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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 (A β) 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 microtubulebinding 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 selfassembly 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 Tauimmunotherapy 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 timedependent fashion. Tau spreading occurs at distance of the injection site and concerns area connected anatomically instead of affecting proximal structures. However, transcellular 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 adenoassociated 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 $A\beta$ -inducing neuroinflammation [60,61]. It was also shown recently to exacerbate Taumediated disease and neuroinflammation independently of A β 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]. PLC γ 2 hydrolyzes the membrane phospholipid PIP₂ to form the secondary messenger inositol triphosphate (IP₃), which promotes the release of calcium into the cytoplasm. Functional alterations of PLC γ 2 impact the IP₃/Ca²⁺ signaling pathway, found determinant for microglial properties [68]. Of interest, Tau misfolding could also impact IP₃ 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 agingdependent 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-1a, Tumor Necrosis Factor (TNFa) 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 proinflammatory 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 $A\beta$ 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-1 β (IL1 β) and cyclooxygenase-2 (Cox2). Microglial activation and reactive GFAP astrocytes have been also reported in Pick's disease [117], and a microgliadriven IL-1^β 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-1 β , TNF α) upregulation through NF- κ B and MAPK signaling pathways [122]. Of interest, recent data emphasize that pathological Tau could promote IL-1ß 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 A2A receptors

reduce both hippocampal Tau phosphorylation and neuroinflammatory 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 hyperphosphorylated Tau and synaptic defects in microglial-neuronal co-culture are mediated by the IL-1 β /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 hyperphosphorylation after the blockade of IL-1β/p38 signaling pathway [119]. Together, these results suggest that activated microglia is prone to secrete IL1^β, or others pro-inflammatory cytokines including TNF β 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-1 β 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 Tcells, 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 $A\beta$ 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 (IFN γ) or TNFa 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 $A\beta$ 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 A β 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 brainrestricted 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 Tauinduced 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, antigenspecific reactive Th1 cells induced by $A\beta$ immunization in APP/IFNy 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-\beta1 (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 /TNF α 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 $A\beta$ 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 IFN_γ-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 spatiotemporal 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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REFERENCES

- Binder LI, Frankfurter A, Rebhun LI. The distribution of tau in the mammalian central nervous system. J Cell Biol 1985;101:1371–8.
- [2] Drechsel DN, Hyman AA, Cobb MH, Kirschner MW. Modulation of the dynamic instability of tubulin assembly by the microtubule-associated protein tau. Mol Biol Cell 1992;3:1141–54.
- [3] Weingarten MD, Lockwood AH, Hwo SY, Kirschner MW. A protein factor essential for microtubule assembly. Proc Natl Acad Sci U S A 1975;72:1858–62.
- [4] Frandemiche ML, De Seranno S, Rush T, Borel E, Elie A, Arnal I, et al. Activity-dependent tau protein translocation to excitatory synapse is disrupted by exposure to amyloidbeta oligomers. J Neurosci 2014;34:6084–97.
- [5] Ittner LM, Ke YD, Delerue F, Bi M, Gladbach A, van Eersel J, et al. Dendritic function of tau mediates amyloid-beta toxicity in Alzheimer's disease mouse models. Cell 2010;142:387–97.
- [6] Kimura T, Whitcomb DJ, Jo J, Regan P, Piers T, Heo S, et al. Microtubule-associated protein tau is essential for longterm depression in the hippocampus. Philos Trans R Soc Lond B Biol Sci 2013;369:20130144.
- [7] Lee G, Newman ST, Gard DL, Band H, Panchamoorthy G. Tau interacts with src-family non-receptor tyrosine kinases. J Cell Sci 1998;111:3167–77.
- [8] Tai HC, Wang BY, Serrano-Pozo A, Frosch MP, Spires-Jones TL, Hyman BT. Frequent and symmetric deposition of misfolded tau oligomers within presynaptic and

postsynaptic terminals in Alzheimer's disease. Acta Neuropathol Commun 2014;2:146.

- [9] Sultan A, Nesslany F, Violet M, Begard S, Loyens A, Talahari S, et al. Nuclear tau, a key player in neuronal DNA protection. J Biol Chem 2011;286:4566–75.
- [10] Mansuroglu Z, Benhelli-Mokrani H, Marcato V, Sultan A, Violet M, Chauderlier A, et al. Loss of Tau protein affects the structure, transcription and repair of neuronal pericentromeric heterochromatin. Sci Rep 2016;6:33047.
- [11] Violet M, Chauderlier A, Delattre L, Tardivel M, Chouala MS, Sultan A, et al. Prefibrillar Tau oligomers alter the nucleic acid protective function of Tau in hippocampal neurons in vivo. Neurobiol Dis 2015;82:540–51.
- [12] Violet M, Delattre L, Tardivel M, Sultan A, Chauderlier A, Caillierez R, et al. A major role for Tau in neuronal DNA and RNA protection in vivo under physiological and hyperthermic conditions. Front Cell Neurosci 2014;8:84.
- [13] Arendt T, Stieler JT, Holzer M. Tau and tauopathies. Brain Res Bull 2016;126:238–92.
- [14] Marciniak E, Leboucher A, Caron E, Ahmed T, Tailleux A, Dumont J, et al. Tau deletion promotes brain insulin resistance. J Exp Med 2017;214:2257–69.
- [15] Guo T, Noble W, Hanger DP. Roles of tau protein in health and disease. Acta Neuropathol 2017;133:665–704.
- [16] Morris M, Knudsen GM, Maeda S, Trinidad JC, Ioanoviciu A, Burlingame AL, et al. Tau post-translational modifications in wild-type and human amyloid precursor protein transgenic mice. Nat Neurosci 2015;18:1183–9.
- [17] Hanger DP, Seereeram A, Noble W. Mediators of tau phosphorylation in the pathogenesis of Alzheimer's disease. Expert Rev Neurother 2009;9:1647–66.
- [18] Sergeant N, Bretteville A, Hamdane M, Caillet-Boudin ML, Grognet P, Bombois S, et al. Biochemistry of Tau in Alzheimer's disease and related neurological disorders. Expert Rev Proteomics 2008;5:207–24.
- [19] Martin L, Latypova X, Wilson CM, Magnaudeix A, Perrin ML, Yardin C, et al. Tau protein kinases: involvement in Alzheimer's disease. Ageing Res Rev 2013;12:289–309.
- [20] Papon MA, El Khoury NB, Marcouiller F, Julien C, Morin F, Bretteville A, et al. Deregulation of protein phosphatase 2A and hyperphosphorylation of tau protein following onset of diabetes in NOD mice. Diabetes 2013;62:609–17.
- [21] Malia TJ, Teplyakov A, Ernst R, Wu SJ, Lacy ER, Liu X, et al. Epitope mapping and structural basis for the recognition of phosphorylated tau by the anti-tau antibody AT8. Proteins 2016;84:427–34.
- [22] Zheng-Fischhofer Q, Biernat J, Mandelkow EM, Illenberger S, Godemann R, Mandelkow E. Sequential phosphorylation of Tau by glycogen synthase kinase-3beta and protein kinase A at Thr212 and Ser214 generates the Alzheimer-specific epitope of antibody AT100 and requires a paired-helical-filament-like conformation. Eur J Biochem 1998;252:542–52.
- [23] Bussiere T, Hof PR, Mailliot C, Brown CD, Caillet-Boudin ML, Perl DP, et al. Phosphorylated serine422 on tau proteins is a pathological epitope found in several diseases with neurofibrillary degeneration. Acta Neuropathol 1999;97:221–30.
- [24] Luna-Munoz J, Chavez-Macias L, Garcia-Sierra F, Mena R. Earliest stages of tau conformational changes are related to the appearance of a sequence of specific phosphodependent tau epitopes in Alzheimer's disease. J Alzheimers Dis 2007;12:365–75.
- [25] Mondragon-Rodriguez S, Basurto-Islas G, Santa-Maria I, Mena R, Binder LI, Avila J, et al. Cleavage and conformational changes of tau protein follow phosphorylation during Alzheimer's disease. Int J Exp Pathol 2008;89:81–90.

- [26] Mondragon-Rodriguez S, Perry G, Luna-Munoz J, Acevedo-Aquino MC, Williams S. Phosphorylation of tau protein at sites Ser(396-404) is one of the earliest events in Alzheimer's disease and Down syndrome. Neuropathol Appl Neurobiol 2014;40:121–35.
- [27] Wang L, Jiang Q, Chu J, Lin L, Li XG, Chai GS, et al. Expression of Tau40 induces activation of cultured rat microglial cells. PLoS One 2013;8:e76057.
- [28] Braak H, Braak E. Neuropathological stageing of Alzheimerrelated changes. Acta Neuropathol 1991;82:239–59.
- [29] Arriagada PV, Growdon JH, Hedley-Whyte ET, Hyman BT. Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. Neurology 1992;42:631–9.
- [30] Duyckaerts C, Bennecib M, Grignon Y, Uchihara T, He Y, Piette F, et al. Modeling the relation between neurofibrillary tangles and intellectual status. Neurobiol Aging 1997;18:267–73.
- [31] Cho H, Choi JY, Hwang MS, Lee JH, Kim YJ, Lee HM, et al. Tau PET in Alzheimer disease and mild cognitive impairment. Neurology 2016;87:375–83.
- [32] Pontecorvo MJ, Devous Sr MD, Navitsky M, Lu M, Salloway S, Schaerf FW, et al. Relationships between flortaucipir PET tau binding and amyloid burden, clinical diagnosis, age and cognition. Brain 2017;140:748–63.
- [33] Ren QG, Liao XM, Chen XQ, Liu GP, Wang JZ. Effects of tau phosphorylation on proteasome activity. FEBS Lett 2007;581:1521–8.
- [34] Keck S, Nitsch R, Grune T, Ullrich O. Proteasome inhibition by paired helical filament-tau in brains of patients with Alzheimer's disease. J Neurochem 2003;85:115–22.
- [35] Ying Z, Wang H, Wang G. The ubiquitin proteasome system as a potential target for the treatment of neurodegenerative diseases. Curr Pharm Des 2013;19:3305–14.
- [36] Santacruz K, Lewis J, Spires T, Paulson J, Kotilinek L, Ingelsson M, et al. Tau suppression in a neurodegenerative mouse model improves memory function. Science 2005;309:476–81.
- [37] Spires TL, Orne JD, SantaCruz K, Pitstick R, Carlson GA, Ashe KH, et al. Region-specific dissociation of neuronal loss and neurofibrillary pathology in a mouse model of tauopathy. Am J Pathol 2006;168:1598–607.
- [38] Olsson B, Lautner R, Andreasson U, Ohrfelt A, Portelius E, Bjerke M, et al. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and metaanalysis. Lancet Neurol 2016;15:673–84.
- [39] Hall GF, Saman S. Death or secretion? The demise of a plausible assumption about CSF-tau in Alzheimer Disease? Commun Integr Biol 2012;5:623–6.
- [40] Medina M, Avila J. The role of extracellular Tau in the spreading of neurofibrillary pathology. Front Cell Neurosci 2014;8:113.
- [41] Seppala TT, Koivisto AM, Hartikainen P, Helisalmi S, Soininen H, Herukka SK. Longitudinal changes of CSF biomarkers in Alzheimer's disease. J Alzheimers Dis 2011;25:583–94.
- [42] Pooler AM, Phillips EC, Lau DH, Noble W, Hanger DP. Physiological release of endogenous tau is stimulated by neuronal activity. EMBO Rep 2013;14:389–94.
- [43] Yamada K, Cirrito JR, Stewart FR, Jiang H, Finn MB, Holmes BB, et al. In vivo microdialysis reveals agedependent decrease of brain interstitial fluid tau levels in P301S human tau transgenic mice. J Neurosci 2011;31:13110–7.
- [44] Plouffe V, Mohamed NV, Rivest-McGraw J, Bertrand J, Lauzon M, Leclerc N. Hyperphosphorylation and cleavage at D421 enhance tau secretion. PLoS One 2012;7:e36873.

- [45] Saman S, Kim W, Raya M, Visnick Y, Miro S, Saman S, et al. Exosome-associated tau is secreted in tauopathy models and is selectively phosphorylated in cerebrospinal fluid in early Alzheimer disease. J Biol Chem 2012;287:3842–9.
- [46] Wang Y, Balaji V, Kaniyappan S, Kruger L, Irsen S, Tepper K, et al. The release and trans-synaptic transmission of Tau via exosomes. Mol Neurodegener 2017;12:5.
- [47] Selenica ML, Davtyan H, Housley SB, Blair LJ, Gillies A, Nordhues BA, et al. Epitope analysis following active immunization with tau proteins reveals immunogens implicated in tau pathogenesis. J Neuroinflammation 2014;11:152.
- [48] McEwan WA, Falcon B, Vaysburd M, Clift D, Oblak AL, Ghetti B, et al. Cytosolic Fc receptor TRIM21 inhibits seeded tau aggregation. Proc Natl Acad Sci U S A 2017;114:574–9.
- [49] Pascual G, Wadia JS, Zhu X, Keogh E, Kukrer B, van Ameijde J, et al. Immunological memory to hyperphosphorylated tau in asymptomatic individuals. Acta Neuropathol 2017;133:767–83.
- [50] Agadjanyan MG, Petrovsky N, Ghochikyan A. A fresh perspective from immunologists and vaccine researchers: active vaccination strategies to prevent and reverse Alzheimer's disease. Alzheimers Dement 2015;11:1246–59.
- [51] Delacourte A, David JP, Sergeant N, Buee L, Wattez A, Vermersch P, et al. The biochemical pathway of neurofibrillary degeneration in aging and Alzheimer's disease. Neurology 1999;52:1158–65.
- [52] Grober E, Dickson D, Sliwinski MJ, Buschke H, Katz M, Crystal H, et al. Memory and mental status correlates of modified Braak staging. Neurobiol Aging 1999;20:573–9.
- [53] Furman JL, Vaquer-Alicea J, White 3rd CL, Cairns NJ, Nelson PT, Diamond MI. Widespread tau seeding activity at early Braak stages. Acta Neuropathol 2017;133:91–100.
- [54] Holmes BB, Furman JL, Mahan TE, Yamasaki TR, Mirbaha H, Eades WC, et al. Proteopathic tau seeding predicts tauopathy in vivo. Proc Natl Acad Sci U S A 2014;111:E4376–85.
- [55] Ahmed Z, Cooper J, Murray TK, Garn K, McNaughton E, Clarke H, et al. A novel in vivo model of tau propagation with rapid and progressive neurofibrillary tangle pathology: the pattern of spread is determined by connectivity, not proximity. Acta Neuropathol 2014;127:667–83.
- [56] Clavaguera F, Bolmont T, Crowther RA, Abramowski D, Frank S, Probst A, et al. Transmission and spreading of tauopathy in transgenic mouse brain. Nat Cell Biol 2009;11:909–13.
- [57] Dujardin S, Lecolle K, Caillierez R, Begard S, Zommer N, Lachaud C, et al. Neuron-to-neuron wild-type Tau protein transfer through a trans-synaptic mechanism: relevance to sporadic tauopathies. Acta Neuropathol Commun 2014;2:14.
- [58] Tardivel M, Begard S, Bousset L, Dujardin S, Coens A, Melki R, et al. Tunneling nanotube (TNT)-mediated neuronto neuron transfer of pathological Tau protein assemblies. Acta Neuropathol Commun 2016;4:117.
- [59] Asai H, Ikezu S, Tsunoda S, Medalla M, Luebke J, Haydar T, et al. Depletion of microglia and inhibition of exosome synthesis halt tau propagation. Nat Neurosci 2015;18:1584–93.
- [60] Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 1993;261:921–3.
- [61] Tai LM, Ghura S, Koster KP, Liakaite V, Maienschein-Cline M, Kanabar P, et al. APOE-modulated Abeta-induced neuroinflammation in Alzheimer's disease: current landscape, novel data, and future perspective. J Neurochem 2015;133:465–88.

- [62] Shi Y, Yamada K, Liddelow SA, Smith ST, Zhao L, Luo W, et al. ApoE4 markedly exacerbates tau-mediated neurodegeneration in a mouse model of tauopathy. Nature 2017;549:523–7.
- [63] Hollingworth P, Harold D, Sims R, Gerrish A, Lambert JC, Carrasquillo MM, et al. Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease. Nat Genet 2011;43:429–35.
- [64] Jones L, Holmans PA, Hamshere ML, Harold D, Moskvina V, Ivanov D, et al. Genetic evidence implicates the immune system and cholesterol metabolism in the aetiology of Alzheimer's disease. PLoS One 2010;5:e13950.
- [65] Lambert JC, Grenier-Boley B, Chouraki V, Heath S, Zelenika D, Fievet N, et al. Implication of the immune system in Alzheimer's disease: evidence from genomewide pathway analysis. J Alzheimers Dis 2010;20:1107–18.
- [66] Tosto G, Reitz C. Genome-wide association studies in Alzheimer's disease: a review. Curr Neurol Neurosci Rep 2013;13:381.
- [67] Sims R, van der Lee SJ, Naj AC, Bellenguez C, Badarinarayan N, Jakobsdottir J, et al. Rare coding variants in PLCG2, ABI3, and TREM2 implicate microglial-mediated innate immunity in Alzheimer's disease. Nat Genet 2017;49:1373–84.
- [68] Sharma P, Ping L. Calcium ion influx in microglial cells: physiological and therapeutic significance. J Neurosci Res 2014;92:409–23.
- [69] Guerreiro R, Hardy J. TREM2 and neurodegenerative disease. N Engl J Med 2013;369:1569–70.
- [70] Jonsson T, Stefansson H, Steinberg S, Jonsdottir I, Jonsson PV, Snaedal J, et al. Variant of TREM2 associated with the risk of Alzheimer's disease. N Engl J Med 2013;368:107–16.
- [71] Seshadri S, Fitzpatrick AL, Ikram MA, DeStefano AL, Gudnason V, Boada M, et al. Genome-wide analysis of genetic loci associated with Alzheimer disease. JAMA 2010;303:1832–40.
- [72] Cantoni C, Bollman B, Licastro D, Xie M, Mikesell R, Schmidt R, et al. TREM2 regulates microglial cell activation in response to demyelination in vivo. Acta Neuropathol 2015;129:429–47.
- [73] Poliani PL, Wang Y, Fontana E, Robinette ML, Yamanishi Y, Gilfillan S, et al. TREM2 sustains microglial expansion during aging and response to demyelination. J Clin Invest 2015;125:2161–70.
- [74] Wang Y, Cella M, Mallinson K, Ulrich JD, Young KL, Robinette ML, et al. TREM2 lipid sensing sustains the microglial response in an Alzheimer's disease model. Cell 2015;160:1061–71.
- [75] Yeh FL, Hansen DV, Sheng M. TREM2, microglia, and neurodegenerative diseases. Trends Mol Med 2017;23:512–33.
- [76] Jay TR, Miller CM, Cheng PJ, Graham LC, Bemiller S, Broihier ML, et al. TREM2 deficiency eliminates TREM2+ inflammatory macrophages and ameliorates pathology in Alzheimer's disease mouse models. J Exp Med 2015;212:287–95.
- [77] Wang Y, Ulland TK, Ulrich JD, Song W, Tzaferis JA, Hole JT, et al. TREM2-mediated early microglial response limits diffusion and toxicity of amyloid plaques. J Exp Med 2016;213:667–75.
- [78] Jiang T, Zhang YD, Chen Q, Gao Q, Zhu XC, Zhou JS, et al. TREM2 modifies microglial phenotype and provides neuroprotection in P301S tau transgenic mice. Neuropharmacology 2016;105:196–206.
- [79] Haure-Mirande JV, Audrain M, Fanutza T, Kim SH, Klein WL, Glabe C, et al. Deficiency of TYROBP, an adapter protein for TREM2 and CR3 receptors, is neuroprotective in a mouse

model of early Alzheimer's pathology. Acta Neuropathol 2017;134:769–88.

- [80] Takahashi H, Klein ZA, Bhagat SM, Kaufman AC, Kostylev MA, Ikezu T, et al. Opposing effects of progranulin deficiency on amyloid and tau pathologies via microglial TYROBP network. Acta Neuropathol 2017;133:785–807.
- [81] Erdei A, Isaak A, Torok K, Sandor N, Kremlitzka M, Prechl J, et al. Expression and role of CR1 and CR2 on B and T lymphocytes under physiological and autoimmune conditions. Mol Immunol 2009;46:2767–73.
- [82] Holen HL, Nustad K, Aasheim HC. Activation of EphA receptors on CD4⁺CD45RO⁺ memory cells stimulates migration. J Leukoc Biol 2010;87:1059–68.
- [83] Nowyhed HN, Chandra S, Kiosses W, Marcovecchio P, Andary F, Zhao M, et al. ATP binding cassette transporter ABCA7 regulates NKT cell development and function by controlling CD1d expression and lipid raft content. Sci Rep 2017;7:40273.
- [84] Ferrari R, Hernandez DG, Nalls MA, Rohrer JD, Ramasamy A, Kwok JB, et al. Frontotemporal dementia and its subtypes: a genome-wide association study. Lancet Neurol 2014;13:686–99.
- [85] Kouri N, Ross OA, Dombroski B, Younkin CS, Serie DJ, Soto-Ortolaza A, et al. Genome-wide association study of corticobasal degeneration identifies risk variants shared with progressive supranuclear palsy. Nat Commun 2015;6:7247.
- [86] Hoglinger GU, Melhem NM, Dickson DW, Sleiman PM, Wang LS, Klei L, et al. Identification of common variants influencing risk of the tauopathy progressive supranuclear palsy. Nat Genet 2011;43:699–705.
- [87] Fernandez-Botran R, Ahmed Z, Crespo FA, Gatenbee C, Gonzalez J, Dickson DW, et al. Cytokine expression and microglial activation in progressive supranuclear palsy. Parkinsonism Relat Disord 2011;17:683–8.
- [88] Gerhard A, Trender-Gerhard I, Turkheimer F, Quinn NP, Bhatia KP, Brooks DJ. In vivo imaging of microglial activation with [11C](R)-PK11195 PET in progressive supranuclear palsy. Mov Disord 2006;21:89–93.
- [89] Gerhard A, Watts J, Trender-Gerhard I, Turkheimer F, Banati RB, Bhatia K, et al. In vivo imaging of microglial activation with [11C](R)-PK11195 PET in corticobasal degeneration. Mov Disord 2004;19:1221–6.
- [90] Ishizawa K, Dickson DW. Microglial activation parallels system degeneration in progressive supranuclear palsy and corticobasal degeneration. J Neuropathol Exp Neurol 2001;60:647–57.
- [91] Liddelow S, Barres B. SnapShot: astrocytes in health and disease. Cell 2015;162:1170–1170.e1.
- [92] Stobart JL, Anderson CM. Multifunctional role of astrocytes as gatekeepers of neuronal energy supply. Front Cell Neurosci 2013;7:38.
- [93] Liddelow SA, Barres BA. Reactive astrocytes: production, function, and therapeutic potential. Immunity 2017;46:957–67.
- [94] Liddelow SA, Guttenplan KA, Clarke LE, Bennett FC, Bohlen CJ, Schirmer L, et al. Neurotoxic reactive astrocytes are induced by activated microglia. Nature 2017;541:481–7.
- [95] Laurent C, Dorothee G, Hunot S, Martin E, Monnet Y, Duchamp M, et al. Hippocampal T cell infiltration promotes neuroinflammation and cognitive decline in a mouse model of tauopathy. Brain 2017;140:184–200.
- [96] Rodriguez-Arellano JJ, Parpura V, Zorec R, Verkhratsky A. Astrocytes in physiological aging and Alzheimer's disease. Neuroscience 2016;323:170–82.

- [97] Forman MS, Lal D, Zhang B, Dabir DV, Swanson E, Lee VM, et al. Transgenic mouse model of tau pathology in astrocytes leading to nervous system degeneration. J Neurosci 2005;25:3539–50.
- [98] Nimmerjahn A, Kirchhoff F, Helmchen F. Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. Science 2005;308:1314–8.
- [99] Koenigsknecht-Talboo J, Landreth GE. Microglial phagocytosis induced by fibrillar beta-amyloid and IgGs are differentially regulated by proinflammatory cytokines. J Neurosci 2005;25:8240–9.
- [100] Paolicelli RC, Bisht K, Tremblay ME. Fractalkine regulation of microglial physiology and consequences on the brain and behavior. Front Cell Neurosci 2014;8:129.
- [101] Walker DG, Lue LF. Understanding the neurobiology of CD200 and the CD200 receptor: a therapeutic target for controlling inflammation in human brains? Future Neurol 2013;8:321–32.
- [102] Wohleb ES. Neuron-microglia interactions in mental health disorders: "For Better, and For Worse". Front Immunol 2016;7:544.
- [103] Guillot-Sestier MV, Doty KR, Town T. Innate immunity fights Alzheimer's disease. Trends Neurosci 2015;38:674–81.
- [104] Heneka MT, Golenbock DT, Latz E. Innate immunity in Alzheimer's disease. Nat Immunol 2015;16:229–36.
- [105] Fan Z, Brooks DJ, Okello A, Edison P. An early and late peak in microglial activation in Alzheimer's disease trajectory. Brain 2017;140:792–803.
- [106] Fan Z, Okello AA, Brooks DJ, Edison P. Longitudinal influence of microglial activation and amyloid on neuronal function in Alzheimer's disease. Brain 2015;138:3685–98.
- [107] Keren-Shaul H, Spinrad A, Weiner A, Matcovitch-Natan O, Dvir-Szternfeld R, Ulland TK, et al. A unique microglia type associated with restricting development of Alzheimer's disease. Cell 2017;169:1276–90e17.
- [108] Simic G, Babic Leko M, Wray S, Harrington CR, Delalle I, Jovanov-Milosevic N, et al. Monoaminergic neuropathology in Alzheimer's disease. Prog Neurobiol 2017;151:101–38.
- [109] Heneka MT, Nadrigny F, Regen T, Martinez-Hernandez A, Dumitrescu-Ozimek L, Terwel D, et al. Locus ceruleus controls Alzheimer's disease pathology by modulating microglial functions through norepinephrine. Proc Natl Acad Sci U S A 2010;107:6058–63.
- [110] Kelly SC, He B, Perez SE, Ginsberg SD, Mufson EJ, Counts SE. Locus coeruleus cellular and molecular pathology during the progression of Alzheimer's disease. Acta Neuropathol Commun 2017;5:8.
- [111] Gabbita SP, Johnson MF, Kobritz N, Eslami P, Poteshkina A, Varadarajan S, et al. Oral TNFalpha modulation alters neutrophil infiltration, improves cognition and diminishes tau and amyloid pathology in the 3xTgAD mouse model. PLoS One 2015;10:e0137305.
- [112] Zenaro E, Pietronigro E, Della Bianca V, Piacentino G, Marongiu L, Budui S, et al. Neutrophils promote Alzheimer's disease-like pathology and cognitive decline via LFA-1 integrin. Nat Med 2015;21:880–6.
- [113] El Khoury J, Toft M, Hickman SE, Means TK, Terada K, Geula C, et al. Ccr2 deficiency impairs microglial accumulation and accelerates progression of Alzheimerlike disease. Nat Med 2007;13:432–8.
- [114] Naert G, Rivest S. CC chemokine receptor 2 deficiency aggravates cognitive impairments and amyloid pathology in a transgenic mouse model of Alzheimer's disease. J Neurosci 2011;31:6208–20.
- [115] Gyoneva S, Kim D, Katsumoto A, Kokiko-Cochran ON, Lamb BT, Ransohoff RM. Ccr2 deletion dissociates cavity

size and tau pathology after mild traumatic brain injury. J Neuroinflammation 2015;12:228.

- [116] Bellucci A, Bugiani O, Ghetti B, Spillantini MG. Presence of reactive microglia and neuroinflammatory mediators in a case of frontotemporal dementia with P301S mutation. Neurodegener Dis 2011;8:221–9.
- [117] Schofield E, Kersaitis C, Shepherd CE, Kril JJ, Halliday GM. Severity of gliosis in Pick's disease and frontotemporal lobar degeneration: tau-positive glia differentiate these disorders. Brain 2003;126:827–40.
- [118] Bellucci A, Westwood AJ, Ingram E, Casamenti F, Goedert M, Spillantini MG. Induction of inflammatory mediators and microglial activation in mice transgenic for mutant human P301S tau protein. Am J Pathol 2004;165:1643–52.
- [119] Maphis N, Xu G, Kokiko-Cochran ON, Jiang S, Cardona A, Ransohoff RM, et al. Reactive microglia drive tau pathology and contribute to the spreading of pathological tau in the brain. Brain 2015;138:1738–55.
- [120] Yoshiyama Y, Higuchi M, Zhang B, Huang SM, Iwata N, Saido TC, et al. Synapse loss and microglial activation precede tangles in a P301S tauopathy mouse model. Neuron 2007;53:337–51.
- [121] Nilson AN, English KC, Gerson JE, Barton Whittle T, Nicolas Crain C, Xue J, et al. Tau oligomers associate with inflammation in the brain and retina of tauopathy mice and in neurodegenerative diseases. J Alzheimers Dis 2017;55:1083–99.
- [122] Kovac A, Zilka N, Kazmerova Z, Cente M, Zilkova M, Novak M. Misfolded truncated protein tau induces innate immune response via MAPK pathway. J Immunol 2011;187:2732–9.
- [123] Heneka MT, Kummer MP, Stutz A, Delekate A, Schwartz S, Vieira-Saecker A, et al. NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. Nature 2013;493:674–8.
- [124] Jiang S, Maphis N, Binder J, Weston L, Bigio E, Geula C, Bhaskar K. Pathological tau activates inflammasomes (and IL-1b) and contributes to neuroinflammation relevant to tauopathies. Poster #61, 5th Venusberg Meeting on Neuroinflammation, Bonn. 2017/05/11–13.
- [125] Laurent C, Burnouf S, Ferry B, Batalha VL, Coelho JE, Baqi Y, et al. A2A adenosine receptor deletion is protective in a mouse model of Tauopathy. Mol Psychiatry 2016;21:97–107.
- [126] Lee DC, Rizer J, Selenica ML, Reid P, Kraft C, Johnson A, et al. LPS- induced inflammation exacerbates phospho-tau pathology in rTg4510 mice. J Neuroinflammation 2010;7:56.
- [127] Kitazawa M, Oddo S, Yamasaki TR, Green KN, LaFerla FM. Lipopolysaccharide-induced inflammation exacerbates tau pathology by a cyclin-dependent kinase 5-mediated pathway in a transgenic model of Alzheimer's disease. J Neurosci 2005;25:8843–53.
- [128] Bennett RE, DeVos SL, Dujardin S, Corjuc B, Gor R, Gonzalez J, et al. Enhanced tau aggregation in the presence of amyloid beta. Am J Pathol 2017;187:1601–12.
- [129] Bhaskar K, Konerth M, Kokiko-Cochran ON, Cardona A, Ransohoff RM, Lamb BT. Regulation of tau pathology by the microglial fractalkine receptor. Neuron 2010;68:19–31.
- [130] Nash KR, Lee DC, Hunt Jr JB, Morganti JM, Selenica ML, Moran P, et al. Fractalkine overexpression suppresses tau pathology in a mouse model of tauopathy. Neurobiol Aging 2013;34:1540–8.
- [131] Bolos M, Llorens-Martin M, Perea JR, Jurado-Arjona J, Rabano A, Hernandez F, et al. Absence of CX₃CR₁ impairs the internalization of Tau by microglia. Mol Neurodegener 2017;12:59.
- [132] Li Y, Liu L, Barger SW, Griffin WS. Interleukin-1 mediates pathological effects of microglia on tau phosphorylation

and on synaptophysin synthesis in cortical neurons through a p38-MAPK pathway. J Neurosci 2003;23:1605–11.

- [133] Gorlovoy P, Larionov S, Pham TT, Neumann H. Accumulation of tau induced in neurites by microglial proinflammatory mediators. FASEB J 2009;23:2502–13.
- [134] Garwood CJ, Cooper JD, Hanger DP, Noble W. Antiinflammatory impact of minocycline in a mouse model of tauopathy. Front Psychiatry 2010;1:136.
- [135] Noble W, Garwood C, Stephenson J, Kinsey AM, Hanger DP, Anderton BH. Minocycline reduces the development of abnormal tau species in models of Alzheimer's disease. FASEB J 2009;23:739–50.
- [136] Maphis N, Xu G, Kokiko-Cochran ON, Cardona AE, Ransohoff RM, Lamb BT, et al. Loss of tau rescues inflammation-mediated neurodegeneration. Front Neurosci 2015;9:196.
- [137] Borsini A, Zunszain PA, Thuret S, Pariante CM. The role of inflammatory cytokines as key modulators of neurogenesis. Trends Neurosci 2015;38:145–57.
- [138] Dioli C, Patricio P, Trindade R, Pinto LG, Silva JM, Morais M, et al. Tau-dependent suppression of adult neurogenesis in the stressed hippocampus. Mol Psychiatry 2017;22:1110–8.
- [139] Rogers J, Luber-Narod J, Styren SD, Civin WH. Expression of immune system-associated antigens by cells of the human central nervous system: relationship to the pathology of Alzheimer's disease. Neurobiol Aging 1988;9:339–49.
- [140] Togo T, Akiyama H, Iseki E, Kondo H, Ikeda K, Kato M, et al. Occurrence of T cells in the brain of Alzheimer's disease and other neurological diseases. J Neuroimmunol 2002;124:83–92.
- [141] Zotova E, Bharambe V, Cheaveau M, Morgan W, Holmes C, Harris S, et al. Inflammatory components in human Alzheimer's disease and after active amyloid-beta42 immunization. Brain 2013;136:2677–96.
- [142] Lueg G, Gross CC, Lohmann H, Johnen A, Kemmling A, Deppe M, et al. Clinical relevance of specific T-cell activation in the blood and cerebrospinal fluid of patients with mild Alzheimer's disease. Neurobiol Aging 2015;36:81–9.
- [143] Pellicano M, Larbi A, Goldeck D, Colonna-Romano G, Buffa S, Bulati M, et al. Immune profiling of Alzheimer patients. J Neuroimmunol 2012;242:52–9.
- [144] Liu C, Cui G, Zhu M, Kang X, Guo H. Neuroinflammation in Alzheimer's disease: chemokines produced by astrocytes and chemokine receptors. Int J Clin Exp Pathol 2014;7:8342–55.
- [145] Wang DB, Dayton RD, Zweig RM, Klein RL. Transcriptome analysis of a tau overexpression model in rats implicates an early pro-inflammatory response. Exp Neurol 2010;224:197–206.
- [146] Burnouf S, Martire A, Derisbourg M, Laurent C, Belarbi K, Leboucher A, et al. NMDA receptor dysfunction contributes to impaired brain-derived neurotrophic factor-induced facilitation of hippocampal synaptic transmission in a Tau transgenic model. Aging Cell 2013;12:11–23.
- [147] Sokolova A, Hill MD, Rahimi F, Warden LA, Halliday GM, Shepherd CE. Monocyte chemoattractant protein-1 plays a dominant role in the chronic inflammation observed in Alzheimer's disease. Brain Pathol 2009;19:392–8.
- [148] Tripathy D, Thirumangalakudi L, Grammas P. RANTES upregulation in the Alzheimer's disease brain: a possible neuroprotective role. Neurobiol Aging 2010;31:8–16.
- [149] Rostene W, Dansereau MA, Godefroy D, Van Steenwinckel J, Reaux-Le Goazigo A, Melik-Parsadaniantz S, et al. Neurochemokines: a menage a trois providing new insights on the functions of chemokines in the central nervous system. J Neurochem 2011;118:680–94.

- [150] Marciniak E, Faivre E, Dutar P, Alves Pires C, Demeyer D, Caillierez R, et al. The Chemokine MIP-1alpha/CCL3 impairs mouse hippocampal synaptic transmission, plasticity and memory. Sci Rep 2015;5:15862.
- [151] Cudaback E, Yang Y, Montine TJ, Keene CD. APOE genotypedependent modulation of astrocyte chemokine CCL3 production. Glia 2015;63:51–65.
- [152] Man SM, Ma YR, Shang DS, Zhao WD, Li B, Guo DW, et al. Peripheral T cells overexpress MIP-1alpha to enhance its transendothelial migration in Alzheimer's disease. Neurobiol Aging 2007;28:485–96.
- [153] Zenaro E, Piacentino G, Constantin G. The blood-brain barrier in Alzheimer's disease. Neurobiol Dis 2017;107:41–56.
- [154] Engelhardt B, Ransohoff RM. Capture, crawl, cross: the T cell code to breach the blood-brain barriers. Trends Immunol 2012;33:579–89.
- [155] Engelhardt B, Vajkoczy P, Weller RO. The movers and shapers in immune privilege of the CNS. Nat Immunol 2017;18:123–31.
- [156] Kipnis J. Multifaceted interactions between adaptive immunity and the central nervous system. Science 2016;353:766–71.
- [157] Bartels AL, Willemsen AT, Kortekaas R, de Jong BM, de Vries R, de Klerk O, et al. Decreased blood-brain barrier Pglycoprotein function in the progression of Parkinson's disease, PSP and MSA. J Neural Transm (Vienna) 2008;115:1001–9.
- [158] Kovac A, Zilkova M, Deli MA, Zilka N, Novak M. Human truncated tau is using a different mechanism from amyloid-beta to damage the blood-brain barrier. J Alzheimers Dis 2009;18:897–906.

- [159] Blair LJ, Frauen HD, Zhang B, Nordhues BA, Bijan S, Lin YC, et al. Tau depletion prevents progressive blood-brain barrier damage in a mouse model of tauopathy. Acta Neuropathol Commun 2015;3:8.
- [160] Fisher Y, Nemirovsky A, Baron R, Monsonego A. T cells specifically targeted to amyloid plaques enhance plaque clearance in a mouse model of Alzheimer's disease. PLoS One 2010;5:e10830.
- [161] Dansokho C, Ait Ahmed D, Aid S, Toly-Ndour C, Chaigneau T, Calle V, et al. Regulatory T cells delay disease progression in Alzheimer-like pathology. Brain 2016;139:1237–51.
- [162] Alves S, Churlaud G, Audrain M, Michaelsen-Preusse K, Fol R, Souchet B, et al. Interleukin-2 improves amyloid pathology, synaptic failure and memory in Alzheimer's disease mice. Brain 2017;140:826–42.
- [163] Liblau RS, Gonzalez-Dunia D, Wiendl H, Zipp F. Neurons as targets for T cells in the nervous system. Trends Neurosci 2013;36:315–24.
- [164] Pool M, Rambaldi I, Darlington PJ, Wright MC, Fournier AE, Bar-Or A. Neurite outgrowth is differentially impacted by distinct immune cell subsets. Mol Cell Neurosci 2012;49:68–76.
- [165] Baruch K, Deczkowska A, Rosenzweig N, Tsitsou-Kampeli A, Sharif AM, Matcovitch-Natan O, et al. PD-1 immune checkpoint blockade reduces pathology and improves memory in mouse models of Alzheimer's disease. Nat Med 2016;22:135–7.
- [166] Baruch K, Rosenzweig N, Kertser A, Deczkowska A, Sharif AM, Spinrad A, et al. Breaking immune tolerance by targeting Foxp3(+) regulatory T cells mitigates Alzheimer's disease pathology. Nat Commun 2015;6:7967.