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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.

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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 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 patients [45,46]. Containing oligomeric pThr181-Tau, exosomal Tau was found in a larger extent in early AD (Braak stage 3) compared to advanced disease progression stage defined by important neuronal loss (Braak stage 5) [45]. Extracellular Tau could then be detected by the immune system and initiates an antigen-driven immune response. For instance, active immunization of the mouse model of Tauopathy rTg4510 with WT or mutated P301L Tau protein induces robust humoral immune responses accompanied by anti-tau antibodies, shown to target 5 immunogenic epitopes found in multiple sites of Tau sequence [47]. Also, circulating tau-specific antibodies were identified in healthy individuals prone to recognize pathological Tau and block *in vitro* Tau aggregation seeding, through notably the cytosolic Fc receptor TRIM21 [48,49]. Therefore, with the aim to achieve successful Tau-immunotherapy and slow down the disease progression, identifying the most immunogenic tau epitopes and the interplay existing between Tau and the immune system remain necessary [50].

Tau inter-cellular transfer

The post-mortem observation of AD brains reveals a characteristic distribution pattern of NFT lesions in the disease course, starting in the transentorhinal cortex and progressively affecting the hippocampus, temporal cortex and polymodal association areas [28,31,32,51]. This sequential and hierarchical pathway defined the six Braak stages and a positive correlation between the affected areas and the clinical symptoms was observed, suggesting an instrumental role in synaptic dysfunction [30,52]. The modalities of the propagation of Tau pathology were investigated. Experimental transfer of brain homogenates containing pathologic Tau from transgenic P301S mice promotes the accumulation of NFT in wild-type (WT) recipient animals in a stereotypical and time-dependent fashion. Tau spreading occurs at distance of the injection site and concerns area connected anatomically instead of affecting proximal structures. However, trans-cellular propagation of Tau in a prion-like fashion was observed as well in the P301S mouse model of Tauopathy or in AD brain [53,54]. Tau seeding activity was shown to be an early manifestation, present in multiple brain regions and associated with disease progression and cognitive decline [53]. Moreover, insoluble Tau is more efficient to be propagated; all without any sign of neurodegeneration, suggesting that molecular forms of Tau responsible for propagation and neurotoxicity are different [55,56]. Of interest, using a lentiviral approach, a trans-synaptic transfer of WT Tau in a dephosphorylated state can also be observed [57]. The cellular mechanisms of this prion-like trans-synaptic transmission were evaluated and different pathways were identified, including free forms, Tunneling nanotubes (TNTs) structures, ectosomes or exosomes [46,58]. Finally, a study revealed a role played by microglial cells, the resident phagocytes of the central nervous system (CNS), in Tau transmission using two different models of Tauopathy: P301S mice and adeno-associated virus (AAV) expressing mutated P301L Tau [59]. Authors observed that microglial cells phagocyte aggregated Tau and that its exosomal secretion is readily transmissible to neurons (Fig. 1). Pharmacological depletion of microglial cells and exosomes synthesis inhibits Tau propagation; highlighting the critical role of microglia in Tau spreading and posit it as a valuable target to slow down disease progression.

AD, Tauopathies and inflammation: genetic evidences

Early onset forms of familial AD concern less than 1% of total cases and are associated with mutations in presenilin 1/2 (*PS-1/2*) and amyloid precursor protein (*APP*) genes. By contrast, the susceptibility of developing sporadic forms of the disease, also called Late-Onset Alzheimer's Disease (LOAD), are conditioned by a combination of environmental and genetic factors. *APOE4* polymorphism is the major genetic risk factor for LOAD, known to intensify brain amyloid-β pathology and described to modulate Aβ-inducing neuroinflammation [60,61]. It was also shown recently to exacerbate Tau-mediated disease and neuroinflammation independently of Aβ pathology using P301S mice [62]. Large genome-wide and rare variant association studies were performed with the purpose of identifying other candidate genes. Authors found a greater amount of single-nucleotide polymorphisms in genes related to immune system, translating an etiology of this pathway in AD development [63–65]. For instance *CR1*, *CD33*, *MS4A4/MS4A6E*, *ABCA7*, *CD2AP*, *CD33* or *EPHA1* genes are involved in complement activation or innate immune response (for review see Ref. [66]). Similarly, polymorphisms in ABI family member 3 (*ABI3*) and Phospholipase C gamma 2 (*PLCG2*) genes were found both highly expressed in microglia [67]. PLCγ2 hydrolyzes the membrane phospholipid PIP_2 to form the secondary messenger inositol triphosphate (IP_3), which promotes the release of calcium into the cytoplasm. Functional alterations of PLCγ2 impact the IP_3/Ca^{2+} signaling pathway, found determinant for microglial properties [68]. Of interest, Tau misfolding could also impact IP_3 production, as it was shown that physiological Tau exerts a tonic inhibition on the phosphatase PTEN reducing the formation of PIP2 [14]. In addition, variants of the triggering receptor expressed on myeloid cells 2 (*TREM2*) gene were also found associated with an increased predisposition to AD [67,69–71]. TREM2 is an immunoglobulin receptor exclusively expressed by microglial cells in the brain, reinforcing the interest on the function of microglia in AD. TREM2 was observed necessary for aging-dependent microglial expansion and for microglial activation and phagocytosis in the context of demyelination [72,73]. Although TREM2 was described to bind apolipoprotein/

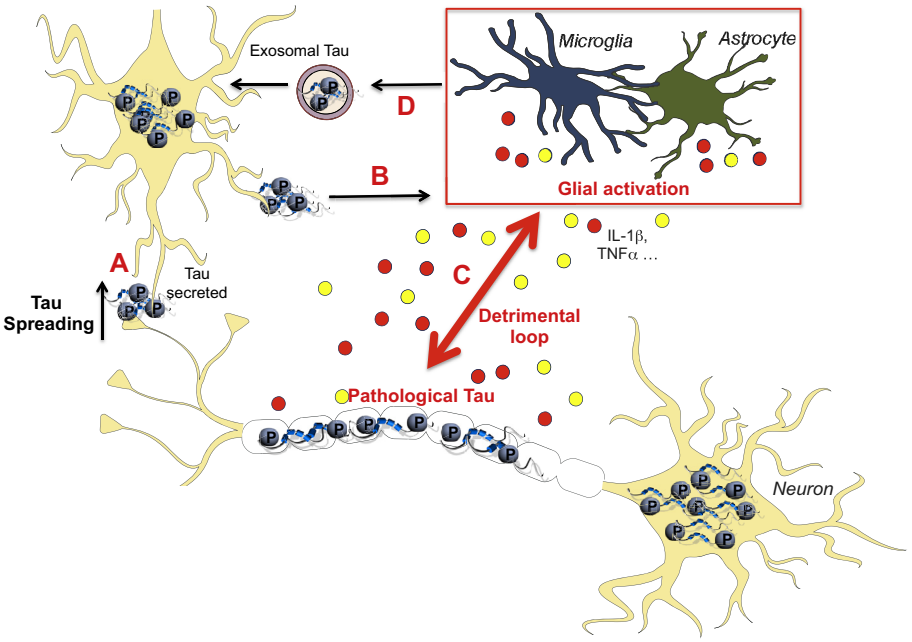

Fig. 1 Innate Immune response and Tau pathology: a vicious circle. Hyperphosphorylated pathological Tau species can be secreted extracellularly, explaining the progressive spread of tauopathy (A). Therefore, it promotes microglial activation/reactive astrocytes which release cytokines or neurotoxic inflammatory molecules including IL1β or TNFα (B). By a modulation of Tau kinases (p38, cdk5…), glial activation enhances Tau pathology, self-perpetuating the detrimental circle (C). Also, microglia was observed to be involved in Tau propagation by releasing exosomal Tau once pathological Tau phagocytosed (D).

phospholipids, promoting microglial survival/activation and increasing amyloid clearance [74,75], its role toward Tau is controversial. Using model of amyloid pathology 5xFAD or APP/PS1 mice, TREM2 was observed to increase or decrease Tau hyper-phosphorylation [76,77]. In addition, while TREM2 mRNA level increases during disease progression in P301S mice, silencing TREM2 by a lentiviral approach was observed to exacerbate Tau pathology, enhance Tau kinase activity, worsening neuroinflammatory response and memory deficits [78]. Also, post mortem analysis of human cortical samples from AD indicates an increase of TREM2 protein associated with Tau pathology and synaptic loss. Finally, TREM2 adapter protein TYROBP or DNAX-activating protein 12 (DAP12) signaling was observed to promote Tau pathology and neuron injuries in APP/PS1 mice [79,80]. Altogether, these genetic studies highlight the critical role played by immune system, in particular microglial cells, in AD pathogenesis even if some evidences indicate an involvement of the adaptive immune system as well. For instance, CR1 and EPHA1 can be expressed on lymphocytes subsets, ABCA7 was shown to promote CD1d surface expression inducing NKT function and ABI3 can indirectly induce T cell activation [67,81–83]. Also, polymorphisms in *HLA-DR* region were found associated in both AD and fronto-temporal dementia (FTD) susceptibility [65,84]. GWAS studies have also been conducted similarly in Corticobasal Degeneration (CBD) or Progressive Supranuclear Palsy (PSP), 2 rare tauopathies [85]. An overlap in genetic risk factors was observed with variants found in genes encoding Tau protein or the myelin-associated oligodendrocyte basic protein (MOBP). PSP susceptibility genes *STX6* or *EIF2AK3* encoding respectively syntaxin 6 and perk were observed as well, highlighting the importance of a dysfunction of vesicular trafficking dysfunction in this disorder [86]. However, no genetic risk factor related to immune function was observed so far in CBD or PSP. Thus, even if microglial activation plays a role in the pathogenesis of these Tauopathies, it might not be a causal factor [87–90].

Glial cells in AD

Besides amyloid and Tau pathologies, another histological feature of AD is the accumulation of reactive astrocytes and microglia in the vicinity of amyloid deposits, commonly referred to as neuroinflammatory response. In the healthy brain, astrocytes provide neuronal energy supply (lactate shuttle hypothesis), participate in synaptic function (recapture/release transmitter – inter-astrocytic communication through calcium wave), induce synaptic pruning and the release of neurotrophic factors [91,92]. However, during neuroinflammatory conditions, activated microglia-driven IL-1α, Tumor Necrosis Factor (TNFα) and C1q release was shown to favor the formation of a neurotoxic subset of reactive astrocytes called A1. A1 astrocytes lose their normal functions and their ability to promote synapse formation, but instead, kill CNS neurons via the secretion of harmful factors [93,94]. A higher proportion of A1 astrocytes producing complement protein C3 was observed in AD brain, suggesting a gain of toxic functions and a loss of physiological properties that could contribute to detrimental effects of reactive astrocytes in AD [94]. Concerning tauopathies, neuronal Tau misfolding as observed in AD and some FTDs is sufficient to induce

morphological changes in astrocytes impacting their physiological role. They shift towards an inflammatory profile, as indicated by GFAP upregulation and the secretion of pro-inflammatory factors, which contribute to the pathogenesis [95,96]. Astrocytic Tau inclusions are pathological hallmarks of PSP and CBD, respectively called tufted astrocytes and astrocytic plaques. To reproduce these pathological features, transgenic mice overexpressing human Tau gene under the GFAP promoter were generated [97]. These mice develop an age-dependent Tau pathology in astrocytes associated with blood-brain-barrier disruption and focal neuron loss, pointing the important role of reactive astrocytes in tauopathies.

Microglia plays a critical role in AD and Tauopathies as well. Microglial cells exhibit highly motile and ramified processes allowing a dynamic and continual survey of the healthy brain as observed using *in vivo* two-photon imaging [98]. They sample, detect and eliminate debris or apoptotic neurons by phagocytosis but this ability is considerably decreased in a pro-inflammatory context [99]. Microglia is involved in multiple processes such as neurogenesis, synapse elimination – in a complement-dependent manner- or synapse plasticity [100]. Moreover, neuronal secretion of CX3CL1 (fractalkine), CD200, the colony-stimulating factor 1 (CSF1) or transforming growth factor-β (TGF-β), among others, favor an inhibitory signaling once fixed to their microglial cognate receptors, keeping these cells in a quiescent state [101,102]. The involvement of microglia on AD pathogenesis was essentially studied in the light of the amyloid side and largely reviewed elsewhere [103,104]. Briefly, these cells appear to have a complex, dynamic and time-dependent impact on amyloid pathology, either promoting the clearance of deposits or associated with neurotoxicity and disease progression due notably to the release of pro-inflammatory cytokines. This is strengthened by the measure of longitudinal changes in microglial activation using imaging and positron emission tomography (PET) scans during the disease course. An initial peak was observed in patients exhibiting mild-cognitive impairments (MCI), and at a latter stage of the disease [105,106]. Although this model will require a larger cohort of patients, the two peaks of activation could reflect a biphasic role of microglia. Therefore, therapeutic avenue targeting microglia require in-depth understanding and a better characterization. In that view, heterogeneity of microglia was deciphered using single-cell RNA sequencing. An individual mapping of immune cell subset identified, in mouse models, a protective and dynamic disease-associated microglia (DAM) involving key genes along the course of AD progression [107]. AD progression can also be impacted by the locus coeruleus (LC), a brain structure early affected (asymptomatic stage) and producing norepinephrine (NE), an anti-inflammatory neurotransmitter (for review see Ref. [108]). Its degeneration induces a disinhibiting effect favoring the establishment of microglial activation and, due to its widespread projections all the major brain structures, facilitates the inflammatory reaction [109,110]. Finally, brain infiltration of peripheral innate immune subsets has been suggested to contribute to AD pathogenesis. For instance, neutrophil infiltration was shown in cerebral parenchyma of AD patients and associated with cognitive damage and an increased Tau/amyloid pathology in 3xTg-AD mice, even if others observed opposite effects [111,112]. Also, recruitment of circulating monocytes via the chemoattractant protein CCL2 and its cognate receptor CCR2 could positively impact the phenotype of APP models. Indeed, deletion of CCR2 in Tg2576 APP mice increases accumulation of microglia around blood vessels possibly through the recruitment of mononuclear phagocytes from the blood and bone marrow and promotes perivascular Aβ deposition [113]. Another study also demonstrated detrimental effect on memory in APP/PS1 mice deficient for CCR2 [113,114]. However, involvement of circulation monocytes in AD remains subject to controversy as most experimental models involved irradiation procedure which open blood-brain barrier. Of interest, the reduction of monocyte infiltration following ccr2 deficiency was involved in Tau hyperphosphorylation in a different disorder called Traumatic Brain Injury (TBI) [115]. Together, innate immune system was shown to participate in disease progression and bidirectional detrimental connections are notably observed with regards to Tau pathology.

Innate immune response and Tau pathology: a vicious circle

Compelling studies revealed that the exclusive presence of Tau pathology is prone to induce microglial/astrocytic activation. For instance, FTD patients carrying the P301S mutation display activated CD68 positive microglial cells around neurons containing hyper-phosphorylated Tau [116]. A strong neuroinflammatory response was also measured as indicated by the upregulation of interleukin-1β (IL1β) and cyclooxygenase-2 (Cox2). Microglial activation and reactive GFAP astrocytes have been also reported in Pick's disease [117], and a microglia-driven IL-1β production was observed in the *substantia nigra* of PSP patients [87]. Tau pathology is thus prone to directly favor the development of neuroinflammation. Indeed, using different transgenic models of Tauopathy, age-dependent astrogliosis/microglial activation and pathological neuroinflammatory changes were observed in CNS structures bearing Tau pathology at a stage where neuronal loss is absent [95,118–120]. The nature of Tau species involved in this process was raised. Since the innate immune response was initiated before the formation of hippocampal NFT, soluble Tau species are more susceptible to be implicated [120]. In that view, a co-localization of activated microglial cells and reactive astrocytes with tau oligomers was observed in both mouse models of Tauopathy and AD/frontotemporal lobar dementia (FTLD) patients' brains [121]. Moreover, it was observed in microglial cultures that misfolded truncated Tau is sufficient to induce pro-inflammatory cytokines (IL-6, IL-1β, TNFα) upregulation through NF-κB and MAPK signaling pathways [122]. Of interest, recent data emphasize that pathological Tau could promote IL-1β secretion by activating the inflammasome, a microglial component of the neuroinflammatory response previously shown to be important regarding amyloid accumulation [123] [124]. Finally, strategies modulating Tau pathology were observed to impact immune response. For instance, active immunization with WT or P301L mutated Tau protein reduces Tau pathology of rTg4510 mice and the number of activated microglia/astrocytic cells [47]. In a similar manner, blockade of adenosine A_{2A} receptors

reduce both hippocampal Tau phosphorylation and neuro-inflammatory response [125].

Reciprocally, the neuroinflammatory response was seen to impact Tau pathogenesis. Indeed, the intra-cerebral administration of LPS, a powerful pro-inflammatory component acting on the myeloid receptor TLR4, promotes a microglial activation and hyper-phosphorylation of Tau as well as the formation of tangles in the conditional rTg4510 model [126]. In addition, microglial activation was observed to be an early event occurring prior the formation of NFTs in P301S mice. Then, it could partially initiate the disease progression since a parallel exists between early synaptic defects and microglial activation in the hippocampus of P301S mice [120]. The underlying mechanisms, which direct the exacerbation of Tau pathology ensuing brain inflammation, were studied and appear mediated by a modulation of Tau kinases. The 3xTg-AD mice, a transgenic model harboring mutations in APP, PS1 and tau gene, received LPS intraperitoneally, which aggravate Tau pathology via CDK5 activation [127]. However, amyloid pathology is present in this model and may create a bias by favoring directly Tau pathology [128]. Transgenic hTau mice, overexpressing human tau gene and depleted for endogenous mouse tau leading to the development of Tau pathology were also used. Genetic deficiency of CX3CR1 induces microglial activation in this model, as the CX3CL1-CX3CR1 regulatory signaling of neuronal-microglial communication is disrupted. Consequently, higher degree of hippocampal Tau phosphorylation/aggregation, loss of synaptic integrity and behavior impairment were observed [119,129]. This is in accordance with the reduced Tau-mediated disease observed in rTg4510 mice overexpressing fractalkine, emphasizing CX3CL1-CX3CR1 axis in the pathogenesis [130]. Notably, it was recently observed that microglial phagocytosis at extracellular Tau is possible through CX3CR1. However, in later stage of AD, both hyper-phosphorylation of Tau and the progressive overexpression of CX3CL1, which competes with Tau in CX3CR1 binding, contribute to Tau clearance impairment by microglia [131]. Interestingly, hTau CX3CR1$^{-/-}$ mice display p38 MAPK upregulation, especially at an early stage [119,129]. Previous observations revealed that LPS-inducing hyper-phosphorylated Tau and synaptic defects in microglial–neuronal co-culture are mediated by the IL-1β/p38 axis [132]. Indeed LPS administration in mice deficient for IL-1 receptor fails to induce Tau hyper-phosphorylation [129]. In addition, experimental transfer of purified microglia from hTau CX3CR1$^{-/-}$ mice is unable to trigger Tau hyper-phosphorylation after the blockade of IL-1β/p38 signaling pathway [119]. Together, these results suggest that activated microglia is prone to secrete IL1β, or others pro-inflammatory cytokines including TNFβ known to favor Tau pathology [133]. Reducing the amount of pro-inflammatory mediator secretion using minocycline treatment was observed to impact directly cortical Tau phosphorylation in hTau mice [134,135]. Both Tau misfolding and neuroinflammatory response favor the progression of pathological changes as loss of synaptic and neuronal integrity, and behavior impairments. In a reciprocal way, Tau is instrumental in LPS-inducing neurotoxicity and neuro-immune response in CX3CR1$^{-/-}$ mice as suggested by the significant reduction of microglial IL-1β secretion and annexin-5/caspase-3 positive neurons in CX3CR1$^{-/-}$ mapt$^{-/-}$ mice [136]. Finally, recent observations indicate that microglia is directly implicated in Tau spreading via the formation of exosomes containing Tau, directly transmissible to neurons [59]. Microglia is then implicated in all the different steps occurring in Tau-driven disease formation (Tau phosphorylation, aggregation, propagation and synaptic alteration), posit it has a valuable target to modulate AD and related Tauopathies progression (Fig. 1). Also, by generating a potent inflammatory response, glial cells can impact adult neurogenesis by reducing progenitor proliferation or neuronal differentiation as extensively detailed elsewhere [137]. A recent study has notably shown that stress inducing Tau hyperphosphorylation reduces dentate gyrus neurogenesis *in vivo*, a phenomenon counteracted by Tau deficiency [138]. Together, it may suggest a possible detrimental loop between neurogenesis, inflammation and Tau pathology.

Adaptive immune response and Tau pathology

Adaptive immune response, in particular brain-infiltrated T-cells, was observed in AD patients and was mainly studied in the light of amyloid pathology [139–141]. So far, little is known on the relationships existing between T cells and Tau pathology. Previous observations are in accordance with such Tau pathology driven T cell process. In AD patients, a positive correlation between the number of parenchymal CD3^{+} T cell and phospho-Tau load was found [141]. Also, a greater amount of activated HLA-DR^{+} CD8 T cells was measured in the CSF of AD patients, associated with structural MRI changes and cognitive deterioration, suggesting a detrimental impact of T cell infiltration [142]. Other findings indicated functional changes in circulating lymphocytes from AD patients. For instance, a greater percentage of late-differentiated CD4 T cells (CD28^{-}CD27^{-}CD45RA^{+}CD45RO^{+}) was observed compared to age-matched controls [143]. In a similar manner, the proportion of activated HLA-DR positive CD4 and CD8 T cells was increased in AD patients' blood [142]. These modifications might result of the chronic stimulation by circulating Aβ while a role of peripheral Tau cannot be excluded. We recently investigated the immune profile of CD4 and CD8 T cells in the blood of Tau transgenic mice (THY-Tau22). Using CD44 and CD62L markers, the proportion of naïve and memory subsets, as well as the amount of interferon-γ (IFNγ) or TNFα was unchanged compared to WT [95]. Regarding Tau, the notion of antigen-specificity remains to be further evaluated. Current results suggest that specific T cell recruitment rather occurs once the CNS is reached, possibly due to the presence of Tau pathology and neuroinflammatory processes, rather than to a preliminar peripheral activation.

Leukocytes trafficking, including tissue-infiltrating T cells, is favored by inflammatory chemoattractant molecules named chemokines. The potential role of chemokines on Aβ pathogenesis and their direct/indirect effects on neurons has been studied and reviewed elsewhere [144]. These mediators are involved in the Tau-driven neuro-inflammatory response characterizing Tauopathies as previously described. Indeed, transcriptome analysis in acute model of rats overexpressing Tau indicates an overexpression of chemokines (C-X-C motif) ligand 10 (CXCL10) and CXCL16 [145]. Moreover, upregulation

of chemokines such as CCL3, CCL4, CCL12 and CXCL2 release was observed in the cortex of hTau mice [134]. In addition, early hippocampal upregulation of microglial CCL3, but also CCL4 and CCL5 were observed in our transgenic mouse model of Tauopathy (THY-Tau22) associated with Tau pathology, and memory impairments [95,146]. Also, a positive correlation was observed between the level of CCL2 and phospho-Tau in the CSF of AD patients, and CCL2, CCL3 and CCL5 were found upregulated in the AD brain supporting the idea of a determinant role of chemokines in chronic inflammation [144,147,148]. Finally, besides their implications in numerous immune functions, chemokines are prone to modulate synaptic plasticity [149]. For instance, *ex-vivo* CCL3 treatment was found to decrease hippocampal LTP in a CCR5-dependent manner. In addition, intra-cerebroventricular injection of CCL3 alters hippocampal synaptic transmission and plasticity, in association with memory impairments, the latter being reversed by CCR5 antagonist administration [150]. Thus, early release of CCL3, acting on its cognate receptor CCR5, may contribute *per se* to progressive synaptic/memory alterations exhibited by THY-Tau22 mice. Of interest, APOE4 genotype, the strongest genetic risk factor for sporadic AD, was observed to favor astrocytic CCL3 production [151].

CCL3-inducing CNS T cell infiltration may also explain the detrimental effects of the chemokine. Using an *in vitro* model of Blood-Brain Barrier (BBB), CCL3 overexpression in AD T cells favors their transendothelial migration by acting on its endothelial cognate receptor CCR5. In addition, cortical T cell infiltration, following acute Aβ administration in rats, is considerably reduced once CCL3 function is neutralized [152]. Therefore, CCL3 could promote brain-infiltrated $CD8^+$ T-cell through the BBB as observed in our THY-Tau22 model, the chemokine being secreted by microglial cells at a stage where T cell infiltration is not present yet [95] (Fig. 2).

Unlike the large majority of tissues, BBB, which is a highly specified structure, restricts drastically the diffusion of cellular components, and so immune cells, from the circulation to brain parenchyma, which confine leukocytes in the vascular compartment in non-pathological conditions [153]. Leukocyte extravasation across the BBB is a multi-step process whose molecular mechanisms have been largely studied in the context of multiple sclerosis [154–156]. BBB disruption has been observed in a certain number of tauopathies including progressive supranuclear palsy (PSP) [157]. *In vitro* experiments found a toxic gain of function of Tau misfolding on BBB integrity [158]. In a similar manner, aged rTg4510 mice exhibit hippocampal Tau accumulation, notably in vascular structure, accompanied by BBB disruption as observed by immunoglobulin G (IgG) extravasation, and $CD4^+$ T cell infiltration, suggesting a passive mechanism of infiltration due to BBB leakage. Tau suppression using doxycycline administration in this conditional model, reverse BBB dysfunction in association with a significant lower number of infiltrated T cells [159]. However, $CD8^+$ T cell infiltration observed in THY-Tau22 mice occur in absence of any BBB disruption, no alteration in tight junction organization or IgG extravasation was observed, suggesting an active model of diapedesis in brain-restricted neuroinflammatory processes [95]. Therefore, even if BBB alteration can occur in association with Tau pathogenesis, it does not appear essential for T cells infiltration.

The functional impact of T cell infiltration on Tau-mediated disease progression has never been evaluated so far. To this end, we chronically suppressed circulating $CD3^+$ T cells using anti-CD3 depleting antibody treatment prior to the development of pathological alterations characterizing THY-Tau22 mice. Paralleling the significant drop of hippocampal CD8 T cells infiltration, treated THY-Tau22 animals displayed a reduction of spatial memory impairments and a recovery of synaptic function, as indicated by the hiuppocampal normalization of Arc and 14.3.3. expressions [95]. Interestingly, the neuroinflammatory response and notably astrocytic/microglial activation was found reduced while no change was

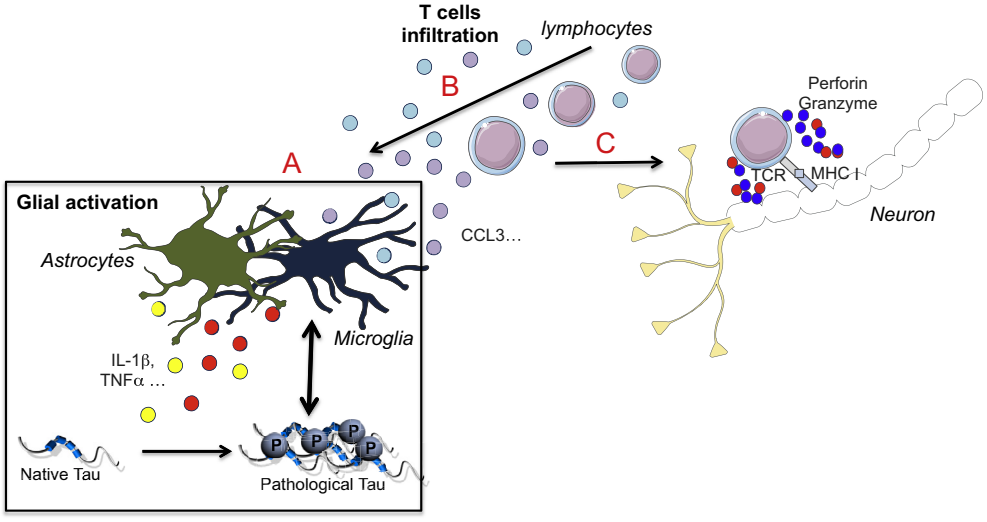

Fig. 2 Consequences of T cell infiltration in Tauopathies. Along the disease formation, innate immune subsets release chemokines (eg. CCL3…) favoring brain T Cell infiltration (A). Consequently, either beneficial or detrimental effects may occur depending on the infiltrated subset. It can modulate the neuroimmune response which may impact tau pathology and synaptic functions (B). Activated T cells can also dampen neurons integrity by the release of neurotoxic factors (granzyme, perforin…) using TCR/MHC I interaction (C). TCR. T-cell receptor, MHC I. Major histocompatibility complex.

observed in term of Tau pathology. Together, this suggests an instrumental role of CD8 T cell infiltration towards Tau-induced cognitive deficits, independent of Tau misfolding, but rather related to a modulate of the innate immune response. This is strongly evocative of previous observations made in the context of amyloid pathology. As a matter of facts, antigen-specific reactive Th1 cells induced by Aβ immunization in APP/IFNγ transgenic mice migrate at site of amyloid plaques to the brain and induce an upregulation of microglial phagocytic markers such as TREM2 and signal regulatory protein-β1 (SIRPβ1) [160]. In a similar manner, pharmacological depletion of FoxP3$^+$ regulatory T cells (Treg) in APP/PS1 mice reduces the amount of plaque-associated microglia and shifts the functionality of microglial cells as observed by transcriptome analysis, all without affecting amyloid deposition [161]. Also, Treg activation induced by IL-2 treatment was associated with an astrocytic recruitment around amyloid plaques in APP/PS1 mice [162]. Although T cell infiltration may impact on microglial activation, a direct effect cannot be excluded to explain the detrimental effects of lymphocytes (Fig. 2). Notably, antigen-specific CD8 T cells may interact with neurons expressing MHCI and exert cytotoxic functions by the release of lytic granules containing granzyme A, B, perforin. The engagement of Fas ligand/Fas signaling pathway and secretion of IFN-γ/TNFα could promote neuronal death as well [163]. Also, CD8 T cells were observed to have an inhibitory effect on neurites outgrowth *in vitro* independently of apoptosis mechanisms [164]. Finally, the impact of regulatory CD4 Treg was evaluated in the light of Aβ pathology. In the amyloid-driven disease model 5xFAD, authors induced a breaking of immune tolerance by a systemic transient depletion of FoxP3$^+$ Treg or programmed death-1 (PD1) immune checkpoint blockade. In both conditions, it favors the trafficking of immunoregulatory myeloid cells and/or Treg cells across the choroid plexus in an IFNγ-dependent pathway, which mitigate amyloid plaque burden and memory impairments [165,166]. This is in apparent discrepancy with the acceleration of cognitive deficits observed in APP/PS1 early depleted in systemic FoxP3$^+$ Treg [161]. Similarly, IL-2 treatment was observed to expand FoxP3$^+$ Treg in the blood and the brain of APP/PS1 mice and rescue hippocampal spatial memory impairments, synaptic defect and amyloid pathology [162], which could actually suggest a dual and time-dependent function of this population [161]. The function of this population is unknown in Tau mediated pathology and more generally deciphering the role played by activated/regulatory subsets along the disease course is necessary to custom therapeutical strategies.

Conclusion

Pathological Tau misfolding as defined in tauopathies and neuroinflammatory processes generated by innate/adaptive components form a detrimental vicious circle and act together in the progression of pathogenesis. Underlying mechanisms are multiples but can be summarized as a toxic gain of function including Tau aggregation, release of inflammatory molecules and a loss of physiological functions such as adult neurogenesis, glial phagocytosis and trophic factor release, Tau-driven axonal transport and RNA/DNA integrity. Also, environmental disease modifiers (for instance obesity, stress, caffeine consumption) can act through an alteration of the neuroimmune response and impact upon the aforementioned vicious circle. Therefore, better understanding of the spatio-temporal pattern of Tau-dependent neuroinflammation in Tauopathies is necessary to better delineate to which extent these innate and adaptive pathways constitute future therapeutical targets for the treatments of AD and Tauopathies.

Conflicts of interest

Authors declare no conflict of interest regarding the present manuscript.

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