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Review Article

# Tau and neuroinflammation: What impact for Alzheimer's Disease and Tauopathies?

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ABSTRACT

Alzheimer's Disease (AD) is a chronic neurodegenerative disorder and the most common type of dementia (60–80% of cases). In 2016, nearly 44 million people were affected by AD or related dementia. AD is characterized by progressive neuronal damages leading to subtle and latter obvious decline in cognitive functions including symptoms such as memory loss or confusion, which ultimately require full-time medical care. Its neuropathology is defined by the extracellular accumulation of amyloid-β (Aβ) peptide into amyloid plaques, and intraneuronal neurofibrillary tangles (NFT) consisting of aggregated hyper- and abnormal phosphorylation of tau protein. The latter, identified also as Tau pathology, is observed in a broad spectrum of neurological diseases commonly referred to as "Tauopathies". Besides these lesions, sustained neuroinflammatory processes occur, involving notably micro- and astro-glial activation, which contribute to disease progression. Recent findings from genome wide association studies further support an instrumental role of neuroinflammation. While the interconnections existing between this innate immune response and the amyloid pathogenesis are widely characterized and described as complex, elaborated and evolving, only few studies focused on Tau pathology. An adaptive immune response takes place conjointly during the disease course, as indicated by the presence of vascular and parenchymal T-cell in AD patients' brain. The underlying mechanisms of this infiltration and its consequences with regards to Tau pathology remain understudied so far. In the present review, we highlight the interplays existing between Tau pathology and the innate/adaptive immune responses.

## Tau: from the gene to the protein, an overview

Tau belongs to the family of microtubule-associated proteins (MAP) and is mainly expressed by neurons with a preferential axonal localization [1]. The gene *mapt* encoding Tau protein is located at locus 17q21, contains 16 exons and can undergo an alternative splicing of the exons 2, 3 and 10 in human brain, generating 6 major isoforms. Depending on the inclusion of the exon 10, the C-terminal microtubule-binding region (MBR) of Tau contains 3 or 4 repeat motifs (3R and 4R tau), ensuring the assembly and stabilization of

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axonal microtubules through their interaction with heterodimers of α- and β-tubulin. Tau was observed *in vitro* to promote tubulin polymerization and decrease the rate of transition between growing and shrinking phases, also called catastrophe, generating a stable but still dynamic state in microtubules [2,3]. Although a large proportion of Tau is located in the axons, a small amount is physiologically distributed in dendrites. The postsynaptic function of Tau remains ill-defined but it may be implicated in synaptic plasticity [4–8]. Besides axons and dendrites, a nuclear function of Tau has been discovered [9]. Nuclear Tau may regulate transcriptional activity and maintain DNA/RNA integrity under physiological and stress conditions [10–12]. Recent data also emphasize the role of Tau as a signaling molecule, owing to a large number of protein partners [13]. For instance, the ability of Tau to regulate brain insulin pathway was observed through a direct interaction and tonic inhibition of the phosphatase PTEN [14].

### *Tau hyperphosphorylation*

Cellular functions of Tau and interactions with its protein partners are impacted by multiple post-translational modifications (PTMs) including acetylation, glycation, glycosylation, methylation, nitration, truncation, ubiquitination and phosphorylation, the most commonly described [15,16]. Tau contains 85 putative phosphorylation sites mainly located in the MBR and the proline-rich domain of the protein [17,18]. Tau phosphorylation state is under the control of many serine/threonine or tyrosine kinases as well as phosphatases; this homeostasis is disrupted in tauopathies favoring Tau hyperphosphorylation [19,20]. Using mass spectroscopy or phospho-specific tau antibodies, an extensive listing of tau phosphorylation sites was obtained, some of being restricted to pathological conditions [16,17]. Interestingly, tau phosphorylation in Alzheimer's Disease (AD) can be viewed as a hierarchical process: some sites are phosphorylated earlier in the disease course generating structural changes promoting the action of secondary kinases and the formation of conformational epitopes. For instance, the epitopes detected by the antibody AT100 and recognizing paired-helical filaments (PHF) was shown to result from a sequential phosphorylation by GSK3-β and PKA at Thr212 and Ser214, in addition to Ser199, Ser202 and Thr205 phosphorylation (AT8 epitope, redefined recently and including also Ser208) [21–23]. Truncation at Asp may facilitate the transition from a natural highly soluble to differential aggregated forms of Tau (oligomers, pre-tangle, tangles), generating the late conformational epitopes AT-100 or Alz50 [24–26] Tau phosphorylation can generate epitopes recognized by immune cells as it will be discussed further. Expression of Tau by microglial cells themselves was also shown to promote their activation [27]. Together, the exact cascade leading to Tau phosphorylation remains ill-defined but subsequent structural changes induce its detachment from microtubules and produce higher levels of soluble free tau. Appearing prior to the formation of NFT [28], Tau hyperphosphorylation favors a dynamic and progressive self-assembly of Tau into oligomeric forms and insoluble materials as PHF along the disease with different degree of neurotoxicity.

### *Tau species-driven neurotoxicity*

The identification of Tau species responsible for neurotoxicity is still a matter of debate. Post-mortem studies showed that density of NFTs was correlated with cognitive impairments characterizing AD patients [29,30]. Recently, imaging studies using selective Tau Positron Emission Tomography (PET) tracers replicate the spreading of pathologic Tau along the disease as defined by Braak stages and observed as well a positive correlation between aggregated Tau and cognitive decline, suggesting a toxic function of insoluble Tau [31,32]. NFT are not inert end products but may be directly detrimental *per se* by disrupting cell metabolism, like proteasome activity as observed *in vitro* using HEK293 cell line transfected with human Tau [33]. In addition, PHF-Tau isolated from AD brains interacts with the 20S-subunit of the proteasome and inhibits its activity [34]. The decline of proteasome activity by NFT may lead to an abnormal accumulation of proteins and initiates a cascade of events ending by neuronal death [35]. Post-synaptic redistribution of pathologic Tau as observed in AD can be involved in neurotoxicity as well. In that view, dendritic Tau was observed *in vivo* to interact with Fyn and mediates amyloid-β toxicity through a Fyn/NMDA receptors (NR)/PSD95 coupling responsible of excitotoxicity [5]. Pathological aggregation of Tau reduces the level of native soluble Tau and consequently its physiological functions, inducing indirectly detrimental effects. Therefore, interactions of Tau with partners are compromised, disrupting microtubule network and axonal transport, RNA/DNA integrity or cell signaling. Also, brain insulin signaling impairments as observed in AD could be explained by a loss of function of Tau [14]. Other studies however revealed that NFT are not a central element of the neurotoxic cascade in comparison with soluble oligomeric Tau. Indeed, using the mouse model of Tauopathy rTg4510, which reversibly expresses the human Tau with P301L mutation that cause inherited frontotemporal dementia, it was found a regional dissociation between neuronal loss and NFT accumulation; suppressing the transgene restored memory formation and stabilized neuron numbers without affecting the accumulation of NFTs [36,37].

### *Tau secretion*

Regardless Tau species driving neurotoxicity, the increase of extracellular cerebrospinal fluid (CSF)-Tau in AD patients was accepted for a long time to be the consequence of a passive release of pathologic Tau from dead neurons generating ghost tangles, even if Tau is also found at low levels in CSF of healthy individuals [38]. However, compelling observations indicate more an active process of Tau secretion [39,40]. Consistent with this view, a longitudinal decrease of CSF Tau phosphorylated at Thr181 was observed in the late stages of AD process, in a context of widespread neuronal death [41]. Also, Tau was found in the CSF of wild type mice in absence of any sign of neurodegeneration and *in vitro* evidences show a physiological Tau secretion upon neuronal activity, in particular after AMPA receptors stimulation [42,43]. Moreover, truncation at Asp421 site and hyper-phosphorylation of Tau were observed to favor its secretion *in vitro* [44]. Interestingly, exosomes-associated Tau were detected in the CSF of AD

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