

Tauopathies

Subjects: **Pathology**

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Tauopathies are neurodegenerative diseases characterized by the pathological accumulation of microtubule associated protein Tau (MAPT) in the form of neurofibrillary tangles and paired helical filaments in neurons and glia, leading to brain cell death. These diseases include frontotemporal dementia (FTD) and Alzheimer's disease (AD) and can be sporadic or inherited when caused by mutations in the MAPT gene. Despite an incredibly high socio-economic burden worldwide, there are still no effective disease-modifying therapies and few Tau-focused experimental drugs have reached clinical trials. One major hindrance for therapeutic development is the knowledge gap in molecular mechanisms of Tau-mediated neuronal toxicity and death. For the promise of precision medicine for brain disorders to be fulfilled, it is necessary to integrate known genetic causes of disease, i.e., MAPT mutations, with understanding of the dysregulated molecular pathways that constitute potential therapeutic targets. Here, the growing understanding of known and proposed mechanisms of disease etiology will be reviewed, together with promising experimental Tau-directed therapeutics, such as recently developed Tau degraders. A particular focus will be given to the application of patient-specific stem cell models to study disease, and a number of current challenges faced by the fields of Tau research and drug discovery will also be addressed, including Tau pathophysiology unanswered questions, limitations of model systems and current challenges faced in developing cell-permeable small molecules that target Tau in disease.

[Tau](#)[Aggregation](#)[Neurodegeneration](#)[Alzheimer's disease](#)[Frontotemporal Dementia](#)[Therapeutics](#)[Tau Degradation](#)

1. Alzheimer's Disease

Over a century after its first described case, Alzheimer's disease (AD) is the most prevalent form of tauopathy and the most common cause of dementia (~60–80% of cases), and its frequency of incidence is rapidly increasing as the world's population aged >65 continues to increase. Approximately 5.8 million Americans lived with AD in 2019, and this is predicted to double by 2050 ^{[1][2]}, together with a financial burden predicted to increase from its current annual US \$259 billion to more than \$1 trillion by 2050. This trend is predicted to be global unless means of delaying, preventing, or treating AD are found ^{[1][3]}.

2. MAPT

The microtubule-associated protein tau (MAPT) is a neuronal protein that regulates microtubule stability and dynamics as well as axonal transport ^{[4][5]}. Tau binds to microtubules via repeat microtubule-binding domains in the

C-terminus, and this process is regulated by phosphorylation of sites within and adjacent the binding region ([Figure 1a,b](#)) [\[6\]](#). The N-terminal projection region plays a role in signal transduction and membrane interactions ([Figure 1a](#)) [\[6\]](#). Other tau physiological functions include interaction with the plasma membrane and scaffold proteins, signal transduction, DNA/RNA protection, and regulation of synaptic function [\[7\]\[8\]](#). In the human central nervous system (CNS), six tau isoforms are expressed by alternative splicing of the *MAPT* exons 2, 3, and 10, of which the longest isoform 2N4R tau (441 amino acids) contains two N-terminal inserts and four repeat domains in the C-terminus region ([Figure 1a](#)) [\[9\]](#). This process is developmentally regulated and specific to each brain region based on physiological function [\[10\]\[11\]](#). Exons 2 and 3 are translated into the N1 and N2 domains, respectively, producing the 0N, 1N, and 2N tau isoforms of the N-terminal projection region ([Figure 1a](#)). In the human adult brain, the 2N isoform is the least expressed while the 1N isoform is the most abundant [\[10\]](#). Exon 10 encodes the second microtubule-binding repeat domain in the C-terminal region ([Figure 1a](#)). Inclusion of exon 10 leads to the expression of three tau isoforms with four microtubule-binding domains (4R-Tau), whereas exclusion of exon 10 leads to expression of three isoforms of 3R-Tau [\[10\]\[12\]](#). These four repeat domains (R1–R4, [Figure 1a](#)) are essential for tau ability to regulate stability of microtubules and support axonal transport. For this reason, relative 3R/4R expression is also developmentally regulated. During the fetal stage, 3R-Tau (0N3R) is the main isoform present, allowing for dynamic axonal properties conducive to synaptogenesis and formation of neural pathways, followed by postnatal expression of all isoforms. In the adult brain, 4R-Tau binds more tightly to microtubules and the overall 3R/4R ratio is maintained at 1:1 [\[10\]\[11\]](#). Despite its protein domains, tau's native state defies the traditional 'structure-function paradigm' by lacking a well-defined three-dimensional structure, being classified as an intrinsically disordered protein. This is a characteristic of proteins that require rapid conformational changes and structural plasticity but is also a characteristic of proteins with high propensity for misfolding that play a role in the pathogenesis of neurodegenerative diseases [\[13\]\[14\]](#). Tau misfolding and aggregation into highly ordered β -sheet-rich paired helical filaments (PHFs) that subsequently deposit in the form of neurofibrillary tangles (NFTs) ([Figure 1b](#)) are implicated in a heterogeneous group of aging-related neurodegenerative disorders referred to as tauopathies, which include Alzheimer's disease (AD), Pick's disease (PiD), frontotemporal dementia (FTD), and progressive supranuclear palsy (PSP) ([Table 1](#)) [\[15\]\[16\]\[17\]\[18\]\[19\]\[20\]\[21\]\[22\]\[23\]\[24\]\[25\]\[26\]\[27\]\[28\]\[29\]](#). While many *MAPT* mutations increase tau's propensity for aggregation and toxicity, and are the cause of dominantly inherited tauopathies [\[30\]](#), the majority of tauopathies are sporadic with variable clinical and pathological presentations [\[15\]](#). Tauopathies are mainly considered gain-of-function proteinopathies but, despite increasing understanding of tau physiology and role in disease, the mechanisms of tau aggregation with disruption of molecular pathways leading to neuronal death are still poorly understood [\[31\]\[32\]\[33\]](#). Evidence indicates that native tau is highly soluble, contains several charged and hydrophilic residues, and shows little tendency for aggregation. Thus, for tau to become aggregation competent, it must undergo conformational and post-translational modifications (PTMs) within and near the hexapeptide motifs in the C-terminal repeat domain ([Figure 1b,c](#)) [\[34\]\[35\]](#), which also makes 4R-Tau more aggregation prone [\[36\]\[37\]](#). Little is known about the consequences of tau loss-of-function, but reduced binding of hyperphosphorylated tau to axonal microtubules may alter their structure and/or function, disrupting axonal transport, driving synaptic dysfunction and loss, and promoting neurotoxicity.

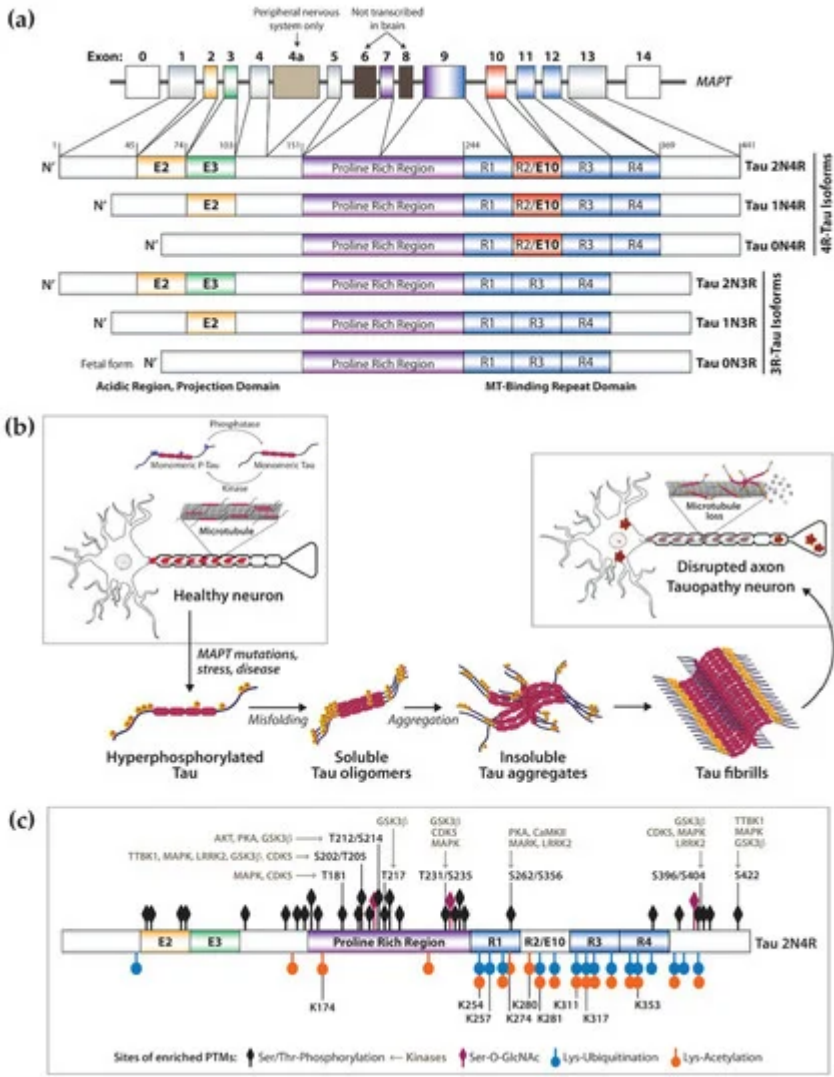


Figure 1. Human microtubule associated protein Tau physiological function and in disease. **(a)** Alternative splicing of the MAPT gene leads to developmentally regulated expression of six Tau isoforms, containing three (3R) or four (4R) microtubule (MT)-binding domains in the C-terminus, and zero, one or two N-terminus domains. **(b)** Simplified representation of Tau function as a regulator of microtubule stability and dynamics in human neurons. Tau binding is regulated by phosphorylation via the concerted action of kinases and phosphatases. In disease Tau becomes hyperphosphorylated and no longer binds microtubules, contributing to axonal dysfunction. Together with post-translational modification, Tau misfolding drives oligomerization and aggregation into larger order insoluble fibrils such as NFTs and PHFs found in the somatodendritic space and processes of CNS neurons. **(c)** Tau undergoes extensive post-translational modification (PTMs), which are exacerbated in disease. Indicated in the 2N4R Tau isoform are the locations of highest PTM density, including phosphorylation, acetylation, O-GlcNAcylation and ubiquitination. Also indicated are sites of phosphorylation prevalent in tauopathies and key regulatory kinases.

Table 1. Summary and key features of primary and secondary tauopathies categorization.

	Clinical	Symptomology	Tau	Neuronal Pathology	Glia Pathology	Affected Brain Regions
Primary Tauopathy	Pick's disease (PiD)	Behavioral change, social disinhibition, eating disorder, absent/late parkinsonism.	3R	Round cytoplasmic inclusions (Pick bodies), rare NFTs.	Ramified astrocytes.	Dentate gyrus of the hippocampus, frontal and temporal neocortical layers II, IV. Frontal, insular and anterior temporal cortices.
	Behavioral variant of FTD (bvFTD)	Behavioral disinhibition, apathy, empathy loss, compulsiveness, executive and cognitive dysfunction.	3R > 4R	Cytoplasmic NFTs, short dystrophic neurites.		Orbitofrontal, dorsolateral prefrontal, medial prefrontal cortices. Subcortical brain nuclei. Temporal-parietal lobes.
	Progressive supranuclear palsy (PSP)	Apathy, anxiety, sleep disturbance. Spectrum from pure motor to pure cognitive presentations.	4R	NFTs, neuropile threads.	Tufted astrocytes, somatodendritic coiled bodies.	Subthalamic nucleus, basal ganglia, brainstem. Posterior mesencephalic cortex.
	Corticobasal syndrome (CBS)	Asymmetric motor symptoms, apraxia, sensory	4R	NFTs, neuropile threads,	Annular clusters of short fuzzy cell processes,	Frontoparietal cortex, striatum,

	Clinical	Symptomology	Tau	Neuronal Pathology	Glia Pathology	Affected Brain Regions
		impairment. Spectrum from pure motor to pure cognitive presentation.		ballooned neurons, pleomorphic inclusions (pre-tangles).	astrocytic Tau plaques, argyrophilic inclusions.	substantia nigra.
	Argyrophilic grain disease (AGD)	Personality change, emotional imbalance, memory failure.	4R	Argyrophilic grains, dendritic straight filaments and smooth tubules.	Thorn-shaped astrocytes, coiled bodies.	Medial temporal lobe, entorhinal cortex, hippocampus, amygdala.
	Aging-related Tau astrogliopathy (ARTAG)	Cognitive decline.	4R	-	Thorn-shaped and granular-fuzzy astrocytes.	Medial temporal lobe, lobar (frontal, parietal, occipital, lateral temporal), subcortical, brainstem.
	Globular glial tauopathy (GGT)	Behavior change, cognitive decline, motor neuron disease (Parkinsonism).	4R	-	Globular inclusions in astrocytes and oligodendrocytes.	White matter, limbic and isocortical regions. Hippocampus.
	Primary progressive	Language deterioration, loss	3R, 4R	NFTs, amyloid plaques	Globular astrocytic inclusions.	Anterior and temporal lobes, parietal

	Clinical	Symptomology	Tau	Neuronal Pathology	Glia Pathology	Affected Brain Regions
	aphasia (PPA)	of semantic memory.				lobe. Frontoinsular cortex
	Primary age-related tauopathy (PART)	Cognitive impairment.	3R, 4R	NFTs, neuropile threads	Medial temporal lobe.	Medial temporal lobe.
	Tangle-only dementia (TOD)	Late-onset dementia.	3R, 4R	Intracellular PHFs, NFTs and neuropil threads.		Hippocampus.
Secondary Tauopathy	Alzheimer's disease (AD)	Memory loss, cognitive dysfunction, social behavior changes.	3R, 4R	NFTs, neuropile threads, neuritic plaques.		Entorhinal cortex, hippocampus, cerebral cortex.
	Chronic traumatic encephalopathy (CTE)	Memory loss, confusion, personality/behavior changes. Motor decline.	3R, 4R	P-Tau aggregates around small vessels, TDP-43 cytoplasmic inclusions.	P-Tau aggregates around small vessels.	Cortical sulci, isocortex layers II–III, hippocampus, subcortical nuclei.

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Diseases where tau has a direct and predominant causal effect on neurodegeneration are referred to as ‘primary tauopathies’, which include progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), Pick’s disease (PiD), aging-related Tau astrogliopathy (ARTAG), argyrophilic grain disease (AGD), primary age-related

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3. Molecular Mechanisms of Tau Pathology

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Figure 2. Summary of proposed mechanisms of Tau pathogenicity and corresponding experimental therapeutic approaches.

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4. Tau Directed Therapeutics

The rate of failure in drug development for tauopathies is relatively high. Promising preclinical data has supported the development of multiple experimental therapies for tauopathy, but showing a pharmacodynamic effect in the brain. However, the BBB is a major barrier to drug delivery. The BBB is a highly selective barrier that prevents the entry of most drugs into the brain. The BBB is composed of endothelial cells, pericytes, and astrocytes. The BBB is a dynamic barrier that can be modulated by various factors, including inflammation, oxidative stress, and aging. The BBB is a major barrier to drug delivery, and therefore, an effective therapy will have to have a super affinity for Tau and/or be administered at high doses, which becomes exceptionally difficult and expensive. Alternatives include intrathecal administration, which can circumvent the BBB but have an immensely high cost of treatment and other medical implications associated that will render the medicinal application worldwide almost prohibitive. Using small molecules that cross the BBB is an attractive and possibly optimal approach, but so far, the majority of experimental Tau drugs with positive pre-clinical data have clear limitations of BBB permeability. Another significant

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