

The Role of Amyloid-Beta Plaques in Disrupting Neural Communication in Alzheimer's Disease

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AUTHOR BIO

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ABSTRACT

Alzheimer's Disease (AD) is defined as a particular onset and course of cognitive and functional decline. Central to AD pathology is the abnormal processing of amyloid precursor proteins (APPs), which produces amyloid-beta ($A\beta$) peptides prone to misfolding and aggregation. Soluble $A\beta$ oligomers are now also recognized as the earliest and most potent disruptors of synaptic communication, leading to the impairment of receptor function and long-term potentiation. These amyloidogenic events serve as an upstream trigger for the hyperphosphorylation and aggregation of tau. As $A\beta$ accumulation progresses, it activates kinases that drive tau hyperphosphorylation, misfolding, and neurofibrillary tangle formation. These effects destabilize microtubules and interrupt axonal transport. The combined effect of $A\beta$ -induced synaptic toxicity, tau-mediated structural breakdown, and chronic neuroinflammation leads to the progressive loss of neural connectivity characteristic of Alzheimer's Disease. This paper will examine how $A\beta$ plaques create disruptions in neural signaling, enabling the transition of tau from a microtubule-stabilizing protein to a neurotoxic aggregate. By evaluating $A\beta$ as the initiator of synaptic stress and tau as the primary driver for structural neurodegeneration and clinical decline, this review aims to show that the loss of neural connectivity in AD is the result of this interdependent proteinopathy, which is further exaggerated by chronic neuroinflammation.

Keywords: *Psychology, Neuroscience, Cognitive Decline, Alzheimer's Disease, Amyloid-Beta, Tau*

INTRODUCTION

AD is a neurodegenerative disease that progressively destroys memory, cognitive skills, and characteristic behavior. The disease was first described by Alois Alzheimer in 1906 based on post-mortem findings of extracellular amyloid-beta plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau (Alzheimer, 1907; Kraepelin, 1910). Currently, AD is considered one of the most prevalent causes of dementia, wherein impaired synaptic signaling, along with disrupted neural networks, forms the core of its pathophysiology (Selkoe & Hardy, 2016).

Amyloid precursor protein (APP) is a transmembrane protein concentrated at synapses, where it participates in normal neuronal communication and signaling. APP cleavage via the amyloidogenic pathway results in the production of A β peptides of variable length and stability, and among these, soluble A β oligomers are the most synaptotoxic. Given its known interference with neurotransmission, weakening of long-term potentiation (LTP), and increased susceptibility to tau-related cytoskeletal breakdown, clarifying the relationship between A β and tau is essential to understanding AD pathophysiology and the early disruptions in neural communication that drive Alzheimer's disease, helping shape future therapeutic approaches.

DISCUSSION

Section 1: Formation of Amyloid-Beta Plaques

1.1 - Origins of Amyloid Pathology: The Amyloid Precursor Protein

Amyloid Precursor Proteins (APPs) are considered the first step to the formation of Amyloid-Beta (A β) Plaques. APP is synthesized in the endoplasmic reticulum (ER), where it is subject to initial folding and post-translational modifications before being transported via the secretory pathway to the trans-Golgi network (TGN), where it undergoes maturation before being transported (Lai et al., 1995). From the TGN, mature APP is delivered to the plasma membrane. Still, it is only transiently retained at the cell surface, as the majority of APP is rapidly internalized into early endosomes through regulated endocytic mechanisms. Within early endosomes, the APP enters a critical sorting phase where it may be recycled to the plasma membrane, directed toward lysosomal degradation, or retrieved to the TGN via “retromer-mediated retrograde transport” (Zhang & Song, 2013). This sorting step is crucial because it determines the exposure of APP to secretases (enzymes that cleave APP) and, consequently, whether APP will follow a non-pathogenic or potentially pathogenic pathway. In fact, alterations in APP trafficking, such as defective endosome-to-TGN retrieval, have been shown to increase the likelihood that APP is processed via the amyloidogenic pathway (i.e., leading eventually to A β production) in cell and animal models of AD (Small et al., 2005), underscoring the importance of trafficking processes before any cleavage events (in-text citation). Taken together, these data demonstrate that APP’s cellular journey, from synthesis, maturation, membrane insertion, endocytosis, and sorting, is an essential upstream determinant of whether APP remains essentially harmless or is overprocessed into pathological A β peptides in AD.

1.2 - Secretases

Another step vital to understanding the production and structure of AB Plaques is the secretases that are produced. The critical step in the production of A β concerns how APP is cut by secretase enzymes. Which secretase cuts APP and where this happens inside the cell determines whether APP is broken down into innocuous fragments or into A β peptides with the potential to drive disease. In the non-amyloidogenic pathway, α -secretase cuts in the middle of the A β region, which prevents A β from forming at all. This action releases sAPP α , a soluble fragment often linked to protective effects in neurons (Selkoe & Hardy, 2016; Postina, 2008). In the amyloidogenic pathway, β -secretase (BACE1) makes the first cut at the start of the A β sequence, producing the membrane-bound C99 fragment. Then, γ -secretase cuts C99 within the membrane to release A β peptides of different lengths (Vassar et al., 1999; De Strooper & Annaert, 2010). The γ -secretase complex, whose core includes presenilin, also determines exactly how long the final A β peptide will be, and disease-related presenilin mutations tend to increase production of longer, more aggregation-prone forms such as A β 42 (De Strooper & Annaert, 2010). Which pathway dominates is greatly dependent on the cellular location of APP and the secretases. For instance, when APP is pulled into acidic endosomes, the function of BACE1 is more efficient, which in turn shifts the processing toward the production of A β (Nixon, 2005; Yan & Vassar, 2014). Consequently, relatively small changes in secretase levels, activity, or localization can strongly affect how much A β accrues during aging or disease (Vassar et al., 1999; Yan & Vassar, 2014).

1.3 - Beta-Amyloid Peptides

One important thing to keep note of when discussing A β peptides is that they aren't a single, uniform species across the entire system. Rather, they are a species where their length and chemical features govern characteristics such as their solubility, propensity to misfold, and their interactions with other cellular components. These are all factors that determine the neurotoxicity of the peptide and, hence, are important to understand.

The two major forms of A β in the brain are A β 40 and A β 42. A β 42 has about two additional hydrophobic amino acids at its tail end, making it more prone to β -sheet formation, a structural pattern that favors aggregation (Selkoe & Hardy, 2016; Benilova et al., 2012). While being amphipathic, that is, having water-loving and a water-repelling part, a single molecule of A β interacts with cellular membranes, metal ions such as copper and zinc, as well as other A β molecules, strongly favoring how the peptide folds and how fast it forms oligomers and fibrils (Knowles et al., 2014; Haass & Selkoe, 2007).

Chemical modifications to A β , such as oxidation or pyroglutamate formation, and conditions in the environment, such as pH, salt concentrations, or presence of lipid membranes, are additional factors that can further drive the peptide toward shapes more disposed to aggregation. The fact that certain mutations to APP or presenilin increase the relative production of A β 42 underlines how important peptide length and its chemistry are in defining disease.

1.4 - Oligomerization

The next step in the formation of Beta-Amyloid Plaques is the formation of oligomers, which are small soluble A β aggregates that form first as the main early drivers of synaptic problems in Alzheimer's disease. Not only do they interfere with learning by blocking long-term potentiation, but they also lead to tau hyperphosphorylation (later discussed in this review).

Studies in experimental models and human tissue indicate that soluble A β oligomers, from dimers and trimers to larger assemblies, disrupt synaptic signaling and correlate much better with cognitive decline than the amount of plaque in the brain (Shankar et al., 2008; Lambert et al., 1998). Their formation follows nucleation dynamics, with a small, unstable "seed" first forming, then recruiting additional A β molecules to grow (Cohen et al., 2013; Knowles et al., 2014). These oligomers are structurally diverse. Whereas some oligomers go on to become fibrils, others never form fibrils but are still highly toxic (Kayed et al., 2003). Environments that concentrate A β , such as lipid raft membrane regions, cell surfaces, or areas rich in metal ions, can accelerate oligomer formation by stabilizing aggregation-prone shapes (Benilova et al., 2012; Kaye et al., 2003). Importantly, A β oligomers extracted from Alzheimer's brains block long-term potentiation and impair memory when introduced into experimental systems, providing direct evidence for their pathogenic role (Shankar et al., 2008; Lambert et al., 1998).

1.5: Fibril formation, β -sheet assembly, and Plaque Deposition

With further assembly, A β oligomers may transition into more ordered β -sheet-rich fibrils. These large structures are highly stable and rigid in nature, thus providing the cores for amyloid plaques. The mechanism of fibril formation involves a process termed nucleation-dependent polymerization. If a small seed is present, there can be rapid addition of monomers, while secondary nucleation on the surface of existing fibrils can further accelerate aggregation (Cohen et al., 2013; Knowles et al., 2014). Such fibrils adopt the characteristic cross- β architecture and are resistant to normal protein-clearing mechanisms, thus enabling persistence in the extracellular space (Knowles et al., 2014).

Although fibrils diffuse less readily than soluble oligomers, they can act as long-term reservoirs, slowly releasing small toxic assemblies and altering the local environment example, by binding metal ions or disturbing ionic balance-which can maintain or amplify neurotoxicity (). Over the years, these fibrils accumulate as macroscopic amyloid plaques, typically consisting of a dense fibrillar core surrounded by reactive glia and damaged neurites. Neuropathological studies consistently show both diffuse and dense-core plaques in AD brains, usually accompanied by dystrophic neurites and clusters of activated microglia and astrocytes. Although plaque burden is one of the two hallmarks of AD pathology, cognitive impairment tends to correlate more strongly with soluble oligomer levels than with plaque load, suggesting that plaques reflect chronic deposition, while oligomers are the more immediate drivers of synaptic injury.

Importantly, plaques also act as local hubs of inflammation: microglia and astrocytes accumulate around them, releasing cytokines and reactive species that can influence both APP processing and A β clearance to create a feedback loop further intensifying local pathology.

Section 2: Tau Pathology + Interaction with A β

2.1 - Tau Protein Dysfunction and Neurofibrillary Tangle Formation

Along with amyloid-beta plaques, Alzheimer's disease is also characterized by significant alterations inside neurons caused by the abnormal actions of tau, a protein that normally stabilizes the cell's transport system. In normal times, tau attaches to microtubules and assists in shuttling nutrients, organelles, and signaling molecules up and down long neuronal pathways. In the case of Alzheimer's, however, tau becomes hyperphosphorylated. In this condition, it has received too many phosphate groups and can no longer attach to the microtubules (Bloom, 2014). When tau lets go, microtubules break down, axonal transport stutters, and the internal framework of the neuron starts to collapse. As hyperphosphorylated tau amasses, it misfolds and aggregates into paired helical filaments. Eventually, neurofibrillary tangles (NFT) are formed; these are a key pathological feature of Alzheimer's disease (Nelson et al., 2012). These tangles physically block the cell's interior and cause needed functions to malfunction. Unlike amyloid-beta plaques, which exist outside of neurons and would not necessarily kill the neuron right away, NFT buildup is indicative that the neuron is degenerating. Moreover, the extent and distribution of tau tangles significantly correlate with memory loss and cognitive decline. In fact, studies have shown it correlates more than plaque burden (Arriagada et al., 1992). All this evidence points to tau's major role in Alzheimer's symptoms.

2.2 - The Synergistic Interaction between A β and Tau Pathology

Although A β plaques and tau tangles were once viewed as separate processes, studies show they are closely linked. A β accumulation appears to come first, usually decades before symptoms, while tau tangles appear to be induced by the A β oligomers through activation of various kinases such as "GSK-3 β " and "CDK5". These places phosphate groups on the tau at irregular sites and further push tau into a pathological state. Once tau is misfolded, it can spread between neurons in a prion-like manner, helping explain the stepwise progression of Alzheimer's pathology: from the entorhinal cortex, the hippocampus, and then the neocortex.

This can be an interaction that works both ways. For example, studies show that reducing tau in mouse models with high A β levels protects neurons from synaptic damage and memory impairment (Roberson et al., 2007). What this data suggests is that while A β may initiate the disease, tau is required for A β to exert its full toxicity. More recently, many researchers have started to think of A β and tau as part of a single reinforcing network. The idea goes that A β sparks the problem, while tau spreads and amplifies it.

2.3 - Impact of Tau on Neuronal Communication + Cognitive Decline

Once tau becomes dysfunctional, its impact on neuronal communication is far-reaching. With microtubules destabilized, axonal transport fails, preventing key molecules such as mitochondria, synaptic

vesicles, and growth factors from reaching their destinations. Even small disruptions in this transport system can quickly amplify, weakening the synapses. It may also prevent long-term potentiation, a biological process that is very important for forming new memories from occurring (Hoover et al., 2010). Tau pathology first impacts brain regions critical for memory, including the entorhinal cortex and hippocampus. These impacts are consistent with the early symptoms of Alzheimer's disease. Deficits in language, reasoning, and daily function emerge as tangles spread. Eventually, the far-reaching neuronal loss driven by tau leads to brain atrophy, characteristic of late-stage cognitive disease. Given that tau deposition strongly correlates with symptom severity, many consider tau to be a strong pathological predictor of clinical decline alongside than A β .

2.4 - Comparing the Roles of A β and Tau in Neurodegeneration

Both A β and tau are critical factors in understanding the onset of Alzheimer's disease, but they do different things at different times within the sequence of the disease. On one hand, A β accumulation begins early and silently, thus often serving as a trigger for downstream pathology. Still, many studies have shown that a lot of people with extensive deposition of A β remain cognitively normal for years, according to Jack et al. in 2013. This data supports the idea that plaque alone is not enough to cause symptoms. Tau pathology, on the other hand, closely tracks cognitive decline. Once tau tangles begin spreading, neuronal dysfunction and memory loss become far more predictable and additionally difficult to reverse.

This distinction shapes current therapeutic strategies for Alzheimer's Disease. Early-stage interventions currently focus on reducing A β accumulation with the aim of preventing tau from becoming abnormal. Later in the intervention, treatments become progressively targeted at tau phosphorylation, tangle formation, and mechanisms that allow tau to spread. Considering A β as an upstream instigator and tau as a direct driver of neurodegeneration gives a clearer basis for explaining Alzheimer's progression and for designing stage-specific therapies.

Section 3: A β Plaques, Tau Pathology & Disruption of Neural Communication

3.1 A β Plaques to Tau Dysregulation

A β plaques mark one of the earliest disturbances in the brain and help set in motion the changes that eventually destabilize neurons. Although plaques form outside cells, the soluble A β oligomers associated with them interfere with normal synaptic signaling and place neurons under stress (Selkoe & Hardy, 2016; Haass & Selkoe, 2007). This stress, in turn, activates kinase enzymes like GSK-3 β and CDK5 that add excessive phosphate groups to tau. Once hyperphosphorylated, tau loses its ability to stabilize microtubules and begins to detach, weakening the cell's internal structure (Ittner et al., 2010; Roberson et al., 2007). This allows A β plaques to initiate the molecular changes that push tau toward dysfunction.

3.2 Plaques Promote Tau Aggregation and Spread

After tau is hyperphosphorylated, neurons are far more vulnerable to tau misfolding and aggregation. A β plaques, along with the inflammation and oxidative stress they provoke, generate an environment that promotes tau aggregation into neurofibrillary tangles (Serrano-Pozo et al., 2011; Heneka, Golenbock & Latz, 2015). These tangles disrupt axonal transport, cutting off delivery of critical cargo, including mitochondria and neurotransmitter receptors. A β -induced synaptic stress and glial activation also contribute to the cell-to-cell dissemination of misfolded tau, further weakening communication between brain regions and hastening network failure (Roberson et al., 2007; Ittner et al., 2010).

3.3 Disruption of Synapses Directly by A β

Studies also show that A β disrupts synaptic function independent of plaque deposition. Specifically, soluble A β oligomers bind to the key synaptic receptors, interfering with calcium homeostasis and blunting long-term potentiation, a cellular process underlying learning and memory (Haass & Selkoe, 2007; Selkoe & Hardy, 2016). This leads to weaker synaptic signaling, reduced stability of dendritic spines, and early disconnection of neural circuits. Consequently, plaques function not only as a long-term repository but also as a source of diffusible A β species that continue to impair synapses even before extensive tau pathology develops.

3.4 Sustained Neuroinflammation and Compromised Neural Homeostasis

A β plaques attract microglia that attempt to clear them, but, in the process, become chronically activated. Over time, these microglia release inflammatory cytokines and reactive oxygen species that damage synapses and stress neurons. This inflammatory environment further promotes tau misfolding and reduces the brain's ability to maintain and repair synaptic connections. As inflammation persists, neurons lose resilience, and communication between neural networks becomes increasingly compromised.

CONCLUSION

A huge question that has been brought up in the study of Alzheimer's Disease concerns the role A β plaques play in disrupting neural communication, specifically in Alzheimer's disease. In two decades of research, it has become clear that A β plaques disrupt neural communication by driving a series of molecular changes that weaken the foundations of healthy signaling. That process starts with how cells handle APP and whether it leads to the formation of longer, aggregation-prone A β peptides. These peptides assemble into soluble oligomers that interfere with synaptic function long before plaques appear. As these oligomers build up, they disturb receptor activity, impair long-term potentiation, and weaken the structural stability of dendritic spines.

Meanwhile, A β exposure turns on intracellular signaling pathways that induce tau to let go of microtubules and start to aggregate into tangles. Tau pathology now contributes prominently to neuronal dysfunction, crumbling transport systems within the cell, and diminishing the neuron's capability to sustain synaptic contacts. In this way, the interrelationship between A β and tau forms a reinforcing loop in which each process accelerates the injury caused by the other.

Where plaques have formed, they continue to emit soluble A β species and attract microglia and astrocytes into a chronic state of inflammation. Chronic inflammation further degrades synapses, promotes the spread of tau pathology, and diminishes the brain's capacity for repair. Over time, these combined effects wear down connectivity across neural networks and directly contribute to the progressive cognitive decline that characterizes Alzheimer's Disease.

In sum, A β plaques have a pivotal and multifaceted role in causing the breakdown of neural communication. They produce toxic oligomers, initiate tau-dependent structural collapse, promote inflammation, and compromise the synaptic systems on which healthy brain function depends. These mutually reinforcing mechanisms contribute to how A β pathology drives the incremental and diffuse impairment of neural communication that characterizes Alzheimer's Disease.

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REFERENCES

- Alzheimer's disease. (2019). In *Handbook of Clinical Neurology* (Vol. 167, pp. 231–255). Elsevier. <https://doi.org/10.1016/B978-0-12-804766-8.00013-3>
- Amyloid- β protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory | *Nature Medicine*. (n.d.). Retrieved December 12, 2025, from <https://www.nature.com/articles/nm1782>
- Arriagada, P. V., Growdon, J. H., Hedley-Whyte, E. T., & Hyman, B. T. (n.d.). *Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease*.
- Arriagada, P. V., Growdon, J. H., Hedley-Whyte, E. T., & Hyman, B. T. (1992). Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. *Neurology*, 42(3), 631–631. <https://doi.org/10.1212/WNL.42.3.631>
- Benilova, I., Karran, E., & De Strooper, B. (2012a). The toxic A β oligomer and Alzheimer's disease: An emperor in need of clothes. *Nature Neuroscience*, 15(3), 349–357. <https://doi.org/10.1038/nn.3028>
- Benilova, I., Karran, E., & De Strooper, B. (2012b). The toxic A β oligomer and Alzheimer's disease: An emperor in need of clothes. *Nature Neuroscience*, 15(3), 349–357. <https://doi.org/10.1038/nn.3028>
- Bloom, G. S. (2014a). Amyloid- β and Tau: The Trigger and Bullet in Alzheimer Disease Pathogenesis. *JAMA Neurology*, 71(4), 505–508. <https://doi.org/10.1001/jamaneurol.2013.5847>
- Bloom, G. S. (2014b). Amyloid- β and Tau: The Trigger and Bullet in Alzheimer Disease Pathogenesis. *JAMA Neurology*, 71(4), 505. <https://doi.org/10.1001/jamaneurol.2013.5847>
- Cohen, S. I. A., Linse, S., Luheshi, L. M., Hellstrand, E., White, D. A., Rajah, L., Otzen, D. E., Vendruscolo, M., Dobson, C. M., & Knowles, T. P. J. (2013). Proliferation of amyloid- β 42 aggregates occurs through a secondary nucleation mechanism. *Proceedings of the National Academy of Sciences*, 110(24), 9758–9763. <https://doi.org/10.1073/pnas.1218402110>
- Common Structure of Soluble Amyloid Oligomers Implies Common Mechanism of Pathogenesis* | *Science*. (n.d.). Retrieved December 12, 2025, from <https://www.science.org/doi/abs/10.1126/science.1079469>
- De Strooper, B., & Annaert, W. (2010). Novel Research Horizons for Presenilins and γ -Secretases in Cell Biology and Disease. *Annual Review of Cell and Developmental Biology*, 26(1), 235–260. <https://doi.org/10.1146/annurev-cellbio-100109-104117>
- FallahBagheri, N., & Akan, Ö. B. (2025). A Molecular Communication Perspective of Alzheimer's Disease: Impact of Amyloid Beta Oligomers on Glutamate Diffusion in the Synaptic Cleft. *IEEE Transactions on Molecular, Biological, and Multi-Scale Communications*, 11(2), 186–200. <https://doi.org/10.1109/TMBMC.2025.3552959>

- Haass, C., & Selkoe, D. J. (2007a). Soluble protein oligomers in neurodegeneration: Lessons from the Alzheimer's amyloid β -peptide. *Nature Reviews Molecular Cell Biology*, 8(2), 101–112. <https://doi.org/10.1038/nrm2101>
- Haass, C., & Selkoe, D. J. (2007b). Soluble protein oligomers in neurodegeneration: Lessons from the Alzheimer's amyloid β -peptide. *Nature Reviews Molecular Cell Biology*, 8(2), 101–112. <https://doi.org/10.1038/nrm2101>
- Haass, C., & Selkoe, D. J. (2007c). Soluble protein oligomers in neurodegeneration: Lessons from the Alzheimer's amyloid β -peptide. *Nature Reviews Molecular Cell Biology*, 8(2), 101–112. <https://doi.org/10.1038/nrm2101>
- Hartl, F. U. (2017). Protein Misfolding Diseases. *Annual Review of Biochemistry*, 86(Volume 86, 2017), 21–26. <https://doi.org/10.1146/annurev-biochem-061516-044518>
- Heneka, M. T., Golenbock, D. T., & Latz, E. (2015a). Innate immunity in Alzheimer's disease. *Nature Immunology*, 16(3), 229–236. <https://doi.org/10.1038/ni.3102>
- Heneka, M. T., Golenbock, D. T., & Latz, E. (2015b). Innate immunity in Alzheimer's disease. *Nature Immunology*, 16(3), 229–236. <https://doi.org/10.1038/ni.3102>
- Hoover, B. R., Reed, M. N., Su, J., Penrod, R. D., Kotilinek, L. A., Grant, M. K., Pitstick, R., Carlson, G. A., Lanier, L. M., Yuan, L.-L., Ashe, K. H., & Liao, D. (2010). Tau Mislocalization to Dendritic Spines Mediates Synaptic Dysfunction Independently of Neurodegeneration. *Neuron*, 68(6), 1067–1081. <https://doi.org/10.1016/j.neuron.2010.11.030>
- Ittner, L. M., Ke, Y. D., Delerue, F., Bi, M., Gladbach, A., Eersel, J. van, Wölfling, H., Chieng, B. C., Christie, M. J., Napier, I. A., Eckert, A., Staufenbiel, M., Hardeman, E., & Götz, J. (2010). Dendritic Function of Tau Mediates Amyloid- β Toxicity in Alzheimer's Disease Mouse Models. *Cell*, 142(3), 387–397. <https://doi.org/10.1016/j.cell.2010.06.036>
- Jack, C. R., Knopman, D. S., Jagust, W. J., Petersen, R. C., Weiner, M. W., Aisen, P. S., Shaw, L. M., Vemuri, P., Wiste, H. J., Weigand, S. D., Lesnick, T. G., Pankratz, V. S., Donohue, M. C., & Trojanowski, J. Q. (2013). Tracking pathophysiological processes in Alzheimer's disease: An updated hypothetical model of dynamic biomarkers. *The Lancet Neurology*, 12(2), 207–216. [https://doi.org/10.1016/S1474-4422\(12\)70291-0](https://doi.org/10.1016/S1474-4422(12)70291-0)
- Kayed, R., Head, E., Thompson, J. L., McIntire, T. M., Milton, S. C., Cotman, C. W., & Glabe, C. G. (2003). Common Structure of Soluble Amyloid Oligomers Implies Common Mechanism of Pathogenesis. *Science*, 300(5618), 486–489. <https://doi.org/10.1126/science.1079469>
- Knowles, T. P. J., Vendruscolo, M., & Dobson, C. M. (2014a). The amyloid state and its association with protein misfolding diseases. *Nature Reviews Molecular Cell Biology*, 15(6), 384–396. <https://doi.org/10.1038/nrm3810>
- Knowles, T. P. J., Vendruscolo, M., & Dobson, C. M. (2014b). The amyloid state and its association with protein misfolding diseases. *Nature Reviews Molecular Cell Biology*, 15(6), 384–396. <https://doi.org/10.1038/nrm3810>
- Lai, A., Sisodia, S. S., & Trowbridge, I. S. (1995). Characterization of Sorting Signals in the β -Amyloid Precursor Protein Cytoplasmic Domain (*). *Journal of Biological Chemistry*, 270(8), 3565–3573. <https://doi.org/10.1074/jbc.270.8.3565>
- Lambert, M. P., Barlow, A. K., Chromy, B. A., Edwards, C., Freed, R., Liosatos, M., Morgan, T. E., Rozovsky, I., Trommer, B., Viola, K. L., Wals, P., Zhang, C., Finch, C. E., Krafft, G. A., &

- Klein, W. L. (1998). Diffusible, nonfibrillar ligands derived from A β 1–42 are potent central nervous system neurotoxins. *Proceedings of the National Academy of Sciences*, 95(11), 6448–6453. <https://doi.org/10.1073/pnas.95.11.6448>
- Majd, S., Power, J. H., & Grantham, H. J. M. (2015). Neuronal response in Alzheimer's and Parkinson's disease: The effect of toxic proteins on intracellular pathways. *BMC Neuroscience*, 16(1), 69. <https://doi.org/10.1186/s12868-015-0211-1>
- Nelson, P. T., Alafuzoff, I., Bigio, E. H., Bouras, C., Braak, H., Cairns, N. J., Castellani, R. J., Crain, B. J., Davies, P., Tredici, K. D., Duyckaerts, C., Frosch, M. P., Haroutunian, V., Hof, P. R., Hulette, C. M., Hyman, B. T., Iwatsubo, T., Jellinger, K. A., Jicha, G. A., ... Beach, T. G. (2012). Correlation of Alzheimer Disease Neuropathologic Changes With Cognitive Status: A Review of the Literature. *Journal of Neuropathology & Experimental Neurology*, 71(5), 362–381. <https://doi.org/10.1097/NEN.0b013e31825018f7>
- Nixon, R. A. (2005). Endosome function and dysfunction in Alzheimer's disease and other neurodegenerative diseases. *Neurobiology of Aging*, 26(3), 373–382. <https://doi.org/10.1016/j.neurobiolaging.2004.09.018>
- Orobets, K. S., & Karamyshev, A. L. (2023). Amyloid Precursor Protein and Alzheimer's Disease. *International Journal of Molecular Sciences*, 24(19), 14794. <https://doi.org/10.3390/ijms241914794>
- Panza, F., Lozupone, M., Logroscino, G., & Imbimbo, B. P. (2019). A critical appraisal of amyloid- β -targeting therapies for Alzheimer disease. *Nature Reviews Neurology*, 15(2), 73–88. <https://doi.org/10.1038/s41582-018-0116-6>
- Penke, B., Bogár, F., & Fülöp, L. (2017). β -Amyloid and the Pathomechanisms of Alzheimer's Disease: A Comprehensive View. *Molecules*, 22(10), 1692. <https://doi.org/10.3390/molecules22101692>
- Roberson, E. D., Scarce-Levie, K., Palop, J. J., Yan, F., Cheng, I. H., Wu, T., Gerstein, H., Yu, G.-Q., & Mucke, L. (2007). Reducing Endogenous Tau Ameliorates Amyloid β -Induced Deficits in an Alzheimer's Disease Mouse Model. *Science*, 316(5825), 750–754. <https://doi.org/10.1126/science.1141736>
- Sadigh-Eteghad, S., Sabermarouf, B., Majdi, A., Talebi, M., Farhoudi, M., & Mahmoudi, J. (2014). Amyloid-Beta: A Crucial Factor in Alzheimer's Disease. *Medical Principles and Practice*, 24(1), 1–10. <https://doi.org/10.1159/000369101>
- Scheltens, P., Strooper, B. D., Kivipelto, M., Holstege, H., Chételat, G., Teunissen, C. E., Cummings, J., & Flier, W. M. van der. (2021). Alzheimer's disease. *The Lancet*, 397(10284), 1577–1590. [https://doi.org/10.1016/S0140-6736\(20\)32205-4](https://doi.org/10.1016/S0140-6736(20)32205-4)
- Sehar, U., Rawat, P., Reddy, A. P., Kopel, J., & Reddy, P. H. (2022). Amyloid Beta in Aging and Alzheimer's Disease. *International Journal of Molecular Sciences*, 23(21), 12924. <https://doi.org/10.3390/ijms232112924>
- Selkoe, D. J., & Hardy, J. (2016). The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO Molecular Medicine*, 8(6), 595–608. <https://doi.org/10.15252/emmm.201606210>
- Serrano-Pozo, A., Frosch, M. P., Masliah, E., & Hyman, B. T. (2011). Neuropathological Alterations in Alzheimer Disease. *Cold Spring Harbor Perspectives in Medicine*, 1(1), a006189. <https://doi.org/10.1101/cshperspect.a006189>

- Shankar, G. M., Li, S., Mehta, T. H., Garcia-Munoz, A., Shepardson, N. E., Smith, I., Brett, F. M., Farrell, M. A., Rowan, M. J., Lemere, C. A., Regan, C. M., Walsh, D. M., Sabatini, B. L., & Selkoe, D. J. (2008). Amyloid- β protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory. *Nature Medicine*, 14(8), 837–842. <https://doi.org/10.1038/nm1782>
- Strooper, B. D., & Annaert, W. (2010). Novel Research Horizons for Presenilins and γ -Secretases in Cell Biology and Disease. *Annual Review of Cell and Developmental Biology*, 26(Volume 26, 2010), 235–260. <https://doi.org/10.1146/annurev-cellbio-100109-104117>
- The Amyloid- β Pathway in Alzheimer's Disease* | *Molecular Psychiatry*. (n.d.). Retrieved December 2, 2025, from <https://www.nature.com/articles/s41380-021-01249-0>
- Vassar, R., Bennett, B. D., Babu-Khan, S., Kahn, S., Mendiaz, E. A., Denis, P., Teplow, D. B., Ross, S., Amarante, P., Loeloff, R., Luo, Y., Fisher, S., Fuller, J., Edenson, S., Lile, J., Jarosinski, M. A., Biere, A. L., Curran, E., Burgess, T., ... Citron, M. (1999). β -Secretase Cleavage of Alzheimer's Amyloid Precursor Protein by the Transmembrane Aspartic Protease BACE. *Science*, 286(5440), 735–741. <https://doi.org/10.1126/science.286.5440.735>
- Yan, R., & Vassar, R. (2014). Targeting the β secretase BACE1 for Alzheimer's disease therapy. *The Lancet Neurology*, 13(3), 319–329. [https://doi.org/10.1016/S1474-4422\(13\)70276-X](https://doi.org/10.1016/S1474-4422(13)70276-X)
- Zhang, X., & Song, W. (2013). The role of APP and BACE1 trafficking in APP processing and amyloid- β generation. *Alzheimer's Research & Therapy*, 5(5), 46. <https://doi.org/10.1186/alzrt211>