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A Brief Overview of Tauopathy: Causes, Consequences, and Therapeutic Strategies

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Abstract

There are currently no disease-modifying therapies for the treatment of tauopathies, a group of progressive neurodegenerative disorders that are pathologically defined by the presence of tau protein aggregates in the brain. Current challenges for the treatment of tauopathy include the inability to diagnose early and to confidently discriminate between distinct tauopathies in patients, alongside an incomplete understanding of the cellular mechanisms involved in pathogenic tau-induced neuronal death and dysfunction. In this review, we describe current diagnostic and therapeutic strategies, known drivers of pathogenic tau formation, recent contributions to our current mechanistic understanding of how pathogenic tau induces neuronal death, and potential diagnostic and therapeutic approaches.

Keywords

tauopathy; tau; neurodegeneration; Alzheimer's disease; traumatic brain injury; metabolic syndrome

Tau and Tauopathies

In 1975, Weingarten and colleagues identified a protein contaminant that co-purified with microtubules. Upon further investigation, this contaminant, now known as the “microtubule-associated protein tau,” or “tau,” was found to be critical for microtubule stability [1]. Later studies identified the tau protein as the major protein constituent of neurofibrillary tangles

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[2, 3], one of the two major pathological hallmarks of human Alzheimer's disease. Subsequent studies found that tau aggregates are the primary pathological feature of clinically heterogeneous neurodegenerative disorders that are now collectively termed “tauopathies.” Tauopathies, including but not limited to Alzheimer's disease, progressive supranuclear palsy, corticobasal syndrome, some frontotemporal dementias, and chronic traumatic encephalopathy, are progressive neurodegenerative disorders that are pathologically defined by tau-positive deposits in the brain.

Current Strategies for Diagnosis and Treatment

Diagnosis

Current clinical diagnosis of distinct tauopathies relies upon clinical history, including symptom onset, progression, and overall course. Though there are numerous neurodegenerative diseases with tau inclusions, clinical research is arguably most attentive to Alzheimer's disease, progressive supranuclear palsy, and corticobasal syndrome. Each clinical syndrome presents with a unique constellation of symptoms thought to represent anatomical regions of vulnerability. Patients with “prototypical” Alzheimer's disease experience an insidious pattern of forgetfulness as pathology builds in the hippocampus and entorhinal cortex [4]. Frequent falls and impaired ocular movements highlight pathology within subcortical structures, suggestive of progressive supranuclear palsy or corticobasal syndrome [4]. The earliest observed changes in cognition and/or behavior occur decades after pathophysiological changes. This extensive prodromal stage provides a wide window for potential therapeutic intervention.

Neuropsychological evaluation—Comprehensive neuropsychological evaluations are instrumental in detecting the earliest signs of neurodegenerative disease. These lengthy assessments evaluate aspects of cognition, behavior and movement, often utilizing demographically-adjusted norms. Distinct cognitive profiles are interpreted within the context of presenting symptoms and reported history, helping to distinguish among competing clinical syndromes. Typical Alzheimer's disease patients show impairments in memory, with rapid forgetting, some degree of anomia, poor visuoconstruction, and impaired category fluency, with preserved phonemic fluency [4]. Subcortical dementias reveal inefficient recall, but preserved recognition memory. Patients with progressive supranuclear palsy often have low letter-cued fluency, varying degrees of executive dysfunction, and difficulty with motorized sequences, while those with suspected corticobasal syndrome often present with asymmetric motor abnormalities and profound apraxia [5].

Neurological evaluation—In conjunction with neuropsychological findings, medical and neurological examination further inform diagnosis, as abnormalities, or the lack thereof, provide additional insight regarding suspected pathology. Axial rigidity, frequent falls, and disturbed eye movements all suggest supranuclear palsy, while asymmetric motor disturbance, alien limb syndrome, and ocular apraxia are associated with corticobasal syndrome [5]. Neurological exam for those with Alzheimer's disease remains largely normal until advanced stages.

Neuroimaging—Neuroimaging is useful for identifying tau-mediated changes in brain structure and function. Magnetic resonance imaging (MRI) captures structural changes of both gray and white matter, while positron emission tomography (PET) imaging utilizes a radioactive tracer measuring brain function [6]. On MRI, Alzheimer's disease patients have hippocampal and parietal atrophy [4]. Patients with progressive supranuclear palsy have notable atrophy of the midbrain, while those with corticobasal syndrome most reliably show changes of the basal ganglia and bilateral frontal lobes [5].

Treatment

Treatment of tau-related neurodegenerative syndromes is limited and largely symptomatic. Currently, there are two classes of medication approved for cognition: cholinesterase inhibitors and an N-methyl-D-aspartate (NMDA) receptor antagonist, each demonstrating modest effects [4] (Table 1). Motor symptoms may respond to dopaminergic regimens [5], speech therapy has shown some efficacy with aphasia syndromes, and physical therapy can prove helpful in prolonging motor function. Symptoms of apathy and depression are quite common and often respond to therapy or pharmacologic intervention, including selective serotonin reuptake inhibitors [5]. There are currently no disease-modifying therapies for tauopathies, including Alzheimer's disease.

Stimulators of Pathogenic Tau Formation

What is “pathogenic” tau?

The most well-described role for physiological tau is that of a microtubule-associated protein that binds to and stabilizes microtubules, particularly microtubules of neuronal axons [7]. In disease states, tau assumes a number of features, including A) Aberrant phosphorylation [8-10] and other posttranslational modifications [11], B) Truncation [2], and C) Aggregation into oligomers and larger insoluble filaments [7] (for a comprehensive review, see Arendt et. al [12]) (Figure 1). In this section, we will discuss stimulators of pathogenic tau formation other than amyloid β and α -synuclein, which have been reviewed extensively [13, 14][15].

Diagnostic potential—Significant research effort has been devoted to developing diagnostic tools based on detection of pathogenic tau in body fluids and brain. A recent meta-analysis analyzing thirty years of published biomarker data from patients with mild cognitive impairment and Alzheimer's disease indicates that levels of total tau (cerebrospinal fluid and plasma) and total phosphotau (plasma) are strongly associated with Alzheimer's disease and mild cognitive impairment due to Alzheimer's disease [16] (available in an interactive format at www.alzforum.org/alzbiomarker). Recently, a mass spectrometry-based assay called “FLEXITau” (Full-Length EXpressed stable Isotope-labeled Tau) was developed for unbiased quantification of post-translational tau modifications *in vitro* and *in vivo*. The FLEXITau technology allows a comprehensive view of the tau post-translational landscape, and has the potential to be adapted for diagnostic purposes [10]. PET-based imaging of pathogenic tau in living humans using 18F-AV-1451 [17, 18] has recently spurred a wealth of studies demonstrating a significant correlation between tau-positive PET, disease severity and post mortem histopathological data for Alzheimer's disease [18, 19].

Tau-based PET provides information regarding the anatomical distribution of pathogenic tau within the brain, which, with the development of better tau tracers, may eventually allow one to differentiate between non-Alzheimer's disease tauopathies. While initial costs and limited accessibility may hinder the use of tau-based imaging in most clinical settings, the use of tau PET in specialized dementia centers will likely transform disease identification, progression, and treatment.

Therapeutic potential—Therapeutic efforts focused on targeting any one of the aforementioned features of pathogenic tau have been recently reviewed [20], and include but are not limited to inhibitors of aberrant tau post-translational modifications, proteolytic processing, and aggregation. A strategy utilizing antisense oligonucleotides to reduce tau mRNA has recently been reported to decrease pathogenic tau, halt neuronal loss, and extend lifespan of mice transgenically expressing human tau harboring the disease-associated P301S mutation (PS19 mouse model), even when administered well after tau deposition [21]. While antisense oligonucleotides targeting tau must undergo further toxicological studies before entering human clinical trials, they were found to be well tolerated in cynomolgus monkeys, and significantly reduced tau mRNA and protein in the brain, spinal cord, and cerebrospinal fluid [21]. Encouragingly, antisense oligonucleotides targeting mutant survival motor neuron protein 1 recently received FDA approval for treatment of spinal muscular atrophy [22], a disease caused by degeneration of lower motor neurons.

Mutations in the tau gene

Mutations in the *microtubule-associated protein tau (MAPT)* gene have been identified in over 150 families with frontotemporal lobar degeneration (termed “FTLD-tau with *MAPT* mutation,” previously known as “FTDP-17”) [23-25]. Clinical manifestations of FTLD-tau with *MAPT* mutation are syndromes of disordered movement, behavioral and personality changes, and cognitive deterioration. Disease phenotypes, age of onset and severity can differ significantly among families with the same mutation, suggesting that other factors (genetic modifiers and/or environment) are likely involved. Of the 57 pathogenic *MAPT* mutations identified, most either occur within the microtubule binding domains or affect the number of microtubule binding domains present in the mature tau protein. Familial tauopathies are associated with aberrantly phosphorylated, inclusion-forming tau protein, clearly demonstrating that mutations in the *MAPT* gene are sufficient to induce formation of pathogenic tau [26].

Brain injury

Chronic traumatic encephalopathy, previously known as “dementia pugilistica,” is a progressive neurodegenerative tauopathy caused by multiple traumatic brain injuries. In humans, post mortem pathological tau staining [27], tau PET [28], and presence of pathogenic tau in plasma exosomes [29] demonstrate an association between chronic traumatic encephalopathy and tauopathy. The defining neuropathological feature of chronic traumatic encephalopathy, an irregular pattern of accumulation of aberrantly phosphorylated tau in neurons and astroglia around small blood vessels at sulcal depths, is distinct from Alzheimer's disease-related tauopathy [27]. In animal models, brain injury is sufficient to induce tau cleavage [30], acute and sustained aberrant tau phosphorylation and aggregation

[31, 32] and cis-trans isomerization of tau, termed “cistauosis” [33, 34]. In mice, traumatic brain injury-induced cistauosis occurs prior to overt tau oligomer or aggregate formation, disrupts axonal microtubule networks and mitochondrial transport, spreads to other neurons, and induces apoptosis [34]. Evidence supports several non-mutually exclusive mechanisms of traumatic brain injury-mediated stimulation of pathogenic tau formation. First, alkaline phosphatase, which dephosphorylates tau, decreases in response to brain injury in rats, causing accumulation of phosphotau [31]. Second, injury-induced severing of neuronal axons may cause tau to dissociate from microtubules, which could facilitate subsequent tau aggregation [35]. Third, the chronic inflammation that results from brain injuries likely exacerbates and sustains the acute tauopathy that occurs shortly after injury [36].

Tau-based PET indicates that the temporal neocortex of most individuals over the age of 65 contain pathogenic tau [37]. Curiously, the presence of pathogenic tau in this context, which is termed “Primary Age-Related Tauopathy” is not always associated with deficits in cognition. Basal ganglia and neocortical neurons of cynomolgus monkeys also exhibit an age-associated accumulation of tau deposits, suggesting that aging-associated tau accumulation may be a general feature of primate aging [38]. A current hypothesis posits that Primary Age-Related Tauopathy, while not a brain injury in the classical sense, is a result of the mild “wear and tear” on the brain that inevitably accumulates over a lifetime [39].

Diagnostic potential—Similar to findings in patients with frontotemporal dementia and Alzheimer's disease [40], a recent study reports higher levels of plasma-isolated exosomal tau in former professional American football players, a population especially vulnerable to chronic traumatic encephalopathy, versus controls [29]. These studies suggest that increased exosomal tau in plasma may be an indicator of tauopathy, but cannot currently be used as a diagnostic to discriminate between distinct tauopathies.

Therapeutic potential—Treating mice subject to a single severe traumatic brain injury with an antibody recognizing cis-phosphotau (cistau) prevents formation of tau oligomers and tangles, prevents cell-to-cell spread of pathogenic tau, reduces brain atrophy and restores long term potentiation [34]. Since cistauosis appears to be an early change in the course of both traumatic brain injury [34]- and Alzheimer's disease-associated tauopathy [33], detecting cistau may be useful for early diagnosis, and targeting cistau may be useful for prevention and therapeutic treatment of various tauopathies. In addition, therapeutic benefits of lithium [41], via inhibition of glycogen synthase kinase-3 β , and a peptide inhibitor (D-JNK1) of c-Jun N-terminal kinase [42], both of which are kinases associated with aberrant tau phosphorylation, have been reported in mouse models of traumatic brain injury.

Metabolic syndrome

Metabolic syndrome is a clinical diagnosis that includes obesity, hyperglycemia, hypertension and dyslipidemia. Affected individuals are at higher risk for developing more serious health conditions including diabetes and Alzheimer's disease [43]. Insulin resistance, a condition in which the body does not respond sufficiently to physiological levels of

insulin, is central to metabolic syndrome. Postmortem brains from patients with tauopathies including Alzheimer's disease, Pick's disease, corticobasal degeneration and progressive supranuclear palsy have increased levels of abnormally phosphorylated insulin receptor substrate 1, a marker of insulin resistance [44]. Within tauopathy brains, neurons with elevated levels of abnormally phosphorylated insulin receptor substrate 1 also harbor pathogenic tau, suggesting a link between impaired insulin signaling and pathogenic tau [44]. Genetic induction of type II diabetes in mice causes disease-associated tau phosphorylation and cleavage [45]. Similarly, streptozotocin, a drug used to artificially induce insulin resistance and a type I diabetes-like phenotype, increases disease-associated tau phosphorylation in wild type mice, but, interestingly, not tau cleavage [45]. An increase in disease-associated phosphotau is also observed in streptozotocin-induced diabetic vervet monkeys [46]. Streptozotocin has also been shown to exacerbate tau phosphorylation and cognitive decline in mice transgenically expressing human tau harboring the P301L mutation alongside proteins associated with familial Alzheimer's disease (3xTg-AD) [47]. The onset of tauopathy in 3xTg-AD mice can also be accelerated by diet-induced diabetes [48]. In mice, streptozotocin-induced cognitive decline is blocked by knocking out the mouse endogenous *MAPT* gene [49], suggesting that tau is the key link between dysregulated insulin signaling and cognitive decline. Taken together, these studies suggest that diabetes is sufficient to drive formation of pathogenic tau. Mechanistically, evidence from cell culture suggests that insulin resistance promotes formation of pathogenic tau through reduced PI3K-Akt activity and subsequent activation of GSK3 β , a kinase known to aberrantly phosphorylate tau in disease settings [50-52].

Therapeutic potential—Based on the link between tauopathy and insulin resistance, several FDA approved therapies developed for managing diabetes, including insulin, liraglutide, linagliptin, and metformin, are being tested in preclinical and clinical settings in the context of tauopathy. Pilot studies in patients with amnesic mild cognitive impairment or Alzheimer's disease have reported cognitive benefits of intranasally-administered insulin [53, 54] and inspired the ongoing clinical trial: The Study of Nasal Insulin in the Fight Against Forgetfulness (SNIFF, NCT01767909). The SNIFF study is examining effects of intranasally-administered insulin on cognition and brain atrophy. While it is currently unknown how intranasal insulin affects tau specifically, the SNIFF study will measure fluid biomarkers, including tau, in cerebrospinal fluid. An advantage of nasally-administered insulin is that insulin will not enter the peripheral bloodstream, which could cause hypoglycemia or insulin resistance.

Liraglutide, a glucagon-like peptide 1 (GLP-1) analog that stimulates insulin secretion, prevents aberrant tau phosphorylation in a mouse model of type II diabetes [55] and significantly reduces aberrantly phosphorylated tau and improves motor function in a mouse model of tauopathy (hTauP301L) [56]. Similarly, linagliptin has also recently been reported to reduce aberrant tau phosphorylation and improve cognition in 3xTg-AD mice [57]. A recent clinical trial reports that liraglutide prevents the decline of brain glucose metabolism that signifies cognitive impairment in Alzheimer's disease patients, but no improvement in cognitive performance was detected over the short six month study [58].

Metformin, a drug that suppresses hepatic glucose production, is commonly prescribed for management of type II diabetes. A small pilot study investigating the effects of metformin treatment in patients with amnesic mild cognitive impairment at risk for developing type II diabetes reports an improvement in one, but not all, measures of cognition [59]. A larger study investigating the effects of lifestyle intervention and metformin on brain glucose metabolism and cognition is currently in phase 4 clinical trials (NCT02409238). In the context of pathogenic tau specifically, metformin has been shown to prevent aberrant tau phosphorylation in a neuronal cell model of insulin resistance [60]. While studies in tau transgenic mice also report a reduction in disease-associated phosphotau in response to metformin treatment, the authors also report a metformin-induced increase in tau cleavage, aggregation, synaptic disruption, and hind limb atrophy. Based on these findings, the authors caution that treatment of diabetic patients with metformin may place them at higher risk for tauopathy [61].

Currently, the best supported and most efficacious intervention to prevent tauopathy associated with metabolic syndrome is a healthy lifestyle. For example, cognitive decline, hippocampal volume and metabolic measures improve in patients participating in the metabolic enhancement for neurodegeneration (MEND) protocol, which focuses on personalized therapeutic needs of the individual using a combination of treatment strategies including exercise and diet [62].

Spread of pathogenic tau from other cells

While not infectious in a classical sense, evidence clearly demonstrates that cells can release pathogenic tau, which “infects” neighboring and synaptically-connected cells in culture and in mice [63-66]. When taken in by neighboring cells, these pathogenic tau seeds stimulate aggregation of natively folded tau within the naïve cell [63, 67]. Studies utilizing recombinant, *in vitro* prepared tau aggregates as well as tau aggregates purified from postmortem Alzheimer's disease brain identify a tau trimer as the minimal unit necessary for cellular uptake of tau aggregates and subsequent seeding of intracellular tau aggregation in culture [67]. Tau may also spread from cell to cell in extracellular secreted microvesicles called “exosomes.” Tau-filled exosomes are present in cerebrospinal fluid and plasma of patients with mild Alzheimer's disease and frontotemporal dementia [40, 68]. Exosomal tau is phosphorylated at threonine 181, a phosphoepitope associated with pathogenic tau in the brain [68]. While exosomal tau has been reported to be secreted by both neurons [68] and microglia [69], blocking exosome formation in mouse microglia stops the spread of pathogenic tau from the entorhinal cortex to the hippocampus [69], suggesting that microglia-derived exosomes could be a vehicle for tau propagation. Studies in cultured cells and a rat model of tauopathy indicate that tau is also packaged into ectosomes, larger vesicles that are shed from cells via plasma membrane budding. When comparing exosomal versus ectosomal tau packaging, the authors report that ectosomal tau packaging occurs when tau is expressed at physiological levels, while exosomal tau packaging only occurs when tau is overexpressed [70]. Tunneling nanotubes, membranous structures that facilitate exchange of factors between cells, could also facilitate transfer of physiological and pathogenic tau between cells [71]. Interestingly, recent studies suggest that neuronal secretion of tau may play a role in normal, physiological brain function, as healthy neurons

secrete tau in response to neuronal activity in cultured cells [72] and in wild-type mice [73]. The potentially “normal” function of neuronal secretion of tau may exacerbate tau spread in pathological conditions, as neuronal activity has also been reported to increase the rate of pathogenic tau spread in mice [74]. It is currently unknown whether pathogenic tau released in response to neuronal activity is free or vesicle-bound. Based on the ever-expanding studies in the field of pathogenic tau spread, it is clear that cells likely have multiple mechanisms to secrete physiological and pathogenic tau *in vivo*. The species of tau multimer and the packaging (or lack thereof) of tau multimer that is most efficient at propagating a misfolded state *in vivo* remains to be determined.

Therapeutic potential—Multiple companies and academic laboratories are working to develop immunotherapy strategies to clear pathogenic tau species from the brain. These active vaccines and anti-tau antibodies, several of which are currently in clinical trials [75], function by binding and clearing pathogenic tau from the brain, thereby preventing intercellular tau spread. Results from phase I trials for AADvac1, a tau vaccine, report favorable safety and immunogenicity outcomes [76]. Anti-tau antibodies are reported to be actively taken up by neurons in *ex vivo* cultured brain slices as well as *in vivo* [77-80], and tau-antibody complexes are proposed to be cleared via the lysosome [78, 79]. In addition to reducing levels of pathogenic tau, the tau antisense oligonucleotide described above also reduces tau seeding activity in tau transgenic mice [21].

Mechanistic target of rapamycin (mTOR) hyperactivity

mTOR is a serine/threonine protein kinase critical for cell survival and growth among cell types, including neurons. Through signal transduction pathways, mTOR integrates messages from the intra- and extracellular environment to modulate cellular functions including but not limited to transcription, translation, autophagy, cell signaling, metabolism, cytoskeletal dynamics, and memory formation [81]. Clinically, mTOR hyperactivity has been described in postmortem brain tissue collected from patients with progressive supranuclear palsy, corticobasal degeneration and Alzheimer's disease [82, 83]. Studies using cultured cells, tau transgenic mice and tau transgenic *Drosophila* have linked mTOR activation to elevated tau protein expression [48, 84, 85], aberrant tau phosphorylation [84, 86] decreased autophagic clearance of pathogenic tau [87-89], initiation of tau secretion [90], and tau-induced activation of the cell cycle in post-mitotic neurons [91]. Taken together, these studies indicate that mTOR activation is a potential driver of pathogenic tau formation, and suggest its relevance as a therapeutic target.

Therapeutic potential—Several mTOR inhibitors are FDA approved for treating cancer, are used as immunosuppressants for organ transplant, and extend lifespan in model organisms ranging from yeast to mammals [92]. The mTOR inhibitor rapamycin reduces pathogenic tau and improves cognition in numerous mouse models by upregulating autophagy [87-89, 93], and prevents neuronal death in tau transgenic *Drosophila* [91]. While treatment of 3xTg-AD mice with rapamycin prior to tau tangle formation significantly reduces formation of tau tangles and cognitive deficits, tangles are not reduced when rapamycin is administered after tangle formation, suggesting that beneficial effects of rapamycin may require an early diagnosis [94]. On the other hand, treatment of human tau

P301S transgenic mice with rapamycin reduces aberrant tau phosphorylation and aggregation when administered early or late within the disease course, suggesting that early treatment with rapamycin may not be required in all contexts [89]. Analogs of rapamycin, or “rapalogs,” are also under investigation for the therapeutic treatment of tauopathies. Temsirolimus, for example, has better stability and pharmacological properties than rapamycin. In two separate studies, temsirolimus-treated tau transgenic mice were reported to have increased autophagy, decreased phosphotau and neurofibrillary tangle load, and improved cognition [95, 96]. Wogonin, a natural compound that inhibits mTOR, also reduces phosphotau in cultured cells [97]. Since several mTOR inhibitors are FDA approved, repurposing them for the treatment of neurodegenerative tauopathies may expedite the discovery of therapeutics. A clinical trial (NCT02874924) is currently underway to investigate the effects of rapamycin in adults aged 70-95; results from this study will provide data for rapamycin's tolerability and efficacy in improving life functions in older individuals. These outcomes will certainly guide future clinical studies.

Cellular Processes That Link Pathogenic Tau to Neuronal Death and Dysfunction

The cellular processes that link pathogenic tau to neuronal death and dysfunction provide additional targets for therapeutic intervention. Studies combining genetic approaches in tau transgenic *Drosophila melanogaster* with comparative studies in post mortem human control versus Alzheimer's disease brain have delineated a detailed cellular cascade that begins with pathogenic tau-mediated over-stabilization of the actin cytoskeleton and ends with neuronal death. The interaction between tau and filamentous actin is thought to play a physiological role in synaptic plasticity [98]. In a pathological setting, however, tau promotes filamentous actin stabilization and formation of filamentous actin bundles [99]. Among the many repercussions that an overly rigid cytoskeleton may have, tau-induced stabilization of filamentous actin is known to impact mitochondrial dynamics, which causes oxidative stress [100]. In addition, excess filamentous actin causes the nuclear envelope to involute, which disrupts the underlying nucleoskeleton [101], a lamin-rich meshwork that lines the nuclear envelope and provides a scaffold for the attachment of highly condensed heterochromatic DNA. Pathogenic tau-induced oxidative stress and lamin depletion cause constitutive heterochromatin to relax, which allows genes that are normally silenced by constitutive heterochromatin to be transcribed [101, 102]. These events activate the cell cycle in neurons [101, 102], which are normally post-mitotic. Activation of the cell cycle in neurons triggers apoptotic cell death [91, 103].

Tau may also have a physiological role in the nucleus where it protects DNA and regulates DNA packaging. Tau binds directly to DNA *in vitro* [104], protects against peroxidation-induced DNA damage [105], binds directly to AT-rich α -satellite heterochromatin in non-neuronal cultured cells [106], and colocalizes with pericentromeric constitutive heterochromatin in primary neuronal cultured from wild-type mice [107]. Markers of constitutive heterochromatin are reduced in neurons of tau knockout mice [107]. Taken together, these studies, combined with studies demonstrating that pathogenic tau induces heterochromatin relaxation via altered nucleoskeletal coupling and dysfunction of the lamin

nucleoskeleton, suggest that the observed loss of markers of constitutive heterochromatin in human Alzheimer's disease brains [102, 108], could be a combined result of both toxic gain of function and loss of normal tau function.

An interaction between physiological tau and actin also regulates the relocalization of tau from dendritic shafts to the postsynaptic density in response to synaptic activity, which is important for synaptic plasticity [98]. In mouse hippocampal slice cultures exposed to amyloid β [98], or when transgenically expressed in mice in a disease-associated acetylated form [109], tau has less dendritic-to-postsynaptic mobility in response to synaptic activity, which is thought to result from a decreased interaction between tau and filamentous actin. Taken together, these data suggest that the physiological interaction between tau and actin is important for synaptic plasticity, that a reduced interaction between tau and actin at the synapse disrupts synaptic plasticity, and that over-stabilization of filamentous actin by pathogenic tau can ignite a chain of events that leads to neuronal death. Additional mechanisms of tau-induced neurotoxicity, including synaptic loss/dysfunction, impaired axonal transport, and microtubule destabilization have also been investigated in the context of tauopathy, and have been reviewed elsewhere [12, 110].

Therapeutic potential

In *Drosophila*, genetic reversal of filamentous actin over-stabilization, nuclear envelope disruption, heterochromatin relaxation, neuronal cell cycle activation, and reduction of oxidative stress significantly reduce tau-induced neurotoxicity [91, 99-102, 111], suggesting that pharmacological approaches that target these pathways may yield therapeutic benefit. Pharmacological approaches to reduce oxidative stress suppress tau-induced toxicity in *Drosophila* [111] and mice [112], however clinical trials in humans with mild to moderate Alzheimer's disease fail to show a cognitive benefit [113].

Concluding Remarks and Future Perspectives

The phenotypic heterogeneity and long disease duration of tauopathies present considerable challenges for diagnosis and development of disease-modifying therapies (see Outstanding Questions). In recent years, however, the tau community has made unprecedented strides toward establishing tools and identifying cellular pathways for diagnostic and therapeutic targeting. Transformative achievements include 1) Entry of tau-based immunotherapy into clinical trials, 2) First reports of tau-targeting antisense oligonucleotides, 3) Development of PET-based *in vivo* tau imaging, 4) A greater understanding of avenues in which pathogenic tau may spread through the brain, and 5) Identification of cellular mechanisms, including significant disruption of nuclear and genomic architecture, that mediate pathogenic tau-induced neuronal death and dysfunction. These advances are rapidly changing the landscape of biological understanding, diagnosis, and treatment for tauopathies, and offer great hope for the future.

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Outstanding Questions

- Will *in vivo* tau imaging be able to differentiate between distinct tauopathies?
- Will tau immunotherapy be effective in slowing cognitive decline in tauopathies?
- What species of tau multimer and what type of multimer packaging is most efficient at propagating a misfolded state *in vivo*?
- Can pharmacologic restoration of genomic architecture be used to prevent or slow tauopathy?

Trends Box

- Current diagnostic strategies cannot detect prodromal tauopathy
- Current therapeutic strategies for tauopathies are not disease-modifying
- Mutations in the tau gene, brain injuries, metabolic syndrome, TOR hyperactivity, and spread from neighboring cells can stimulate formation of pathogenic tau
- Pathogenic tau-induced alterations in genomic architecture cause neuronal death

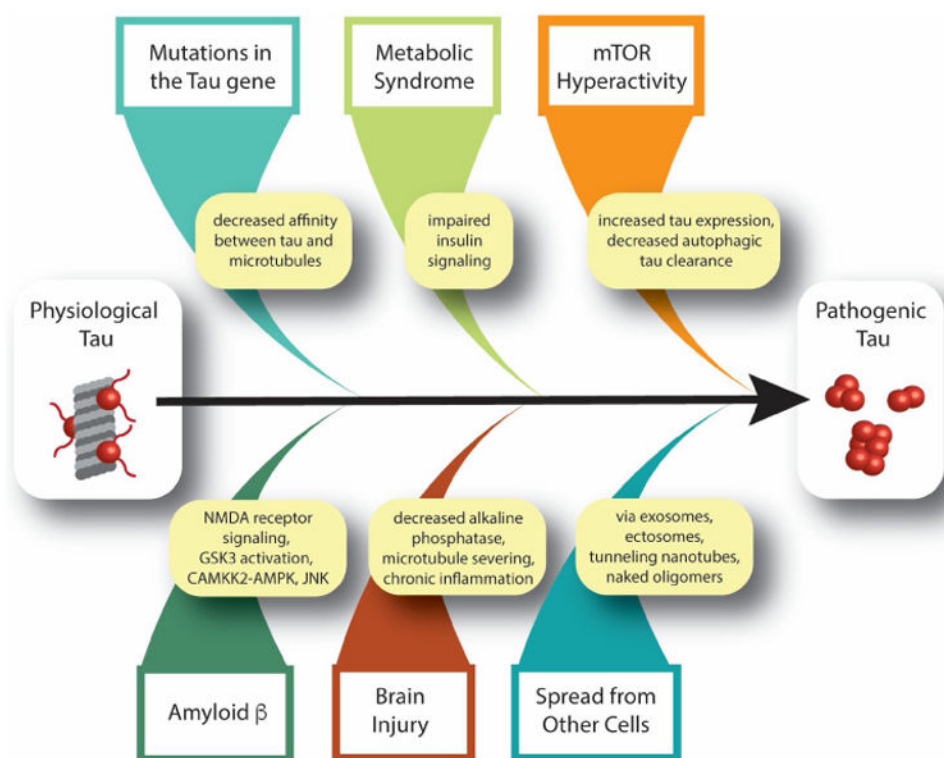


Figure 1.
Known stimulators of pathogenic tau formation.

Table 1

Current pharmacological strategies for treatment of cognitive deficits in tauopathies.

Year Approved	Drug	Brand Name	Disease Stage	Mechanism of Action	Disease Modifying	Delay Disease Progression
1996	Donepezil	Aricept	All stages	Cholinesterase inhibitor	No	No
2000	Rivastigmine	Exelon	All stages	Cholinesterase inhibitor	No	No
2001	Galantamine	Razadyne	Mild to moderate	Cholinesterase inhibitor	No	No
2003	Memantine	Namenda	Moderate to Severe	NMDA receptor antagonist	No	No
2014	Donepezil+ Memantine	NAMZARIC	Moderate to Severe	Cholinesterase inhibitor + NMDA receptor antagonist	No	No