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The Role of Amyloid Beta and Tau in the Pathology of Alzheimer's Disease

By Alisa Zhou

AUTHOR BIOGRAPHY

Alisa Zhou is a rising high school senior in FL, United States. She is interested in studying human disease and hopes to research within the field of biomaterials and biotechnology.

ABSTRACT

Neurotoxic amyloid beta plaques and neurofibrillary tau tangles are often known as the two main proteins attributed to the pathological hallmarks of Alzheimer's disease (AD). This disease is a prevalent type of dementia that is often known to be associated with aging, memory loss, and no cure. This review examines the amyloidogenic processing of amyloid-β precursor protein (APP) into the amyloid β-42 peptide, the encoding of microtubule-associated protein tau (MAPT) through RNA splicing and phosphorylation, and the genetic factors (isoforms, alleles, chromosomal locations, and regulatory enzymes) that contribute to mutation risk in Alzheimer's disease. Recent studies suggest that tau may play a more critical role, as the distribution and density of tau aggregates had a stronger correlation with the clinical stage of AD. This suggestion challenges the ongoing debate on the amyloid cascade hypothesis: amyloid-beta oligomers, rather than plaque, play a more critical role in Alzheimer's disease pathology by triggering downstream events that lead to tau tangles. The amyloid beta peptide activates glycogen synthase kinase 3 (GSK3), which phosphorylates tau protein. This sequence leads to the formation of insoluble toxic aggregates that protein phosphatases cannot effectively dephosphorylate in some patients.

Keywords: *Alzheimer's Disease, Tau tangles, Amyloid Beta, Oligomers, APP, Hyperphosphorylation, amyloid cascade hypothesis, glycogen synthase kinase 3 (GSK3), Down Syndrome*

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INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disease of dementia that is characterized by memory loss, cognitive decline, and behavior changes. It was first studied in 1907 by Alois Alzheimer. He reported the results of the autopsy performed on a 55-year-old woman named Auguste Deter, who had died from a progressive behavioral and cognitive disorder (O'Brien & Wong, 2011). He had noted the presence of abnormal extracellular deposits and intracellular aggregates–now recognized as amyloid beta plaques and neurofibrillary tangles, respectively–that played a major role in the pathogenesis of this disease (O'Brien & Wong, 2011).

Amyloid beta forms during the amyloidogenic pathway of amyloid-β precursor protein (APP). It is first cleaved by β-secretase, resulting in amyloid peptides with an N-terminus. Then cleaved by γ-secretase and result in the C-terminus, which are prone to form oligomers and fibrils (Rukmangadachar & Bollu, 2019).

For tau tangles, during tau formation, the increased RNA splicing complexity of specific exons in tau genes leads to the formation of distinct isoforms (Corsi et al., 2022). Later, abnormal post-translational modification (hyperphosphorylation) after the splicing further affects the tau protein, and potentially leads to tau's dysfunction and detachment from microtubules (National Institute on Aging, 2024). Eventually, the neurotoxic aggregates and deposits disrupted neuronal function and led to cell death.

METHODS

The literature review process began with exploring over ten resources regarding Alzheimer's disease's symptoms and the protein involved from Google to ensure information consistency and determine the thematic area of focus. Then, after noting some key words from the general sources to set up the outline, detailed information included in this paper was chosen from the PubMed database by entering key terms such as "amyloid beta peptide", and applying a filter for "Books and Documents", "Systematic Review" with published date (within five years from July 2025). Next, searched with the key term "Amyloid Precursor Protein" in the same database and published date (within fifteen years from July 2025 for major information; doesn't apply for image). This process continued for every key term encountered throughout the entire research process. The selected paper was mainly based on information consistency and its alignment with this literature's review thematic focus after scanning at least five papers/its abstract for each specific term.

A similar method was applied when selecting papers for tau protein literature. Additional searches were conducted using key terms such as 'tauopathies,' 'tau isoform,' 'GSK3,' and 'Alzheimer's disease,' for the purpose of understanding the encoding process and pathogenesis of amyloid beta and tau protein. All key terms and

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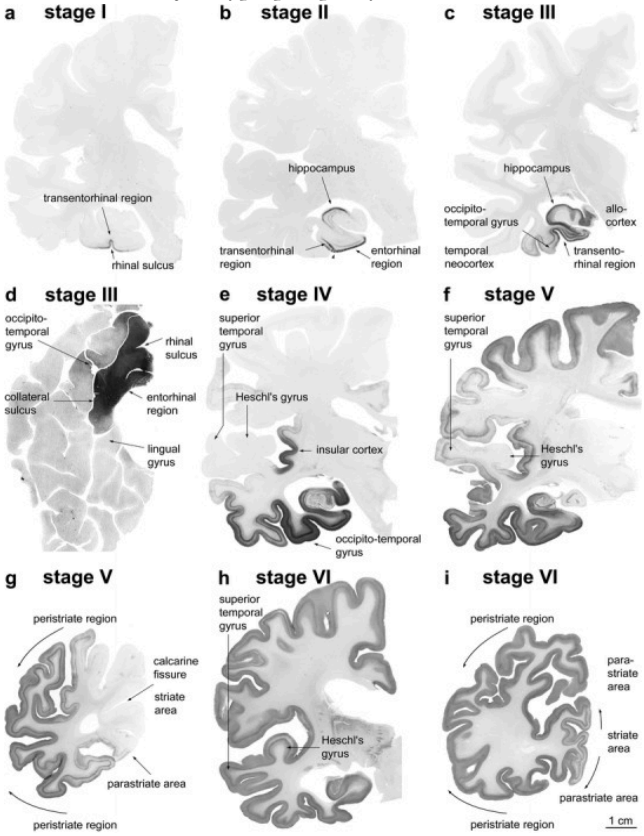
claims mentioned in this article were validated through appearing in at least three different papers published in PubMed to ensure information consistency, general direction, and minimize bias. In total, over a hundred papers' abstracts were being read for the entire review.

PATHOLOGICAL FEATURES OF ALZHEIMER'S DISEASE

Alzheimer's disease first started to affect the brain's region responsible for memory. When brain cells become affected, neurotransmitters such as acetylcholine decrease and eventually shrink in different areas of the brain (National Health Service, 2024). This can be shown by hyperphosphorylated tau for different stages (see Figure 1).

Figure 1

Stages I–VI of cortical neurofibrillary pathology in 100 µm polyethylene glycol-embedded hemisphere sections immunostained for hyperphosphorylated tau (Braak & Braak, 2006).



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In the early stage of diagnosis, the person will encounter problems such as memory loss, difficulty in completing daily tasks, wandering, losing direction, increased anxiety, etc. Then, as Alzheimer's disease becomes more severe, symptoms like shortened attention span, hallucinations, paranoia, impulsive behavior (using vulgar language, inappropriate emotional outbursts), as well as difficulty with language and getting dressed, may begin to show in patients. Finally, at a severe stage, which is usually near the end of life, the person will have no awareness of surroundings, seizures, physical body decline, and will completely rely on others for their care (National Institute on Aging, 2022). In addition, a common cause of death in people with Alzheimer's disease is aspiration pneumonia, which occurs when people are unable to swallow properly and inhale food or liquids into their lungs instead of air (National Institute on Aging, 2022).

The pathology of this disease involves abnormal buildup of tau proteins, which form neurofibrillar tangles on the microtubule within the brain cell, and amyloid-β peptide deposits that form extracellular plaque (Rukmangadachar & Bollu, 2019). And this formation of the toxic protein starts in the preclinical stage of Alzheimer's, which is often a decade before memory loss and other cognitive impairment syndromes appear (National Institute on Aging, 2022). In general cases, it starts to affect people in their mid-60s, and risks will double every 5 years after that. However, for early-onset Alzheimer's, it may start affecting people from around the age of 40 (National Health Service, 2024), with death often occurring within 10 years of diagnosis (Rukmangadachar & Bollu, 2019). People with Down syndrome (trisomy 21) have a higher chance of getting AD because of the amyloid beta encoded on chromosome 21.

ROLE OF AMYLOID-B

APP Processing

The production and accumulation of amyloid-β plays one of the central roles in the pathogenesis of Alzheimer's Disease. The buildup of amyloid-β peptide is derived from a larger precursor called amyloid-β precursor protein (APP). It is a single-pass transmembrane protein with a large domain that plays roles in several cellular processes, with the gene encoding it located on chromosome 21. In fact, the alternate splicing of the APP transcript generates 8 isoforms, but the most common three are APP695, which is predominantly expressed in the central nervous system (CNS); APP751 and APP770 are more ubiquitously expressed across tissues (O'Brien & Wong, 2011).

The sequential cleavage of the amyloid precursor protein occurs mainly through two different pathways. In the non-amyloidogenic pathway, APP is first cleaved by α-secretase and then by γ-secretase, thereby

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preventing the formation of Aβ and generating soluble ectodomains sAPPα and its intracellular C-terminal fragment (AICD) (Rukmangadachar & Bollu, 2019).

In contrast, in the amyloidogenic pathway, APP is first cleaved by BACE1 (β-secretase) and produces amyloid β 1-40 with the N-terminus. Then cleaved by γ-secretase, resulting in amyloid β 1-42 with extra residues at the C-terminus. This sequence ultimately generates amyloid beta peptides, soluble ectodomains sAPPβ, and intracellular C-terminal fragment (AICD) (O'Brien & Wong, 2011; Rukmangadachar & Bollu, 2019).

Some research indicates a synergistic relationship between the amyloid-β peptide and tauopathy(pathologies related to tau protein) through GSK3. GSK3 is able to modulate the cleavage of APP by regulating α-secretase, β-secretase, and γ-secretase activity, favoring the amyloidogenic pathway, which is associated with aβ toxicity (Zhao et al., 2024). In the bidirectional relationship, amyloid beta peptide can also activate GSK3 and potentially, through increasing the kinase's enzymatic activity, GSK3 later enhances tau post-modification, leading to hyperphosphorylation (Zhao et al., 2024).

The resulting amyloid beta peptides containing 42 amino acids only account for 10% of the peptide, but they are the primary pathogenic species of Alzheimer's Disease because of their hydrophobic nature (largely attributed to the amino acids located on the C-terminal), which are prone to aggregation into oligomers and fibrils. The resulting fibrils form β-pleated sheet configurations, which contribute to the formation of amyloid plaques that can be detected by H&E staining or amyloid-specific dyes under polar light (Rukmangadachar & Bollu, 2019).

Genetic Risk Factors

The early onset of Alzheimer's disease is rare (2-3% of cases). It may be due to genetic factors and familial cases (Rukmangadachar & Bollu, 2019). In early-onset Alzheimer's, the patients developed amyloid plaque by their 30s and clinical symptoms of Alzheimer's disease dementia in their 40s (National Institute on Aging, 2022). APP mutation is also one of the first implicated in familial Alzheimer's disease, which accounts for approximately 10% to 15% of the familial cases (Rukmangadachar & Bollu, 2019). Some findings suggest that APP overexpression or aberrant processing plays a role in disease development; therefore, people with Down syndrome, who carry an extra chromosome 21, tend to have higher levels of APP since APP is encoded on chromosome 21 (Rukmangadachar & Bollu, 2019).

Another genetic risk factor for late-onset Alzheimer's disease is apolipoprotein E (ApoE) polymorphism. The ApoE gene (*APOE*) encodes 3 major isoforms: ApoE2, ApoE3, and ApoE4 alleles. Although one of ApoE's functions is to serve as a chaperone protein that facilitates the clearance of amyloid

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plaques, ApoE4 appears to be less efficient in this role, thereby promoting amyloid-β accumulation and deposition. In fact, the risk is even higher with homozygous (ApoE4/4) than heterozygous (ApoE4/3) in this dose-dependent effect gene, which is associated with increased risk of sporadic Alzheimer's disease (Rukmangadachar & Bollu, 2019). Moreover, mutations affecting the catalytic subunit of the γ-secretase complex (the enzyme responsible for processing APP) have also been implicated in the disease. For instance, a mutation in the presenilin 1 (PSEN1) gene, which is located on chromosome 14, is also very common and accounts for up to 80% of autosomal dominant early-onset familial Alzheimer's disease cases (Rukmangadachar & Bollu, 2019).

ROLE OF TAU

Tauopathies

Abnormal accumulation, modification–excessive phosphorylation in certain pathological conditions–of tau proteins can lead to numerous neurodegenerative diseases, collectively known as tauopathies (Li et al., 2024). In Alzheimer's disease, the mutated tau proteins form neurofibrillary tangles that first appear in the transentorhinal and hippocampal regions. They then gradually progress to medial temporal lobes, neocortical association areas, and subcortical nuclei (Whitwell et al., 2008; see Fig. 1 above). This pattern makes tau tangles a reliable predictor and early indicator of Alzheimer's disease, since the quantity and location of tangles correlate directly with disease severity (Findley, 2024).

The formation of tau protein is associated with the morphology and physiology of neurons. Morphology differentiation involves the rearrangement of the three components of the cytoskeleton: microtubules, microfilaments, and intermediate filaments (Congdon & Sigurdsson, 2018). The microtubule is a tube-like structure that spans through the axon of the neuron, with the system inside transporting important molecules back and forth across the cell (Congdon & Sigurdsson, 2018). It is stabilized by microtubule-associated proteins(MAPs) like Tau and others, such as MAP1A, MAP1B, and MAP2 (Findley, 2024). A healthy tau protein promotes the polymerization of tubulin into microtubules in the brain (Findley, 2024). But in a disease state, the tau protein detaches from microtubules and forms insoluble aggregates that clump together inside neurons, therefore disrupting the neuron's transport system (National Institute on Aging, 2024) (see Fig. 2).

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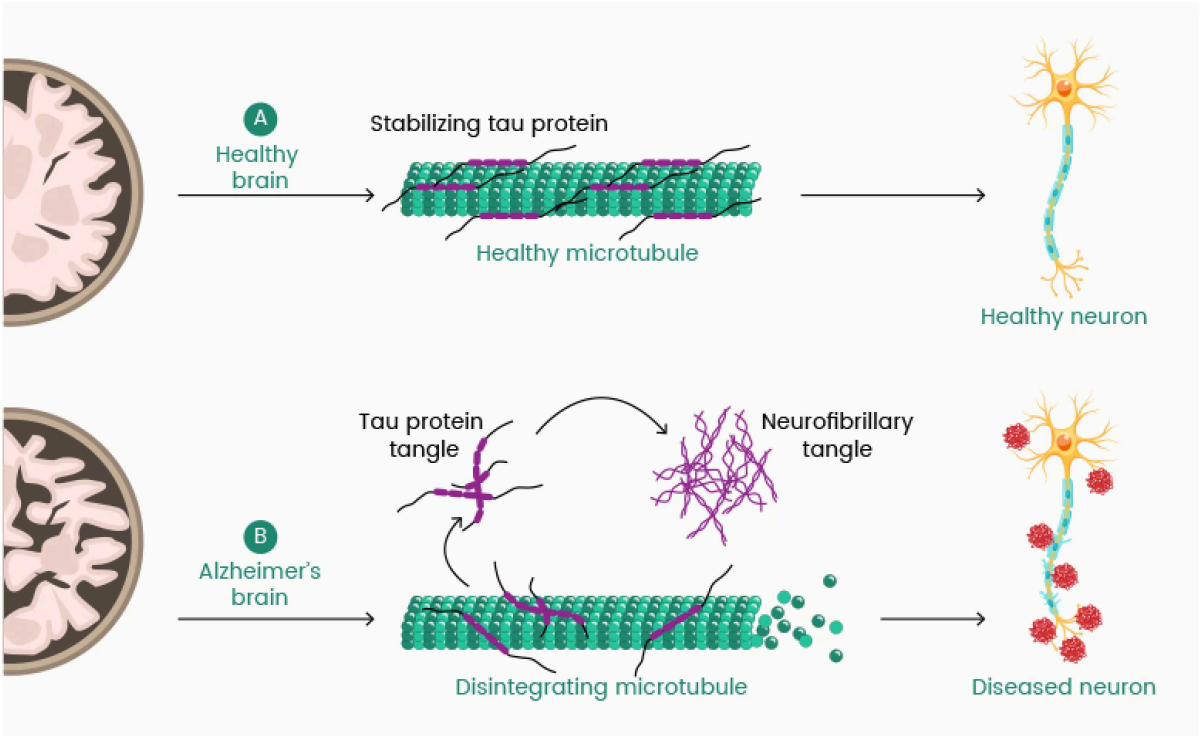
Figure 2

Tau protein detached from the microtubule in a pathological state versus in the healthy brain, tau protein attached to the microtubule (BioSpace, 2024).



Physiological and Pathological Role of Tau Proteins

Tau gene encoding process

The encoding process of the tau gene into protein takes place on chromosome 17q21, which involves two major haplotypes (H1 and H2). They are differentiated by a block of eight common single-nucleotide polymorphisms (SNPs) (Corsi et al., 2022). It is important to highlight that the H1 haplotype is strongly associated with overexpression in several neurodegenerative diseases (Avila et al., 2004).

During the encoding process of tau protein, the human tau gene–often known as microtubule-associated protein tau (MAPT)–is transcribed into nuclear RNA and yields several different tau mRNAs (see Fig. 3) through alternative splicing of the coding exons 2, 3, and 10. This process results in six

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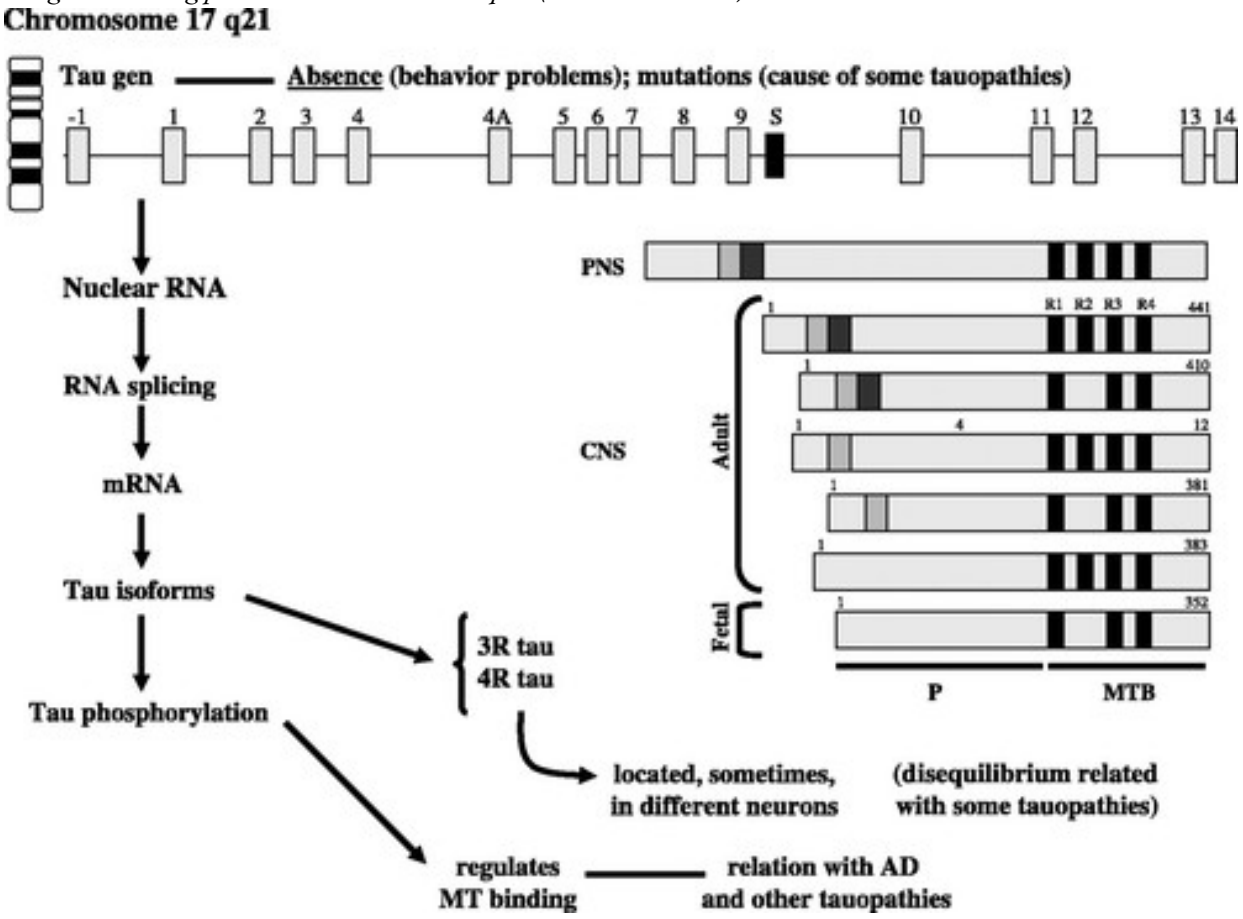
different tau isoforms through translation in the adult central nervous system (CNS) (Avila et al., 2004; Bowles et al., 2022).

Figure 3

Tau gene encoding process on chromosome 17 q21. (Avila et al., 2004)



In the CNS, exon 10 of the MAPT gene plays a crucial role in microtubule stability as it contributes to one of the encoding processes of microtubule-binding repeat domains. The alternative splicing process is regulated by splicing factors, such as SC35-like proteins, which influence the inclusion or exclusion of exon 10 (Bowles et al., 2022). This inclusion or exclusion will form two major isoforms: 3R tau, which lacks exon 10 and comprises three tubulin/microtubule binding regions; and 4R tau, which includes exon 10 and comprises four tubulin/microtubule binding regions (Bowles et al., 2022). The balance between 3R and 4R is also associated

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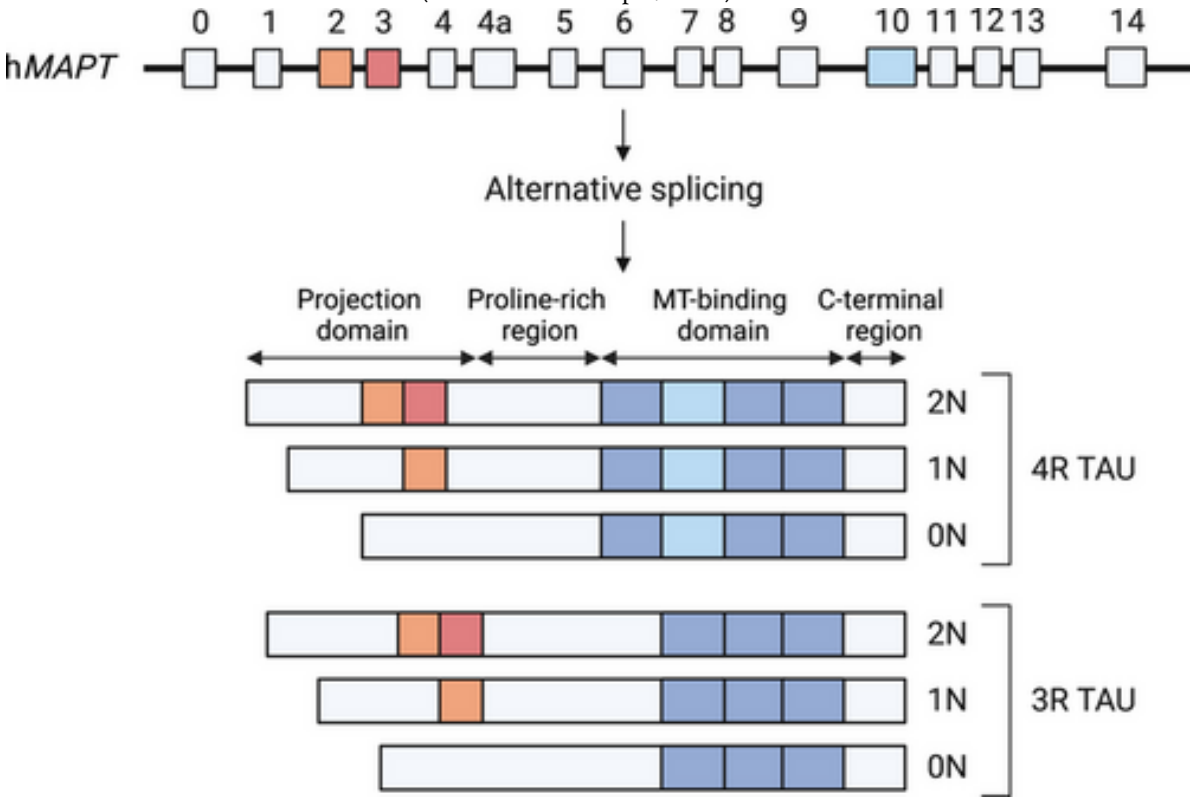
with the brain developmental stage. Importantly, splicing dysregulations of exon 10 lead to an imbalance between 4R and 3R isoforms (see Fig. 4), also associated with tauopathies (Corsi et al., 2022).

Figure 4
4R and 3R isoform with N-terminus (Buchholz & Zempel, 2024).



Note. light blue represents exon 10

Additionally, alternative splicing at the N-terminal region results in different isoforms through three N-terminus variant: N0 (absence of both exons 2 and 3), N1 (inclusion of exon 2 only), and N2(inclusion of both exons 2 and 3), in approximate ratio of 37%, 54%, and 9% of the total tau respectively (Corsi et al., 2022).

Finally, the complexity of tau isoforms further increases after undergoing post-translational modifications such as phosphorylation. During the modification, Glycogen synthase kinase 3(GSK3) was the kinase enzyme that played a major role in phosphorylating tau (Zhao et al., 2024).

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Hyperphosphorylation

Recall that aberrant accumulation of tau proteins plays a critical role in the pathology of Alzheimer's disease due to excessive phosphorylation, also known as hyperphosphorylation (Li et al., 2024). In a physiological state, phosphorylation is regulated by both phosphatases and kinases. Phosphatases such as protein phosphatase (PP)1, PP2A, and PP2B (calcineurin) dephosphorylate–removing excess phosphate group, especially in hyperphosphorylated tau (Li et al., 2024).

On the other hand, kinases such as glycogen synthase kinase 3(GSK3), tau protein kinase II (cdk5), MARK, PKA, CamKII, PKC, MAPK, JNK, or ROCK, carry out the phosphorylation (Sayas & Ávila, 2021). For instance, GSK3, core to multiple neuronal processes that are dysregulated in AD pathogenesis, performs phosphorylation by binding directly to tau and transferring phosphate from ATP to specific serine and threonine residues on tau (Sayas & Ávila, 2021).

In the pathological state of AD, mutations in the tau gene occur in the tubulin-binding region, where healthy tau initially promotes polymerization of tubulin into microtubules (Avila et al., 2004). This also makes it difficult for PP2A to perform its dephosphorylation function (remove the phosphate group); therefore, tau phosphorylation increases. In fact, hyperphosphorylation caused by excess GSK3 activity is usually treated with inhibitors like okadaic acid (Kamat et al., 2014).

CONCLUSION

Currently, according to recent reviews, substantial breakthroughs have been achieved in the clinical development of amyloid beta antibodies. Several drugs like lecanemab and aducanumab have been approved by the Food and Drug Administration (FDA) in the U.S. to target AD (Suzuki et al., 2024). On the other hand, tau-targeting therapies have failed to show clinical benefit, although the amounts and distribution of neurofibrillary tau tangles have a stronger correlation to the severity of the disease, compared to amyloid beta (Suzuki et al., 2024). Thus, for potential therapeutic targets on AD, it is important to study each individual role and analyze ongoing debates regarding the connection between them.

There may be limits on this paper due to access to resources only published in English and selection on certain databases. They are selected because they provide comprehensive information and consistency in data among recent reviews. However, the limited number of studies reviewed may restrict the understanding of other significant factors, such as GSK3 and mutation in PSEN2 and ApoE, which may also play a crucial role in studying Alzheimer's disease.

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Overall, it's undeniable that both of the proteins are major hallmarks of AD, and each plays a significant role in the pathology of Alzheimer's disease. For instance, the amyloid beta 1-42 peptide is prone to being configured into toxic oligomers and disrupts neurotransmitters. Mutated tau genes and abnormal phosphorylation led to aggregated neurofibrillary tangles, which detached and no longer helped stabilize the microtubules. Lastly, future studies should focus on GSK3, since several studies have suggested it may serve as a molecular linkage between tauopathies and amyloid beta pathology.

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