Type-I interferon pathway in neuroinflammation and neurodegeneration: focus on Alzheimer's disease.

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Abstract

Past research in Alzheimer's disease (AD) has been largely driven by the amyloid hypothesis; the accompanying neuroinflammation seen in AD has been assumed to be consequential and not disease modifying or causative. However, recent data from both clinical and preclinical studies have established that the immune-driven neuroinflammation contributes to AD pathology. Key evidence for the involvement of neuroinflammation in AD includes enhanced microglial and astroglial activation in the brains of AD patients, increased proinflammatory cytokine burden in AD brains and epidemiological evidence that chronic non-steroidal anti-inflammatory drug use prior to disease onset leads to a lower incidence of AD. Identifying critical mediators controlling this neuroinflammation will prove beneficial in developing anti-inflammatory therapies for the treatment of AD. The type-I interferons (IFNs) are pleiotropic cytokines that control pro-inflammatory cytokine secretion and are master regulators of the innate immune response that impact on disorders of the central nervous system. This review provides evidence that the type-I IFNs play a critical role in the exacerbation of neuro-inflammation and actively contribute to the progression of AD.

Key words; Type-I Interferon, Alzheimer's disease, neuroinflammation, neurodegeneration, amyloid, microglia, astrocytes

Introduction

The causation and propagation of Alzheimer's disease (AD) is a multistep process in which neuroinflammation plays an important role. The central nervous system (CNS) exhibits features of inflammation in response to injury, infection, or disease, whereby resident cells generate inflammatory mediators, including cytokines, prostaglandins, free radicals, complement factor, chemokines, and adhesion molecules, that stimulate recruitment of additional immune cells and activate astrocytes and microglia. This glial reactivity is initially beneficial and required for the efficient removal of the inflammatory stimulus and controlled return to physiological homeostasis, however prolonged and dysregulated neuroinflammation can elicit deleterious effects on the central nervous system (CNS). The concept that neuroinflammation plays a role in the progression and exacerbation of neurodegeneration is one that is gaining credence, with recent data from both clinical and preclinical studies establishing that immune-driven neuroinflammation contributes to AD pathology. This review will analyse the role that the type-I interferons (IFNs) play in the control and regulation of neuroinflammation in chronic neurodegeneration.

Type-I IFN signalling cascades

Originally named for their ability to "interfere" with viral replication (Isaacs and Lindenmann 1957), IFNs are a superfamily of pleiotropic cytokines associated with varied immunomodulatory functions related to host infection, pathogen and disease (de Weerd and Nguyen 2012). There are three classes of IFNs based on their cognate receptor: type-I IFNs consisting of 14 subtypes, with the most studied of these being IFNα and IFNβ; type-II IFNs solely consisting of IFN-γ; and type-III IFNs which contains three IFNλ subtypes (de Weerd and Nguyen 2012). These IFNs possess pro-inflammatory properties through the activation of a number of signalling pathways. Of these, the classical Janus-associated kinase (JAK) and signal transducer and activator of transcription (STAT) pathway (JAK-STAT) is the most critical and well defined (Platanias 2005) (Figure 1).

Type-I IFN signalling occurs through their cognate receptor, the IFNα/β receptor (IFNAR) (de Weerd and Nguyen 2012). The IFNAR is composed of two subunits, IFNAR1 and IFNAR2. Lacking intrinsic kinase activity, these subunits recruit JAKs to induce downstream phosphorylation. These are Tyk-2 and Jak1 for IFNAR1 and IFNAR2 respectively. These

residues act as docking sites for the phosphorylation of a number of STATs, which upon phosphorylation translocate to the nucleus, resulting in pro-inflammatory gene transcription of interferon-regulated genes (IRGs) (Platanias 2005). A number of IFN-regulated factors (IRFs) are also able to bind to the STAT complex prior to nuclear translocation. Of importance is IRF7, which is crucial in the autocrine production and exacerbation of the type-I IFN response (Honda et al. 2005). Type-I IFN signalling is plastic in nature with over 2000 activated or repressed from ligand-receptor interactions (Schreiber and Piehler 2015). It is now important to note that IFNβ is capable of inducing JAK-STAT independent of the IFNAR2 subunit, via interaction with IFNAR1 alone (de Weerd et al. 2013). Indeed, much remains unknown regarding the diverse biological outcomes of type-I IFN signalling (Ng et al. 2016).

Type-I IFN CNS toxicity

The complexity of type-I IFN signalling, and the differential effects it has in the central and peripheral nervous systems, ultimately leads to different outcomes. It is known that interferons play important roles in a number of physiological processes apart from antiviral and antimicrobial defence, with processes such as cell survival and immunomodulation requiring a low level of tonic type-I IFN release (Gough et al. 2012). In multiple sclerosis (MS), an autoimmune disease leading to demyelination and peripheral motor neurodegeneration, IFN□□□□ and IFN□□□□ have been used as an effective therapy for reducing attacks in secondary progressive cases of the disease (Wingerchuk and Carter 2014). Interestingly IFN□ has been shown to be a major driver of microglial phagocytosis of myelin in a murine autoimmune encephalitis (EAE) model suggesting that microglial generated IFN□ is of benefit in combating the progression of MS (Kocur et al. 2015). However, while these therapies have been beneficial in reducing the severity of the symptoms of MS, an epidemiological study has shown that there have been cases of IFN□□treated MS patients developing Parkinson's disease (PD)-like symptoms following ongoing type-I IFN therapy (Manouchehrinia and Constantinescu 2012). These include common symptoms such as impaired motor function, as well as other cognitive deficits and depression. In the murine EAE model of MS, elevations in microglial and brain-infiltrating leukocyte IRF7 expression has been reported and indicates an increased capacity for brain type-I IFN production (Salem et al. 2011). Furthermore, genome-wide association analyses

within these models has revealed a type-I IFN-dependent upregulation of pro-inflammatory genes in brain-residing astrocytes alongside anti-inflammatory activity in the periphery (Rothhammer et al. 2016). This illustrates that while the IFNs may be beneficial in the periphery, entry into the CNS and their activity within this tightly regulated environment can be detrimental and exacerbate the degeneration of healthy neurons, leading to the development of many neurodegenerative disorders. Clearly the regulation of IFN production and specificity in type-I IFN signalling in the CNS is of importance. This concept is highlighted by the studies of Ejerskov and colleagues who reported that the absence of IFN led to Lewy body and PD like symptoms in the IFN$^{-/-}$ mouse (Ejlerskov et al. 2015). In contrast, the work of Main and colleagues proposes that blocking type-I IFN signalling, by genetic and pharmacological means, leads to a neuroprotection in the MPTP-toxin model of PD (Main et al. 2016a; Main et al. 2016b). This seeming contradiction underscores our limited understanding of how type-I IFNs function in specific pathological contexts.

An increasing body of evidence suggests that accumulation of IFN within the brain leads to cellular toxicity and deleterious phenotypes. Transgenic mice that overexpress IFNα in glial cells show brain pathology and behavioural deficits such as Wallerian degeneration of myelinated fibres, alterations in synaptic strength and plasticity, increased seizure activity, and impaired learning ability (Campbell et al. 1999). In addition, when IFN repressors such as SOCS1 are inactivated in mouse models, the mice die from excessive inflammation driven by IFNs (Alexander et al. 1999). Ubiquitin-specific peptidase 18 (USP18) has recently been shown to be a key negative regulator of type-I IFN signalling. With USP18 deficiency leading to severely enhanced IFN-induced inflammation resulting in neuronal calcification and polymicrogyria (Meuwissen et al. 2016). Increased expression of IFN in the brain and cerebrospinal fluid (CSF) is also associated with cognitive decline in patients with human immunodeficiency virus (HIV) encephalopathy (Rho et al. 1995). The 'sickness behaviours' that accompany West Nile virus infection have been associated with increased CNS-residing IFN(Cunningham et al. 2007). Moreover, the neonatal Aicardi-Goutières syndrome is associated with excessive IFNα production in the CSF and serum, resulting in calcification of the basal ganglia and white matter, demyelination, and brain atrophy (Crow et al. 2006a; Crow et al. 2006b). The type-I IFN response has also been implicated in aging, with genome-wide analysis showing that the choroid plexus, an interface between the brain and

circulation, displays a type-I IFN expression profile in both aged mice and humans (Baruch et al. 2014). Further, this study showed that inhibition of the type-I IFN signalling restored cognitive function in these mice. Based on the aforementioned evidence, prolonged type-I IFN exposure in the CNS appears to contribute to a myriad of neurodegenerative disorders.

Neuroinflammation in Alzheimer's disease (AD)

Pathologically, AD is primarily characterised by the loss of pyramidal neurons and synapses in the cerebral cortex and certain subcortical regions, in particular the hippocampus, resulting in gross atrophy of the brain and expansion of ventricular volume. Post mortem histological examination also reveals two distinctive lesions in AD affected individuals, neurofibrillary tangles (NFTs) and senile plaques (SPs) (Selkoe 2001). NFTs are composed of intracellular hyper phosphorylated aggregates of the microtubule associated protein tau, whilst SPs consist of extracellular deposits of amyloid-β (Aβ) aggregates. These aggregates contain a number of Aβ peptide species comprising between 37–43 amino acids, with the most abundant being Aβ1-42 (Borchelt et al. 1997). The deposition of Aβ is considered to occur prior to elevated tau hyper-phosphorylation and decades before AD cognitive symptoms become apparent (Jack et al. 2013). Giving this pathological timing event intervening with Aβ production within early stages of disease proposes an attractive therapeutic window in support of the amyloid hypothesis.

Alongside amyloidosis, neuroinflammation has been implicated throughout the progression of AD. Initially, the coordinated neuro-inflammatory response to Aβ seeding is required for efficient microglial-mediated phagocytic removal and astrocytic-mediated enzymatic breakdown of amyloid peptides to maintain healthy brain function. Excessive Aβ deposition and NFTs in AD impair the Aβ-related clearance abilities of recruited microglia and astrocytes that manifests as a chronically dysregulated neuro-inflammatory phenotype (Eikelenboom et al. 2006; Minter et al. 2016b). This impaired clearance results in continued microglial stimulation and excessive pro-inflammatory cytokine production. Heightened levels of inflammatory cytokines levels are able to cause degeneration and death of otherwise healthy proximal neurons, directly contributing to AD pathology (Minter et al. 2016b). Additionally, release of cellular debris and damage associated molecular patterns by these degenerating neurons can further stimulate microglia and inflammatory mediator

production. As such, this neuroinflammatory process has the potential to become self-perpetuating, with removal of the initial Aβ stimulus unlikely to produce a resolution (Heneka et al. 2013).

Further evidence for the contribution of neuroinflammation in AD pathology includes a number of long-term epidemiological studies of individuals prescribed non-steroidal anti-inflammatory drugs (NSAIDs). Reviews of both prospective and retrospective studies demonstrate that individuals administered NSAIDs display a lower prevalence of AD compared to respective controls and this occurrence is strongly related to the length and time of commencement for therapy (Imbimbo et al. 2010). In particular, numerous epidemiological studies have demonstrated that individuals taking these drugs prior to age of onset periods can halve their risk of developing AD (Vlad et al. 2008; Zandi et al. 2002; in t' Veld et al. 2001). Contrary to these epidemiological studies, interventional use of NSAIDs in the treatment of clinically diagnosed AD has failed to display patient efficacy thus far (Group et al. 2008a; Group et al. 2007; Group et al. 2008b). These clinical observations suggest that modulation of neuroinflammation prior to, or early in AD progression may alleviate disease severity however this therapeutic window narrows significantly in latter stages.

Cytokine systems mediating microglial activity in AD

Pro-inflammatory cytokines secreted in AD not only induce neuroinflammatory and neuropathic mechanisms, but also influence classical neurodegenerative pathways such as amyloid precursor protein (APP) processing. For example, interleukin-1β (IL-1β) can regulate APP processing and Aβ production *in vitro* (Blasko et al. 1999), and conversely, Aβ induces a range of pro-inflammatory mediator secretion in cultured microglia (Floden and Combs 2006; Hanisch 2002). Together, Aβ-stimulated production of pro-inflammatory mediators and their feedback activation of APP processing (Sastre et al. 2003; Sastre et al. 2006) contribute to a self-perpetuating, vicious cycle. In this manner, post mortem analyses of AD-affected individuals reveal that microglia are skewed to a pro-inflammatory phenotype (Sudduth et al. 2013) and remain inefficient in Aβ phagocytosis and clearance (Mosher and Wyss-Coray 2014). Considering these observations, identifying mechanisms that alleviate the pro-inflammatory activity of microglia or perhaps promote anti-inflammatory phenotypes may provide a novel means of AD therapy.

A number of *in vivo* studies have investigated the modulation of pro-inflammatory cytokine systems in various mouse models of AD. Increased levels of TNFα, IL1β and IL-6 in the $APP_{SWE}/PS1_{M146L}$ mouse model skew microglia to an pro-inflammatory phenotype (Patel et al. 2005). Either removal or inhibition of iNOS in $APP_{SWE}/PS1_{\Delta E9}$ mice shifts microglia from an activated pro-inflammatory state to an anti-inflammatory phenotype, resulting in decreased levels of Aβ. Subsequent behavioural analysis of these mice revealed a rescue from the induced cognitively impaired AD phenotype (Kummer et al. 2011). Deletion of tumour necrosis factor death receptor (TNFR1), the endogenous receptor for TNFα, in APP_{23} mice leads to decreased levels of Aβ as well as diminished levels of microglial activation (He et al. 2007). A□□can stimulate IL-1β production by activating the NALP3 inflammasome expressed in neural tissue (Halle et al. 2008). Activating the NALP3 inflammasome also directly contributes to amyloid load, constrained microglial Aβ phagocytosis, and behavioural deficits in $APP_{SWE}/PS1_{\Delta E9}$ mice (Heneka et al. 2013). In contrast to the aforementioned studies, hippocampal injections of an adeno associated virus (AAV) expressing IL-β into $APP_{SWE}/PS1_{\Delta E9}$ mice leads to increased numbers of arginase-1 (ARG-1) positive microglia with increased levels of the anti-inflammatory marker ARG-1 shown to be able to clear Aβ plaques (Cherry et al. 2015). These studies support the notion that timing of inflammatory interventions in the potential treatment of AD is of utmost importance and drastically alters disease phenotype.

Additional *in vivo* studies investigating the effects of modulating hallmark anti-inflammatory cytokine systems in preclinical AD models have been contrasting. Using an AAV to deliver IL-4 or IL-10 to hippocampal regions of $APP_{SWE}/PS1_{M146L}$ mice, reductions in microgliosis and improvements in cognition have been reported (Kiyota et al. 2010). A decrease in Aβ levels is also seen in AAV delivery of IL-4 to the hippocampus of these mice (Kiyota et al. 2012). Contrary to these studies, Chakraborty *et al.,* has demonstrated that AAV delivery of IL-10 via intra-cerebroventricular (ICV) injection into multiple APP transgenic models (TgCRND8 and Tg2576 mice) confers alleviated amyloidosis, worsened cognitive deficits and reductions in microglial-mediated Aβ phagocytosis (Chakrabarty et al. 2015). Furthermore, genetic ablation of *IL-10* in $APP_{SWE}/PS1_{\Delta E9}$ mice confers enhanced microglial Aβ clearance resulting in attenuated amyloidosis (Guillot-Sestier et al. 2015). Similar discrepancies have been

observed in findings regarding the anti-inflammatory cytokine TGFβ. In $APP_{SWE/V717F}$ transgenic mice containing up-regulated astrocytic expression of TGFβ, decreased Aβ levels in parallel with increases in overall microglial activation have been reported (Wyss-Coray et al. 2001). However, blockade of TGFβ signalling in innate immune cells of Tg2576 mice facilitated the infiltration of Aβ-clearing peripheral macrophages and significantly reduced amyloid burden (Town et al. 2008). These seemingly conflicting studies highlight the complexity of anti-inflammatory cytokine signalling in AD models of amyloidosis but also re-enforce the importance of the peripheral immune response, not just microglial reactivity, in driving neuroinflammation. Ongoing studies are now focused on identifying how genetic variants in these anti-inflammatory cytokines confer altered risk for the onset of AD in numerous demographic populations (Di Bona et al. 2012; Li et al. 2014; Luedecking et al. 2000; Su et al. 2016).

The emergence of microglia as an important cell type in the regulation of the inflammatory environment in the CNS has led to various terminology being adopted to describe their activation states. Microglial cells of the brain are derived from yolk sac-localised macrophage progenitors that invade the brain at very early embryonic stages (Alliot et al. 1999; Kierdorf et al. 2013). This developmental lineage and the ability of microglia to respond to injury or inflammation by performing phagocytosis and producing cytokines and chemokines has led them to be categorised as 'resident macrophages' by many researchers. This categorisation has meant that they are often delineated into the pro-inflammatory or M1 camp or the anti-inflammatory or M2 camp. This M1/M2 delineation has been used for ease of identification of the function of microglial cells. However, description of peripheral macrophages has moved past the M1/M2 delineation (Murray and Wynn 2011; Murray et al. 2014). Like most CNS processes an 'all or nothing' delineation has led to confusion over the nomenclature of microglial polarisation, when this very polarisation phenomenon itself is in the early stages of research. It is known that microglia exist in a spectrum of activation states as recent transcriptomic analysis suggests that microglial function and phenotype are influenced by brain region, age and microenvironment (Wes et al. 2016). In a recent review, Ransohoff (Ransohoff 2016b) mounts a persuasive argument that the M1/M2 categorisation is one that hinders the field of microglial research and is best discarded as an outdated hypothesis.

Interplay of amyloidosis and type-I IFN-mediated neuro-inflammation

Crucially, type-I IFN signalling is involved in the initiation and regulation of all the aforementioned Aβ-stimulated pro-inflammatory cytokine systems (Akira et al. 2006). In recent years, our laboratory has focused on investigating how type-I IFN signalling shapes the neuro-inflammatory landscape in AD. We have demonstrated that soluble Aβ1-42 initiates a type-I IFN response in neurons *in vitro*, and, importantly, that this response occurs prior to the up-regulation of other pro-inflammatory cytokines (Taylor et al. 2014). This preliminary evidence supports the notion that an amyloid-induced type-I IFN response may be an early-stage critical component in develop of neuroinflammation in response to Aβ insult.

Our analysis of human post-mortem AD patients reports an up-regulation of hallmark pro-inflammatory cytokines and type-I IFNs (Taylor et al. 2014). This finding suggests that type-I IFNs are mediators released during neuro-inflammatory cascades and highlights their potential to contribute to AD pathology. This up-regulation of type-I IFN expression coincided with elevated pre-frontal cortical IRF-7 expression, crucial for type-I IFN production, suggesting an increased type-I IFN production capacity in diseased patients. Taken together with findings presented in primary cultured IFNAR1$^{-/-}$ neurons and glia and the $APP_{SWE}/PS1_{\Delta E9}$ x IFNAR1$^{-/-}$ mouse (discussed below) it is likely that this type-I IFN response is perpetuating a deleterious neuro-inflammatory cycle and actively contributing to disease progression (Minter et al. 2016a). The hypothesis that type-I IFNs facilitate deleterious neuro-inflammation and contribute to neuro-degeneration is supported by further findings implicating a deleterious role of type-I IFN signalling on hippocampal neurogenesis and brain function in response to ageing (Baruch *et al.*, 2014; Zheng *et al.*, 2014).

Comprehensive analysis of $APP_{SWE}/PS1_{\Delta E9}$ mice reveals a positive correlation between age, pro-inflammatory cytokine burden (including type-I IFNs) and cognitive decline (Francois et al. 2014). These preclinical analyses support the notion that neuro-inflammatory severity may be a true correlate of cognitive decline in AD (Heneka et al. 2015; Ransohoff 2016a; Latta et al. 2015). As previously described, the neuroinflammatory response is multi-faceted and the exact cell-type specific contributions to its propagation in AD remain unclear. Our

investigation of type-I IFN signalling mechanisms revealed a neuronal contribution to neuro-inflammation in the $APP_{SWE}/PS1_{\Delta E9}$ mouse by which phosphorylation of Stat-3 was co-localised with FOX-3 (NeuN) using immunohistochemical techniques (Minter et al. 2016a). Additionally, type-I IFN response genes are up-regulated in the choroid plexus of the J20 mouse model of AD and epithelial cells isolated from this tissue exhibit an IFNα response to soluble Aβ1-42 challenge (Mesquita et al. 2015). These findings identify that whilst astrocytes and microglia are considered the primary mediators of CNS neuro-inflammation, other brain-residing cell types should not be overlooked. Indeed, removal of type-I IFN signalling in neuronal cultures is protective against amyloid insult (Taylor et al. 2014) implicating the importance of neuronal type-I IFN signalling in the response to neurotoxic Aβ peptides.

The neuroprotection seen in $IFNAR1^{-/-}$ neurons to Aβ peptides led us to cross the $IFNAR1^{-/-}$ mouse with the $APP_{SWE}/PS1_{\Delta E9}$ to generate the $APP_{SWE}/PS1_{\Delta E9}$ x $IFNAR1^{-/-}$ mouse, a murine model of AD lacking type-I IFN signalling. We found that although there was no alteration in amyloid plaque deposition and only modest reductions in monomeric A load, there was improved spatial cognitive performance as measured by the Morris water maze test (Minter et al. 2016a). These mice also displayed a predominantly anti-inflammatory glial phenotype which was confirmed with *in vitro* studies that demonstrated that A1-42-conditioned media from $IFNAR1^{-/-}$ glia was significantly less toxic to primary cultured neurons than the corresponding wild-type glia media, suggestive that type-I IFN signalling is required in the neuro-toxic response to A1-42. It is important to note that our investigation into the neuro-inflammation driving an AD-like phenotype in aged $APP_{SWE}/PS1_{\Delta E9}$ mice and in AD itself does not discredit the amyloid cascade hypothesis. Rather our findings reported in Taylor et al., (Taylor et al. 2014) and Minter et al., (Minter et al. 2016a) support amyloidosis as a trigger of type-I IFN-mediated neuro-inflammation that, in a chronically active setting, drives further neurodegeneration and contributes to AD progression.

These findings also suggest that alleviating neuro-inflammation, specifically through modulation of type-I IFN signalling, may delay cognitive decline and reduce neurotoxicity irrespective of Aβ load. Neurons produce and respond to type-I IFNs (Prehaud et al. 2005; Wang and Campbell 2005), inducing pro-apoptotic signalling mechanisms (Hertzog et al.

1994), that likely explain the type-IFN-mediated brain toxicity observed in overexpression models (Campbell et al. 1999). As type-I IFNs are master regulators of hallmark pro-inflammatory cytokines that also induce neurodegeneration (Akassoglou et al. 1997; Kawai and Akira 2006; Thornton et al. 2006), it is likely that blockade of type-I IFN signalling also prevents downstream hallmark cytokine-induced toxicity irrespective of amyloid load. Thus, there may still be therapeutic value in reducing inflammatory severity in AD despite the maintenance of amyloid burden.

A critical issue within the current field is identifying how Aβ species are detected by the innate immune system to induce sustained neuroinflammation in AD. Investigation of the pattern recognition receptor sub-family, the toll-like receptors (TLRs), highlights these first-line response entities of the innate immune system as prime candidates for Aβ detection (Salminen et al. 2009; Minter et al. 2016b). The majority of TLR signalling requires recruitment of the myeloid differentiation factor-88 (Myd88) adaptor protein that confers activation of pro-inflammatory nuclear factor kappa B and IRF dependent pathways (Barton 2007; Downes and Crack 2010). We have demonstrated, through the use of Myd88$^{-/-}$, IRF7 siRNA knockdown (KD) and IRF3 KD neuronal cell culture systems, that the TLR network is involved in the initial production of type-I IFN in response to soluble Aβ1-42 (Minter et al. 2015). Furthermore, these genetically manipulated cultures display similar levels of protection against Aβ1-42 toxicity when compared to the aforementioned neuronal cultures lacking type-I IFN signalling (Taylor et al. 2014). Thus, we propose that Aβ-TLR signalling, in part, drives the up-regulated type-I IFN production and signalling observed in our models of AD (Minter et al. 2015; Minter et al. 2016a; Taylor et al. 2014), maintaining significant implications for the propagation of neuro-inflammation and neuronal toxicity in AD.

Juxtaposed to this proposal, *in vivo* studies targeting the regulation of TLR-Myd88 signalling in murine models of AD remain confounded. One study has demonstrated reduced amyloid pathology in $APP_{SWE}/PS1_{\Delta E9}$ mice upon genetic ablation of *Myd88* (Lim et al. 2011) in contrast to other studies illustrating that TLR inhibition or removal of the Myd88 adaptor protein impedes the microglial ability to detect Aβ and worsens disease pathology (Michaud et al. 2011; Michaud et al. 2013). However, a more recent study suggests that Myd88 may not be a key entity in amyloid detection as genetic ablation of this TLR adaptor molecule in

$APP_{SWE}/PS1_{\Delta E9}$ mice fails to influence amyloid deposition nor plaque-localised gliosis (Weitz et al. 2014). We demonstrate that removal of Myd88 in primary cultured neurons confers protection against Aβ1-42, correlating with an attenuated type-I IFN response (Minter et al. 2015). Hence, further investigation into the precise mechanisms of Aβ-TLR-signalling resulting in cell-type specific type-I IFN production is required to unravel possible therapeutic targets.

Referenced evidence throughout this review suggest that, Aβ sensing by TLRs and subsequent IRF-mediated gene transcription can lead to the production of type-I IFNs. Of these IRFs, IRF-7 is a critical regulator of IFNα production in response to viral and bacterial infection (Honda et al. 2005). It is of interest that IRF-7 is upregulated in human AD post-mortem brains alongside IFNα levels (Taylor et al. 2014) and that these levels are reduced in $APP_{SWE}/PS1_{\Delta E9}$ mice that lack type-I IFN signalling (Minter et al. 2016a). Additionally, Minter et al confirmed that the neuronal type-I IFN response to soluble amyloid is mediated primarily through the TLRs and that production is dependent upon Myd88 and IRF-7 signalling (Minter et al. 2015). Hence the IRF-7 dependent production of type-I IFN appears to be a critical element of the pro-inflammatory response to Aβ both *in vitro* and *in vivo*. Interestingly, genetic variants of *IRF7* and *IFNα* are prevalent amongst the human population, impacting directly on an individual's ability to fight infection from common pathogens (Lee et al. 2014). Mutations in IRF7 have been linked to increased viral titres of Epstein Barr virus in AD patients (Licastro et al. 2015), with CNS viral infection being a common comorbidity in AD (Porcellini et al. 2010; Licastro et al. 2011). Furthermore, the natural ageing type-I IFN response is deleterious to neuronal function and can inhibit hippocampal neurogenesis (Baruch et al. 2014; Zheng et al. 2014). Taken collectively, common genetic abnormalities in the IRF7-dependant type-I IFN production mechanism may pre-dispose individuals to initiate an excessive neuro-inflammatory response to Aβ and drive an AD phenotype. This hypothesis is supported by epidemiological studies concluding a strong correlation between the occurrence of a midlife neuro-inflammatory event (hypertension, stroke and brain trauma) and significantly elevated risk of late onset-AD (Faraco and Iadecola 2013; Iadecola 2014).

Throughout this review we propose that type-I IFNs are critical mediators of the neuro-inflammatory response observed in AD. A key question arising from this hypothesis was: *Are the type-I IFNs crucial for the activation of inflammatory responses themselves or are they regulators of subsequent inflammatory events?* Data from our laboratory suggest the latter. By removing type-I IFN signalling in our *in vitro* (Taylor et al. 2014) and *in vivo* (Minter et al. 2016a) models of AD we do not observe complete ablation of neuro-inflammation but an altered inflammatory environment is evident. Firstly, primary cultured IFNAR1$^{-/-}$ neurons and glia still initiate an IL-6 response to Aβ1-42 insult similar to wildtype cells despite the absence of type-I IFN signalling (Taylor et al. 2014). Secondly, whilst microgliosis is attenuated in $APP_{SWE}/PS1_{\Delta E9}$ x IFNAR1$^{-/-}$ mice, the recruitment and activation of these cells to plaque burdened areas was not completely ablated (Minter et al. 2016a). Thirdly, $APP_{SWE}/PS1_{\Delta E9}$ x IFNAR1$^{-/-}$ mice display increased astrogliosis and cortical IL-1β levels compared to $APP_{SWE}/PS1_{\Delta E9}$ alone (Minter et al. 2016a). This enhanced astrocyte recruitment facilitated by IL-1β pro-inflammatory cytokine release in a largely anti-inflammatory environment clearly suggests that type-I IFNs are master modulators and/or regulators of inflammation. This modulatory characteristic remains important as inflammation is required for effective Aβ clearance from the CNS, it is only when this process becomes dysregulated and excessive that it contributes to neuro-degeneration (Heneka *et al.*, 2014). Data presented from the studies of Taylor et al., and Minter et al., implicate neuro-inflammatory processes as key mechanisms by which Aβ induces neuronal dysfunction and toxicity and associates type-I IFN signalling as a critical modulator of these mechanisms.

Conclusions

Our work and that of others provide strong evidence in implicating neuro-inflammation as a key pathological mechanism contributing to the progression of AD. Specifically, the neuro-inflammatory response to Aβ is regulated by the type-I IFNs from the time of initial soluble amyloid detection through to later stages of disease in $APP_{SWE}/PS1_{\Delta E9}$ mice. This robust type-I IFN response is deleterious to neuronal viability and cognition and modulation of this IFNAR1-dependent signalling shows great promise in the development of novel anti-inflammatory therapy for the treatment of AD. We hypothesise that type-I IFN signalling is crucial in the regulation of the neuroinflammation in AD and other forms of dementia. If type-I IFN signalling can be regulated, then the avenue is open for a viable alternative

strategy to reduce the neural cell death and subsequent cognitive decline in AD. A better understanding of the neuroinflammatory and immunoregulatory processes in the disease will aid the development of anti-neuroinflammatory approaches that may not cure AD, but may slow the progression or delay the onset of this devastating disorder.

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Author contribution statement
JMT, ZM, MRM and PJC all contributed to the writing of this manuscript.

Conflict of interest statement
The authors declare that they have no competing interests.

Figure Legend
Figure 1. Schematic representation of the type-I IFN signalling pathway.

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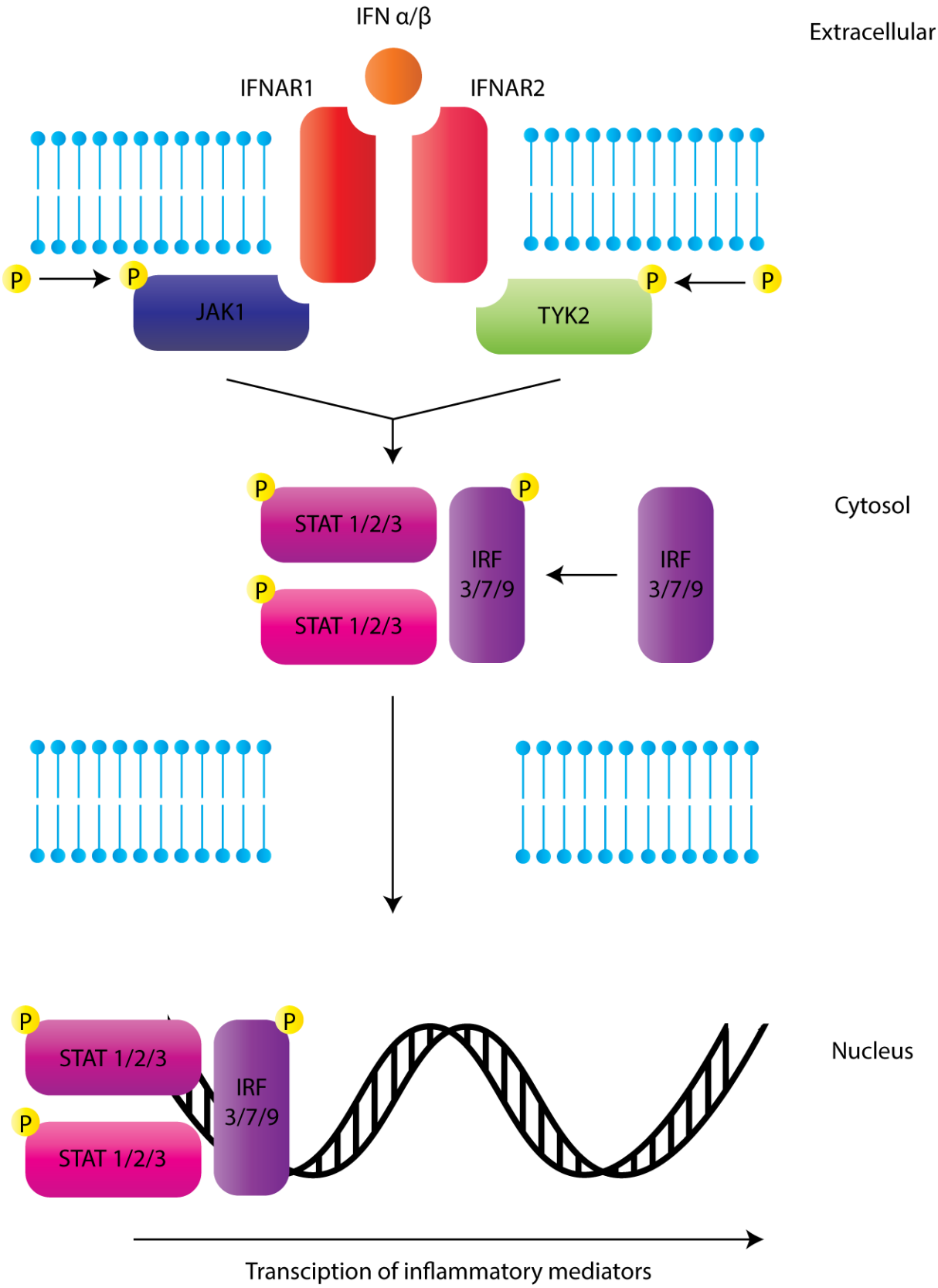
IFN α/β
Extracellular
IFNAR1
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JAK1
TYK2
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STAT 1/2/3
IRF
3/7/9
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STAT 1/2/3
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STAT 1/2/3
Nucleus
Transciption of inflammatory mediators

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