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Interferons: A molecular switch between damage and repair in ageing and Alzheimer's disease

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ABSTRACT

Alzheimer's disease was first described over 100 years ago, yet it remains incurable and affects 44 million people worldwide. Traditionally, research has largely focused on the amyloid cascade hypothesis, but interest in the importance of inflammation in the progression of the disease has recently been increasing. Interferons, a large family of cytokines that trigger the immune system, are believed to play a crucial role in the pathology of Alzheimer's disease. This review focuses on how interferons affect the brain during ageing and whether they could be candidate therapeutic targets for the treatment of Alzheimer's disease.

1. Introduction

Alzheimer's disease is the most common form of dementia and affects 44 million patients worldwide. These patients experience progressive memory loss and cognitive decline, and their brain is characterised by extracellular accumulation of amyloid beta (Aβ) in senile plaques. Although Aloïs Alzheimer described the pathological hallmarks of Alzheimer's disease back in 1907 (Alzheimer, 1907), no treatment to reverse, slow down or halt the disease exists. As populations age, the number of patients double every 20 years, creating an urgent need for a therapy (Prince et al., 2013).

Over the last decades, research has been mostly focused on the amyloid cascade hypothesis (Karran and De Strooper, 2016). This hypothesis states that accumulation of Aβ peptides, derived from amyloidogenic cleavage of APP (β-amyloid precursor protein), causes a neurodegenerative process in the brain (Bolos et al., 2017). More recently, the progression of Alzheimer's disease is believed to correlate with the increased levels of soluble $A\beta_{1-42}$ oligomers (McLean et al., 1999), which lead to activation of cytokines, complement proteins, and chemokines, causing inflammation (Akiyama et al., 2000). Moreover, a positive correlation between pro-inflammatory cytokines and cognitive decline has been reported (Taylor et al., 2014; Holmes et al., 2009). Furthermore, genome-wide studies revealed various inflammation-related proteins as risk factors for Alzheimer's disease, such as triggering receptor expression on myeloid cells 2 (TREM2), complement receptor 1 (CR1), and CD33 (Zhang et al., 2013). Clearly, neuroinflammation plays an important role in Alzheimer's disease and occurs early during disease progression, even before the appearance of the pathological hallmarks of the disease (Wright et al., 2013). However, until now, anti-inflammatory drugs have not been useful for the treatment of Alzheimer's disease (Miguel-Alvarez et al., 2015; Anti-inflammatory drugs fall short in Alzheimer's disease, 2008). In this review, we will focus on inflammation, and particularly the role of interferons (IFNs), at the brain barriers and its role in Alzheimer's disease.

2. Immune surveillance in the brain

To ensure proper communication in the central nervous system (CNS), a balanced and well-controlled micro-environment is necessary (De Bock et al., 2014). Tight barriers, such as the blood–brain barrier (BBB) and the blood–cerebrospinal fluid (CSF) barrier, separate the brain from the periphery to establish brain homeostasis (Fig. 2) (De Bock et al., 2014; Redzic, 2011; Abbott et al., 2010).

The BBB is formed by the neurovascular unit, which consists of tightly connected endothelial cells associated with perivascular astrocytic end-feet, pericytes, and microglia (De Bock et al., 2014). The plasma membranes of the astrocytic end-feet are contiguous with the basal lamina (Hawkins and Davis, 2005). This provides structural support around the pericytes and endothelial cells. The blood–CSF barrier is formed by a tightly connected single layer of choroid plexus epithelial (CPE) cells. These cells rest on a basal lamina and stroma, which contain capillaries, dendritic cells, and macrophages (Demeestere et al., 2015a). In contrast to the BBB, the capillaries of the choroid plexus are highly fenestrated (Gorle et al., 2016).

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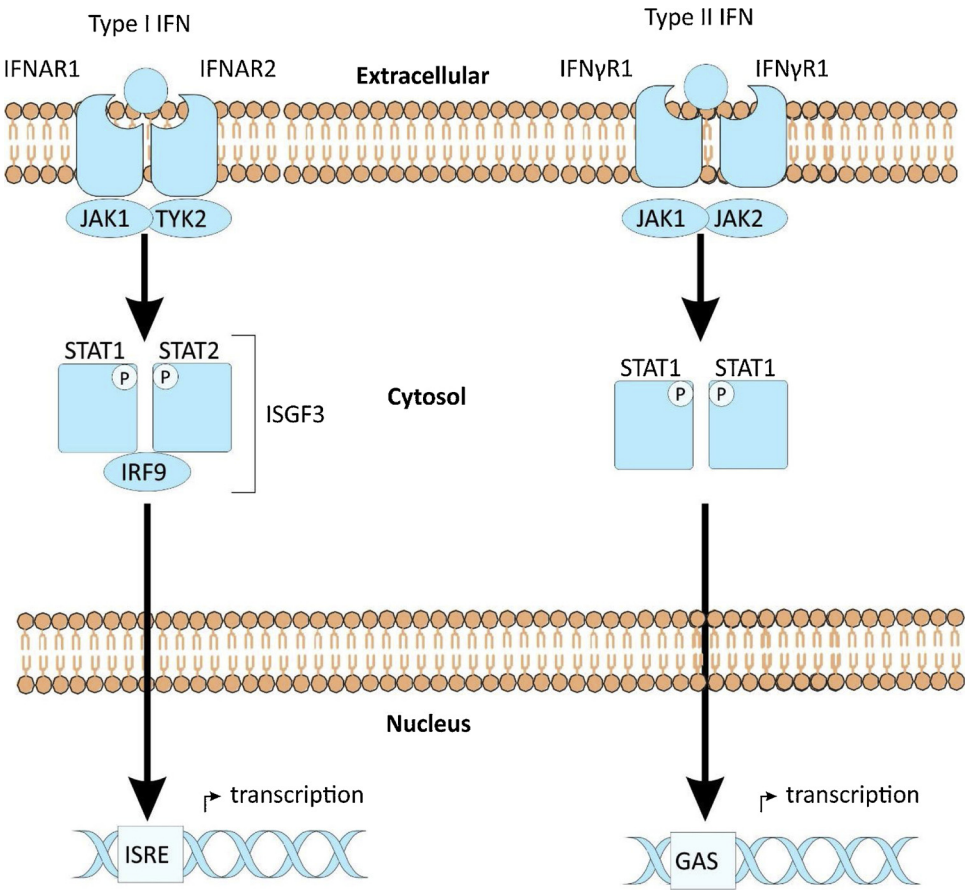

Fig. 1. Overview of the type I and type II IFN signalling pathways. (Left) Upon binding of type I IFN ligands, the IFNAR1/2 complex, associated with JAK1 and TYK2, causes phosphorylation of the STAT1–STAT2 complex, which binds to IRF9 to form ISGF3. The ISGF3 complex translocates to the nucleus and binds to the ISRE signature sequences to induce gene expression. **(Right)** Binding of IFNγ to IFNγR1 leads to activation of JAK1 and JAK2, leading to phosphorylation of STAT1, which in turn leads to the formation of a STAT1-STAT1 homodimer. This complex translocates to the nucleus, where it activates genes with a GAS signature. IFN: interferon; IFNAR: interferon-α/β receptor; JAK: Janus kinase; TYK2: tyrosine kinase; STAT: signal transducer and activator of transcription; IRF9: interferon regulatory factor; ISGF3: interferon-stimulated gene factor 3; ISRE: interferon-sensitive response element; GAS: gamma-activated sequence.

The brain was long thought to be an 'immune-privileged site' free of immune reactions, in part due to the presence of brain barriers (Perry, 1998; Galea et al., 2007). Although the entry of immune cells into the brain is limited, it is important in normal physiology, immune pathology, and host defence (Galea et al., 2007). Furthermore, the entry of immune cells plays a role in surveillance of the brain (Engelhardt and Coisne, 2011; Ransohoff et al., 2003), and it is essential for CNS maintenance and repair (Demeestere et al., 2015b; Kipnis et al., 2004; Wolf et al., 2009) and in learning processes (Ziv et al., 2006). The theory of the brain being 'immune-privileged' has been revised; the brain is no longer seen as absolutely immune privileged but rather as immunologically unique compared to the other organs (Galea et al., 2007; Louveau et al., 2015).

At the choroid plexus, the immune response is similar to that of the body (Galea et al., 2007). In fact, the CPE cells are thought to be important sensors of inflammatory stimuli in both the periphery and the CNS because of their unique position between the peripheral blood and the CNS (Marques et al., 2007; Vandenbroucke et al., 2012; Brkic et al., 2015; Balusu et al., 2016; Gorle et al., 2017). Although the BBB is described as an absolute immunological barrier that blocks entry of leukocytes into the CNS (Shechter et al., 2013a), immune cell trafficking can occur under inflammatory circumstances (Lutz et al., 2017; Larochelle et al., 2011; Banks and Erickson, 2010). The blood–CSF barrier acts as a permissive gate allowing selective immune trafficking and immunologic inspection of cells (Demeestere et al., 2015b; Shechter et al., 2013a; Strazielle and Ghersi-Egea, 2000). Indeed, the choroid plexus can produce molecules involved in leukocyte adhesion to enable activated immune cells to pass (Demeestere et al., 2015b; Marques et al., 2007; Meeker et al., 2012; Engelhardt and Ransohoff, 2005; Marques et al., 2009).

In some neuroinflammatory conditions, entry of circulating leukocytes *via* the BBB or the blood–CSF barrier worsens the damage. Nevertheless, infiltration of leukocytes can also contribute to repair (Demeestere et al., 2015b). For example, infiltrating leukocytes promote tissue recovery after CNS injuries such as stroke and spinal cord injury (Schwartz and Baruch, 2014; Shechter et al., 2013b). However, in traumatic brain injury and multiple sclerosis, infiltration of leukocytes is believed to worsen the disease (Shechter et al., 2013a; Aube et al., 2014; Semple et al., 2010; Chen et al., 2003; Dimitrijevic et al., 2007). Therefore, tightly controlled mechanisms are in place to maintain the balance between damage and repair (Demeestere et al., 2015b; Becher, 2008; Stolp et al., 2013).

3. IFNs and their influence on the CNS

IFNs constitute a superfamily of pleiotropic, helical cytokines that are important for the development of innate and acquired immune defences. They were discovered by Isaacs and Lindenmann based on their ability to interfere with viral infections (Isaacs and Lindenmann, 1957) and to form the first line of defence against pathogenic infections. IFNs are involved in the initiation and regulation of pro-inflammatory cytokines and activate several signalling pathways (de Weerd et al., 2007). However, they also play a role in behaviour, thermoregulation, and neuronal activity and plasticity (de Weerd et al., 2007; de Weerd and Nguyen, 2012).

IFNs can be divided in three classes based on their receptors: types I, II, and III (Nallar and Kalvakolanu, 2014). Type I IFNs are the best known IFNs and consist of 14 subtypes that bind to the IFNα/β receptor (IFNAR1/2); IFNα and IFNβ are the most studied type I IFNs. On the other hand, IFNγ is the only type II IFN and it signals *via* the IFNγ receptor complex (IFNγR1). Type III IFNs include IFNλ1, IFNλ2, and IFNλ3 and use a receptor complex consisting of interleukin 10 receptor 2 (IL10R2) and IL-28 receptor alpha (IL28RA) (de Weerd and Nguyen, 2012).

Binding of IFNs to their respective receptors induces a signalling cascade *via* the classical Janus-associated kinase (JAK) pathway and the signal transducer and activator of transcription (STAT) pathway (Fig. 1). After type I IFNs bind to the IFNAR1/2 complex, Tyk-2 and Jak1 phosphorylate the STAT1–STAT2 complex, which in turn binds to interferon regulatory factor 9 (IRF9) to form interferon signalling factor 3 (ISGF3). This complex translocates to the nucleus and binds to interferon regulatory elements (ISRE) to induce the expression of the corresponding genes (Fig. 1) (Schneider et al., 2014). Binding of IFNγ to IFNγR1 leads to activation of JAK1 and JAK2. This heterodimer phosphorylates STAT1, inducing the formation of a STAT1 homodimer that translocates to the nucleus, activating genes with a gamma IFN activation site (GAS) (Fig. 1) (de Weerd and Nguyen, 2012). Type III IFNs activate the JAK–STAT pathway in a way resembling that of type I IFNs (de Weerd and Nguyen, 2012).

Type I IFNs are produced by almost every cell type in the body, but plasmacytoid dendritic cells (pDC) are the strongest producers of these IFNs. These cells can migrate to the brain during inflammation (Owens et al., 2014). In the brain, type I IFNs are produced mainly by microglia and astrocytes, but neurons have also been shown to express type I IFNs (Owens et al., 2014). Production of type I IFNs is induced by Toll-like receptors (TLR) *via* TIR domain-containing adapter inducing IFNβ (TRIF) or myeloid differentiation primary response-88 (MyD88) (Hofer and Campbell, 2013).

T cells and natural killer (NK) cells are the main sources of IFNγ in the body. In the non-inflamed brain, IFNγ is released in small amounts by astrocytes, fibroblasts, neurons, and endothelial cells (Rady et al., 1995; De Simone et al., 1998; Neumann et al., 1997; Wei et al., 2000), as well as by activated microglia (Li et al., 2001; Bogdan and Schleicher, 2006). Production of IFNγ is regulated by cytokines: interleukin (IL)-12 and IL-18 induce the expression of IFNγ, whereas IL-4 and IL-10 diminish its expression (Schroder et al., 2004).

The levels of type III IFNs are low in the brain (Owens et al., 2014), and in contrast to IFNAR1/2 and IFNγR1, which are expressed on numerous cell types in the CNS, the receptor for type III IFNs is expressed only on neurons, pDCs, and epithelial cells (Owens et al., 2014). Therefore, in this review we will focus on type I and type II IFNs.

The effects of type I and type II IFNs on the CNS depends on numerous factors, such as the subtype, the concentration, the duration of the signal, the cell type involved, and the presence of other cytokines (Deczkowska et al., 2016). Below, a few examples of the influence of type I and type II IFNs on the CNS are described.

3.1. Type I IFNS

Type I IFNs are important for limiting infection in both the periphery and the CNS (Halford et al., 1997; Paul et al., 2007). However, several studies have shown that increased levels of type I IFNs are detrimental to the brain. Overexpression of IFNα in glial cells leads to brain pathology and behavioural deficits (Campbell et al., 1999), and increased expression of IFNα in astrocytes leads to encephalopathy associated with gliosis and neurodegeneration (Akwa et al., 1998). Moreover, several neural diseases are associated with excessive IFNα in the serum and CSF, such as Aicardi-Goutières syndrome (Lebon et al., 2002), HIV associated encephalitis (Rho et al., 1995), and systemic lupus erythematosus (SLE) (Meyer, 2009).

Furthermore, behavioural and cognitive changes are driven by the expression of IFNAR1 on endothelial and epithelial cells (Blank et al., 2016). Type I IFNs decrease the expression of brain-derived neurotrophic factor (BDNF), insulin-like growth factor 1 (IGF1), and other neurotrophic factors (Baruch et al., 2014), but they also induce pro-apoptotic signals in neurons (Hertzog et al., 1994).

Since type I IFNs can modulate the immune response, they are used in the form of intramuscular injections to treat, for example, multiple sclerosis and hepatitis. In addition to its immunomodulatory effects, IFN treatment was also shown to stabilise the BBB (Kraus and Oschmann, 2006). However, patients treated with type I IFNs have an increased risk of depression and cognitive decline (Reichenberg et al., 2005; Dieperink et al., 2000; Raison et al., 2005). Although IFNα is used as a treatment for hepatitis, patients sometimes develop Parkinson-like symptoms (Kajihara et al., 2010; Almeida et al., 2009; Mizoi et al., 1997). Likewise, type I IFNs aggravate disease in two mouse models of Parkinson's disease, namely, the α-synuclein model and the rotenone model (Qin et al., 2016; Main et al., 2017). Moreover, mice in which type I IFN signalling is induced by stimulation of TLR3 signalling develop symptoms resembling Alzheimer's disease (Krstic et al., 2012) whereas blocking type I IFN signalling leads to neuroprotection in the MPTP-toxin model of Parkinson's disease (Main et al., 2016). In contrast, mice and humans deficient in IFNβ develop Parkinson-like symptoms (Ejlerskov et al., 2015). These contradictory results show that type I IFNs have both beneficial and detrimental effects in the brain and that maintaining a tight balance is important.

3.2. Type II IFNs

IFNγ is needed to respond to and control CNS infections, such as by *Toxoplasma gondii* (Kang and Suzuki, 2001) and measles virus (Fantetti et al., 2016). However, IFNγ leads to caspase-1 mediated neuronal apoptosis (Hallam et al., 2000). Both pro-neurogenic (Whitley and Gnann, 2002; Baron et al., 2008; Johansson et al., 2008; Barish et al., 1991) and anti-neurogenic (LaFerla et al., 2000; Kim et al., 2002; Ben-Hur et al., 2003; Walter et al., 2011; Wong et al., 2004) roles for IFNγ have been described, depending on age, model system and whether inflammation is present. Moreover, IFNγ plays a role in social behaviour *via* inhibitory neurons: mice lacking IFNγ ignore other mice and have overactive neurons in the prefrontal cortex; injection of IFNγ restores normal social behaviour (Filiano et al., 2016).

IFNγ injection after brain injury reduces astrocyte activation (Pawlinski and Janeczko, 1997). But in experimental autoimmune encephalomyelitis (EAE), both inflammatory and protective roles have been described for IFNγ (Ottum et al., 2015). Injection of IFNγ in the CNS of healthy mice induces events resembling EAE, comparable inflammation, cellular infiltration, and demyelination (Simmons and Willenborg, 1990; Vass and Lassmann, 1990; Vass et al., 1992; Sethna and Lampson, 1991). In EAE, IFNγ deficiency causes atypical symptoms of multiple sclerosis (Lee et al., 2012) while treatment with IFNγ improves clinical symptoms (Voorthuis et al., 1990; Heremans et al., 1996; Naves et al., 2013; Billiau et al., 1988). Altogether, IFNγ seems to lead to inflammation in the spinal cord but has a protective role in the brain (Lees et al., 2008; Stromnes et al., 2008; Pierson et al., 2012).

4. Importance of interferons at the brain barriers during ageing and Alzheimer's disease

Ageing, a major risk factor for Alzheimer's disease, is often referred to as 'inflammageing' because it is accompanied by chronic low-grade inflammation (Franceschi, 2007). Studying the changes that occur during ageing could give a deeper insight into the development of age-related diseases such as Alzheimer's disease. Indeed, during ageing, several changes are observed at the brain barriers, and these changes are aggravated in Alzheimer's disease (Gorle et al., 2016; Vandenbroucke, 2016).

During ageing, the choroid plexus shifts from a Th1 towards a Th2 profile, which means that type I IFN signalling increases while type II IFNs decrease (Baruch et al., 2013). Blocking the type I IFN signalling in old mice resulted in improvements in memory and lower levels of inflammation in the hippocampus (Baruch et al., 2014). Moreover, the observed increase in the level of C-C motif chemokine ligand (*Ccl*)-11 in the choroid plexus might play a role in the cognitive decline (Villeda et al., 2011). This effect could be reversed by administering IFNγ (Baruch et al., 2013).

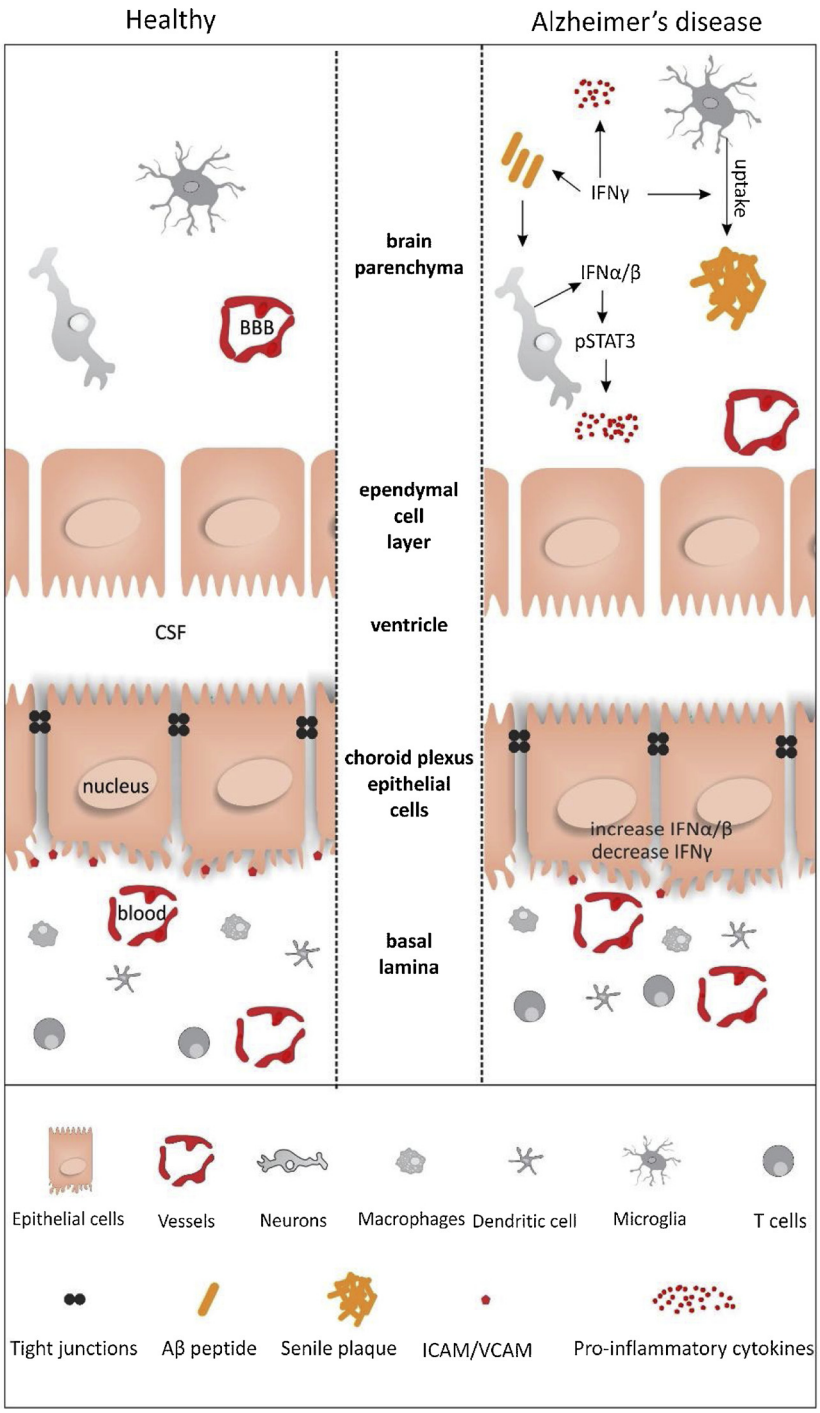

Fig. 2. Schematic representation of the brain and choroid plexus in healthy conditions and in Alzheimer's disease. (Left) The blood–cerebrospinal fluid barrier is formed by choroid plexus epithelial (CPE) cells connected by tight junctions. The CPE cells rest on the basal lamina, which contains fenestrated capillaries, dendritic cells, macrophages and T cells. **(Right)** In CPE cells, there is an increase in type I IFNs and a decrease in type II IFNs, which is associated with decreased expression of molecules needed for leukocyte trafficking. The influences of interferons during Alzheimer's disease are shown. They include increased type I IFN signalling, uptake of Aβ, production of Aβ, and inflammation. BBB: blood–brain barrier; CSF: cerebrospinal fluid; IFN: interferon; pSTAT3: phosphorylated signal transducer and activator of transcription 3; Aβ: amyloid β; ICAM: intercellular adhesion molecule; VCAM: vascular cell adhesion molecule.

4.1. Type I IFN

Activation of the type I IFN pathway has also been shown in two mouse models of Alzheimer's disease: $APP_{SWE}/PS1_{\Delta E9}$ and J20 mice. In $APP_{SWE}/PS1_{\Delta E9}$ mice increased levels of IFNα and phosphorylated STAT3 were found in brain lysates; more specifically, STAT3 phosphorylation was found in neurons surrounding amyloid plaques (Taylor et al., 2014; Wan et al., 2010). In J20 mice type I IFNs were shown to be upregulated and the presence of IFNα in the CSF was correlated with changes in behavioural performance (Mesquita et al., 2015). In the post-mortem brain of Alzheimer's disease patients increased levels of IFNα and phosphorylated STAT3 were found, while on the mRNA level both *Ifnα* and *Ifnβ* were upregulated and increased signalling was observed (Fig. 2) (Taylor et al., 2014).

Primary CPE cells, in contrast to astrocytes and neurons, were shown to produce IFNα in response to stimulation with $A\beta_{1\text{-}42}$ (Mesquita et al., 2015). Interestingly, $A\beta_{1\text{-}42}$ treatment of neurons *in vitro* drives pro-inflammatory cytokine expression, which is dependent on type I IFN signalling (Taylor et al., 2014). Several of these pro-inflammatory cytokines, such as tumour necrosis factor (TNF), IL-6, and IL-1β, have been reported to be involved in Alzheimer's disease, and type I IFNs play a role in the initiation and regulation of these cytokines (Fig. 2) (de Weerd et al., 2007; Akira et al., 2006). Furthermore, neurons deficient in IFNAR1 are protected against $A\beta_{1\text{-}42}$-induced inflammation and less cell death was observed in IFNAR1-deficient neurons (Taylor et al., 2014). While the brain of $APP_{SWE}/PS1_{\Delta E9}$ mice

deficient in IFNAR1 shows no change in plaque deposition and only a small reduction in monomeric Aβ load, these mice do show improved spatial cognitive performance (Minter et al., 2016).

4.2. Type II IFN

As in ageing, a decrease in IFNγ at the choroid plexus was reported in the 5xFAD and $APP_{SWE}/PS1_{\Delta E9}$ mouse models of Alzheimer's disease (Fig. 2) (Baruch et al., 2015a). When CPE cells were stimulated with $A\beta_{1\text{-}42}$, no change in *Ifn*γ gene expression was found. Therefore, the changes in IFNγ at the choroid plexus during Alzheimer's disease may be related to the immune cells residing in the choroid plexus (Mesquita et al., 2015). In fact, within the CP stroma, CD4 + T cells and possibly NK cells produce IFNγ (Phillips et al., 2013; Kunis et al., 2013). Interestingly, in old mice the changes in type II IFN signalling in the choroid plexus could be partially reversed by infusion of blood from young mice (Baruch et al., 2014). This effect could have been mediated by the immune cells in the young blood.

Increasing levels of IFNγ are found in the brain of the mouse model Tg2576 (Abbas et al., 2002) as well as in Alzheimer's disease patients (Belkhelfa et al., 2014). In astrocytes, production of $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ is induced by IFNγ (Blasko et al., 2000). Moreover, in combination with TNF, IFNγ causes not only higher Aβ production, but also reduces its clearance in Tg2576 mice (Yamamoto et al., 2007). IFNγ treatment also makes neurons more sensitive to $A\beta_{1\text{-}42}$-induced cell death in a dose-dependent way (Bate et al., 2006). Delivery of IFNγ *via* injection of an adeno-associated virus vector (AAV) in the hippocampus of 3xTg mice causes increased inflammation, activation of microglia, and increased levels of $A\beta_{1\text{-}42}$ in the brain (Mastrangelo et al., 2009). In contrast, IFNγ overexpression induced by injection of AAV in the ventricles of newborn pups leads to a decrease in Aβ deposition and to infiltration of peripheral monocytes (Chakrabarty et al., 2010a). In line with this observation, a polymorphism in the IFNγ gene that causes lower production of IFNγ is associated with fast cognitive decline in Alzheimer's disease (Asselineau et al., 2015). Likewise, expression of IFNγ in oligodendrocytes in APP transgenic mice enhances neurogenesis and improves spatial learning and memory (Baron et al., 2008).

4.3. Immune surveillance

Leukocytes have been shown to play a role in the clearance of Aβ (Naert and Rivest, 2013; Town et al., 2008; Hawkes and McLaurin, 2009; El Khoury et al., 2007; Rezai-Zadeh et al., 2009). While no data are available on IFNs at the BBB during ageing and in Alzheimer's disease, *in vitro* experiments show that IFNβ treatment reduces the expression of adhesion molecules and transendothelial migration of T cells and monocytes (Kraus and Oschmann, 2006). At the blood–CSF barrier, immune surveillance is altered with age and recruitment of immune cells to the CNS is reduced, impairing the ability to resolve brain pathology (Baruch et al., 2015a). Infiltration of leukocytes into the brain through the blood–CSF barrier depends on IFNγ signalling (Kunis et al., 2013) because IFNγ induces the expression of key integrins and chemokines involved in leukocyte trafficking by the choroid plexus (Kunis et al., 2013; Raposo et al., 2014). Mice deficient in IFNγR1, in which IFNγ signalling is abolished, display cognitive decline, possibly related to reduced leukocyte infiltration (Baruch et al., 2014). As in ageing, a decrease in IFNγ at the choroid plexus was reported in the 5xFAD and $APP_{SWE}/PS1_{\Delta E9}$ murine models of Alzheimer's disease (Baruch et al., 2015a). This decrease in IFNγ at the choroid plexus in 5xFAD mice is accompanied by lower levels of intercellular adhesion molecule 1 (*Icam1*), vascular cell adhesion molecule 1 (*Vcam1*), C-X-C motif chemokine ligand 10 (*Cxcl10*), and *Ccl22*, which are needed for the migration of leukocytes (Fig. 2) (Baruch et al., 2015a). Interestingly, the use of a scavenger of nitric oxide (NO), which is a negative regulator of leukocyte trafficking at the choroid plexus (Baron et al., 2000), attenuates disease in 5xFAD mice reflected by an increased number of infiltrating cells (Baruch et al., 2015b). Moreover, when trafficking of leukocytes at the choroid plexus was enhanced with Copaxone, the resultant increase in *Bdnf* and *Igf1* expression led to improved cognition (Baruch et al., 2015a). However, the timing and the type of T cells infiltrating in the brain determine the effect, since Tregs delay disease when they are amplified in an early stage of the disease (Dansokho et al., 2016), whereas Aβ-specific T cells at a later stage worsen the disease (Browne et al., 2013).

With age, the brain's resident innate immune cells, microglia, contribute to Alzheimer's disease (Hammond et al., 2019) by adopting a phenotype that negatively affects brain functioning. Recently, it was shown that the increased level of type I IFNs in the ageing brain is responsible for the exaggerated microglial response leading to impaired cognitive performance (Deczkowska et al., 2017).

In the early stages of the disease, activation of microglia is beneficial because it results in the clearance of Aβ (Wyss-Coray et al., 2002; Chakrabarty et al., 2010b; Shaftel et al., 2007). IFNγ-producing cells increase the microglial phagocytosis of Aβ (Monsonego et al., 2006). However, treatment of microglia with Aβ combined with IFNγ increases their production of TNF (Meda et al., 1995). Indeed, prolonged activation of microglia leads to sustained pro-inflammatory signalling, neuronal damage and exacerbation of Alzheimer's disease (Meda et al., 1995; Hickman et al., 2008; Sheng et al., 1998).

5. Conclusion

It has become clear from the study of human genetics and mouse models of Alzheimer's disease that the immune system plays an important role in the pathogenesis of this disease. Targeting the immune system is therefore a potential new therapy to halt or reverse disease progression (Schwartz, 2017). However, recent studies did not observe improvement with immune therapy in mouse models of Alzheimer's disease (Latta-Mahieu et al., 2018). Our knowledge of the exact mechanisms of inflammation and the immune system in Alzheimer's disease is too limited, and more research is needed to pave the way to new therapies.

The balance between type I and type II IFNs, which is crucial in the normal functioning of the brain, is a promising route of investigation. An imbalance between type I and type II IFNs is observed in Alzheimer's disease. The two types of IFNs seem to antagonise each other's functions at the blood–CSF barrier (Deczkowska et al., 2016), and the imbalance that develops during ageing and in Alzheimer's disease is associated with impaired immune surveillance at the choroid plexus. Further research is needed to elucidate the mechanism of IFNs because a better understanding of the balance between type I IFN and type II IFN might lead to development of potential therapeutic strategies. Inflammatory cytokines other than IFNs might be interesting targets as well. For example, our lab recently showed the potential of targeting TNFR1 in Alzheimer's disease (Steeland et al., 2018; Steeland and Vandenbroucke, 2019). Clearly, targeting inflammation is a promising path towards new therapies.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

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