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Relationship Between Amyloid-beta Deposition and Tau Deposition in Alzheimer's Disease

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Abstract: So far, the primary culprits in the onset of Alzheimer's disease are the deposits of amyloid-β (Aβ) proteins and the formation of tau protein knots. These markers are crucial for a conclusive pathological diagnosis. Despite the significance of both amyloid-β deposits and tau protein knots, the nature of their interaction remains largely unexplained, and the scientific inquiries into this relationship yield a patchy and inconclusive body of research. In this paper, we find out Aβ plaques accelerate neurotic plaque tau aggregation and propagation and apply fluorescent biotechnique to detect and measure Aβ oligomers in normal and tau seed condition. The findings indicate that upon introducing varied concentrations of Aβ aggregates into culture mediums devoid of lipofectamine, both Aβ filaments and newly synthesized Aβ enhance tau nucleation in correlation with their concentration. Moreover, Aβ oligomers exhibit a more pronounced stimulatory effect, strongly suggesting an interaction between Aβ and tau.

Keywords: amyloid-β (Aβ) protein, tau protein, Alzheimer's disease (AD), interaction.

1. Introduction

Alzheimer's, an insidious neurodegenerative condition, typically initiates with gradual onset and continually exacerbates over time, accounting for 60–70% of all dementia instances. Memory lapses concerning recent occurrences are frequently the initial manifestation. As the malady progresses, affected individuals may encounter linguistic difficulties, spatial disorientation, which may result in frequent instances of becoming lost, emotional instability, diminished drive, neglect of personal care, and conduct disorders. As the sufferer's health deteriorates, social withdrawal from loved ones and community becomes prevalent. Eventually, the decline encompasses physical capabilities, culminating in mortality. Despite variations in the rate of deterioration, the median survival period post-diagnosis spans approximately three to twelve years.

The origins of Alzheimer's remain a mystery, yet the prevailing theories essentially boil down to a pair of concepts: the amyloid-β (Aβ) pathway and the excessive phosphorylation of the tau protein. According to the Aβ pathway theory, the accumulation of Aβ in the form of inflammatory plaques in the brain leads to the onset of AD by harming the neurons. However, there is no content results in AD clinical treatment for disposing Aβ oligomers. Lately, there has been a surge of interest in the tau protein, as neurotic knots laden with excessively phosphorylated tau are indicative of Alzheimer's disease pathology, and tau plays a pivotal role in the toxic effects of Aβ. Since Aβ oligomers and tau tangles are the prime pathological signs, we want to find out the relationship and interaction between them. In this work, we have analyzed and concluded experiment data. We aspire that this document

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aids in enhancing the comprehension of the relationship between Aβ and tau in the context of Alzheimer's disease pathogenesis, thereby encouraging additional studies into the interplay mechanics of Aβ and tau.

2. Main body

The amyloid precursor protein (APP) is anchored within the cellular membrane, with one segment residing inside the cell and the other protruding externally. It facilitates the growth and post-injury recuperation of neurons. Being a protein, APP undergoes utilization and eventually degrades, undergoing a recycling process. Typically, it is cleaved by enzymes known as α-secretase and γ-secretase, resulting in a soluble peptide that is easily disposable. However, when the enzyme β-secretase collaborates with γ-secretase, the resulting residual fragment is insoluble and forms a monomer known as Aβ. These adhesive monomers adhere to one another outside neuronal cells, leading to the formation of Aβ plaques. These monomers constitute oligomers (os), and Aβos serve as intermediate stages in the aggregation of Aβ, occurring during both the lag phase and the growth phase. (Figure 1)

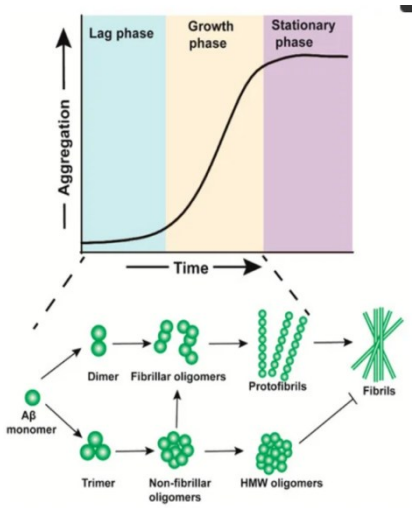

Figure 1: Schematic representation of the process of β-amyloid (Aβ) aggregation

Tau protein basically is a low molecular weight and related to tubulin protein. It mainly exists inside neuron. The role of it is like a transport tool, connecting electrical signal between each neuron. To promote it, there are some modifications on it and the most common one is phosphorate acid. However, it will hyperphosphorylation in AD patient's neurons. In a comprehensive breakdown, the formation of Aβ plaques exterior to the neuron sets off concurrent internal pathways. This results in the triggering of kinase activity, which is an enzymatic process that attaches phosphate groups to the tau protein. The precise locations wherephosphorate acid are situated within the N-terminal segment (including Ser46, Thr123, Ser198, Ser199, Ser202, Ser208, Ser210, Thr212, Ser214, Thr217, Thr231, and Ser235), the repeat domain (Ser262 and Ser356), and the C-terminal area (Ser396, Ser400, Thr403, Ser404, Ser409, Ser412, Ser413, and Ser422), as depicted in Figure 1. Multiple enzymes are responsible for the hyperphosphorylation of these sites, among them A-kinase, C-kinase, cyclin-dependent kinase-5 (CDK-5), CaM kinase II, glycogen synthase kinase-3β (GSK-3β), and MAPKs, as outlined in Table 1. Consequently, the tau protein undergoes a structural transformation due to its detachment from microtubules (MTs) and the subsequent formation of intracellular neurofibrillary tangles. This disrupts the tau protein's role in supporting the MTs within the cytoskeleton, leading to aggregation with other tau proteins and forming tangled structures known as neurofibrillary tangles.

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Neurons affected by these tangles and malfunctioning microtubules suffer impaired signaling and may eventually undergo apoptosis, or controlled cell death. To encapsulate, the Aβ protein acts as a catalyst, exacerbating the hyperphosphorylation of the tau protein.

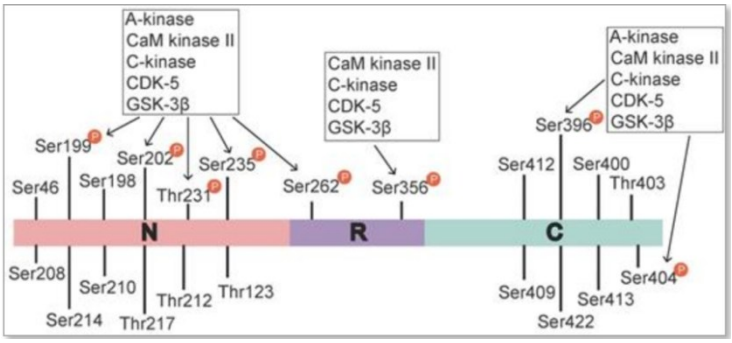

Figure 2: Tau phosphorylation sites and associated kinases

Table 1: Sites on tau phosphorylated by different kinases

Phosphorylation stage	Kinase	Phosphorylation sites	Whether Aβ is involved
Prephosphorylation	A-kinase	Ser262,Ser294,Ser305, Ser324,Ser356	No
	C-kinase	Ser305	No
	CaM kinase	Ser416/Ser262	No
	CDK-5	Ser195,Ser202,Thr231, Ser235,Ser396,Ser404	Yes
Phosphorylation	GSK-3β	Ser199*,Ser202,Thr231*, Ser235,Ser262,Ser396*, Ser404*	Yes
	MAPK	Thr181,Ser202*,Thr205*, Ser396*,Ser404*,Ser422, Ser199*,Thr50*	Yes
Prephosphorylation+Phosphorylation	A-kinase+GSK-3β	Ser199*,Ser202*,Thr231, Ser235,Ser262,Ser396*, Ser404[d]*	Yes
	CaM kinase+GSK-3β	Ser199*,Ser202*,Thr231*, Ser235*,Ser262*,Ser396*, Ser404*	Yes
	CDK-5+GSK-3β	Ser199,Ser202,Thr231*, Ser235,Ser262,Ser396, Ser404[d]	Yes

Aβ plaques accelerate neurotic plaque tau aggregation and propagation. A new hypothesis states that the medium of it is τ protein. This protein also can be phosphorylated. The propagation of Aβ and phosphorylated-τ pathologies across the brain follows a structured, stepwise progression. Notably, an aggregation of phosphorylated-τ is evident within the locus coeruleus, raphenuclei, substantia nigra, the dorsal nucleus of the vagus nerve, and the basal nucleus of Meynert. Subsequent to their maturation, Aβ deposits become visible in distinct brain areas. Latest findings depict that the cellular prion protein (PrPC) acts as a receptor for harmful Aβ variants and -synuclein aggregates. PrPC is present in the neuropil and has been identified within amyloid deposits and neurons in Alzheimer's disease patients. Concentrated in postsynaptic densities, PrPC triggers the activation of Fyn kinase.

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This activated kinase phosphorylates the GluN2B subunit of NMDA receptors and engages with the phosphorylation of tau. As Aβ aggregates prompt PrPC-Fyn mediated phosphorylation of tau, PrPC could be involved in the interaction between Aβ and phosphorylated-τ either directly or indirectly. Synaptic terminals release soluble phosphorylated-τ. P-τ can either form inside the cell or outside the cell. When it form ouside the cell, there is opputunity forsoluble p-τ combine with PrPC. Aβ is also combines eith PrPC and stimulates Fyn, through pyk2 related tau phosphorylation increases degree of p-τ. Neurons lacking tau demonstrate an immunity to the degenerative effects caused by either synthetic or human origin Aβ peptides, whereas an increase in tau expression intensifies the detrimental impact of Aβ. In this context, the interaction between Aβ and PrPC, the activation of Fyn, and the phosphorylation of the tau protein could offer different perspectives on the observation that Aβ deposits expedite the spread of tau phosphorylation through a PrPC-associated pathway, potentially promoting tau accumulation in brain regions with Aβ buildup. Consequently, phosphorylated tau might serve as an additional protein involved in the interplay between Aβ and tau. The interconnections observed at the site of damage further illustrate the complex network of direct and indirect relationships between Aβ deposits and tau clumping.

This study aims to gauge the impact of Aβ and tau protein clumping. Utilizing tau HEK293T cells equipped with a biosensor, these cells carry the P301S mutated tau repeat domain (RD) fused with either yellow or cyan fluorescent proteins. As tau proteins clump together within these cells, the yellow and cyan fluorescent proteins create a FRET pair, enabling the spectral quantification of the aggregate clusters. The cells are initially exposed to various Aβ species (recently prepared, oligomeric, and fibrillar) via lipofectamine, followed by the introduction of fibrillar tau RD seeds 24 hours into the process. Post this interval, fluorescent microscopy is employed to capture imagery. In the absence of tau seed transduction, the biosensor cells exhibit a diffused fluorescent signal, suggesting the baseline expression of non-clumped, native tau. When the cells are seeded with tau RD at a concentration of 10 nM, they reveal intracellular tau aggregates as bright fluorescent spots. An increase in the concentration of Aβ oligomers results in a marked rise in the visibility of these fluorescent puncta. The findings indicate that the stimulation of tau aggregation by Aβ oligomers is proportional to their concentration, with the influence of newly prepared and fibrillar Aβ being significantly subtler. To further delineate these varying influences, the quantity of tau fibril seeds in the aggregation assay was manipulated.

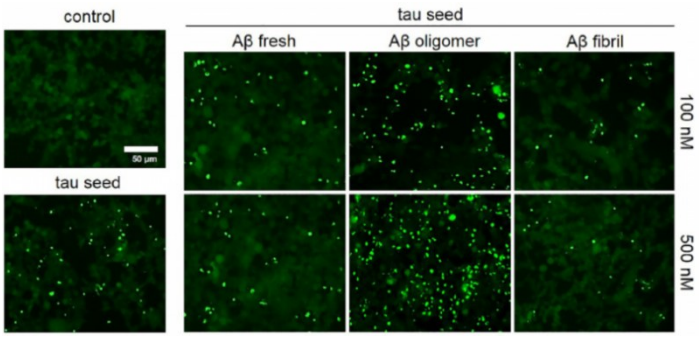

Figure 3: Fluorescent microscope images of seeded biosensor cells

3. Conclusion

In summary, Aβ and tau proteins are pivotal in Alzheimer's disease, contributing to the characteristic observed in the brains of deceased patients, namely amyloid deposits and neurofibrillary tangles. Despite their significant contribution to the disease's onset, monotherapies directed at Aβ or tau have failed to yield satisfactory therapeutic outcomes in clinical trials. Thus, people should pay concentration on the interaction or relationship research and make detailed and logical conclusion.

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Now we know Beta-amyloid hastens the phosphorylation process of the tau protein, while it concurrently disrupts the aggregation of tau into oligomers. The detrimental impact of beta-amyloid is contingent upon its interaction with tau, as both proteins collaborate to compromise mitochondrial function. Investigations both in the laboratory and in clinical settings have been carried out, affirming the theory that the synergy between beta-amyloid and tau magnifies the deleterious impact of both. Attempts have been undertaken to disrupt the association between beta-amyloid and the tau protein, including research into inhibitors of GSK-3β and CDK-5. Nevertheless, the therapeutic effectiveness in a clinical context remains undetermined, and the inquiry into the relationship between beta-amyloid and tau persists. Given that Alzheimer's disease is a multifaceted condition, likely stemming from a confluence of genomic, epigenetic, atomic, and environmental factors, it is imperative to concentrate not solely on medicinal treatments but also on the intricate biopsychosocial dimensions of managing AD, such as devising psychological therapies. Additionally, the pursuit of novel pharmacological agents capable of addressing AD through diverse pathways warrants further exploration.

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