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Connecting the dots between tau dysfunction and neurodegeneration

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Tauopathies are devastating and ultimately fatal neurodegenerative diseases, which are histopathologically defined by insoluble filamentous deposits of abnormally phosphorylated tau protein within neurons and glia. Identifying the causes of abnormal tau phosphorylation and subsequent aggregation has been the focus of much research, and is currently a major target for the development of therapeutic interventions for tauopathies, including Alzheimer's disease (AD). Much has recently been learned about the sequence of events that lead from tau dysfunction to neuronal death. This review focuses on the cascade of events that are catalyzed by pathological tau, and highlights current and potential therapeutic strategies to target this pathway.

Involvement of tau in neurodegenerative diseases

In 1907, Alois Alzheimer first described neurofibrillary tangles [1], which are now known to be a key pathological feature of a number of neurodegenerative diseases. Eight decades later the major component of neurofibrillary tangles was identified, a hyperphosphorylated, filamentous form of the tau protein [2]. The subsequent discovery of a group of inherited tauopathies, termed frontotemporal dementia with parkinsnism associated with chromosome 17 (FTDP-17), that are caused by dominant mutations in the tau gene (*MAPT*) [3–5], unequivocally demonstrated that tau dysfunction can drive neurodegeneration.

Current treatments for AD, the most common tauopathy, are solely symptomatic. Given the close association between tau pathology and severity of disease, together with evidence that tau acts downstream of amyloid β (Aβ) to induce neuronal death [6,7], it has become increasingly recognized that tau-based therapies may be effective in treating AD – with the added benefit of also applying to other comparatively rarer tauopathies. Current strategies include decreasing tau aggregation, blocking abnormal tau phosphorylation, or stopping the spread of tau pathology through the brain (Table 1). These targets have been reviewed elsewhere [8,9]. We instead highlight recent work that provides significant insight into the mechanisms downstream of tau dysfunction that promote neuronal death. The genetic players in this pathway represent potentially untapped targets for therapeutic intervention.

Mechanisms of tau neurotoxicity

The aggregation of misfolded tau protein, the autosomal dominant inheritance pattern in familial tauopathies [3–5], and the lack of an obvious neurodegenerative phenotype in tau knockout animal models [10], suggests a dominant gain of function pathogenic mechanism. Accordingly, transgenic expression of human wild type or mutant tau causes progressive neuronal death in various animal models of tauopathy [11,12]. These models have enabled identification and characterization of key cellular processes that promote apoptosis in tauopathy, including synapse loss, impaired axonal transport, overstabilization of filamentous actin, mitochondrial dysfunction, oxidative stress, DNA damage, epigenetic changes, and aberrant cell cycle activation in postmitotic neurons (Figure 1). We describe in further detail the evidence that supports a role for each of these processes in tauopathy.

Unplugged – synapse loss in tauopathy

Synapse loss can be elicited either by the failure of neurons to maintain functional axons and dendrites, or by neuronal death [13]. In AD, with its slow progression, many studies indicate that synapse loss precedes neuronal loss by several decades. Not only does the initial decrease in synapse number and density seem to be disproportionate to the loss of neuronal cell bodies, suggesting that pruning of synaptic endings precedes neuronal loss [14], but synapse loss also appears to be an early event in pathogenesis – as shown in patients with mild cognitive impairment and early AD [15–17].

Soluble, extracellular species of Aβ are capable of triggering both acute neuronal death and synaptic dysfunction [18]. Whereas in a pathocascade Aβ has been placed upstream of tau [7], the toxic effects of Aβ depend at least in part on soluble, cytoplasmic tau, as shown by crossing Aβ plaque-forming mice onto a tau knockout background [6,19]. Here, reducing tau levels was sufficient to improve or even rescue fully the features that characterize mice with Aβ deposition, including reduced lifespan, memory impairment, and susceptibility to experimentally induced excitotoxic seizures. Importantly, these improvements occurred in the absence of any changes to Aβ levels or plaque load. A recent study in transgenic mice overexpressing mutant forms of human amyloid precursor protein (APP)

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Table 1. Mechanisms of tau-induced toxicity that are current and potential targets for therapeutic intervention

Mechanism	Potential targets[a]	Drug effort
Tau hyperphosphorylation/ misfolding	PAR-1[b] GSK-3β[b] HSPs[b]	Lithium[c] Methylene blue[c] Tideglusib[d] Nicotinomide[d] Valproic acid[d] LMT-X[d] Sodium selenate[d] Compound A[b] Thiamet-G[b] SNR-003-556[b]
Tau spread	HSPGs	MC1 antibody[b] PHF1 antibody[b]
Synapse loss	STEP NMDAR Fyn	MEM 1003[c] Neramexane[c] Sabeluzole[c]
Microtubule destabilization		AL-108[c] Epothilone D[d] TPI-287[d] AL-208[d] Paclitaxel[b]
Impaired axonal transport	JIP1 KLC1/2 DIC	
Actin stabilization	CFL2[b] GSN[b] ACTB[b]	
Mitochondrial dysfunction/oxidative stress	DRP1[b] MFN2[b] OPA1[b] Complex V PRDX2[b] SOD2[b] REST	Lithium[c] ALCAR[c] Idebenone[c] Propentofylline[c] AC-1204[d] α-Tocopherol[d] Resveratrol[d] Curcumin[d] NSAIDs[b]
DNA damage	p53[b] MDM4 ART	
Heterochromatin relaxation/aberrant gene expression	BPTF[b] PPA2[b] PIWIL1[b] ASH1L[b] SFPQ	
Cell cycle activation	CDK1[b] TSC2[b] RBL2[b] Rb	Olomoucine[b] Rapamycin[b]

[a]Proteins selected as potential therapeutic targets are those discussed in the text and/or whose genetic manipulation suppresses aspects of tau toxicity, and do not represent the entirety of proteins implicated in tauopathy. For proteins that were identified as dysfunctional in animal models of tauopathy, the human homolog is listed in the table. Information about clinical trials was obtained from http://www.clinicaltrials.gov.

[b]Drug or protein whose genetic manipulation suppresses aspects of tau toxicity in animal models.

[c]Discontinued clinical trial.

[d]Clinical trial.

and presenilin-1 (PSEN1) even suggests a feedback mechanism with tau also regulating Aβ because, in addition to protecting from neuronal and synaptic loss, removing tau resulted in a lower plaque load [20]. With evidence increasing that spontaneous seizures have a role in the pathogenesis of AD, interestingly, tau reduction is also capable of preventing spontaneous epileptiform activity in multiple lines of Aβ plaque-forming mice, as shown by electroencephalography (EEG) recordings [21].

How do Aβ and tau interact in the spine? In mediating Aβ toxicity via tau, the Src kinase Fyn has a crucial role. Tau is necessary to target Fyn to the spine where Fyn mediates the downstream toxicity of Aβ by directly or indirectly overactivating cellular receptors such as the NMDA-type glutamate receptor [19] (Figure 1). Aβ further causes a mis-sorting of tau into dendrites as well as a loss of spines [22]. A time-resolved model for how Aβ, via Fyn, ultimately causes neuronal demise, posits that Aβ in a first step activates Fyn, causing downstream excitotoxicity, and that Aβ later in disease activates striatal-enriched protein tyrosine phosphatase (STEP), a Fyn-phosphatase that eventually inactivates Fyn, leading to the loss of synapses [23]. Whether this inactivation of Fyn then results in the reduction of tau in the spine remains to be determined.

Although tau is traditionally perceived as an axonal protein, with a somatodendritic relocalization characterizing AD and related tauopathies, under physiological conditions tau is localized – albeit at lower levels as known for the axon – to the dendritic compartment including spines [19]. This localization is tightly regulated. Both depolarization and the induction of long-term potentiation (LTP) target tau to the spine, as does exposure to Aβ; however, depending on the type of trigger tau seems to be specifically phosphorylated, and manipulating these phosphorylation sites abrogates the localization of tau to spines [24]. Together these studies present tau as a scaffolding protein with diverse functions in a physiological and pathological context, many of which await elucidation. More research into the cellular role of distinct phospho-species of tau is needed, as well as the role of tau's many isoforms.

Derailed – impaired axonal transport in tauopathy

Concerning the axonal transport of tau, there are two important questions in the field. One relates to how tau is actually transported, and the second how pathologically elevated tau (which is inevitably hyperphosphorylated) impairs axonal transport. Both processes are highly interrelated.

Several models have been presented to understand tau transport: motor protein-dependent cotransport with microtubule fragments, diffusion, and kinesin-driven transport that is tau phosphorylation-dependent [25]. Recent studies suggest that tau diffuses along the microtubule lattice, a behavior also adopted by non-microtubule-associated proteins such as antibodies [26]. It was further found that about half of the tau molecules on microtubules are in fact not stationary but instead move bidirectionally along these microtubules. By using a range of tau concentrations it was suggested that tau molecules that diffuse along the length of a microtubule do not block each other but instead pass each other, either because they are bound