

The Role of Amyloid- β and Tau Proteins in Alzheimer's Disease

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ABSTRACT: Alzheimer's disease is a complex neurodegenerative disorder associated with the buildup of amyloid- β plaques and tau neurofibrillary tangles, but the exact relationship between them is unclear. Understanding their interaction is important since therapies targeting only amyloid- β have not been entirely effective. This review synthesizes studies to clarify whether amyloid- β and tau act independently or together in Alzheimer's disease. Based on prior clinical trials of anti-A β antibodies, it has been demonstrated that plaque reduction has had inconsistent cognitive improvement. Early-phase tau-targeted therapies, on the other hand, are currently being developed, but not yet widely effective or researched. Mechanistic studies and combination therapies have suggested that A β and tau have a combined effect, which supports dual-targeted interventions. Imaging studies also show that amyloid and tau have an interconnected effect. These findings show that neurodegeneration acceleration in Alzheimer's is due to both proteins instead of a single pathology. Developing early detection techniques through biomarkers, combined with therapies focused on both A β and tau, may improve clinical outcomes in terms of prevention and treating symptoms. This topic was chosen because Alzheimer's disease is one of the leading causes of dementia worldwide, and understanding the combined roles of amyloid- β and tau may contribute to the development of more effective treatments.

KEYWORDS: Genetics and Molecular Biology of Disease, Neurobiology, Alzheimer's Disease, Amyloid- β , Tau.

■ Introduction

Alzheimer's disease (AD) is one of the most complex neurodegenerative disorders, which is why its exact underlying causes are still not fully understood.¹ After decades of research, two key proteins have been identified as central to its pathology. These proteins are amyloid- β and tau. The question, however, is how these abnormalities occur and interact to accelerate neurodegeneration. This lack of clarity has created a significant research gap within Alzheimer's studies. Due to the lack of understanding surrounding these two proteins, the development of effective diagnostic, clinical, and therapeutic strategies has been significantly limited.

Previous studies have provided insights into the roles of amyloid- β and tau in Alzheimer's disease, but their findings often focus on different aspects. Research on amyloid- β has emphasized its early accumulation in the brain and potential role in initiating the neurodegenerative process, such as studies involving amyloid PET imaging that detected plaque build-up years before symptoms were detected.² On the other hand, studies on tau suggest that its presence is more closely linked with cognitive decline than amyloid- β .³ For instance, autopsy and tau PET imaging studies show that the spread of neurofibrillary tangles strongly correlates with memory impairment and disease severity.³ Overall, some studies support a sequential interaction between the proteins, while others indicate that their pathways are independent. So, despite these advances in research, the relationship between the two proteins remains unclear. Further, clinical trials targeting amyloid- β alone have had limited cognitive improvement, which shows the need for a perspective that considers the combined effects of these proteins.⁴

Clarifying the relationship between amyloid- β and tau proteins is needed to improve our understanding of AD progression. Current evidence shows that focusing on one protein alone has not resulted in effective therapies, further showing the importance of considering both of their effects. This review addresses a critical gap by combining the roles of both proteins to offer a more comprehensive understanding that can inform future research, early detection strategies, and the development of treatments.

■ Methodology

The objective of this study is to examine the roles of amyloid- β and tau proteins in the development and progression of Alzheimer's disease. Specifically, the study aims to evaluate whether amyloid- β accumulation and tau hyperphosphorylation act sequentially or independently in Alzheimer's disease. This review also aims to understand how these findings affect current and future therapeutic and clinical strategies.

Given that this study is a literature review, the goal is to synthesize findings from peer-reviewed scientific research that investigate amyloid- β and tau pathologies in Alzheimer's disease. No experimental manipulation, data collection from human subjects, or in-field studies were conducted. The data for this study were gathered through searches of academic databases. Peer-reviewed journal articles, systematic reviews, and meta-analyses were included. Only studies published in English and studies containing data and models regarding amyloid- β and tau pathologies were selected.

The primary sources included original peer-reviewed research articles that contained experimental findings, imaging results, or analyses on A β and tau in human subjects or animal models. Secondary sources included review articles, systemat-

ic analyses, and meta-analyses that showed trends, evaluated different hypotheses, or analyzed results from multiple studies.

Because this study is entirely a review of literature, no human or animal subjects were involved, so no ethical approval was required. The study did not use any physical tools or laboratory materials. All the data was gathered from publicly accessible academic sources.

■ Discussion

Background: Amyloid and Tau:

The amyloid precursor protein (APP) is a protein found in many cells in the body, but it is especially common in neurons. In the healthy brain, APP helps with neuron growth, communication between brain cells, and repair after injury.⁵ In healthy cells, this protein can be broken down, or cleaved, by enzymes in two different ways. These two ways are different because one way is healthy, whereas the other can become harmful.²

In the healthy, also known as a non-amyloidogenic pathway, APP is cut by an enzyme called α -secretase. This produces a fragment called soluble APP- α (sAPP α). sAPP α helps protect neurons and also supports memory and learning.⁶ In the amyloidogenic pathway (unhealthy), however, APP is cut by two different enzymes. These are β -secretase (also known as BACE1) and γ -secretase. This process produces short protein pieces called amyloid-beta (A β) peptides, including A β_{40} and A β_{42} .² A β_{40} is the more common form, but A β_{42} is more likely to build up and aggregate, which makes it especially harmful.²

On the other hand, tau is a protein that is mainly found inside neurons, where it helps stabilize microtubules. Microtubules are long, tube-like structures that act as the “tracks” for transporting nutrients, organelles, and other molecules within the cell.⁷ These microtubules are important in neurons because they have long extensions called axons, which need efficient transport to connect different parts of the brain. Tau assists in keeping the microtubules straight and strong by attaching to them, which allows materials to move smoothly and neurons to function properly.⁸ Tau can also be modified by adding phosphate groups through the process of phosphorylation. In healthy brains, this is strictly regulated and helps control tau’s interaction with microtubules. So, when tau works correctly, it supports neuron stability, communication, and overall brain health.⁷

However, in Alzheimer’s disease, these normal processes become disrupted. APP is processed through the amyloidogenic pathway, which leads to an excessive accumulation of A β peptides that can aggregate into plaques. At the same time, abnormal hyperphosphorylation of tau causes it to detach from microtubules and form neurofibrillary tangles, which hinders neuronal transport and contributes to neurodegeneration. Together, these pathological changes interfere with communication between neurons, which contributes to cognitive decline.

The Amyloid Hypothesis:

The amyloid hypothesis supports that the accumulation of amyloid- β (A β) plaques outside neurons is the initiating factor in Alzheimer’s disease.⁹ Under normal conditions, small

amounts of A β are produced and efficiently cleared by the brain. However, dysregulation in this process leads to excessive accumulation. When A β peptides, especially A β_{42} , build up in the brain, they can form small clusters called oligomers, which are prone to aggregation. These oligomers are highly toxic and interfere with communication between neurons at synapses.¹⁰ Synapses are the connections that allow neurons to send signals to each other. Over time, the oligomers grow into larger, insoluble plaques that are even visible in postmortem brains of Alzheimer’s patients.¹⁰

The amyloid hypothesis suggests that this buildup of A β triggers downstream harmful events inside neurons. One major effect is the abnormal modification of tau proteins. Normally, tau helps stabilize microtubules inside neurons, but exposure to A β oligomers can activate enzymes like glycogen synthase kinase-3 β (GSK-3 β) that add excessive phosphate groups to tau, a process known as hyperphosphorylation.¹¹ Hyperphosphorylated tau detaches from microtubules, causing them to collapse and form neurofibrillary tangles. These tangles disrupt intracellular transport, reduce neuron survival, and contribute to the cognitive decline seen in Alzheimer’s disease.¹²

Additionally, A β plaques can cause oxidative stress and inflammation. Microglial cells, which are the brain’s immune cells, try to clear the excess A β . However, this response can backfire by producing inflammatory molecules that damage surrounding neurons.⁵ Synapses are weakened, neurons die, and the brain experiences the neurodegeneration that is commonly seen in Alzheimer’s disease. According to the amyloid hypothesis, this sequence from A β accumulation to tau pathology to neuron death is the cascade that ultimately causes the symptoms of Alzheimer’s, which include memory loss, confusion, and impaired reasoning.¹⁰

Studies supporting the amyloid hypothesis use two strong lines of evidence: genetic mutations in familial Alzheimer’s disease and imaging studies of amyloid- β (A β) in living brains. First, rare inherited mutations in genes such as APP, PSEN1, and PSEN2 have been associated with early-onset Alzheimer’s disease. These mutations increase the ratio of the A β_{42} form (which aggregates more easily) to A β_{40} , indicating that excessive and abnormal amyloid production can initiate disease processes. Secondly, advanced positron emission tomography (PET) imaging studies show that high A β accumulation can be detected years before cognitive symptoms appear in individuals.¹³ For example, a large multicenter PET study found that cognitively unimpaired participants who were both A β -PET positive and tau-PET positive had a much higher risk of progression, mild cognitive impairment (MCI), and dementia compared to those who were negative.¹³ Further, recent studies show that a high A β -PET signal predicts future cognitive and functional decline in clinically normal older adults.¹⁴ Overall, these findings reinforce the idea that A β accumulation is likely an early cause of the cascade from A β buildup to tau pathology to the death of neurons.

Despite decades of research focused on reducing amyloid- β (A β) plaques, the outcomes from many clinical trials have been low. This has raised questions about the validity of the amyloid cascade hypothesis in guiding Alzheimer’s disease therapies.

One major criticism is that while many anti-A β treatments successfully reduce plaque load or lower A β biomarkers, this reduction often does not correlate with meaningful cognitive or functional improvement for patients.^{4,15} For example, although plaque reduction has been achieved with monoclonal antibodies like aducanumab and lecanemab, the clinical benefit of slowing cognitive decline remains inconsistent.¹⁶ Another significant issue is regarding the timing of intervention and the disease stage of the patient. Many anti-amyloid trials were conducted in participants who already had mild to moderate dementia, a stage where amyloid has likely triggered the cascade. So, it is likely that the buildup of tau neurofibrillary tangles, synaptic loss, and neurodegeneration has already taken place. In these situations, removing A β may not significantly reverse damage that has already occurred.¹⁷ Accordingly, reviews have suggested that interventions in later stages of Alzheimer's are less effective and that earlier intervention in preclinical or prodromal stages may be required.¹⁸ These issues have led many researchers to conclude that focusing solely on A β is too narrow. Evidence from clinical trials and biomarker analyses has suggested that amyloid removal does not always prevent cognitive decline, raising questions about whether amyloid is the main cause of Alzheimer's or one of the many significant causes of the disease.^{17,18}

The Tau Pathology Hypothesis:

In Alzheimer's disease, tau becomes abnormally modified through the process of hyperphosphorylation. During this process, multiple phosphate groups are added to amino acids that make up tau, which include serine, threonine, and tyrosine. This modification is typically regulated by glycogen synthase kinase-3 β , cyclin-dependent kinase 5, and microtubule affinity-regulating kinase, all of which become dysregulated in Alzheimer's patients.¹² Hyperphosphorylation changes tau's normal conformation, which reduces its ability to bind to microtubules. As tau detaches from these microtubules, the structure of the microtubules weakens, which causes microtubule destabilization and hence the weakening of axon transport pathways. So, the cells' transport system for transporting organelles, vesicles, and other essential proteins along the axon is damaged. Mitochondria, synaptic vesicles, and neurotrophic factors fail to reach the synapses due to the impaired microtubules, which result in weakened neurotransmission and synaptic dysfunction.¹² These factors contribute directly to cognitive decline. The detached tau proteins self-aggregate to form soluble oligomers that are neurotoxic and eventually aggregate into insoluble neurofibrillary tangles (NFTs) within the soma and dendrites.⁷ The NFTs disrupt signaling pathways, cause oxidative stress, and trigger inflammatory responses from neighboring cells. Over time, the accumulation of NFTs leads to neuronal atrophy and cell death, which increases neurodegeneration across the brain's regions.⁷

The tau pathology hypothesis specifically claims that these tau tangles are more directly correlated with cognitive decline and symptom severity than amyloid- β plaques. Research has shown that the amount and location of tau tangles in the brain correspond closely with regions responsible for mem-

ory, reasoning, and other higher cognitive functions, such as the hippocampus, entorhinal cortex, and neocortex.^{3,19} For example, patients with high tau accumulation in the hippocampus often show severe memory loss, while individuals with significant amyloid plaque deposits may not yet show severe cognitive symptoms.¹⁹ This has led researchers to believe that tau pathology may be a better indicator of the progression and severity of Alzheimer's disease than amyloid alone.¹⁹

The tau hypothesis emphasizes that the presence and spread of the tangles closely align with the cognitive decline observed in patients, showing that tau is an important indicator for understanding and potentially treating Alzheimer's disease.^{3,20} Once tau proteins become abnormal and form tangles inside neurons, they don't just stay in one cell. Instead, evidence shows that tau can spread from one neuron to another.²¹ Abnormal tau acts as a template, causing normal tau proteins in neighboring neurons to misfold and aggregate. This propagation explains why tau pathology follows a predictable pattern in the brain. In Alzheimer's disease, tau tangles typically appear first in the entorhinal cortex, which is critical for memory formation. From there, tau spreads to the hippocampus and eventually to widespread regions of the neocortex, correlating with progressive memory loss, cognitive decline, and behavioral changes.¹⁹ Understanding how tau propagates is essential because it shows why targeting tau early, before widespread spread occurs, could be more effective in slowing or preventing cognitive decline. By slowing the transmission of misfolded tau between neurons, therapies could simultaneously treat symptoms and potentially slow the progression of Alzheimer's disease.²²

The role of tau in Alzheimer's disease has been strongly supported by multiple types of evidence, including neuroimaging studies, post-mortem analyses, and emerging tau-targeted therapies. Imaging studies have been essential in tracking tau accumulation in living patients. By using positron emission tomography (PET) scans with tau-specific tracers such as 18F-flortaucipir, researchers can visualize tau deposition in different brain regions.²³ These studies consistently show that tau accumulation correlates closely with cognitive decline, particularly in memory and executive function, whereas amyloid plaques alone often show a weaker correlation.²⁴ Longitudinal imaging studies also suggest that tau spreads in a predictable pattern, which is from the entorhinal cortex to the hippocampus and neocortex.^{3,19} Autopsy findings provide additional support for tau's role in Alzheimer's disease. The examination of post-mortem brains reveals that the amount of neurofibrillary tangles strongly correlates with the extent of the disease, even more than the density of amyloid plaques.²⁵ Studies also show that individuals with high amyloid- β levels but low tau often remain cognitively normal, further showing tau as a more pressing cause of the symptoms.²⁶

Amyloid vs. Tau - Are They Competing or Linked?:

One of the most prominent debates in Alzheimer's research is how amyloid- β (A β) and tau proteins interact in the brain. The amyloid cascade hypothesis states that A β accumulation occurs first and triggers downstream tau pathology, ultimately

leading to the death of neurons and, therefore, cognitive decline.^{9,10} According to this model, amyloid plaques act as an initiator that initiates a cascade of molecular events, including tau hyperphosphorylation, synaptic dysfunction, and neuroinflammation. Experimental studies in transgenic mouse models support this idea. The mice engineered to overexpress human APP develop A β plaques first, followed by tau tangles and neuronal loss.²⁷ These findings suggest that A β may act as a trigger for tau pathology.

However, some research challenges this sequential view. Observations in both human and animal models indicate that tau pathology can sometimes occur without significant amyloid accumulation, particularly in brain regions like the entorhinal cortex.²⁸ This has led to the concept of independent pathways, where amyloid and tau may contribute to neurodegeneration separately, and their combined presence accelerates disease progression. In this scenario, targeting one protein without addressing the other explains why many anti-amyloid therapies have had limited clinical improvement.^{10,13}

More recent studies propose a combined model, where A β and tau interact in a feedback loop. In this model, early amyloid deposition promotes tau misfolding and spread, which in turn intensifies amyloid toxicity, creating a constant cycle of neurodegeneration.²⁹ Misfolded tau can increase synaptic dysfunction and neuroinflammation, which then leads to further amyloid accumulation.³ This model is supported by longitudinal imaging and biomarker studies. These show that amyloid accumulation occurs before detectable tau pathology, but tau spread correlates more closely with clinical symptoms. Therefore, this reinforces the idea that both proteins are critical in Alzheimer's and that their roles are interdependent.^{3,30}

Understanding whether amyloid triggers tau or whether they act independently is crucial for developing effective therapies. If amyloid truly initiates tau pathology, then early anti-amyloid interventions could prevent downstream tau tangles. In contrast, if tau can propagate independently, then therapies must target both proteins or focus on tau directly to halt cognitive decline.³¹

Positron emission tomography (PET) imaging using A β tracers shows plaques in cognitively normal older adults, indicating that amyloid deposition can begin 15-20 years before noticeable memory decline.^{30,32} Similarly, cerebrospinal fluid (CSF) analysis shows decreased A β_{42} levels early in the pre-clinical stage, which correlates with the initial deposition of plaques in the brain.³³ In contrast, tau pathology appears closer to the onset of cognitive symptoms. Tau PET imaging and autopsy studies demonstrate that neurofibrillary tangles begin in the entorhinal cortex and hippocampus before spreading to the neocortex.^{24,34} These findings reinforce the idea that while amyloid may initiate a pathological cascade, tau accumulation is more closely tied to functional impairment. Additionally, there is an increasing amount of evidence supporting the overlap between the processes. Some studies show that tau deposition can begin in specific brain regions even when amyloid levels are low, suggesting that tau may also have independent triggers or be influenced by other factors such as aging, inflammation, or vascular changes.^{25,35} In summary, amyloid pathology gen-

erally precedes tau pathology, but tau's appearance and spread are more predictive of symptom onset and disease progression, overall proving that both amyloid and tau are closely linked to the progression of Alzheimer's Disease, rather than just a single protein pathology.

Therapeutic Implications and Clinical Trials:

Over the past decade, anti-amyloid therapies have been the primary focus of clinical trials aiming to slow Alzheimer's disease progression. Monoclonal antibodies such as aducanumab and lecanemab have been designed to selectively target amyloid- β (A β) plaques and assist in clearing them from the brain.^{30,36} Aducanumab was approved by the FDA in 2021 under accelerated approval, based on its ability to reduce amyloid plaques, although its clinical benefits on cognitive outcomes remain debated.^{30,36} Similarly, lecanemab has shown promising results in Phase 3 trials, demonstrating modest slowing of cognitive decline in early Alzheimer's patients.^{37,38} The results that these treatments have shown, along with donanemab, can be seen in Table 1.³⁹

Table 1: Clinical trials targeting amyloid- β consistently show effective plaque reduction; however, cognitive outcomes remain inconsistent. These findings suggest that amyloid removal alone may not be sufficient to significantly alter disease progression, especially in later stages of Alzheimer's disease.

Therapy	Trial Phase	Target/Mechanism	Outcome Summary	References
Aducanumab	3	Selective A β plaque removal via monoclonal antibody	Reduced amyloid burden on PET but had inconsistent cognitive benefits ^{30,36}	Sevigny et al., 2018; Knopman et al., 2021
Lecanemab	3	Targets soluble A β protofibrils	Slowed cognitive decline by 27% in early AD ^{37,38}	Swanson et al., 2021; van Dyck et al., 2023
Donanemab	3	Binds pyroglutamate, which is modified A β	Reduced plaques and slowed cognitive decline ³⁹	Mintun et al., 2021

The growing recognition of tau's importance has also led to the development of tau-focused therapies. Current approaches include monoclonal antibodies targeting pathological tau, which are small molecules that inhibit tau aggregation or phosphorylation.³¹ There are also strategies to stabilize microtubules disrupted by tau tangles.³¹ Early-phase clinical trials are testing compounds such as gosuranemab and tilavonemab, which aim to reduce tau propagation and improve cognitive outcomes in patients with mild Alzheimer's disease.³¹ Other approaches involve microtubule stabilizers, which aim to counteract the loss of tau function and maintain neuronal cytoskeleton integrity, thereby reducing synaptic dysfunction.⁴⁰ The results of these approaches are summarized in Table 2. While tau-targeted therapies are still largely in early-phase clinical trials, evidence suggests that they may provide cognitive benefits when administered during the early disease stage.³¹

Table 2: Tau-targeting therapies have shown limited clinical success, with most trials failing to demonstrate cognitive improvement. This suggests that timing and combination approaches may be more critical.

Therapy	Trial Phase	Mechanism	Outcome summary	References
Gosuranemab	2	Antibody against extracellular tau	Safe, but no significant cognitive benefit ³¹	Congdon & Sigurdsson, 2018
Tilavonemab	2	Prevents trans-synaptic tau spread	Did not meet efficacy endpoints ³¹	Congdon & Sigurdsson, 2018
TPI-287	1	Microtubule stabilizer	Limited efficacy, along with some safety issues ⁴⁰	Goldlust et al., 2024

Current therapies suggest that combining amyloid- and tau-targeted strategies may be more effective than focusing on either pathology alone. Clinical trials are beginning to explore sequential interventions, aiming to reduce amyloid deposition while also preventing tau-mediated neurodegeneration.⁴¹ This supports the idea that it is not amyloid or tau that individually accelerate neurodegeneration, but rather it is both of them. Studies targeting both amyloid-β and tau pathologies are summarized in the tables below, with Table 3 focused on therapeutic strategies and Table 4 focused on mechanistic evidence.

Table 3: The method of combining approaches that target amyloid-β and tau produces stronger effects on neurodegeneration than single-pathway approaches. These strategies support the view that Alzheimer’s disease requires multi-targeted approaches to slow progression.

Therapeutic Focus	Intervention Strategy	Outcome summary	References
Combination therapy	Anti-Aβ antibody and anti-tau antibody in sequential administration	Demonstrated that combination therapy had a large effect on reducing biomarkers of neurodegeneration ⁴¹	Cummings <i>et al.</i> , 2022
Mechanistic insight	Combined suppression of Aβ and tau in preclinical models	Found interdependent toxicity, meaning dual targeting improved neuronal function ⁴²	Busche & Hyman, 2020
Clinical trial perspective	Early amyloid clearance, followed by tau-targeted therapy	Proposed that early Aβ removal delays tau accumulation and clinical decline ³⁸	van Dyck <i>et al.</i> , 2023

Table 4 shows mechanistic evidence that demonstrates how amyloid-β and tau interact in Alzheimer’s. The studies performed using transgenic mouse models show that amyloid-β accumulation pushes tau to spread and therefore increases neuronal hyperactivity. So, when both proteins are inhibited, neuronal hyperactivity will be decreased. Cell culture and animal experiments have shown that Aβ-induced kinase activation influences tau. This shows that therapeutics targeting Aβ first, followed by tau, can slow the progression of Alzheimer’s disease. In addition, human PET imaging studies show that amyloid plaques can be consistently seen before NFTs form, which supports that their relationship is interlinked.

Table 4: Experimental and imaging studies provide strong evidence that amyloid-β and tau pathologies are biologically interconnected, with amyloid often accelerating tau spread. These findings support therapeutic strategies that intervene early in amyloid accumulation to prevent tau-related neurodegeneration.

Experimental Model	Outcome Summary	Implication	References
Transgenic mouse model	Aβ accumulation accelerates the spread of tau	Dual inhibition reduces neuronal hyperactivity ⁴²	Busche & Hyman, 2020
Cell culture and animal model	Tau pathology depends on Aβ-induced kinase activation	Sequential therapy, first targeting Aβ, followed by tau, may delay AD ⁴⁷	He <i>et al.</i> , 2018
PET imaging study on humans	The presence of amyloid precedes tau accumulation and predicts it	Supports the idea that early amyloid clearance is necessary to prevent tau accumulation ⁴⁸	Palmqvist <i>et al.</i> , 2020

Gaps in Knowledge:

One of the current gaps in Alzheimer’s research is that a significant proportion of elderly individuals have substantial amyloid-β (Aβ) deposition in their brains, but do not show severe cognitive impairment.⁴³ This suggests that the presence of amyloid plaques alone is not sufficient to cause dementia. Several explanations have been proposed to explain this phenomenon. First, cognitive reserve may play a protective role. Individuals with higher education levels and more engagement appear to tolerate higher amyloid loads without developing clinical symptoms, potentially due to compensatory neural

mechanisms that preserve cognitive function.⁴⁴ Second, co-existing pathologies may regulate the impact of amyloid. For example, tau pathology, neuroinflammation, and vascular dysfunction can interact with Aβ to determine whether cognitive symptoms occur. In some people, amyloid accumulation occurs without significant tau aggregation, possibly explaining why cognitive function remains intact.⁴⁵ Finally, the solubility of amyloid may matter. Soluble oligomeric forms of Aβ are more synaptotoxic than the insoluble fibrillar plaques that accumulate in the brain, meaning that individuals with primarily fibrillar deposits may experience less neuronal dysfunction.⁴⁶ Together, these findings go against the idea that amyloid is a straightforward factor in Alzheimer’s disease and show the importance of studying amyloid in combination with other pathological markers, including tau, to fully understand disease progression.

Implications for Future Research:

Research over the past decades has established that both amyloid-β (Aβ) and tau proteins play crucial roles in Alzheimer’s disease, but their relationship is complex. Aβ accumulation is often one of the earliest detectable changes in the brain and can initiate a cascade of events that promote tau hyperphosphorylation and neurofibrillary tangle formation.^{10,32} However, tau pathology correlates more closely with cognitive decline and symptom severity than amyloid burden, suggesting that tau tangles may be the more direct cause of the symptoms.³

Together, these findings suggest that Alzheimer’s is not caused by a single protein pathology. Rather, Aβ and tau interact with each other. The combination of tau and amyloid reveals why therapeutic strategies targeting only one protein have often produced mixed results, and why a more comprehensive understanding is essential for designing effective therapeutics and interventions. Given the interdependent relationship between amyloid-β and tau, there is a growing consensus that interventions in the preclinical or early stages of Alzheimer’s disease are likely to be more effective than treatments administered after significant neurodegeneration has occurred. Early detection through biomarkers, including cerebrospinal fluid (CSF) Aβ and tau measurements, PET imaging, and emerging blood tests, can identify individuals at risk before cognitive symptoms appear.⁴⁷⁻⁴⁹ With the combination of early detection and a treatment for both protein pathologies, more effective treatments can be developed. By focusing more on prevention and early intervention, and also by recognizing the interdependence between amyloid and tau, researchers can aim to slow disease progression, offering the potential to improve Alzheimer’s in the overall at-risk populations.²³

Conclusion

In summary, both amyloid-β and tau proteins play key roles in Alzheimer’s disease, but their relationship is not yet fully understood. While amyloid accumulation may initiate pathological cascades, tau pathology correlates more closely with cognitive decline, suggesting that both contribute to disease progression. This complexity shows the importance of early

detection using biomarkers and imaging techniques to identify at-risk individuals before significant neurodegeneration occurs.

The overall findings indicate that effective treatment may require a combined therapeutic approach that targets both amyloid and tau, alongside addressing other contributing factors such as inflammation and vascular changes. Future research should further investigate how these other factors interact with protein pathologies. Future research should also explore new biomarkers and intervention strategies to improve early detection and prevention of disease progression. Additionally, future studies should prioritize multi-model approaches, such as combining PET imaging, blood-based biomarkers, and genetic analyses, to better understand how amyloid and tau change over time. Researchers should also investigate combination therapies administered during preclinical stages of Alzheimer's disease to find whether early intervention can prevent cognitive decline. By researching various aspects of Alzheimer's disease, researchers can develop more effective methods to slow progression and hence improve patient treatments.

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