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A Systematic Review of Amyloid-β and Tau's contribution to Neuroinflammation in Alzheimer's Disease Progression

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ABSTRACT: Alzheimer's Disease (AD) is classified as the most common neurodegenerative disease that triggers and furthers the onset of neuronal cell death as a consequence of hallmark pathological changes. Since there is yet no cure for dementias such as Alzheimer's Disease, there is perpetual cognitive function and developmental decline in diseased patients. The hallmarks of AD include abnormal amyloid-β plaques, neurofibrillary tangles, and neuroinflammation. While these neuronal processes are interlinked, it is not entirely understood how they are related or regulate each other. This review will focus on the association of neuronal processes and Alzheimer's Disease pathology - more specifically the influence of amyloid-β peptide aggregation on tau tangles, and microglial inflammation. In this paper, the interaction between amyloid-β and tau tangles including how this interaction leads to proinflammatory patterns, which results in neuroinflammation observed in Alzheimer's Disease, was analyzed. In context, evidence for induction and progression of tau hyperphosphorylation and neuroinflammation were observed through analysis of iPSC neurons. In examining the pathological hallmarks for Alzheimer's Disease, neuronal abnormalities and dysfunctions have been analyzed with the intent of uncovering new potential therapeutic approaches for rescuing degenerative cell function and structure.

KEYWORDS: Cellular and Molecular Biology; Neurobiology; Alzheimer's Disease; Hallmarks.

Introduction

Alzheimer's Disease (AD) is a specific dementia that accounts for 60–80% of all dementia cases and affects 33.9 million people worldwide - a number that is expected to triple in the next 40 years.[1] AD is characterized as loss of cognitive function, such as thinking, remembering, reasoning, and behavioral abilities that affects patients' daily lives. Late-onset Alzheimer's Disease (LOAD), the most common form, is present with an onset of ~65 years of age, while early-onset Alzheimer's Disease (EOAD) is present in the younger population, with the age of onset between 35 through 60 years of age.[2] Although the age of onset can vary, according to the current criteria, the process to diagnose a patient is common and widely accepted. Diagnosis is only determined with varying degrees of certainty as possible or probable Alzheimer's Disease when all other causes have been excluded. However, currently, an unambiguous detection of AD depends on verification of typical Alzheimer's Disease pathological changes in brain tissue by autopsy reports and post-mortem analysis. As the disease progresses, patients develop increasingly severe disabilities and become completely dependent on patient care at later stages of disease.[3] The accumulation of hallmark AD pathology, first identified in the medial temporal lobe and hippocampus regions, ultimately triggers the clinical symptoms of dementia and short-term memory loss. Early stages of dementia also include subtle cognitive impairment and health issues, such as anxiety and delusions, which then develop in the lateral and parietal lobe, furthering cognitive impairment. These include failing to recall personal history, poor recognition and direction sense, and withdrawing socially. As it proliferates into the frontal lobe, occipital lobe, and cerebellum, patients fail to perform rudimentary skills, lose vision and sense of direction, and become unable to communicate.[3,4] This progression is due to cell death, the loss of neurons and neuronal connections, which is influenced by the pathological hallmarks of Alzheimer's Disease. These include amyloid-β peptide aggregation, neurofibrillary tangles, and neuroinflammation. Investigating and targeting the primary cause of Alzheimer's Disease may provide a foundation to tackle a defective component before it damages the nervous system.

Amyloid-β and Alzheimer's Disease Pathology:

A prominent hallmark pathology and primary indicator of Alzheimer's disease is the extracellular plaque deposits of the β-amyloid peptide. As suggested by the Amyloid-Cascade hypothesis, β-amyloid is the main cause of Alzheimer's and the misfolding of the extracellular Aβ protein accumulated in senile plaques causes memory loss and confusion, resulting in personality changes and cognitive decline over time.[5] Dysfunction in the mechanisms of Aβ production, specifically APP (β-amyloid precursor protein) proteolysis, has been linked to plaque formation.[6] APP is a type-I oriented membrane protein that plays a vital role in biological transport, such as neuronal development, signaling, and intracellular transport.[7] APP is processed through two principal pathways: the amyloidogenic pathway and the non-amyloidogenic pathway.[8] In the non-amyloidogenic pathway, APP is cleaved by the protease enzyme α-secretase. This processing produces a partial APP CTF, which lacks the amino terminal of the Aβ domain, thus creating a non-toxic byproduct. On the other hand, the amyloidogenic pathway produces the two forms of the amyloid-β peptide, Aβ40 and Aβ42, through cleavage of APP using β-secretase and γ-secretase.[9] A defect in the APP processing system or in the APP itself will yield accumulation

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of amyloid-β. A mutation in APP, such as the duplication of chromosome 21 or duplication of the APP gene, accelerates generation of amyloid-β after being cleaved by β-secretase 1 (BACE1) and γ-secretase, therefore, furthering the progression of Alzheimer's Disease at a younger age. Similarly, a mutation in the genes that constitute the γ-secretase catalytic subunit, presenilin 1 (PSEN1) and presenilin 2 (PSEN2), alters gamma secretase function which leads to dysfunction in the proteolysis of APP and production of amyloid-β.[7] Whereas Aβ40 accounts for approximately 90% of amyloid-β production, the Aβ42 product is more hydrophobic and is suggested to be involved in amyloid-β aggregation when mutated, leading to amyloid plaque deposition in the AD brain.[9,10] As accepted and useful as the Amyloid Cascade Hypothesis may seem, there are growing amounts of research findings that contradict this theory. Current research suggests that individuals with substantial plaque aggregation can have normal cognition.[11] Research has also shown after Alzheimer's Disease onset, immunoclearing of senile plaques may not always improve cognition, although Alzheimer's Disease itself is based on plaques and plaque deposits.[5] This seems to indicate that amyloid-β deposits alone are not always sufficient to cause dementia.[11-13]

Neurofibrillary Tangles and Alzheimer's Disease Pathology:

Neuropathological studies of Alzheimer's Disease link clinical symptoms to accumulation of neurofibrillary tangles (NFTs), which are constituted by aggregates of hyperphosphorylated tau protein. Abnormal NFTs accumulation occurs within the neuronal cell bodies, including limbic and association cortices, which undergo degeneration during the course of AD.[14] These are present in the regions responsible for various cognitive domains that are impaired in AD, with the density of tau correlating with the region experiencing cognitive decline.[15] Each of these fibrillary lesions contains microtubule associated protein tau (MAPT), which is characterized as a paired helical filament structure (PHFs), and in a decreased amount, straight filaments.[16] Neuronal tau assists tubule networking by assembling and stabilizing microtubules through binding to microtubule filaments, in turn improving cytoskeleton structure and allowing neurite extension.[17] Tau is modified post-translationally through phosphorylation, which inhibits its binding to microtubules and could ultimately lead to tau hyperphosphorylation when all potential sites are fully phosphorylated. Upregulated phosphorylation at specific microtubule associated proteins (MAP), however, promotes tau self-aggregation into filaments.[18] Thus, tau hyperphosphorylation impairs microtubular structure and tau itself becomes destabilized. This destabilization generates dystrophic neurites, triggers formation of neurofibrillary tangles and neuropil threads, which are enlarged filament-containing dendrites, axons, and terminals.[18,19] Abnormally hyperphosphorylated tau, a key component of PHFs in Alzheimer's Disease, gains a toxic ability to sequester regular tau and other MAPs, causing microtubule disassembly.[18] NFTs, as the most mature form of hyperphosphorylated tau, leads to neurofibrillary degeneration, which degrades neurons and dendrites to influence the onset of AD.[19]

Neuroinflammation and Alzheimer's Disease Pathology:

Alongside amyloid-β plaques and neurofibrillary tangles, neuroinflammation plays a significant role in AD pathology. The term "neuroinflammation" suggests an inflammatory response in the central nervous system (CNS) when there is an insufficiency in eliminating the foreign intruder. Inflammation is, therefore, intended for neuroprotection, but overexpression promotes tissue damage and neurodegeneration pathology.[20] Neuroinflammation was originally observed near aggregated amyloid-β peptides in autopsy reports of neuropathological disorders, including AD.[21] Glial cells in the CNS, specifically astrocytes and microglia, are involved in the inflammatory response. Astrocytes are a type of macroglia that are vital for mediating glutamate levels, providing structural support for the blood brain barrier (BBB), and releasing pro-inflammatory cytokines, such as TNFα, to moderate extravasation from blood to the CNS parenchyma. These reactive astrocytes lead to degradation of synapses.[22] Microglia are macrophages that are vital for neuronal plasticity, neurogenesis, regeneration, and defense. They have the potential to phagocytose neurotoxic components, secrete cytotoxic entities, and produce and provide antigens.[23] In the absence of invasive pathogens, microglia remain in an inactive state during which they scan and monitor the parenchyma of the brain sporadically, without disruption of neuronal activity and other glial cells. When any potential damage is detected, microglia activate and transform into mobile amoeboids in order to reach the defective module.[24] These glial cells release cytokines and neurotoxins for a sustained period of time, sometimes up to hours, further worsening pathology in the CNS.[25] Neurotrophic factors secreted by activated neurons, cytokines, are linked to inhibition of the expression of Class II Major Histocompatibility Complex (MHC II) in regards to microglial cells.[26] Thus, the anti-inflammatory phenotype transforms into a pro-inflamsmatory combative phenotype. This stimulation begins a chronic inflammatory response, resulting in behavioral changes, neuronal death, and rapid progression of Alzheimer's Disease.[27]

■ Discussion

Amyloid-β and Tau During Alzheimer's Disease Progression:

To investigate the interaction between tau and amyloid-β, it is relevant to understand the effects of hyperphosphorylated tau and amyloid-β during Alzheimer's Disease progression. Chen and colleagues performed an analysis on 82 patients in the following treatment groups: mild cognitive impairment (MCI), Alzheimer's Disease, and healthy controls.[27] This model displayed significant changes in amyloid-β biomarkers, Aβ42 and Aβ40, and tau biomarkers t-tau (total tau) and p-tau (phosphorylated tau) over the course of a 3-year study period. T-tau and p-tau are suggested to be released during neuronal degradation, with p-tau correlating with NFTs and t-tau correlating with impaired axonal transport. While the Aβ42 levels represented through Aβ42-related biomarkers changed as a function of time in patients with stable AD, tau-related biomarkers changed linearly as a function of clinical diagnostic classifications over the AD cognitive spectrum. These findings associate amyloid-β and tau with ongoing indepen-

dent progression in etiological processes.[28] It is important to recognize that the trials that were done cannot quantify levels of amyloid-β and tau, and thus, only correlations and associations can be observed. Growing research suggests that Aβ and tau change in a sequential, dynamic and temporarily overlapping manner.[29,30] Furthermore, a neuropsychological cohort study with a MCI group showed, at baseline, a negative correlation of Aβ42 with global cognition. In the second year, Aβ42 and phosphorylated tau correlated negatively with memory, function, and cognition, while in the third year the amyloid-β biomarkers displayed positive correlation with episodic memory, semantic memory, and attention, and Aβ42 and hyperphosphorylated tau represented a positive correlation with all cognitive functions. Therefore, there is negative association of Aβ42 with cognitive function during the first- and second-year trials, and a positive association in the third trial. This displays that cognitive impairment in the early stages better fits with hyperphosphorylated tau increase than with amyloid-β. Yet, amyloid-β is more expressive in the Alzheimer's Disease group (including stable AD subjects and MCI that progressed to AD subjects).[28] Given the strong correlation between hyperphosphorylated tau accumulation, rather than amyloid-β, and early stages of AD, it is unclear whether the overlapping processes and hyperphosphorylated tau interactions within the brain parenchyma and destabilization of the cytoskeleton caused further expression in amyloid-β seen in Stage 3 of the study. Altogether, this data suggests that hyperphosphorylated tau is a better indicator of Alzheimer's Disease, and there are possible implications on amyloid-β production. It is important to note that Chen and collaborators were measuring biomarkers from blood samples, and researchers are currently uncertain of how hallmarks, such as amyloid-β aggregation and tau, correlate with AD in plasma.

To confirm and further explore the idea of tau and amyloid-β interactions, Barthélemy and colleagues analyzed tau and amyloid-β pathophysiology throughout AD development, which was measured using clinical assessments, cerebral spinal fluid (CSF), and brain imaging techniques. Through observations of a study cohort consisting of non-familial at-risk and symptomatic participants, tau isoforms were compared to the stages and proliferation of amyloid plaques using mass spectrometry methods. When amyloid plaques are initiated, there is an increase in levels of tau phosphorylation sites, pT217 and pT181. As neuronal degradation begins to occur, dictated upon decreased cortical metabolic activity, levels of the pT205 phosphorylation site and tau isoform, t-tau, begin to increase as well. Based on clinical and cortical atrophy decline, tau-PET tangles (NFTs) evolve, although pT217 and pT181 decrease. It is evident that tau sequentially changes with disease stage, amyloid plaques, and cortical atrophy. This confirms that the hyperphosphorylation of tau is dynamic and, in early stages, depends on the proportion of mutated amyloid-β present, and later, on the degree of cognitive decline. This also demonstrates tau isoforms are contingent upon aggregated amyloid plaques, therefore providing a possible link between amyloid-β and tau. Additionally, given the predictability of tau as stages progress, abnormal production or alterations to tau may be used to identify early stages of AD. Then, to assess whether amyloid-β aggregation in varying cortices is associated with tau phosphorylation, Barthélemy and colleagues used cross-sectional correlations, based on bivariate regressions, between phosphorylation sites for p-tau and cortical regions of amyloid plaque accumulation through PiB-PET SUVR, which is a protein that binds to amyloid-β and can be detected through PET imaging. The results demonstrate a positive correlation between pT217/T217, pT181/T181 and pT205/T205 phosphorylation and PiBPET SUVR, although pS202/S202 was negatively correlated with the amyloid plaque biomarker.[33] This data signifies that although tau is the most accurate marker for AD, amyloid-β initiation occurred first. The variable levels of correlation further the hypothesis of tau influencing aggregation of amyloid-β, with different cortical metabolic activities and presence triggering positive and negative correlations.

Effect of Tau on Amyloid-β Pathology:

To understand if there is an effect of tau expression on amyloid-β production, Pickett and collaborators performed recent research on pathology and behavior in context of AD using transgenic mice models APP/PS1+Tau mice and three control genotypes: control (MAPT -/-), APP/PS1 only (MAPTnull x APP/PS1), and human tau only (MAPTnull x rTg21221). APP/PS1+Tau mice contained APP, PSEN1, and Tau, while the MAPT -/- mice lacked the MAPT gene due to double knockout. In APP/PS1+Tau mice and APP/PS1 mice, onset of amyloid senile plaques appeared in cortex and hippocampus after six months, with plaque burden positively correlating with age. Plaque deposition was observed through the pan-Aß antibody and stained with 0.05% thioflavine S in 50% ethanol.[31] Remarkably, lower plaque deposits were identified in APP/PS1+Tau mice, rather than in APP/PS1 mice, which is unusual compared to previous studies in which larger plaques were identified.[32] Although both mice were expressing the APP/PS1 transgene, senile plaque deposits differed. In a post-mortem analysis of mice of the same cohort that were being tested, percentage accumulation of amyloid-β in pre- and post-synaptic terminals in APP/PS1 and APP/PS1+Tau mice were higher than the controls, although the amyloid-β levels in these mice showed similar percentages of amyloid-β concentration. There was also no effect on amyloid-β aggregates in synapses when lowering tau levels. Tau was also not detected in mice that didn't express tau (controls and APP/PS1). Furthermore, in contrast with amyloid-β, the percentage of tau near synapses did not vary significantly, but the number of synapses with tau notably changed.[31] Damaged synapses are a strong pathological indication and driver of cognitive decline within Alzheimer's Disease.[30,32] These findings suggest that tau and amyloid-β was observed in both pre and post synapses and supports the hypothesis of the interaction of tau and amyloid-β in dysfunction and cognitive impairment. Yet, decreasing hyperphosphorylated tau displayed no effect on amyloid-β generation, implying that hyperphosphorylated tau does not factor in on mutated amyloid-β, although lower plaque deposits were identified in mice with tau (MAPTnull x rTg

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21221). This suggests that hyperphosphorylated tau does not affect amyloid-β initiation and progression. It also suggests the possibility of either tau function in mice varying from the function of tau in the human nervous system, or the temporal and spatial expression generated through Ca2+/calmodulin-dependent protein inaccurately depicting the endogenous tau. Additionally, deregulation of tau levels in APP/PS1+Tau mice did not alter amyloid-β aggregation. Yet, APP/PS1+Tau mice contained decreased amyloid plaque depositions in comparison to APP/PS1 mice, thus suggesting that while stabilized tau does not impact amyloid plaque levels, tau after hyperphosphorylation influences amyloid-β progression.

Effect of Neuroinflammation on Amyloid-β Pathology:

The first signs of neuroinflammation stimulating Alzheimer's Disease was noticed when microglia upregulation was seen in post-mortem analysis of patients with neuropathological disorders.[34-36] These early studies observed microglial activation near amyloid-β aggregation sites, leading them to believe neuroinflammation amplified cognitive decline and onset of AD.[21] Multiple studies have already determined that anti-inflammatory microglia promote Aβ clearance to halt progression of AD, although continuous microglial accumulation will release cytotoxins, such as proinflammatory cytokines, reactive oxygen species (ROS), chemokine, and complement proteins. Microglia and astrocytes will then experience loss of function and BBB structural integrity, and the toxic molecules secreted will upregulate Aβ production, while a lowered expression of degradative enzymes decreases Aβ clearance.[37]

To further analyze the effects of neuroinflammation on amyloid-β pathology in AD, Marsh and colleagues backcrossed 5xfAD mice onto a Rag2-/-/Il2rγ-/- double-knockout to create mice that lacked immune system cells, specifically, T cells, B cells, and natural killer (NK) cells. These mice, Rag-5xfAD, and wild-type mice, Rag-WT, were corresponded with immune-competent Alzheimer's Disease transgenic and wild-type mice, WT-5xfAD and WT-WT. Then they performed a highly sensitive multiplex ELISA, a protein measurement technique, to detect amyloid-β levels. Marsh and colleagues found that all amyloid-β species in Rag-5xfAD half-brains were increased twofold in comparison to WT-5xfAD half-brains. Rag-5xfAD mice also displayed a highly significant increase of plaque volume. Marsh and collaborators then had to determine if this substantial increase of amyloid-β was prompted by increased Aβ production or decreased clearance. Thus, they analyzed a Western blot of the protein level of APP and Presenilin 1. Rag-5xfAD and WT-5XfAD mice displayed an expected increase in APP and Presenilin 1 in comparison to wild-type controls, yet there was no difference in protein expression between Rag-5xfAD and WT-5xfAD. Then, they performed a hierarchical cluster analysis of microglial- enriched genes that were recognized from a recently published online RNA-seq database. Those genes strongly implied microglial dysfunction, which brings up the question if alterations in microglial number and formation could be the reason for increased amyloid peptides. Using immunohistochemical and unbiased IMARIS 3D rendering of microglia, Marsh and colleagues were able to quantify and model the microglial process. Their findings were that WT-5xfAD mice displayed increased microglia cells and decreased microglial branching processing in comparison to WT-WT mice, suggesting an activated phenotype. Additionally, Rag-5xfAD mice displayed a substantial increase in microglial number and decreased branching and process length when compared to WT-5xfAD mice. Surprisingly, Rag-WT microglia had a longer process and a smaller increase in branching on average, when compared to WT-WT microglia.[39] All this data suggests that the loss of immune cells modulates microglial phenotypes and processes. Differentiation between Rag-5xfAD and WT-5xfAD suggests that microglia in Rag-5xfAD mice are further or alternatively activated. It also appears that the observed elevations of senile plaque load in Rag-5xfAD are not due to increased or abnormal APP production and/or processing, but rather are likely mediated because of altered Aβ clearance, which is the primary function of microglia. Thus, it can be concluded that defective microglial activation and processing leads to aggregation of amyloid plaques.

Amyloid-β and Tau with Neuroinflammation

It is crucial to investigate the correlation between tau, amyloid-β, and pro-inflammatory patterns regarding the stages of AD pathology. To do so, Dani and colleagues used a cohort study of 26 patients with varying degrees of Alzheimer's Disease and mild cognitive impairment (MCI). They examined PET imaging of tau, amyloid-β, and microglia using biomarkers, 18F-AV-1451 (tau biomarker) and 11C-PK11195 (microglia biomarker) and analyzed it through Z-score mapping. Z-score mapping is used to statistically compare data points by measuring standard deviations above or below the mean. As expected, in amyloid-positive individuals, there was a high positive correlation with microglia, and higher correlation coefficients were identified in the MCI group, rather than the AD group. When those same individuals were tested for tau correlations, there were strong positive correlations with microglia, especially in the temporal lobe of AD subjects. Then, they observed tau in amyloid-negative individuals (AD without appearance of senile plaques). Tau aggregation and microglial activation were positively correlated, yet the correlation coefficients were smaller and the Z-score was lower in comparison to amyloid-positive patients. Microglial activation, amyloid-β deposition, and tau aggregation displayed a strong positive correlation in the temporal lobe.[38] This data supports amyloid-β uptake by microglia as being a probable stimulus of pro-inflammatory patterns. The positive correlation of microglia and tau also suggests an association between the two processes, although what is specifically being influenced cannot be determined without further testing and a meta-cohort study. It is important to recognize, however, that the strongest positive correlation between the two was seen in the temporal lobe, which is where tau aggregation increases aggressively during the Braak stages. This could suggest tau's rapid increase is due to neuroinflammatory patterns, which is influenced by aggre-

gation of amyloid-β in early stages, or that neuroinflammatory patterns occur because of the sudden aggregation of tau and amyloid-β exacerbates the effect.

Given microglial activation is stimulated by amyloid-β, it is important to analyze the correlation between neuroinflammation and amyloid-β and tau pathology to understand AD. Prokop and colleagues recently established a cohort of 66 patients with varying stages of Alzheimer's Disease progression, primary age-related tauopathy (PART), and pathological aging conditions. They initially analyzed tau's effect on microglia activation with insignificant deposits of amyloid-β in the temporal lobe. Although PART patients displayed high levels of NFTs and neuropil threads with no simultaneous amyloid-β progression, there was a negligible increase of activated microglia in AD patients. On the other hand, patients with severe AD displayed high levels of plaques, tau, and activated microglia in respect to the controls. Then, Prokop and collaborators analyzed neuroinflammation in twelve pathological aging cases, or those with the presence of senile plaques and nearly no tau indications. Comparatively, microglial activation in PART cases was still significantly low, and severe AD cases again showed a major increase in neuroinflammation. Yet it is important to consider that in both groups, subjects presented overall higher averages than the controls, suggesting amyloid-β and tau pathology is not exclusively due to ageing. Since amyloid-β pathology appeared to have a significant influence on microglia activation, it was also observed that higher microglia levels related with amyloid-β plaques through PHF-1 immunohistochemical staining. Moreover, a detailed computer-assisted image analysis was performed to correlate the percentage of area covered by plaque deposits and progression of anatomical progression of AD, in which there was an increased aggregation of amyloid-β deposits. Although, the area covered by hyperphosphorylated tau increased with disease progression, there were comparatively lower amounts of hyperphosphorylated tau observed in all brain cortices.[40] This data shows that tau pathology alone cannot induce substantial pro-inflammatory patterns, and concurrent amyloid-β is necessary. Similarly, this data suggests it can be confirmed that amyloid-β pathology alone can trigger severe neuroinflammation, with tau exacerbating that effect.

Conclusion

Alzheimer's Disease is recognized by the exacerbation of amyloid-β peptides, hyperphosphorylated tau, and neuroinflammation. Over the years, studies have associated these hallmark pathologies, although the exact interactions are unclear. Analysis of AD pathology literature suggests amyloid-β has a strong correlation with tau hyperphosphorylation, although a meta-analysis must be done to confirm findings of studies in AD patients. Tau, which becomes hyperphosphorylated, is the greatest and most influential on cognitive decline. Cognitive decline translates to a rapid progression of AD pathology. Amyloid-β, additionally, has the potential to provoke pro-inflammatory patterns. Tau, however, cannot trigger neuroinflammation alone, and co-occurrent amyloid-β pathology is necessary for substantial microglia activation. Inflamed microglia can lead to cognitive decline, which will lead to a more rapid progression of AD. Additionally, pro-inflammatory patterns display causation of the spread of tau, similar to the pathology seen in Braak stages. Yet, a thorough analysis must be done to fully confirm neuroinflammation can cause hyperphosphorylation of tau, which then leads to cognitive decline that furthers the development of AD. These interactions shed light on progression of Alzheimer's Disease, and specifically targeting these hallmarks using multiple strategies to downregulate all other hallmarks will provide potential therapies. Future studies should specifically aim to target tau phosphorylation sites, to decelerate production of abnormal tau, while concurrently targeting APP and its processing to inhibit mutated amyloid-β. This literature review analyzed and suggested how specific pathological hallmarks interact within the brain to worsen Alzheimer's Disease symptoms. There will likely be more potential in therapies if they target two pathological hallmarks, instead of only focusing on one. This also narrows the possible pathways to test and expands current knowledge about AD pathology.

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The author, Avni Kabra, is a high schooler in Connecticut interested in neuroscience research. This literature review was written to better understand Alzheimer's Disease and it's causes, which can ultimately assist in finding a cure. She hopes to pursue this further with an interest in mathematical application to scientific problems.

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