BBA - Molecular Basis of Disease 1866 (2020) 165584

Contents lists available at ScienceDirect

BBA - Molecular Basis of Disease

journal homepage: www.elsevier.com/locate/bbadis

Review

N-terminal tau truncation in the pathogenesis of Alzheimer's disease (AD): Developing a novel diagnostic and therapeutic approach

G. Amadoro[a,b,1,*], V. Latina[a,1], V. Corsetti[a], P. Calissano[a]

[a] European Brain Research Institute (EBRI), Viale Regina Elena 295, 00161 Rome, Italy
[b] Institute of Translational Pharmacology (IFT)-CNR, Via Fosso del Cavaliere 100, 00133 Rome, Italy

ARTICLE INFO

Keywords:
Tau truncation
Synapse(s)
Neurodegeneration
Tauopathies
Alzheimer's disease (AD)

ABSTRACT

Tau truncation occurs at early stages during the development of human Alzheimer's disease (AD) and other tauopathy dementias. Tau cleavage, particularly in its N-terminal projection domain, is able to drive *per se* neurodegeneration, regardless of its pro-aggregative pathway(s) and in fragment(s)-dependent way. In this short review, we highlight the pathological relevance of the 20-22 kDa NH_2-truncated tau fragment which is endowed with potent neurotoxic "gain-of-function" action(s), both *in vitro* and *in vivo*. An extensive comment on its clinical value as novel progression/diagnostic biomarker and potential therapeutic target in the context of tau-mediated neurodegeneration is also provided.

1. Introduction

Alzheimer's Disease (AD) is a progressive neurodegenerative disease with gradual deterioration of cognition/behaviour characterized by a long prodromal phase (20 years) and an average clinical duration of 8–10 years. This chronic illness has an estimated prevalence of 10–30% in the worldwide population > 65 years of age with an incidence of 1–3% which is expected to worsen in the years to come. A large number of affected patients (> 95%) suffer from late-onset (80–90 years of age) sporadic form of disease with primary, antagonistic and integrative aging hallmarks as risk factors of increased susceptibility [1]. Conversely, a small proportion (< 1%) -which carries familiar inherited mutations in genes that, directly and/or indirectly, affect the metabolism of Amyloid Precursor Protein (APP)- is destined to develop symptoms at a much younger age (mean age of ~45 years) [1,2]. Both in humans and preclinical animal models, the characteristic histopathological lesions of the disease are tau-laden neurofibrillary tangles (NFT) and Amyloid β (Aβ)-positive deposits located in selective brain regions involved in the memory/learning processes, such as the basal forebrain, hippocampus and neocortex [1,3]. Neuropathological changes are paralleled by functional alterations in neuronal plasticity and early disruption of connectivity with perturbed activity in Default Mode Network (DMN), a circuit including different cortical areas whose deterioration occurs prior to the onset of obvious clinical symptoms and mnestic disabilities [2]. In AD development, Aβ and tau aggregates spread throughout the brain following stereotyped and predictable patterns. In detail, progressive severity of tau neuropathology (Braak staging) has been classified into six phases, designated as Braak/Braak (B/B) stages. At early-stages B/B I-II, neurofibrillary pathology is restricted to the transentorhinal and entorhinal cortices. At middle-stages B/B III-IV, tau inclusions disseminate into the limbic system with engagement of the hippocampus (CA1–4), areas of the frontal and temporal neocortices and the amygdala. At late-stages B/B V-VI, the neocortex is compromised by tau deposition [3].

Clinicopathologic evaluations have shown that the cortical density of NFT better correlates with the cognitive decline than the Aβ-neuritic plaques in patients suffering from AD [3–8]. Consistently, the NFT tau load is considered a more reliable predictor of functional networks deterioration than measures of Aβ deposition in imaging studies on patients transitioning from Mild Cognitive Impairment (MCI) to full-

Abbreviations: AD, Alzheimer's Disease; MCI, Mild Cognitive Impairment; NFT, NeuroFibrillary Tangles; SF, Straight Filaments; PHF, Paired Helical Filaments; Aβ, Amyloid-β peptides; SDS-PAGE, Sodium Dodecyl Sulfate-PolyAcrylamide Gel Electrophoresis; NGF, Nerve Growth Factor; BDNF, Brain-Derived Neurotrophic Factor; STS, STauroSporin; AMPA receptor, α-Amino-3-hydroxy-5-Methyl-4-isoxazole Propionic Acid; NMDA, N-Methyl-D-Aspartate; NR2B, receptor subunits 2B; CREB protein, cAMP Response Element Binding; APPSwe, Amyloid Precursor Protein KM670/671NL Swedish mutation; PS-1, Presenilin-1; ANT-1, Adenine Nucleotide Translocator-1; iPSC, induced Pluripotent Stem Cell; CSF, CerebroSpinal Fluid; Tg, Transgenic; Wt, Wild-type; DMN, Default Mode Network; PET, Positron Emission Tomography; MRI, Magnetic Resonance Imaging; EEG, ElectroEncephaloGraphy

* Corresponding author at: Institute of Translational Pharmacology (IFT)-CNR, Via Fosso del Cavaliere 100, 00133 Rome, Italy.
E-mail address: g.amadoro@inmm.cnr.it (G. Amadoro).

[1] Equal contribution.

https://doi.org/10.1016/j.bbadis.2019.165584
Received 23 May 2019; Received in revised form 23 September 2019; Accepted 24 September 2019
Available online 29 October 2019

blown AD [9]. Tau tangle neuropathology is associated with deficits of episodic-memory performance and atrophy of temporal lobes in cognitively-intact healthy adults regardless of Aβ, indicating that tau may be the actual driver for neurodegeneration *in vivo*. In this regard, longitudinal positron emission tomography (PET), structural magnetic resonance imaging (MRI) and neuropsychological assessments have revealed that Aβ does not seem to underlie age-related memory impairments, although it can accelerate the development of tau pathology outside the medial temporal lobe (MTL), a brain region which is early involved by tau deposition and whose damage is associated with loss of mental processes in aging and dementia [10]. Recent findings demonstrating that tau dysfunction is linked to cognitive decay in a region-specific manner in AD cases [11], while pure amyloidosis is *per se* asymptomatic, have raised further concerns about the validity of classical amyloid cascade hypothesis and on whether Aβ is the primary culprit in disease etiopathogenesis [12]. In keeping with these observations, *in vitro* and *in vivo* studies have outlined the necessary, not-dispensable role of tau dyshomeostasis in cellular and animal models with AD phenotype [13–18] especially in provoking the prodromal, pathologically-relevant changes of synaptic plasticity and neurotransmission [19–21]. Notwithstanding these compelling clinical, epidemiological and experimental evidence, Aβ-directed intervention has been mainly pursued during the last couples of decades until the more recent discovery that tau is not only present in the cytoplasm but also actively secreted into the extracellular space and transmitted from one cell to another. A growing number of studies have confirmed that the transynaptic propagation of released tau occurs in a stereotyped and strain-specific manner across anatomically-interconnected neuronal networks and *via* a mechanism of prionoid-like template/seeding spreading [22–26]. These advances in basic knowledge of tau pathobiology have collectively generated great interest in the field because of their important “bench-to-bedside” implications for the cure of human AD and non-AD tauopathies. The beneficial effects of antibodies, small molecules or other pharmacological agents aimed at decreasing the production, uptake/binding, internalization, release and/or extracellular action mechanism(s) of toxic tau species are under current investigation [27,28]. Owing to the occurrence of severe adverse side-effects and the failure in improving cognitive performance referred by Phase II trials targeting Aβ, immunotherapeutic approaches based on the clearance/neutralization of diffusible, soluble conformers of tau have been alternatively employed for AD treatment in human beings [29–32]. In this context, tau fragments derived from the N-terminal projection domain of full-length protein turn out to be interesting, being prevailing in the biological fluids from diseased patients [33–38].

One of the most unexpected and intriguing findings which has encouraged efforts towards a better comprehension of the underlying tau-mediated pathogenic processes and the design of molecularly-targeted therapeutics is that, in addition to its classical axonal distribution in post-mitotic neurons, tau also localizes within synaptic compartments under physiopathological conditions [39–45]. To date, there is proof that pathogenic tau species affect, directly and indirectly, the synaptic plasticity and neurotransmission along both pre- and post-synaptic pathways including: (i) regulation of targeting, metabolic and/or energetic activities of synapse-resident mitochondria; (ii) control of glutamatergic (NMDA/AMPA) receptors distribution into dendritic spines and/or direct interaction with scaffolding protein and/or signaling complexes; (iii) modulation of synaptic vesicles clustering/mobilization [39–45].

Of particular relevance is the fact that, among tau post-translational modifications, truncation is critically involved in the onset/progression of AD because of its ability to promote both misfolding/aggregation and neurodegeneration [46–48], in tight association with progressive detriment of cognitive and mnestic functions [49–53]. In AD, proteolysis enhances the capacity of tau protein to aggregate and, then, to accumulate as protease(s)-resistant NFTs into brains from affected patients [50,51,54–58]. By cryo-electron microscopy and atomistic resolution carried out on the insoluble materials isolated from cerebral specimens of AD subjects, the Straight Filaments (SF) and Paired Helical Filaments (PHF) -which accumulate into the soma (as NFT) and into the dystrophic neurites (as neuropil threads and dystrophic neurites surrounding the Aβ-positive neuritic plaques), respectively- appear to be mainly constituted by a 12 kDa β-sheet helical core including the proteolytic fragments of tau [46,47,57]. Tau cleavage promotes glycation and ubiquitination, two other pathological protein modifications occurring as PHF maturate during their time-dependent evolution into late-stage filamentous inclusions [47,48]. However, truncation results in tau fragments which can induce *per se* neurodegeneration independently of the pro-aggregative pathway(s) and along fragment-specific pattern [47,59], as consequence of their: (i) deleterious action (s) on pre- and/or post-synaptic functions [18,60–63]; (ii) interference with vital cellular processes (axonal transport, microtubule organization, mitochondria metabolism, gene expression) [57]; (iii) secretion into extracellular space and cell-to-cell propagation [64]. Moreover, tau cleavage also contributes -both directly and indirectly- to the execution of apoptotic signal, as suggested by the extensive co-localization of truncated tau with DNA fragmentation in AD neurons [65] and the activation of effector protease(s) followed by stimulation of pro-death downstream signaling(s) [51–53,66–68]. Individual tau fragments have been recently detected in body fluids such as CerebroSpinal Fluid (CSF), plasma and saliva from AD-afflicted patients by paving the way for their quantification as reliable biomarkers for diagnosing dementia, monitoring disease's progression and/or patient's stratification and response to treatment efficacy. Therapeutic strategies aimed at targeting/blocking the toxicity associated with tau cleavage, including inhibitors of protease-substrate interaction and antibody-mediated immunodepletion, are being undertaken, especially in consideration that the deleterious effects of pathological tau appear to be fully reversible within a certain time frame [57,59,64].

Here, we provide an overview of experimental findings by our and other research groups highlighting the importance of tau proteolysis, particularly in its N-terminal projection domain, in the context of tau-mediated synaptic dysfunction and neurodegeneration. We discuss the potential clinical and translational impact of the 20–22 kDa fragment (NH_2htau), a NH_2-derived tau peptide endowed with potent “gain-of-function” action(s), both *in vitro* and *in vivo*, which is released in activity-dependent manner from nerve endings and found at high level in CSF of subjects suffering from both AD and other associated dementias.

2. Pathological N-terminal cleavage of tau is a contributing factor to early synaptic failure and neurodegeneration during the AD progression

Synaptic impairment and loss of nerve endings occurring prior to overt neuronal death are largely recognized as the principal biological correlates of memory and cognitive disintegration in AD and other human non-AD tauopathies [69,70]. Interestingly, although Aβ can cause downstream tau dysmetabolism, Aβ-driven synaptotoxicity is tau-dependent, in particular on its N-terminal region which protrudes away from the surface of microtubule-track towards the plasma membrane [15,18]. Studies in post-mortem AD brains, as well as in AD transgenic animal models, have also demonstrated the concomitant occurrence of synaptic failure and mitochondrial stress [71,72]. Indeed, the nerve terminal ends are largely enriched of these organelles, more than in other cellular regions [73], due to their high-energy demand and local need of elevated calcium in response to neurotransmission [74]. Interestingly, a complex interplay between pathological Aβ and tau in precipitating the structural and functional demise of synaptic boutons, has been reported to take place *via* parallel and convergent mitochondrial pathways in numerous *in vitro* and *in vivo* investigations [75–77]. As a consequence, preclinical research focusing on the changes in synaptic integrity, function and bioenergetics is pivotal for clinical studies aimed at improving symptomatic and disease-modifying approaches to

halt AD at its inception [69,70].

To gain further insights into the tau-driven pathomechanisms at synapses, our research group first developed a neoepitope antibody directed against the N-terminal sequence of human tau protein $DRKD_{(25)}$-QGGYTMHQDQE which encompasses a conserved caspase(s)-cleavage site [64,78]. This antibody recognizes the newly-created Δ-$_{25}NH_2$tau(Q26-36aa)-terminus of degradation product(s) of tau without cross-reaction towards the same aminoacidic stretch from full-length, intact isoforms of protein [79]. In this framework, we found out that a NH_2-terminal tau peptide of 20-22 kDa molecular weight (MW) (aka NH_2htau) on SDS-PAGE separation was early generated in strong correlation with the activation of effector proteases and with the extent of cell death, in different human and rodent *in vitro* paradigms. This NH_2-terminally cleaved form of tau was clearly visible in: (i) differentiated SH-SY5Y cells undergoing apoptosis following Brain-Derived Neurotrophic Factor (BDNF) withdrawal or acute treatment with STauroSporine (STS); (ii) rat pheochromocytoma PC12 neurons deprived of Nerve Growth Factor (NGF) as trophic support for death induction; (iii) Cerebellar Granule primary cultures (CGN) exposed to low concentration of extracellular potassium ($K5^+$) in culture milieu [79]. By combining Western blotting analysis with commercial tau antibodies directed against different epitopes of protein and immunohistochemistry studies, it turned out to be included within the 26 and 230 aminoacids on the N-terminal domain of the longest full-length tau isoform (htau40) [79], two consensus-sequences known to be specific substrates for caspase(s) and calpain-mediated proteolysis, respectively [64,78] (Fig. 1). The pathological relevance of the 20–22 kDa NH_2htau was further validated *in vivo* [79], in hippocampi from 15 month-old AD11 transgenic mice. In this animal model for sporadic AD, the progressive disease-associated neurochemical, behavioural and electrophysiological hallmarks are recapitulated by chronic inactivation of the NGF/TrkA signaling during adulthood by means of the intracellular expression of specific anti-neurotrophin neutralizing antibody [80–82]. Remarkably, the 20–22 kDa tau-derived peptide appeared to preferentially accumulate into synaptic compartment(s) from pathological terminal nerve endings [63], as further confirmed on isolated hippocampal crude synaptosomal preparations from 3-month-old aging (huAPP695·K670 N/M671 L)2576 (Tg2576) transgenic mice and from autoptic specimens of early-middle (Braak stage = 3) patients affected from AD [63] (Fig. 2).

Taken together and in agreement with other following studies [58,83], these findings suggest a "cell death-model" in the AD pathogenesis in which, at initial stages of neurodegeneration, apoptogenic stimuli, by themselves and/or synergically even without leading to complete execution of death program [84–86], can operate in vulnerable populations of post-mitotic neurons, through aberrant activation of effector proteases. This, in turn, would cause downstream the proteolytic cleavage of tau protein with generation of one or more of its toxic soluble truncated species, including the 20–22 kDa NH_2htau, which *per se* may further contribute to propagate and/or facilitate the cellular collapse during the disease progression. In line with causal role of tau dyshomeostasis in excitotoxicity and network hyperexcitability linked to AD and non-AD neurodegenerative disorders [14,18,87–89], the high-efficient, adenovirus-mediated transduction of the NH_2-26-230 human tau fragment exerted in hippocampal and cortical primary cultures a potent, harmful "gain-of-function" effect(s) [90,91]. The "death signaling", involving the NMDAR-mediated and caspase-independent excitotoxicity, was accompanied by dephosphorylation of cAMP-response-element-binding protein (CREB) and it was significantly inhibited by ifenprodil, a selective antagonist of extrasynaptic NR2B-subunit-containing NMDARs [90,91].

Since the subcellular localization of a protein into synaptic compartments represents a strong rationale of addressing its plausible role in synaptic function(s) under physiopathological conditions, the molecular mechanism(s) underlying the neurotoxicity of the 20-22 kDa NH_2htau and the biochemical interactome engaged by its preferential accumulation at nerve terminals were next investigated. In this regard, a synthesized NH_2-26-44 peptide -which is the minimal active moiety retaining the *in vitro* deleterious effect of longer overexpressed parental NH_2-26-230 human tau fragment [90,91]- was found to markedly inhibit the oxidative phosphorylation (OXPHOS) and cause an increased production of Reactive Oxygen Species (ROS) when *ex-vivo* tested in

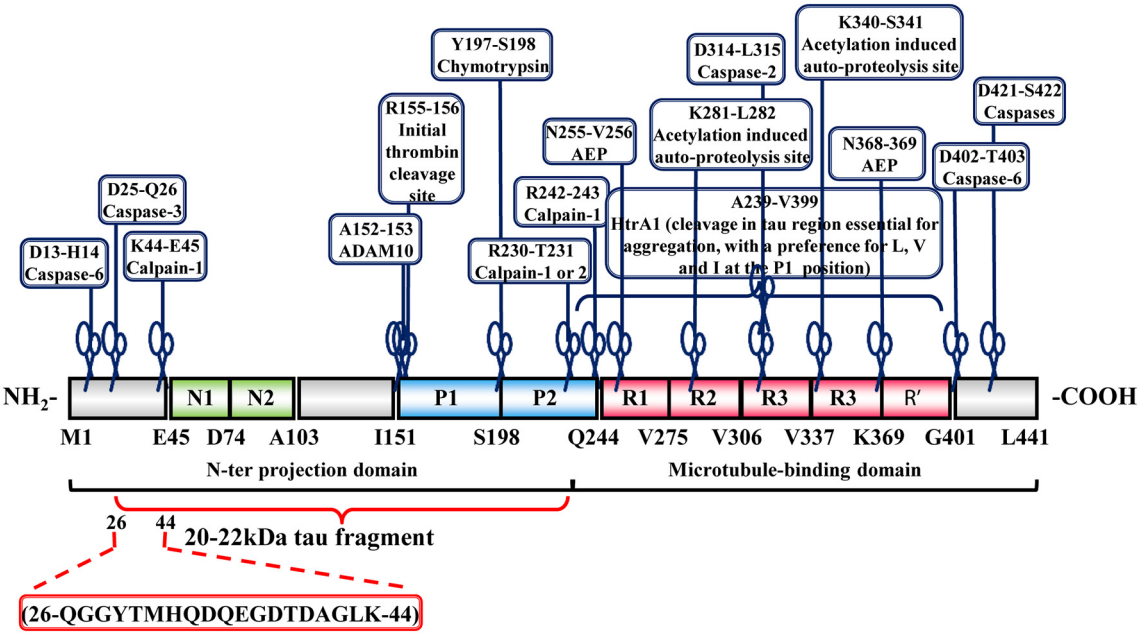

Fig. 1. Schematic representation of the truncation sites on the 2N4R full-length human tau protein.
Schematic of tau proteolysis of the full-length human isoform (2N4R; 1–441 aminoacids) which is typically divided into a N-terminal projection domain and a C-terminal microtubule-binding domain. N1 and N2 are the N-terminal inserts, P1 and P2 are the prolin-rich domains, R1, R2, R3 and R4 are the repeat domains and R' is the flanking domain. Letters refer to the single aminoacid code while the number refers to the position along the length of the tau441 isoform. The 20–22 kDa fragment encompassing the D25-Q26 and R231-T231 caspase(s) and calpain cleavage-sites and the smaller 2.0 kDa peptide are shown. Figure adapted from [64].

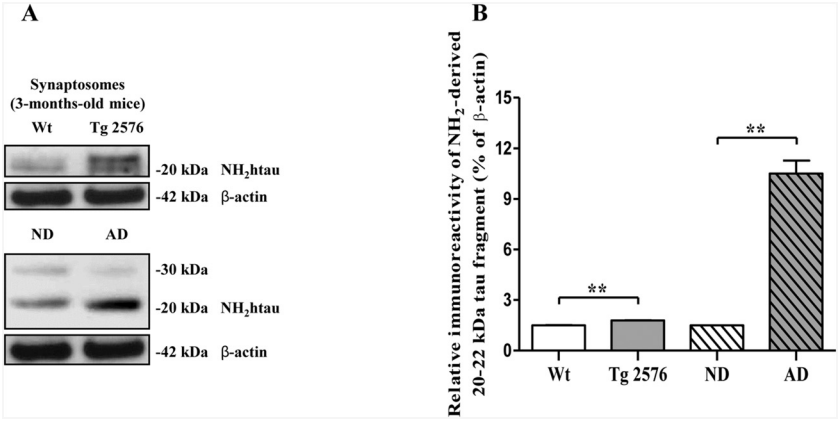

Fig. 2. Identification of the NH_2-derived 20-22 kDa tau fragment in preclinical AD animal model and in autoptic human specimens.

(A–B): Crude synaptosomal preparations from hippocampi were isolated from 3-month-old Tg2576 AD mice and littermate wild-type controls (Wt) (upper panels) and from human early-middle AD-affected cases (Braak stage = 3) and age-matched not-demented (ND) healthy subjects (lower panels). Patients demographic details (age, Braak-stage, number of analyzed cerebral samples, brain weight, sex) and detailed experimental procedures were previously reported in [63,94,96]. Equal amounts of total protein extract (40 μg) were analyzed by SDS-PAGE/Western blotting for the expression levels of the endogenous 20-22 kDa NH_2htau by probing with cleavage-specific anti-tau Δ-25 NH_2tau (Q26-36aa) mAb (A). Bar graph shows the densitometric quantification of immunoreactivity levels normalized by calculating the ratio of the intensity of the signal for the 20-22 kDa NH_2htau to that of β-actin which was used as loading control for each sample/lane (B). Values were mean ± SEM of at least of five independent experiments and were expressed with respect to corresponding control counterpart. Statistically significant differences were calculated at the respective experimental points by unpaired-two tailed t-Student's test (**$p < 0.01$ vs controls).

functional assays on intact/active mitochondria isolated from primary neuronal cultures. Although the precise sequence of events has not been completely understood, the intracellular bioavailability of ATP appeared to be significantly reduced by treatment with NH_2-26-44 tau peptide -but not with its biologically-harmless NH_2-1-25 counterpart [90,91]. This effect was discovered to result from the blockage in the thiol group/s located into the active site of Adenine Nucleotide Translocator-1 (ANT-1), the inner membrane component of the Mitochondrial Permeability Transition Pore (MPTP) [92,93]. The involvement of the 20–22 kDa NH_2htau in synaptic derangement *in vivo* was addressed thanks to studies showing that this NH_2-truncated tau peptide, but not the physiological full-length protein: (i) was selectively enriched into human mitochondria from AD crude synaptoneurosomes in correlation with the synaptic loss/disassembly and with the organelle functional disturbance [94]; (ii) interacted with Aβ specie(s) and cooperated with it in inhibiting the ANT-1-dependent ADP/ATP exchange at human AD nerve terminals [63] along a mechanism(s) involving both the catalytic -SH group/s and the Aβ-stimulated production of Complex I-derived superoxide anions [93].

Subsequent investigations clarified that the 20–22 kDa NH_2htau could contribute to synaptic injury not only directly, by functional inactivation of ANT-1 mitochondrial carrier [63] but also, indirectly, by improper recruitment of Parkin, an ubiquitin-ligase which triggers the selective degradation of these organelles along the autophagic-lysosomal pathway (mitophagy). The traslocation of cytosolic Parkin to neuronal mitochondria was strongly promoted by NH_2htau which make them more prone to undergo indiscriminate and detrimental autophagic flux [95,96], a physiopathological clearance process in which ubiquitin-binding adaptors recruit these organelles when damaged/oxidated to the degradative autophagosome by binding to LC3. These *in vitro* and *in vivo* findings fit well with the emerging “dual-hit” hypothesis of the AD onset/development in which both pathological Aβ and tau provoke damage of synaptic terminal boutons at early stages of disease progression by impinging, directly or indirectly, on the mitochondrial metabolic function(s) and dynamics (changes in number, shape and sub-cellular distribution) [75–77].

In conclusion, by means of morphological, biochemical and functional experimental approaches, we report that the 20–22 kDa NH_2htau: (i) is pathologically relevant, being present at high levels into synaptic compartment(s) from cellular, animal experimental AD models and post-mortem humans brains of cognitively-impaired AD subjects [96]; (ii) is able to induce alterations in mitochondrial trafficking, morphology and bioenergetics which, in turn, could contribute to the synaptic deterioration and imbalanced neurotransmission likely by impairing the energy-consuming clearance/re-uptake of extracellular glutamate [92,97]. These findings are in line with the early deficits in energy metabolism and turnover of mitochondria (biogenesis, transport, degradation and selective quality control) detected in brains from different lines of AD transgenic mice [71,98–100] and from AD patients [75,101], which occur in correlation with clinical disability [102] and with modifications of synaptic plasticity in susceptible neurocircuitries of limbic system [77,103,104]. As shown by other research groups, the 20–22 kDa NH_2htau is also discernible in: (i) hippocampal cultured neurons [105] and organotypic slices [106] exposed to low concentration of extracellular Aβ oligomers; (ii) 3xTg mice carrying mutated human APPSwe, tauP301L, PS1M146V [107] which are *in vitro* and *in vivo* AD systems characterized by marked mitochondrial and synaptic disablement. Furthermore, in support of its deleterious effect (s) on the progression of AD and related disorders, the *in vivo* expression of two overlapping pathologically-relevant, NH_2-derived tau fragments lacking the extreme N-end -such as tau 26-330 [108] or calpain-cleaved tau 45-230 [109]- is able to recapitulate a few key hallmarks of neuropathology in transgenic animals by inducing neuronal degeneration, synaptic abnormalities and behavioural deficits in memory/learning tasks.

3. Extracellular NH_2-derived tau fragment(s) is a potential diagnostic biomarker and therapeutic target for human tauopathies, including AD

Due to its canonical function(s) of microtubule-associated protein (MAP) involved in the cytoskeleton stabilization, axonal motor-based transport, neuritic elongation and maturation, intracellular tau has been largely accepted to be localized into the cytoplasm of neurons. However, a growing number of data supports the idea that tau is also physiologically secreted following the neuronal activity, likely within extracellular vesicles (exosomes and ectosomes) and through an unconventional pathway [25]. Consistently, intervention strategies which intercept the bioactive seeds of extracellular pathological tau have been actually proved to attenuate the early Aβ-dependent and/or independent synaptic dysfunction(s) in preclinical AD models with significant improvement in animals' cognitive or motor functions [29,110]. Tau is released into the extracellular space both in its full-length [111,112] and truncated forms [35,113], not only in the conditioned media of human tau-expressing cell lines [114,115], primary neurons [116] and induced Pluripotent Stem Cell (iPSC)-derived neurons [35,114,117] but also in the brain InterStitial Fluid (ISF) and CerebroSpinal Fluid (CSF) of mice [118] and human [119]. Of note, CSF-AD tau is detected mainly as a heterogeneous population of fragments, including the NH_2-terminal and/or prolin-rich domain of protein [34,37,38,120–124], irrespective of cell death or neurodegeneration [125]. Relevantly, elevated levels of mid-region and N-terminal

containing fragments are largely abundant both in CSF and in plasma from AD and MCI-AD patients, suggesting that NH_2-derived species are actively secreted during the pathological aging [125] by escaping neurons more preferentially than COOH-derived ones [126].

Consistent with these observations, high levels of the 20–22 kDa NH_2htau were detectable by Western blotting analysis on peripheral CSF from living patients affected from tau-dependent neurodegenerative diseases associated with mnestic disability, providing thus a biomarker for AD and non-AD human tauopathies [33]. Strikingly, we found out that the 20-22 kDa NH_2htau: (i) was not a normal constituent of CSF, unlike t-tau and p-tau, being rarely detected in patients without cognitive impairment; (ii) discriminated, with a weak specificity of 65% but a high sensitivity of 85%, subjects carrying neurodegenerative diseases associated with cognitive deterioration (*i.e.*, AD, frontotemporal lobar degeneration, Parkinson's disease with dementia, vascular dementia, mixed dementia, *etc.*) from those affected by other neurological disorders without memory/learning deficits [33]. Interestingly, by immunoprecipitation followed by high-resolution mass spectrometry and immunoassays, a recent longitudinal study has confirmed that this tau peptide is actually present in individual CSF and specifically upregulated in AD subjects, in correlation with the progressive decrease of their cognitive performance [36]. In support of the finding that the extracellular abundance of NH_2-derived tau fragments is prominent in AD environments, additional *ex-vivo* and *in vitro* evidence has demonstrated that the soluble and unaggregated C-terminally truncated forms of tau, including the 20–22 kDa NH_2htau, are preferentially secreted from synaptosomes of AD brains [127] and in conditioned media from patient-derived induced Pluripotent Stem Cells (iPSC) cortical neurons of affected subjects [35,113]. More recently, we reported that a 2.0 kDa peptide which encompasses the smaller and more potent NH_2-26-44 tau aminoacidic stretch included into the parental 20–22 kDa NH_2htau: (i) was actually endogenously detected *in vivo*, being present in hippocampal synaptosomal preparations from AD subjects [128]; (ii) was able to induce brain pathology by altering the normal synaptic function(s), both *in vitro* [129] and *in vivo* [128], when exogenously-added to neurons. Elevated levels of intracellular calcium load, structural and functional alterations of synaptic connections, cognitive impairments in the absence of signs of frank neuronal death were clearly detected in NH_2-26-44 tau-exposed hippocampi, a pathological phenotype which is recapitulated by well-established cell-culture and mouse models of tauopathy [128,129].

Given that the identification of the molecular identity of neurotoxic intracellular/extracellular tau species is required to develop more effective immunotherapeutical approaches [28,31], these experimental studies might also have far-reaching translational implications, by providing a remarkable opportunity for developing unexplored tau-based vaccination regimen useful in future AD trials. Consistently, antibodies targeting the N-terminal projection domain of human tau are proved to be beneficial following intra-cerebroventricular (i.c.v.) and peripheral administrations in AD transgenic mice by counteracting their cognitive deficits [130–133] and preventing the age-dependent seeding/spreading of neuropathology [134]. *In vivo* delivery of HJ8.5 -a monoclonal antibody (mAb) which recognizes the N-terminal region of tau (epitope residues 25–30) and is endowed with potent ability to block its seeding activity *in vitro*- markedly reduces the accumulation of hyperphosphorylated (AT8)/insoluble pathological aggregates, the microglial activation and the brain atrophy of 6-month-old P301S tau transgenic mice [130,131] with consequent improvement in their motor/sensorimotor and cognitive deficits. Intraperitoneal injection of anti-tau 43D mAb (epitope residues 6–18) significantly ameliorates the reference memory of 14–17-months-old 3xTg-AD mice when tested in the Morris water maze task, by diminishing the level of both total and AD-like hyperphosphorylated tau (Ser202/Thr205 (AT8), Thr205, Ser262/356 (12E8), and Ser396/404 (PHF-1)) [132]. Passive immunization of this aggressive AD animal model with 43D mAb also prevents the phospho-tau seeding in the ipsilateral hippocampus and inhibits its propagation to the contralateral side [133]. Taken together, these compelling findings indicate that immunotherapy against the N-terminal extremity of tau can be a productive treatment strategy to prevent *in vivo* the associated trans-cellular propagation of neuropathology mediated by its extracellular aggregates. Besides, in okadaic acid (OA)-treated rats showing an accumulation of pathological tau induced by selective inhibition of PP2A, the infusion of polyclonal antibody against the N-terminal region of tau (phospho-residue cluster 68–71) evokes appreciable neuroprotective effects on its site-specific AD-like hyperphosphorylation and, thus, on the animals' cognitive performance [134]. Relevantly, there is also strong evidence that the N-terminal of human tau which interacts with the plasma membrane [135] can contribute to its pathological action at synaptic extensions [18,136], not only by facilitating the secretion to the extracellular space [137], but also by triggering the initial nucleation/oligomerization processes which underlies the higher-order aggregative pattern [138]. Nevertheless, the development of anti-tau antibodies which selectively target the toxic components of its N-terminal region will be of great therapeutic interest for the cure of AD by avoiding the clearance of the normal full-length protein endowed with important physiological functions and whose reduction *in vivo*, even if partial, is known to be extremely harmful in terminally-differentiated post-mitotic neurons [27–31]. Interestingly, the species-specific differences in the expression and protein sequences of tau at its N-terminal domain [139], along with the occurrence of extrinsic post-translational determinants, might, at least in part, account for increased vulnerability of human beings to develop mature AD neurodegeneration [140]. To this point, several tau-dependent mechanisms have been proposed, such as: (i) different control in protein-protein interactions with a subset of disease-relevant components involved in vesicle-associated machinery assembly and synaptic transmission [35,141,142]; (ii) facilitation in secretion through a mechanism involving recruitment of End Binding proteins which belong to the group of microtubule plus-end tracking proteins (+TIPs) [137].

In summary, several pieces of data demonstrate that targeting tau pathology might be prove more effective in preventing/delay the clinical symptoms of AD, considered that the Aβ-directed therapies have been unsuccessful to date. Evidence from APP-overexpressing transgenic animal models [143] and longitudinal clinical trials have also demonstrated that Aβ-associated cognitive deficits in healthy normal older subjects develop only in the presence of elevated CSF levels of phospho-tau [144]. In AD progression, hyperphosphorylated tau is closely linked with memory impairments whereas Aβ deposition does not correlate with cognition but rather with early functional deterioration of integrity and dynamics of critical brain networks, as measured by functional MRI and electroencephalography (EEG). In particular, Aβ pathology shows topographical correspondence with the DMN whose disruption in AD initially involves the medial temporal lobe and posterior cingulate cortex/precuneus and later progresses to the lateral parietal and medial frontal regions with the increasing disease severity [145]. However, it's worth noting that promising results from tau-directed interventions in the field of AD cure should be interpreted with caution given the complexity of targeting extracellular soluble toxic tau whose precise nature *in vivo* remains to be clearly identified [34,110]. On the other hand, tau-based human clinical trials are still in progress and a synergy between Aβ and other risk factors and/or pathogenic proteins can also contribute to neuron death and cognitive deficits at sufficient level to warrant a dementia diagnosis [146,147]. Multiple-targeted approaches taking into account the multi-factorial nature of AD pathology which involves different underlying causative mechanisms (*i.e.* Aβ, tau, inflammation, neurotrophic factor imbalance and others) should be considered to achieve the best outcomes in managing this devastating illness in human beings [148].

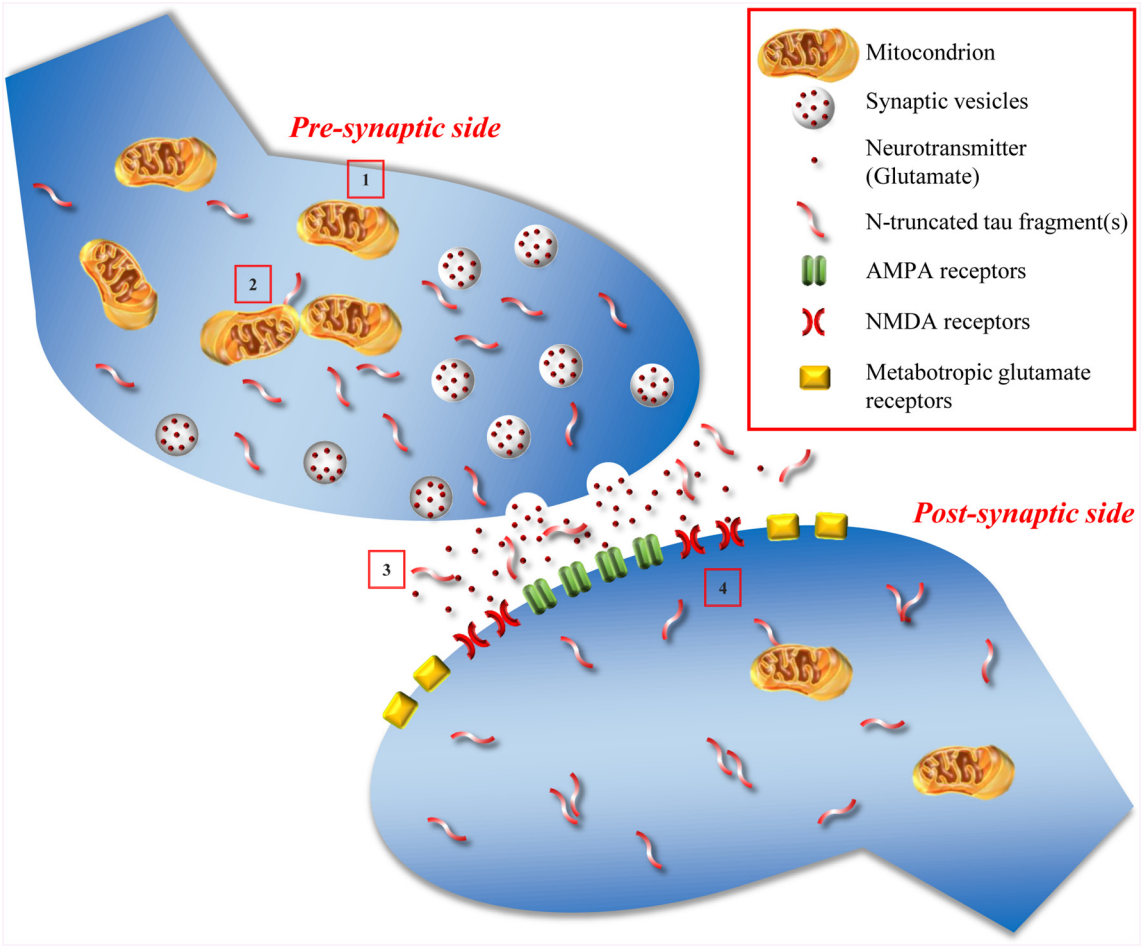

Fig. 3. Putative pathological mechanisms by which the N-terminally truncated tau fragment(s) (*i.e.* NH_2htau) may impair the synaptic functions in AD.
1. NH_2htau affects mitochondrial bioenergetics by inhibiting the ANT-1-dependent ADP/ATP exchange [92–94]; 2. NH_2htau impairs mitochondrial dynamics (fusion/fission and selective autophagic clearance) [95,96]; 3. NH_2htau is released into the extracellular space [127] where it may perturb the plasma membrane and be internalized [128,129]; 4. NH_2htau is involved in extrasynaptic NMDA2B receptor-dependent excitotoxicity [90,91].

4. Conclusions and future directions

Compelling experimental and clinical studies show that pathological tau accumulation within specific brain regions and/or its CSF levels better correlate in AD with impaired cognitive functions and synapse loss than Aβ does, suggesting that neurodegeneration may be ultimately driven during the disease progression by changes in normal metabolism of tau. Truncation at N-terminal domain of tau is an important pathogenetic mechanism which is early and causally involved in the initiation/development of human AD and other related brain dementias, collectively named tauopathies. Tau cleavage at its NH_2 extremity contributes to neuropathology propagation by increasing the propensity of protein to aggregate into insoluble NFTs and/or by disrupting the cellular machinery and synaptic function which lead, eventually, to end-stage neuronal death (Fig. 3). Novel diagnostic/prognostic disease biomarkers and therapeutic strategies focused on the tau proteolysis at its amino-terminus domain, are currently pursued offering a new hope for treatment of these fatal neurodegenerative disorders with a high burden of tau pathology.

Funding

This research was supported by Magnetic Diagnostic Assay for neurodegenerative diseases H2020-ICT-2016-2017 “SSI - Smart System Integration” Proposal 732678 SEP 210349930. The funders had no role in study design, data collection and analysis, decision to publish or preparation of manuscript.

Author contribution

G.A., V.L. and P.C. designed and outlined the structure and contents of the review. V.C. contributed to critical discussion and reading. G.A., V.L. and P.C. contributed to the literature review, discussion and writing of the manuscript.

Transparency document

The Transparency document associated this article can be found, in online version.

Declaration of competing interest

The authors declare that they have no actual or potential conflicts of interest and that these data are not published elsewhere.

Acknowledgments

We wish to thank Pina Moliterno for suggestions in the final editing of the manuscript.

Consent for publication

All authors approve the study described in this report and give their consent for publication.

References

[1] A. Kumar, A. Singh, Ekavali, A review on Alzheimer's disease pathophysiology and its management: an update, Pharmacol. Rep. 67 (2015) 195–203, https://doi.org/10.1016/j.pharep.2014.09.004.

[2] C.L. Masters, R. Bateman, K. Blennow, C.C. Rowe, R.A. Sperling, J.L. Cummings, Alzheimer's disease, Nat. Rev. Dis. Primers 1 (2015) 15056, https://doi.org/10.1038/nrdp.2015.56.

[3] I. Alafuzoff, K. Iqbal, H. Friden, R. Adolfsson, B. Winblad, Histopathological criteria for progressive dementia disorders: clinical-pathological correlation and classification by multivariate data analysis, Acta Neuropathol, 74 74 (1987) 209–225.

[4] P.V. Arriagada, J.H. Growdon, E.T. Hedley-Whyte, B.T. Hyman, Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease, Neurology 42 (1992) 631–639.

[5] K.P. Riley, D.A. Snowdon, W.R. Markesbery, Alzheimer's neurofibrillary pathology and the spectrum of cognitive function: findings from the Nun study, Ann. Neurol. 51 (2002) 567–577.

[6] Y. Huang, L. Mucke, Alzheimer mechanisms and therapeutic strategies, Cell 148 (2012) 1204–1222, https://doi.org/10.1016/j.cell.2012.02.040.

[7] P. Sharma, P. Srivastava, A. Seth, P.N. Tripathi, A.G. Banerjee, S.K. Shrivastava, Comprehensive review of mechanisms of pathogenesis involved in Alzheimer's disease and potential therapeutic strategies, Prog. Neurobiol. (2018) pii: S0301-0082(18)30139-4, doi: https://doi.org/10.1016/j.pneurobio.2018.12.006.

[8] D.J. Selkoe, J. Hardy, The amyloid hypothesis of Alzheimer's disease at 25 years, EMBO. Mol. Med. 8 (2016) 595–608, https://doi.org/10.15252/emmm.201606210.

[9] P.T. Nelson, I. Alafuzoff, E.H. Bigio, C. Bouras, H. Braak, N.J. Cairns, R.J. Castellani, B.J. Crain, P. Davies, K. Del Tredici, C. Duyckaerts, M.P. Frosch, V. Haroutunian, P.R. Hof, C.M. Hulette, B.T. Hyman, T. Iwatsubo, K.A. Jellinger, G.A. Jicha, E. Kövari, W.A. Kukull, J.B. Leverenz, S. Love, I.R. Mackenzie, D.M. Mann, E. Masliah, A.C. McKee, T.J. Montine, J.C. Morris, J.A. Schneider, J.A. Sonnen, D.R. Thal, J.Q. Trojanowski, J.C. Troncoso, T. Wisniewski, R.L. Woltjer, T.G. Beach, Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature, J. Neuropathol. Exp. Neurol. 71 (2012) 362–381, https://doi.org/10.1097/NEN.0b013e31825018f7.

[10] A. Maass, S.N. Lockhart, T.M. Harrison, R.K. Bell, T. Mellinger, K. Swinnerton, S.L. Baker, G.D. Rabinovici, W.J. Jagust, Entorhinal tau pathology, episodic memory decline, and neurodegeneration in aging, J. Neurosci. 38 (2018) 530–543, https://doi.org/10.1523/JNEUROSCI.2028-17.2017.

[11] A. Bejanin, D.R. Schonhaut, R. La Joie, J.H. Kramer, S.L. Baker, N. Sosa, N. Ayakta, A. Cantwell, M. Janabi, M. Lauriola, J.P. O'Neil, M.L. Gorno-Tempini, Z.A. Miller, H.J. Rosen, B.L. Miller, W.J. Jagust, G.D. Rabinovici, Tau pathology and neurodegeneration contribute to cognitive impairment in Alzheimer's disease, Brain 140 (2017) 3286–3300, doi: https://doi.org/10.1093/brain/awx243.

[12] M.E. Murray, V.J. Lowe, N.R. Graff-Radford, A.M. Liesinger, A. Cannon, S.A. Przybelski, B. Rawal, J.E. Parisi, R.C. Petersen, K. Kantarci, O.A. Ross, R. Duara, D. S. Knopman, C.R. Jr Jack, D.W. Dickson, Clinicopathologic and 11C-Pittsburgh compound B implications of Thal amyloid phase across the Alzheimer's disease spectrum, Brain 138 (2015) 1370–1381, doi: https://doi.org/10.1093/brain/awv050.

[13] M. Rapoport, H.N. Dawson, L.I. Binder, M.P. Vitek, A. Ferreira, Tau is essential to beta -amyloid-induced neurotoxicity, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 6364–6369, https://doi.org/10.1073/pnas.092136199.

[14] E.D. Roberson, K. Scearce-Levie, J.J. Palop, F. Yan, I.H. Cheng, T. Wu, H. Gerstein, G.Q. Yu, L. Mucke, Reducing endogenous tau ameliorates amyloid beta-induced deficits in an Alzheimer's disease mouse model, Science 316 (2007) 750–754, https://doi.org/10.1126/science.1141736.

[15] M.E. King, H.M. Kan, P.W. Baas, A. Erisir, C.G. Glabe, G.S. Bloom, Tau-dependent microtubule disassembly initiated by prefibrillar beta-amyloid, J, Cell. Biol. 175 (2006) 541–546, https://doi.org/10.1083/jcb.200605187.

[16] K.A. Vossel, K. Zhang, J. Brodbeck, A.C. Daub, P. Sharma, S. Finkbeiner, B. Cui, L. Mucke, Tau reduction prevents Abeta-induced defects in axonal transport, Science 330 (2010) 198, https://doi.org/10.1126/science.1194653.

[17] O.A. Shipton, J.R. Leitz, J. Dworzak, C.E. Acton, E.M. Tunbridge, F. Denk, H.N. Dawson, M.P. Vitek, R. Wade-Martins, O. Paulsen, M. Vargas-Caballero, Tau protein is required for amyloid {beta}-induced impairment of hippocampal long-term potentiation, J. Neurosci. 31 (2011) 1688–1692, https://doi.org/10.1523/JNEUROSCI.2610-10.2011.

[18] L.M. Ittner, Y.D. Ke, F. Delerue, M. Bi, A. Gladbach, J. van Eersel, H. Wölfing, B.C. Chieng, M.J. Christie, I.A. Napier, A. Eckert, M. Staufenbiel, E. Hardeman, J. Götz, Dendritic function of tau mediates amyloid-beta toxicity in Alzheimer's disease mouse models, Cell 142 (2010) 387–397, https://doi.org/10.1016/j.cell.2010.06.036.

[19] D. Liao, E.C. Miller, P.J. Teravskis, Tau acts as a mediator for Alzheimer's disease-related synaptic deficits, Eur. J. Neurosci. 39 (2014) 1202–1213, https://doi.org/10.1111/ejn.12504.

[20] S. Forner, D. Baglietto-Vargas, A.C. Martini, L. Trujillo-Estrada, F.M. LaFerla, Synaptic impairment in Alzheimer's disease: a dysregulated symphony, Trends Neurosci. 40 (2017) 347–357, https://doi.org/10.1016/j.tins.2017.04.002.

[21] T.L. Spires-Jones, B.T. Hyman, The intersection of amyloid beta and tau at synapses in Alzheimer's disease, Neuron 82 (2014) 756–771, https://doi.org/10.1016/j.neuron.2014.05.004.

[22] M.G. Spillantini, M. Goedert, Tau pathology and neurodegeneration, Lancet Neurol. 12 (2013) 609–622, https://doi.org/10.1016/S1474-4422(13)70090-5.

[23] M. Goedert, M.G. Spillantini, Propagation of tau aggregates, Mol. Brain 10 (2017) 18, https://doi.org/10.1186/s13041-017-0298-7.

[24] M.E. Orr, A.C. Sullivan, B.A. Frost, Brief overview of tauopathy: causes, consequences, And Therapeutic Strategies, Trends Pharmacol. Sci. 38 (2017) 637–648, https://doi.org/10.1016/j.tips.2017.03.011.

[25] D.P. Hanger, D.H. Lau, E.C. Phillips, M.K. Bondulich, T. Guo, B.W. Woodward, A.M. Pooler, W. Noble, Intracellular and extracellular roles for tau in neurodegenerative disease, J. Alzheimers Dis. 40 (2014) S37–S45, https://doi.org/10.3233/JAD-132054.

[26] A. Mudher, M. Colin, S. Dujardin, M. Medina, I. Dewachter, S.M. Alavi Naini, E.M. Mandelkow, E. Mandelkow, L. Buée, M. Goedert, J.P. Brion, What is the evidence that tau pathology spreads through prion-like propagation? Acta Neuropathol. Commun. 5 (2017) 99, https://doi.org/10.1186/s40478-017-0488-7.

[27] M.R. Khanna, J. Kovalevich, V.M. Lee, J.Q. Trojanowski, K.R. Brunden, Therapeutic strategies for the treatment of tauopathies: hopes and challenges, Alzheimers Dement. 12 (2016) 1051–1065, https://doi.org/10.1016/j.jalz.2016.06.006.

[28] P. Novak, E. Kontsekova, N. Zilka, M. Novak, Ten years of tau-targeted immunotherapy: the path walked and the roads ahead, Front. Neurosci. 12 (2018) 798, https://doi.org/10.3389/fnins.2018.00798.

[29] J.T. Pedersen, E.M. Sigurdsson, Tau immunotherapy for Alzheimer's disease, Trends Mol. Med. 21 (2015) 394–402, https://doi.org/10.1016/j.molmed.2015.03.003.

[30] E.M. Sigurdsson, Immunotherapy targeting pathological tau protein in Alzheimer's disease and related tauopathies, J. Alzheimers Dis. 15 (2008) 157–168.

[31] E.M. Sigurdsson, Tau immunotherapy, Neurodegener. Dis. 16 (2016) 34–38, https://doi.org/10.1159/000440842.

[32] A.M. Pooler, M. Polydoro, S. Wegmann, S.B. Nicholls, T.L. Spires-Jones, B.T. Hyman, Propagation of tau pathology in Alzheimer's disease: identification of novel therapeutic targets, Alzheimers Res. Ther. 5 (2013) 49, https://doi.org/10.1186/alzrt214.

[33] G. Amadoro, V. Corsetti, G.M. Sancesario, A. Lubrano, G. Melchiorri, S. Bernardini, P. Calissano, G. Sancesario, CSF levels of a 20-22kDa NH2-fragment of human tau provide a novel neuronal injury biomarker in Alzheimer's disease and other dementias, J. Alzheimers Dis. 42 (2014) 211–226, https://doi.org/10.3233/JAD-140267.

[34] J.E. Meredith, S. Sankaranarayanan, V. Guss, A.J. Lanzetti, F. Berisha, R.J. Neely, J.R. Slemmon, E. Portelius, H. Zetterberg, K. Blennow, H. Soares, M. Ahlijanian, C.F. Albright, Characterization of novel CSF tau and ptau biomarkers for Alzheimer's disease, PLoS One 8 (2013) e76523, , https://doi.org/10.1371/journal.pone.0076523.

[35] J. Bright, S. Hussain, V. Dang, S. Wright, B. Cooper, T. Byun, C. Ramos, A. Singh, G. Parry, N. Stagliano, I. Griswold-Prenner, Human secreted tau increases amyloid-b production, Neurobiol. Aging 36 (2015) 693–709, https://doi.org/10.1016/j.neurobiolaging.2014.09.007.

[36] C. Cicognola, G. Brinkmalm, J. Wahlgren, E. Portelius, J. Gobom, N.C. Cullen, O. Hansson, L. Parnetti, R. Constantinescu, K. Wildsmith, H.-H. Chen, T.G. Beach, T. Lashley, H. Zetterberg, K. Blennow, K. Höglund, Novel tau fragments in cerebrospinal fluid: relation to tangle pathology and cognitive decline in Alzheimer's disease, Acta Neuropathol. (2018), https://doi.org/10.1007/s00401-018-1948-2.

[37] N.R. Barthélemy, F. Fenaille, C. Hirtz, N. Sergeant, S. Schraen-Maschke, J. Vialaret, L. Buée, A. Gabelle, C. Junot, S. Lehmann, F. Becher, Tau protein quantification in human cerebrospinal fluid by targeted mass spectrometry at high sequence coverage provides insights into its primary structure heterogeneity, J. Proteome Res. 15 (2016) 667–676, https://doi.org/10.1021/acs.jproteome.5b01001.

[38] N.R. Barthélemy, A. Gabelle, C. Hirtz, F. Fenaille, N. Sergeant, S. Schraen-Maschke, J. Vialaret, L. Buée, C. Junot, F. Becher, S. Lehmann, Differential mass spectrometry profiles of tau protein in the cerebrospinal fluid of patients with Alzheimer's disease, progressive Supranuclear palsy, and dementia with Lewy bodies, J. Alzheimers Dis. 51 (2016) 1033–1043, https://doi.org/10.3233/JAD-150962.

[39] M.L. Frandemiche, S. De Seranno, T. Rush, E. Borel, A. Elie, I. Arnal, F. Lanté, A. Buisson, Activity-dependent tau protein translocation to excitatory synapse is disrupted by exposure to amyloid-beta oligomers, J. Neurosci. 34 (2014) 6084–6097, https://doi.org/10.1523/JNEUROSCI.4261-13.2014.

[40] J.C. Polanco, C. Li, L.G. Bodea, R. Martinez-Marmol, F.A. Meunier, J. Götz, Amyloid-β and tau complexity - towards improved biomarkers and targeted therapies, Nat. Rev. Neurol. 14 (2010) 22–39, https://doi.org/10.1038/nrneurol.2017.162.

[41] I. Sotiropoulos, M.C. Galas, J.M. Silva, E. Skoulakis, S. Wegmann, M.B. Maina, D. Blum, C.L. Sayas, E.M. Mandelkow, E. Mandelkow, M.G. Spillantini, N. Sousa, J. Avila, M. Medina, A. Mudher, L. Buee, Atypical, non-standard functions of the microtubule associated tau protein, Acta Neuropathol. Commun. 5 (2017) 91, https://doi.org/10.1186/s40478-017-0489-6.

[42] B.R. Hoover, M.N. Reed, J. Su, R.D. Penrod, L.A. Kotilinek, M.K. Grant, R. Pitstick, G.A. Carlson, L.M. Lanier, L.L. Yuan, K.H. Ashe, D. Liao, Tau mislocalization to dendritic spines mediates synaptic dysfunction independently of neurodegeneration, Neuron 68 (2010) 1067–1081, https://doi.org/10.1016/j.neuron.2010.11.

030.
[43] H-C. Tai, B.Y. Wang, A. Serrano Pozo, M.P. Frosch, T.L. Spires-Jones, B.T. Hyman, Frequent and symmetric deposition of misfolded tau oligomers within presynaptic and postsynaptic terminals in Alzheimer's disease, Acta Neuropathol. Commun. 2 (2014) 146, doi: https://doi.org/10.1186/s40478-014-0146-2.
[44] H. Moreno, G. Morfini, L. Buitrago, G. Ujlaki, S. Choi, E. Yu, J.E. Moreira, J. Avila, S.T. Brady, H. Pant, M. Sugimori, R.R. Llinás, Tau pathology-mediated presynaptic dysfunction, Neuroscience 325 (2016) 30–38, https://doi.org/10.1016/j.neuroscience.2016.03.044.
[45] P. Regan, D.J. Whitcomb, K. Cho, Physiological and pathophysiological implications of synaptic tau, Neuroscientist 23 (2017) 137–151, https://doi.org/10.1177/1073858416633439.
[46] A.L. Guillozet-Bongaarts, F. Garcia-Sierra, M.R. Reynolds, P.M. Horowitz, Y. Fu, T. Wang, M.E. Cahill, E.H. Bigio, R.W. Berry, L.I. Binder, Tau truncation during neurofibrillary tangle evolution in Alzheimer's disease, Neurobiol. Aging 26 (2005) 1015–1022, https://doi.org/10.1016/j.neurobiolaging.2004.09.019.
[47] F. García-Sierra, S. Mondragón-Rodríguez, G. Basurto-Islas, Truncation of tau protein and its pathological significance in Alzheimer's disease, J. Alzheimers Dis. 14 (2008) 401–409.
[48] L. Martin, X. Latypova, F. Terro, Post-translational modifications of tau protein: implications for Alzheimer's disease, Neurochem. Int. 58 (2011) 458–471, https://doi.org/10.1016/j.neuint.2010.12.023.
[49] R.A. Rissman, W.W. Poon, M. Blurton-Jones, S. Oddo, R. Torp, M.P. Vitek, F.M. LaFerla, T.T. Rohn, C.W. Cotman, Caspase-cleavage of tau is an early event in Alzheimer disease tangle pathology, J. Clin. Invest. 114 (2004) 121–130, https://doi.org/10.1172/JCI20640.
[50] G. Basurto-Islas, J. Luna-Munoz, A.L. Guillozet-Bongaarts, L.I. Binder, R. Mena, F. Garcia-Sierra, Accumulation of aspartic acid421- and glutamic acid391-cleaved tau in neurofibrillary tangles correlates with progression in Alzheimer disease, J. Neuropathol. Exp. Neurol. 67 (2008) 470–483, https://doi.org/10.1097/NEN.0b013e31817275c7.
[51] T.C. Gamblin, F. Chen, A. Zambrano, A. Abraha, S. Lagalwar, A.L. Guillozet, M. Lu, Y. Fu, F. Garcia-Sierra, N. LaPointe, R. Miller, R.W. Berry, L.I. Binder, V.L. Cryns, Caspase cleavage of tau: linking amyloid and neurofibrillary tangles in Alzheimer's disease, Proc. Natl. Acad. Sci. U. S. A. 100 (2003) 10032–10037, https://doi.org/10.1073/pnas.1630428100.
[52] H. Guo, S. Albrecht, M. Bourdeau, T. Petzke, C. Bergeron, A.C. LeBlanc, Active caspase-6 and caspase-6-cleaved tau in neuropil threads, neuritic plaques, and neurofibrillary tangles of Alzheimer's disease, Am. J. Pathol. 165 (2004) 523–531, https://doi.org/10.1016/S0002-9440(10)63317-2.
[53] P.M. Horowitz, K.R. Patterson, A.L. Guillozet-Bongaarts, M.R. Reynolds, C.A. Carroll, S.T. Weintraub, D.A. Bennett, V.L. Cryns, R.W. Berry, L.I. Binder, Early N-terminal changes and caspase-6 cleavage of tau in Alzheimer's disease, J. Neurosci. 24 (2004) 7895–7902, https://doi.org/10.1523/JNEUROSCI.1988-04.2004.
[54] A. Abraha, N. Ghoshal, T.C. Gamblin, V. Cryns, R.W. Berry, J. Kuret, L.I. Binder, C-terminal inhibition of tau assembly in vitro and in Alzheimer's disease, J. Cell Sci. 113 (2000) 3737–3745.
[55] R.W. Berry, A. Abraha, S. Lagalwar, N. LaPointe, T.C. Gamblin, V.L. Cryns, L.I. Binder, Inhibition of tau polymerization by its carboxy-terminal caspase cleavage fragment, Biochemistry 42 (2003) 8325–8331, https://doi.org/10.1021/bi027348m.
[56] H. Yin, J. Kuret, C-terminal truncation modulates both nucleation and extension phases of tau fibrillization, FEBS Lett. 580 (2006) 211–215, https://doi.org/10.1016/j.febslet.2005.11.077.
[57] T. Guo, W. Noble, D.P. Hanger, Roles of tau protein in health and disease, Acta Neuropathol. 133 (2017) 665–704, https://doi.org/10.1007/s00401-017-1707-9.
[58] A. de Calignon, L.M. Fox, R. Pitstick, G.A. Carlson, B.J. Bacskai, T.L. Spires-Jones, B.T. Hyman, Caspase activation precedes and leads to tangles, Nature 464 (2010) 1201–1204, https://doi.org/10.1038/nature08890.
[59] Y. Wang, S. Garg, E.M. Mandelkow, E. Mandelkow, Proteolytic processing of tau, Biochem. Soc. Trans. 38 (2010) 955–961, https://doi.org/10.1042/BST0380955.
[60] X. Zhao, L.A. Kotilinek, B. Smith, C. Hlynialuk, K. Zahs, M. Ramsden, J. Cleary, K.H. Ashe, Caspase-2 cleavage of tau reversibly impairs memory, Nat. Med. 22 (2016) 1268–1276, https://doi.org/10.1038/nm.4199.
[61] L. Zhou, J. Mcinnes, K. Wierda, M. Holt, A.G. Herrmann, R.J. Jackson, Y.C. Wang, J. Swerts, J. Beyens, K. Miskiewicz, S. Vilain, I. Dewachter, D. Moechars, B. De Strooper, T.L. Spires-Jones, J. De Wit, P. Verstreken, Tau association with synaptic vesicles causes presynaptic dysfunction, Nat. Commun. 8 (2017) 15295, doi: https://doi.org/10.1038/ncomms15295.
[62] J.M. Decker, L. Krüger, A. Sydow, S. Zhao, M. Frotscher, E. Mandelkow, E.M. Mandelkow, Pro-aggregant tau impairs mossy fiber plasticity due to structural changes and Ca++ dysregulation, Acta Neuropathol. Commun. 3 (2015) 23, https://doi.org/10.1186/s40478-015-0193-3.
[63] G. Amadoro, V. Corsetti, A. Atlante, F. Florenzano, S. Capsoni, R. Bussani, D. Mercanti, P. Calissano, Interaction between NH2-tau fragment and Aß in AD mitochondria contributes to the synaptic deterioration, Neurobiol. Aging 33 (2012) 833.e1-25, doi: https://doi.org/10.1016/j.neurobiolaging.2011.08.001.
[64] J.P. Quinn, N.J. Corbett, K.A.B. Kellett, N.M. Hooper, Tau proteolysis in the pathogenesis of tauopathies: neurotoxic fragments and novel biomarkers, J. Alzheimers Dis. 63 (2018) 13–33, https://doi.org/10.3233/JAD-170959.
[65] G. Ugolini, A. Cattaneo, M. Novak, Co-localization of truncated tau and DNA fragmentation in Alzheimer's disease neurones, Neuroreport 8 (1997) 3709–3712.
[66] C.W. Chung, Y.H. Song, I.K. Kim, W.J. Yoon, B.R. Ryu, D.G. Jo, H.N. Woo, Y.K. Kwon, H.H. Kim, B.J. Gwag, I.H. Mook-Jung, Y.K. Jung, Proapoptotic effects of tau cleavage product generated by caspase-3, Neurobiol. Dis. 8 (2001) 162–172, https://doi.org/10.1006/nbdi.2000.0335.
[67] L. Fasulo, G. Ugolini, M. Visintin, A. Bradbury, C. Brancolini, V. Verzillo, M. Novak, A. Cattaneo, The neuronal microtubule-associated protein tau is a substrate for caspase-3 and an effector of apoptosis, J. Neurochem. 75 (2000) 624–633.
[68] M. Blurton-Jones, F.M. Laferla, Pathways by which Abeta facilitates tau pathology, Curr. Alzheimer Res. 3 (2006) 437–448.
[69] Y. Chen, A.K.Y. Fu, N.Y. Ip. Synaptic dysfunction in Alzheimer's disease: Mechanisms and therapeutic strategies, Pharmacol. Ther. (2018) pii: S0163-7258(18)30203-1, doi: https://doi.org/10.1016/j.pharmthera.2018.11.006.
[70] J. Pozueta, R. Lefort, M.L. Shelanski, Synaptic changes in Alzheimer's disease and its models, Neuroscience 251 (2013) 51–65, https://doi.org/10.1016/j.neuroscience.2012.05.050.
[71] H. Du, L. Guo, S. Yan, A.A. Sosunov, G.M. McKhann, S.S. Yan, Early deficits in synaptic mitochondria in an Alzheimer's disease mouse model, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 18670–18675, https://doi.org/10.1073/pnas.1006586107.
[72] F.A. Cabezas-Opazo, K. Vergara-Pulgar, M.J. Pérez, C. Jara, C. Osorio-Fuentealba, R.A. Quintanilla, Mitochondrial dysfunction contributes to the pathogenesis of Alzheimer's disease, Oxidative Med. Cell. Longev. 509654 (2015), https://doi.org/10.1155/2015/509654.
[73] Z. Li, K. Okamoto, Y. Hayashi, M. Sheng, The importance of dendritic mitochondria in the morphogenesis and plasticity of spines and synapses, Cell 119 (2004) 873–887, https://doi.org/10.1016/j.cell.2004.11.003.
[74] M. Vos, E. Lauwers, P. Verstreken, Synaptic mitochondria in synaptic transmission and organization of vesicle pools in health and disease, Front. Synaptic Neurosci. 2 (2010) 139, https://doi.org/10.3389/fnsyn.2010.00139.
[75] Q. Cai, P. Tammineni, Mitochondrial aspects of synaptic dysfunction in Alzheimer's disease, J. Alzheimers Dis. 57 (2017) 1087–1103, https://doi.org/10.3233/JAD-160726.
[76] A.M. Pooler, W. Noble, D.P. Hanger, A role for tau at the synapse in Alzheimer's disease pathogenesis, Neuropharmacology 76 (2014) 1–8, https://doi.org/10.1016/j.neuropharm.2013.09.018.
[77] P.H. Reddy, Abnormal tau, mitochondrial dysfunction, impaired axonal transport of mitochondria, and synaptic deprivation in Alzheimer's disease, Brain Res. 1415 (2011) 136–148, https://doi.org/10.1016/j.brainres.2011.07.052.
[78] N. Canu, L. Dus, C. Barbato, M.T. Ciotti, C. Brancolini, A.M. Rinaldi, M. Novak, A. Cattaneo, A. Bradbury, P. Calissano, Tau cleavage and dephosphorylation in cerebellar granule neurons undergoing apoptosis, J. Neurosci. 18 (1998) 7061–7074.
[79] V. Corsetti, G. Amadoro, A. Gentile, S. Capsoni, M.T. Ciotti, M.T. Cencioni, A. Atlante, N. Canu, T.T. Rohn, A. Cattaneo, P. Calissano, Identification of a caspase-derived N-terminal tau fragment in cellular and animal Alzheimer's disease models, Mol. Cell. Neurosci. 38 (2008) 381–392, https://doi.org/10.1016/j.mcn.2008.03.011.
[80] S. Capsoni, G. Ugolini, A. Comparini, F. Ruberti, N. Berardi, A. Cattaneo, Alzheimer-like neurodegeneration in aged antinerve growth factor transgenic mice, Proc. Natl. Acad. Sci. U. S. A. 97 (2000) 6826–6831.
[81] S. Capsoni, S. Giannotta, A. Cattaneo, Nerve growth factor and galantamine ameliorate early signs of neurodegeneration in anti-nerve growth factor mice, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 12432–12437, https://doi.org/10.1073/pnas.192442999.
[82] S. Capsoni, S. Giannotta, A. Cattaneo, Beta-amyloid plaques in a model for sporadic Alzheimer's disease based on transgenic anti-nerve growth factor antibodies, Mol. Cell. Neurosci. 21 (2002) 15–28.
[83] T.T. Rohn, V. Vyas, T. Hernandez-Estrada, K.E. Nichol, L.A. Christie, E. Head, Lack of pathology in a triple transgenic mouse model of Alzheimer's disease after overexpression of the anti-apoptotic protein Bcl-2, J. Neurosci. 28 (2008) 3051–3059, https://doi.org/10.1523/JNEUROSCI.5620-07.2008.
[84] A.K. Raina, X. Zhu, S. Shimohama, G. Perry, M.A. Smith, Tipping the apoptotic balance in Alzheimer's disease: the abortosis concept, Cell Biochem. Biophys. 39 (2003) 249–255, https://doi.org/10.1385/CBB:39:3:249.
[85] P. Calissano, C. Matrone, G. Amadoro, Apoptosis and in vitro Alzheimer disease neuronal models, Commun. Integr. Biol. 2 (2009) 163–169.
[86] M. Obulesu, M.J. Lakshmi, Apoptosis in Alzheimer's disease: an understanding of the physiology, pathology and therapeutic avenues, Neurochem. Res. 39 (2014) 2301–2312, https://doi.org/10.1007/s11064-014-1454-4.
[87] H.C. Hunsberger, C.C. Rudy, S.R. Batten, G.A. Gerhardt, M.N. Reed, P301L tau expression affects glutamate release and clearance in the hippocampal trisynaptic pathway, J. Neurochem. 132 (2015) 169–182, https://doi.org/10.1111/jnc.12967.
[88] J.M. Decker, L. Kruger, A. Sydow, F. Dennissen, Z. Siskova, E. Mandelkow, E.M. Mandelkow, The tau/A152T mutation, a risk factor for frontotemporal-spectrum disorders, leads to NR2B receptor-mediated excitotoxicity, EMBO Rep. 17 (2016) 552–569, https://doi.org/10.15252/embr.201541439.
[89] E.D. Roberson, B. Halabisky, J.W. Yoo, J. Yao, J. Chin, F. Yan, T. Wu, P. Hamto, N. Devidze, G.Q. Yu, J.J. Palop, J.L. Noebels, L. Mucke, Amyloid-β/Fyn-induced synaptic, network, and cognitive impairments depend on tau levels in multiple mouse models of Alzheimer's disease, J. Neurosci. 31 (2011) 700–711, doi: https://doi.org/10.1523/JNEUROSCI.4152-10.2011.
[90] G. Amadoro, A.L. Serafino, C. Barbato, M.T. Ciotti, A. Sacco, P. Calissano, N. Canu, Role of N-terminal tau domain integrity on the survival of cerebellar granule neurons, Cell Death Differ. 11 (2004) 217–230, https://doi.org/10.1038/sj.cdd.4401314.
[91] G. Amadoro, M.T. Ciotti, M. Costanzi, V. Cestari, P. Calissano, N. Canu, NMDA receptor mediates tau-induced neurotoxicity by calpain and ERK/MAPK

activation, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 2892–2897, https://doi.org/10.1073/pnas.0511065103.
[92] A. Atlante, G. Amadoro, A. Bobba, L. de Bari, V. Corsetti, G. Pappalardo, E. Marra, P. Calissano, S. Passarella, A peptide containing residues 26-44 of tau protein impairs mitochondrial oxidative phosphorylation acting at the level of the adenine nucleotide translocator, Biochim. Biophys. Acta 1777 (2008) 1289–1300, https://doi.org/10.1016/j.bbabio.2008.07.004.
[93] A. Bobba, G. Amadoro, V.A. Petragallo, P. Calissano, A. Atlante, Dissecting the molecular mechanism by which NH2htau and Aβ1-42 peptides impair mitochondrial ANT-1 in Alzheimer disease, Biochim. Biophys. Acta 1827 (2013) 848–860, https://doi.org/10.1016/j.bbabio.2013.04.001.
[94] G. Amadoro, V. Corsetti, A. Stringaro, M. Colone, S. D'Aguanno, G. Meli, M. Ciotti, G. Sancesario, A. Cattaneo, R. Bussani, D. Mercanti, P. Calissano, A NH2 tau fragment targets neuronal mitochondria at AD synapses: possible implications for neurodegeneration, J. Alzheimers Dis. 21 (2010) 445–470, doi: https://doi.org/10.3233/JAD-2010-100120.
[95] G. Amadoro, V. Corsetti, F. Florenzano, A. Atlante, M.T. Ciotti, M.P. Mongiardi, R. Bussani, V. Nicolin, S.L. Nori, M. Campanella, P. Calissano, AD-linked, toxic NH2 human tau affects the quality control of mitochondria in neurons, Neurobiol. Dis. 62 (2014b) 489–507, Corrigendum in Neurobiol. Dis. 74C (2014b) 102–103, doi: 10.1016/j.nbd.2013.10.018.
[96] V. Corsetti, F. Florenzano, A. Atlante, A. Bobba, M.T. Ciotti, F. Natale, F. Della Valle, A. Borreca, A. Manca, G. Meli, C. Ferraina, M. Feligioni, S. D'Aguanno, R. Bussani, M. Ammassari-Teule, V. Nicolin, P. Calissano, G. Amadoro, NH2-truncated human tau induces deregulated mitophagy in neurons by aberrant recruitment of Parkin and UCHL-1: implications in Alzheimer's disease, Hum. Mol. Genet. 24 (2015) 3058–3081, https://doi.org/10.1093/hmg/ddv059.
[97] D.A. Di Monte, I. Tokar, J.W. Langston, Impaired glutamate clearance as a consequence of energy failure caused by MPP(+) in astrocytic cultures, Toxicol. Appl. Pharmacol. 158 (1999) 296–302, https://doi.org/10.1006/taap.1999.8717.
[98] S. Hauptmann, I. Scherping, S. Drose, U. Brandt, K.L. Schulz, M. Jendrach, K. Leuner, A. Eckert, W.E. Müller, Mitochondrial dysfunction: an early event in Alzheimer pathology accumulates with age in AD transgenic mice, Neurobiol. Aging 30 (2009) 1574–1586, https://doi.org/10.1016/j.neurobiolaging.2007.12.005.
[99] V. Rhein, X. Song, A. Wiesner, L.M. Ittner, G. Baysang, F. Meier, L. Ozmen, H. Bluethmann, S. Dröse, U. Brandt, E. Savaskan, C. Czech, J. Götz, A. Eckert, Amyloid-beta and tau synergistically impair the oxidative phosphorylation system in triple transgenic Alzheimer's disease mice, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 20057–20062, https://doi.org/10.1073/pnas.0905529106.
[100] M. Balietti, B. Giorgetti, T. Casoli, M. Solazzi, F. Tamagnini, C. Burattini, G. Aicardi, P. Fattoretti, Early selective vulnerability of synapses and synaptic mitochondria in the hippocampal CA1 region of the Tg2576 mouse model of Alzheimer's disease, J. Alzheimers Dis. 34 (2013) 887–896, https://doi.org/10.3233/JAD-121711.
[101] E.K. Pickett, J. Rose, C. McCrory, C.A. McKenzie, D. King, C. Smith, T.H. Gillingwater, C.M. Henstridge, T.L. Spires-Jones, Region-specific depletion of synaptic mitochondria in the brains of patients with Alzheimer's disease, Acta Neuropathol. 136 (2018) 747–757, https://doi.org/10.1007/s00401-018-1903-2.
[102] J.P. Blass, Cerebrometabolic abnormalities in Alzheimer's disease, Neurol. Res. 25 (2003) 556–566, https://doi.org/10.1179/016164103101201995.
[103] P.H. Reddy, R. Tripathi, Q. Troung, K. Tirumala, T.P. Reddy, V. Anekonda, U.P. Shirendeb, M.J. Calkins, A.P. Reddy, P. Mao, M. Manczak, Abnormal mitochondrial dynamics and synaptic degeneration as early events in Alzheimer's disease: implications to mitochondria-targeted antioxidant therapeutics, Biochim. Biophys. Acta 1822 (2012) 639–649, https://doi.org/10.1016/j.bbadis.2011.10.011.
[104] L. Guo, J. Tian, H. Du, Mitochondrial dysfunction and synaptic transmission failure in Alzheimer's disease, J. Alzheimers Dis. 57 (2017) 1071–1086, https://doi.org/10.3233/JAD-160702.
[105] J. Reifert, D. Hartung-Cranston, S.C. Feinstein, Amyloid beta-mediated cell death of cultured hippocampal neurons reveals extensive tau fragmentation without increased full-length tau phosphorylation, J. Biol. Chem. 286 (2011) 20797–20811, https://doi.org/10.1074/jbc.M111.234674.
[106] Y.H. Chong, Y.J. Shin, E.O. Lee, R. Kayed, C.G. Glabe, A.J. Tenner, ERK1/2 activation mediates Abeta oligomer-induced neurotoxicity via caspase-3 activation and tau cleavage in rat organotypic hippocampal slice cultures, J. Biol. Chem. 281 (2006) 20315–20325, https://doi.org/10.1074/jbc.M601016200.
[107] D. Baglietto-Vargas, M. Kitazawa, E.J. Le, T. Estrada-Hernandez, C.J. Rodriguez-Ortiz, R. Medeiros, K.N. Green, F.M. LaFerla, Endogenous murine tau promotes neurofibrillary tangles in 3xTg-AD mice without affecting cognition, Neurobiol. Dis. 62 (2014) 407–415, https://doi.org/10.1016/j.nbd.2013.10.019.
[108] A. Pristerà, D. Saraulli, S. Farioli-Vecchioli, G. Strimpakos, M. Costanzi, M.G. di Certo, S. Cannas, M.T. Ciotti, F. Tirone, E. Mattei, V. Cestari, N. Canu, Impact of N-tau on adult hippocampal neurogenesis, anxiety, and memory, Neurobiol. Aging 34 (2013) 2551–2563, https://doi.org/10.1016/j.neurobiolaging.2013.05.010.
[109] A.E. Lang, D.N. Riherd Methner, A. Ferreira, Neuronal degeneration, synaptic defects, and behavioral abnormalities in tau_{45-230} transgenic mice, Neuroscience 275 (2014) 322–339, https://doi.org/10.1016/j.neuroscience.2014.06.017.
[110] K. Yamada, Extracellular tau and its potential role in the propagation of tau pathology, Front. Neurosci. 11 (2017) 667, https://doi.org/10.3389/fnins.2017.00667.
[111] C.M. Karch, A.T. Jeng, A.M. Goate, Calcium phosphatase calcineurin influences tau metabolism, Neurobiol. Aging 34 (2013) 374–386, https://doi.org/10.1016/j.neurobiolaging.2012.05.003.
[112] A.M. Pooler, E.C. Phillips, D.H. Lau, W. Noble, D.P. Hanger, Physiological release of endogenous tau is stimulated by neuronal activity, EMBO Rep. 14 (2013) 389–394, https://doi.org/10.1038/embor.2013.15.
[113] D. Kanmert, A. Cantlon, C.R. Muratore, M. Jin, T.T. O'Malley, G. Lee, T.L. Young-Pearse, D.J. Selkoe, D.M. Walsh, C-terminally truncated forms of tau, but not full-length tau or its C-terminal fragments, are released from neurons independently of cell death, J. Neurosci. 35 (2015) 10851–10865, https://doi.org/10.1523/JNEUROSCI.0387-15.2015.
[114] X. Chai, J.L. Dage, M. Citron, Constitutive secretion of tau protein by an unconventional mechanism, Neurobiol. Dis. 48 (2012) 356–366, https://doi.org/10.1016/j.nbd.2012.05.021.
[115] T. Katsinelos, M. Zeitler, E. Dimou, A. Karakatsani, H.M. Müller, E. Nachman, J.P. Steringer, C. Ruiz de Almodovar, W. Nickel, T.R. Jahn, Unconventional secretion mediates the trans-cellular spreading of tau, Cell Rep. 23 (2018) 2039–2055, https://doi.org/10.1016/j.celrep.2018.04.056.
[116] C.M. Karch, A.T. Jeng, A.M. Goate, Extracellular tau levels are influenced by variability in tau that is associated with tauopathies, J. Biol. Chem. 287 (2012) 42751–42762, https://doi.org/10.1074/jbc.M112.380642.
[117] N.W. Hu, G.T. Corbett, S. Moore, I. Klyubin, T.T. O'Malley, D.M. Walsh, F.J. Livesey, M.J. Rowan, Extracellular forms of Aβ and tau from iPSC models of Alzheimer's disease disrupt synaptic plasticity, Cell Rep. 23 (2018) 1932–1938, https://doi.org/10.1016/j.celrep.2018.04.040.
[118] K. Yamada, J.R. Cirrito, F.R. Stewart, H. Jiang, M.B. Finn, B.B. Holmes, L.I. Binder, E.M. Mandelkow, M.I. Diamond, V.M. Lee, D.M. Holtzman, In vivo microdialysis reveals age-dependent decrease of brain interstitial fluid tau levels in P301S human tau transgenic mice, J. Neurosci. 31 (2011) 13110–13117, https://doi.org/10.1523/JNEUROSCI.2569-11.2011.
[119] S. Magnoni, T.J. Esparza, V. Conte, M. Carbonara, G. Carrabba, D.M. Holtzman, G.J. Zipfel, N. Stocchetti, D.L. Brody, Tau elevations in the brain extracellular space correlate with reduced amyloid-β levels and predict adverse clinical outcomes after severe traumatic brain injury, Brain 135 (2012) 1268–1280, https://doi.org/10.1093/brain/awr286.
[120] M. Novak, R. Jakes, P.C. Edwards, C. Milstein, C.M. Wischik, Difference between the tau protein of Alzheimer paired helical filament core and normal tau revealed by epitope analysis of monoclonal antibodies 423 and 7.51, Proc. Natl. Acad. Sci. U.S.A. 88 (1991) 5837–5841.
[121] Y. Zhou, J. Shi, D. Chu, W. Hu, Z. Guan, C.X. Gong, K. Iqbal, F. Liu, Relevance of phosphorylation and truncation of tau to the etiopathogenesis of Alzheimer's disease, Front. Aging Neurosci. 10 (2018) 27, https://doi.org/10.3389/fnagi.2018.00027.
[122] G.V. Johnson, P. Seubert, T.M. Cox, R. Motter, J.P. Brown, D. Galasko, The tau protein in human cerebrospinal fluid in Alzheimer's disease consists of proteolytically derived fragments, J. Neurochem. 68 (1997) 430–433.
[123] E. Portelius, S.F. Hansson, A.J. Tran, H. Zetterberg, P. Grognet, E. Vanmechelen, K. Höglund, G. Brinkmalm, A. Westman-Brinkmalm, E. Nordhoff, K. Blennow, J. Gobom, Characterization of tau in cerebrospinal fluid using mass spectrometry, J. Proteome Res. 7 (2008) 2114–2120, https://doi.org/10.1021/pr7008669.
[124] D. Wagshal, S. Sankaranarayanan, V. Guss, T. Hall, F. Berisha, I. Lobach, A. Karydas, L. Voltarelli, C. Scherling, H. Heuer, M.C. Tartaglia, Z. Miller, G. Coppola, M. Ahlijanian, H. Soares, J.H. Kramer, G.D. Rabinovici, H.J. Rosen, B.L. Miller, J. Meredith, A.L. Boxer, Divergent CSF tau alterations in two common tauopathies: Alzheimer's disease and progressive supranuclear palsy, J. Neurol. Neurosurg. Psychiatry 86 (2015) 244–250, https://doi.org/10.1136/jnnp-2014-308004.
[125] Z. Chen, D. Mengel, A. Keshavan, R.A. Rissman, A. Billinton, M. Perkinton, J. Percival-Alwyn, A. Schultz, M. Properzi, K. Johnson, D.J. Selkoe, R.A. Sperling, P. Patel, H. Zetterberg, D. Galasko, J.M. Schott, D.M. Walsh, Learnings about the complexity of extracellular tau aid development of a blood-based screen for Alzheimer's disease, Alzheimers Dement. (2018) pii: S1552–5260(18)33561–1, doi: https://doi.org/10.1016/j.jalz.2018.09.010.
[126] C. Sato, N.R. Barthélemy, K.G. Mawuenyega, B.W. Patterson, B.A. Gordon, J. Jockel-Balsarotti, M. Sullivan, M.J. Crisp, T. Kasten, K.M. Kirmess, N.M. Kanaan, K.E. Yarasheski, A. Baker-Nigh, T.L.S. Benzinger, T.M. Miller, C.M. Karch, R.J. Bateman, Tau kinetics in neurons and the human central nervous system, Neuron 97 (2018) 1284–1298.e7, doi: https://doi.org/10.1016/j.neuron.2018.02.015.
[127] S. Sokolow, K.M. Henkins, T. Bilousova, B. Gonzalez, H.V. Vinters, C.A. Miller, L. Cornwell, W.W. Poon, K.H. Gylys, Pre-synaptic C-terminal truncated tau is released from cortical synapses in Alzheimer's disease, J. Neurochem. 133 (2015) 368–379, https://doi.org/10.1111/jnc.12991.
[128] A. Borreca, V. Latina, V. Corsetti, S. Middei, S. Piccinin, F. Della Valle, R. Bussani, M. Ammassari-Teule, R. Nisticò, P. Calissano, G. Amadoro, AD-related N-terminal truncated tau is sufficient to recapitulate in vivo the early perturbations of human neuropathology: implications for immunotherapy, Mol. Neurobiol. 55 (2018) 8124–8153, https://doi.org/10.1007/s12035-018-0974-3.
[129] F. Florenzano, C. Veronica, G. Ciasca, M.T. Ciotti, A. Pittaluga, G. Olivero, M. Feligioni, F. Iannuzzi, V. Latina, M.F.M. Sciacca, A. Sinopoli, D. Milardi, G. Pappalardo, M. De Spirito, M. Papi, A. Atlante, A. Bobba, A. Borreca, P. Calissano, G. Amadoro, Extracellular truncated tau causes early presynaptic dysfunction associated with Alzheimer's disease and other tauopathies, Oncotarget 8 (2017) 64745–64778, https://doi.org/10.18632/oncotarget.17371.
[130] K. Yanamandra, N. Kfoury, H. Jiang, T.E. Mahan, S. Ma, S.E. Maloney, D.F. Wozniak, M.I. Diamond, D.M. Holtzman, Anti-tau antibodies that block tau aggregate seeding in vitro markedly decrease pathology and improve cognition in vivo, Neuron 80 (2013) 402–414, https://doi.org/10.1016/j.neuron.2013.07.046.
[131] K. Yanamandra, H. Jiang, T.E. Mahan, S.E. Maloney, D.F. Wozniak, M.I. Diamond, D.M. Holtzman, Anti-tau antibody reduces insoluble tau and decreases brain atrophy, Ann. Clin. Transl. Neurol. 2 (2015) 278–288, https://doi.org/10.1002/

acn3.176.
[132] C.L. Dai, X. Chen, S.F. Kazim, F. Liu, C.X. Gong, I. Grundke-Iqbal, K. Iqbal, Passive immunization targeting the N-terminal projection domain of tau decreases tau pathology and improves cognition in a transgenic mouse model of Alzheimer disease and tauopathies, J. Neural Transm. (Vienna) 122 (2015) 607–617, https://doi.org/10.1007/s00702-014-1315-y.
[133] C.L. Dai, W. Hu, Y.C. Tung, F. Liu, C.X. Gong, K. Iqbal, Tau passive immunization blocks seeding and spread of Alzheimer hyperphosphorylated tau-induced pathology in 3 × Tg-AD mice, Alzheimers Res. Ther. 10 (2018) 13, https://doi.org/10.1186/s13195-018-0341-7.
[134] S. Subramanian, G. Savanur, S. Madhavadas, Passive immunization targeting the N-terminal region of phosphorylated tau (residues 68-71) improves spatial memory in okadaic acid induced tauopathy model rats, Biochem. Biophys. Res. Commun. 483 (2017) 585–589, https://doi.org/10.1016/j.bbrc.2016.12.101.
[135] R. Brandt, J. Léger, G. Lee, Interaction of tau with the neural plasma membrane mediated by tau's amino-terminal projection domain, J. Cell, Biol. 131 (1995) 1327–1340.
[136] A. Ittner, L.M. Ittner, Dendritic tau in Alzheimer's disease, Neuron 99 (2018) 13–27, https://doi.org/10.1016/j.neuron.2018.06.003.
[137] C.L. Sayas, M. Medina, R. Cuadros, I. Ollá, E. García, M. Pérez, I. Ferrer, F. Hernández, J. Avila, Role of tau N-terminal motif in the secretion of human tau by end binding proteins, PLoS One 14 (2019) e0210864, , https://doi.org/10.1371/journal.pone.0210864.
[138] H.E. Feinstein, S.J. Benbow, N.E. LaPointe, N. Patel, S. Ramachandran, T.D. Do, M.R. Gaylord, N.E. Huskey, N. Dressler, M. Korff, B. Quon, K.L. Cantrell, M.T. Bowers, R. Lal, S.C. Feinstein, Oligomerization of the microtubule-associated protein tau is mediated by its N-terminal sequences: implications for normal and pathological tau action, J. Neurochem. 137 (2016) 939–954, https://doi.org/10.1111/jnc.13604.
[139] T.T. Rohn, R.A. Rissman, M.C. Davis, Y.E. Kim, C.W. Cotman, E. Head, Caspase-9 activation and caspase cleavage of tau in the Alzheimer's disease brain, Neurobiol. Dis. 11 (2002) 341–354.
[140] L.C. Walker, M. Jucker, The exceptional vulnerability of humans to Alzheimer's disease, Trends Mol. Med. 23 (2017) 534–545, https://doi.org/10.1016/j.molmed.2017.04.001.
[141] M.L. Selenica, H. Davtyan, S.B. Housley, L.J. Blair, A. Gillies, B.A. Nordhues, B. Zhang, J. Liu, J.E. Gestwicki, D.C. Lee, M.N. Gordon, D. Morgan, C.A. Dickey, Epitope analysis following active immunization with tau proteins reveals immunogens implicated in tau pathogenesis, J. Neuroinflammation 11 (2014) 152, https://doi.org/10.1186/s12974-014-0152-0.
[142] K. Stefanoska, A. Volkerling, J. Bertz, A. Poljak, Y.D. Ke, L.M. Ittner, M.A. Ittner, An N-terminal motif unique to primate tau enables differential protein-protein interactions, J. Biol. Chem. 293 (2018) 3710–3719, https://doi.org/10.1074/jbc.RA118.001784.
[143] F.M. LaFerla, K.N. Green, Animal models of Alzheimer disease, Cold Spring Harb Perspect Med. 2 (2012), pii: a006320. doi: https://doi.org/10.1101/cshperspect.a006320.
[144] R.S. Desikan, L.K. McEvoy, W.K. Thompson, D. Holland, J.B. Brewer, P.S. Aisen, R.A. Sperling, A.M. Dale, Alzheimer's disease neuroimaging initiative. Amyloid-β–associated clinical decline occurs only in the presence of elevated P-tau, Arch. Neurol. 69 (2012) 709–713, https://doi.org/10.1001/archneurol.2011.3354.
[145] M. Pievani, W. de Haan, T. Wu, W.W. Seeley, G.B. Frisoni, Functional network disruption in the degenerative dementias, Lancet Neurol. 10 (2011) 829–843, https://doi.org/10.1016/S1474-4422(11)70158-2.
[146] H.K. Ashe, K.R. Zahs, Probing the biology of Alzheimer's disease in mice, Neuron 66 (2010) 631–645, https://doi.org/10.1016/j.neuron.2010.04.031.
[147] E. Giacobini, G. Gold, Alzheimer disease therapy–moving from amyloid-β to tau, Nat. Rev. Neurol. 9 (2013) 677–686, https://doi.org/10.1038/nrneurol.2013.223.
[148] X.Q. Chen, W.C. Mobley, Alzheimer disease pathogenesis: insights from molecular and cellular biology studies of oligomeric Aβ and tau species, Front Neurosci. 21 (2019) 13:659, doi: https://doi.org/10.3389/fnins.2019.00659.