Review Article on Role of Amyloid and Tau Proteins in Alzheimer's Disease

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***Abstract*—The Amyloid Cascade Hypothesis has dominated the Alzheimer's disease (AD) field in the last 25 years. It posits that the increase of amyloid-β (Aβ) is the key event in AD that triggers tau pathology followed by neuronal death and eventually, the disease. However, therapeutic approaches aimed at decreasing Aβ levels have so far failed, and tau-based clinical trials have not yet produced positive findings. Here we have examined literature on the role of Aβ and tau in synaptic dysfunction, memory loss, and seeding and spreading of AD, highlighting important parallelisms between the two proteins. We discuss novel findings showing binding of both Aβ and tau oligomers to amyloid-β protein precursor (AβPP), and the requirement for the presence of this protein for both Aβ and tau to enter neurons and induce abnormal synaptic function and memory. We propose a novel view of AD pathogenesis in which extracellular oligomers of Aβ and tau act in parallel and upstream of AβPP.**

***Index Terms*—Amyloid-β peptide, amyloid-β protein precursor, oligomers, synaptic dysfunction, tau, Alzheimer's disease.**

I. INTRODUCTION

Alzheimer's disease (AD) is characterized by the accumulation of amyloid-beta (Aβ) plaques and neurofibrillary tangles of hyperphosphorylated tau protein, which together drive synaptic dysfunction, neuronal death, and cognitive decline. Extracellular plaques disrupt neural communication, while intracellular tau tangles compromise axonal transport. These pathologies act synergistically, often with Aβ triggering tau propagation, leading to widespread neurodegeneration.

- **Amyloid-Beta Plaques:** Derived from the cleavage of Amyloid Precursor Protein (APP), Aβ peptides aggregate into extracellular senile plaques. Imbalance between production and clearance results in accumulation, believed to start decades before clinical symptoms.
- **Tau Protein Tangles:** Normally, tau stabilizes microtubules within neurons. In Alzheimer's, hyperphosphorylation causes tau to detach, aggregate, and form intracellular neurofibrillary tangles (NFTs), leading to cellular structure failure.
- **Synergistic Relationship:** While Aβ is considered an early upstream initiator, tau pathology is more closely associated with cognitive decline. Research suggests that plaques can promote tau phosphorylation, creating a "vicious cycle" of toxicity.
- **Therapeutic Targets:** Current research focuses on targeting both proteins, including monoclonal antibodies that remove aggregates.

II. EARLY HISTORY OF THE AMYLOID-B PATHWAY IN AD

The Aβ is a 4 kDa fragment of the amyloid precursor protein (APP), a larger precursor molecule widely produced by brain neurons, vascular and blood cells, and, to a lesser extent, astrocytes. Two subsequent proteolytic cleavages of APP by β-secretase (BACE1) at the ectodomain and γ-secretase at intra-membranous sites generate Aβ. In 1984, Aβ and its amino acid sequence were reported for the first time as a primary constituent of meningovascular polymorphic deposits in patients with Down Syndrome. Neuropathological studies indicate a spatial-temporal evolution of brain Aβ accumulation that occurs initially in cerebral regions with high

metabolic activity and spreads from neocortex to allocortex to brainstem, eventually reaching the cerebellum.

Fig. No. 1: Advance Stages of Alzheimer's Disease

III. STRUCTURE RELATED TOXICITY

Aβ is classified based on molecular weight, microscopic dimensions and length. The first and smallest among the three types are the very short oligomers, also referred to as dimers or hexamers, with a molecular weight of 5–55 kDa. The second type is the Aβ-derived diffusible ligands with the molecular weight of 17–42 kDa. The third type comprises the protofibrils, which are transient structures appearing before the formation of matured amyloid fibrils.

IV. PATHOPHYSIOLOGY OF TAU PROTEINS

Normally, tau proteins are found on the inside of neurons' axons to maintain their correct structure. In some forms of dementia, including Alzheimer's disease and frontotemporal dementia, tau proteins become damaged and detach from their axons. Now moving freely inside the neuron, the abnormal tau proteins clump together to form neurofibrillary tangles. This dysfunctional tau is toxic to neurons and causes them to die. When neurons in a chain die, that chain is broken, and messages cannot be delivered as effectively through the brain.

Fig. No. 2: Tau Proteins in Neurodegeneration

V. DIAGNOSIS

An important part of diagnosing Alzheimer's disease includes being able to explain symptoms, with input from a close family member or friend. Tests of memory and thinking skills also help diagnose Alzheimer's disease. Blood and imaging tests can rule out other potential causes of symptoms and check for proteins in the brain linked to Alzheimer's disease. Today, healthcare professionals can diagnose Alzheimer's disease during life using biomarker tests including specific types of PET scans of the brain. Amyloid and tau proteins can also be measured in the cerebrospinal fluid and, recently, in blood biomarker tests.

VI. RISK FACTORS

Researchers have identified several risk factors that affect the likelihood of developing dementia. Non-modifiable factors include age (the risk of Alzheimer's disease increases significantly with advancing age) and genetics/family history. Modifiable risk factors include smoking, high alcohol consumption, atherosclerosis, high LDL cholesterol, elevated plasma homocysteine, diabetes, and mild cognitive impairment. Many people with Down's syndrome show neurological and behavioral signs of Alzheimer's disease by the time they reach middle age.

VII. AB AND TAU OLIGOMERS: IMPACT ON MEMORY

How do Aβ and tau induce memory loss? According to most studies, the answer should be sought at the synapse. A subtle effect exerted by soluble forms of Aβ and tau at the synapse seems to be the earlier event underlying memory loss. Several studies have demonstrated that administration of different preparations of oligomeric Aβ and tau impaired synaptic plasticity and memory. Both Aβ and tau interfere with the transcription factor CREB, whose phosphorylation at Ser133 is thought to be one of the fundamental events in memory formation. Aβ inhibits the physiological increase of CREB phosphorylation during LTP. Tau overexpression and hyperphosphorylation was also found to be accompanied by a reduction of CREB phosphorylation.

Both Aβ and tau also target Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), another key molecule needed for LTP and memory formation. CaMKII is dysregulated in the hippocampus of AD mouse models and patients. The deleterious effects of Aβ and tau also involved BDNF, a critical factor linked to neuronal survival and function. A decrease of BDNF levels in serum and brains of AD patients correlates with cognitive impairment. These findings suggest that restoring synaptic-related molecules and second messenger systems regulating memory mechanisms might be a viable therapeutic strategy to counteract AD.

VIII. CONCLUSION

Alzheimer's disease is a complex and progressive neurodegenerative disorder in which both amyloid-β and tau proteins play crucial and interconnected roles. Amyloid-β accumulation is considered an early initiating factor, while tau pathology is more closely associated with neuronal damage and cognitive

decline. The interaction between these two proteins creates a synergistic effect that accelerates synaptic dysfunction, neuronal loss, and memory impairment.

Recent evidence suggests that rather than acting in isolation, amyloid-β and tau oligomers work in parallel pathways, influencing key molecular mechanisms involved in synaptic plasticity and neuronal communication. Despite extensive research, therapeutic strategies targeting amyloid-β and tau individually have shown limited success, indicating the need for a more integrated approach. Future research should focus on understanding their combined mechanisms, early diagnostic biomarkers, and novel therapeutic targets such as amyloid precursor protein (APP) and synaptic signaling pathways.

REFERENCES

[1] J. Hardy and G. Higgins, "Alzheimer's disease: the amyloid cascade hypothesis," Science, vol. 256, no. 5054, pp. 184–185, 1992.

[2] D. J. Selkoe and J. Hardy, "The amyloid hypothesis of Alzheimer's disease at 25 years," EMBO Molecular Medicine, vol. 8, no. 6, pp. 595–608, 2016.

[3] G. S. Bloom, "Amyloid-β and tau: the trigger and bullet in Alzheimer disease pathogenesis," JAMA Neurology, vol. 71, no. 4, pp. 505–508, 2014.

[4] Y. Wang and E. Mandelkow, "Tau in physiology and pathology," Nature Reviews Neuroscience, vol. 17, no. 1, pp. 5–21, 2016.

[5] J. M. Long and D. M. Holtzman, "Alzheimer disease: an update on pathobiology and treatment strategies," Cell, vol. 179, no. 2, pp. 312–339, 2019.

[6] H. W. Querfurth and F. M. LaFerla, "Alzheimer's disease," New England Journal of Medicine, vol. 362, no. 4, pp. 329–344, 2010.

[7] C. R. Jack Jr. et al., "NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease," Alzheimer's & Dementia, vol. 14, no. 4, pp. 535–562, 2018.

[8] M. A. Busche and B. T. Hyman, "Synergy between amyloid-β and tau in Alzheimer's disease," Nature Neuroscience, vol. 23, no. 10, pp. 1183–1193, 2020.

[9] D. S. Knopman et al., "Alzheimer disease," Nature Reviews Disease Primers, vol. 7, no. 1, p. 33, 2021.

[10] C. Haass and D. J. Selkoe, "Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid-β peptide," Nature Reviews Molecular Cell Biology, vol. 8, no. 2, pp. 101–112, 2007.