv, Y., Schwartz, M., 2004. T cell deficiency leads to cognitive dysfunction: implications for therapeutic vaccination for schizophrenia and other psychiatric conditions. Proc. Natl. Acad. Sci. U. S. A. 101 (21), 8180–8185. doi:http://dx.doi.org/10.1073/pnas.0402268101.
Kivisakk, P., Mahad, D.J., Callahan, M.K., Trebst, C., Tucky, B., Wei, T., Wu, L., Baekkevold, E.S., Lassmann, H., Staugaitis, S.M., Campbell, J.J., Ransohoff, R.M., 2003. Human cerebrospinal fluid central memory CD4+ T cells: evidence for trafficking through choroid plexus and meninges via P-selectin. Proc. Natl. Acad. Sci. U. S. A. 100 (14), 8389–8394. doi:http://dx.doi.org/10.1073/pnas.1433000100.
Kunis, G., Baruch, K., Miller, O., Schwartz, M., 2015. Immunization with a myelin-derived antigen activates the brain's choroid plexus for recruitment of immunoregulatory cells to the CNS and attenuates disease progression in a mouse model of ALS. J. Neurosci. 35 (16), 6381–6393. doi:http://dx.doi.org/10.1523/JNEUROSCI.3644-14.2015.
Kunis, G., Baruch, K., Rosenzweig, N., Kertser, A., Miller, O., Berkutzki, T., Schwartz, M., 2013. IFN-gamma-dependent activation of the brain's choroid plexus for CNS immune surveillance and repair. Brain 136 (Pt 11), 3427–3440. doi:http://dx.doi.org/10.1093/brain/awt259.
Kustova, Y., Sei, Y., Morse Jr., H.C., Basile, A.S., 1998. The influence of a targeted deletion of the IFNgamma gene on emotional behaviors. Brain Behav. Immun. 12 (4), 308–324. doi:http://dx.doi.org/10.1006/brbi.1998.0546.
Kwak, Y., Lundkvist, G.B., Brask, J., Davidson, A., Menaker, M., Kristensson, K., Block, G.D., 2008. Interferon-gamma alters electrical activity and clock gene expression in suprachiasmatic nucleus neurons. J. Biol. Rhythms 23 (2), 150–159. doi:http://dx.doi.org/10.1177/0748730407313355.
LaFerla, F.M., Sugarman, M.C., Lane, T.E., Leissring, M.A., 2000. Regional hypomyelination and dysplasia in transgenic mice with astrocyte-directed expression of interferon-gamma. J. Mol. Neurosci. 15 (1), 45–59. doi:http://dx.doi.org/10.1385/JMN:15:1:45.
Lassmann, H., Schmied, M., Vass, K., Hickey, W.F., 1993. Bone marrow derived elements and resident microglia in brain inflammation. Glia 7 (1), 19–24. doi:http://dx.doi.org/10.1002/glia.440070106.
Lau, L.T., Yu, A.C., 2001. Astrocytes produce and release interleukin-1, interleukin-6, tumor necrosis factor alpha and interferon-gamma following traumatic and metabolic injury. J. Neurotrauma 18 (3), 351–359. doi:http://dx.doi.org/10.1089/08977150151071035.
Lee, H., Brott, B.K., Kirkby, L.A., Adelson, J.D., Cheng, S., Feller, M.B., Datwani, A., Shatz, C.J., 2014. Synapse elimination and learning rules co-regulated by MHC class I H2-Db. Nature 509 (7499), 195–200. doi:http://dx.doi.org/10.1038/nature13154.
Lee, M., McGeer, E., McGeer, P.L., 2013. Neurotoxins released from interferon-gamma-stimulated human astrocytes. Neuroscience 229, 164–175. doi:http://dx.doi.org/10.1016/j.neuroscience.2012.10.033.
Li, A., Ceballos-Diaz, C., DiNunno, N., Levites, Y., Cruz, P.E., Lewis, J., Golde, T.E., Chakrabarty, P., 2015. IFN-gamma promotes tau phosphorylation without affecting mature tangles. FASEB J. 29 (10), 4384–4398. doi:http://dx.doi.org/10.1096/fj.15-275834.
Li, L., Walker, T.L., Zhang, Y., Mackay, E.W., Bartlett, P.F., 2010. Endogenous interferon gamma directly regulates neural precursors in the non-inflammatory brain. J. Neurosci. 30 (27), 9038–9050. doi:http://dx.doi.org/10.1523/JNEUROSCI.5691-09.2010.
Li, X., Chauhan, A., Sheikh, A.M., Patil, S., Chauhan, V., Li, X.M., Ji, L., Brown, T., Malik, M., 2009. Elevated immune response in the brain of autistic patients. J. Neuroimmunol. 207 (1–2), 111–116. doi:http://dx.doi.org/10.1016/j.jneuroim.2008.12.002.
Litteljohn, D., Cummings, A., Brennan, A., Gill, A., Chunduri, S., Anisman, H., Hayley, S., 2010. Interferon-gamma deficiency modifies the effects of a chronic stressor in mice: implications for psychological pathology. Brain Behav. Immun. 24 (3), 462–473. doi:http://dx.doi.org/10.1016/j.bbi.2009.12.001.
Litteljohn, D., Nelson, E., Hayley, S., 2014. IFN-gamma differentially modulates memory-related processes under basal and chronic stressor conditions. Front. Cell. Neurosci. 8, 391. doi:http://dx.doi.org/10.3389/fncel.2014.00391.
Lockrow, J.P., Fortress, A.M., Granholm, A.C., 2012. Age-related neurodegeneration and memory loss in down syndrome. Curr. Gerontol. Geriatr. Res. 2012, 463909. doi:http://dx.doi.org/10.1155/2012/463909.
Louveau, A., Harris, T.H., Kipnis, J., 2015a. Revisiting the mechanisms of CNS immune privilege. Trends Immunol. 36 (10), 569–577. doi:http://dx.doi.org/10.1016/j.it.2015.08.006.
Louveau, A., Smirnov, I., Keyes, T.J., Eccles, J.D., Rouhani, S.J., Peske, J.D., Derecki, N.C., Castle, D., Mandell, J.W., Lee, K.S., Harris, T.H., Kipnis, J., 2015b. Structural and functional features of central nervous system lymphatic vessels. Nature doi:http://dx.doi.org/10.1038/nature14432.
Maes, M., Scharpe, S., Meltzer, H.Y., Okayli, G., Bosmans, E., D'Hondt, P., Vanden Bossche, B.V., Cosyns, P., 1994. Increased neopterin and interferon-gamma secretion and lower availability of L-tryptophan in major depression: further evidence for an immune response. Psychiatry Res. 54 (2), 143–160.
Maes, M., Song, C., Lin, A., De Jongh, R., Van Gastel, A., Kenis, G., Bosmans, E., De Meester, I., Benoy, I., Neels, H., Demedts, P., Janca, A., Scharpe, S., Smith, R.S., 1998. The effects of psychological stress on humans: increased production of pro-inflammatory cytokines and a Th1-like response in stress-induced anxiety. Cytokine 10 (4), 313–318.
Maes, M., Song, C., Lin, A.H., Bonaccorso, S., Kenis, G., De Jongh, R., Bosmans, E., Scharpe, S., 1999. Negative immunoregulatory effects of antidepressants: inhibition of interferon-gamma and stimulation of interleukin-10 secretion. Neuropsychopharmacology 20 (4), 370–379. doi:http://dx.doi.org/10.1016/S0893-133X(98)00088-8.
Maher, F.O., Clarke, R.M., Kelly, A., Nally, R.E., Lynch, M.A., 2006. Interaction between interferon gamma and insulin-like growth factor-1 in hippocampus impacts on the ability of rats to sustain long-term potentiation. J. Neurochem. 96 (6), 1560–1571. doi:http://dx.doi.org/10.1111/j.1471-4159.2006.03664.x.
Makela, J., Koivuniemi, R., Korhonen, L., Lindholm, D., 2010. Interferon-gamma produced by microglia and the neuropeptide PACAP have opposite effects on the viability of neural progenitor cells. PLoS ONE 5 (6), e11091. doi:http://dx.doi.org/10.1371/journal.pone.0011091.
Mastrangelo, M.A., Sudol, K.L., Narrow, W.C., Bowers, W.J., 2009. Interferon-{gamma} differentially affects Alzheimer's disease pathologies and induces neurogenesis in triple transgenic-AD mice. Am. J. Pathol. 175 (5), 2076–2088. doi:http://dx.doi.org/10.2353/ajpath.2009.090059.
Medawar, P.B., 1948. Immunity to homologous grafted skin; the fate of skin homografts transplanted to the brain, to subcutaneous tissue, and to the anterior chamber of the eye. Br. J. Exp. Pathol. 29 (1), 58–69.
Mesquita, S.D., Ferreira, A.C., Gao, F., Coppola, G., Geschwind, D.H., Sousa, J.C., Correia-Neves, M., Sousa, N., Palha, J.A., Marques, F., 2015. The choroid plexus transcriptome reveals changes in type I and II interferon responses in a mouse model of Alzheimer's disease. Brain Behav. Immun. doi:http://dx.doi.org/10.1016/j.bbi.2015.06.008.
Michailidou, I., Willems, J.G., Kooi, E.J., van Eden, C., Gold, S.M., Geurts, J.J., Baas, F., Huitinga, I., Ramaglia, V., 2015. Complement C1q-C3-associated synaptic changes in multiple sclerosis hippocampus. Ann. Neurol. 77 (6), 1007–1026. doi:http://dx.doi.org/10.1002/ana.24398.
Mizuno, T., Zhang, G., Takeuchi, H., Kawanokuchi, J., Wang, J., Sonobe, Y., Jin, S., Takada, N., Komatsu, Y., Suzumura, A., 2008. Interferon-gamma directly induces neurotoxicity through a neuron specific, calcium-permeable complex of IFN-gamma receptor and AMPA GluR1 receptor. FASEB J. 22 (6), 1797–1806. doi:http://dx.doi.org/10.1096/fj.07-099499.
Monteiro, S., Ferreira, F.M., Pinto, V., Roque, S., Morais, M., de Sa-Calcada, D., Mota, C., Correia-Neves, M., Cerqueira, J.J., 2016. Absence of IFN[gamma] promotes hippocampal plasticity and enhances cognitive performance. Transl. Psychiatry 6, e707. doi:http://dx.doi.org/10.1038/tp.2015.194.
Mosser, D.M., 2003. The many faces of macrophage activation. J. Leukoc. Biol. 73 (2), 209–212.
Mount, M.P., Lira, A., Grimes, D., Smith, P.D., Faucher, S., Slack, R., Anisman, H., Hayley, S., Park, D.S., 2007. Involvement of interferon-gamma in microglial-mediated loss of dopaminergic neurons. J. Neurosci. 27 (12), 3328–3337. doi:http://dx.doi.org/10.1523/JNEUROSCI.5321-06.2007.
Muller, M., Fontana, A., Zbinden, G., Gahwiler, B.H., 1993. Effects of interferons and hydrogen peroxide on CA3 pyramidal cells in rat hippocampal slice cultures. Brain Res. 619 (1–2), 157–162.
Munder, M., Mallo, M., Eichmann, K., Modolell, M., 1998. Murine macrophages secrete interferon gamma upon combined stimulation with interleukin (IL)-12 and IL-18: a novel pathway of autocrine macrophage activation. J. Exp. Med. 187 (12), 2103–2108.
Myint, A.M., Bondy, B., Baghai, T.C., Eser, D., Nothdurfter, C., Schule, C., Zill, P., Muller, N., Rupprecht, R., Schwarz, M.J., 2013. Tryptophan metabolism and immunogenetics in major depression: a role for interferon-gamma gene. Brain Behav. Immun. 31, 128–133. doi:http://dx.doi.org/10.1016/j.bbi.2013.04.003.
Nelson, S.B., Valakh, V., 2015. Excitatory/inhibitory balance and circuit homeostasis in autism spectrum disorders. Neuron 87 (4), 684–698. doi:http://dx.doi.org/10.1016/j.neuron.2015.07.033.
Neumann, H., Schmidt, H., Cavalie, A., Jenne, D., Wekerle, H., 1997a. Major histocompatibility complex (MHC) class I gene expression in single neurons of the central nervous system: differential regulation by interferon (IFN)-gamma and tumor necrosis factor (TNF)-alpha. J. Exp. Med. 185 (2), 305–316.

Neumann, H., Schmidt, H., Wilharm, E., Behrens, L., Wekerle, H., 1997b. Interferon gamma gene expression in sensory neurons: evidence for autocrine gene regulation. J. Exp. Med. 186 (12), 2023–2031.
O'Connor, J.C., Andre, C., Wang, Y., Lawson, M.A., Szegedi, S.S., Lestage, J., Castanon, N., Kelley, K.W., Dantzer, R., 2009a. Interferon-gamma and tumor necrosis factor-alpha mediate the upregulation of indoleamine 2,3-dioxygenase and the induction of depressive-like behavior in mice in response to bacillus Calmette-Guerin. J. Neurosci. 29 (13), 4200–4209. doi:http://dx.doi.org/10.1523/JNEUROSCI.5032-08.2009.
O'Connor, J.C., Lawson, M.A., Andre, C., Moreau, M., Lestage, J., Castanon, N., Kelley, K.W., Dantzer, R., 2009b. Lipopolysaccharide-induced depressive-like behavior is mediated by indoleamine 2,3-dioxygenase activation in mice. Mol. Psychiatry 14 (5), 511–522. doi:http://dx.doi.org/10.1038/sj.mp.4002148.
Olsson, T., Zhi, W.W., Hojeberg, B., Kostulas, V., Jiang, Y.P., Anderson, G., Ekre, H.P., Link, H., 1990. Autoreactive T lymphocytes in multiple sclerosis determined by antigen-induced secretion of interferon-gamma. J. Clin. Invest. 86 (3), 981–985. doi:http://dx.doi.org/10.1172/JCI114800.
Oxenkrug, G.F., 2011. Interferon-gamma-inducible kynurenines/pteridines inflammation cascade: implications for aging and aging-associated psychiatric and medical disorders. J. Neural Transm. 118 (1), 75–85. doi:http://dx.doi.org/10.1007/s00702-010-0475-7.
Panitch, H.S., Hirsch, R.L., Haley, A.S., Johnson, K.P., 1987. Exacerbations of multiple sclerosis in patients treated with gamma interferon. Lancet 1 (8538), 893–895.
Paul-Samojedny, M., Owczarek, A., Suchanek, R., Kowalczyk, M., Fila-Danilow, A., Borkowska, P., Kucia, K., Kowalski, J., 2011. Association study of interferon gamma (IFN-gamma) +874T/A gene polymorphism in patients with paranoid schizophrenia. J. Mol. Neurosci. 43 (3), 309–315. doi:http://dx.doi.org/10.1007/s12031-010-9442-x.
Pellicano, E., 2010. The development of core cognitive skills in autism: a 3-year prospective study. Child Dev. 81 (5), 1400–1416. doi:http://dx.doi.org/10.1111/j.1467-8624.2010.01481.x.
Pereira, L., Medina, R., Baena, M., Planas, A.M., Pozas, E., 2015. IFN gamma regulates proliferation and neuronal differentiation by STAT1 in adult SVZ niche. Front. Cell. Neurosci. 9, 270. doi:http://dx.doi.org/10.3389/fncel.2015.00270.
Piccio, L., Rossi, B., Scarpini, E., Laudanna, C., Giagulli, C., Issekutz, A.C., Vestweber, D., Butcher, E.C., Constantin, G., 2002. Molecular mechanisms involved in lymphocyte recruitment in inflamed brain microvessels: critical roles for P-selectin glycoprotein ligand-1 and heterotrimeric G(i)-linked receptors. J. Immunol. 168 (4), 1940–1949.
Pitt, D., Werner, P., Raine, C.S., 2000. Glutamate excitotoxicity in a model of multiple sclerosis. Nat. Med. 6 (1), 67–70. doi:http://dx.doi.org/10.1038/71555.
Popko, B., Corbin, J.G., Baerwald, K.D., Dupree, J., Garcia, A.M., 1997. The effects of interferon-gamma on the central nervous system. Mol. Neurobiol. 14 (1–2), 19–35. doi:http://dx.doi.org/10.1007/BF02740619.
Querfurth, H.W., LaFerla, F.M., 2010. Alzheimer's disease. N. Engl. J. Med. 362 (4), 329–344. doi:http://dx.doi.org/10.1056/NEJMra0909142.
Radjavi, A., Smirnov, I., Derecki, N., Kipnis, J., 2014a. Dynamics of the meningeal CD4 (+) T-cell repertoire are defined by the cervical lymph nodes and facilitate cognitive task performance in mice. Mol. Psychiatry 19 (5), 531–533. doi:http://dx.doi.org/10.1038/mp.2013.79.
Radjavi, A., Smirnov, I., Kipnis, J., 2014b. Brain antigen-reactive CD4+ T cells are sufficient to support learning behavior in mice with limited T cell repertoire. Brain Behav. Immun. 35, 58–63. doi:http://dx.doi.org/10.1016/j.bbi.2013.08.013.
Ransohoff, R.M., Engelhardt, B., 2012. The anatomical and cellular basis of immune surveillance in the central nervous system. Nat. Rev. Immunol. 12 (9), 623–635. doi:http://dx.doi.org/10.1038/nri3265.
Ransohoff, R.M., Kivisakk, P., Kidd, G., 2003. Three or more routes for leukocyte migration into the central nervous system. Nat. Rev. Immunol. 3 (7), 569–581. doi:http://dx.doi.org/10.1038/nri1130.
Reale, M., Iarlori, C., Thomas, A., Gambi, D., Perfetti, B., Di Nicola, M., Onofrj, M., 2009. Peripheral cytokines profile in Parkinson's disease. Brain Behav. Immun. 23 (1), 55–63. doi:http://dx.doi.org/10.1016/j.bbi.2008.07.003.
Schafer, D.P., Lehrman, E.K., Kautzman, A.G., Koyama, R., Mardinly, A.R., Yamasaki, R., Ransohoff, R.M., Greenberg, M.E., Barres, B.A., Stevens, B., 2012. Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. Neuron 74 (4), 691–705. doi:http://dx.doi.org/10.1016/j.neuron.2012.03.026.
Schmidt, F.M., Lichtblau, N., Minkwitz, J., Chittka, T., Thormann, J., Kirkby, K.C., Sander, C., Mergl, R., Fasshauer, M., Stumvoll, M., Holdt, L.M., Teupser, D., Hegerl, U., Himmerich, H., 2014. Cytokine levels in depressed and non-depressed subjects, and masking effects of obesity. J. Psychiatr. Res. 55, 29–34. doi:http://dx.doi.org/10.1016/j.jpsychires.2014.04.021.
Schwartz, M., 2015. Neuroimmunity: How New Brain Science will Revolutionize the Way We Live and Age. Yale University Press, New Haven, CT.
Scimemi, A., Meabon, J.S., Woltjer, R.L., Sullivan, J.M., Diamond, J.S., Cook, D.G., 2013. Amyloid-beta1-42 slows clearance of synaptically released glutamate by mislocalizing astrocytic GLT-1. J. Neurosci. 33 (12), 5312–5318. doi:http://dx.doi.org/10.1523/JNEUROSCI.5274-12.2013.
Seifert, H.A., Collier, L.A., Chapman, C.B., Benkovic, S.A., Willing, A.E., Pennypacker, K. R., 2014. Pro-inflammatory interferon gamma signaling is directly associated with stroke induced neurodegeneration. J. Neuroimmune Pharmacol. 9 (5), 679–689. doi:http://dx.doi.org/10.1007/s11481-014-9560-2.
Serre-Miranda, C., Roque, S., Santos, N.C., Portugal-Nunes, C., Costa, P., Palha, J.A., Sousa, N., Correia-Neves, M., 2015. Effector memory CD4(+) T cells are associated with cognitive performance in a senior population. Neurol. Neuroimmunol. Neuroinflamm. 2 (1), e54. doi:http://dx.doi.org/10.1212/NXI.0000000000000054.
Smeltz, R.B., Chen, J., Ehrhardt, R., Shevach, E.M., 2002. Role of IFN-gamma in Th1 differentiation: IFN-gamma regulates IL-18R alpha expression by preventing the negative effects of IL-4 and by inducing/maintaining IL-12 receptor beta 2 expression. J. Immunol. 168 (12), 6165–6172.
Spencer, N.G., Schilling, T., Miralles, F., Eder, C., 2016. Mechanisms underlying interferon-gamma-induced priming of microglial reactive oxygen species production. PLoS ONE 11 (9), e0162497. doi:http://dx.doi.org/10.1371/journal.pone.0162497.
Stellwagen, D., Malenka, R.C., 2006. Synaptic scaling mediated by glial TNF-alpha. Nature 440 (7087), 1054–1059. doi:http://dx.doi.org/10.1038/nature04671.
Sun, L., Tian, Z., Wang, J., 2010. A direct cross-talk between interferon-gamma and sonic hedgehog signaling that leads to the proliferation of neuronal precursor cells. Brain Behav. Immun. 24 (2), 220–228. doi:http://dx.doi.org/10.1016/j.bbi.2009.09.016.
Supekar, K., Uddin, L.Q., Khouzam, A., Phillips, J., Gaillard, W.D., Kenworthy, L.E., Yerys, B.E., Vaidya, C.J., Menon, V., 2013. Brain hyperconnectivity in children with autism and its links to social deficits. Cell Rep. 5 (3), 738–747. doi:http://dx.doi.org/10.1016/j.celrep.2013.10.001.
Suzuki, Y., Claflin, J., Wang, X., Lengi, A., Kikuchi, T., 2005. Microglia and macrophages as innate producers of interferon-gamma in the brain following infection with *Toxoplasma gondii*. Int. J. Parasitol. 35 (1), 83–90. doi:http://dx.doi.org/10.1016/j.ijpara.2004.10.020.
Tanner, D.C., Cherry, J.D., Mayer-Proschel, M., 2011. Oligodendrocyte progenitors reversibly exit the cell cycle and give rise to astrocytes in response to interferon-gamma. J. Neurosci. 31 (16), 6235–6246. doi:http://dx.doi.org/10.1523/JNEUROSCI.5905-10.2011.
Tostes, M.H., Teixeira, H.C., Gattaz, W.F., Brandao, M.A., Raposo, N.R., 2012. Altered neurotrophin, neuropeptide, cytokines and nitric oxide levels in autism. Pharmacopsychiatry 45 (6), 241–243. doi:http://dx.doi.org/10.1055/s-0032-1301914.
Traugott, U., Lebon, P., 1988. Interferon-gamma and Ia antigen are present on astrocytes in active chronic multiple sclerosis lesions. J. Neurol. Sci. 84 (2–3), 257–264.
Tsurimoto, T., Stillman, B., 1990. Functions of replication factor C and proliferating-cell nuclear antigen: functional similarity of DNA polymerase accessory proteins from human cells and bacteriophage T4. Proc. Natl. Acad. Sci. U. S. A. 87 (3), 1023–1027.
Van Laar, V.S., Roy, N., Liu, A., Rajprohat, S., Arnold, B., Dukes, A.A., Holbein, C.D., Berman, S.B., 2015. Glutamate excitotoxicity in neurons triggers mitochondrial and endoplasmic reticulum accumulation of Parkin, and, in the presence of N-acetyl cysteine, mitophagy. Neurobiol. Dis. 74, 180–193. doi:http://dx.doi.org/10.1016/j.nbd.2014.11.015.
Vardjan, N., Gabrijel, M., Potokar, M., Svajger, U., Kreft, M., Jeras, M., de Pablo, Y., Faiz, M., Pekny, M., Zorec, R., 2012. IFN-gamma-induced increase in the mobility of MHC class II compartments in astrocytes depends on intermediate filaments. J. Neuroinflammation 9, 144. doi:http://dx.doi.org/10.1186/1742-2094-9-144.
Vasek, M.J., Garber, C., Dorsey, D., Durrant, D.M., Bollman, B., Soung, A., Yu, J., Perez-Torres, C., Frouin, A., Wilton, D.K., Funk, K., DeMasters, B.K., Jiang, X., Bowen, J.R., Mennerick, S., Robinson, J.K., Garbow, J.R., Tyler, K.L., Suthar, M.S., Schmidt, R.E., Stevens, B., Klein, R.S., 2016. A complement-microglial axis drives synapse loss during virus-induced memory impairment. Nature 534 (7608), 538–543. doi:http://dx.doi.org/10.1038/nature18283.
Vetlugina, T.P., Lobacheva, O.A., Sergeeva, S.A., Nikitina, V.B., Nevidimova, T.I., Semke, A.V., 2016. Adjunctive use of interferon gamma inducer for treatment of patients with schizophrenia. Acta Neuropsychiatr. 28 (3), 149–156. doi:http://dx.doi.org/10.1017/neu.2015.60.
Vikman, K.S., Duggan, A.W., Siddall, P.J., 2007. Interferon-gamma induced disruption of GABAergic inhibition in the spinal dorsal horn in vivo. Pain 133 (1–3), 18–28. doi:http://dx.doi.org/10.1016/j.pain.2007.02.010.
Vikman, K.S., Owe-Larsson, B., Brask, J., Kristensson, K.S., Hill, R.H., 2001. Interferon-gamma-induced changes in synaptic activity and AMPA receptor clustering in hippocampal cultures. Brain Res. 896 (1–2), 18–29.
Vom Berg, J., Prokop, S., Miller, K.R., Obst, J., Kalin, R.E., Lopategui-Cabezas, I., Wegner, A., Mair, F., Schipke, C.G., Peters, O., Winter, Y., Becher, B., Heppner, F.L., 2012. Inhibition of IL-12/IL-23 signaling reduces Alzheimer's disease-like pathology and cognitive decline. Nat. Med. 18 (12), 1812–1819. doi:http://dx.doi.org/10.1038/nm.2965.
Walter, B.A., Valera, V.A., Takahashi, S., Matsuno, K., Ushiki, T., 2006. Evidence of antibody production in the rat cervical lymph nodes after antigen administration into the cerebrospinal fluid. Arch. Histol. Cytol. 69 (1), 37–47.
Walter, J., Honsek, S.D., Illes, S., Wellen, J.M., Hartung, H.P., Rose, C.R., Dihne, M., 2011. A new role for interferon gamma in neural stem/precursor cell dysregulation. Mol. Neurodegener. 6, 18. doi:http://dx.doi.org/10.1186/1750-1326-6-18.
Wang, J., Lin, W., Popko, B., Campbell, I.L., 2004. Inducible production of interferon-gamma in the developing brain causes cerebellar dysplasia with activation of the Sonic hedgehog pathway. Mol. Cell. Neurosci. 27 (4), 489–496. doi:http://dx.doi.org/10.1016/j.mcn.2004.08.004.
Wang, X., Suzuki, Y., 2007. Microglia produce IFN-gamma independently from T cells during acute toxoplasmosis in the brain. J. Interferon Cytokine Res. 27 (7), 599–605. doi:http://dx.doi.org/10.1089/jir.2006.0157.
Wei, M., Li, L., Meng, R., Fan, Y., Liu, Y., Tao, L., Liu, X., Wu, C., 2010. Suppressive effect of diazepam on IFN-gamma production by human T cells. Int. Immunopharmacol. 10 (3), 267–271. doi:http://dx.doi.org/10.1016/j.intimp.2009.11.009.
Wei, Y.P., Kita, M., Shinmura, K., Yan, X.Q., Fukuyama, R., Fushiki, S., Imanishi, J., 2000. Expression of IFN-gamma in cerebrovascular endothelial cells from aged

mice. J. Interferon Cytokine Res. 20 (4), 403–409. doi:http://dx.doi.org/10.1089/107999000312342.
Wheelock, E.F., 1965. Interferon-Like Virus-Inhibitor Induced in Human Leukocytes by Phytohemagglutinin. Science 149 (3681), 310–311. doi:http://dx.doi.org/10.1126/science.149.3681.310.
Wolf, S.A., Steiner, B., Akpinarli, A., Kammertoens, T., Nassenstein, C., Braun, A., Blankenstein, T., Kempermann, G., 2009. CD4-positive T lymphocytes provide a neuroimmunological link in the control of adult hippocampal neurogenesis. J. Immunol. 182 (7), 3979–3984. doi:http://dx.doi.org/10.4049/jimmunol.0801218.
Xiao, B.G., Link, H., 1998. IFN-gamma production of adult rat astrocytes triggered by TNF-alpha. Neuroreport 9 (7), 1487–1490.
Yamamoto, M., Kiyota, T., Horiba, M., Buescher, J.L., Walsh, S.M., Gendelman, H.E., Ikezu, T., 2007. Interferon-gamma and tumor necrosis factor-alpha regulate amyloid-beta plaque deposition and beta-secretase expression in Swedish mutant APP transgenic mice. Am. J. Pathol. 170 (2), 680–692. doi:http://dx.doi.org/10.2353/ajpath.2007.060378.
Ye, J., Ortaldo, J.R., Conlon, K., Winkler-Pickett, R., Young, H.A., 1995. Cellular and molecular mechanisms of IFN-gamma production induced by IL-2 and IL-12 in a human NK cell line. J. Leukoc. Biol. 58 (2), 225–233.
Yilmaz, G., Arumugam, T.V., Stokes, K.Y., Granger, D.N., 2006. Role of T lymphocytes and interferon-gamma in ischemic stroke. Circulation 113 (17), 2105–2112. doi:http://dx.doi.org/10.1161/CIRCULATIONAHA.105.593046.
Yoshimoto, T., Okamura, H., Tagawa, Y.I., Iwakura, Y., Nakanishi, K., 1997. Interleukin 18 together with interleukin 12 inhibits IgE production by induction of interferon-gamma production from activated B cells. Proc. Natl. Acad. Sci. U. S. A. 94 (8), 3948–3953.
Zhu, P.J., Huang, W., Kalikulov, D., Yoo, J.W., Placzek, A.N., Stoica, L., Zhou, H., Bell, J.C., Friedlander, M.J., Krnjevic, K., Noebels, J.L., Costa-Mattioli, M., 2011. Suppression of PKR promotes network excitability and enhanced cognition by interferon-gamma-mediated disinhibition. Cell 147 (6), 1384–1396. doi:http://dx.doi.org/10.1016/j.cell.2011.11.029.
Ziv, Y., Ron, N., Butovsky, O., Landa, G., Sudai, E., Greenberg, N., Cohen, H., Kipnis, J., Schwartz, M., 2006. Immune cells contribute to the maintenance of neurogenesis and spatial learning abilities in adulthood. Nat. Neurosci. 9 (2), 268–275. doi:http://dx.doi.org/10.1038/nn1629.