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A state of delirium: Deciphering the effect of inflammation on tau pathology in Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD), the predominant form of dementia, is highly correlated with the abnormal hyperphosphorylation and aggregation of tau. Immune responses are key drivers of AD and how they contribute to tau pathology in human disease remains largely unknown. This review summarises current knowledge on the association between inflammatory processes and tau pathology. While, preclinical evidence suggests that inflammation can indeed induce tau hyperphosphorylation at both pre- and post-tangles epitopes, a better understanding of whether this develops into advanced pathological features such as neurofibrillary tangles is needed. Microglial cells, the immune phagocytes in the central nervous system, appear to play a key role in regulating tau pathology, but the underlying mechanisms are not fully understood. Their activation can be detrimental *via* the secretion of pro-inflammatory mediators, particularly interleukin-1β, but also potentially beneficial through phagocytosis of extracellular toxic tau oligomers. Nevertheless, anti-inflammatory treatments in animal models were found protective, but whether or not they affect microglial phagocytosis of tau species is unknown. However, one major challenge to our understanding of the role of inflammation in the progression of tau pathology is the preclinical models used to address this question. They mostly rely on the use of septic doses of lipopolysaccharide that do not reflect the inflammatory conditions experienced AD patients, questioning whether the impact of inflammation on tau pathology in these models is dose-dependent and relevant to the human disease. The use of more translational models of inflammation corroborated with verification in clinical investigations are necessary to progress our understanding of the interplay between inflammation and tau pathology.

1. Introduction

Alzheimer's disease (AD) is classified under a group of neurodegenerative diseases termed tauopathies owing to its association with tau pathology. Tau is a microtubule-associated protein predominately expressed in neurons, which stabilizes microtubules under physiological conditions, and as such regulates axonal stability and cell morphology (Avila et al., 2004). Under pathological conditions such as AD, tau is abnormally hyperphosphorylated leading to a decrease in its affinity for microtubules, a process represented in Fig. 1. Soluble hyperphosphorylated tau then aggregates into pathological soluble and insoluble aggregates known as neurofibrillary tangles (NFT), a hallmark of AD. In addition to NFT, amyloid-beta (Aβ) plaques are identified in AD brains, however cognitive decline correlates to a greater extent with tau pathology (Schöll et al., 2016).

Inflammation is considered a key mechanistic driver in AD where both Aβ plaques and NFT co-localize with microglia and astrocytes, the resident immune cells of the brain (Serrano-Pozo et al., 2011). Genome wide association studies (GWAS) suggest a strong association between AD and genes involved in the regulation of immunological function (Lambert et al., 2013), whereas epidemiological studies have revealed a reduced risk of developing the disease following long-term anti-inflammatory treatments (Vlad et al., 2008) and disease-exacerbating effects of infectious agents (Honjo et al., 2009). Corroborating these observations, pro-inflammatory stimuli have been shown to induce both amyloid and tau pathologies in animal models (Zilka et al., 2012).

To date, several randomised trials of anti-inflammatory agents have been conducted in AD. Despite the use of multiple types anti-inflammatory treatments, whether non-steroidal anti-inflammatory drugs (NSAID) or steroidal, all have failed to demonstrate clear clinical efficacy in AD patients (Jaturapatporn et al., 2012). Pathogenesis in AD develops years prior to symptom manifestation, and therefore, anti-inflammatory agents were suggested to be beneficial when administered

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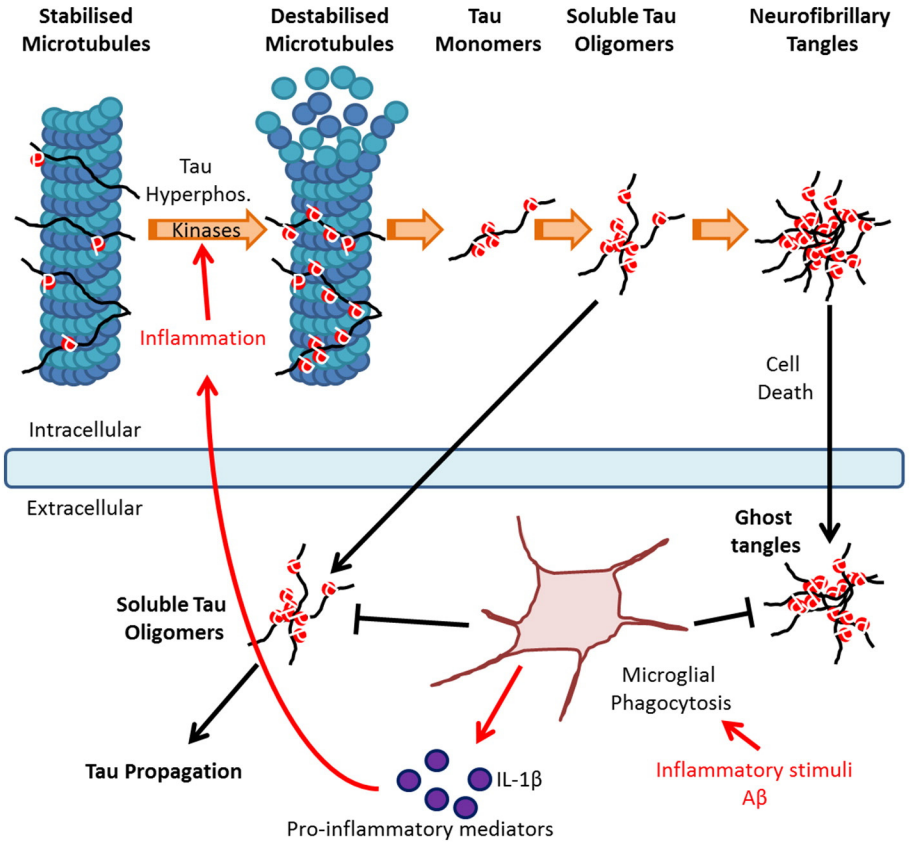

Fig. 1. Progression of tau pathology: Under physiological conditions tau regulates microtubule stabilisation. In tauopathies, tau hyperphosphorylation triggers a loss in microtubule affinity. Soluble tau aggregates into pathological soluble tau oligomers, ultimately forming pathological insoluble neurofibrillary tangles (NFT). Tau oligomers are secreted into the extracellular compartment contributing to the propagation of tau pathology into neighbouring neurons. Inflammatory stimuli, such as Aβ, stimulate microglial production of pro-inflammatory mediators such as IL-1β leading to the up-regulation of kinases involved in tau phosphorylation and exacerbation of the pathology. However, inflammation can have beneficial effects on tau pathology by inducing microglial phagocytosis of extracellular tau species. Image adapted from National Institute of Ageing.

prodromal. Although the largest trials assessing NSAIDs on subjects at risk of developing AD have failed to show benefits on AD incidence (Breitner et al., 2013) a recent updated systematic review still argues in favor of their use for prevention of AD (Wang et al., 2015).

The mechanisms underlying the involvement of immune responses in AD pathogenesis remain poorly understood because inflammation has both beneficial and detrimental effects which can be very context dependent (Heneka et al. 2016). Aβ pathology is exacerbated through the induction of pro-inflammatory mediators secreted from active immune cells such as microglia (Brugg et al., 1995) but conversely, activation of these cells can stimulate clearance of Aβ plaques *via* induction of phagocytosis (Fiala et al., 2007), demonstrating a dual role for inflammation on amyloid pathology. Less is known about the specific role of inflammatory processes on tau pathology, and to our knowledge, the effect of anti-inflammatory treatments on tau pathogenesis in humans is unknown. In preclinical models inflammation is generally seen as an exacerbating factor (Zilka et al., 2012) but recent data suggest that it may be beneficial as well (Majerova et al., 2014). Here, we will review the preclinical findings to shed light on the interplay between inflammation and tau pathology in AD.

2. Inflammation induces tau phosphorylation

Table 1 summarises the outcomes of studies assessing the effect of pro-inflammatory stimuli on tau pathology.

2.1. Systemic immune stimuli induce neuroinflammation

The majority of our understanding for the role played by inflammation on tau pathology relies on the use of systemic immune challenges, and particularly of the toll-like receptor 4 (TLR-4) agonist; lipopolysaccharide (LPS) which fails to cross the blood brain barrier (Banks and Robinson, 2010), thereby mimicking systemic infections. LPS nevertheless induces central inflammatory responses through a variety of including neural routes such as vagal afferents, humoral routes through circumventricular organs, infiltration of peripheral monocytes and through effects on brain endothelial cells (Miller and Raison, 2016; Pardon, 2015), and as such can affect tau pathology.

2.2. Inflammation induces tau phosphorylation in tau models

The first direct evidence for a role of inflammation in exacerbating tau pathology stemmed from *in vitro* studies with primary microglial cells stimulated with Aβ or LPS prior to being co-cultured with primary neocortical neurons (Li et al., 2003). This landmark study showed that secretion of the pro-inflammatory cytokine interleukin-1β (IL-1β) by microglial stimulation causes an increase in tau phosphorylation through activation of p38-mitogen-activated protein kinases (MAPK). This has been confirmed *in vivo* predominantly using the 3xTg model which exhibits both tau and amyloid pathologies (Oddo et al., 2003). A chronic treatment regimen with LPS (0.5 mg/kg twice a week for 6 weeks) triggered tau hyperphosphorylation at multiple phosphorylation sites associated with both pre- and post-tangle tau pathology in 3xTg mice, and at both early and advanced pathological stages (Kitazawa et al., 2005; Sy et al., 2011). Again, microglial activation and resulting secretion of IL-1β were implicated, *via* activation of either cyclin dependent kinase-5 (CDK-5) (Kitazawa et al., 2005) or glycogen synthase kinase-3β (GSK-3β) (Sy et al., 2011). The discrepancy in the kinases involved is likely due to differences in age and pathological

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