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REVIEW ARTICLE

The six brain-specific TAU isoforms and their role in Alzheimer's disease and related neurodegenerative dementia syndromes

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Abstract

INTRODUCTION: Alternative splicing of the human *MAPT* gene generates six brain-specific TAU isoforms. Imbalances in the TAU isoform ratio can lead to neurodegenerative diseases, underscoring the need for precise control over TAU isoform balance. Tauopathies, characterized by intracellular aggregates of hyperphosphorylated TAU, exhibit extensive neurodegeneration and can be classified by the TAU isoforms present in pathological accumulations.

METHODS: A comprehensive review of TAU and related dementia syndromes literature was conducted using PubMed, Google Scholar, and preprint server.

RESULTS: While TAU is recognized as key driver of neurodegeneration in specific tauopathies, the contribution of the isoforms to neuronal function and disease development remains largely elusive.

DISCUSSION: In this review we describe the role of TAU isoforms in health and disease, and stress the importance of comprehending and studying TAU isoforms in both, physiological and pathological context, in order to develop targeted therapeutic interventions for TAU-associated diseases.

KEYWORDS
alternative splicing, Alzheimer's disease, genetic tauopathy, MAPT, TAU isoforms, tauopathy

Highlights

- *MAPT* splicing is tightly regulated during neuronal maturation and throughout life.
- TAU isoform expression is development-, cell-type and brain region specific.
- The contribution of TAU to neurodegeneration might be isoform-specific.
- Ineffective TAU-based therapies highlight the need for specific targeting strategies.

1 | INTRODUCTION

The microtubule-associated protein TAU plays a pivotal role in the regulation of fundamental neuronal processes. TAU's manifold physiological roles include stabilizing microtubules (MTs), facilitating axonal transport, and modulating synaptic plasticity.[1] Under physiological conditions TAU supports neuronal plasticity by regulating the structural dynamics of MTs necessary for neuronal growth and function. The complexity of TAU functions is further enhanced by alternative splicing of the TAU-encoding *MAPT* gene, theoretically enabling the

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expression of over 30 different splice isoforms in the human central and peripheral nervous system, each of which could potentially exhibit distinct functions.[2–5] Notably, *MAPT* alternative splicing and TAU isoform expression are highly species dependent. While six isoforms are expressed in the adult human brain (2N4R, 1N4R, 0N4R, 2N3R, 1N3R, 0N3R), only three are detected in adult rodents (2N4R, 1N4R, 0N4R) (Table 1).[3,6–8]

The importance of TAU exceeds its physiological role, as dysregulation and loss of the microtubule-stabilizing function has been intricately linked to neurodegenerative diseases (NDDs) (reviewed, e.g., in[9,10]). In sporadic forms of Alzheimer's disease (AD), TAU undergoes abnormal phosphorylation (often referred to as hyperphosphorylation) and eventually changes its subcellular localization, leading to its accumulation and the formation of neurofibrillary tangles (NFTs).[11–16] TAU pathology has been observed in a variety of neurodegenerative diseases, such as frontotemporal dementia (FTD), progressive supranuclear palsy (PSP), Pick's disease (PiD), and corticobasal degeneration (CBD), therefore termed tauopathies. The majority of these diseases occur sporadically, and the underlying triggers remain elusive.[17] However, over 50 variants in *MAPT* have been associated with FTD (Alzforum database 12/2023), which i.a. lead to imbalances in TAU isoform expression[18–21] (reviewed, e.g., in[22,23]), clearly demonstrating a pathogenic role of TAU isoforms in at least a subset of FTD. Tauopathies can be further classified according to the TAU isoforms present in the pathological inclusions. For instance, PiD is characterized by tangles containing 3R-TAU isoforms (0N3R, 1N3R, and 2N3R), whereas 4R-TAU (0N4R, 1N4R, and 2N4R) accumulates in disorders like PSP and CBD. In AD, aggregates consist of all TAU isoforms (as reviewed in[24,25]). Despite the pivotal role of TAU in the pathogenesis of these disorders, our understanding of the contribution of individual TAU isoforms remains limited. Most studies have predominantly focused on "full-length" or mature 2N4R-TAU or specific mutants associated with FTD, and often rely on rodent model systems that express only 4R-TAU. While whole classification systems of tauopathies are based on subsets of isoforms present in the tauopathy-typical accumulations of TAU (e.g., 3R and 4R tauopathies), the role the isoforms in physiology and disease is underappreciated. We here point out that TAU isoforms are not only important for the established histopathological classification, but apparently also for physiological neuronal and brain development, intracellular distribution, and mediation of neuronal dysfunction. We should appreciate the differences of the human TAU isoforms for the design of preclinical studies (in particular for the use and generation of transgenic mice, which are currently based overwhelmingly on single and not representative isoforms), which may well pave the way for the selective targeting of a subset of TAU species (e.g. isoforms) as a therapeutic avenue.

Hence, in this review, we summarize the diverse physiological functions of the six major brain TAU isoforms, the implications of alternative splicing, and variations observed across species. Furthermore, we describe the pathological role of TAU isoforms in NDDs, with a special focus on AD, and stress the importance of comprehending and studying TAU isoforms in both physiological and pathological context in order to develop targeted therapeutic interventions for TAU-associated NDDs.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using databases, such as PubMed and Google Scholar, meeting abstracts, and preprint servers with a special focus on brain TAU isoforms, TAU biology, and TAU-related neurodegenerative dementia syndromes.
2. **Interpretation**: While the TAU protein is intricately linked to pathophysiology of several tauopathies, the relevance and contribution of its isoforms remains relatively unexplored. Our review summarizes the current state of TAU research with a special focus on the human brain-specific TAU isoforms, their physiological characteristics, and their implications in tauopathies and neurodegenerative diseases.
3. **Future directions**: The failure of a variety of TAU-targeting therapies in tauopathies highlights the urgent need for improved targeting strategies. Our review emphasizes the importance of comprehending and studying TAU isoforms in both physiological and pathological context in order to develop targeted therapeutic interventions for TAU-related dementia syndromes that address TAU pathology while maintaining essential cellular TAU functions.

2 | *MAPT* ALTERNATIVE SPLICING AND TAU ISOFORMS

The TAU protein is a natively unfolded, intrinsically disordered, soluble protein, which is abundantly expressed in the central and peripheral nervous system, especially in neurons. However low levels of TAU can be also detected in astrocytes and oligodendrocytes.[26–32] In addition, TAU is widely expressed in other tissues, such as the pancreas, breast, kidney, and skeletal muscle, however at much lower levels than in neuronal tissues.[33,34]

The human TAU protein is encoded by the *MAPT* gene on chromosome 17q21.31. Alternative splicing gives rise to a diverse array of isoforms in the human central and peripheral nervous system, with over 30 different predicted isoforms.[2–5] The primary targets of the alternative splicing process are exons 2, 3, and 10, resulting in the expression of six brain-associated TAU isoforms in mature human neurons characterized by the number of N-terminal inserts (0N, 1N, or 2N) and C-terminal repeat domains (3R or 4R) (Figure 1 and Table 1).[2] Exon 10 inclusion or exclusion determines the number of C-terminal repeat domains, while splicing of exons 2 and 3 determine

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TABLE 1 TAU isoform expression in human and murine brains.

Parameter	Human TAU				Murine TAU			
Fetal isoform	0N3R				0N3R			
Adult isoforms (CNS)		Length [aa]	Molecular weight [kDa]	Expression level*		Length [aa]	Molecular weight [kDa]	Expression level*
	0N3R	352	36.76	10%–20 %				
	0N4R	383	40.01	8%–13%	0N4R	350	36.74	20%
	1N3R	381	39.72	23%–30%				
	1N4R	412	42.97	20%–25%	1N4R	372	38.96	40%
	2N3R	410	42.60	3%–5%				
	2N4R	441	45.85	5%–15%	2N4R	430	44.89	40%

*Based on [37,87].

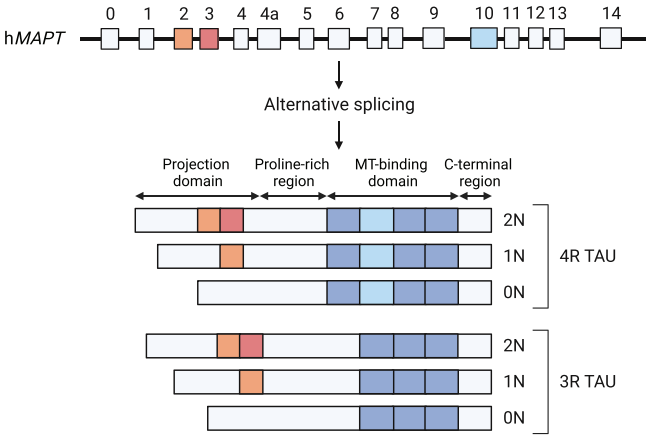


FIGURE 1 Alternative splicing of the human *MAPT* gene. The human *MAPT* gene encodes for six brain-specific TAU isoforms based on alternative splicing of exons 2, 3, and 10. The TAU protein can be structured into four different domains: The N-terminal projection domain, which projects away from the microtubules (MTs), acts as a spacer and interacts with components of the plasma membrane. The proline-rich region is involved in cellular signalling by interacting with Src-familiy kinases such as Fyn. The MT-binding domain mediates MT polymerization and stability, and the C-terminal region additionally contributes to MT polymerization and TAU's interaction with the plasma membrane. Figure created with BioRender.com

the number of N-terminal inserts. Of note, exon 3 inclusion depends on the inclusion of exon 2 due to a weak branch point that favors exclusion of exon 3 from the final mRNA transcript.[33,35]

While the shortest isoform, 0N3R, is exclusively expressed during neurogenesis, the isoform composition switches upon neuronal maturation toward larger TAU isoforms, particularly 2N (comprising 2N3R and 2N4R) and 4R (comprising 0N4R, 1N4R, and 2N4R), resulting in nearly equal ratios of 3R and 4R-TAU isoform expression in adult brains.[8,36] Even though 3R and 4R isoforms are present in nearly equal amounts, the relative abundance of 0N, 1N, and 2N TAU isoforms in humans differs significantly: While 1N TAU isoforms account for approx. 50% of all TAU species, 0 and 2N TAU isoforms each make up only up to 20% (Table 1).[37] Further, the isoform composition and protein abundance can differ in brain regions and cellular subtypes.[37–40] Notably, inclusion of exon 4a upon neuronal maturation results in the additional expression of a high molecular weight TAU isoform in the peripheral nervous system, referred to as big TAU, which might play a role in the regulation of axonal transport of large projecting neurons.[5,6,41,42]

MAPT is not exclusively expressed in the brain, but TAU can be found in a variety of tissues. Briefly, several studies indeed show that TAU found in the periphery, in particular the peripheral nervous system, so-called, "Big TAU," includes exon 4a (5), but other isoforms are expressed as well. Interestingly, the fetal brain isoform 0N3R is usually not expressed elsewhere, but data are limited to adult tissue.[43,44] One study specifically looking at the enteric nervous system (ENS) detected expression of brain-typical TAU isoforms (but not big TAU), indicating that the ENS may have particular, brainlike properties. In rats, the adult ENS did not express 0N3R-TAU, while primary cultures thereof (which usually maintain some degree of immaturity) did, indicating that, at least in some peripheral tissues, also the brain-typical isoforms are expressed.[45] Also, in Western blots of typical PNS-tissues (like rat sciatic nerve), there are usually faint bands at the size of the brain-specific isoforms, suggesting that the inclusion of the typical PNS-exons is far from perfect.[45] We note that exon 4 is expressed in the PNS, exon 6 is expressed in the brain and the spinal cord, while for exon 8, there are no data that would allow to deduce its expression in a specific or any tissue.[33] Expression of *MAPT* in non-brain tissues and the PNS has received very little interest, so data are scarce (see recent reviews[41,42]), and often unclear. Of note, expression of TAU in cell lines derived from pancreatic beta cells have been detected[46,47], but not in the actual tissue. As pancreatic beta cells share important features with neurons, it is conceivable that in paradigms of de-differentiation, creation of cell lines or cancerous behavior, these cells may express TAU, but not under physiological conditions.

What are molecular factors mediating TAU splicing? Over 10 serine/arginine-rich splicing factors (SRs) and heterogenous nuclear ribonucleoproteins (hnRNPs) are implicated in the splicing of exons 2, 3, and 10,[48–50] and developmental stage specific splicing inhibitors have been described in the regulation of exon 10 splicing.[50,51] The ratio of 3R to 4R TAU isoforms is crucial for normal neuronal

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function and imbalances are directly linked to various neurodegenerative diseases (see also section 3. The contribution of TAU isoforms to tauopathies). Notably, exon 10 is a focal point of splicing regulation due to its pivotal role in familial tauopathies like progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), Pick's disease (PiD), and frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17).[48,49,52] Pathogenic variants at the exon 10-intron 10 boundary disturb proper exon 10 splicing leading to an altered 3R and 4R TAU isoform balance and are directly associated with FTD.[18–20,48,49,53–56] Under normal conditions, exon 10 splicing is regulated by a variety of *cis*- and *trans*-acting elements. Deletion of the SC35-like element at the 5′ end of exon 10, for example, promotes exon 10 inclusion in several cell culture models.[57] Furthermore a polypurine enhancer (PPE) and an A/C rich enhancer (ACE) further add to the complex regulation of exon 10 splicing regulation, and mutations in these elements are directly linked to FTD and other neurodegenerative diseases by promoting exon 10 inclusion.[58–60] Due to high self-complementary between the 3′ end of exon 10 and the 5′ end of intron 10, a stem loop is usually formed that increases availability for U1 snRNP and enhancing 4R TAU expression.[61,62] Exon 10 alternative splicing is further regulated by various SR proteins, that either promote (e.g., SRSF1, SRSF2, SC35), SRSR6, and SRSR9, or suppress its inclusion (e.g., SRSF3, SRSF4, SRSF11) (reviewed, e.g., in[33]). Kinases regulating the activity of SR proteins, such as Dyrk1A,[57,63] PKA,[64] and CLK1, 2, and 3[65] have been additionally shown to regulate the alternative splicing of *MAPT*. Further proteins affecting exon 10 splicing are the polypyrimidine tract-binding Protein 1 (PTBP1) that represses exon 10 inclusion,[66] and Nova-1.[67] Muscleblind-like (MBNL) proteins are involved in developmental splicing and could potentially influence *MAPT* splicing, although direct evidence remains sparse.[68,69] Their known roles in modulating splicing in various contexts make them candidates for future research in TAU isoform regulation. The same is true for CELF2 (also known as ETR3): CELF2 belongs to the CELF family, known for its involvement in developmental splicing regulation. While its direct role in TAU splicing is not extensively documented, CELF proteins' broad regulatory functions suggest a possible influence on *MAPT* splicing patterns.[68]

MicroRNAs (miRNAs) regulate *MAPT* alternative splicing by targeting specific sites within the mRNA. Several brain miRNAs, including miR-124, miR-9, miR-132, and miR-137, have been identified as important regulators of *MAPT* alternative splicing, particularly in the context of exon 10 splicing (reviewed, e.g., in[70]). These miRNAs can indirectly regulate the expression of exon 10 *trans*-acting factors, thereby affecting the balance between 3R and 4R TAU isoforms. While the specific mechanisms by which these miRNAs regulate *MAPT* alternative splicing are still being elucidated, it is clear that miRNAs play a significant role in modulating the splicing of TAU pre-mRNA, particularly in the context of tauopathies (reviewed in[71,72]).

For the technical and molecular mechanism of *MAPT* alternative splicing, we refer the interested reader to recent exhaustive reviews (for example[33,50,68,70–75]).

In addition to the above mentioned splicing factors, two major haplotypes influence *MAPT* gene expression and alternative splicing.[76] The H1 haplotype, found in approximately 75% of the European population, promotes exon 10 inclusion and increases susceptibility to tauopathies like Parkinson's disease (PD), PSP, and CBD.[76–81] Conversely, the H2 haplotype, characterized by a ~970 kb inversion spanning the entire *MAPT* locus, reduces AD risk and enhances exon 3 inclusion.[82–84] The H2 haplotype is nearly exclusive to the European population, with an occurrence rate of around 25%.[85]

Although the coding sequence of *MAPT* is relatively conserved among mammals, and humans and rodents share the same intron-exon organization, the splicing pattern diverges significantly across phylogenetic groups[3,6,38,86] (reviewed, e.g., in[7]). In adult human and primate brains, six TAU isoforms (0N3R, 0N4R, 1N3R, 1N4R, 2N3R, and 2N4R) are present, whereas in murine brains only up to four TAU isoforms (0N3R, 0N4R, 1N4R, 2N4R) are expressed (Figure 1, Table 1). Similar to human neuronal development, murine neuronal development is characterized by exclusive expression of 0N3R; however, adult murine neurons predominantly contain 4R TAU isoforms (0N4R, 1N4R, and 2N4R) with roughly equal expression ratios (Table 1).[6,38,86–88] These dissimilarities may at least partially explain human vulnerability to *MAPT* splicing abnormalities and the absence of TAU pathology in many transgenic mouse models of AD, as summarized, for example, in [25,89].

In summary, the intricate splicing patterns and diverse isoform landscape of the TAU protein underscore its central role in both physiological neuronal function and the pathogenesis of neurodegenerative diseases. The differential expression of TAU isoforms in different brain regions, cell types, and species underscores the complexity of its regulation and suggests specific vulnerabilities in certain contexts.

3 | STRUCTURE, LOCALIZATION, AND PRIMARY FUNCTION OF THE TAU ISOFORMS

3.1 | TAU domain structure and canonical primary function of microtubule stabilization

The TAU protein is structured into four different domains, depending on the amino acid sequence and the interactions with other proteins[90,91]: (1) the N-terminal projection domain comprising the N-terminal inserts and is hence different for 0N, 1N, and 2N isoforms, (2) a proline-rich region consistent among CNS isoforms, (3) the MT-binding domain that harbors either three (3R) or four (4R) repeat domains, and (4) the C-terminal region, which is identical between the CNS isoforms (Figure 1). The six human brain-specific TAU isoforms differ in their size ranging from 352 aa for the smallest, fetal TAU isoform 0N3R, to 441 aa for the largest 2N4R-TAU isoform (Table 1). While 3R-TAU isoforms comprise three MT-binding repeats (R1, R3, and R4), 4R-TAU isoforms have an additional repeat domain (R2), due to the inclusion of exon 10 during alternative splicing. Under physiological conditions, TAU is mainly bound to neuronal MTs, however, TAU phosphorylation at specific sites (in particular the KxGS-motifs phosphorylated by the microtubule affinity regulating kinases (MARKs) (see, e.g.,[92]), but also hyperphosphorylation under pathological conditions lead to detachment from MTs. Underhyperphosphorylated conditions, a "paperclip" fold can be observed, in particular for the

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largest TAU isoform (2N4R). This fold is based on interactions between the N-terminus with the repeat domains (R1-R4) and increases the aggregation propensity of this TAU species.[93–95] Together with the proline-rich and the C-terminal pseudo-repeat region, the MT-binding domain enables tubulin binding and regulates MT-polymerization efficiency, while the N-terminal region projects away from MTs, which could regulate MT-spacing.[96] The differences in the N-terminal exons may thus result in different distances between MTs, but this has not been addressed experimentally.

By binding to monomeric tubulin subunits, TAU promotes the assembly and stability of MTs, also enabling them to have long labile domains necessary for rapid MT assembly and disassembly,[97] without evidence of differential impact of the different isoforms. Complete loss of TAU (e.g., in *Mapt* KO mice or *MAPT* KO in human neurons) does not lead to overt loss of MTs, but only to subtle defects in neuronal outgrowth (which is usually connected to MT function).[98–101] It is thus obvious that loss of TAU does not automatically cause loss or destabilization of MTs. The concept that TAU facilitates dynamic lability of MTs in physiological conditions (see, e.g.,[97,102]), and the concept that TAU (as well as i.a. many other axonal MAPs and MAP-associated kinases) certainly play a role not only in MT stability, but also in MT dynamics, underlines the experimental evidence that TAU may be crucial for proper MT dynamics in physiological conditions. Accordingly, loss of TAU might not directly lead to MT destabilization, but rather towards a disturbed ratio between labile and stable MT domains. Either way, even if TAU makes MTs more dynamic (or more stable), pathological TAU (which does not necessarily mean loss of TAU) may result in "overdynamic" or fragile MT, which may even result in excessive severing of MTs, as outlined previously,[101,103] which could cause MT loss. TAU further serves as a spacer and anchors MTs to the cellular plasma membrane via its interaction with actin and annexins.[104–106]

MT-binding affinity is tightly regulated by phosphorylation, with 85 predicted phosphorylatable sites (reviewed in[107]), and more than 50 of which have already been demonstrated experimentally.[108–110] Most phosphorylation sites identified in *post mortem* brains are located within the isoform independent proline-rich and C-terminal region.[110] While the N-terminal domain is also often phosphorylated, there has been so far no experimental evidence of phosphorylation in the second insert of TAU, which may be due to the lower abundance of 2N-isoforms, but could also hint toward joint regulation of 1N/2N isoforms versus 0N isoforms, as there are many phosphorylated sites experimentally confirmed in the first insert (e.g., S46, S56, S68, T69, T71). In contrast, there are few phosphorylation sites present in the repeat domains, and those present (in particular the KxGS-motifs) may be redundant. The second MT-binding repeat domain (only present in 4R-TAU) contains three phosphorylation sites (S289, S293, S305) phosphorylated in *post mortem* brains. Due to the repetitive nature of the repeat domains, however, specific or individual regulation seems unlikely (for summary and discussion about PTMs of TAU, see[111]). The additional MT-binding repeat in 4R-TAU isoforms does increase their MT-binding affinity, leading to faster and more efficient MT assembly compared to 3R-TAU isoforms in vitro.[112–114] These differential effects, however, have not been observed in human neuroblastoma cells (SH-SY5Y) expressing individual TAU isoforms.[115] In this model, 4R-TAU isoforms reduced the cellular size, whereas 3R-TAU isoforms resulted in an increase, but no significant differences in regard to MT number, stability, length, and growth rate were observed between individual isoforms.[115] This suggests that all isoforms can mediate the canonical function of TAU, i.e. MT stabilization, at least in an isolated context in human neuron-like cells.

3.2 | TAU sorting and localization

In the developing brain and particularly during neuronal polarization, TAU is efficiently sorted into the axon. Nevertheless, in the mature brain, a minor proportion is also detectable in the soma, dendrites, and was even reported in the nucleus.[116–122] Axonal enrichment of TAU is likely achieved by various strategies, such as active transport of *MAPT* mRNA mediated by an axonal localization signal in the 3′ untranslated region (UTR), free protein diffusion, active protein transport along MTs, rapid degradation of somatic TAU, and inhibition of retrograde diffusion by a TAU diffusion barrier (TDB) at the axon initial segment (AIS)[123–130]; for review see, e.g.,[131]. Furthermore, the MT-binding affinity, which is influenced by posttranslational modifications (PTMs) like phosphorylation and acetylation, tends to be higher in the axon, and dependent on the number of C-terminal repeat domains encoded by exon 10.[74,112–114,132–134] Compartment-specific enzymes, e.g. the p38γ kinase at the postsynaptic density[135] or PP2A phosphatase in dendrites,[136,137] enable differential modification of TAU and fine-tuning of its MT-affinity and subcellular localization. Overall, TAU is considered an axonal protein and is often used as a marker of such. However, several studies have demonstrated that the axonal sorting efficiency among the six TAU isoforms differs significantly: While the smaller human 0N isoforms are efficiently sorted into axons, the 1N and 2N isoforms tend to be partially retained in dendrites and cell bodies of rodent primary and hiPSC-derived neurons.[100,124,138] In the murine brain, 0N4R and 2N4R TAU isoforms are enriched in the CA3 mossy fiber region that contains axonal projections from dentate granule cells.[139] Further, 1N4R and 2N4R isoforms are enriched in the dendritic fractions, which could be explained by the stronger interaction of these isoforms with dendritic or postsynaptic proteins.[139] TAU phosphorylation at isoform-independent epitopes, such as T231 (AT180), S262 (12E8), and S396/404 (PHF1) were shown to regulate dendritic localization of TAU.[140] Furthermore, a truncated TAU variant lacking the MT-binding domain is uniformly distributed in the neuron.[140] Therefore, the differences in the subcellular localization of the TAU isoforms likely depend on the presence and number of N-terminal inserts, which could be explained by differences in PTMs, MT-binding affinity, and protein-protein interactions of TAU isoforms (see also the TAU isoform-specific functions beyond MT stabilization section).[117,132–134] Further, the isoform composition and protein abundance can differ in brain regions and cellular subtypes,[37–40] indicative of tight brain region-, cellular compartment-, and neuronal subtype-specific regulation.

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4 | TAU ISOFORM-SPECIFIC FUNCTIONS BEYOND MT STABILIZATION

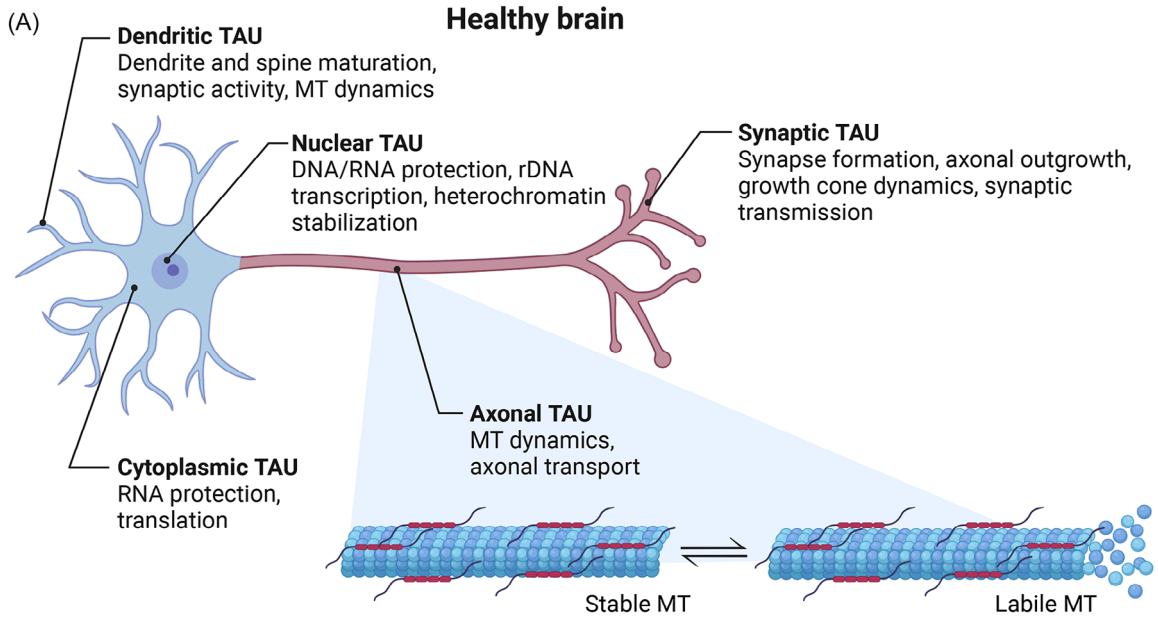
In addition to its primary function in stabilizing neuronal MTs, TAU interacts with various other proteins, influencing a wide range of cellular processes (Figure 2A) (for review see [25,141,142]). Limited data are available on the functional diversity of individual TAU isoforms. Several studies have revealed distinct intracellular distributions of TAU isoforms in primary neuronal cultures, mouse brains, and hiPSC-derived neurons, indicating their potential differential roles in TAU-related functions (see the TAU sorting and localization section).[100,124,139] In accordance with these differential localizations, co-immunoprecipitation (Co-IP) experiments using endogenous murine 0N4R, 1N4R, and 2N4R-TAU isoforms have revealed distinct isoform-specific interactions: Proteins binding to murine 0N4R-TAU were enriched in cellular homeostasis, the cellular respiration pathway, and glycolysis pathway and include α- and β-synuclein, synapsin-1, and synaptogyrin-3. 1N4R-TAU binding proteins, such as ATPase, neuromodulin, calmodulin, and sodium- and chloride-dependent GABA transporter 3, were also enriched in glycolysis, while proteins that preferentially bind to 2N4R-TAU were involved in ATP synthesis and synaptic transmission, including, for example, ApoA1, ApoE, and synaptotagmin.[143,144] However, specific interaction domains or motifs have not been identified that could explain the differential binding of TAU isoforms to these proteins. Notably, also none such isoform-specific interactome studies have been conducted in human brain lysates or neurons to date.

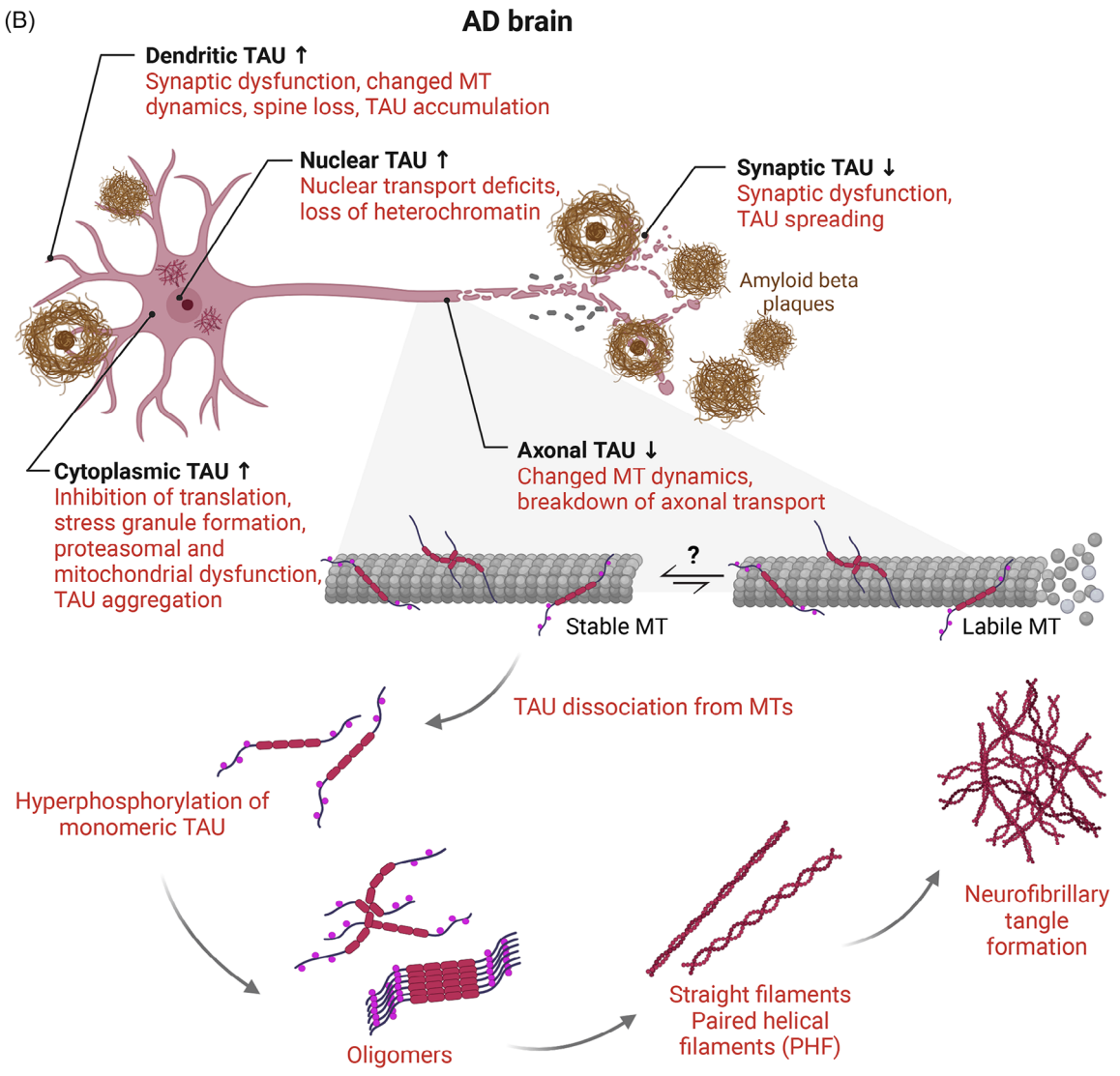
A recent study using hiPSC-derived neurons revealed that TAU interactions encompass a broad spectrum of functions beyond cytoskeletal organization, and include pre-synaptic vesicle dynamics, proteasomal processes, RNA binding, and mitochondrial activities, implying diverse additional roles for TAU (Figure 2A).[144] Interestingly, differences between the interactome of N- and C-terminally APEX-tagged 2N4R-TAU were observed: N-terminally tagged TAU interacted mainly with active zone proteins, such as Dynamin 1, α-/β-SNAP, RAB3GAP1, and Liprin α3, and with postsynaptic proteins like ABI2, Cadherin-2, and Nectin, while C-terminally tagged TAU was involved in vesicle fusion and interacted with proteins, such as Syntaxin 1A/1B, RAB3A, RIMS1, and Mint1. Furthermore, N-terminally tagged TAU interacted with a SNARE protein present in autophagosomes, YKT6, which plays important roles in lysosomal fusion.[144] Differential labeling of TAU interacting proteins by N- and C- terminal APEX point toward subdomain-, and likely isoform-specific interactions, which might depend on the number of N-terminal inserts and C-terminal repeat domains that potentially are influenced by changes in the alternative splicing pattern of the *MAPT* gene. However, these likely domain-specific interactions have not been further addressed in this study. In SH-SY5Y cells, overexpressed 2N4R-TAU interactions where significantly enriched for components of the translational and RNA-processing machinery.[145] Using truncated TAU variants, the study further unraveled that RNA-binding proteins (RNPs), ribosomal subunits, and heteronuclear ribonucleoproteins (hnRNPs) among others, preferentially bind to the N-terminal domains (in this case containing both inserts (exon 2 and exon 3), while 14-3-3 proteins, heat-shock proteins (HSPs), and actin-related proteins interact mainly with the C-terminal domains of 2N4R-TAU.[145] A study using IMR neuroblastoma cells and human neurons differentiated from a neural progenitor cell line (ReN VM), that both express equal amounts of 2N4R and 2N3R, further consistently showed the interactions of TAU with HSPs, 14-3-3 proteins, hnRNPs, and RNPs.[146] The studies performed in human cellular context are in line with results obtained from human post-mortem tissue and consistently identified proteasomal proteins and RNPs, such as hnRNPs, FUS, SFPQ, and PTBP1, to interact with TAU.[142,147–149] In a comprehensive study using the HT22 murine neuronal cell line cells, 2N4R, 1N4R, and 0N4R TAU demonstrated different capabilities to undergo liquid-liquid phase separation (LLPS),[150] a process used for membrane-less compartmentalization, and implicated in pathological protein aggregation observed in neurodegenerative diseases (reviewed in[151]). While p62 positive condensates were formed upon presence of 2N4R TAU, these were absent upon expression of 1N4R and 0N4R, suggesting that these isoforms are involved in other physiological processes.[150]

Although human and murine TAU are highly similar due to strong *MAPT* sequence homology,[3,6,7,25] the interactome of TAU differs remarkably between species (reviewed in[142]), which hints towards differential functions of TAU between these two species. In a rodent context, a variety of TAU species have been studied, ranging from WT rat TAU (which corresponds to all 4R-TAU isoforms) to transgenic mice overexpressing human 1N4R- or 2N4R-TAU with FTD-associated mutations (P301S or P301L). Likely due to these differences, both in isoforms and pathogenicity, the TAU interactome varies strongly between individual studies. Nevertheless, interactions of TAU with HSPs, and synaptic and trafficking components are consistently found, suggesting further roles of TAU in these processes.[142,152–155] Notably, a significant amount of the interacting partners identified in human studies did not appear in the screenings performed in rodent models, however some interactions of TAU with vesicle proteins and proteins involved in the unfolded protein response remain consistent between human and rodents (reviewed in [142]).

The vast majority of functions and interactions of TAU have been primarily studied in pathological contexts, either using TAU variants associated with FTD, or by using cellular stressors, such as amyloid beta oligomers (see also the The contribution of TAU isoforms to AD pathology section), but with no attention to the individual isoforms. Briefly, in these studies, TAU has been directly linked to impairments of the proteasomal system, reduced protein synthesis by interacting with ribosomal components, excitotoxicity by interaction with components of the NMDA receptor complex and spine loss by destabilization of local MTs (Figure 2B).[101,142,147,156–164] Furthermore, nuclear localization of TAU has been observed. While TAU protects RNA and DNA under physiological conditions, the interaction of TAU with RNPs and RNA can also increase its aggregation propensity.[88,165–170] TAU further plays a role in regulating synaptic plasticity at the postsynaptic site through its interactions with NMDA and AMPA receptors, as well as other components of the postsynaptic density, including PSD95, Fyn

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kinase, and GSK-3β.[156,159,164,171,172] Here, the role of the individual isoforms remains unresolved.

In summary, the functions of TAU extend beyond MT stabilization to encompass diverse roles in cellular processes. Isoform-specific studies in murine brains together with data from human neurons reveal unique patterns of interactions, emphasizing the importance of considering different TAU isoforms when studying TAU physiology. Recent investigations in hiPSC-derived neurons further highlight the involvement of TAU in pre-synaptic vesicle dynamics, proteasomal processes, translation, and mitochondrial function, expanding the functional spectrum. Despite high sequence homology, the TAU interactome differs between species, emphasizing the need for species-specific considerations. While pathological implications have been extensively studied, the roles of TAU isoforms in physiological conditions, such as translational regulation and synaptic plasticity, remain relatively unexplored. Collectively, these findings advance our understanding of the diverse contributions of TAU to cellular function, with potential implications for health and disease.

5 | THE EFFECT OF TAU DEPLETION AND (RE-)EXPRESSION OF (INDIVIDUAL) TAU ISOFORMS

Through MT-binding, TAU influences various neuronal processes such as axonal differentiation, morphogenesis, outgrowth, branching, cargo transport, and neuronal plasticity.[97,103,119,173–175] TAU depletion is in general well tolerated in rodents, possibly due to the compensatory upregulation of other microtubule-associated proteins (MAPs), such as MAP1A and MAP6 during neuronal development.[97,99,102,176] However, *Mapt* knockout (KO) mice show some strain-dependent mild age-related characteristics, such as changes in sleep-wake patterns, motor deficits (parkinsonism), deterioration of cardiovascular function, and impairments of fear conditioning.[177–184]

In contrast, TAU depletion in adult animals enhances hippocampal neurogenesis and leads to resistance against depressive behaviour.[185] In primary cultures, KO, knockdown (KD), or antibody mediated suppression of TAU however results in a mild but detectable reduction of axonal growth, decreased MT density, reduced neurite length, and reduced synaptic spines in some studies, but does not cause axonal transport deficits, changes in MT-stability, neuronal activity and synaptic spines.[97,99,101,176,186–188] Similar effects have also been observed in hiPSC-derived neurons, which in addition exhibit changes in the AIS but do not show impairments in neuronal activity.[100,189,190] The expression of all six human TAU isoforms from an artificial chromosome in murine *Mapt* KO background resulted in increased dendritic localization of TAU, TAU hyperphosphorylation and aggregation, memory deficits, and neuronal loss.[191–194] These phenotypes are likely caused by the imbalance between 3R and 4R expression observed in these animals, which is also associated with several tauopathies[191–194] (see the TAU isoforms in tauopathies section). In contrast, humanization of the entire murine *Mapt* locus similarly resulted in a human-like expression of TAU isoforms but does not lead to any overt phenotype or impairments in *Mapt* KO animals.[195] Heterozygous deletion of exon 10 (encoding for the fourth repeat domain) in mice resulted in a one-to-one ratio of 3R and 4R murine TAU isoform expression, mimicking the physiological abundance of TAU in human brains. While the deletion of exon 10 did not result in apparent morphological changes of the brain, an age-dependent decline of sensorimotor function was observed in these animals,[196] which hint toward an isoform-specific haploinsufficiency pathomechanism. While this is in line with a recent study claiming *MAPT*-haploinsufficiency-based loss of dopaminergic neurons and decreased viability due to a lack of MAP1A compensation,[197] there is to date little evidence supporting (isoform-specific) TAU haploinsufficiency. There is, however, a clear selection against loss of function (LoF) mutations in the brain-development-specific isoform 0N3R-TAU (but not the other isoforms), indicating that in humans, and at least during neuronal development, haploinsufficiency of 0N3R-TAU is not tolerated or prevents further procreation (e.g., because of severe enough intellectual disability).[198] However, these results highlight the importance of a tight regulation of TAU isoform expression, underline the differences between human and murine *Mapt* splicing and the importance of a (species-specific) splicing pattern for proper physiological function of TAU.

The effects of individual TAU isoforms are also remarkably different depending on the model system studied, the technique used to express TAU and which isoform is chosen. Expression of human 2N4R-TAU in a murine *Mapt* KO background increased hippocampal neurogenesis and improved cognitive function compared to TAU depleted animals.[199,200] Notably, mild toxic effects of overexpressed human 0N4R-TAU have been observed, which induced Golgi fragmentation in isolated murine

FIGURE 2 TAU functions in health and disease. In healthy neurons, TAU is enriched in the axon, where it binds and enables MTs to form long labile/ dynamic domains. A small fraction of TAU is reported to be localized in in the soma, dendrites and the nucleus. Interactome and functional studies highlight the diverse roles of TAU in various cellular contexts. For example, by interacting with DNA and RNA, TAU can influence transcription and translation.[142] Dendritic TAU enhances dendrite and spine maturation and may be important for synaptic activity. During neuronal development, TAU facilitates axonal outgrowth and growth cone dynamics and later has a role in synapse formation and synaptic transmission. Under pathological conditions, such as extracellular aggregation of amyloid beta plaques, TAU dissociates from axonal MTs, accumulates in in the somatodendritic compartment, and gets hyperphosphorylated. Due to the phosphorylation, TAU changes its conformation, which increases its aggregation propensity and results in the accumulation of TAU assemblies in NFTs. Reduction of the MT-bound TAU results in changes of MT dynamics and leads to impairments of downstream functions, such as axonal transport, which ultimately drives synaptic dysfunction and neuronal cell death. Furthermore, TAU missorting into the dendrites causes postsynaptic spine loss and NMDA receptor mediated excitotoxicity driving cognitive decline. Furthermore, somatic or missorted TAU can inhibit translation, and cause proteasomal and mitochondrial dysfunction. At the pre-synapse TAU further contributes to synaptic dysfunction and can spread trans-synaptically to receiving neurons, possibly mediating the progression of the pathology. Figure created with BioRender.com

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hippocampal neurons.[201] Furthermore, overexpression of human TAU isoforms in WT primary murine neurons significantly affected spine and dendrite maturation: especially 2N4R-TAU expression enhanced neuronal maturation, accelerated spine formation and dendritic growth.[124] Depletion of TAU in the SH-SY5Y neuroblastoma cell line, resulted in an increased resistance to induced DNA double-strand breaks (DSBs) but lead to cellular senescence in a p53 dependent manner.[202] The re-expression of 2N4R- or 2N3R-TAU, restored cellular sensitivity to DSBs and ameliorated the pro-survival effects of TAU depletion, but other isoforms were not evaluated.[202] Re-expression of individual TAU isoforms in hiPSC-derived *MAPT* KO neurons restored neurite length and AIS length to wild-type (WT) levels and did not affect neuronal activity.[100]

All in all, the results from human TAU knock-in (KI) and murine *Mapt* KO animals and derived primary neurons, and recent evidence from hiPSC-derived *MAPT*-KO neurons, suggest that TAU depletion can be tolerated relatively well in rodents likely because of compensation by other MAPs, however, also implies important modulatory roles of TAU in neuronal development and maturation, in particular in human cells. In humans, mutations in *MAPT* which lead to a loss of its primary function by altering the MT binding affinity or reduce its ability to promote MT assembly, are causative for FTD, but usually also come along with a gain of function, namely increased aggregation propensity.[198,203] Furthermore, tauopathies can be classified according to the TAU isoforms present in neuronal inclusions (see also the TAU isoforms in other tauopathies section). In humans, true haploinsufficiency of *MAPT* alone has not been reported. Microdeletions at chromosome 17q21.3, which encompassed *MAPT* and *CRHR1* (corticotropin-releasing hormone receptor 1, a gene that is currently not associated with a genetic disease),[204,205] were later found to also include the gene *KANSL1*, which is causative for the phenotype of the (*KANSL1*-associated) Koolen-De Vries syndrome, independent of the absence or presence of *MAPT*.[206] This, and the fact that up to date there are no homozygous LoF mutation carriers of *MAPT* reported, hint towards at least some selection against (haplo-) insufficiency or LoF mutations in human development, but whether LoF is a contributor to (age-associated) neurodegeneration is unclear. This underlines the differences between human and murine neurons regarding the tolerance of TAU loss and the importance of TAU function especially during neuronal development.

6 | THE CONTRIBUTION OF TAU ISOFORMS TO TAUOPATHIES

Tauopathies are a heterogenous group of more than 20 neurodegenerative diseases characterized by mislocalization and accumulation of hyperphosphorylated TAU in the somatodendritic compartment.[7] They are categorized based on the presence or absence of co-pathologies, the genetic background, the TAU isoforms present in the insoluble aggregates, or the conformation of the TAU filaments (reviewed in[9,25,207–209]). Primary tauopathies, such as PSP, CBD, PiD, and FTDP-17, are diseases in which TAU pathology is the major contributing factor or hallmark. In contrast, secondary tauopathies, such as AD, PD, and Huntington's disease (HD) involve the aggregation of an additional amyloidogenic protein (Amyloid beta (Aβ), α-synuclein, or huntingtin, respectively). The majority of tauopathies are sporadic, and endo-lysosomal and mitochondrial dysfunction, changes in splice factors, aberrant ROS production, and epigenetic dysregulations together with certain risk factors, such as TAU haplotype, an unhealthy lifestyle (e.g., alcohol abuse, smoking, overweight), cardiovascular factors (such as hypertension or diabetes) and head injuries have been implicated in the disease pathogenesis (reviewed in[207,210–212]).

Over 50 *MAPT* variants are linked to FTD spectrumdisorders, contributing to up to 20% of familial cases (Alzforum database 12/2023) (reviewed in[22,25,209]). These mutations, often centered around exons 9-12, or found within intronic regions, frequently lead to impaired splicing of exon 10. This disruption results in an imbalance between 3R and 4R TAU isoforms (e.g., ΔK280, ΔN296, P301L, P301S).[54,213] Other missense mutations or deletions diminish the MT binding affinity of TAU, reduce its ability to promote MT assembly (e.g., P301L, P301S, V337M), enhance protein aggregation propensity (e.g., ΔK280 and P301L), disrupt interactions with other proteins (e.g., R406W), or alter its phosphorylation pattern (e.g., P301L, V337M, G272V).[21,25,213–215] Moreover, the dysfunction of other proteins has been associated with the misregulation of TAU splicing in sporadic tauopathies, which leads to an elevated inclusion of exon 10, and resulting in a higher expression of 4R TAU isoforms.[216,217] Depending on the altered splicing pattern, tauopathies can be classified as either 3R or 4R tauopathies. For example, PiD is distinguished by tangles containing 3R isoforms (0N3R, 1N3R, and 2N3R), while 4R-TAU (0N4R, 1N4R, and 2N4R) accumulates in disorders such as PSP and CBD. In AD patients, aggregates comprise all isoforms.[24,25] The disease-specific aggregation of TAU isoforms can be explained by differences in the seeding potential of individual isoforms: 3R TAU seeds, for example, can recruit both 3R and 4R monomers, whereas 4R isoform seeds contain only 4R monomers.[218–220] Of note, TAU aggregation propensity is significantly affected by its PTMs and the specific isoform(s) expressed (see the The contribution of TAU isoforms to AD pathology section). A recent in vitro study demonstrated, for example, that while acetylation can specifically drive 3R-TAU aggregation, acetylation of lysine residues within the second MT-binding repeat unique to 4R-TAU isoforms prevents TAU fibril formation.[221] Cryo-EM characterization of fibrils derived from brains of patients with distinct tauopathies revealed that distinct TAU filament structures characterize different tauopathies, implying substantial variations in the mechanisms underlying these diseases and underscoring the necessity for disease-modifying treatments that account for these variations.[208,222–225]

In myotonic dystrophy type 1 (DM1), a CTG microsatellite repeat expansion in the 3′ UTR of dystrophia myotonica protein kinase (DMPK) gene causes the expression of a toxic RNA. This RNA aggregates as so-called nuclear foci and ultimately results in aberrant splicing of various genes, leading to multisystemic symptoms including heterogeneous brain involvement.[226,227] Notably, NFTs of DM1 patients exhibit a selective buildup of the 0N3R TAU isoform due to altered splicing of the *MAPT* gene, primarily marked by reduced exon

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2 and 3 inclusion.[228–230] Dysregulation of the splicing factor embryonic lethal abnormal vision-like RNA-binding protein-3 (ETR3/CELF2) has been shown to repress exon 2, 3, and 10 inclusion in DM1, thereby contributing to the pathological TAU protein accumulation and NFT formation.[227,229,231,232] In addition, MBNL1 and MBNL2 dysregulation disrupts the developmental regulation of TAU splicing, leading to missplicing of TAU exon 2.[228,229,233]

The contribution of the TAU isoforms to pathological processes has been mainly studied in the context of FTD by the use of mutated TAU variants, which are directly associated with genetic forms of the disease. In human neurons generated from an immortalized neural progenitor cell line (ReN VM), the presence of mutant 2N4R-TAU^{P301L} in addition to endogenously expressed WT 3R-TAU (mainly 0N3R) led to the disruption of specific TAU interactions with non-muscle myosins.[146] These myosins play crucial roles in regulating the morphology of dendritic spines, underlining the essential role of TAU in maintaining dendritic spine integrity.[146,234–236] Additionally, in hiPSC-derived neurons, the presence of 2N4R-TAU^{P301L} or 2N4R-TAU^{V337M} resulted in a reduction of TAU interactions with ribosomal and mitochondrial proteins, causing impairments in mitochondrial biogenesis.[144] Moreover, a decrease in the levels of these disrupted TAU-interacting proteins observed in vitro was also observed in AD patient brains and correlated with the progression of AD.[144] Expression of 2N4R^{P301L} in SH-SY5Y neuroblastoma cells resulted in a reduced interaction of TAU and proteasomal subunits but increased interactions with ribosomal subunits, translation initiation factors and hnRNPs.[145] Comparison of the WT rat 2N4R-TAU interactome with a truncated human 4R-TAU (hTAU151-391) variant in transgenic rats lead to the identification of novel interacting proteins, for example, Baiap2, Gpr37l1, and Nptx1, that were further validated by Co-IP of human AD brains and could play a role in TAU pathology.[152] Enhanced expression of 0N4R- and 1N4R-TAU in hiPSC-derived neurons mediated by introducing point mutations at the 3′ and 5′ ends of exon 10 that prevent splicing of the pre-mRNA, did not result in obvious phenotypes and treatment with aggregation-prone TAU seeds did not induce TAU accumulation.[237] However, when neurons express 0N4R^{P301S} and 1N4R-TAU^{P301S} under the same conditions, progressive TAU accumulation can be observed. Expression of mutant TAU further resulted in impairments of endo-lysosomal function and neuronal activity. In addition, a recent CRISPRi screen in these neurons identified components of the endo-lysosomal system and proteins mediating UFMylation of TAU as novel factors promoting the initial seeding and propagation of TAU.[237]

Proteomic analysis of murine neurons expressing human 0N4R^{P301L} revealed changes in the interaction of TAU with RNPs, that upon disease progression specifically co-localize with TAU inclusions.[153] Further, 1N4R^{P301L} expression in mice confirmed interactions of TAU with HSPs and found a novel link between the ubiquitin-proteasomal system and TAU pathology.[155] In a *Drosophila melanogaster* tauopathy model, overexpression of the 0N4R isoform led to neurodegeneration and impairments in learning and memory.[238]

In conclusion, studies in diverse cellular models, including hiPSC-derived neurons and transgenic rodents, highlight isoform-specific interactions, and their relevance to disease progression. It is crucial to note that the studies discussed here predominantly utilized isolated and mutated TAU isoforms for their analyses to uncover novel disease mechanisms. While some findings are consistent between studies, the question of whether these mechanisms are truly isoform-specific remains elusive, especially concerning that often isolated 2N4R or 1N4R TAU isoforms are studied. The considerable differences between studies, including variations in the isoform studied, the use of FTD-associated mutants, and the diverse model systems employed, underscore the complexity of TAU in disease pathology. The relevance of these findings to disease pathology and the functional role of TAU in this context therefore remains to be explored.

7 | AD PATHOLOGY: GENERAL INTRODUCTION AND ISOFORM-SPECIFIC CONTRIBUTIONS OF TAU

In general, AD is a slowly progressive disease that is characterized by the decline of memory, language, visuospatial, and executive functions over time.[239] Although individuals in the initial phases remain cognitively normal, slight changes in the brain can be detected many years to decades before symptoms manifest.[11,13,239] In the advanced stages of AD, individuals lose the ability to perform daily tasks independently, often requiring full-time care. At the molecular level, the following key characteristics of AD (as reviewed elsewhere,[11–13,240]) can be detected in the brain: (1) The deposition of amyloid beta (Aβ) peptides in insoluble extracellular amyloid plaques and intracellular aggregation of hyperphosphorylated TAU protein in NFTs and neuropil threads. (2) Significant synaptic loss and neuronal cell death which correlate with the onset of cognitive impairment and severity of symptoms. (3) Impairment of the blood-brain barrier integrity, resulting in the activation of microglia and astrocytes and subsequent neuroinflammation.

7.1 | Familial and sporadic AD: Risk factors and their impact on amyloid pathology

Briefly, the majority of AD cases emerge in a sporadic fashion, primarily affecting individuals over the age of 65 (late-onset /sporadic AD). Nevertheless, a smaller proportion of cases (< 5%), results from autosomal dominant inheritance (familial AD), associated with early onset of the disease between the age of 30 and 65. Pathogenic variants are identified in the genes encoding for the amyloid precursor protein (*APP*) or proteases involved in APP processing (*PSEN1* or *PSEN2*). These variations lead to an enhanced production of aggregation prone Aβ peptides, or directly influence the propensity for Aβ aggregation[241] (reviewed, e.g., in[11,242]). These peptides, namely Aβ_{40} and Aβ_{42}, which accumulate in insoluble extracellular plaques in AD, are produced through sequential cleavage of APP by the β-secretase and γ-secretase complex.[243,244] Under normal physiological conditions and at low concentrations, Aβ peptides facilitate synapse formation and synaptic signaling. The processing and release of Aβ peptides is therefore closely linked to synaptic activity.[245–250] At higher

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concentrations, Aβ peptides, particularly $A\beta_{42}$, may aggregate into β-sheet conformations such as oligomers and (proto) fibrils leading to significant downstream consequences, including neuronal dysfunction (mainly through interaction with NMDA and insulin receptors), TAU hyperphosphorylation, and synapse loss, that ultimately result in neurodegeneration[247] (reviewed, e.g., in[251–253]). Furthermore, various APP mutations are linked to familial AD, for instance, the Swedish (K670_M671delinsNL), London (V717I), or Indiana (V717F) mutations that result in amplified production of amyloidogenic Aβ peptides or structural modifications which enhance the propensity of the peptides to aggregate (reviewed in[243]). Additionally, variations in *PSEN1* or *PSEN2*, which encode for presenilin 1 (PS1) and 2 (PS2) that are part of the γ-secretase complex, result in a dominant-negative effect on γ-secretase activity and alter the balance between $A\beta_{42}$ and $A\beta_{40}$ peptides.[254,255]

More than 40 alleles have been implied as susceptibility factors for late-onset sporadic AD (reviewed in[11]). The *APOE* ε4 allele, the most prominent risk allele, for example, increases the AD risk up to 15 times when present on both alleles.[256] Other risk genes, such as *TREM2*, *SORL1*, *ABCA7*, *BIN1*, *CD33*, and *CLU*, are primarily associated with APP processing, immune response, microglial function, cholesterol lipid dysfunction, endocytosis, and vascular factors, implying central roles of these pathways for disease pathology.[257–260] Interestingly, variants in *MAPT* are not associated with an increased risk for AD, although several of TAU's interaction partners, such as *BIN1*, *FERMT2*, and *PTK2B*, have been identified as risk factors.[259]

On the other hand, several protective alleles that reduce the risk of developing AD, have been identified, including the *APOE* ε2 allele leading to a two times reduced risk of AD.[261,262] In addition, the rare Icelandic APP mutation (A647T) has been shown to protect against cognitive decline by reducing the production of $A\beta_{42}$ by up to 40%.[263] Remarkably, a homozygous mutation in APOE ε3 (R136S, "Christchurch"), identified in one individual with an inherited *PSEN1* variant, protected against neurodegeneration and cognitive decline for decades after the expected onset of disease symptoms.[264]

7.2 | The general role of TAU as a disease mediator in AD

While TAU protein pathology has been intricately linked to AD and, in contrast to Aβ pathology, correlates well with the cognitive decline observed in patients, no disease-causing variants in *MAPT* have been associated with AD and co-occurring Aβ pathology is necessary to drive TAU accumulation and disease progression.[265–269] The significance of TAU in disease progression is underscored by the absence of cognitive symptoms in some individuals with Aβ pathology and the protection of *Mapt* KO animals from Aβ-induced neurotoxicity, memory impairments, and premature mortality.[98,270–277] TAU reduction in hAPP, APP23, and pR5 transgenic mice for example prevented memory loss, premature mortality, and reduced excitotoxicity induced by Aβ.[164,270] This is likely mediated by the reduced expression of the tyrosine kinase Fyn upon TAU depletion, as *Fyn* KO animals exhibit the same protective effect as *Mapt* KO mice.[278] This protective mechanism can be observed also in primary cultures and slice cultures from TAU depleted animals, which show sustained long-term potentiation (LTP) and functional axonal transport of mitochondria and vesicles.[164,279] This effect has been recently also demonstrated in *MAPT* KO hiPSC-derived neurons that are protected from Aβ oligomer (AβO)-induced neuronal toxicity.[100,190] Of note, the protective effect of TAU reduction or depletion is specific to AD and does not protect from pathology in animal models of other tauopathies, such as ALS and PD, and even exacerbates the phenotype of Niemann-Pick disease type C models.[279–281]

In contrast to Aβ peptides, TAU pathology manifests as intracellular NFTs, neuropil threads, and dystrophic neurites. The pattern of TAU pathology in the brain of AD patients is highly reproducible and follows determined trajectories: TAU accumulation appears first in the locus coeruleus (LC), and then spreads to the entorhinal cortex, hippocampus, and finally, in advanced stages, throughout the frontal cortex.[15,282–284] Similar to the spread of Aβ pathology, TAU pathology also propagates to anatomically connected regions of the brain in a prion-like manner: TAU aggregates either synthetically prepared or derived from AD-affected brains trigger pathological TAU aggregation in mouse models of AD.[285–291] The self-assembly of TAU into larger oligomers and filaments significantly depends on the presence of two hexapeptide motifs, PHF6 ($_{306}$VQIVYK$_{311}$) and PHF6* ($_{275}$VQIINK$_{280}$), within the MT-binding domain. Deletion of the PHF6 sequence, which enables the assembly of TAU into β-sheet conformations similar to that of TAU fibrils observed in vivo, for example is sufficient to prevent TAU assembly.[292] TAU aggregation can be further enhanced by the interaction with RNA and RNPs, as interaction of TAU with the RNP TIA1 for example increases stress granule formation and toxic TAU aggregation.[166]

Normally, TAU is efficiently sorted into the axon. In the presence of pathological Aβ species, however, TAU undergoes abnormal phosphorylation, detaches from MTs, and accumulates in the cell body and dendrites (Figure 2B).[25,252,293–297] Specifically dendritic TAU has been implemented as an early driver of Aβ-induced neurotoxicity: TAU locally destabilizes dendritic MTs by recruiting Tubulin-Tyrosin-Ligase-Like-6 (TTLL6s). TTLL6 polyglutamylates dendritic MTs, which triggers spastin-mediated MT severing and causes synaptic and specifically dendritic spine dysfunction.[101,103,298,299] Furthermore, dendritic TAU recruits Fyn to the postsynaptic NMDA receptor complex, which causes the phosphorylation of NMDA receptor subunits and ultimately results in excitotoxicity[164] (reviewed in[156]). PTMs of TAU, such as phosphorylation and acetylation increase the dendritic localization of TAU and influence its aggregation propensity, contributing to local MT destabilization and synapse dysfunction.[134,156,300]

As a MT-associated protein, TAU plays a significant role in regulating the transport of proteins and organelles along the axon by influencing cytoskeletal motor proteins such as dynein and kinesin.[301] PTMs of TAU result in a reduced MT-binding affinity, detachment from axonal MTs, and lead to altered MT dynamics. Pathological TAU directly impedes the binding of motor proteins to axonal MTs, leading to deficient axonal transport and the accumulation of organelles and axonal proteins in the cell body (Figure 2B).[211] Breakdown of axonal transport,

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together with local disruption of MT dynamics, directly contributes to the synaptic impairments observed in AD. The therapeutic benefit of MT-stabilizing drugs as demonstrated in preclinical AD models further supports the importance of TAU-mediated MT dynamics in AD.[302–305] However, it may be more appropriate to correct the imbalanced ratio between labile and stable microtubules rather than solely concentrating on stabilizing MTs (reviewed, e.g., in[102]). In sum, TAU aggregation and loss of physiological TAU function contribute significantly to the synaptic dysfunction and neuronal cell death observed in AD through altered cytoskeleton dynamics and axonal transport deficits (Figure 2B).[25,211,240]

7.3 | The contribution of TAU isoforms to AD pathology

While the role of TAU as a key mediator of Aβ-induced neurotoxicity is well established, the contribution of individual isoforms remains largely unexplored.[143] Studies performed in disease context often focus on one specific TAU isoform, mainly 2N4R (= "full-length TAU"), and make use of mutated TAU variants (associated with FTD) to induce TAU pathology. In WT mice, the 2N4R-TAU interactome has been specifically linked to neurological diseases.[143 14]. In the human brain, however, 1N-TAU isoforms are the predominantly expressed isoforms, that make up to 50% of the whole TAU protein expression.[37] While TAU depletion protects neurons and mice from AD pathology, re-expression of 1N4R-TAU, but not the other human TAU isoforms, restored the vulnerability of *MAPT* KO hiPSC-derived neurons to AβO-induced neuronal dysfunction.[100] In primary neurons, KD of 2N4R-TAU by RNAi or a 2N-TAU specific antibody specifically prevented AβO-induced synaptotoxicity, suggesting that specific TAU isoforms might be sufficient to drive neurodegeneration in these model systems.[138] Overexpression of the human 0N4R and 0N3R TAU isoforms in *Drosophila melanogaster* resulted in a reduced lifespan upon 0N3R expression, but also lead to greater neurodegeneration upon 0N4R expression, suggesting that upon overexpression, and due to different interactions, TAU isoforms exhibit a differential toxicity.[238] Furthermore, a comprehensive study performed in flies characterized the effect of individual human TAU isoform overexpression and demonstrated that overall lifespan is affected equally by all isoforms. Interestingly, specifically 4R TAU isoforms (0N, 1N, and 2N) lead to significant learning and memory deficits, that were not observed in 3R expressing animals.[306] TAU has been shown to interact with RNPs and ribosomal subunits (reviewed in[142]), and TAU oligomers formed by 1N4R induce a translational stress response and inhibit translation, resulting in stress granule formation and changes of dendrite length and morphology that further drive neuronal dysfunction in primary murine neurons.[163,170,307,308] Besides the likely contribution of the N-terminal inserts to disease pathology, the presence of an additional repeat domain has been shown to enhance the aggregation propensity of TAU isoforms in vitro. The additional repeat domain of 4R TAU isoforms results in faster assembly into oligomers, which is further enhanced by the presence of additional N-terminal inserts, present in 1N- and 2N-TAU isoforms that reduce the critical concentration to form fibrils in vitro.[112,223] Furthermore, due to the additional repeat domain present in 4R-TAU isoforms, these isoforms can be subjected to a higher number of PTMs, such as phosphorylation. Especially phosphorylation of the KxGS motifs, that are located within the MT-binding domain, could further contribute to local disruption of MT dynamics and drive synapse loss in AD.[101] Furthermore, TAU spreading or seeding could be isoform-specific: A recent study demonstrated that exposure of human iPSC-derived astrocytes to extracellular vesicles isolated from 1N3R and 1N4R overexpressing primary rat neurons lead to similar uptake of 3R and 4R TAU; however, 3R-containing vesicles were more toxic to the cells compared to 4R-containing extracellular vesicles (EVs).[309] As TAU spreading has been shown to be mediated (among other pathways) via EVs (reviewed, e.g., in[310]), these initial results support our hypothesis that rather individual TAU isoforms mediate TAU toxicity in disease context.

In conclusion, studies investigating the contribution of individual TAU isoforms to AD pathology remain sparse. Available results suggest a significant contribution of the 1N- and 2N4R-TAU isoforms to AD pathology; however, in vivo validations of these experiments are needed to gain a better understanding of these processes. Clarifying the specific contributions of individual TAU isoforms will be critical for unraveling the intricate mechanisms underlying TAU-related neurodegenerative disorders.

8 | TAU-TARGETING THERAPIES FOR AD AND OTHER TAUOPATHIES

Among the seven currently U.S. Food and Drug Administration (FDA) -approved drugs for the treatment of AD, five (donepezil, rivastigmine, galantamine, memantine, and the combination of memantine with donepezil) primarily target disease symptoms, such as behavioral psychological, and cognitive impairments (e.g., agitation, aggression, memory loss), without substantially improving cognition or halting disease progression.[239] Two antibodies designed to target Aβ, aducanumab (Biogen) and lecanemab (Eisai and Biogen), have gained approval as disease-modifying treatments (DMTs). Both drugs received FDA approval via the accelerated approval pathway, which relies on a "surrogate endpoint" anticipated to correlate with a positive impact on cognitive function. For full FDA approval, both medications must demonstrate their clinical efficacy in subsequent trials.

With respect to TAU, several agents are currently investigated in preclinical and clinical settings, which use diverse strategies to diminish or avert pathological TAU build-up in the context of AD and other tauopathies (for an overview of current clinical trials for AD, see[311]). For example, reducing overall *MAPT* expression by an antisense oligonucleotide (ASO) significantly reduced TAU pathology and improved cognition in AD/tauopathy mouse models and has proven safety in a phase Ib clinical study.[277,312,313] The ASO, termed $MAPT_{Rx}$ (Ionis Pharmaceuticals), binds to intron 9 of the *MAPT* pre-mRNA, thereby targeting it for degradation and achieving up to 50% reduction of TAU levels in the cerebrospinal fluid (CSF) of human subjects.[312] A successful and significant reduction of TAU

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expression and neuronal degeneration has been achieved also by a single systemic injection of an AAV-based engineered zinc finger protein transcription factor in APP/PS1 mice.[314] While some antibody-based therapies for the clearance of extracellular Aβ have shown clinical benefit and have been approved for use in AD patients, no effective therapy targeting TAU has yet shown efficacy. Several antibodies are currently investigated in clinical studies to target toxic TAU species, such as highly phosphorylated and aggregation-prone TAU or TAU assemblies. Unlike Aβ, the majority of (toxic) TAU species may remain intracellularly, and it needs to be demonstrated whether antibodies can successfully prevent pathology and improve cognition by targeting mostly extracellular TAU species (for review, see e.g.,[315,316]). Besides enhancing the clearance of pathological TAU, several compounds have been designed to inhibit TAU aggregation. Leuco-Methylthioninium Bis(Hydromethanesulphonate) (LMTM/ TauRx Pharmaceuticals), a derivative of methylene blue, has demonstrated a significant reduction of TAU pathology. In TAU transgenic mice, LMTM improved cognitive impairments,[317] and a recent phase III study on early AD patients demonstrated an improvement of cognitive deficits and a reduction of brain atrophy.[316,318,319] ACI-3024 (AC Immune) is another small compound TAU aggregation inhibitor. Even though preclinical data have not been published yet, data presented at conferences show that the compound disrupts TAU aggregates in vitro, in primary neuronal cultures and in a tauopathy mouse model[320] (as discussed in[316]). Further, it prevents microglial activation and neuronal cell death induced by toxic TAU species. A phase I study was started in 2019 to evaluate the safety and tolerability of ACI-3024 in healthy volunteers, however results have not yet been reported (reviewed in[316]). Other therapeutic strategies aim to target specific PTMs of TAU, for example, (1) by inhibiting GSK3β and preventing (hyper)phosphorylation of TAU[66,321,322]; (2) by targeting acetylation of TAU, which has been demonstrated to increase the aggregation propensity of TAU[134,156,300]; or (3) by inhibiting O-GlcNAcase (OGA) activity, to increase O-GlcNAcetylation of TAU, which has been reported to prevent aggregation of TAU, and stabilize it in a soluble form.[323,324] While promising results have been demonstrated in preclinical models for GSK3β inhibitors Lithium, valproic acid, and Tideglusib,[66,321,322,325] none of the compounds demonstrated beneficial effects on cognition in clinical trials.[326–328] Salsalate, which has been found to inhibit TAU acetylation in animal models for FTD and TBI, did not show any clinical benefit in PSP patients.[329–331] While inhibiting phosphorylation and acetylation of TAU did not demonstrate beneficial outcomes in clinical studies so far, three OGA activity inhibitors, MK-8719 (Alectos Therapeutics/ Merck), ASN90 (Asceneuron SA), and LY3884963 (Eli Lilly & Co) received orphan drug designation by the FDA for the treatment of PSP (MK-8719, ASN90), and FTD (LY3884963).[332–334]

Despite the variety of TAU-targeting therapeutic strategies, to our knowledge, no DMT for AD or other TAU-related neurodegenerative disease that specifically targets a particular TAU isoform or alters *MAPT* splicing is currently being evaluated in preclinical or clinical trials for AD. While an imbalance in TAU 3R-to-4R isoform expression has been directly linked to disease pathogenesis in several tauopathies,[9,10,207,212] data on the contribution of individual TAU isoforms on AD are scarce. Nevertheless, some recent results imply benefits in disease models when individual isoforms are suppressed, or demonstrate isoform-specific mediation of neuronal dysfunction.[100,138] (see the The contribution of TAU isoforms to AD pathology section) A strategy to enhance exon 10 incorporation through a lentivirus-mediated *trans*-splicing event has shown beneficial results in the humanized TAU mouse model of Andorfer and colleagues, restoring equal ratios of 3R and 4R TAU expression and reducing TAU pathology and cognitive impairments.[191,335–337] Targeting specific TAU isoforms in AD may be advantageous over total protein reduction strategies, as total TAU reduction can lead to mild age-related phenotypes in animal models and is associated with a severe developmental disorder in humans (see the The effect of TAU depletion and (re-)expression of (individual) TAU isoforms section).

9 | CONCLUSION AND PERSPECTIVE

The species-dependent and tissue-specific complexity of *MAPT* splicing and the resulting diversity of TAU isoforms may have evolutionary advantages: Based on studies on TAU isoforms performed in murine and human model systems, we can assume that the isoforms adopt distinct functions in dependence of, for example, their expression timing during development, brain-region specific expression, PTM-sites, interactors, and subcellular localization.

While *MAPT* splicing regulation may provide evolutionary advantages in a physiological context as outlined above, their regulation in humans apparently has to be maintained in a tight fashion: Dysregulation of *MAPT* splicing, altered subcellular localizations, and differences in PTMs influencing the aggregation propensity of the protein significantly contribute to disease pathogenesis and neuronal dysfunction, all proven by clinical disease manifestation or experimental evidence. The failure of a variety of Aβ- and TAU-targeting therapies in AD, the most prevalent tauopathy, highlights the urgent need for better targeted therapies. The following points should be considered: (1) Therapeutic strategies targeting TAU isoforms, including splicing modifiers and interventions that restore the correct isoform ratio, hold promise as effective therapies for TAU-related diseases, in particular for diseases where TAU isoform balance per se is affected; (2) The development of TAU-based (independent of whether strategies are isoform-based or not) therapeutic approaches must take into consideration that *MAPT* splicing patterns show developmental stage-, region-, and cell type-specificity in the brain, suggesting selective susceptibility to changes in TAU isoform expression, and that the role of TAU in neuronal development needs to be carefully assessed, as 0N3R-TAU may be essential for proper human brain development, which would imply also an important function for adult neurogenesis; and finally, (3) Future disease models of Alzheimer's or other tauopathies should be developed on the basis of systems that enable the study of the different TAU isoforms, for example, mice or human neurons expressing all human TAU isoforms. Better understanding of TAU biology and the involvement of the TAU isoforms in physiology and disease mechanisms will ultimately help to develop specific therapies, which must target the

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pathological processes underlying tauopathies, all while preserving the essential functions of TAU in normal cellular physiology.

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