Type-I Interferons in Alzheimer's Disease and Other Tauopathies

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Abstract

The detection of pathogen-associated molecular patterns can elicit the production of type-I interferons (IFNs), soluble cytokines that induce a transcriptional state inhibitory to viral replication. Signatures of type-I IFN-driven gene expression, and type-I IFNs themselves, are observed in the central nervous system during neurodegenerative diseases including Alzheimer's disease and other tauopathies, the umbrella term for diseases that feature aggregation of the cytosolic protein tau. The contribution of the type-I IFN response to pathological progression of these diseases, however, is not well understood. The wholesale transcriptional changes that ensue from type-I IFN production can both promote protective effects and lead to damage dependent on the context and duration of the response. The type-I IFN system therefore represents a signalling pathway with a potential disease-modifying role in the progression of neurodegenerative disease. In this review we summarise the evidence for a type-I IFN signature in AD and other tauopathies and examine the role of aggregated proteins as inflammatory stimuli. We explore both the protective role of IFN against protein pathologies as well as their downstream toxic consequences, which include the exacerbation of protein pathology as a potentially destructive feed-forward loop. Given the involvement of type-I IFNs in other neurogenerative diseases, we draw comparisons with other categories of homotypic protein aggregation. Understanding how type-I IFN influences progression of AD and other tauopathies may yield important insight to neurodegeneration and identify new targets in an area currently lacking disease-modifying therapies.

Introduction

Alzheimer's disease (AD) is the most common form of dementia and is anticipated to affect more than 113 million people worldwide by 2050 (Knopman *et al.*, 2021). AD is characterised by two distinct pathologies in the post-mortem brain (Alzheimer, 1907). Plaques of beta-amyloid (Aβ) peptide, a cleavage product of the transmembrane protein, amyloid precursor protein (APP), accumulate in the extracellular spaces of the brain. In addition, fibrillar and hyperphosphorylated assemblies of the microtubule-associated protein tau accumulate in the cytoplasm of neurons (Goedert and Spillantini, 2006). Mutations in *APP* can lead to dominantly inherited, early-onset variants of AD, though these inherited forms make up less than 1% of AD cases (Laurent, Buée and Blum, 2018a). The 'amyloid cascade hypothesis' places Aβ pathology as an upstream, causative insult that unleashes a range of ensuing consequences including tau pathology and neurotoxicity (Hardy and Higgins, 1992). However, clinically targeting Aβ has so far failed to yield cognitive benefit (Karran and De Strooper, 2022). This has directed focus towards other targets such as tau lesions, which correlate strongly with cognitive decline (Nelson *et al.*, 2007).

Tau assemblies are present in a range of neurodegenerative diseases alongside AD, classed as tauopathies. Several non-synonymous point mutations in *MAPT*, the gene that encodes tau, give rise to familial inherited tauopathies such as frontotemporal lobar degeneration with tau-immunoreactive inclusions (FTLD-tau) (Goedert, 2018). These findings establish tau as a causative factor in pathological progression, at least in these rare diseases and potentially more broadly in the tauopathies. In Pick's disease (PiD), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), tau pathology is the main, often sole observed protein pathology (Spillantini and Goedert, 2013). The mechanism that leads to the assembly of tau during neurodegeneration is uncertain. Cell-autonomous mechanisms likely drive the earliest tau pathology, which is apparent in the majority of human brains by the age of 30 years (Braak and Del Tredici, 2015). Misfolded tau may also act in a 'prion-like' manner promoting its propagation through iterative rounds of seeded aggregation. Injection of mouse brains with tau assemblies can induce tau aggregation in the neurons of the recipient animal (Clavaguera *et al.*, 2009; De Calignon *et al.*, 2012; L. Liu *et al.*, 2012). Similar results can also be obtained in cell-based and *ex vivo* models (Frost, Jacks and Diamond, 2009; Guo and Lee, 2011; McEwan *et al.*, 2017; Miller *et al.*, 2021). While the contribution of this process to disease progression remains undetermined, a unifying feature of AD and several tauopathies is inflammation.

Microglia are a critical component of the brain's innate immune response, the first line of defence against foreign pathogens during infection. This response limits the early replication of pathogens while adaptive immune responses are generated (Le Bon and Tough, 2002).

Pathogen-associated molecular patterns (PAMPs) or host-derived danger-associated molecular patterns (DAMPs) are recognised by germ-line encoded pattern recognition receptors (PRRs) on the surface of, and inside, host cells (Iwasaki and Medzhitov, 2004; Roh and Sohn, 2018). Microglia are the major site of PRR expression in the brain, though other cell types, particularly astrocytes, also contribute. Engagement of PRRs can result in the transcription of cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), tumour necrosis factor (TNF) and type-I interferons. Each of these have specific roles, including recruitment of professional immune cells and the orchestration of the adaptive immune response. Type-I IFNs comprise IFN-α and IFN-β and have a critical role in inducing an antiviral state in infected and neighbouring cells. They exert this function by binding to the type I IFN receptor complex (IFNAR) and initiating signalling through kinases JAK1/TYK2 which in turn phosphorylate STAT1 and STAT2 transcription factors (**Figure 1**). This leads to the upregulation of around 2,000 genes in humans, a response that is conserved across mammals (Shaw *et al.*, 2017). As well as their antiviral effects, type-I IFNs have a further role in dampening pro-inflammatory cytokines (Prinz *et al.*, 2008; Goldmann, Blank and Prinz, 2016). Each of the major cell types of the CNS retain the ability to both produce and respond to type-I IFN (**Supplementary Tables 1, 2 and 3)**, though astrocytes and microglia are considered the major sources of production (Scheu *et al.*, 2019).

Inflammation is a key feature of the degenerating brain. In AD, inflammatory markers, including TNF, IL-1β and type-I IFN precede the appearance of symptoms (Taylor *et al.*, 2014; Taipa *et al.*, 2019). and chronically activated, dysfunctional microglia are widespread in the post-mortem brain (Tarkowski *et al.*, 2003; Navarro *et al.*, 2018). Reactive microglia can be found associated with sites of both tau and Aβ pathologies (Serrano-Pozo *et al.*, 2011). In tauopathies that do not feature Aβ plaques, activated microglia increase proportionately with tau pathology and are found in close proximity to sites of aggregation (Paulus, Bancher and Jellinger, 1993; Gerhard *et al.*, 2006; Malpetti *et al.*, 2020). It is now understood that prolonged immune activation can exacerbate protein aggregation in AD and tauopathies (reviewed by (Wyss-Coray and Mucke, 2002a; Laurent, Buée and Blum, 2018b)). As major players in the response to infection, and in the degenerating brain, the role of type-I IFNs has come under scrutiny.

Type-I IFN signature of Alzheimer's Disease and Tauopathies

Transcripts of IFNα/β and downstream IFN-stimulated genes (ISGs), are significantly higher in brains of AD and clinical dementia patients compared to controls (Taylor *et al.*, 2014; Roy *et al.*, 2020). The expression of IRF7, a transcription factor regulating type-I IFN production, and itself an ISG, is strongly correlated with Braak stage and clinical stage. This elevated

IRF7 expression is reflected at the protein level in the prefrontal cortex of AD patients (Taylor *et al.*, 2014; Roy *et al.*, 2020). Larger scale transcriptomic approaches in AD and other tauopathies also show that there is a complex signature of type-I IFN-mediated immune suppression and activation (Rexach *et al.*, 2020). Genome wide association studies (GWAS) implicate genetic variation in innate immune response pathways as important contributors for AD and tau-associated dementias. Polymorphisms in several innate immune genes, including ISGs, are associated with AD risk (Salih *et al.*, 2019). This includes OAS1, a cytosolic RNA sensor responsible for degrading cellular and viral RNAs (Magusali *et al.*, 2021). Primary tauopathies have also been associated with mutations in TBK1, a key kinase involved in type-I IFN production. A type-I IFN signature is therefore a key characteristic in AD and other tauopathies with a potential disease-modifying role.

Protein pathologies and ageing contribute to a type-I IFN signature

Protein assemblies are themselves agonists of the type-I IFN response. $A\beta_{1-42}$ assemblies stimulate IFNα/β production in primary neurons, as well as in glial and choroid plexus epithelial cell cultures (Taylor *et al.*, 2014; Mesquita *et al.*, 2015; Minter *et al.*, 2016). Pattern recognition receptors such as toll-like receptor 2 (TLR2) and TLR4, have been identified as receptors for assemblies of $A\beta_{1-42}$ (S. Liu *et al.*, 2012; Hughes *et al.*, 2020) and of phosphorylated tau (Meng *et al.*, 2022). This signalling can elicit a downstream IFN response. Tau assemblies can further stimulate type-I IFN via a cytosolic microglial receptor, polyglutamine binding protein 1 (PQBP1) (Jin *et al.*, 2021) and can activate STAT1 (Li *et al.*, 2019) (**Table 1)**. Protein assemblies may therefore be considered as endogenously-derived molecular patterns that provoke innate immune responses similar to PAMPs.

In mouse models of Aβ pathology, transcriptomic analysis shows that there is an increased population of IFN-responsive microglia which highly express ISGs (Sala Frigerio *et al.*, 2019; LC *et al.*, 2021; Yang *et al.*, 2021). Lineage tracing reveals that these ISG-expressing microglia accumulate progressively in amyloid disease models until a majority of microglia displays evidence of ISG expression (Roy *et al.*, 2022). Similarly, for tau, animal models demonstrate a type-I IFN signature early in the neurogenerative process (Rexach *et al.*, 2020). Genetic deletion of Ifnar reduces the phagocytic capacity of microglia and dampens the production of pro-inflammatory cytokines in response to $A\beta_{1-42}$. This suggests that type-I IFNs are produced and are important for mediating downstream clearance of aggregates and onward inflammatory events.

Ageing itself has been shown to be associated with high levels of type-I IFN in the CNS. Baruch et al. report an age-dependent type-I IFN production at the choroid plexus (Baruch *et al.*, 2014). This has a detrimental effect on cognition which can be reversed by anti-IFNAR

antibody administration. Therefore, even in the absence of specific protein pathology, age-related effects contribute to a type-I IFN signature in the brain. Taken together the above data suggest that stimuli for the production of type-I IFN likely derive from multiple sources: age-related activation of innate immunity, protein aggregates engaging PRRs and, once disease is established, DAMPs arising from tissue damage related to neurodegeneration. The consequences of chronic type-I IFN production in the CNS on the development of further pathology are not fully elucidated. However, accumulating evidence suggests that a chronic IFN response in the brain is a source of toxicity and potentially exacerbates protein aggregation, thereby setting in motion a destructive feed-forward loop.

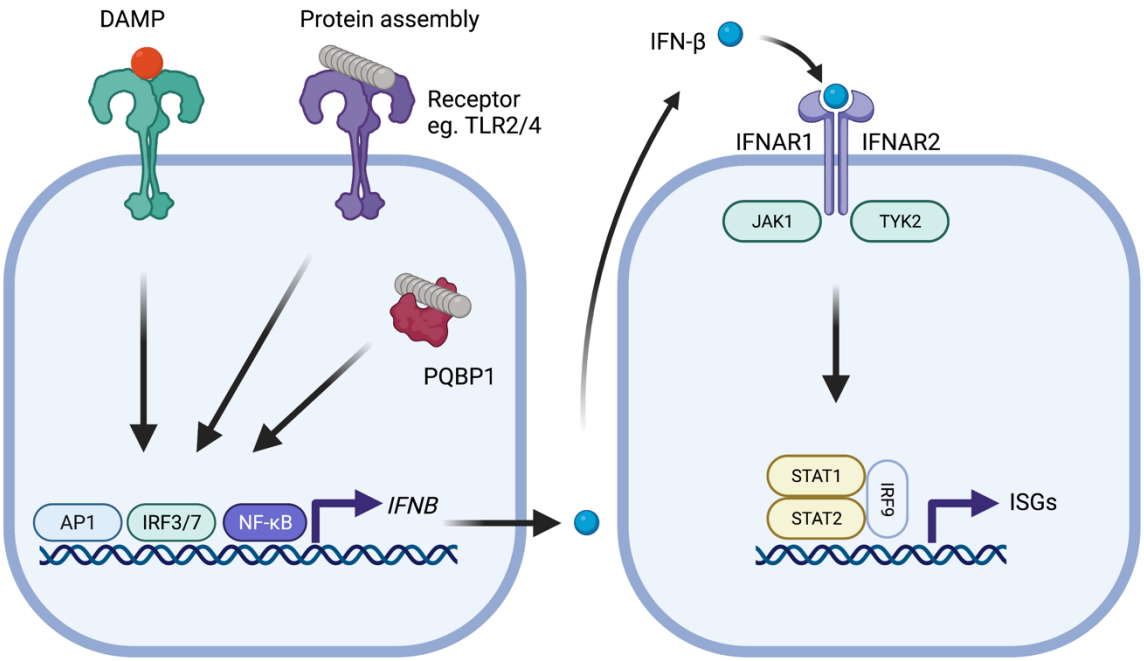
Table 1: Summary of studies addressing the production of type-I IFNs in *ex vivo* and *in vitro* models of AD and tauopathy.

Reference	*Study Design*	*Key Observation*
Taylor et al., 2014	$A\beta_{1-42}$ treated primary neurons from WT or Ifnar1-/- mice	Upregulation of IFN-α/ β. Reduced proinflammatory cytokine production in Ifnar1-/- neurons
Xue et al., 2021	Oligomeric Aβ-treated organotypic slice cultures	Anti-IFNAR administration reduces Aβ-stimulated microglial phagocytosis of synapses
Roy et al., 2020	Nucleic acid-amyloid-treated organotypic slice cultures	Secretion of IFN-α/ β. Anti-IFNAR administration reduces nucleic acid-amyloid-stimulated complement C3 expression
Mesquita et al., 2015	$A\beta_{1-42}$ treated choroid plexus epithelial cells	Upregulation of IFN-α/ β and IFN response genes
Minter et al., 2016	$A\beta_{1-42}$ treated primary glial cultures	Upregulation of IFN-α/ β. Supernatants from $A\beta_{1-42}$ treated Ifnar1-/- cultures are less neurotoxic and have reduced proinflammatory cytokines
Jin et al., 2021	Oligomeric/fibrillar tau-treated primary microglia	Upregulation of IFN-α/ β and IFN response genes
Li et al., 2019	Tau overexpression in HEK293 cells	Increased activation of STAT1. IFN not measured.
Meng et al. 2022	THP-1 human macrophages treated with hyperphosphorylated tau aggregates	Upregulation of IFN-β and CCL5

The role of Type-I IFNs in disease pathology

In the periphery, type-I IFNs provide potent protection against infection, yet lead to toxic consequences when over-produced. Dysregulated IFN production leads to severe disease states, exemplified by inherited interferonopathies which have severe symptoms that mirror viral infection (Crow and Stetson, 2021). In neurodegeneration, type-I IFN is emerging as a central mediator of cascading toxic consequences. Loss of type-I IFN signalling is protective in APP/PS1 mice and 5xFAD mice, alleviating synapse loss and microglial activation (Minter *et al.*, 2016; Roy *et al.*, 2020, 2022) (**Table 2**). Consistent with this model, administration of IFN-β to WT mice promotes microglial activation, neurotoxicity and synapse loss (Roy *et al.*, 2020). In transgenic mice expressing human tau, cognitive impairment is ameliorated when STAT1 signalling is blocked (Li *et al.*, 2019). Beyond a model of toxicity, further evidence suggests that type-I IFNs can promote further protein aggregation. In mouse models, β-amyloid pathology is ameliorated under conditions of *Ifnar* genetic deletion (Roy *et al.*, 2020, 2022). The effect of IFN on tau aggregation remains unclear, though agonists of the IFN response such as LPS exacerbate pathology (Lee *et al.*, 2010). This raises the prospect that an inappropriate innate immune response to protein aggregates sets in motion a destructive feed-forward loop by inducing further protein aggregation via type-I IFN.

Despite these multiple toxic effects of type-I IFN in the CNS, the view that its production is universally detrimental is not supported by other findings, particularly in acute settings. APP overexpression by lentiviral transduction or $A\beta_{1\text{-}42}$ peptide delivery to the mouse brain induces pro-inflammatory cytokine production. This can be reduced by administration of IFN-β, consistent with the anti-inflammatory effects of type-I IFN (Chavoshinezhad *et al.*, 2019; Mudò *et al.*, 2019). Furthermore, genetic knockout of IFN-β is associated with reduced autophagic clearance and accumulation of ubiquitinated alpha-synuclein aggregates in mice (Ejlerskov *et al.*, 2015). One possibility is that IFNs, while protective in acute settings, lead to damage when chronically over-produced, consistent with the ‘double-edged sword’ hypothesis of innate immune activation in neurodegeneration (Wyss-Coray and Mucke, 2002b). This would broadly align with our understanding of IFN in peripheral infection: that IFNs are highly protective when appropriately expressed yet can unleash severe damage when dysregulated or chronically over-produced.



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181 ***Figure 1. Type-I IFN signalling in the context of neurodegenerative disease.*** *Protein*
182 *assemblies such as β-amyloid and tau activate innate immune signalling through interactions*
183 *with cell surface receptors such as TLR2 and TLR4 or intracellular receptors such as*
184 *PQBP1. Damage associated molecular patterns similarly provoke activation of signalling.*
185 *Activation of downstream signalling pathways, notably AP1, IRF3 or IRF7 and NF-kB, leads*
186 *to production of IFN-b which subsequently binds to the type-I IFN receptor complex*
187 *comprising IFNAR1 and IFNAR2 that is expressed on all nucleated cells. Following type-I*
188 *IFN binding, the IFNAR receptor complex initiates signalling through the adaptor kinases*
189 *JAK1 and TYK2 leading to activation of STAT1/STAT2/IRF9 heteromultimers. This complex,*
190 *referred to as ISGF3, migrates to the nucleus and induces transcription of interferon-*
191 *stimulated genes (ISGs) that possess interferon-sensitive response element (ISRE). The*
192 *protein products of these genes help establish an antiviral state and include several innate*
193 *immune sensors.*

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Table 2: Summary of studies evaluating type-I IFNs in *in vivo* models of AD and tauopathy

Reference	*Study Design*	*Key Observation*	*Type-I IFN: Helpful/ Harmful in disease?*
Taylor et al., 2014	Chimaeric mouse/human APP (Swedish mutation) and mutant human Presenilin overexpression in mice (APP/PS1)	Upregulation of IFN-α in whole brain	
Xue et al., 2021	Human APP and presenilin with five AD-linked mutations overexpressed in mice (5xFAD)	Upregulation of IFN signalling in microglia	
Roy et al., 2020	5XFAD, APP/PS1 mice and knock-in humanised APP mice with three AD-linked mutations (APP^{NL-G-F})	Upregulation of IFN response genes in hippocampus	
Mesquita et al., 2015	Human APP (Swedish and Iberian mutations) overexpression in mice (J20)	Upregulation of IFN response genes in choroid plexus	
Rexach et al., 2020	Human tau (P301L mutation) overexpression in mice (Tg4510)	Phosphorylated tau pathology correlates with transcription of IFN response genes	
Li et al. 2019	WT mice overexpressing human tau	Upregulation of phosphorylated STAT1. Blocking STAT1 signalling ameliorates synapse loss and cognitive impairment	**Harmful**

Minter et al., 2016	Ifnar1-/- APP/PS1 mice	Ifnar1-/- reduces microgliosis, proinflammatory cytokine secretion and ameliorates cognitive impairment	**Harmful**
Ejlerskov et al., 2015	IFN-β-/- and WT mice	Increased neuronal apoptosis and cognitive impairment in IFN-β-/- mice. Lewy bodies containing phosphorylated tau are increased in IFN-β-/- mice	**Helpful**
Chavoshinezhad et al., 2019	IFN-β administration to APP overexpressing mice (lentivirus)	IFN-β alleviates memory impairments and reduces proinflammatory cytokines (IL-1β, TNFα)	**Helpful**
Mudò et al., 2019	IFN-β administration to $A\beta_{1-42}$ injected rats	IFN-β alleviates memory impairments and reduces proinflammatory cytokine production induced by $A\beta_{1-42}$	**Helpful**
Roy et al., 2020	IFN-β administration to WT mice	IFN-β increases synapse loss and microglial activation	**Harmful**
Roy et al., 2020	Anti-IFNAR administration to 5xFAD mice	Anti-IFNAR administration alleviates synapse loss and microglial activation	**Harmful**
Roy et al., 2022	Microglia/Neuron specific Ifnar1 knockout in 5xFD mice	Ifnar1-/- in microglia reduces post-synaptic loss and in neurons reduces Aβ plaque accumulation	**Harmful**
Barnett et al. 2022	Human APP (Swedish), Mutated tau and presenillin overexpressing mice (3xTg-AD)	PTau181 and $A\beta_{1-42}$ correlate strongly with IFNα in the hippocampus of mice with adolescent intermittent ethanol	

Type-I IFNs in models of prion and Parkinson's disease

Interesting parallels for tauopathies can be sought by examining other protein misfolding diseases of the CNS. Parkinson's disease (PD) is characterised by the aggregation of the cytosolic protein alpha-synuclien. Prion diseases such as Creutzfeld-Jakob disease in humans and scrapie in other animals are driven by the conversion of a membrane-anchored protein, PrP, to a misfolded variant. Genetic depletion of signalling components such as IRF3, Ifnar, TLR4 and TLR2 render mice more susceptible to the scrapie variant of PrP, PrP^{Sc}. This suggests a protective role for type-I IFNs in the recognition and control of prion assemblies (Ishibashi *et al.*, 2012, 2019; Carroll *et al.*, 2018). However even here, type-I IFN production comes at a cost, as Nazmi et al. show that neuronal death is accelerated by Ifnar-dependent signalling (Nazmi *et al.*, 2019).

In PD, type-I IFN and ISG transcripts are upregulated, similar to observations in AD and other tauopathies (Main *et al.*, 2016). The effects of type-I IFN appear to be model-dependent. In one model of PD, neuronal loss is induced by 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) injection. Blockade of IFN signalling using anti-Ifnar antibodies supressed dopaminergic neuronal death, suggesting that type-I IFN signalling is neurotoxic (Main *et al.*, 2016). In contrast, genetic deletion of IFN-β caused the formation of α-syn-positive Lewy body structures and reduced autophagic clearance (Ejlerskov *et al.*, 2015). As in the tauopathies, these findings again point to production of type-I IFN having an important role in protection against protein aggregation, but with over-production likely toxic. Any therapeutic intervention by manipulation of the type-I IFN pathway in proteopathies must therefore seek to target the over-production of IFN whilst ensuring that its essential functions in the control of proteinopathy are not unduly compromised.

Discussion

Type-I IFN plays a critical role in the brain during pathogen infection. Like classical pathogens, aggregated proteins including Aβ and tau can provoke an immune reaction that includes the production of type-I IFN. *In vivo*, the literature lacks clarity on whether IFNs are harmful or beneficial. Protective effects of type-I IFN have been observed for Aβ, prion and α-syn especially in short-term challenge experiments, suggesting that common protective mechanisms may be at play. However, type-I IFNs promote downstream toxic consequences which may be amplified in a positive-feedback manner in response to ongoing tissue damage and further protein aggregation. Our understanding of these effects is in its infancy and remains largely without mechanistic detail. Further, for tau pathology, there remains little insight to the effect of IFN signalling due to the lack of studies using genetic knockout or experimental IFN-blockade. Future research should seek to dissect the IFN response at the level of specific ISGs to identify those that aid in limiting protein aggregation versus those that promote toxic downstream consequences. An understanding at this level may allow selective pharmacological intervention to prevent the chronic toxic consequences of IFN signalling in neurodegeneration.

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Author Contributions

Both authors wrote and edited the manuscript. SS collated information used in the tables and supplementary tables.

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