

REVIEW

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Interaction Between A β and Tau in the Pathogenesis of Alzheimer's Disease

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Abstract: Extracellular neuritic plaques composed of amyloid- β (A β) protein and intracellular neurofibrillary tangles containing phosphorylated tau protein are the two

hallmark proteins of Alzheimer's disease (AD), and the separate neurotoxicity of these protein in AD has been extensively studied. However, interventions that target A β or tau individually have not yielded substantial breakthroughs. The interest in the interactions between A β and tau in AD is increasing, but related drug investigations are in their infancy. This review discusses how A β accelerates tau phosphorylation and the possible mechanisms and pathways by which tau mediates A β toxicity. This review also describes the possible synergistic effects between A β and tau on microglial cells and astrocytes. Studies suggest that the coexistence of A β plaques and phosphorylated tau is related to the mechanism by which A β facilitates the propagation of tau aggregation in neuritic plaques. The interactions between A β and tau mediate cognitive dysfunction in patients with AD. In summary, this review summarizes recent data on the interplay between A β and tau to promote a better understanding of the roles of these proteins in the pathological process of AD and provide new insights into interventions against AD.

Keywords: Alzheimer's disease, amyloid- β , tau, interaction, phosphorylation

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease that is characterized by the progressive deterioration of cognition and memory [1]. AD is defined pathologically by an extensive loss of neurons and two characteristic protein deposits in the brain, extracellular amyloid plaques and intracellular neurofibrillary tangles (NFTs), which are caused by tau hyperphosphorylation [1, 2]. Several hypotheses related to the pathogenesis of AD were studied [3], and the amyloid- β (A β) cascade and the hyperphosphorylation of tau protein are the two main hypotheses. The A β cascade hypothesis states that A β , deposited in the form of neuroinflammatory plaques, induces AD by damaging neuronal cells [4]. A β facilitates the development of AD and initiates a deleterious cascade involving tau pathology and neurodegeneration [5]. However, the development of many AD drugs examined in clinical trials and laboratory studies focused on the reduction of amyloid deposition and the clearance of A β oligomers and have not yielded satisfactory effects

[6-8]. A β may not be the only disease-causing protein during the course of AD. Intraneuronal tangles containing hyperphosphorylated tau are a hallmark of AD pathology [9], and tau is a mediator of A β cytotoxicity [7]. Therefore, the pathological changes to tau in AD also attracted attention. However, extensive studies focused solely on the neurotoxicity of A β or tau have not shown significant efficacy in the treatment of AD [8-11]. Therefore, focusing solely on the role of A β or tau in AD lesions while ignoring the interaction between A β and tau may not be entirely correct. A β and tau may interact via intermediate materials, such as kinases (e.g., GSK-3 β , CDK-5 and ERK) [12]. The removal of A β or tau alone does not completely terminate the interaction pathway, which continues to play a role in the acceleration of the pathological process [11, 13]. The pathological process likely involves an interplay between A β and tau in which these proteins amplify toxic effects rather than a strictly hierarchical mode of interaction [13]. Therefore, suppression of the interaction may be of more practical significance than simply focusing on the neurotoxicity of A β or tau alone [14]. The present review describes the following interactions between A β and tau. A) A β drives tau pathology by inducing tau hyperphosphorylation, and hyperphosphorylated tau mediates toxicity in neurons. B) Tau mediates A β toxicity, and A β toxicity is critically dependent on the presence of tau. C) A β and tau target cellular processes or organelles synergistically and may amplify each other's toxic effects. D) A β and tau may coexist in pathological locations [11]. We hope that this review provides a better understanding of the role of A β and tau in the pathological development of AD to promote further research on the mechanism of the interaction between A β and tau and the development of more effective therapies for AD.

A β mediates tau toxicity

A β accelerates the phosphorylation of tau protein

Tau is a microtubule (MT)-binding protein, and tau phosphorylation at multiple sites controls its binding to MTs [15]. The identified phosphorylation sites are located in the N-terminal region (Ser46 [16], Thr123 [17], Ser198, Ser199, Ser202, Ser208,

Ser210, Thr212, Ser214, Thr217, Thr231, and Ser235), the repeat region (Ser262 and Ser356), and the C-terminal region (Ser396, Ser400, Thr403, Ser404, Ser409, Ser412, Ser413, and Ser422 [18]) (Figure 1). These sites are phosphorylated by several enzymes, including A-kinase, C-kinase, cyclin-dependent kinase-5 (CDK-5), CaM kinase II, glycogen synthase kinase-3 β (GSK-3 β) and MAPKs [12, 19] (Table 1). Under pathological conditions, these kinases contribute to the hyperphosphorylation of tau protein, which subsequently leads to the dissociation of tau protein from MTs and the formation of NFTs [20, 21]. Hyperphosphorylated tau protein results in abnormal increases in cytoskeletal proteins, axoplasmic transport disorders and neuronal degeneration [22]. Tau hyperphosphorylation is the product of deregulated Ser/Thr kinases, such as CDK-5 and GSK-3 β [23]. Tau protein is prephosphorylated by A-kinase, C-kinase, CDK-5, and CaM kinase II and subsequently phosphorylated by GSK-3 β . Ser262/Ser356 is first prephosphorylated by CDK-5, CaM kinase II and C-kinase, and this prephosphorylation makes it more accessible to GSK-3 β for further phosphorylation [24]. The prephosphorylation of Ser262/Ser356 may cause tau to assume a more favourable conformation such that Thr231, Ser235, Ser396, Ser404 [19, 24] and other sites may be rapidly recognized by GSK-3 β in the subsequent phosphorylation step [25]. A β accelerates the hyperphosphorylation of tau by mediating the activation of CDK-5 [23] and GSK-3 β [26]. GSK-3 β , which is inextricably related to A β , is an important factor in the phosphorylation of tau, and it aggravates tau-induced neurotoxicity [15, 27] (Table 1). Tau phosphorylation at Ser262 is equally critical for A β 42-induced tau toxicity [11]. In conclusion, aggregated A β induces tau hyperphosphorylation by enhancing the activity of GSK-3 β and CDK-5, which are involved in the phosphorylation of tau at multiple Ser/Thr sites [28] (Figure 1). Hyperphosphorylated tau protein detaches from MTs and is more likely to form NFTs [23, 27, 30], which causes neurofibrillary degeneration. Therefore, CDK-5 and GSK-3 β kinase inhibitors may help inhibit A β -mediated tau hyperphosphorylation. For example, inhibitors of GSK-3 β and CDK-5, such as lithium, AZD1080 and roscovitine, significantly lowered the levels of tau phosphorylation and significantly reduced the levels of

aggregated, insoluble tau [31-33]. However, their clinical efficacy has not been established [34]. This result further suggests that proteins other than A β act on tau hyperphosphorylation or phosphorylation caused by kinases other than CDK-5 and GSK-3 β , that A β is not the only protein that activates CDK-5 and GSK-3 β , and that other tau phosphorylation sites should be further explored. Further studies have demonstrated that mitogen-activated protein kinases (MAPKs) and GSK-3 β were involved in the formation of PHF-tau in the AD brains [35-37]. Similarly, A β -induced tau phosphorylation in neurons is mediated via activation of both MAPK and GSK-3 β [12, 36-38]. MAPKs, including ERK1/2, SAPKs and p38, are activated by tyrosine phosphorylation and are involved in the phosphorylation of tau in AD [36-38]. Therefore, further exploration is needed to develop new drugs that act at different specific phosphorylation sites of tau via various mechanisms.

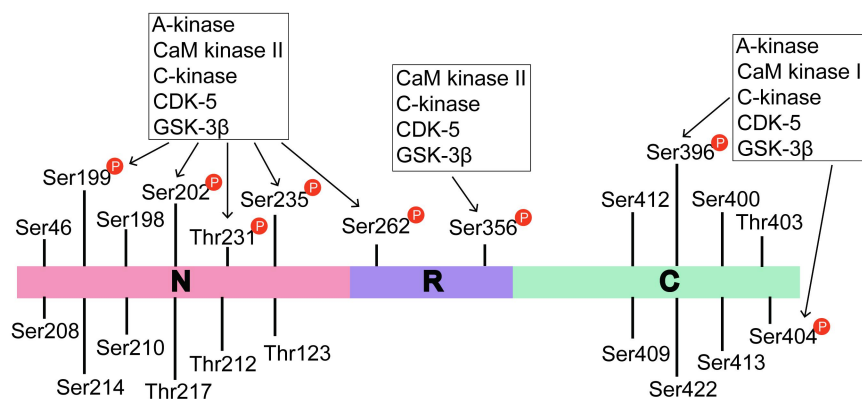


Figure 1. Tau phosphorylation sites and associated kinases. The identified tau phosphorylation sites are located in the N-terminal region (Ser46 [16], Thr123 [17], Ser198, Ser199, Ser202, Ser208, Ser210, Thr212, Ser214, Thr217, Thr231, and Ser235), the repeat region (Ser262 and Ser356), and the C-terminal region (Ser396, Ser400, Thr403, Ser404, Ser409, Ser412, Ser413, and Ser422 [18]). Ser199, Ser202, Thr231, Ser235, Ser262, Ser396, and Ser404 are phosphorylated by various activated kinases, namely A-kinase, C-kinase, CaM kinase II, CDK-5 and Gsk-3 β , and Ser356 is phosphorylated by C-kinase, CaM kinase II, CDK-5 and Gsk-3 β . A-kinase, C-kinase, CaM kinase II and CDK-5 are primarily involved in the prephosphorylation of tau. This prephosphorylation increases the affinity of GSK-3 β to these sites, which ultimately leads to tau hyperphosphorylation.

Table 1. Sites on tau phosphorylated by different kinases

Phosphorylation stage	Kinase	Phosphorylation sites	Whether A β is involved	References
Prephosphorylation	A-kinase	Ser262, Ser293, Ser305, Ser324, Ser356	No	[18, 19, 24]
	C-kinase	Ser305	No	[24]
	CaM kinase II	Ser416 / Ser262	No	[19, 24]
	CDK-5	Ser195, Ser202, Thr231, Ser235, Ser396, Ser404	Yes	[19, 23, 24, 28]
Phosphorylation	GSK-3 β	Ser199*, Ser202, Thr231*, Ser235, Ser262, Ser396*, Ser404*	Yes	[19, 23, 24, 28]
	MAPK	Thr181, Ser202*, Thr205*, Ser396*, Ser404*, Ser422, Ser199*, Thr50*	Yes	[36-38]
Prephosphorylation + Phosphorylation	A-kinase + GSK-3 β	Ser199*, Ser202*, Thr231, Ser235, Ser262, Ser396*, Ser404*	Yes	[24, 25]
	C-kinase + GSK-3 β	Ser199, Ser202, Thr231*, Ser235*, Ser262, Ser396*, Ser404 ^d *	Yes	[24, 25]
	CaM kinase II + GSK-3 β	Ser199*, Ser202*, Thr231*, Ser235*, Ser262*, Ser396*, Ser404*	Yes	[24, 25]
	CDK-5 + GSK-3 β	Ser199, Ser202, Thr231*, Ser235*, Ser262, Ser396, Ser404 ^d	Yes	[23-26]

Note: * Phosphorylation of these sites is significantly enhanced.

A β also interferes with tau oligomerization

In addition to its driving effect on tau phosphorylation, A β also interferes with tau oligomerization and aggregation. Tau oligomers, which are an intermediate form of tau that occurs prior to NFT formation, are toxic [39]. Hyperphosphorylated tau dislodges from MTs, and its affinity for other tau monomers induces binding between individual tau proteins to form tau oligomers, which are detergent-soluble aggregates, by acting on the phosphorylation sites. This process is mediated by A β -activated

CDK-5 and GSK-3 β . These tau oligomers potentiate neuronal damage, which leads to neurodegeneration [40, 41]. A β also triggers caspase-3 (CASP3) cleavage of tau at Asp421 in the C-terminus to yield an N-terminal caspase cleavage product (amino acids 1-421) [42] (Figure 2). Truncated tau lacking its C-terminal 20 amino acids assembles more rapidly into filaments than full-length tau [42]. A β also induces the generation of a 17-kDa tau fragment via the activation of calpain-1 in hippocampal neurons. The expression of this tau fragment leads to neurite degeneration and cell death in neurons and nonneuronal cell types [43]. Cleaved tau protein self-aggregates and misfolds, and these self-aggregated and misfolded products are further assembled into soluble oligomers [42]. Tau oligomers may act as “seeds” by inducing endogenous tau misfolding and redistribution to the somatodendritic compartment, which suggests the existence of a unifying mechanism for the propagation of amyloid proteins [44, 45]. Oligomers in this aggregation process are the most neurotoxic form of tau and may be transmitted between neuronal cells [39]. Tau oligomers in neurons induce neuroinflammatory factors, which bind to astrocytes and microglia and induce apoptosis [39, 46]. Therefore, the inhibition of tau oligomer formation is also worth further examination. For example, a targeted inhibitor of caspase-3 may be developed to reduce tau cleavage.

A β toxicity is dependent on tau

Extracellular deposits of fibrillar A β form senile plaques and accelerate tau hyperphosphorylation, which induces neurotoxicity. However, whether the neurotoxicity of A β is dependent on tau is not clear. One study showed that the absence of tau in glutamate N-methyl-D-aspartate (NMDA) receptor subunit GluN2B-bearing spines, where tau is typically located, prevented the toxic effect of the binding of A β to NMDA receptors (NMDARs) [47]. A recent study proposed that the phosphorylation of tau at Tyr 18 by Fyn kinase also blocks A β toxicity [48, 49]. A β may be the initiator of tau pathology and play a role in downstream neuronal injury [50, 51]. Tau mediates A β toxicity by interacting with Fyn kinase via its amino-terminal projection domain (PD) [50]. A β

promotes Fyn phosphorylation, and phosphorylated tau and Fyn are transferred to postsynaptic membrane receptors, which are denoted by NMDARs. Fyn phosphorylates the NR subunit 2 (NR2) to facilitate the interaction with postsynaptic density protein 95 (PSD95) [47, 52], which leads to excitotoxic downstream signalling [47, 53]. Soluble A β binds to or near NMDARs, which indicates that NMDARs are potential targets of A β , and the NMDAR and PSD95 complex participates in NMDAR-mediated A β neurotoxicity [54, 55]. Therefore, the activation of Fyn, which migrates into dendritic spines via tau facilitation, is a key event in A β oligomer-induced synaptic toxicity [45, 56]. Some studies have also indicated that a reduction in tau levels prevented the cognitive impairment in AD transgenic mice overexpressing A β and that overexpression of Fyn can enhance their cognitive impairment [57, 58]. The absence of tau prevents A β toxicity and tau phosphorylation by GSK3 [59, 60] or another kinase (p38 γ) [61] at a specific residue (threonine 205) [62]. P38 γ regulates PSD95-tau-Fyn complexes by phosphorylating tau at Thr205, which interferes with the postsynaptic excitotoxic signalling complexes engaged by A β . Tau-dependent A β toxicity is modulated by site-specific tau phosphorylation, which inhibits postsynaptic PSD95-tau-Fyn complexes, which reveals an A β toxicity-limiting role of p38 γ in AD [61]. A new study found that A β alone caused hyperactivity, and tau alone suppressed activity and promoted the silencing of many neurons [62]. Neuronal silencing dominates hyperactivity in the presence of both A β and tau, and this finding was corroborated in a recent in vitro study using extracellular field recordings of entorhinal cortex (EC) slices [62]. Tau blocks A β -dependent hyperactivity, which results in the profound silencing of circuits in the presence of A β and tau in the cortex [63]. This result suggests that tau and A β exert antagonistic effects on neural circuit activation. Caspase-cleaved tau may also be an important downstream event in A β -induced cascades, such as the poisonous 17-kDa tau fragment, which leads to neurite degeneration and cell death [43]. Therefore, A β -induced neurotoxicity may be mediated not only by A β overdeposition but also, at least in part, by protease activation, which leads to the generation of neurotoxic tau fragments, such as the

17-kDa neurotoxic tau fragment. A β may serve as the trigger, and tau may be the bullet [45, 53]. All of these results further support the notion that the toxicity of A β is dependent on tau (Figure 2). In summary, tau protein may play a key role in the A β -induced mechanism, and the recombinant expression of human tau protein in tau-depleted neurons restores the sensitivity of neurons to A β toxicity.

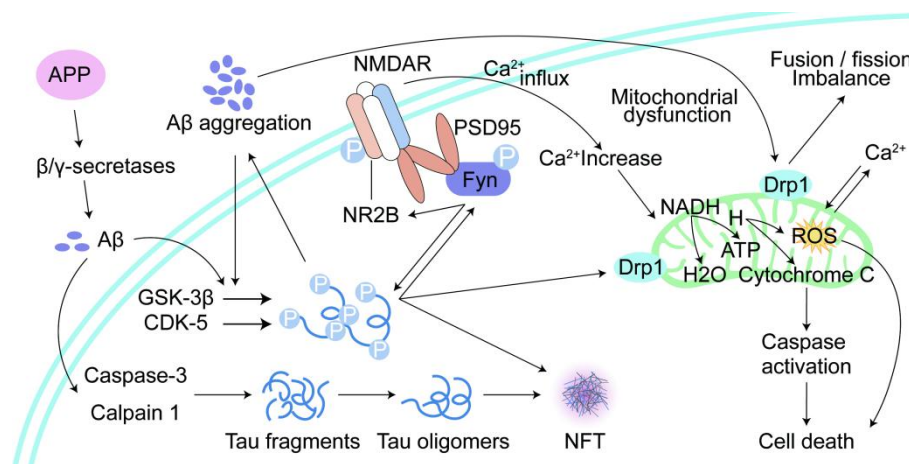


Figure 2. Reciprocal toxicity between A β and tau. A β precursor protein (APP) is cleaved by β/γ secretases to form A β . A β activates GSK-3 β and CDK-5 to phosphorylate tau protein and activate caspase-3 and calpain 1 to hydrolyse tau protein and form tau oligomers. Phosphorylated tau protein interacts with Fyn. A β -activated Fyn also accelerates tau phosphorylation and binds to tau. Phosphorylated Fyn acts on NR2B to form the NMDAR-PSD95-Fyn complex. NMDARs are activated to increase Ca²⁺, which affects the function of mitochondria. A β and phosphorylated tau induce the fusion and fission of mitochondria by acting on Drp1, which induces the dysfunction of mitochondrial dynamics and ultimately leads to reactive oxygen species (ROS) overproduction and apoptosis.

A β and tau work together to damage mitochondria

Another cellular compartment in which A β and tau work together to damage neurons is the mitochondrion [45]. Mitochondrial dysfunction is widely implicated in the aetiology of AD [64]. A β deposition, NFT formation, and neurodegeneration may be consequences of mitochondrial malfunctioning [65]. The overexpression of APP and treatment with amyloid- β -derived diffusible ligands induce mitochondrial fragmentation and abnormal distribution without cell death [66, 67], which suggests that A β -induced abnormal mitochondrial dynamics may play a role in the early pathogenesis of AD [68]. A β induces axonal and dendritic swelling and decreases

axonal transport in hippocampal neurons [69], which contribute to an altered mitochondrial distribution. Excessive mitochondrial fission correlates with increased reactive oxygen species (ROS) production [66, 67, 70], which leads to the progression of extensive macromolecular oxidative damage and amyloid lesions caused by ROS [71]. Intracellular A β interacts with 3-hydroxyacyl-CoA dehydrogenase type-2 (HSD17B10, also known as ABAD), and this interaction promotes mitochondrial dysfunction and ROS leakage [72]. Another protein localized at the outer mitochondrial membrane, dynamin-1-like protein Drp1 (DNM1L), interacts with A β and phosphorylated tau, which likely leads to excessive mitochondrial fragmentation and neuronal damage [73]. Tau is a substrate for mitochondrial caspase-3 in vitro [41, 74], which contributes to mitochondrial fragmentation in AD brains. Caspase-cleaved tau and tau truncated at Asp421, which mimics the product obtained with caspase cleavage (T4C3), induce mitochondrial fragmentation and mitochondrial fission in a calcineurin-dependent manner [75]. The expression of caspase-cleaved tau fragments in neurons impairs mitochondrial function, and this impairment leads to changes in the mitochondrial membrane potential, the dysregulation of mitochondrial calcium levels and mitochondrial integrity and an increase in mitochondrial O $^{2-}$ [68, 75]. The introduction of tau in mature hippocampal neurons results in the degeneration of synapses via perturbation of mitochondrial transport and ATP levels at the synapse [76]. N-terminal tau fragments exert toxic effects on mitochondria and lead to mitochondrial dysfunction associated with impairments in oxidative phosphorylation by distorting the structure of the complex V enzyme and the level of adenine nucleotide translocator, which ultimately perturb the synthesis of ATP in mitochondria [77]. The dysregulation of Ca $^{2+}$ and its secondary processes directly affect tau phosphorylation, APP processing and lysosome function, and in turn, tau and A β further aggravate Ca $^{2+}$ dyshomeostasis [78]. A β stimulates neurons to cause a large amount of Ca $^{2+}$ influx and intracellular Ca $^{2+}$ overload then damage to mitochondria, which results in the impairment of neuronal productivity, activation of apoptosis-related proteins and factors and the initiation of apoptosis [79]. The dysregulation of Ca $^{2+}$ homeostasis further promotes mitochondrial dysfunction,

impairments in synaptic transmission and plasticity and oxidative stress, which contribute to the age-related cognitive impairment. A β and tau exert deleterious effects on mitochondria, and these effects result in ROS accumulation, ATP synthesis and Ca²⁺ dysregulation [80] (Figure 2).

Joint action of A β and tau in nonneuronal cells

Combined effects of A β and tau on microglia in AD

Microglial activation is a key neuropathological feature of AD, and clinical studies found reduced levels of glial cell activation in more benign cases of AD [81]. Soluble A β and subsequent plaques trigger microglial activation and the release of proinflammatory cytokines, such as interleukin-1 β and tumour necrosis factor- α (TNF- α), ROS and reactive nitrogen species [82]. The neuroinflammatory reaction in the brain caused by activated glial cells primarily occurs around capillary sites where A β is deposited [83]. The expression of mutant tau also drives microglial activation, even prior to tangle formation [84] (Figure 3). Young APP/PS1-rTg4510 mice without plaques and tangles exhibit a synergistically enhanced tau aggregation phenotype, which may be an early consequence of microglial changes. This result directly implicate microglial changes in the progression of tau pathology [85]. Microglial depletion protected against the propagation of tau pathology from the EC to the dentate gyrus (DG) in PS19 transgenic mice and rescued tau-dependent DG hypoexcitability [86]. Glial tau pathology reportedly occurs in tauopathies [87] and AD [88]. Microglia take up and decompose seed-competent tau [89], albeit ineffectively [90], and tau uptake may reciprocally lead to microglial activation. Activated microglia may be directly involved in the repackaging of tau into exosomes or indirectly involved in the enhancement of tau phosphorylation via proinflammatory cytokine signalling [85, 91]. Microglia activated as a consequence of neuronal injury may also be related to the induction of neurodegeneration, which leads to tau hyperphosphorylation and aggregation [92]. Enhanced microglial activation and accelerated onset and progression of tau pathology may be caused by the absence of the microglial fractalkine receptor CX3CR1 [85, 91]. Tau associated with exosomes

and phosphorylated at Thr181 (AT270⁺ tau) was identified in human cerebrospinal fluid (CSF) samples from patients with AD [93]. Therefore, microglia may phagocytose tau-containing neurons or synapses and secrete tau protein via exosomes [93, 94]. During this process, microglia may facilitate the spread of tau pathology via exosomal vesicles. Variation in the TREM2 gene is a major risk factor for AD. TREM2 deletion and the secondary loss of plaque-associated microglia enhance the seeding and spreading of tau pathology, which suggests that TREM2 mitigates tau pathology by directing microglia to scavenge plaques [95]. Microglia may also neutralize A β or toxic tau species to delay propagation and neurodegeneration. Briefly, activated microglia may play a role in A β toxicity and tau pathology and the formation of neuritic plaques and tau hyperphosphorylation, which contribute to microglial activation.

2. Interaction of A β and tau with astrocytes in AD

Astrocytes are abundant in the brain and perform many functions in the central nervous system (CNS), such as modulating synaptic formation, maintaining neuronal homeostasis via metabolic support [96], and comprising part of the blood-brain barrier (BBB) [97]. Astrocytes may be activated in the preclinical stages of AD [98]. One of the earliest neuropathological changes in AD is the accumulation of astrocytes at sites of A β deposition [99]. Activated astrocytes surround amyloid plaques and NFTs, which are the neuropathological hallmarks of advanced AD [100]. A β deposition and the NFTs formed by tau hyperphosphorylation may promote the activation and accumulation of astrocytes. Reactive astrocytes release proinflammatory mediators and cytotoxic molecules in neuroinflammation, and these effects exacerbate the pathology of AD [101]. However, astrocytes also express genes involved in phagocytosis, which may attenuate the pathology via the uptake and clearance of protein aggregates [102]. This phagocytic capacity was demonstrated for A β [103, 104]. Insights from animal models indicate that impairing astrocyte activation via the ablation of glial fibrillary acidic protein (GFAP) and vimentin resulted in an increased plaque load [105]. A β is taken up and trafficked to lysosomes for degradation in

astrocytes [103]. The impairment of lysosome function with ageing [106] or the loss of presenilin is likely the underlying mechanism for the accumulation of A β and phagocytosed amyloid material within astrocytes [107], which may be the key to promoting amyloid plaque progression [100]. Transcription factor EB (TFEB) plays an important role in this process. Astrocytic TFEB expression attenuates amyloid plaque accumulation by enhancing A β uptake from the interstitial fluid (ISF) and facilitating clearance via lysosomal degradation in the brain. TFEB directly stimulates astrocytes to degrade A β , which reduces the pathogenesis of amyloid plaques (Figure 3). In a transgenic model of tau spreading, astrocytes took up hyperphosphorylated tau as the synapses degenerated [108]. The accumulation of abnormally phosphorylated tau in astrocytes is named ageing-related tau astroglipathy (ARTAG) [109]. ARTAG may play a role in mediating the formation of pathological tau inclusions in astrocytes or indicate astrocyte involvement in the early stages of transsynaptic tau spreading [109]. TFEB in astroglia stimulated the uptake and clearance of aberrant extracellular tau, which prevented the neuronal spreading of tau pathology in a mouse model of tauopathy [110]. In conclusion, A β and tau may share a common site of action in astrocytes, which promotes the expression of TFEB activated by A β deposition and the over-deposition of hyperphosphorylated tau. Damage to astrocytes reduces TFEB expression, which results in reduced clearance and increased aggregation of A β and tau. In contrast, A β over-deposition and tau hyperphosphorylation accelerate astrocyte injury by releasing neuroinflammatory cytokines. However, excessive damage to astrocytes worsens the inadequate removal of A β and tau, which further aggravates self-injury and the progression of AD.

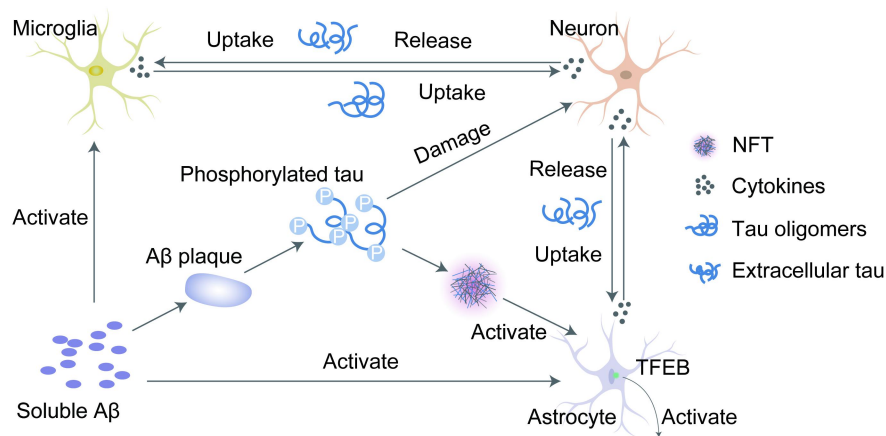


Figure 3. Interaction of Aβ and tau with microglia and astrocytes. In response to Aβ or tau, microglia and astrocytes are converted into a reactive state, which triggers the inflammatory cascade. These cells reciprocally activate each other via this cascade, which leads to neuronal injury. Inflammatory cytokines (such as interleukin-1β and TNF-α) induce the neuronal release of tau, and activated microglia take up extracellular tau. Cytokines also accelerate tau phosphorylation to ultimately induce the formation of neurofibrillary tangles (NFTs). Transcription factor EB (TFEB) activates astrocytes to take up extracellular tau. This process consists of a cycle of Aβ deposition, tau phosphorylation, release and uptake, and the roles of cytokines to ultimately lead to cell death and the NFT-mediated exacerbation of neurodegenerative changes.

Aβ and tau may be involved in damage to the BBB, endothelial cells, and pericytes during the pathological process of AD. Aβ and tau activate microglia and astrocytes. Activated microglia disrupt chemokine and cytokine secretion from the BBB. [111]. Microglia-mediated BBB alterations in AD are also reflected by the destruction of pericytes and basement membrane (BM) by microglia. Activated microglia also promote pericyte apoptosis in vitro via the upregulation of NADPH oxidase in pericytes [112]. Activated astrocytes secrete vascular permeability factors, such as vascular endothelial growth factors (VEGFs), nitric oxide (NO) [113], and endothelin (ET) [114], which aggravate the destruction of the BBB. Aβ and tau may exert indirect or direct effects on BBB components. Currently available data are insufficient. Therefore, the specific mechanism must be further examined, and a further understanding may help identify new methods for the treatment and prevention of AD.

Aβ plaques facilitate neuritic plaque tau aggregation and propagation

Widespread deposition of A β plaques in the neocortex and a hierarchically organized pattern of NFTs (composed largely of tau aggregates) in limbic and cortical association areas are the neuropathological hallmarks of AD [5]. A β and p- τ pathology spread throughout the brain in a hierarchical pattern. However, prior to NFT formation in the transentorhinal region, an accumulation of p- τ is observed in the locus coeruleus, raphenuclei, substantia nigra, dorsal nucleus of the vagus nerve, and basal nucleus of Meynert [115-117]. A β plaques and NFTs are found in neocortical brain regions after a certain stage [118, 119]. This finding suggests that neurodegenerative lesions spread or propagate from one brain region to another [120]. Nevertheless, the mechanisms of A β and tau pathology interactions and whether other proteins are involved in this process are not clear and should be the focus of our attention and thinking.

A recent study showed that cellular prion protein (PrPC) was a receptor for toxic A β species and α -synuclein oligomers [121]. PrPC occurs in the neuropil [122, 123], and it was detected in amyloid plaques and neurons in patients with AD [124, 125]. PrPC is enriched in postsynaptic densities, which leads to Fyn kinase activation, and activated Fyn kinase phosphorylates the GluN2B subunit of NMDA receptors [126] and interacts with the phosphorylation of tau [127, 128]. A β oligomers initiate PrPC-Fyn-related phosphorylation of tau [129]. PrPC may be directly or indirectly involved in the interplay between A β and p- τ pathology propagation. Soluble p- τ may be released at synapses [130] and may be present in the extracellular space, which creates the conditions for the binding of soluble p- τ to PrPC. A β and PrPC combine with an interaction partner to activate Fyn [126, 131], which increases the levels of p- τ via Pyk2-related phosphorylation of tau [132, 133]. Tau appears to spread into neocortical regions almost solely in people with coexistent A β pathology [134, 135]. Tau-knockout neurons are resistant to neuritic degeneration induced by synthetic or human-derived A β species, and tau overexpression exacerbates A β -induced damage [136]. During this process, the binding of A β to PrPC [137], Fyn activation, and τ -protein phosphorylation may provide alternative explanations for the finding that

A β plaques accelerate tau phosphorylation propagation via a PrPC-related mechanism, which may encourage the deposition of tau in areas of the brain where A β aggregates. These correlations at the lesion site again demonstrate direct and indirect interactions between A β plaques and tau aggregation.

Relationships between A β , tau and cognition

A β and p-tau interact to cause neuronal loss and synaptic damage, which lead to cognitive decline in patients with AD [68, 138]. The accumulation of plaques and tangles induce changes in the behavioural symptoms of patients with AD, which are a direct consequence of the damage and destruction of synapses that mediate memory and cognition [53]. Previous longitudinal PET studies tracked A β [139, 140] and tau [141, 142] accumulation. Clinical studies observed greater cognitive decline in clinically healthy older individuals with abnormalities of CSF A β and phospho-tau [143, 144]. PET and CSF data indicate that synergy between A β and tau is associated with brain dysfunction [145, 146] and cognitive decline [144, 147]. A β and tau in the inferior temporal neocortex interact and potentiate tauopathy and cognitive decline. One clinical study indicated that memory progressively declined in individuals with posterior cingulate hypometabolism, which is the region most strongly linked to the tau-A β interaction [145]. During AD progression, A β and tau proteins are readily excreted from the brain into the peripheral blood through disruption of the BBB and receptor-mediated mechanisms [148, 149]. A β and tau are detected in plasma using highly sensitive and accurate analytical techniques. Single-molecule array (SIMOA) and xMAP technology determined that A β 42 levels, which are positively correlated with CSF A β 42 levels but negatively correlated with the CSF t-tau levels, were higher at the mild cognitive impairment (MCI) stage than the AD stage, and the t-tau levels were positively associated with the burden of brain tau deposition on tau PET across the AD spectrum; i.e., the A β 42 levels are elevated during the MCI stage and reach a plateau prior to the demented stage, whereas the t-tau levels increased with AD-associated tau pathology [150, 151]. These findings are also consistent with laboratory findings, which suggested that tau was likely the primary mechanism of

A β -related neurotoxicity [136] and previous work identifying other imaging markers of neurodegeneration [145, 152, 153], which indicated that A β pathology alone may be insufficient to drive imminent cognitive decline [154, 155]. Previous autopsy studies [156] also support the notion that A β pathology precedes and accelerates neocortical tau pathology, which together precipitate cognitive decline. These findings also explain why the clinical treatment of A β has not yielded satisfactory results. Tau and amyloid pathology may begin independently, but the spread of tau beyond the mesial temporal lobe is associated with and may be dependent on amyloid accumulation [157]. Therefore, higher plasma A β 42 and t-tau levels at the MCI stage are predictors of greater risk for the development of cognitive decline at the prodementia stage of AD. The combination of the two plasma biomarkers with other markers may help identify subjects with MCI who are at risk for developing AD, which may be beneficial for the administration of early and preventative pharmacological interventions.

Conclusions and future directions

A β and tau proteins play well-established roles in AD and form the two hallmark pathologies that are visible in postmortem AD brains as amyloid plaques and NFTs, respectively. Although these two proteins play important roles in the pathogenesis of AD, treatments that target A β or tau alone have not achieved good clinical results [6-11]. Related experimental and clinical studies were performed, which support the hypothesis that the interplay between A β and tau amplifies the toxic effects of each protein [13-15, 27, 47, 48]. Some efforts have been made to interfere with the interaction between A β and tau protein, such as studies on GSK-3 β and CDK-5 inhibitors [31-33]. However, the exact clinical efficacy is not certain [34]. The p38/JNK MAPK pathway also mediates cortical neuronal apoptosis [158], and ERK is related to memory and learning [159]. Inhibition of ERK1/2, p38 and JNK kinases may be efficacious for the treatment of AD through attenuation of A β -induced neurotoxicity via activation of the Erk1/2, p38 and JNK pathways [158, 159]. However, the pharmacological inhibition of ERK1/2 in mice and SH-SY5Y cells did

not reduce the basal levels of phospho-tau or hypothermia-induced tau hyperphosphorylation [160, 161]. This result may be due to the multiple mechanisms involved in the interaction between A β and tau protein, and inhibitors cannot simultaneously inhibit the pathways of multiple targets. Clinical drugs for the treatment of AD primarily include cholinesterase inhibitors (donepezil, rivastigmine, and galantamine), which are effective for cognition in mild-to-moderate AD, and NMDAR antagonists (memantine), which are effective for moderate-to-severe AD [162]. Combination therapy (cholinesterase inhibitors and memantine) may be beneficial for moderate-to-severe dementia [153]. However, neither cholinesterase inhibitors nor memantine are effective in patients with mild cognitive impairment [162]. AD is a multifactorial disease that likely is the result of different interactions of genomic, epigenetic, interatomic, and environmental aspects [163, 164]. Therefore, a multidisciplinary approach is needed. We need to focus not only on pharmacological therapy but also on the complex biopsychosocial aspects of caring for patients with AD, such as by developing psychological interventions. Moreover, the development of new drugs that can treat AD via multiple pathways should be further examined.

Abbreviations

A β : amyloid- β ; AD: Alzheimer's disease; NFTs: neurofibrillary tangles; MT: microtubule; CDK-5: cyclin-dependent kinase-5; GSK-3 β : glycogen synthase kinase-3 β ; MAPKs: mitogen-activated protein kinases; CASP3: caspase-3; PHF: paired helical filament; PD: projection domain; NMDA: N-methyl-D-aspartate; NMDAR: N-methyl-D-aspartic acid receptor; NR2: NR subunit 2; EC: entorhinal cortex; PSD-95: postsynaptic density protein 95; APP: amyloid precursor protein; ROS: reactive oxygen species; DNMI1L: dynamin-1-like protein Drp1; TNF- α : tumour necrosis factor- α ; DG: dentate gyrus; TREM2: triggering receptor expressed on myeloid cells 2; CNS: central nervous system; BBB: blood-brain barrier; GFAP: glial fibrillary acidic protein; CSF: cerebrospinal fluid; TFEB: transcription factor EB;

ISF: interstitial fluid; ARTAG: ageing-related tau astroglipathy; BM: basement-membrane; NADPH: nicotinamide adenine dinucleotide 2'-phosphate reduced tetrasodium salt; NADH: nicotinamide adenine dinucleotide; β -APP: amyloid- β precursor protein; VEGFs: vascular endothelial growth factors; NO: nitric oxide; ET: endothelin; PrPC: prion protein; PET: positron emission tomography; SIMOA: single-molecule array; MCI: mild cognitive impairment.

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Author Contributions

H.Z., W.W. and Y.C. wrote the manuscript. H.L., Y.C., L.M. and H.P. revised the manuscript. X.J. and M.Z. revised the figures. All the authors provided intellectual input and read the manuscript.

Competing Interests

The authors declare that no competing interests exist.

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