

Review

A β and Tau Interact with Metal Ions, Lipid Membranes and Peptide-Based Amyloid Inhibitors: Are These Common Features Relevant in Alzheimer's Disease?

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Abstract: In the last two decades, the amyloid hypothesis, i.e., the abnormal accumulation of toxic A β assemblies in the brain, has been considered the mainstream concept sustaining research in Alzheimer's Disease (AD). However, the course of cognitive decline and AD development better correlates with tau accumulation rather than amyloid peptide deposition. Moreover, all clinical trials of amyloid-targeting drug candidates have been unsuccessful, implicitly suggesting that the amyloid hypothesis needs significant amendments. Accumulating evidence supports the existence of a series of potentially dangerous relationships between A β oligomeric species and tau protein in AD. However, the molecular determinants underlying pathogenic A β /tau cross interactions are not fully understood. Here, we discuss the common features of A β and tau molecules, with special emphasis on: (i) the critical role played by metal dyshomeostasis in promoting both A β and tau aggregation and oxidative stress, in AD; (ii) the effects of lipid membranes on A β and tau (co)-aggregation at the membrane interface; (iii) the potential of small peptide-based inhibitors of A β and tau misfolding as therapeutic tools in AD. Although the molecular mechanism underlying the direct A β /tau interaction remains largely unknown, the arguments discussed in this review may help reinforcing the current view of a synergistic A β /tau molecular crosstalk in AD and stimulate further research to mechanism elucidation and next-generation AD therapeutics.

Keywords: Alzheimer's Disease; neurodegeneration; metal complexes; amyloid; membranes; peptides



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1. Introduction

At the end of 1901, Alois Alzheimer, a German neuropathologist, described the presence of neurofibrillary tangles (NFTs) and "senile plaques" in post-mortem neuronal tissues of a patient that experienced memory failure and gradual mental decline [1]. That pioneering article is considered the first report describing senile dementia, a chronic neurodegenerative condition that will be later commonly identified as Alzheimer's Disease (AD). AD is known to be the prevalent form of dementia especially in aged people: 60–70% of all cases of dementia are diagnosed with AD [2] and about 32% of people 85 years old and older are affected by AD [3]. Presently, the different types of protein aggregates i.e., extracellular deposits of amyloid β (A β) peptide [4] and the intracellular hyperphosphorylated forms of tau protein, NFTs, [5] observed in AD brains represent the two distinctive pathological traits of AD [6]. Accumulating evidence suggests that A β plays a significant role in AD while human genetics established the relationship between tau malfunction and neurodegeneration. It is demonstrated that inherited Frontotemporal Dementia (FTD) and parkinsonism, with extensive filamentous tau deposits in the brain in the absence of A β deposits, are caused by mutations in the *MAPT*, the microtubule associated protein tau gene [7]. These pathological mutations involve tau hyperphosphorylation which leads to detachment of the functional protein from the microtubules, with consequent intracellular

cumulation [8,9]. In AD, abnormal tau levels promote protein aggregation as paired helical filaments (PHFs) or straight filaments (SFs) in the cytosol [8,9].

Although initially A β and tau misfolding follows different routes and district of propagation, as the disease progresses, A β plaques and NFT are both formed in neocortical regions [10]. Tau levels have been also measured in the extracellular space where the protein can interact with A β [11].

As far as the intracellular trafficking of A β is concerned, it is quite clear that the peptide may be present in many cytosolic compartments. This is witnessed by observing that extracellular A β preparations are commonly used in in vitro AD experimental models [10]. Their toxicity is mediated via receptor recognition and death signaling, as well as intracellular internalization. Extracellular A β can be internalized in the cell via endocytic pathways aided by cell surface heparan sulfate or a variety of receptors and transporters such as the formyl peptide receptor-like protein 1 (FPRL1) or the scavenger receptor for advanced glycation end-products (RAGE) [12–14]. Interactions with intracellular proteins such as GM1, prefoldin (PFD), and other molecular chaperones redistribute the internalized A β through the neuronal bodies where interaction with tau protein may also occur [15,16].

The hypothesis of an existing crosstalk between tau and A β toxic aggregation is further supported by several studies [17]. Many reports have demonstrated that the toxic crosstalk between tau and A β aggregation initiates with the disruption of the mitochondrial membrane [18]. A β and tau have been found to co-localize in neurons and astrocytes. Particularly, A β accumulates primarily in synapses surrounding senile plaques, and synapses from tau-null animals are protected from A β damage [19]. On the other hand, a recent study reported that only 0.02% percent of synapses were found positive for both A β and tau, an evidence that argues against a direct A β /tau interaction at the synapses [20]. Therefore, this view has been questioned by some recent findings revealing that A β and tau accumulate in both pre- and postsynaptic terminals [20]. Remarkably, in both human AD and *Drosophila* models, tau has been found to attach to presynaptic vesicles, impairing neurotransmitter release [21], accordingly it's becoming evident that A β has an impact on presynaptic function [22]. Intracellular A β /tau complexes could conceivably accelerate tau hyperphosphorylation and A β nucleation [23,24].

Therefore, tau/A β reciprocal interaction appears to influence the aggregation and toxicity of both molecules [25] and most of the above observations reinforce the idea that A β aggregated forms (i.e., plaques, oligomers) may provide a microenvironment that promotes tau aggregation and propagation fostering disease progression [26].

Nevertheless, the growing knowledge on the A β -tau cross interactions suggests that for a truly effective therapeutic approach to AD to be pursued, next generation drugs should target both A β and tau [27]. A possible approach to achieve this goal should also consider the environmental conditions, as well as the molecular partnerships the two A β and tau proteins might interact with.

In this paper we reviewed some current studies concerning A β or tau interactions with metal ions, biological membranes or anti-fibrillogenic peptide systems.

In this review, the A β and tau interactions with metal ions are revisited, giving emphasis to the respective peptide domains involved in the cross-interaction also in the presence of lipid membranes. Our discussion will include the use of designed peptide-based compounds able to interfere with the A β /tau potentially harmful contacts. The multifactorial nature of A β and tau interplay suggests a new approach for the design of small peptide-based molecules endowed with metal chelating and anti-fibrillogenic properties. These multifunctional molecules could be considered as a useful tool to tackle the multiple pathological aspects of neurodegenerative disorders.

2. A β and Tau Proteins: Molecular Structure and Physiological Functions

The high degree of conservation of the A β sequence among vertebrates (>90% sequence homology that reaches 95% in mammals), suggests that it must play an important role in the survival of the species.

When present in low quantities, soluble A β isoforms play a vital physiological role in the CNS, contributing to normal brain function [28]. Due to its hydrophobic interaction with lipidic membranes, vesicles, and transmembrane receptors [29], as well as neurotrophic or neurotoxic effects depending on its concentration, monomeric A β homeostasis appears to be crucial in the modulation of synaptic function. In addition to its role in synapsis regulation, the A β monomer has neuroprotective properties that are mediated through the activation of several pathways. A β monomers have been shown to increase neuronal survival by activating the phosphatidylinositol-3-kinase (PI-3-K) pathway, which appears to be mediated by IGF-1/insulin receptor stimulation [30]. The activation of this route in neurons has been shown to cause functional synaptogenesis, or the development of new synapses [31].

Additional non-toxic yet atypical functions of soluble A β have been observed. These include: protective antimicrobial properties [32]; protection against cancer [33]; assisting the brain to recover from traumatic and ischemic injuries by participating to the blood-brain barrier repair; regulation of the synaptic function [34].

The two 40 or 42 residues long A β peptides (A β 40 or A β 42, respectively) are produced by the concerted proteolysis of the amyloid precursor protein (APP) [4,35,36]. APP processing may occur via two distinct pathways, i.e., non-amyloidogenic and amyloidogenic. The generation of A β peptides belongs to the activity of two transmembrane proteolytic enzymes (the β -secretase and the γ -secretase), on the membrane-bound APP. APP can be also processed by a different protease (α -secretase) that cleaves APP between amino acids 16 and 17 of the A β peptide, thus blocking A β peptides generation [37,38]. A β 's primary structure is composed of a hydrophilic N-terminal region (1–16) alongside a hydrophobic C-terminal domain (17–40/42).

Tau is a microtubule-associated protein (MAP) mainly concentrated in the axons of neurons [39]. Six different tau isoforms are present in the brain, each one encompassing from 352 to 441 amino acids residues and including four tubulin-binding domains termed, R1, R2, R3 and R4. In general, tau primary structure can be divided into C-terminal domain, microtubule binding domain, N-terminal projection domain (alternative inserts 0N, 1N or 2N) and Pro-rich region domain (Figure 1). Tau, include 12 histidyl residues as potential metal binding sites [39]. Tau(273–284) and A β (25–35), containing both an hydrophobic hexapeptide sequence (VQIINK and GAIIGL, respectively), promote aberrant aggregates (see the section below) [40].

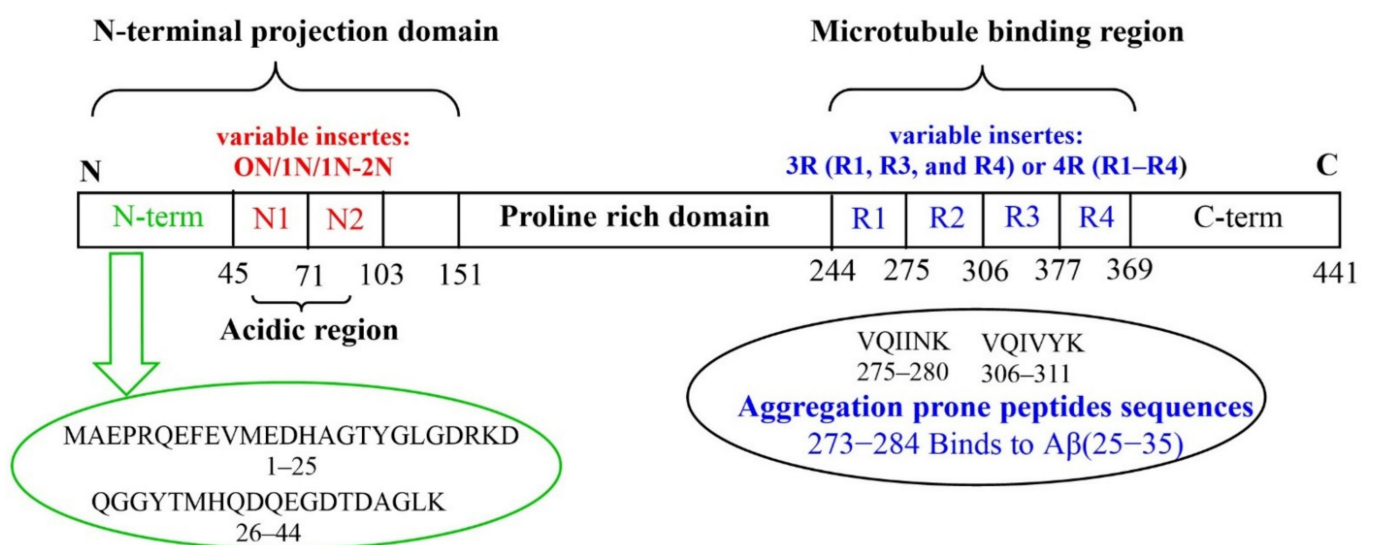


Figure 1. Tau protein: longest tau isoform (441 amino acids) containing the variable inserts (N1, N2, R1, R2, R3 and R4).

The second and third microtubule binding domain repeats exhibit a propensity to form an ordered β -sheet structure. The biological role of tau protein mainly involves the stabilization of microtubules, but also different biological pathways such as synaptic activity [41], anxiety-related behavior [42], regulation of myelination [43], glucose metabolism, regulation of iron homeostasis and genomic stability [44,45].

Tau is also a substrate for the ubiquitin–proteasome system (UPS) and for chaperone-mediated autophagy [46]. A role for tau in regulating the functional maturation and survival of new-born neurons, the selectivity of neuronal death following stress, and neuronal responses to external stimuli was also reported [47]. Tau is subject to different post-translational modifications i.e., phosphorylation, glycosylation, glycation, prolyl-isomerization, cleavage or truncation, nitration, polyamination, ubiquitination, sumoylation, oxidation and aggregation [48].

3. Could A β and Tau Be Colocalized in Lipid Membranes?

The role played by lipid membranes in modulating amyloid aggregation and toxicity has been largely investigated [49,50]. Plasma cell membrane is not a simple target for amyloidogenic proteins, but it is rather an active actor which can foster peptide aggregation.

Many reports suggest that lipid abnormalities exist in the AD brain, implying that aberrant A β amyloid interactions with the plasma membrane may cause toxicity [23,51]. A β -membrane interactions can occur when the peptide is inserted into the membrane and a pore-like structure forms, or when it is bound to the membrane's surface [23]. The channels generated in the plasma membrane have the potential to harm neuronal cells by impairing signal transmission and ultimately causing apoptosis. Surprisingly, just as A β peptide can influence the property and state of the membrane, so the membrane can influence the fibrillation process of A β peptides.

Due to the easy accessibility of cytosolic tau to cellular and organelle membranes, research into tau-lipid bilayer interactions has become more helpful in understanding disease pathophysiology, with multiple studies implicating membranes as major targets for oligomeric tau aggregation [24]. Indeed, similar to A β peptide, tau protein is able to interact with both biological and artificial membranes [24,52–55]. Moreover, binding of tau to membranes *in vitro* is enhanced by the presence of anionic lipid, as observed for A β peptide [56,57]. Interestingly, Katsinelos and colleagues showed that tau is also capable of disrupting large unilamellar vesicle (LUV) membranes in a PI(4,5)P₂-dependent manner [58]. Thus, such similarities in the mechanism and topology of the interactions of A β and tau peptide with lipidic membrane raise a question: could lipid membranes be the interface that mediates the cross correlation between A β and tau in the etiology of Alzheimer's Disease?

Each lipid component of cell membrane is an active molecule which can affect conformation, function and behavior of several transmembrane protein [59]. Cholesterol, gangliosides, in particular monosialotetrahexosylganglioside (GM1), and sphingomyelin have shown to play a pivotal role in Alzheimer's Disease [60,61] and are all strictly correlated with raft domain [62]. A significant alteration in raft domains lipid composition in the frontal cortex of AD patients were described [63,64]. Interestingly, there is some evidence that both tau protein and amyloid beta are strictly correlated, directly and/or indirectly, with raft domain in membrane, and, in particular, with Cholesterol and gangliosides [23,55].

Cholesterol could interact with A β monomer, protofibrils and fibrils [65–67]. Matsuzaki et al. showed that a reduction in cholesterol almost abolished the formation of A β 42 amyloids in rat pheochromocytoma PC12 cells [68]. Moreover, Cholesterol and sphingomyelin are also involved in tau secretion through plasma membrane. Treatment with methyl- β -cyclodextrin to reduce cell membrane cholesterol decreased tau secretion by 47%, while increasing cellular cholesterol increased tau secretion by 75% [69]. Thus, an increase in cholesterol contents in membrane, associated with Alzheimer's Disease [70] could potentially promote a local coexistence of high concentration of both proteins. Yet, recent studies suggest that gangliosides play essential and complicated roles in Alzheimer's Disease,

by accelerating the oligomerization of A β in neuronal membrane environment [71,72]. According to the studies by Matsuzaki et al., in GM1 cluster containing sphingomyelin and cholesterol, A β 40 specifically bound to a GM1 cluster. Confocal laser microscopic study further demonstrated that fluorescein-labeled A β selectively bound to GM1 enriched domains of cell membranes in a time and concentration-dependent manner [73]. Tau protein also requires the presence of cholesterol and sphingomyelin to interact and penetrate membranes, indicating that raft domains play a key role in this process [69,74,75]. The interactions between lipid membranes and tau have not been fully characterized, particularly the mutually disruptive structural perturbations. Several works suggest that tau aggregation may be modulated by plasma membranes [55]. Tau has been shown to interact with the plasma membrane through its amino-terminal domain and accumulates with A β in raft microdomains [54,74,76]. Moreover, anionic lipid vesicles have been shown to promote the aggregation of the microtubule binding domain of tau (K18) at sub- μ M concentrations [77]. Tau also has been shown to have a strong tendency to associate with and intercalate into negatively charged lipid monolayers and bilayers being able to seed the formation of paired helical filament in the inner leaflet of plasma membranes. Furthermore, tau interaction with anionic lipid membranes has been demonstrated to disrupt lipid packing and compromise membrane structural integrity [78].

The whole of these data suggest that raft lipid domain could play a role of “mediator”. Indeed, accumulating evidence suggests the possibility of a local and transient co-presence of A β and tau, at high local concentration, in the microdomain raft region of plasma membrane, enhanced by pathological condition [74,79]. Thus, lipid membrane could be the interface where A β and tau proteins mutually cross interact. Whether this cross interaction occurs directly or indirectly must be determined yet and more investigation is necessary.

Plasma membrane might also mediate the mutual modulation of the activity of A β and tau without a direct cross-interaction. The importance of tau in mediating A β toxicity has been clearly demonstrated by the resistance of tau knock-out neurons to A β -induced neurotoxicity [80].

A β is known to activate calpain and increase tau proteolysis in primary neurons [81]. Membrane cholesterol content regulates the rate of calcium influx and calpain activation in neurons by increasing the activity of glutamatergic receptors and membrane associated calcium transporters. Nicholson and Ferreira [82] suggested a link between cholesterol levels in plasma membranes and tau toxicity in the context of AD, by showing that A β -mediated production of 17 kDa calpain cleaved tau fragments increase with neuronal development and is correlated with membrane cholesterol level in neurons. However a direct neurotoxic effect of the calpain-cleaved 17 kDa tau species has not yet been demonstrated [83].

4. A β and Tau Can Interact with Metal Ions

It is widely accepted that unbalanced metal homeostasis is associated to neurodegeneration through different pathogenic pathways including oxidative stress, microglia activation, and inflammation [57,84]. In AD, metals ions are directly and indirectly involved in the A β /tau processing [85–90] and can impact the physiological functions of these proteins. In particular, A β production is regulated by zinc-(α -secretase) and copper-dependent (β -secretase) enzymes that will not properly work if metal ions are dysregulated. On this ground, abnormally high concentrations of zinc increase the resistance of A β peptides to α -secretase cleavage and, therefore, promote an increase in A β content [91]. Moreover, it has been found that zinc can inhibit the α -secretase cleavage activity of APP, resulting in elevated β - and γ -secretase processing of APP and a further increased generation of extracellular A β plaques [85]. Some proteases responsible for A β degradation are the zinc-dependent neprilysin (NEP) and insulin degrading enzyme (IDE) [92]. Metal ion dyshomeostasis could result in improperly metal complexes of NEP or IDE, thereby affecting the A β turn-over and the formation of toxic aggregates. Likewise, tau phosphorylation and aggregation could be influenced by metals as zinc, copper and iron, which have been shown to modulate kinases that phosphorylate tau, further worsening tau pathology [93].

Moreover, zinc has also been demonstrated to induce tau hyperphosphorylation by activating the glycogen synthase kinase-3beta (GSK-3 β) and inactivating phosphatase such as protein phosphatase 2A (PP2A) [94,95] and it has been implicated in tau aggregation and neurotoxicity as suggested by a recent study carried out on a tau-R3(303–336) peptide fragment [96].

Metals can also directly interact either with A β peptides or tau proteins in AD by influencing their respective folding stability as well as their mutual interaction. As an example, Cu(II) and Zn(II) ions have been reported to catalyze toxic A β or tau self-assembly and, in turn, generate toxic amyloid fibrils promoting neuronal loss [97,98].

In addition to its effects on amyloid aggregation, metal ions could play multifaceted effects on protein clearance [99].

In particular, it has been reported that the reuptake of transition metal ions as Zn(II) and Cu(II), after neuronal signaling, is slower in AD brains. As a result, higher concentrations of metal ions may be allowed to persist within the synapse, which in turn might promote A β aggregation [100–102].

Another important consequence of metal ion dyshomeostasis is oxidative stress caused by production of reactive oxygen species (ROS) by Fenton-like reactions [97]. Metal–A β complexes [i.e., Cu(I/II)–A β and Fe(II/III)–A β] have been observed to generate ROS similar to redox-active metal ions [103,104].

Several studies indicated the reduction of Cu(II)–A β to Cu(I)–A β and transfer of one electron to O₂ to yield O₂•– [105,106]. Moreover, the D1, H13/H14, and M35 residues in A β may also be involved in the mechanism proposed for the ROS generation mediated by Cu(I/II)–A β [107,108].

From the above it is clear that an interplay among A β , tau, and metal ion dyshomeostasis plays a significant role in AD pathogenesis [109]. All these factors have been shown to mutually influence each other with adverse effects on disease progression. A better understanding of their relationship at a molecular level, could be beneficial for elucidating AD pathogenesis. In this regard, determining the affinity of metal ions for tau and A β proteins is essential to understand the biological relevance of these metal complexes and predict which biomolecule could effectively compete with A β and/or tau for metal ion complexation. Affinity measurements of the copper complexes with A β and tau indicated dissociation constants in the range from nanomolar to attomolar values [110–112] and from micromolar to high picomolar [113,114], respectively. Since extracellular Cu(II) levels in the brain interstitial fluid are 100 nM, a picomolar affinity for Cu(II) would allow A β or Tau to compete for Cu(II) ions with other extracellular Cu(II) ligands [110]. This is especially true in the synaptic region where Cu(II) can be released during neurotransmission [115]. In particular, the concentrations of ionic copper in the synaptic cleft, after excitatory release, may reach 15 mM [116]. A β is also present in the synaptic cleft region [117] while recent studies indicate that tau can be detected into the synaptic vesicles under pathological conditions [118]. The data above mentioned indicate the ability of A β and tau proteins to interact with copper ions at physiological conditions.

The binding sites, the conformational changes, and affinity constants of Cu(II) and Zn(II) complexes with A β have been widely investigated [119,120]. Different coordination modes, stability constant values, and metal-assisted polypeptide secondary structure changes have been proposed. The 1–16 residue domain was generally considered the binding region for the Cu(II) ion in A β (1–42) [121,122].

In particular, at a low metal to A β ratio and physiological pH, macrochelate complex species mainly form while, upon increasing the metal to ligand ratio, more than one complex species can form with different coordination modes, as a consequence of the metal-assisted deprotonation of the amide nitrogens [123].

Little is known on the Cu(II) complex with oligomeric A β species. Recently, the Cu(II) coordination properties of synthetic A β (1–16) dimer, has been investigated [124]. Interestingly, an increased affinity of Cu(II) for His13 and His14 residues, compared with the Cu(II) coordination modes reported in the A β (1–16) monomer, was observed. This

result was in keeping with a recent study that reported the involvement of imidazole nitrogen of His13 and His14 in Cu(II) coordination with A β (1–40) fibrils [125].

Studies of the Zn(II) complexes with the N-terminal region of A β demonstrates that Zn(II) is preferentially placed in the 8–16 amino acidic region of A β (1–16), where it forms macrochelate complex species through the imidazole nitrogens of His13 or His14. This preference is different from that found for the Cu(II) ion that forms more stable complexes with the N-terminus domain [126].

Interestingly, a solid state NMR study on A β fibrils indicated that Zn²⁺ causes structural changes in the N-terminal domain of A β 42 by interaction of the metal ion with the side chain of His13 and His14 residues. Moreover, the metal ion is able to disrupt the salt bridge, between the side chains of Asp23 and Lys28, considered to be critical in the A β 42 aggregation process [127].

The studies reported above revealed that Cu(II) or Zn(II) exhibit a different binding site preference within the N-terminal region of A β peptide. Indeed, the addition of Zn(II) in excess is not able to completely remove Cu(II) from its primary binding sites. In particular, the copper ion cannot be displaced from the N-terminal group, which is its preferred coordinating site. Interestingly, Cu(II) can be shifted from the binding to the two His residues, His13 and His14, when Cu(II) to Zn(II) ratios are low [128]. The formation of this ternary metal complex may play a role in the redox activity of metals-A β complexes and justify the protective role of zinc in comparison with copper [85,129].

The amino acid sequence of tau protein is relatively rich in histidine residues and the imidazole side chain can be considered as potential metal binding sites of proteins [see Figure 2]. Almost all complexation studies reported in literature have been focused on the pseudo-repeats (R1–R4 domains) placed in the microtubule-binding region of tau protein [86–89,114].

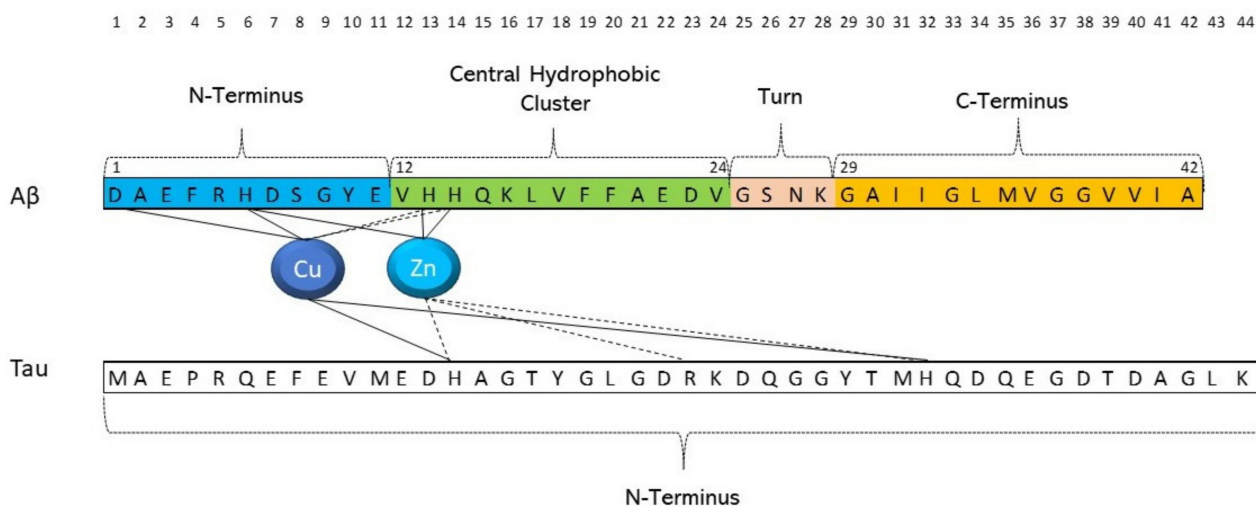


Figure 2. Cu(II) and Zn(II) binding sites in tau and A β peptide fragments.

These studies confirmed the involvement of the histidyl residue and the deprotonated amide nitrogens as the primary metal binding sites of the microtubule region. Few works have been reported about the metal complexes with peptides derived from the region outside the microtubule-binding domain of tau protein. In particular, recent studies described for the first time the Cu(II) binding ability of tau peptides from the N-terminal region of tau protein [130,131]. The results indicate that Cu(II) can bind the N-terminal domain using the histidine residues or amino group as anchoring sites. The results revealed that the complexes formed with the peptides containing the H32 residue predominate over those of H14 at physiological pH values with the formation of imidazole- and amide-coordinated species. Interestingly, the copper binding affinity of the histidyl residue (H32) is greater than the one of the histidines in the microtubule domain, suggesting that the N-terminal domain of tau

protein could be an additional coordinating site for copper ions [86]. No data are available on the formation of mixed metal complexes involving A β and tau despite molecular in vitro evidence for a direct A β /tau interaction. In particular, computational simulations revealed a metal binding affinity of peptide fragments bearing the metal interacting sequence from tau protein lower than those reported for the Cu(II)-A β system [90].

In these conditions, the formation of an a ternary complex A β -Cu-tau complex might occur as observed in the study of the copper complexes with A β N-terminus and octarepeat peptide fragments derived from the N-terminal part of the prion protein where computational simulations revealed that the amino terminus is a more effective anchoring site for metal binding [132,133].

Therefore, the possibility for a direct, Cu-mediated interaction between A β and Tau cannot be ruled out. Cu-bridging coordination might have an important impact on the aggregation behavior because the overall affinity of the peptide-peptide interactions, could be considerably increased.

5. Can Targeted Peptide-Based Inhibitors Prevent A β /Tau Cross-Seeding AD?

The interplay between the tau protein and A β is revealing more than casual in AD [134,135], and the search of the cross-interaction sites on both proteins may lead to the design of new molecules capable of inhibiting cross-seeded toxic aggregation [136]. While a variety of peptide-based inhibitors of A β aggregation have been developed and extensively reported [137–140], less examples of peptide inhibitors of tau protein aggregation exist in the literature [86,141]. So far, most AD therapeutic research has focused on A β , fewer efforts have been directed to developing therapeutic compounds targeting tau.

The development of peptide drugs can be hampered by their short half-life in vivo due to protease susceptibility, however the bioavailability of peptides, as well their blood-brain barrier (BBB) permeability, can be overcome by chemical modifications i.e., incorporation of conformationally constrained amino acids, modifications of the peptide backbone, end-protection and the use of D-enantiomeric amino acids.

A β /tau interactions may be reciprocally mediated by specific amino acid sequences of their respective primary structures. Guo et al. [142] studied, through a peptide membrane array, the sites of interaction between tau and A β . They found that the following A β fragments are involved in the interaction with non-phosphorylated tau: EVHHQK (residues 11–16), NKGAI (residues 27–32), and GGVVIA (residues 37–42) (see Figure 3). Likewise, the aggregation prone peptides sequences VQIINK (residues 275–280) and VQIVYK (residues 306–311) located at the beginning of repeat 2 (R2) and repeat 3 (R3) of the microtubule domain (K18), respectively, were found to bind A β [142].

Recently, Cuadros et al. [143] showed that the w-tau peptide (KKVKGVGWVGCCP-WVYGH), containing two tryptophan residues and derived from the 18-residue unique sequence of w-tau (a new tau human-specific splicing isoform) is able to inhibit not only tau protein assembly but also amyloid β peptide polymerization.

Computational seeding model predicts that the amyloid core of A β can form intermolecular β -sheet interactions with VQIINK or VQIVYK [144]. It is plausible that cross-seeding of tau by A β promotes tangle formation in AD, which could be prevented not only by inhibiting A β aggregation, but also by disrupting the binding site of A β with tau. On this basis, it can be hypothesized that an inhibitor capable of targeting the amyloid core, which itself is an important sequence for A β aggregation [145–147], might block both A β aggregation and tau seeding by A β . The design and synthesis of small peptides and/or peptidomimetics might be a viable strategy to break pathological cross interaction and prevent protein aggregation. Rationally designed peptides should prevent polypeptide chain aggregation by an ensemble of concurrent mechanisms operating at (i) the intermolecular interfaces that may include hampering the electrostatic interaction, (ii) hydrophobic capping of the “hot spot” responsible of molecular recognition or (iii) managing the metal coordination properties of either A β or tau.

Many studies have been inspired by the well-known hydrophobic core A β 16–20 (KLVFF) [148] and the β -sheet breaker peptide LPFFD [149] (see Figure 3) sequences to generate a variety of β -sheet breaker modified peptides [150]. For instance, considering the key role of the hydrogen-bridging or electrostatic interactions in the inhibitory property. β -sheet breaking peptides, based on the KLVFF sequence, the incorporation of N-methyl-amino acids [151–153], the addition of “disrupter” groups such as oligolysine chains to the C-terminus (KLVFFKKKKK) [154,155] or RG-/-GR residues at their N- and C-terminal end (RGKLVFFGR or RGKLVFFGR-NH₂) have been designed [156]. Other KLVFF derived synthetic peptides include a multiple-peptide conjugate such as a 4-branched KLVFF-dendrimer [157] and six copies of fvlk (retro-inverse analogue of KLVFF) linked to branched hexameric polyethylene glycol (PEG) [158]. Moreover, reducing the conformational freedom of the peptide, a cyclic KLVFF-derived peptide aggregation inhibitor was developed as well [159,160]. The introduced modification positively impacted with the inhibitory effect on A β aggregation compared to the unmodified sequence KLVFF or LPFFD, allowing a potential use of the compounds as therapeutic in Alzheimer’s Disease.

The antifibrillogenic and neuroprotective ability of a zinc-porphyrin-KLVFF conjugate was also reported [161]. Authors demonstrated an enhanced amyloid suppression properties and inhibition of the cytotoxic effects of A β 42’s oligomers by this derivative with respect the unconjugated KLVFF parent peptide [161]. Yet, the fluorescent porphyrin endows this peptide conjugate with theragnostic properties enabling the identification and visualization of soluble A β aggregates in biological fluids and the photodynamic therapy.

The β -sheet breaker peptide LPFFD has been subjected to chemical modifications as well. LPFFD-PEG [162], LPFFD containing at the N-terminus an N,N-di-methyltaurine or a taurine moiety [163], N- and C-terminal protections to minimize exopeptidase cleavage, modifications at the catabolic sites of the sequence to prevent proteolytic degradation have been reported [164].

Furthermore, LPFFD-modified analogues were screened by a set of *in vitro* and *in vivo* assays to study their application as peptide drug candidates, increasing stability and simultaneously maintaining (or enhancing) potency, brain uptake, compound solubility, and low toxicity [164]. The authors suggest that introducing a series of chemical modifications, the pharmacological profile of LPFFD can be improved and these strategies could be beneficial in the treatment of Alzheimer’s Disease.

A trehalose moiety has been covalently attached to the LPFFD peptide in different sites of the sequence to endow these systems with optimal bioavailability in terms of higher stability toward proteolytic degradation within biological fluids and hence better opportunities for potential clinical trials [165–167]. Trehalose has been chosen because of its protein stabilizing ability and neuroprotective action [165–167]. All the LPFFD conjugates interfered with the A β ’s fibrillation process by recognizing the “hot spots” responsible for A β oligomerization and fibril formation. A significant cytoprotective effect, toward pure cultures of rat cortical neurons, was also observed for all the synthesized derivatives alongside a concomitant activation of cell viability signal pathways [167].

It would be of interest to explore whether the above described peptides, known to prevent aggregation of amyloid- β , would exhibit a promising dual role in preventing amyloid- β as well as tau aggregation, as demonstrated by Gorantla et al. who screened LPFFD, KLVFF, and related derivatives containing thymine and sarcosine units (Table 1) [168].

Griner et al., designed several peptide-based inhibitors whose effectiveness for both A β and tau suggested that there was a common binding interface on the A β and tau aggregates [169] (Table 1). Starting from the crystal structure of the segment 16–26, containing the mutation D23N, the authors identified two octapeptides of the D-series designed against A β 16–26 D23N: (D)-LYIWIWRT e (D)-LYWIQKT. Moreover, they found that solvent accessible residues K16, V18 and E22 of A β are important for tau seeding. The dual efficacy of the inhibitor (D)-LYIWIWRT suggests that A β and tau, share a common structural motif in AD and that there is a direct interaction between the A β core and the amyloid-prone

regions of tau. Interestingly, these inhibitors are specific for A β and tau, and not for others protein such as hIAPP [169].

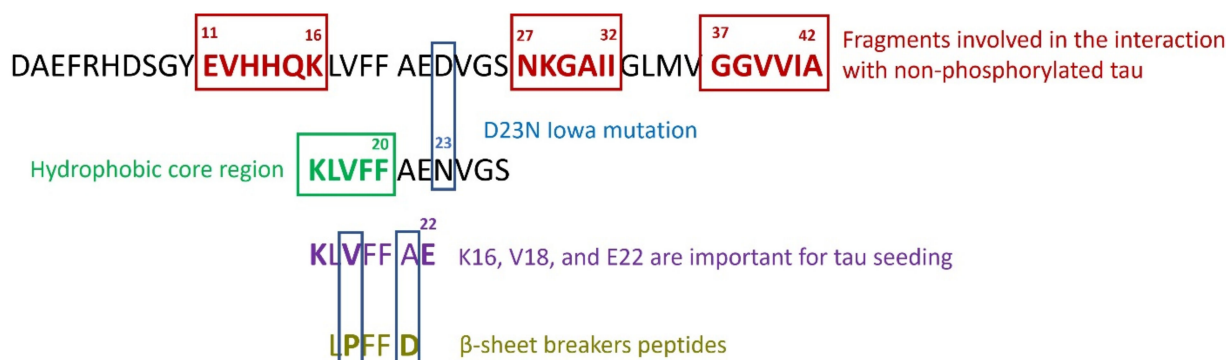


Figure 3. A β 1–42: fragments involved in the interaction with non-phosphorylated tau: EVHHQK (residues 11–16), NKGAI (residues 27–32), and GGVVIA (residues 37–42) [142]; the hydrophobic core region (KLVFF) [148,169] and the β -sheet breaker peptide LPFFD [149].

The VQIVYK fragment has been used as a model system for the development of cyclic tau aggregation peptide inhibitors: the cyclic D,L- α -peptides [IJwHsK] (square brackets indicate the cyclopeptide; upper and lower case letters represents L- and D-amino acids, respectively; J indicates norleucine) whose self-assembled structure is similar to amyloids. These designed cyclic D,L- α -peptides (Table 1) may cross-react with A β through a complementary sequence of hydrogen-bond donors and acceptors to modulate A β aggregation and toxicity. These cyclic peptides can inhibit the formation of toxic aggregates and can disassemble preformed A β fibrils by interacting with several regions of the soluble A β sequence and inducing structural changes to unfolded A β [170,171].

Other authors used the A β (25–35)-NH₂ and tau(273–284) peptide fragments, both acetylated and amidated, as an experimental model to investigate on the A β /Tau cross-interaction. The tau fragment could act as a fibrillogenic inhibitor of the A β counterpart. In particular, the incorporation of the tau fragment into the β -rich A β (25–35) oligomers reduced the propensity of A β (25–35) to aggregate but does not completely abolish fibril formation [40].

Table 1. Peptide designed for a dual property of inhibiting aggregates of tau and amyloid- β .

Peptides	Description	References
Ac-EVMEDHAKLVFF-NH ₂ (τ 9-16-KLVFF)	Chimera Tau/A β tau 9–16/A β 16–20	[90,141]
Ac-QGGYTMHQKLVFF-NH ₂ (τ 26-33-KLVFF)	tau 26–33/A β 16–20	
(D)-LYIWIWRT (D)-LYWIQKT	Peptide-based inhibitors effectiveness for both A β and tau designed against A β 16–26 D23N	[169]
Thymine-Sr-L-Sr-F-Sr-A Thymine-K-Sr-V-Sr-F-A	Introduction of thymine and sarcosine (Sr) inhibiting aggregates of tau and β -amyloid.	[168]
cyclic D,L- α -peptides [IJwHsK] ¹	Designed tau aggregation peptide inhibitors that may cross-react with A β	[170,171]

¹ Square brackets indicate the cyclopeptide; upper and lower case letters represents L- and D-amino acids, respectively; J indicates norleucine.

More recently a rational designed peptide inhibitor of tau aggregation, RI-AG03 (Ac-rrrrrrrGpkyk(Ac)iqvGr-NH₂), was developed. This peptide, based on the tau fragment 306–311(VQIVYK), is the proteolytically stable retro-inverted version of AG03 (Ac-RG-VQIK(Ac)YKP-GRRRRRRRR) containing a poly-arginine chain in order to reduce aggregation [172].

An emerging approach relies on the use of multifunctional peptides, having metal chelating and antifibrillogenic as potential elements to counteract metal-induced amyloid toxic aggregation [173]. To this regard, two A β /tau chimera peptides, namely Ac-EVMEDHAKLVFF-NH₂ (τ 9–16-KLVFF) and Ac-QGGYTMHQKLVFF-NH₂ (τ 26–33-KLVFF), have been designed and synthesized (Table 1) [90,141]. These peptides present at their respective C-terminal part, the A β recognizing hydrophobic sequence A β 16–20, whereas the metal binding sites are represented by the amino acid strings of the 9–16 or 26–33 tau's protein N-terminal region. The interaction between the A β and chimera peptides was studied by means of thioflavin-T (ThT) fluorescence and limited proteolysis MALDI-TOF spectrometry. These studies aimed at determining the anti-fibrillogenic activity of the two "chimera" peptides exploring different environmental conditions. The study was carried out in the presence of lipid membranes consisting of TLBE as well as in the presence of copper or zinc ions and the peptides were proposed as a potential candidate for future in vitro studies addressing the inhibition of pathogenic A β /tau accumulation. Forthcoming studies are in progress to elucidate cross-interaction with tau related peptides/protein.

6. Conclusions

Beyond the initial amyloid cascade hypothesis, postulating no interaction between A β and tau, several lines of evidence, either molecular or clinical, indicates the existence of an interplay between A β and tau accumulation.

It is now well-established that A β peptide and tau protein are mutually interconnected in AD pathogenesis, but neither how the misfolding of one of these two amyloid proteins may affect the other, nor the molecular pathways underlying aberrant A β /tau cross-interaction, have been fully elucidated yet. Accumulating evidence suggests that tau is physiologically released into the extracellular space, independently of cell death or neurodegeneration, where it can interact with the A β peptides [174,175].

Several hypotheses suggest that peptide patches of both A β and tau can interact together, either in the monomeric or aggregated forms, to facilitate cross-seeding [25,142,176]. Interestingly, in the case of the A β peptide, the mainly involved amino acids patches may include the A β 16–21 region [142], whereas the repeat domains or PHF6 peptide fragments have been invoked for the tau protein [177].

However, for a more comprehensive understanding of the molecular events triggering A β /tau interactions, additional tau's amino acid regions should be considered [178]. In this review, we have extended the discussion by also including those papers describing the cross-relationships between the full-length A β peptides and some peptide fragments belonging to N-terminal domain of the tau protein [130,141].

These studies have only recently appeared in the literature and dedicated emphasis on the role played by metal ions in modulating the A β /tau interplay also in different environmental conditions. Indeed, beside a brief description of the putative physiological role of A β and tau, the present review illustrates the recent studies carried out on the potential role of membranes in the A β /tau cross-interactions, with the aim to better define whether membranes could be the preferred site where protein-protein interactions may occur [179].

It turned out that lipid membrane can effectively drive tau's structural transition from random coil to β -sheet and this might potentially occur also in the presence of A β . Finally, this review addressed the importance of appropriately designed multifunctional peptides as modulator of the protein-protein interactions also in the presence of metal ions. In this context, we believe that there are margins for potentially therapeutic interventions against AD, using multifunctional peptides that are capable of inhibiting A β /tau co-aggregation by also modulating metal driven cross-interactions between A β and tau protein in specific, biologically relevant, compartments including the cell membrane interface.

Considering all the above, we can conclude that most of the literature cited in this review supports the theory that mutual A β and tau interactions strongly contribute to exac-

erbate AD pathology [26]. However, the understanding of the molecular relationship and mechanism of A β and tau interaction remains at its infancy. Such a conclusion comes from the awareness that, at present, there is no clear experimental evidence in vivo describing the molecular association between A β and tau in the various regions of the central nervous system. Nevertheless, the emerging scenario continues to stimulate the scientific research towards therapeutic solutions that consider both A β and tau, as a therapeutic target for an effective fight against Alzheimer's Disease. This is a quite ambitious, yet compelling goal to achieve, but other intrinsic (i.e., genetic), environmental and lifestyle aspects must be taken into consideration, in addition to the molecular traits we have considered in this review. In any case, it is apparent that the latest research developments in the molecular events underlying AD, increasingly underscores the need to restrict the pathological synergism downstream the aberrant interaction between A β and tau proteins.

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References

1. Stelzmann, R.A.; Norman Schnitzlein, H.; Reed Murtagh, F. An English Translation of Alzheimer's 1907 Paper, "Über Eine Eigenartige Erkrankung Der Hirnrinde". *Clin. Anat.* **1995**, *8*, 429–431. [[CrossRef](#)] [[PubMed](#)]
2. *Towards a Dementia Plan: A WHO Guide*; World Health Organization: Geneva, Switzerland, 2018.
3. 2015 Alzheimer's Disease Facts and Figures. *Alzheimers Dement. J. Alzheimers Assoc.* **2015**, *11*, 332–384. [[CrossRef](#)] [[PubMed](#)]
4. Glenner, G.G.; Wong, C.W. Alzheimer's Disease: Initial Report of the Purification and Characterization of a Novel Cerebrovascular Amyloid Protein. *Biochem. Biophys. Res. Commun.* **1984**, *120*, 885–890. [[CrossRef](#)]
5. Lee, V.M.; Balin, B.J.; Otvos, L.; Trojanowski, J.Q. A68: A Major Subunit of Paired Helical Filaments and Derivatized Forms of Normal Tau. *Science* **1991**, *251*, 675–678. [[CrossRef](#)] [[PubMed](#)]
6. Selkoe, D.J.; Hardy, J. The Amyloid Hypothesis of Alzheimer's Disease at 25 Years. *EMBO Mol. Med.* **2016**, *8*, 595–608. [[CrossRef](#)] [[PubMed](#)]
7. Goedert, M. Alzheimer's and Parkinson's Diseases: The Prion Concept in Relation to Assembled A β , Tau, and α -Synuclein. *Science* **2015**, *349*, 1255–1255. [[CrossRef](#)] [[PubMed](#)]
8. Crowther, R.A. Straight and Paired Helical Filaments in Alzheimer Disease Have a Common Structural Unit. *Proc. Natl. Acad. Sci. USA* **1991**, *88*, 2288–2292. [[CrossRef](#)]
9. Meraz-Ríos, M.A.; Lira-De León, K.I.; Campos-Peña, V.; De Anda-Hernández, M.A.; Mena-López, R. Tau Oligomers and Aggregation in Alzheimer's Disease. *J. Neurochem.* **2010**, *112*, 1353–1367. [[CrossRef](#)]
10. Wang, Z.-X.; Tan, L.; Liu, J.; Yu, J.-T. The Essential Role of Soluble A β Oligomers in Alzheimer's Disease. *Mol. Neurobiol.* **2016**, *53*, 1905–1924. [[CrossRef](#)]
11. Blennow, K.; Zetterberg, H. The Past and the Future of Alzheimer's Disease CSF Biomarkers—A Journey toward Validated Biochemical Tests Covering the Whole Spectrum of Molecular Events. *Front. Neurosci.* **2015**, *9*, 345. [[CrossRef](#)]
12. Sandwall, E.; O'Callaghan, P.; Zhang, X.; Lindahl, U.; Lannfelt, L.; Li, J.-P. Heparan Sulfate Mediates Amyloid-Beta Internalization and Cytotoxicity. *Glycobiology* **2010**, *20*, 533–541. [[CrossRef](#)] [[PubMed](#)]
13. Iribarren, P.; Zhou, Y.; Hu, J.; Le, Y.; Wang, J.M. Role of Formyl Peptide Receptor-like 1 (FPRL1/FPR2) in Mononuclear Phagocyte Responses in Alzheimer Disease. *Immunol. Res.* **2005**, *31*, 165–176. [[CrossRef](#)]
14. Wang, H.; Chen, F.; Du, Y.-F.; Long, Y.; Reed, M.N.; Hu, M.; Suppiramaniam, V.; Hong, H.; Tang, S.-S. Targeted Inhibition of RAGE Reduces Amyloid- β Influx across the Blood-Brain Barrier and Improves Cognitive Deficits in Db/Db Mice. *Neuropharmacology* **2018**, *131*, 143–153. [[CrossRef](#)]
15. Yuyama, K.; Yamamoto, N.; Yanagisawa, K. Accelerated Release of Exosome-Associated GM1 Ganglioside (GM1) by Endocytic Pathway Abnormality: Another Putative Pathway for GM1-Induced Amyloid Fibril Formation. *J. Neurochem.* **2008**, *105*, 217–224. [[CrossRef](#)] [[PubMed](#)]
16. Sakono, M.; Zako, T.; Ueda, H.; Yohda, M.; Maeda, M. Formation of Highly Toxic Soluble Amyloid Beta Oligomers by the Molecular Chaperone Prefoldin. *FEBS J.* **2008**, *275*, 5982–5993. [[CrossRef](#)] [[PubMed](#)]
17. Ittner, L.M.; Götz, J. Amyloid- β and Tau—A Toxic Pas de Deux in Alzheimer's Disease. *Nat. Rev. Neurosci.* **2011**, *12*, 67–72. [[CrossRef](#)]
18. Naveh Tassa, S.; Ben Zichri, S.; Lacham-Hartman, S.; Oren, O.; Slobodnik, Z.; Eremenko, E.; Toiber, D.; Jelinek, R.; Papo, N. A Mechanism for the Inhibition of Tau Neurotoxicity: Studies with Artificial Membranes, Isolated Mitochondria, and Intact Cells. *ACS Chem. Neurosci.* **2021**, *12*, 1563–1577. [[CrossRef](#)] [[PubMed](#)]
19. Ittner, L.M.; Ke, Y.D.; Delerue, F.; Bi, M.; Gladbach, A.; van Eersel, J.; Wölfing, H.; Chieng, B.C.; Christie, M.J.; Napier, I.A.; et al. Dendritic Function of Tau Mediates Amyloid- β Toxicity in Alzheimer's Disease Mouse Models. *Cell* **2010**, *142*, 387–397. [[CrossRef](#)]

20. Pickett, E.K.; Herrmann, A.G.; McQueen, J.; Abt, K.; Dando, O.; Tulloch, J.; Jain, P.; Dunnett, S.; Sohrabi, S.; Fjeldstad, M.P. Amyloid Beta and Tau Cooperate to Cause Reversible Behavioral and Transcriptional Deficits in a Model of Alzheimer's Disease. *Cell Rep.* **2019**, *29*, 3592–3604. [[CrossRef](#)]
21. McInnes, J.; Wierda, K.; Snellinx, A.; Bounti, L.; Wang, Y.-C.; Stancu, I.-C.; Apóstolo, N.; Gevaert, K.; Dewachter, I.; Spires-Jones, T.L.; et al. Synaptogyrin-3 Mediates Presynaptic Dysfunction Induced by Tau. *Neuron* **2018**, *97*, 823–835.e8. [[CrossRef](#)]
22. Ovsepian, S.V.; O'Leary, V.B.; Zaborszky, L.; Ntziachristos, V.; Dolly, J.O. Synaptic Vesicle Cycle and Amyloid β : Biting the Hand That Feeds. *Alzheimers Dement.* **2018**, *14*, 502–513. [[CrossRef](#)] [[PubMed](#)]
23. Niu, Z.; Zhang, Z.; Zhao, W.; Yang, J. Interactions between Amyloid β Peptide and Lipid Membranes. *Biochim. Biophys. Acta-Biomembr.* **2018**, *1860*, 1663–1669. [[CrossRef](#)] [[PubMed](#)]
24. Georgieva, E.R.; Xiao, S.; Borbat, P.P.; Freed, J.H.; Eliezer, D. Tau Binds to Lipid Membrane Surfaces via Short Amphipathic Helices Located in Its Microtubule-Binding Repeats. *Biophys. J.* **2014**, *107*, 1441–1452. [[CrossRef](#)] [[PubMed](#)]
25. Wallin, C.; Hiruma, Y.; Wärmländer, S.K.T.S.; Huvent, I.; Jarvet, J.; Abrahams, J.P.; Gräslund, A.; Lippens, G.; Luo, J. The Neuronal Tau Protein Blocks In Vitro Fibrillation of the Amyloid- β ($A\beta$) Peptide at the Oligomeric Stage. *J. Am. Chem. Soc.* **2018**, *140*, 8138–8146. [[CrossRef](#)] [[PubMed](#)]
26. Busche, M.A.; Hyman, B.T. Synergy between Amyloid- β and Tau in Alzheimer's Disease. *Nat. Neurosci.* **2020**, *23*, 1183–1193. [[CrossRef](#)]
27. Mangialasche, F.; Solomon, A.; Winblad, B.; Mecocci, P.; Kivipelto, M. Alzheimer's Disease: Clinical Trials and Drug Development. *Lancet Neurol.* **2010**, *9*, 702–716. [[CrossRef](#)]
28. Morley, J.E.; Farr, S.A. Hormesis and Amyloid- β Protein: Physiology or Pathology? *J. Alzheimers Dis. JAD* **2012**, *29*, 487–492. [[CrossRef](#)]
29. Hillen, H. The Beta Amyloid Dysfunction (BAD) Hypothesis for Alzheimer's Disease. *Front. Neurosci.* **2019**, *13*, 1154. [[CrossRef](#)]
30. Giuffrida, M.L.; Caraci, F.; Pignataro, B.; Cataldo, S.; De Bona, P.; Bruno, V.; Molinaro, G.; Pappalardo, G.; Messina, A.; Palmigiano, A.; et al. Beta-Amyloid Monomers Are Neuroprotective. *J. Neurosci. Off. J. Soc. Neurosci.* **2009**, *29*, 10582–10587. [[CrossRef](#)]
31. Cuesto, G.; Enriquez-Barreto, L.; Caramés, C.; Cantarero, M.; Gasull, X.; Sandi, C.; Ferrús, A.; Acebes, Á.; Morales, M. Phosphoinositide-3-Kinase Activation Controls Synaptogenesis and Spinogenesis in Hippocampal Neurons. *J. Neurosci.* **2011**, *31*, 2721–2733. [[CrossRef](#)]
32. Mi, G.; Hm, B.; Sr, R. Alzheimer's Amyloid- β Is an Antimicrobial Peptide: A Review of the Evidence. *J. Alzheimers Dis. JAD* **2018**, *62*, 1495–1506. [[CrossRef](#)]
33. Freedman, D.M.; Wu, J.; Chen, H.; Kuncl, R.W.; Enewold, L.R.; Engels, E.A.; Freedman, N.D.; Pfeiffer, R.M. Associations between Cancer and Alzheimer's Disease in a U.S. Medicare Population. *Cancer Med.* **2016**, *5*, 2965–2976. [[CrossRef](#)] [[PubMed](#)]
34. Brothers, H.M.; Gosztyla, M.L.; Robinson, S.R. The Physiological Roles of Amyloid- β Peptide Hint at New Ways to Treat Alzheimer's Disease. *Front. Aging Neurosci.* **2018**, *10*, 118. [[CrossRef](#)] [[PubMed](#)]
35. Masters, C.L.; Simms, G.; Weinman, N.A.; Multhaup, G.; McDonald, B.L.; Beyreuther, K. Amyloid Plaque Core Protein in Alzheimer Disease and Down Syndrome. *Proc. Natl. Acad. Sci. USA* **1985**, *82*, 4245–4249. [[CrossRef](#)]
36. Selkoe, D.J. Normal and Abnormal Biology of the Beta-Amyloid Precursor Protein. *Annu. Rev. Neurosci.* **1994**, *17*, 489–517. [[CrossRef](#)]
37. Thornton, E.; Vink, R.; Blumbergs, P.C.; Van Den Heuvel, C. Soluble Amyloid Precursor Protein Alpha Reduces Neuronal Injury and Improves Functional Outcome Following Diffuse Traumatic Brain Injury in Rats. *Brain Res.* **2006**, *1094*, 38–46. [[CrossRef](#)]
38. Wang, Y.-Q.; Qu, D.-H.; Wang, K. Therapeutic Approaches to Alzheimer's Disease through Stimulating of Non-Amyloidogenic Processing of Amyloid Precursor Protein. *Eur. Rev. Med. Pharmacol. Sci.* **2016**, *20*, 2389–2403.
39. Luna-Viramontes, N.I.; Campa-Córdoba, B.B.; Ontiveros-Torres, M.Á.; Harrington, C.R.; Villanueva-Fierro, I.; Guadarrama-Ortiz, P.; Garcés-Ramírez, L.; de la Cruz, F.; Hernandez-Alejandro, M.; Martínez-Robles, S.; et al. PHF-Core Tau as the Potential Initiating Event for Tau Pathology in Alzheimer's Disease. *Front. Cell. Neurosci.* **2020**, *14*, 247. [[CrossRef](#)]
40. Do, T.D.; Economou, N.J.; Chamas, A.; Buratto, S.K.; Shea, J.-E.; Bowers, M.T. Interactions between Amyloid- β and Tau Fragments Promote Aberrant Aggregates: Implications for Amyloid Toxicity. *J. Phys. Chem. B* **2014**, *118*, 11220–11230. [[CrossRef](#)]
41. Jadhav, S.; Cubinkova, V.; Zimova, I.; Brezovakova, V.; Madari, A.; Cigankova, V.; Zilka, N. Tau-Mediated Synaptic Damage in Alzheimer's Disease. *Transl. Neurosci.* **2015**, *6*, 214–226. [[CrossRef](#)]
42. Gonçalves, R.A.; Wijesekara, N.; Fraser, P.E.; De Felice, F.G. Behavioral Abnormalities in Knockout and Humanized Tau Mice. *Front. Endocrinol.* **2020**, *11*, 124. [[CrossRef](#)] [[PubMed](#)]
43. LoPresti, P. Tau in Oligodendrocytes Takes Neurons in Sickness and in Health. *Int. J. Mol. Sci.* **2018**, *19*, 2408. [[CrossRef](#)] [[PubMed](#)]
44. Kent, S.A.; Spires-Jones, T.L.; Durrant, C.S. The Physiological Roles of Tau and $A\beta$: Implications for Alzheimer's Disease Pathology and Therapeutics. *Acta Neuropathol.* **2020**, *140*, 417–447. [[CrossRef](#)] [[PubMed](#)]
45. Guo, T.; Noble, W.; Hanger, D.P. Roles of Tau Protein in Health and Disease. *Acta Neuropathol.* **2017**, *133*, 665–704. [[CrossRef](#)]
46. Rodríguez-Martín, T.; Cuchillo-Ibáñez, I.; Noble, W.; Nyenya, F.; Anderton, B.H.; Hanger, D.P. Tau Phosphorylation Affects Its Axonal Transport and Degradation. *Neurobiol. Aging* **2013**, *34*, 2146–2157. [[CrossRef](#)]
47. Pallas-Bazarra, N.; Jurado-Arjona, J.; Navarrete, M.; Esteban, J.A.; Hernández, F.; Ávila, J.; Llorens-Martín, M. Novel Function of Tau in Regulating the Effects of External Stimuli on Adult Hippocampal Neurogenesis. *EMBO J.* **2016**, *35*, 1417–1436. [[CrossRef](#)]

48. Martin, L.; Latypova, X.; Terro, F. Post-Translational Modifications of Tau Protein: Implications for Alzheimer's Disease. *Neurochem. Int.* **2011**, *58*, 458–471. [[CrossRef](#)]
49. Sciacca, M.F.M.; Tempa, C.; Scollo, F.; Milardi, D.; La Rosa, C. Amyloid Growth and Membrane Damage: Current Themes and Emerging Perspectives from Theory and Experiments on A β and HIAPP. *Biochim. Biophys. Acta Biomembr.* **2018**, *1860*, 1625–1638. [[CrossRef](#)]
50. García-Viñuales, S.; Sciacca, M.F.M.; Lanza, V.; Santoro, A.M.; Grasso, G.; Tundo, G.R.; Sbardella, D.; Coletta, M.; Grasso, G.; La Rosa, C.; et al. The Interplay between Lipid and A β Amyloid Homeostasis in Alzheimer's Disease: Risk Factors and Therapeutic Opportunities. *Chem. Phys. Lipids* **2021**, *236*, 105072. [[CrossRef](#)]
51. Drolle, E.; Negoda, A.; Hammond, K.; Pavlov, E.; Leonenko, Z. Changes in Lipid Membranes May Trigger Amyloid Toxicity in Alzheimer's Disease. *PLoS ONE* **2017**, *12*, e0182194. [[CrossRef](#)]
52. Künze, G.; Barré, P.; Scheidt, H.A.; Thomas, L.; Eliezer, D.; Huster, D. Binding of the Three-Repeat Domain of Tau to Phospholipid Membranes Induces an Aggregated-like State of the Protein. *Biochim. Biophys. Acta* **2012**, *1818*, 2302–2313. [[CrossRef](#)] [[PubMed](#)]
53. Maas, T.; Eidenmüller, J.; Brandt, R. Interaction of Tau with the Neural Membrane Cortex Is Regulated by Phosphorylation at Sites That Are Modified in Paired Helical Filaments. *J. Biol. Chem.* **2000**, *275*, 15733–15740. [[CrossRef](#)] [[PubMed](#)]
54. Brandt, R.; Léger, J.; Lee, G. Interaction of Tau with the Neural Plasma Membrane Mediated by Tau's Amino-Terminal Projection Domain. *J. Cell Biol.* **1995**, *131*, 1327–1340. [[CrossRef](#)]
55. Sallaberry, C.A.; Voss, B.J.; Majewski, J.; Biernat, J.; Mandelkow, E.; Chi, E.Y.; Vander Zanden, C.M. Tau and Membranes: Interactions That Promote Folding and Condensation. *Front. Cell Dev. Biol.* **2021**, 2632. [[CrossRef](#)] [[PubMed](#)]
56. Ait-Bouziad, N.; Lv, G.; Mahul-Mellier, A.-L.; Xiao, S.; Zorludemir, G.; Eliezer, D.; Walz, T.; Lashuel, H.A. Discovery and Characterization of Stable and Toxic Tau/Phospholipid Oligomeric Complexes. *Nat. Commun.* **2017**, *8*, 1678. [[CrossRef](#)] [[PubMed](#)]
57. Elbaum-Garfinkle, S.; Ramlall, T.; Rhoades, E. The Role of the Lipid Bilayer in Tau Aggregation. *Biophys. J.* **2010**, *98*, 2722–2730. [[CrossRef](#)]
58. Katsinelos, T.; Zeitler, M.; Dimou, E.; Karakatsani, A.; Müller, H.-M.; Nachman, E.; Steringer, J.P.; Ruiz de Almodovar, C.; Nickel, W.; Jahn, T.R. Unconventional Secretion Mediates the Trans-Cellular Spreading of Tau. *Cell Rep.* **2018**, *23*, 2039–2055. [[CrossRef](#)]
59. Fabiani, C.; Antollini, S.S. Alzheimer's Disease as a Membrane Disorder: Spatial Cross-Talk Among Beta-Amyloid Peptides, Nicotinic Acetylcholine Receptors and Lipid Rafts. *Front. Cell. Neurosci.* **2019**, *13*, 309. [[CrossRef](#)]
60. Lahdo, R.; De La Fournière-Bessueille, L. Insertion of the Amyloid Precursor Protein into Lipid Monolayers: Effects of Cholesterol and Apolipoprotein E. *Biochem. J.* **2004**, *382*, 987–994. [[CrossRef](#)]
61. Matsuzaki, K. Physicochemical Interactions of Amyloid β -Peptide with Lipid Bilayers. *Biochim. Biophys. Acta BBA-Biomembr.* **2007**, *1768*, 1935–1942. [[CrossRef](#)]
62. Lin, M.-S.; Chen, L.-Y.; Wang, S.S.S.; Chang, Y.; Chen, W.-Y. Examining the Levels of Ganglioside and Cholesterol in Cell Membrane on Attenuation the Cytotoxicity of Beta-Amyloid Peptide. *Colloids Surf. B Biointerfaces* **2008**, *65*, 172–177. [[CrossRef](#)] [[PubMed](#)]
63. Fabelo, N.; Martín, V.; Marín, R.; Moreno, D.; Ferrer, I.; Díaz, M. Altered Lipid Composition in Cortical Lipid Rafts Occurs at Early Stages of Sporadic Alzheimer's Disease and Facilitates APP/BACE1 Interactions. *Neurobiol. Aging* **2014**, *35*, 1801–1812. [[CrossRef](#)] [[PubMed](#)]
64. Kosicek, M.; Hecimovic, S. Phospholipids and Alzheimer's Disease: Alterations, Mechanisms and Potential Biomarkers. *Int. J. Mol. Sci.* **2013**, *14*, 1310–1322. [[CrossRef](#)] [[PubMed](#)]
65. Beel, A.J.; Sakakura, M.; Barrett, P.J.; Sanders, C.R. Direct Binding of Cholesterol to the Amyloid Precursor Protein: An Important Interaction in Lipid-Alzheimer's Disease Relationships? *Biochim. Biophys. Acta* **2010**, *1801*, 975–982. [[CrossRef](#)] [[PubMed](#)]
66. Harris, J.R. Cholesterol Binding to Amyloid-Beta Fibrils: A TEM Study. *Micron. Oxf. Engl.* **2008**, *39*, 1192–1196. [[CrossRef](#)]
67. Barrett, P.J.; Song, Y.; Van Horn, W.D.; Hustedt, E.J.; Schafer, J.M.; Hadziselimovic, A.; Beel, A.J.; Sanders, C.R. The Amyloid Precursor Protein Has a Flexible Transmembrane Domain and Binds Cholesterol. *Science* **2012**, *336*, 1168–1171. [[CrossRef](#)]
68. Wakabayashi, M.; Matsuzaki, K. Formation of Amyloids by A β -(1–42) on NGF-Differentiated PC12 Cells: Roles of Gangliosides and Cholesterol. *J. Mol. Biol.* **2007**, *371*, 924–933. [[CrossRef](#)]
69. Merezhko, M.; Brunello, C.A.; Yan, X.; Vihinen, H.; Jokitalo, E.; Uronen, R.-L.; Huttunen, H.J. Secretion of Tau via an Unconventional Non-Vesicular Mechanism. *Cell Rep.* **2018**, *25*, 2027–2035. [[CrossRef](#)]
70. Feringa, F.M.; van der Kant, R. Cholesterol and Alzheimer's Disease; From Risk Genes to Pathological Effects. *Front. Aging Neurosci.* **2021**, *13*, 333. [[CrossRef](#)]
71. Matsuzaki, K. How Do Membranes Initiate Alzheimer's Disease? Formation of Toxic Amyloid Fibrils by the Amyloid β -Protein on Ganglioside Clusters. *Acc. Chem. Res.* **2014**, *47*, 2397–2404. [[CrossRef](#)]
72. Matsuzaki, K.; Kato, K.; Yanagisawa, K. A β Polymerization through Interaction with Membrane Gangliosides. *Biochim. Biophys. Acta BBA-Mol. Cell Biol. Lipids* **2010**, *1801*, 868–877. [[CrossRef](#)] [[PubMed](#)]
73. Wakabayashi, M.; Okada, T.; Kozutsumi, Y.; Matsuzaki, K. GM1 Ganglioside-Mediated Accumulation of Amyloid β -Protein on Cell Membranes. *Biochem. Biophys. Res. Commun.* **2005**, *328*, 1019–1023. [[CrossRef](#)] [[PubMed](#)]
74. Kawarabayashi, T.; Shoji, M.; Younkin, L.H.; Wen-Lang, L.; Dickson, D.W.; Murakami, T.; Matsubara, E.; Abe, K.; Ashe, K.H.; Younkin, S.G. Dimeric Amyloid β Protein Rapidly Accumulates in Lipid Rafts Followed by Apolipoprotein E and Phosphorylated Tau Accumulation in the Tg2576 Mouse Model of Alzheimer's Disease. *J. Neurosci.* **2004**, *24*, 3801–3809. [[CrossRef](#)] [[PubMed](#)]

75. Klein, C.; Krämer, E.-M.; Cardine, A.-M.; Schraven, B.; Brandt, R.; Trotter, J. Process Outgrowth of Oligodendrocytes Is Promoted by Interaction of Fyn Kinase with the Cytoskeletal Protein Tau. *J. Neurosci.* **2002**, *22*, 698–707. [[CrossRef](#)] [[PubMed](#)]
76. Williamson, R.; Usardi, A.; Hanger, D.P.; Anderton, B.H. Membrane-Bound β -Amyloid Oligomers Are Recruited into Lipid Rafts by a Fyn-Dependent Mechanism. *FASEB J.* **2008**, *22*, 1552–1559. [[CrossRef](#)] [[PubMed](#)]
77. Campos-Peña, V.; Tapia-Ramírez, J.; Sánchez-Torres, C.; Meraz-Rios, M.A. Pathological-like Assembly of Tau Induced by a Paired Helical Filament Core Expressed at the Plasma Membrane. *J. Alzheimers Dis. JAD* **2009**, *18*, 919–933. [[CrossRef](#)]
78. Jones, E.M.; Dubey, M.; Camp, P.J.; Vernon, B.C.; Biernat, J.; Mandelkow, E.; Majewski, J.; Chi, E.Y. Interaction of Tau Protein with Model Lipid Membranes Induces Tau Structural Compaction and Membrane Disruption. *Biochemistry* **2012**, *51*, 2539–2550. [[CrossRef](#)]
79. Kawarabayashi, T.; Nakamura, T.; Sato, K.; Seino, Y.; Ichii, S.; Nakahata, N.; Takatama, M.; Westaway, D.; George-Hyslop, P.S.; Shoji, M. Lipid Rafts Act as a Common Platform for Amyloid- β Oligomer-Induced Alzheimer's Disease Pathology. *J. Alzheimers Dis. JAD* **2022**, *87*, 1189–1203. [[CrossRef](#)]
80. Roberson, E.D.; Scearce-Levie, K.; Palop, J.J.; Yan, F.; Cheng, I.H.; Wu, T.; Gerstein, H.; Yu, G.-Q.; Mucke, L. Reducing Endogenous Tau Ameliorates Amyloid Beta-Induced Deficits in an Alzheimer's Disease Mouse Model. *Science* **2007**, *316*, 750–754. [[CrossRef](#)]
81. Park, S.-Y.; Ferreira, A. The Generation of a 17 kDa Neurotoxic Fragment: An Alternative Mechanism by Which Tau Mediates β -Amyloid-Induced Neurodegeneration. *J. Neurosci.* **2005**, *25*, 5365–5375. [[CrossRef](#)]
82. Nicholson, A.M.; Ferreira, A. Increased Membrane Cholesterol Might Render Mature Hippocampal Neurons More Susceptible to β -Amyloid-Induced Calpain Activation and Tau Toxicity. *J. Neurosci.* **2009**, *29*, 4640–4651. [[CrossRef](#)] [[PubMed](#)]
83. Wray, S.; Noble, W. Linking Amyloid and Tau Pathology in Alzheimer's Disease: The Role of Membrane Cholesterol in A β -Mediated Tau Toxicity. *J. Neurosci.* **2009**, *29*, 9665–9667. [[CrossRef](#)] [[PubMed](#)]
84. Dexter, D.T.; Jenner, P.; Schapira, A.H.; Marsden, C.D. Alterations in Levels of Iron, Ferritin, and Other Trace Metals in Neurodegenerative Diseases Affecting the Basal Ganglia. *Ann. Neurol.* **1992**, *32* (Suppl. 1), S94–S100. [[CrossRef](#)] [[PubMed](#)]
85. Cuajungco, M.P.; Goldstein, L.E.; Nunomura, A.; Smith, M.A.; Lim, J.T.; Atwood, C.S.; Huang, X.; Farrag, Y.W.; Perry, G.; Bush, A.I. Evidence That the β -Amyloid Plaques of Alzheimer's Disease Represent the Redox-Silencing and Entombment of A β by Zinc. *J. Biol. Chem.* **2000**, *275*, 19439–19442. [[CrossRef](#)] [[PubMed](#)]
86. Balogh, B.D.; Szakács, B.; Di Natale, G.; Tabbi, G.; Pappalardo, G.; Sóvágó, I.; Várnagy, K. Copper (II) Binding Properties of an Octapeptide Fragment from the R3 Region of Tau Protein: A Combined Potentiometric, Spectroscopic and Mass Spectrometric Study. *J. Inorg. Biochem.* **2021**, *217*, 111358. [[CrossRef](#)] [[PubMed](#)]
87. Ahmadi, S.; Wu, B.; Song, R.; Zhu, S.; Simpson, A.; Wilson, D.J.; Kraatz, H.B. Exploring the Interactions of Iron and Zinc with the Microtubule Binding Repeats R1 and R4. *J. Inorg. Biochem.* **2020**, *205*, 110987. [[CrossRef](#)] [[PubMed](#)]
88. Ahmadi, S.; Zhu, S.; Sharma, R.; Wilson, D.J.; Kraatz, H.B. Interaction of Metal Ions with Tau Protein. The Case for a Metal-Mediated Tau Aggregation. *J. Inorg. Biochem.* **2019**, *194*, 44–51. [[CrossRef](#)]
89. Ma, Q.F.; Li, Y.M.; Du, J.T.; Kanazawa, K.; Nemoto, T.; Nakanishi, H.; Zhao, Y.F. Binding of Copper (II) Ion to an Alzheimer's Tau Peptide as Revealed by MALDI-TOF MS, CD, and NMR. *Biopolymers* **2005**, *79*, 74–85. [[CrossRef](#)]
90. Sciacca, M.F.M.; Di Natale, G.; Tosto, R.; Milardi, D.; Pappalardo, G. Tau/A β Chimera Peptides: Evaluating the Dual Function of Metal Coordination and Membrane Interaction in One Sequence. *J. Inorg. Biochem.* **2020**, *205*, 110996. [[CrossRef](#)]
91. Bush, A.I.; Pettingell, W.H.; Paradis, M.D.; Tanzi, R.E. Modulation of A Beta Adhesiveness and Secretase Site Cleavage by Zinc. *J. Biol. Chem.* **1994**, *269*, 12152–12158. [[CrossRef](#)]
92. Jakob-Roetne, R.; Jacobsen, H. Alzheimer's Disease: From Pathology to Therapeutic Approaches. *Angew. Chem. Int. Ed.* **2009**, *48*, 3030–3059. [[CrossRef](#)] [[PubMed](#)]
93. Savelieff, M.G.; Lee, S.; Liu, Y.; Lim, M.H. Untangling Amyloid- β , Tau, and Metals in Alzheimer's Disease. *ACS Chem. Biol.* **2013**, *8*, 856–865. [[CrossRef](#)] [[PubMed](#)]
94. Xiong, Y.; Luo, D.-J.; Wang, X.-L.; Qiu, M.; Yang, Y.; Yan, X.; Wang, J.-Z.; Ye, Q.-F.; Liu, R. Zinc Binds to and Directly Inhibits Protein Phosphatase 2A in Vitro. *Neurosci. Bull.* **2015**, *31*, 331–337. [[CrossRef](#)]
95. Boom, A.; Authelet, M.; Dedecker, R.; Frédéric, C.; Van Heurck, R.; Daubie, V.; Leroy, K.; Pochet, R.; Brion, J.-P. Bimodal Modulation of Tau Protein Phosphorylation and Conformation by Extracellular Zn²⁺ in Human-Tau Transfected Cells. *Biochim. Biophys. Acta BBA-Mol. Cell Res.* **2009**, *1793*, 1058–1067. [[CrossRef](#)] [[PubMed](#)]
96. Lee, G.; Neve, R.L.; Kosik, K.S. The Microtubule Binding Domain of Tau Protein. *Neuron* **1989**, *2*, 1615–1624. [[CrossRef](#)]
97. Greenough, M.A.; Camakaris, J.; Bush, A.I. Metal Dyshomeostasis and Oxidative Stress in Alzheimer's Disease. *Neurochem. Int.* **2013**, *62*, 540–555. [[CrossRef](#)] [[PubMed](#)]
98. Huang, Y.; Wu, Z.; Cao, Y.; Lang, M.; Lu, B.; Zhou, B. Zinc Binding Directly Regulates Tau Toxicity Independent of Tau Hyperphosphorylation. *Cell Rep.* **2014**, *8*, 831–842. [[CrossRef](#)]
99. Grasso, G.; Santoro, A.M.; Lanza, V.; Sbardella, D.; Tundo, G.R.; Ciaccio, C.; Marini, S.; Coletta, M.; Milardi, D. The Double Faced Role of Copper in A β Homeostasis: A Survey on the Interrelationship between Metal Dyshomeostasis, UPS Functioning and Autophagy in Neurodegeneration. *Coord. Chem. Rev.* **2017**, *347*, 1–22. [[CrossRef](#)]
100. Kepp, K.P. Bioinorganic Chemistry of Alzheimer's Disease. *Chem. Rev.* **2012**, *112*, 5193–5239. [[CrossRef](#)]
101. Que, E.L.; Domaille, D.W.; Chang, C.J. Metals in Neurobiology: Probing Their Chemistry and Biology with Molecular Imaging. *Chem. Rev.* **2008**, *108*, 1517–1549. [[CrossRef](#)]

102. Duce, J.A.; Bush, A.I. Biological Metals and Alzheimer's Disease: Implications for Therapeutics and Diagnostics. *Prog. Neurobiol.* **2010**, *92*, 1–18. [[CrossRef](#)]
103. Cheignon, C.; Jones, M.; Atrián-Blasco, E.; Kieffer, I.; Faller, P.; Collin, F.; Hureau, C. Identification of Key Structural Features of the Elusive Cu–A β Complex That Generates ROS in Alzheimer's Disease. *Chem. Sci.* **2017**, *8*, 5107–5118. [[CrossRef](#)] [[PubMed](#)]
104. Eskici, G.; Axelsen, P.H. Copper and Oxidative Stress in the Pathogenesis of Alzheimer's Disease. *Biochemistry* **2012**, *51*, 6289–6311. [[CrossRef](#)] [[PubMed](#)]
105. Cheignon, C.; Tomas, M.; Bonnefont-Rousselot, D.; Faller, P.; Hureau, C.; Collin, F. Oxidative Stress and the Amyloid Beta Peptide in Alzheimer's Disease. *Redox Biol.* **2018**, *14*, 450–464. [[CrossRef](#)] [[PubMed](#)]
106. Dikalov, S.I.; Vitek, M.P.; Mason, R.P. Cupric–Amyloid β Peptide Complex Stimulates Oxidation of Ascorbate and Generation of Hydroxyl Radical. *Free Radic. Biol. Med.* **2004**, *36*, 340–347. [[CrossRef](#)]
107. Ali, F.E.; Separovic, F.; Barrow, C.J.; Cherny, R.A.; Fraser, F.; Bush, A.I.; Masters, C.L.; Barnham, K.J. Methionine Regulates Copper/Hydrogen Peroxide Oxidation Products of A β . *J. Pept. Sci.* **2005**, *11*, 353–360. [[CrossRef](#)]
108. Cassagnes, L.-E.; Hervé, V.; Nepveu, F.; Hureau, C.; Faller, P.; Collin, F. The Catalytically Active Copper–Amyloid-Beta State: Coordination Site Responsible for Reactive Oxygen Species Production. *Angew. Chem. Int. Ed.* **2013**, *52*, 11110–11113. [[CrossRef](#)]
109. Kim, A.C.; Lim, S.; Kim, Y.K. Metal Ion Effects on A β and Tau Aggregation. *Int. J. Mol. Sci.* **2018**, *19*, 128. [[CrossRef](#)]
110. Sarell, C.J.; Wilkinson, S.R.; Viles, J.H. Substoichiometric Levels of Cu²⁺ Ions Accelerate the Kinetics of Fiber Formation and Promote Cell Toxicity of Amyloid- β from Alzheimer Disease. *J. Biol. Chem.* **2010**, *285*, 41533–41540. [[CrossRef](#)]
111. Garzon-Rodriguez, W.; Yatsimirsky, A.K.; Glabe, C.G. Binding of Zn(II), Cu(II), and Fe(II) Ions to Alzheimer's A β Peptide Studied by Fluorescence. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2243–2248. [[CrossRef](#)]
112. Atwood, C.S.; Scarpa, R.C.; Huang, X.; Moir, R.D.; Jones, W.D.; Fairlie, D.P.; Tanzi, R.E.; Bush, A.I. Characterization of Copper Interactions with Alzheimer Amyloid Beta Peptides: Identification of an Attomolar-Affinity Copper Binding Site on Amyloid Beta₁₋₄₂. *J. Neurochem.* **2000**, *75*, 1219–1233. [[CrossRef](#)] [[PubMed](#)]
113. Soragni, A.; Zambelli, B.; Mukrasch, M.D.; Biernat, J.; Jeganathan, S.; Griesinger, C.; Ciurli, S.; Mandelkow, E.; Zweckstetter, M. Structural Characterization of Binding of Cu(II) to Tau Protein. *Biochemistry* **2008**, *47*, 10841–10851. [[CrossRef](#)] [[PubMed](#)]
114. Bacchella, C.; Gentili, S.; Bellotti, D.; Quartieri, E.; Draghi, S.; Baratto, M.C.; Remelli, M.; Valensin, D.; Monzani, E.; Nicolis, S.; et al. Binding and Reactivity of Copper to R1 and R3 Fragments of Tau Protein. *Inorg. Chem.* **2020**, *59*, 274–286. [[CrossRef](#)] [[PubMed](#)]
115. D'Ambrosi, N.; Rossi, L. Copper at synapse: Release, binding and modulation of neurotransmission. *Neurochem. Int.* **2015**, *90*, 36–45. [[CrossRef](#)]
116. Hung, Y.H.; Bush, A.I.; Cherny, R.A. Copper in the Brain and Alzheimer's Disease. *JBIC J. Biol. Inorg. Chem.* **2010**, *15*, 61–76. [[CrossRef](#)]
117. Shankar, G.M.; Walsh, D.M. Alzheimer's Disease: Synaptic Dysfunction and A β . *Mol. Neurodegener.* **2009**, *4*, 48. [[CrossRef](#)]
118. Zhou, L.; McInnes, J.; Wierda, K.; Holt, M.; Herrmann, A.G.; Jackson, R.J.; Wang, Y.-C.; Swerts, J.; Beyens, J.; Miskiewicz, K.; et al. Tau Association with Synaptic Vesicles Causes Presynaptic Dysfunction. *Nat. Commun.* **2017**, *8*, 15295. [[CrossRef](#)]
119. Faller, P.; Hureau, C. Bioinorganic Chemistry of Copper and Zinc Ions Coordinated to Amyloid- β Peptide. *Dalton Trans.* **2009**, 1080–1094. [[CrossRef](#)]
120. Faller, P. Copper and Zinc Binding to Amyloid-Beta: Coordination, Dynamics, Aggregation, Reactivity and Metal-Ion Transfer. *ChemBiochem Eur. J. Chem. Biol.* **2009**, *10*, 2837–2845. [[CrossRef](#)]
121. Syme, C.D.; Nadal, R.C.; Rigby, S.E.J.; Viles, J.H. Copper Binding to the Amyloid-Beta (A β) Peptide Associated with Alzheimer's Disease: Folding, Coordination Geometry, pH Dependence, Stoichiometry, and Affinity of A β (1–28): Insights from a Range of Complementary Spectroscopic Techniques. *J. Biol. Chem.* **2004**, *279*, 18169–18177. [[CrossRef](#)]
122. Kowalik-Jankowska, T.; Ruta, M.; Wiśniewska, K.; Lankiewicz, L. Coordination Abilities of the 1–16 and 1–28 Fragments of Beta-Amyloid Peptide towards Copper(II) Ions: A Combined Potentiometric and Spectroscopic Study. *J. Inorg. Biochem.* **2003**, *95*, 270–282. [[CrossRef](#)]
123. Damante, C.A.; Ösz, K.; Nagy, Z.; Pappalardo, G.; Grasso, G.; Impellizzeri, G.; Rizzarelli, E.; Sóvágó, I. The Metal Loading Ability of β -Amyloid N-Terminus: A Combined Potentiometric and Spectroscopic Study of Copper(II) Complexes with β -Amyloid(1–16), Its Short or Mutated Peptide Fragments, and Its Polyethylene Glycol (PEG)-Ylated Analogue. *Inorg. Chem.* **2008**, *47*, 9669–9683. [[CrossRef](#)]
124. Natale, G.D.; Sinopoli, A.; Grenács, Á.; Sanna, D.; Sóvágó, I.; Pappalardo, G. Copper(II) Coordination Properties of the A β (1–16)₂ Peptidomimetic: Experimental Evidence of Intermolecular Macrochelate Complex Species in the A β Dimer. *New J. Chem.* **2016**, *40*, 10274–10284. [[CrossRef](#)]
125. Parthasarathy, S.; Long, F.; Miller, Y.; Xiao, Y.; McElheny, D.; Thurber, K.; Ma, B.; Nussinov, R.; Ishii, Y. Molecular-Level Examination of Cu²⁺ Binding Structure for Amyloid Fibrils of 40-Residue Alzheimer's β by Solid-State NMR Spectroscopy. *J. Am. Chem. Soc.* **2011**, *133*, 3390–3400. [[CrossRef](#)] [[PubMed](#)]
126. Damante, C.A.; Osz, K.; Nagy, Z.; Pappalardo, G.; Grasso, G.; Impellizzeri, G.; Rizzarelli, E.; Sóvágó, I. Metal Loading Capacity of A β N-Terminus: A Combined Potentiometric and Spectroscopic Study of Zinc(II) Complexes with A β (1–16), Its Short or Mutated Peptide Fragments and Its Polyethylene Glycol-Ylated Analogue. *Inorg. Chem.* **2009**, *48*, 10405–10415. [[CrossRef](#)] [[PubMed](#)]

127. Mithu, V.S.; Sarkar, B.; Bhowmik, D.; Chandrakesan, M.; Maiti, S.; Madhu, P.K. Zn(++) Binding Disrupts the Asp(23)-Lys(28) Salt Bridge without Altering the Hairpin-Shaped Cross- β Structure of A β (42) Amyloid Aggregates. *Biophys. J.* **2011**, *101*, 2825–2832. [[CrossRef](#)]
128. Damante, C.A.; Ósz, K.; Nagy, Z.; Grasso, G.; Pappalardo, G.; Rizzarelli, E.; Sóvágó, I. Zn²⁺'s Ability to Alter the Distribution of Cu²⁺ among the Available Binding Sites of A β (1-16)-Polyethyleneglycol-Ylated Peptide: Implications in Alzheimer's Disease. *Inorg. Chem.* **2011**, *50*, 5342–5350. [[CrossRef](#)]
129. Moreira, P.; Pereira, C.; Santos, M.S.; Oliveira, C. Effect of Zinc Ions on the Cytotoxicity Induced by the Amyloid β -Peptide. *Antioxid. Redox Signal.* **2000**, *2*, 317–325. [[CrossRef](#)]
130. Di Natale, G.; Bellia, F.; Sciacca, M.F.M.; Campagna, T.; Pappalardo, G. Tau-Peptide Fragments and Their Copper(II) Complexes: Effects on Amyloid- β Aggregation. *Inorganica Chim. Acta* **2018**, *472*, 82–92. [[CrossRef](#)]
131. Lukács, M.; Szunyog, G.; Grenács, A.; Lihi, N.; Kállay, C.; Di Natale, G.; Campagna, T.; Lanza, V.; Tabbi, G.; Pappalardo, G.; et al. Copper(II) Coordination Abilities of the N-Terminal Peptide Fragments of Tau Protein: A Combined Potentiometric, Spectroscopic and ESI-MS Study. *ChemPlusChem* **2019**, *84*, 1697–1708. [[CrossRef](#)]
132. Magri, A.; Di Natale, G.; Rizzarelli, E. Copper-Assisted Interaction between Amyloid- β and Prion: Ternary Metal Complexes with A β N-Terminus and Octarepeat. *Inorganica Chim. Acta* **2018**, *472*, 93–102. [[CrossRef](#)]
133. Di Natale, G.; Pappalardo, G.; Milardi, D.; Sciacca, M.F.M.; Attanasio, F.; La Mendola, D.; Rizzarelli, E. Membrane Interactions and Conformational Preferences of Human and Avian Prion N-Terminal Tandem Repeats: The Role of Copper(II) Ions, PH, and Membrane Mimicking Environments. *J. Phys. Chem. B* **2010**, *114*, 13830–13838. [[CrossRef](#)] [[PubMed](#)]
134. Ciccone, L.; Shi, C.; di Lorenzo, D.; Van Baelen, A.-C.; Tonalì, N. The Positive Side of the Alzheimer's Disease Amyloid Cross-Interactions: The Case of the A β 1-42 Peptide with Tau, TTR, CysC, and ApoA1. *Molecules* **2020**, *25*, 2439. [[CrossRef](#)] [[PubMed](#)]
135. Subedi, S.; Sasidharan, S.; Nag, N.; Saudagar, P.; Tripathi, T. Amyloid Cross-Seeding: Mechanism, Implication, and Inhibition. *Molecules* **2022**, *27*, 1776. [[CrossRef](#)] [[PubMed](#)]
136. Roda, A.R.; Serra-Mir, G.; Montoliu-Gaya, L.; Tiessler, L.; Villegas, S. Amyloid-Beta Peptide and Tau Protein Crosstalk in Alzheimer's Disease. *Neural Regen. Res.* **2022**, *17*, 1666.
137. Malafaia, D.; Albuquerque, H.M.T.; Silva, A.M.S. Amyloid- β and Tau Aggregation Dual-Inhibitors: A Synthetic and Structure-Activity Relationship Focused Review. *Eur. J. Med. Chem.* **2021**, *214*, 113209. [[CrossRef](#)]
138. Szalaj, N.; Godyń, J.; Jończyk, J.; Pasięka, A.; Panek, D.; Wichur, T.; Więckowski, K.; Zareba, P.; Bajda, M.; Pislár, A.; et al. Multidirectional In Vitro and in Cellulo Studies as a Tool for Identification of Multi-Target-Directed Ligands Aiming at Symptoms and Causes of Alzheimer's Disease. *J. Enzyme Inhib. Med. Chem.* **2020**, *35*, 1944. [[CrossRef](#)]
139. Lv, P.; Xia, C.-L.; Wang, N.; Liu, Z.-Q.; Huang, Z.-S.; Huang, S.-L. Synthesis and Evaluation of 1,2,3,4-Tetrahydro-1-Acridone Analogues as Potential Dual Inhibitors for Amyloid-Beta and Tau Aggregation. *Bioorg. Med. Chem.* **2018**, *26*, 4693–4705. [[CrossRef](#)]
140. Okuda, M.; Fujita, Y.; Hijikuro, I.; Wada, M.; Uemura, T.; Kobayashi, Y.; Waku, T.; Tanaka, N.; Nishimoto, T.; Izumi, Y.; et al. PE859, A Novel Curcumin Derivative, Inhibits Amyloid- β and Tau Aggregation, and Ameliorates Cognitive Dysfunction in Senescence-Accelerated Mouse Prone 8. *J. Alzheimers Dis. JAD* **2017**, *59*, 313–328. [[CrossRef](#)]
141. Sciacca, M.F.M.; Di Natale, G.; Milardi, D.; Pappalardo, G. Tau/A β Chimera Peptides: A Thioflavin-T and MALDI-TOF Study of A β Amyloidosis in the Presence of Cu(II) or Zn(II) Ions and Total Lipid Brain Extract (TLBE) Vesicles. *Chem. Phys. Lipids* **2021**, *237*, 105085. [[CrossRef](#)]
142. Guo, J.-P.; Arai, T.; Miklossy, J.; McGeer, P.L. A β and Tau Form Soluble Complexes That May Promote Self Aggregation of Both into the Insoluble Forms Observed in Alzheimer's Disease. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 1953–1958. [[CrossRef](#)] [[PubMed](#)]
143. Cuadros, R.; Pérez, M.; Ruiz-Gabarré, D.; Hernández, F.; García-Escudero, V.; Avila, J. Specific Peptide from the Novel W-Tau Isoform Inhibits Tau and Amyloid β Peptide Aggregation In Vitro. *ACS Chem. Neurosci.* **2022**, *13*, 1974–1978. [[CrossRef](#)] [[PubMed](#)]
144. Miller, Y.; Ma, B.; Nussinov, R. Synergistic Interactions between Repeats in Tau Protein and A β Amyloids May Be Responsible for Accelerated Aggregation via Polymorphic States. *Biochemistry* **2011**, *50*, 5172–5181. [[CrossRef](#)] [[PubMed](#)]
145. Tjernberg, L.O.; Callaway, D.J.E.; Tjernberg, A.; Hahne, S.; Lilliehöök, C.; Terenius, L.; Thyberg, J.; Nordstedt, C. A Molecular Model of Alzheimer Amyloid β -Peptide Fibril Formation. *J. Biol. Chem.* **1999**, *274*, 12619–12625. [[CrossRef](#)] [[PubMed](#)]
146. Bernstein, S.L.; Wyttenbach, T.; Baumketner, A.; Shea, J.-E.; Bitan, G.; Teplow, D.B.; Bowers, M.T. Amyloid Beta-Protein: Monomer Structure and Early Aggregation States of Abeta42 and Its Pro19 Alloform. *J. Am. Chem. Soc.* **2005**, *127*, 2075–2084. [[CrossRef](#)] [[PubMed](#)]
147. Marshall, K.E.; Vadukul, D.M.; Dahal, L.; Theisen, A.; Fowler, M.W.; Al-Hilaly, Y.; Ford, L.; Kemenes, G.; Day, I.J.; Staras, K.; et al. A Critical Role for the Self-Assembly of Amyloid-B1-42 in Neurodegeneration. *Sci. Rep.* **2016**, *6*, 30182. [[CrossRef](#)] [[PubMed](#)]
148. Tjernberg, L.O.; Näslund, J.; Lindqvist, F.; Johansson, J.; Karlström, A.R.; Thyberg, J.; Terenius, L.; Nordstedt, C. Arrest of Beta-Amyloid Fibril Formation by a Pentapeptide Ligand. *J. Biol. Chem.* **1996**, *271*, 8545–8548. [[CrossRef](#)]
149. Soto, C.; Kindy, M.S.; Baumann, M.; Frangione, B. Inhibition of Alzheimer's Amyloidosis by Peptides That Prevent Beta-Sheet Conformation. *Biochem. Biophys. Res. Commun.* **1996**, *226*, 672–680. [[CrossRef](#)]
150. Funke, S.A.; Willbold, D. Peptides for Therapy and Diagnosis of Alzheimer's Disease. *Curr. Pharm. Des.* **2012**, *18*, 755–767. [[CrossRef](#)]

151. Gordon, D.J.; Sciarretta, K.L.; Meredith, S.C. Inhibition of β -Amyloid(40) Fibrillogenesis and Disassembly of β -Amyloid(40) Fibrils by Short β -Amyloid Congeners Containing N-Methyl Amino Acids at Alternate Residues. *Biochemistry* **2001**, *40*, 8237–8245. [[CrossRef](#)]
152. Soto, P.; Griffin, M.A.; Shea, J.-E. New Insights into the Mechanism of Alzheimer Amyloid- β Fibrillogenesis Inhibition by N-Methylated Peptides. *Biophys. J.* **2007**, *93*, 3015–3025. [[CrossRef](#)]
153. Kokkoni, N.; Stott, K.; Amijee, H.; Mason, J.M.; Doig, A.J. N-Methylated Peptide Inhibitors of β -Amyloid Aggregation and Toxicity. Optimization of the Inhibitor Structure. *Biochemistry* **2006**, *45*, 9906–9918. [[CrossRef](#)] [[PubMed](#)]
154. Bett, C.K.; Serem, W.K.; Fontenot, K.R.; Hammer, R.P.; Garno, J.C. Effects of Peptides Derived from Terminal Modifications of the A β Central Hydrophobic Core on A β Fibrillization. *ACS Chem. Neurosci.* **2010**, *1*, 661–678. [[CrossRef](#)]
155. Pallitto, M.M.; Ghanta, J.; Heinzelman, P.; Kiessling, L.L.; Murphy, R.M. Recognition Sequence Design for Peptidyl Modulators of β -Amyloid Aggregation and Toxicity. *Biochemistry* **1999**, *38*, 3570–3578. [[CrossRef](#)] [[PubMed](#)]
156. Austen, B.M.; Paleologou, K.E.; Ali, S.A.E.; Qureshi, M.M.; Allsop, D.; El-Agnaf, O.M.A. Designing Peptide Inhibitors for Oligomerization and Toxicity of Alzheimer's β -Amyloid Peptide. *Biochemistry* **2008**, *47*, 1984–1992. [[CrossRef](#)] [[PubMed](#)]
157. Chafekar, S.M.; Malda, H.; Merckx, M.; Meijer, E.W.; Viertl, D.; Lashuel, H.A.; Baas, F.; Scheper, W. Branched KLVFF Tetramers Strongly Potentiate Inhibition of β -Amyloid Aggregation. *ChemBioChem* **2007**, *8*, 1857–1864. [[CrossRef](#)]
158. Zhang, G.; Leibowitz, M.J.; Sinko, P.J.; Stein, S. Multiple-Peptide Conjugates for Binding Beta-Amyloid Plaques of Alzheimer's Disease. *Bioconjug. Chem.* **2003**, *14*, 86–92. [[CrossRef](#)]
159. Kino, R.; Araya, T.; Arai, T.; Sohma, Y.; Kanai, M. Covalent Modifier-Type Aggregation Inhibitor of Amyloid- β Based on a Cyclo-KLVFF Motif. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 2972–2975. [[CrossRef](#)]
160. Arai, T.; Sasaki, D.; Araya, T.; Sato, T.; Sohma, Y.; Kanai, M. A Cyclic KLVFF-Derived Peptide Aggregation Inhibitor Induces the Formation of Less-Toxic off-Pathway Amyloid- β Oligomers. *Chembiochem Eur. J. Chem. Biol.* **2014**, *15*, 2577–2583. [[CrossRef](#)]
161. Villari, V.; Tosto, R.; Natale, G.D.; Sinopoli, A.; Tomasello, M.F.; Lazzaro, S.; Micali, N.; Pappalardo, G. A Metalloporphyrin-Peptide Conjugate as an Effective Inhibitor of Amyloid- β Peptide Fibrillation and Cytotoxicity. *ChemistrySelect* **2017**, *2*, 9122–9129. [[CrossRef](#)]
162. Rocha, S.; Cardoso, I.; Börner, H.; Pereira, M.C.; Saraiva, M.J.; Coelho, M. Design and Biological Activity of β -Sheet Breaker Peptide Conjugates. *Biochem. Biophys. Res. Commun.* **2009**, *380*, 397–401. [[CrossRef](#)]
163. Giordano, C.; Sansone, A.; Masi, A.; Masci, A.; Mosca, L.; Chiaraluce, R.; Pasquo, A.; Consalvi, V. Inhibition of Amyloid Peptide Fragment A β 25–35 Fibrillogenesis and Toxicity by N-Terminal β -Amino Acid-Containing Esapeptides: Is Taurine Moiety Essential for In Vivo Effects? *Chem. Biol. Drug Des.* **2012**, *79*, 30–37. [[CrossRef](#)]
164. Adessi, C.; Frossard, M.-J.; Boissard, C.; Fraga, S.; Bieler, S.; Ruckle, T.; Vilbois, F.; Robinson, S.M.; Mutter, M.; Banks, W.A.; et al. Pharmacological Profiles of Peptide Drug Candidates for the Treatment of Alzheimer's Disease. *J. Biol. Chem.* **2003**, *278*, 13905–13911. [[CrossRef](#)]
165. Bona, P.D.; Giuffrida, M.L.; Caraci, F.; Copani, A.; Pignataro, B.; Attanasio, F.; Cataldo, S.; Pappalardo, G.; Rizzarelli, E. Design and Synthesis of New Trehalose-Conjugated Pentapeptides as Inhibitors of A β (1–42) Fibrillogenesis and Toxicity. *J. Pept. Sci.* **2009**, *15*, 220–228. [[CrossRef](#)] [[PubMed](#)]
166. Sinopoli, A.; Giuffrida, A.; Tomasello, M.F.; Giuffrida, M.L.; Leone, M.; Attanasio, F.; Caraci, F.; De Bona, P.; Naletova, I.; Saviano, M.; et al. Ac-LPFFD-Th: A Trehalose-Conjugated Peptidomimetic as a Strong Suppressor of Amyloid- β Oligomer Formation and Cytotoxicity. *ChemBioChem* **2016**, *17*, 1541–1549. [[CrossRef](#)] [[PubMed](#)]
167. Attanasio, F.; Cascio, C.; Fisichella, S.; Nicoletti, V.G.; Pignataro, B.; Savarino, A.; Rizzarelli, E. Trehalose Effects on α -Crystallin Aggregates. *Biochem. Biophys. Res. Commun.* **2007**, *354*, 899–905. [[CrossRef](#)] [[PubMed](#)]
168. Gorantla, N.V.; Sunny, L.P.; Rajasekhar, K.; Nagaraju, P.G.; Cg, P.P.; Govindaraju, T.; Chinnathambi, S. Amyloid- β -Derived Peptidomimetics Inhibits Tau Aggregation. *ACS Omega* **2021**, *6*, 11131–11138. [[CrossRef](#)]
169. Griner, S.L.; Seidler, P.; Bowler, J.; Murray, K.A.; Yang, T.P.; Sahay, S.; Sawaya, M.R.; Cascio, D.; Rodriguez, J.A.; Philipp, S.; et al. Structure-Based Inhibitors of Amyloid Beta Core Suggest a Common Interface with Tau. *eLife* **2019**, *8*, e46924. [[CrossRef](#)] [[PubMed](#)]
170. Richman, M.; Wilk, S.; Chemerovski, M.; Wärmländer, S.K.T.S.; Wahlström, A.; Gräslund, A.; Rahimipour, S. In Vitro and Mechanistic Studies of an Antiamyloidogenic Self-Assembled Cyclic d,l- α -Peptide Architecture. *J. Am. Chem. Soc.* **2013**, *135*, 3474–3484. [[CrossRef](#)] [[PubMed](#)]
171. Belostozky, A.; Richman, M.; Lisniansky, E.; Tovchychrechko, A.; Chill, J.H.; Rahimipour, S. Inhibition of Tau-Derived Hexapeptide Aggregation and Toxicity by a Self-Assembled Cyclic D,L- α -Peptide Conformational Inhibitor. *Chem. Commun.* **2018**, *54*, 5980–5983. [[CrossRef](#)]
172. Aggidis, A.; Chatterjee, S.; Townsend, D.; Fullwood, N.J.; Ortega, E.R.; Tarutani, A.; Hasegawa, M.; Lucas, H.; Mudher, A.; Allsop, D. Peptide-Based Inhibitors of Tau Aggregation as a Potential Therapeutic for Alzheimer's Disease and Other Tauopathies. *bioRxiv* **2021**, preprint. [[CrossRef](#)]
173. Shamloo, A.; Asadbegi, M.; Khandan, V.; Amanzadi, A. Designing a New Multifunctional Peptide for Metal Chelation and A β Inhibition. *Arch. Biochem. Biophys.* **2018**, *653*, 1–9. [[CrossRef](#)] [[PubMed](#)]
174. Tripathi, T.; Khan, H. Direct Interaction between the β -Amyloid Core and Tau Facilitates Cross-Seeding: A Novel Target for Therapeutic Intervention. *Biochemistry* **2020**, *59*, 341–342. [[CrossRef](#)]

175. Yamada, K. Extracellular Tau and Its Potential Role in the Propagation of Tau Pathology. *Front. Neurosci.* **2017**, *11*, 667. [[CrossRef](#)] [[PubMed](#)]
176. Lewis, J.; Dickson, D.W.; Lin, W.-L.; Chisholm, L.; Corral, A.; Jones, G.; Yen, S.-H.; Sahara, N.; Skipper, L.; Yager, D.; et al. Enhanced Neurofibrillary Degeneration in Transgenic Mice Expressing Mutant Tau and APP. *Science* **2001**, *293*, 1487–1491. [[CrossRef](#)]
177. Seidler, P.M.; Boyer, D.R.; Rodriguez, J.A.; Sawaya, M.R.; Cascio, D.; Murray, K.; Gonen, T.; Eisenberg, D.S. Structure-Based Inhibitors of Tau Aggregation. *Nat. Chem.* **2018**, *10*, 170–176. [[CrossRef](#)] [[PubMed](#)]
178. Doğanyığıt, Z.; Erbakan, K.; Akyuz, E.; Polat, A.K.; Arulsamy, A.; Shaikh, M.F. The Role of Neuroinflammatory Mediators in the Pathogenesis of Traumatic Brain Injury: A Narrative Review. *ACS Chem. Neurosci.* **2022**, *13*, 1835–1848. [[CrossRef](#)]
179. Majewski, J.; Jones, E.M.; Vander Zanden, C.M.; Biernat, J.; Mandelkow, E.; Chi, E.Y. Lipid Membrane Templated Misfolding and Self-Assembly of Intrinsically Disordered Tau Protein. *Sci. Rep.* **2020**, *10*, 13324. [[CrossRef](#)]