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REVIEW ARTICLE

Tau at the interface between neurodegeneration and neuroinflammation

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Abstract

Tau is an evolutionary conserved protein that promotes the assembly and stabilization of microtubules in neuronal axons. Complex patterns of posttranslational modifications (PTMs) dynamically regulate tau biochemical properties and consequently its functions. An imbalance in tau PTMs has been connected with a broad spectrum of neurodegenerative conditions which are collectively known as tauopathies and include Alzheimer's disease (AD), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD) among others. The hallmark of these neurological disorders is the presence in the brain of fibrillary tangles constituted of misfolded species of hyper-phosphorylated tau. The pathological events leading to tau aggregation are still largely unknown but increasing evidence suggests that neuroinflammation plays a critical role in tangle formation. Moreover, tau aggregation itself could enhance inflammation through feed-forward mechanisms, amplifying the initial neurotoxic insults. Protective effects of tau against neuroinflammation have been also documented, adding another layer of complexity to this phenomenon. Here, we will review the current knowledge on tau regulation and function in health and disease. In particular, we will address its emerging role in connecting neurodegenerative and neuroinflammatory processes.

Introduction

Tau protein is mainly expressed in neuronal cells and at lower levels in glia, either oligodendrocytes or astrocytes [1, 2]. Tau is a microtubule-binding protein [3], thus localizes predominantly in the axonal tracts of neurons where it stabilizes the microtubules and promotes their assembly [4]. In addition to its role in cytoskeletal dynamics, tau regulates axonal transport by competing with the molecular motors kinesin and dynein for microtubule binding [5]. Tau also participates in axonal elongation and adult neurogenesis [6, 7], and recent evidence supports a function in modulating synaptic plasticity, iron transport, and actin polymerization [8–10]. Lastly, tau has been detected within the nuclear compartment, where it helps maintaining DNA integrity [11].

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Tau belongs to the evolutionary conserved family of microtubule-associated proteins (MAPs). In humans, tau is encoded by the *MAPT* gene mapping to chromosome 17q21.31 and includes 16 exons (Fig. 1a). The genomic region spanning the *MAPT* locus (1.8 Mb) is characterized by a high degree of linkage disequilibrium due to a 900 kb inversion which suppresses recombination and defines two extended haplotypes, H1 and H2 [12]. H2 is common only in people with European ancestry [13]. In the adult brain, tau exists in six different isoforms due to alternative splicing of exons 2, 3, and 10 (Fig. 1b). Additional tau variants including exons 4a, 6, and 8 have been described in peripheral tissues and animal models [14]. The six main isoforms differ in the number of specific inserts localized at the N-terminus (0N, 1N or 2N, exons 2 and 3) and in the microtubule-binding region (MTBR) (3R or 4R, exon 10) of the protein [15]. The N-terminal inserts consist of acidic sequences of 29 amino acids each, which control microtubule spacing as well as tau subcellular localization [16, 17]. The MTBR inserts are instead imperfect acid repeats of 31–32 amino acids, which mediate electrostatic interactions with the outer microtubule surface [18]. A proline-rich domain is situated in the central portion of all tau isoforms. Tau is

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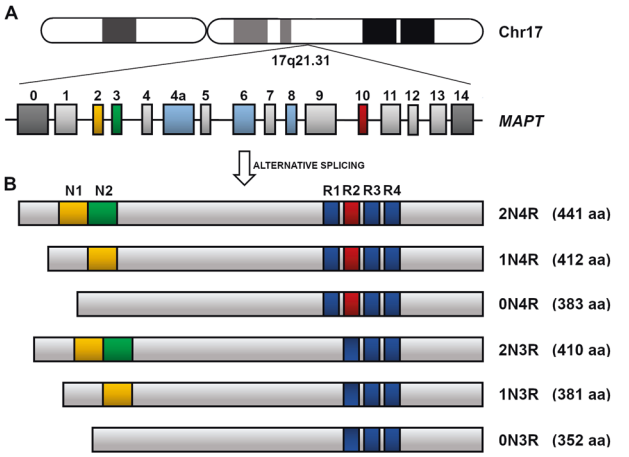

Fig. 1 Schematic representation of human *MAPT* genetic structure and tau protein isoforms. a The human *MAPT* gene maps to chromosome 17q21.31 and contains a total of 16 exons. Exon 2 (E2), E3, E4, E5, E7, E9, E11, E12, and E13 are constitutively expressed (light gray boxes). E0 and E14 are transcribed but not translated (dark gray boxes). E4a, E6, and E8 are not transcribed in the central nervous system (light blue boxes). E2 (yellow box), E3 (green box), and E10 (red box) are subjected to alternative splicing, generating six isoforms in the adult brain. **b** These tau isoforms differ in the number of N-terminal inserts (0N, 1N, or 2N) and C-terminal repeats (3R or 4R). The length of each isoform in terms of amino acid (aa) number is also given.

considered an "intrinsically disordered" protein as it does not acquire a specific tertiary structure in solution [19]. However, interactions between tau N- and C-terminus may induce a "paper-clip" conformation under physiological conditions [20].

Tau cellular functions and biochemical properties are strictly regulated in both space and time by specific post-translational modification (PTM) patterns. More than 60 residues throughout the tau sequence are subjected to several PTMs including phosphorylation, acetylation, methylation, ubiquitination, nitration, and glycosylation [21]. Tau PTM dysregulation is associated with a heterogeneous group of incurable neurological disorders collectively known as tauopathies.

Converging evidence recognizes the involvement of an immune component in the etiology and pathophysiology of many tauopathies. More recent data suggest CNS inflammatory responses might contribute to or even trigger tau aggregation [22, 23]. Hereafter, we will build on this innovative concept to revise the canonical working model of tau dysmetabolism in neurodegeneration. Furthermore, we will discuss the emerging role of tau in classical neuroinflammatory disorders such as multiple sclerosis (MS). This chronic autoimmune disease represents a paradigmatic example of the tight overlap existing between neurodegeneration and neuroinflammation, and provides a strong rationale to position tau at the interface of these two pathogenic processes.

Tau pathology in classic tauopathies

Tauopathies are characterized by the deposition of insoluble aggregates constituted of misfolded tau species in the central nervous system (CNS) (Table 1). These inclusions are believed to interfere with neuronal physiology at multiple levels and eventually cause neuronal loss.

Tau deposits named neurofibrillary tangles (NFTs) were first described in the Alzheimer's disease (AD) brain as thick bundles near the cell surface of affected neurons, reactive to Bielschowsky silver stain [24]. Ultrastructural characterization of these aggregates by electron microscopy highlighted distinctive assemblies named paired helical filaments (PHFs) and straight filaments (SFs), constituted of two smaller filaments of 10 nm diameter that wrap around one another with regular periodicity [25]. Subsequently, other types of tau inclusions were identified in different tauopathies. For instance, round shaped tau aggregates known as Pick bodies are found in neurons of Pick's disease (PiD) patients [26], whereas granular deposits that are negative to silver stain are present in astrocytes of globular glial tauopathy (GGT) patients [27], and star-like tufts of dense fibers are common in progressive supranuclear palsy (PSP) [28]. Alternative folds to PHFs have been recently described for tau isolated from PiD and corticobasal degeneration (CBD) inclusions [29, 30]. Different combinations of tau isoforms contribute to these inclusions. Both 3R and 4R isoforms are present in AD. Tau 4R isoforms are instead predominant in PSP, GGT, and CBD, while PiD is driven mainly by 3R isoforms.

Tau isolated from NFTs and other inclusions is hyperphosphorylated and this aberrant PTM is considered the main trigger for aggregation as it precedes the formation of insoluble deposits [31]. Phosphorylation is by far the most abundant tau modification with 85 potential phosphorylation sites in its longest isoform (2N4R) [32]. In physiological conditions, tau phosphorylation is the result of the concerted activity of several protein kinases and phosphatases such as glycogen synthase kinase 3, PAR-1/microtubule affinity-regulating kinases, and protein phosphatase 2A [33]. An imbalance in this well-orchestrated mechanism is postulated to take place in tauopathies. Phosphorylation at specific KXGS motifs within the MTBR decreases tau affinity for microtubules [34], and this mechanism is believed to drive tau aggregation by favoring tau self-organization into high-ordered structures such as PHFs. Alternatively, hyper-phosphorylation may cause aggregation by enhancing tau biochemical stability and in turn promoting its pathological buildup within the cell [35]. Another possibility is that aberrant phosphorylation triggers tau aggregation by disrupting its physiological trafficking to the axon, thus increasing tau local concentration in the somatodendritic compartment [36]. In this regard,

Table 1 Principal features of canonical tauopathies.

Disease	Prevalence	Tau isoforms	Tau inclusions	Genetic mutations	Genetic associations ($P < 10^{-8}$)	References
Alzheimer's disease (AD)	3.9% in people aged 60+ years	3R/4R	Neurofibrillary tangles (NFTs)	*APP, PSEN1, PSEN2*	*ADAMTS4, CR1, BIN1, INPPD5, HESX1, CLNK, HLA-DRB1, TREM2, CD2AP, ZCWPW1, EPHA1, CNTNAP2, CLU/ PTK2B, ECHDC3, MS4A6A, PICALM, SORL1, SLC24A4, ADAM10, APH1B, KAT8, SCIMP, ABI3, ALPK2, ABCA7, APOE, AC074212.3, CD33,* and *CASS4*	[155, 156]
Progressive supranuclear palsy (PSP)	5–6 cases/100,000	4R	Globose NFTs, tufted astrocytes, and coiled bodies	*MAPT, LRKK2*	*MAPT, MOBP, STX6, RUNX2, SLCO1A2,* and *EIF2AK3*	[85, 157, 158]
Corticobasal degeneration (CBD)	5–7/100,000	4R	Astrocytic plaques, balloons neurons, and neuropil threads	*MAPT*	*MAPT, lnc-KIF13B-1*	[159, 160]
Pick's disease (PiD)	Rare (10 time less than AD)	3R	Pick bodies, swollen neurons	*MAPT*	–	[161, 162]
Frontotemporal dementia with parkinsonism-17 (FTDP-17)	Unknown	4R	NFTs, glial inclusions	*MAPT, GRN*	–	[163]
Argyrophilic grain disease (AgD)	9.3% in patients 65 years old	4R	Spindle-shaped argyrophilic grains in neuronal processes, coiled bodies in oligodendrocytes	*MAPT*	–	[164, 165]
Globular glial tauopathy (GGT)	Unknown	4R	Globose inclusions in oligodendrocytes	*MAPT*	–	[166]
Chronic traumatic encephalopathy (CTE)	Unknown	3R/4R	NFTs	–	–	[167]
Parkinsonism–dementia complex of Guam	42–274:100,000 in Guam population	3R/4R	NFTs	*TRPM7*	–	[168–170]

phosphorylated tau has been recently shown to undergo liquid–liquid phase separation and form high concentrated cytosolic droplets [37]. Lastly, hyper-phosphorylation may directly force tau into three-dimensional conformations more prone to self-assembly [38]. In contrast with these scenarios, there is also evidence that hyper-phosphorylation might represent a physiological mechanism responding to environmental stresses. For example, hibernating animals display reversible PHF-like phosphorylation of tau without fibril formation [39].

In addition to phosphorylation, other PTMs have been connected with tau pathology. Truncated tau species at both N- and C-terminal sites (D13, D25, N368, E391, and D421) have been isolated from NFTs [40–44]. Aberrant proteolytic cleavage of tau by cellular endopeptidases is believed to promote aggregation by disrupting the paper-clip conformation that stabilizes the protein in the healthy brain. Tau acetylation at lysine 174 (K174) has been recently detected as an early change in AD brain and was shown to cause cognitive deficits in animal models of the disease. This PTM was demonstrated to increase tau propensity toward aggregation by reducing its physiological turnover and promoting its mislocalization to the soma [45, 46]. Acetylation of K280 is another AD-specific PTM and similarly drives tau aggregation [47]. Tau from AD inclusions was also found deamidated at asparagine 279 and this irreversible modification decreases tau ability to bind microtubules [48]. In addition, PHFs contain methylated tau at seven different lysine residues but the role of this PTM is still debated [49]. Cross-talk between PTMs has been reported as well. N-glycosylation can promote tau aggregation via enhancing the phosphorylation process [50]. On the contrary, O-glycosylation of tau inhibits its aggregation by protecting relevant residues from phosphorylation [51]. Acetylation at KXGS motifs equally prevents tau phosphorylation and aggregation [52].

Tau aggregation can also be triggered by specific mutations in the *MAPT* gene as first reported in the context of frontotemporal dementia with parkinsonism-17 (FTDP-17) [53–55]. Over 50 different pathogenic missense, silent, and intronic mutations have been reported so far [56]. Similar to hyper-phosphorylation, those mapping to the MTBR promote aggregation by reducing tau affinity for microtubules [57]. Other mutations, especially the intronic and silent ones, are instead able to cause an imbalance in the physiological 3R:4R isoform ratio by affecting *MAPT* splicing [54, 58], which may lead to increased concentration of free cytosolic tau and favor its self-association. Finally, there is evidence that multiple missense mutations may promote local changes in tau structure that directly confer the ability to form aggregates when tested in vitro [59, 60].

It is still unclear how tau aggregates exert their pathogenic activity. The disruption of tau native interactions may affect cytoskeletal stability and eventually increase neuronal vulnerability [61]. Alternatively, tau aggregates may induce neuronal loss trough a toxic gain-of-function mechanism. Insoluble inclusions could indeed sequester important cellular factors from the pool of biologically available molecules [62]. Additionally, there is evidence that misfolded tau can interact with the proteasome and inhibit its activity [63]. Tau aggregates might also physically block axonal transport through steric hindrance [64]. On the other hand, some authors have questioned the pathogenicity of tau aggregates, pinpointing soluble tau oligomers as the real toxic species. Larger tau assemblies would instead be protective by removing oligomers from the cytosol [65, 66].

Mechanisms of misfolded tau spreading

For many years, the pathogenic mechanisms underlying protein misfolding were believed to be cell-autonomous, occurring independently in a large number of neurons throughout the brain. However, recent experimental evidence suggests that non-cell-autonomous events may also contribute to the spread of protein aggregates in the diseased brain. For example, in a mouse model expressing the FTDP-17 associated P301L tau mutant only in the entorhinal cortex, tau pathology propagates to other brain regions without detectable transgene expression [67]. Subsequent experiments involving injection of synthetic tau fibrils in the mouse brain demonstrated time-dependent propagation of tau pathology to areas distant from the injection site [68]. In vivo tracing of tau deposition patterns via positron emission tomography also supports the non-cell-autonomous propagation model [69].

One possible mechanism of tau spreading is the self-replicating mechanism first discovered in prion diseases. This peculiar form of propagation can be described as molecular infectivity, where preexisting aggregates can imprint their pathological conformation on naive proteins in neighboring cells. In support of this hypothesis, tau aggregates from a variety of different human tauopathies have been successfully transmitted to transgenic mouse and cell biosensor models, suggesting they adopt a prion conformation upon misfolding [70–73]. The transmission of patient-derived tau aggregates in experimental settings does not directly imply that they are infectious in real-life conditions, but provides nevertheless a mechanistic framework to explain the progressive spread of misfolded tau.

Another proposed mechanism by which misfolded tau can diffuse throughout the CNS is cell secretion. The elevated levels of phosphorylated tau in the cerebrospinal fluid (CSF) of tauopathy patients were initially considered the mere result of passive release from necrotic neurons. Conversely, recent evidence indicates that tau is actively

exported to the extracellular space and this process depends on neuronal activity [74]. The lack of a signal peptide in the tau sequence suggests that its secretion does not follow the canonical endoplasmic reticulum-to-Golgi pathway. Two pools of extracellular tau have been characterized so far. The first consists of membrane-free tau that is secreted by direct translocation across the plasma membrane. Late endosomes and the small GTPase RAB7A seem to mediate this particular form of tau trafficking in physiological conditions [75], while Golgi fragmentation is associated with augmented tau secretion upon disease [76]. The second pool is constituted by tau associated to extracellular vesicles such as ectosomes and exosomes [77, 78]. Microglia are the principal cytotype spreading tau via exosome secretion upon disease, and the inhibition of exosome synthesis in this cell compartment reduces tau propagation in vitro and in vivo [79]. Tau-containing exosomes can cross the blood–brain barrier (BBB) and their detection in the peripheral blood is being currently under evaluation as a potential biomarker to monitor disease progression [80].

Synapses appear to be the major site for intercellular tau secretion. One observation in support of transsynaptic propagation is the spatial overlap between tau deposition patterns and functional brain networks in different tauopathies [81, 82]. Experiments conducted with microfluidic devices mechanistically confirmed that synaptic contacts are required for exosome-mediated transmission of tau [78]. The low-density lipoprotein receptor-related protein 1 represents the main regulator of tau uptake on post-synaptic membranes [83]. Prion-like propagation and secretion are not mutually exclusive mechanisms; they likely co-exist and are possibly interdependent. Thus, postsynaptic terminals may represent the first site of misfolded tau seeding activity.

Immune responses in tauopathies: genetic evidence

With the exception of a small proportion of familial cases, the vast majority of tauopathies are sporadic and present a complex genetic architecture, without clear Mendelian patterns of inheritance [84]. The tau H1 haplotype is strongly associated with increased risk of PSP, CBD and late-onset AD (LOAD) [85–87], while the H2 haplotype confers protection to LOAD by influencing *MAPT* expression [88]. Apolipoprotein E (*APOE*) ε4 represents the strongest genetic risk factor for LOAD and was the first gene found associated with the disease outside the *MAPT* region [89]. *APOE* ε4 influences LOAD risk via modulating the clearance of amyloid-β (Aβ), the other main protein undergoing aggregation in AD [90]. Another *APOE* allele (ε2) has been recently implicated in PSP risk and progression through direct effects on tau pathology [91]. In addition to these functions, apolipoprotein E exerts immunomodulatory roles [92–95], pinpointing the possible involvement of immune processes in the pathophysiology of tauopathies. The advent of large genome-wide association studies (GWASs) has allowed the systematic identification of genes associated with the risk of developing these disorders (Table 1), and many show immune-related functions.

The *HLA-DRB1* locus was found associated with LOAD risk in a large meta-analysis of four GWASs of European ancestry [96]. Human leukocyte antigen (*HLA*) genes encode membrane glycoproteins involved in antigen presentation, and represent key regulators of adaptive immunity. A subsequent fine-mapping effort further refined the association to the five-allele *HLA* haplotype *A*03:01~B*07:02~DRB1*15:01~DQA1*01:02~DQB1*06:02* [97]. The inability of certain *HLA* alleles to completely eliminate foreign antigens such as viral proteins has been argued to cause immunoregulatory disturbance and ultimately increase the risk of developing AD and other neurodegenerative diseases [98].

The same meta-analysis highlighted additional LOAD candidate susceptibility genes with immune functions, namely cluster of differentiation 33 (*CD33*), clusterin (*CLU*), complement receptor 1 (*CR1*), ephrin type-A receptor 1 (*EPHA1*), ATP-binding cassette subfamily A member 7 (*ABCA7*), membrane spanning 4 domains A4A and A6E (*MS4A4A*/*MS4A6E*), and CD2-associated protein (*CD2AP*) [96]. Some of these genes contribute to the development and homeostasis of the immune system such as *CD33* being involved in myelopoiesis [99]. Others are implicated in inflammatory responses—this is the case of *CR1* regulating the activation of the complement cascade [100]. In a more recent screening using a whole-exome microarray approach, rare coding variants in phospholipase C gamma 2 (*PLCG2*), ABI family member 3 (*ABI3*), and triggering receptor expressed on myeloid cells 2 (*TREM2*) were found associated with LOAD susceptibility [101]. A polymorphism located within the *TREM* gene cluster also correlates with phosphorylated tau levels in the CSF [102]. Importantly, these genes are highly expressed in microglial cells and interact with the previously identified risk genes as part of a large protein network. Another exome sequencing study also detected risk variants in the immunoglobulin heavy constant gamma 3 (*IGHG3*) gene [103].

The involvement of the microglia compartment similarly emerged from GWAS efforts in other tauopathies. In particular, the C-X-C chemokine receptor type 4 (*CXCR4*) gene regulating microglia activation was found associated with risk of PSP, FTD, and CBD [104]. A subsequent study confirmed the extensive genetic overlap between FTD and autoimmune diseases, particularly in genes associated with microglial function such as leucine-rich repeat kinase

2 (*LRRK2*), and acyloxyacyl hydrolase (*AOAH*), and the *HLA* genes *HLA-DRA*, *HLA-A*, and *HLA-C* [105]. A significant genetic overlap was similarly measured for AD [106]. Altogether, these data corroborate the notion that aberrant microglia-dependent responses may directly contribute to disease.

Immune responses in tauopathies: the role of glia

Neuroinflammation has been documented in brain tissues from different tauopathies. Consistent with the genetic data, histological analysis has identified the glial compartment as the primary mediator of this process. In particular, both microglia and astroctyes synergistically contribute to CNS inflammation in tauopathies. The effects of neuroinflammation on tau pathology can be either beneficial or detrimental, depending on the magnitude and timing of the response.

Microglial cells belong to the innate arm of the immune system and represent the resident macrophages of the CNS. They can uptake various extracellular materials such as cell debris, apoptotic cells, and microbes. Consequently, their phagocytic activity takes part in a plethora of physiological processes including CNS development, adult neurogenesis, synaptic homeostasis, and pathogen defense. Microglia activation is also a common feature of neurodegenerative diseases and aging [107]. In the context of tauopathies, reactive microglia are observed around NFTs in AD brain as well as in PiD, PSP, and CBD [108–111]. Their main function at these pathological sites is likely the clearance of misfolded tau. Microglia are able to internalize tau aggregates both in vitro and in vivo, and this process depends at least in part on CX3C chemokine receptor 1 signaling [112]. Microglia can also contribute to the rapid elimination of dying neurons and nonfunctional synapses. This activity seems to be regionally regulated by specific epigenetic programs, possibly explaining the differential vulnerability of distinct brain regions to tau aggregation [113].

Microglia become activated upon interaction with misfolded tau [114]. Loss of neuronal integrity also contributes to microglia activation through the decrease of specific inhibitory molecules on the neuronal membrane such as cluster of differentiation 200 (CD200) [115], and the concomitant upregulation of stimulatory mediators including matrix metalloproteinase 3 and substance P [116]. In the initial stages of the pathogenic process, this status is associated with the production of the anti-inflammatory interleukins IL-10, IL-4, IL-13, and transforming growth factor β (M2 phenotype), which contributes to the control of the local immune response and promotes tissue repair. However, as the disease progresses, persistent microglia activation results in the switch from M2 to M1 phenotype, eventually aggravating tau pathology through the exaggerated release of reactive oxygen species, nitric oxide (NO), and pro-inflammatory cytokines such as the interleukins IL-1β, IL-6, IL-12, IL-23, and tumor necrosis factor α (TNF-α) [117].

Astrocytes are the most abundant cells and are ubiquitous in all regions of the CNS. Their functions include physical and metabolic support for neurons, detoxification, cell migration guidance, and regulation of energy metabolism. In response to injury and disease, astrocytes undergo chronic activation called astrogliosis [118]. Mirroring the microglia, reactive astrocytes can acquire a pro-inflammatory A1 phenotype or an A2 status defined by the upregulation of neuroprotective molecules such as brain derived neurotrophic factor, vascular endothelial growth factor, and basic fibroblast growth factor, which can promote neuronal survival and synaptic repair [119]. A1 astrocytes are more prevalent in AD brain and such imbalance in A1/A2 ratio is directly caused by microglia dysregulation. IL-1α, TNF-α, and C1q secreted by activated microglia are necessary and sufficient to polarize astrocytes toward the A1 phenotype [120].

Immune responses in tauopathies: the involvement of peripheral lymphocytes

In addition to CNS innate immunity, the activation of the peripheral immune system also takes place in tauopathies. This phenomenon has been principally studied in AD. Higher proportions of activated HLA-DR positive $CD4^+$ and $CD8^+$ T lymphocytes were measured in peripheral blood of AD patients [121]. Infiltrating T cells were also found in the brain parenchyma of both AD patients and animal models [122, 123]. More recently, clonally expanded $CD8^+$ T effector memory $CD45RA^+$ (T_{EMRA}) cells have been identified in the CSF of AD patients by single-cell T cell receptor (*TCR*) sequencing [124], providing evidence of antigen-experienced T cells patrolling the intrathecal space of AD brains.

The exact mechanism of T cell recruitment into the CNS is still debated. However, alterations in BBB selective permeability seem to play a crucial role in lymphocyte extravasation upon disease, and a leaky BBB represents a biomarker of different tauopathies [125, 126]. Microglia migrate toward and accumulate around cerebral vessels in response to CNS inflammation. Initial contact maintains BBB integrity via expression of the tight-junction protein claudin-5. In contrast, microglia phagocytose astrocytic end-feet and impair BBB function upon sustained inflammation [127]. Pro-inflammatory factors released by activated microglial cells such as TNF-α and monocyte chemoattractant protein 1 also contribute to BBB disruption [128]. Notably, tau depletion was shown to prevent

progressive BBB damage, demonstrating that tau alone can initiate the breakdown and that BBB dysfunctions might be reversible [129].

The fact that the total number of infiltrating $CD3^+$ T cells correlates with the phospho-tau load implies the possible participation of adaptive immunity to disease progression [130]. Chronic T cell depletion was indeed able to prevent T cell hippocampal infiltration and revert spatial memory deficits in a transgenic AD model [131]. T cells can exacerbate the pathogenic process by boosting the pre-existing inflammation in the brain. In fact, interferon γ (IFN-γ) released by infiltrating Th1 $CD4^+$ T cells is able to promote microglia activation and increase plaque burden [132]. At the same time, T cell-mediated protective effects have been documented as well. In particular, depletion of $CD25^+$ regulatory T cells was demonstrated to aggravate cognitive deficits, increase the plaque burden, and amplify microglia responses in AD transgenic mice [133, 134]. Also, $CD4^+$ T helper 1 (Th1) cells can induce a purinergic receptor P2Y, G-protein coupled 12 $(P2ry12)^+$ $MHCII^+$ subset of microglia that attenuates AD pathology [135].

Tau pathology and neuroinflammation: lessons from noncanonical tauopathies

MS is a chronic autoimmune disease characterized by lymphocyte infiltration into the CNS, focal demyelination, and variable grades of axonal degeneration. The activation of both microglia and astrocytes is another pathological hallmark of the disease [136]. At the genetic level, MS risk variants are linked to genes expressed in inflammatory and brain-resident immune cells, especially microglia [137]. From a clinical standpoint, MS typically starts with an acute phase dominated by inflammatory bursts followed by a total or partial resolution (relapsing-remitting MS). Over time, it evolves into a secondary progressive course with irreversible deterioration of motor and cognitive functions, due to accumulating neuronal injury. However, a small portion of MS cases exhibits a progressive course from the onset of clinical signs (primary progressive MS) [138]. Although not typically considered a tauopathy, aggregates of misfolded tau have been documented within demyelinated lesions from patients with progressive MS, either primary or secondary [139]. In agreement with the human data, tau aggregates are also found in the CNS of rodents at chronic stages of experimental autoimmune encephalomyelitis (EAE), a disease model that recapitulates many features of MS phenotype [139–141]. At the molecular level, tau species constituting these insoluble inclusions display hyperphosphorylation patterns overlapping with AD and other conventional tauopathies [139]. A traditional PHF purification protocol was employed to isolate tau aggregates from MS and EAE brains. It remains unknown whether such aberrant phosphorylation is associated with the same pathological folds described in canonical tauopathies. Interestingly, a patient suffering from an early aggressive form of MS displayed hyper-phosphorylated but still soluble tau in acute lesions, possibly capturing the early stages of the aggregation process [142].

The direct pathogenicity of these aggregates has not been yet demonstrated in the context of MS, but there is growing evidence of their detrimental potential by affecting tau physiological function. We have shown that tau-null mice experience an exacerbated EAE course due to the destabilization of the axonal microtubule lattice [143]. This neuroprotective function of tau seems to be part of an adaptive homeostatic mechanism evolved to preserve axonal integrity against chronic neuroinflammatory stress. In addition, peptides deriving from the tau amyloidogenic domain can activate B-1a lymphocytes and two populations of resident macrophages (MΦs), and in turn ameliorate EAE signs via increased IL-10 production [144].

Concluding remarks and future directions

Tauopathies cluster with proteinopathies, neurodegenerative disorders caused by the dysmetabolism of certain proteins, and are characterized by the aggregation of pathological forms of tau in affected brains. A significant effort has been invested toward the characterization of the structural and molecular determinants of tau neurotoxicity. In contrast, very little is known about the primary causes of tau aggregation. Here, we have shown that tau dysmetabolism and neuroinflammation are deeply entwined, mechanistically correlated processes. A limited, yet consistent body of evidence suggests that neuroinflammatory responses might precede tau misfolding and neurodegeneration. Increased levels of IL-1β, TNF-α, and GM-CSF have been detected in the CSF of patients with mild cognitive impairment, before full manifestation of AD pathology [145]. Concurrently, hippocampal neuronal loss with impaired synaptic function and prominent microglia activation was detected in a humanized AD mouse model before fibrillary tau tangles emerged [146]. TNF-α and IL-1β secreted from activated microglia are sufficient to promote tau hyper-phosphorylation and aggregation via cyclin-dependent kinase 5 and p38 mitogen-activated protein kinase [22, 147–149], and the ablation of microglia from AD brain is able to prevent neuronal and synaptic loss [150]. The assembly of NLRP3 inflammasome in activated microglia has been recently revealed as a key driver for tau aberrant phosphorylation and misfolding in a calcium/calmodulin-dependent protein kinase type II α (CaMKII-α) dependent manner [23]. According to this scenario, the neuroinflammatory process would act as a trigger for tau pathology

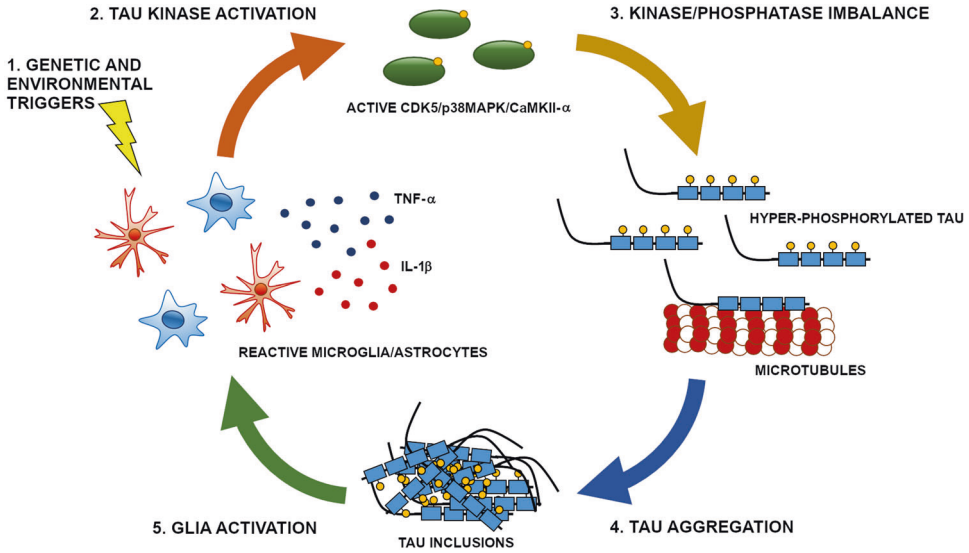

Fig. 2 Alternative model for neuroinflammation in tau pathology. The combination of (yet to be discovered) exposure factors and genetic predisposition initiates neuroinflammatory responses in the central nervous system (CNS) via chronic activation of microglia and astrocytes. Reactive glial cells release pro-inflammatory cytokines including tumor necrosis factor α (TNF-α) and interleukin 1 β (IL-1β), which in turn activate tau-specific protein kinases such as cyclin-dependent kinase 5 (CDK5), p38 mitogen-activated protein kinase (p38MAPK), and calcium/calmodulin-dependent protein kinase type II α (CaMKII-α) in neurons. The imbalance in the finely tuned activity of these enzymes results in aberrant phosphorylation of tau molecules, which detach from microtubules and self-assemble into insoluble aggregates. These tau inclusions exert neurotoxic activities and are able to further activate the glial compartment, eventually amplifying the initial pathogenic signals through feed-forward mechanisms.

rather than being only a secondary response to neuronal damage (Fig. 2). Although provocative and still missing full empirical validation, this model might help explaining the failure of those therapeutic attempts targeting exclusively protein aggregation and neglecting the inflammatory component of the disease. In this regard, it is noteworthy that TNF-blocking agents are able to reduce the risk of AD in patients with rheumatoid arthritis and psoriasis [151]. Also, nasal administration of amyloid-beta peptides was shown to reduce plaque burden in AD mice via antigen-specific anti-inflammatory immune responses [152].

Clinical trials have recently tested compounds with anti-inflammatory properties in AD. Some of them such as minocyline showed promising results, although they did not reach statistical significance [153]. However, minocycline was not initially designed to be an immunosuppressant drug and its targets are not entirely clear, which may have resulted in unpredicted detrimental side effects [154]. For the future, it will be important to test chemicals and biologicals with known mechanisms of action in order to target pro-inflammatory pathways in microglia and astrocytes with higher specificity. Moreover, efforts should focus on characterizing the influence of specific genetic makeups on the immune response in subjects at risk for tauopathies. In this regard, a critical challenge will be to translate the current GWAS associations into a biologically meaningful framework, deciphering all the molecular mechanisms and cellular pathways in which the known risk variants play a role. Altogether, these action items will allow defining novel and perhaps more effective therapeutic targets to tackle neuroinflammation in tau pathologies. At the same time, the gained knowledge may pave the way to tau targeting therapies also in classical neuroinflammatory diseases.

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Compliance with ethical standards

Conflict of interest The author declares no conflict of interest.

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