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Tau Acts as a Mediator for Alzheimer's Disease-Related Synaptic Deficits

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Abstract

The two histopathological hallmarks of Alzheimer's disease (AD) are amyloid plaques containing multiple forms of A β and neurofibrillary tangles containing phosphorylated tau proteins. As mild cognitive impairment frequently occurs long before the clinical diagnosis of Alzheimer's disease, the scientific community has been increasingly interested in the roles of A β and tau in earlier cellular changes that lead to functional deficits. Therefore, great progress has recently been made in understanding how A β or tau causes synaptic dysfunction. However, the interaction between the A β and tau-initiated intracellular cascades that lead to synaptic dysfunction remains elusive. The cornerstone of the two decade-old hypothetical amyloid cascade model is that amyloid pathologies precede tau pathologies. Although the premise of A β -tau pathway remains valid, the model keeps evolving as new signaling events are discovered that lead to functional deficits and neurodegeneration. Recent progress has been made in understanding A β -PrP^C-Fyn-mediated neurotoxicity and synaptic deficits. Although still elusive, many novel upstream and downstream signaling molecules have been found to modulate tau mislocalization and tau hyperphosphorylation. Here we will discuss the mechanistic interactions between A β -PrP^C-mediated neurotoxicity and tau-mediated synaptic deficits in an updated amyloid cascade model with calcium and tau as the central mediators.

Keywords

Alzheimer's disease; amyloid cascade hypothesis; soluble proteins; dendritic spines; synaptic dysfunction; A β ₁₋₄₂ oligomers; amyloid beta; tau; Alzheimer's disease mouse models; Alzheimer

Introduction

Alzheimer's disease (AD) was first described by Alois Alzheimer more than a century ago (Alzheimer, 1907), the disease is characterized by progressive memory loss and inability to form new memories. AD is thought to be responsible for 50–60% of dementia cases (Blennow *et al.*, 2006); in fact, there are currently more than 25 million individuals living with AD worldwide (Alzheimer's Association, www.alz.org). Even though cures for AD and

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related dementias have not yet been identified our understanding of the disease process has expanded greatly since the time of Alois Alzheimer. This review will examine the recent discoveries that reveal how soluble forms of A β and tau proteins lead to synaptic deficits.

Shifting Winds: Plaques and tangles give way to soluble A β and tau

The brains from AD patients contain amyloid plaques and neurofibrillary tangles, which are considered the two pathological hallmarks of AD; this pathology was initially thought to be responsible for neurotoxicity in AD patients (Alzheimer, 1907; Blennow *et al.*, 2006). Nearly three decades ago, amyloid β -peptide (A β) was discovered to be the main component of neuritic plaques (Masters *et al.*, 1985) and the product of proteolytic cleavage of the amyloid- β precursor protein (APP) (Haass *et al.*, 1992). Humans with AD related mutations in APP, presenilin (affecting production of A β) or APOE (affecting clearance of A β) have been correlated with cognitive deficits (Blennow *et al.*, 2006). Soon after A β was found to be the primary component of plaques, the microtubule-associated protein tau in its hyperphosphorylated state was discovered to be the chief component of neurofibrillary tangles (Grundke-Iqbal *et al.*, 1986; Nukina & Ihara, 1986).

Initial research into AD focused on the neuritic plaques and neurofibrillary tangles found at later time points in the disease. Much has been learned about these hallmarks of AD pathology, but the focus of the research community has shifted towards understanding the disease at earlier stages (Selkoe, 2002; Ashe & Zahs, 2010; Crimins *et al.*, 2013). This is due to findings that have indicated that AD has a long preclinical phase preceding cell death and brought the relationship between plaques, tangles, and neurotoxicity into question. In AD the number of neurofibrillary tangles, but not neuritic plaques, has been positively correlated with the severity of dementia (Arriagada *et al.*, 1992). A β plaques are found in 40% of elderly adults who have not been clinically diagnosed with dementia (Hulette *et al.*, 1998). Further inquiry has confirmed that many aged persons who do not have dementia and who are aging “normally” show AD pathology (Bennett *et al.*, 2006; Price *et al.*, 2009). Neurofibrillary tangles do not correlate well with neural death as dying neurons often don't contain tangles (Gómez-Isla *et al.*, 1997; Andorfer *et al.*, 2005; Spire *et al.*, 2006). Additionally, the novel mutation APP_{E693 Δ} causes dementia and synaptic deficits without the accumulation of neuritic plaques (Tomiya *et al.*, 2010). Evidence from AD transgenic mice with increased A β levels indicates that cognitive deficits develop before plaques form, if they form at all (Westerman *et al.*, 2002; Lesné *et al.*, 2006). Multiple studies have demonstrated that soluble tau, rather than insoluble tau found in neurofibrillary tangles, is responsible for neurotoxic effects (Santacruz *et al.*, 2005; Oddo *et al.*, 2006). These results downplay the importance of plaques and tangles in AD progression, directing the attention of researchers towards earlier time points in the disease and soluble species of A β and tau.

Of Mice and Men: Pushing AD researchers towards the synapse

The creation of transgenic mouse models of AD has advanced the study of the disease, but has lead to new questions as well. These transgenic mice show significant increases in A β levels and undergo neuritic plaque formation. However, the degree of widespread neuronal loss is marginal even at ages when behavioral deficits are detected indicating that synaptic dysfunction, not cell death, causes these early behavioral deficits (Games *et al.*, 1995; Hsiao *et al.*, 1996; Bondolfi *et al.*, 2002; Zahs & Ashe, 2010; Rupp *et al.*, 2011). A number of groups researching AD have investigated synaptic changes in the hippocampus, a brain area highly associated with memory. Widespread synapse loss has long been identified in the brain tissue of dementia patients, often via the imaging of the presynaptic terminal marker synaptophysin (Gonatas *et al.*, 1967; Davies *et al.*, 1987; Masliah *et al.*, 1989; Heinonen *et al.*, 1995; Arendt, 2009). In fact, synapse loss has a stronger correlation with cognitive

decline than plaque or tangle load in humans with dementia (Davies *et al.*, 1987; Masliah *et al.*, 1989; DeKosky & Scheff, 1990; Terry *et al.*, 1991; Sze *et al.*, 1997; Selkoe, 2002). Loss of synapses has also been identified in multiple AD mouse models as early as 2 months of age (Mucke *et al.*, 2000; Lanz *et al.*, 2003; Hsieh *et al.*, 2006; Perez-Cruz *et al.*, 2011). Baseline synaptic properties (AMPA and NMDA glutamate receptor currents) are altered in AD transgenic mice 3 weeks of age and older (Hsia *et al.*, 1999; Kamenetz *et al.*, 2003; Hsieh *et al.*, 2006; Roberson *et al.*, 2011). At 8 months of age many AD transgenic mice also develop a deficiency in long term potentiation (LTP, a well-developed theory of memory in which synapses are strengthened by a battery of activity) (Chapman *et al.*, 1999; Gureviciene *et al.*, 2004; Malenka & Bear, 2004). The research using AD transgenic mice shows that synapses can be affected at early time points in the disease progression, before profound neuronal loss is observed, suggesting that these changes may be related to the development of dementia.

In AD transgenic mice, synaptic deficits oftentimes do not correlate with A β plaque formation, however, deficits often do coincide with elevations in soluble A β peptides (McLean *et al.*, 1999; Näslund *et al.*, 2000; Selkoe, 2002; Oddo *et al.*, 2003; Sheng *et al.*, 2012). Furthermore, genetic mutations correlated with AD in humans are associated with an increase in the levels of A β or an increase in the proportion of A β ₁₋₄₂ to A β ₁₋₄₀ (two common truncations of the protein found in humans) (Tanzi & Bertram, 2005; Blennow *et al.*, 2006). Recently, research has shifted to understanding the effect of A β ₁₋₄₂ on synapses and the findings have reframed the amyloid hypothesis to focus upon soluble A β oligomers (also more descriptively referred to as A β -derived diffusible ligands or A β micro-aggregates), rather than neuritic plaques (Haass & Selkoe, 2007; Krafft & Klein, 2010; Sheng *et al.*, 2012). One such soluble A β oligomer, A β *56 has been shown to cause cognitive deficits in mice (Lesné *et al.*, 2006; Cheng *et al.*, 2007). Numerous studies have shown that soluble A β oligomers cause the collapse of spines in hippocampal cell- and brain slice-cultures after 5–15 days of treatment (Hsieh *et al.*, 2006; Shrestha *et al.*, 2006; Lacor *et al.*, 2007; Shankar *et al.*, 2007; 2008). Electrophysiological and immunocytochemical studies have shown that treatment with soluble A β oligomers leads to deficits in both AMPA and NMDA glutamate receptor signaling and expression at the synapse (Chen *et al.*, 2002; Snyder *et al.*, 2005; Hsieh *et al.*, 2006; Shankar *et al.*, 2007; Zhao *et al.*, 2010). The recapitulation of synaptic changes found in AD transgenic mice by the treatment of cultured neurons with soluble A β oligomers validates the hypothesis that soluble A β oligomers are responsible for these changes. In our two recent studies, A β oligomers induce effects that are similar to those caused by the expression of mutant P301L tau proteins, suggesting that A β and tau may share a common signaling pathway (Figure 1).

Revisiting Amyloid Cascade Hypothesis: A β as the trigger and tau as the mediator

Proposed in 1991, the amyloid cascade hypothesis attempted to explain the mechanistic interaction between amyloid and tau pathologies (Hardy & Allsop, 1991). In its original form the amyloid cascade hypothesis laid down the corner stone of the popular model: A β $\rightarrow$ tau $\rightarrow$ neuronal damage (Figure 2A). In its second version, abnormal increase in intracellular calcium was added as a central piece (Hardy & Higgins, 1992; Figure 2B). Aberrant cleavage of APP or a mutation of APP leads to increased deposition of A β . From this point A β increases intracellular calcium levels; the hypothesis states that this loss of calcium homeostasis causes two distinct effects: 1) the hyperphosphorylation of tau, resulting in neurofibrillary tangles and 2) neurodegeneration (Hardy & Higgins, 1992). A later revision have incorporated synaptic deficits into this cascade (Hardy & Selkoe, 2002), proposing that tau hyperphosphorylation is an effect secondary to synaptic deficits and

cellular injuries (Figure 2C). In our recent study, A β -induced synaptic deficits were blocked by the expression of AP (a phosphorylation blocking mutation) tau (Miller *et al.*, 2014), clearly placing tau phosphorylation before synaptic dysfunction. Therefore, we propose a revision to the amyloid cascade hypothesis in Figure 2D, framing tau hyperphosphorylation as a cellular event between A β triggering and final synaptic deficits.

Clinicians seeking to develop treatments for AD have focused on A β interventions due to years of research indicating that A β mediates AD pathogenesis (Hardy & Selkoe, 2002; Tanzi & Bertram, 2005). Unfortunately, the results of drug trials that target A β have not yielded substantive results (Gilman *et al.*, 2005; Green *et al.*, 2009). This fact has led researchers to broaden the range of proteins targeted, one such protein is tau (Golde *et al.*, 2010). A growing body of literature now implicates tau as both necessary and sufficient to drive cognitive impairment in AD mouse models and ostensibly AD in humans. When a P301L mutant tau transgene is turned off for a period of time mice recover from the cognitive deficits found while the transgene is active, indicating the necessity of the mutant tau for deficits (Santacruz *et al.*, 2005). The pathology found in transgenic tau mice is exacerbated by increased A β levels (Götz *et al.*, 2001; Lewis *et al.*, 2001; Bolmont *et al.*, 2007). In the 3xTg-AD mouse expressing the APP_{Swe}, tau_{P301L}, and PS1_{M146V} transgenes, A β pathology is detected before tau pathology suggesting the possibility of a causal relationship between the two protein (Oddo *et al.*, 2003; Santacruz *et al.*, 2005). In this mouse severe cognitive deficit are not observed until tau pathology is detected (Oddo *et al.*, 2004; Billings *et al.*, 2005). Interestingly, cognitive deficits in 3xTg-AD are only mitigated when both A β and tau, not A β alone, are reduced via immunotherapy (Oddo *et al.*, 2006). Furthermore, reduction of tau in an AD mouse expressing human APP prevented cognitive deficits without affecting elevated A β plaque levels (Roberson *et al.*, 2007). Still more evidence of the mediatory role of tau has also been found in humans: the presence of neurofibrillary tangles is a strong indicator of the whether A β pathology is correlated to cognitive deficits (Bennett *et al.*, 2004).

Tau protein binds to microtubules and plays a role in cytoskeletal development and regulation in neurons; the protein's phosphorylation state is controlled by kinases and phosphates such as GSK3 β and PP1 respectively (Buée *et al.*, 2000; Avila *et al.*, 2004). Pathology outside of neuritic plaques and neurofibrillary tangles, e.g. Lewy bodies and vascular infarctions, has been found in many patients with clinical AD diagnoses – it is estimated that between 1/3–1/2 of AD patients have a mixed pathology (Kovacs *et al.*, 2008). Furthermore, patients with mixed pathology have a much higher chance of experiencing dementia than those who exhibit pathology consistent with only one disease (Langa *et al.*, 2004; Fotuhi *et al.*, 2009; Schneider, 2009). Interestingly, alterations in tau are found in a number of other neurodegenerative diseases. Tau inclusions and hyperphosphorylation are also found in frontotemporal dementia, corticobasal degeneration, Pick's disease, and other dementias (Buée *et al.*, 2000; Avila *et al.*, 2004). Tau hyperphosphorylation has also been implicated in Parkinson's disease; many Parkinson's patients experience dementia in addition to motor disturbances (Ishizawa *et al.*, 2003; Aarsland *et al.*, 2008; Reichmann, *et al.*, 2009; Svenningsson *et al.*, 2012). The ubiquitous role of tau in multiple neurodegenerative disorders clearly supports the central role of tau in the cellular cascades that lead to dementia.

The above multiple lines of research all emphasize the role of tau as a downstream mediator of A β -induced dementia, supporting the cornerstone of amyloid cascade: the A β -tau-neuronal damage pathway (see reviews by Reitz, 2012; Zahs & Ashe, 2013). However, consistent with mainstream thought at that time, the initial form of amyloid cascade argued for the central roles of insoluble deposits of A β and tau (Hardy & Allsop, 1991). Although it is still controversial which species of A β and tau are the main culprits for dementia in AD

(see reviews by Karran *et al.*, 2011; Wischik *et al.*, 2013; Zahs & Ashe, 2013), as discussed earlier recent studies favor the roles of soluble species of A β and tau over its insoluble deposits in AD progression. Curiously, interstitial tau proteins have also been shown to affect the A β -tau cascade although the cellular mechanism remains to be determined (Yamada *et al.*, 2011). Therefore, the first and second forms of amyloid cascade hypothesis may need some modifications even though the central premise that A β initiates the cellular events leading to dementia remains valid.

As synaptic deficits attracted greater attention in the field of AD research, a revised version of amyloid cascade was proposed (Hardy & Selkoe, 2002). The updated hypothetical cascade placed progressive synaptic and neuritic injuries before tau pathologies (Figure 2C). However, due to our evolving understanding of the roles that tau plays in AD pathogenesis, the temporal sequence of A β initiation, synaptic deficits, tau hyperphosphorylation, tangle formation and neuronal death is still being debated (Morris *et al.*, 2011). Our recent studies indicate that tau mediates early synaptic deficits before overt neurodegeneration and formation of tau tangles (Hoover *et al.*, 2010). Furthermore, A β oligomer-induced synaptic deficits are blocked in cultured neurons expressing AP (phosphorylation blocking) tau; this tau construct may act as a dominant negative modulator, blocking the mislocalization of endogenous tau (Miller *et al.*, 2014). In both of our studies, AMPA receptor-mediated excitatory synaptic responses were impaired when the density of dendritic spines had not yet been altered and no significant neuronal loss had yet occurred. Therefore, at least some elements of synaptic deficits such as loss of postsynaptic AMPA receptors are mediated by tau hyperphosphorylation at a very early stage of the disease, putting tau before synaptic deficits in our revised cascade (Figure 2D)

Calcium and tau serve as the central pieces of multiple signaling loops in the entangled A β -tau cascade

One of the biggest challenges to the amyloid cascade hypothesis comes from studies using AD mouse models. Many transgenic mice that specifically overproduce A β proteins do not demonstrate robust tau pathologies such as tau tangles or severe neuronal loss (Games *et al.*, 1995; Hsiao *et al.*, 1996; Sturchler-Pierrat *et al.*, 1997; Holcomb *et al.*, 1998; Mucke *et al.*, 2000; Jankowsky *et al.*, 2001). Additional tau, presenilin or other human transgenes are needed to produce the full spectrum of the AD hallmarks including amyloid plaques, neurofibrillary tangles, chronic inflammation and neuronal loss in transgenic animals (Oddo *et al.*, 2003; Padmanabhan *et al.*, 2006; Colton *et al.*, 2008; Wilcock *et al.*, 2008; Cohen *et al.*, 2013). Another big challenge for the amyloid cascade hypothesis comes from recent clinical trials (see review by Yoshiyama *et al.*, 2013). A β removal, reduction of A β production and active immunization with A β have shown limited efficacy and do not prevent tau pathology or neurodegeneration (Holmes *et al.*, 2008; Green *et al.*, 2009).

To address these challenges, many competing hypotheses have been proposed, including the inflammation hypothesis (see review by McGeer & McGeer 2013), mitochondrial cascade hypothesis (see review by Swerdlow *et al.*, 2010), capillary dysfunction hypothesis (see review by Østergaard *et al.*, 2013) and cholesterol hypothesis (see review by Castello & Soriano 2013). However, the competing hypotheses often propose distinct parallel signaling pathways that directly or indirectly interact with the core A β -tau signaling pathway. Therefore, the central premise of classical amyloid cascade remains valid. To the present, there are at least four parallel signaling pathways that affect intracellular calcium and tau, which subsequently lead to neuronal death, loss of dendritic spines and loss of AMPA receptors (Figure 3). If inflammation, mitochondrial dysfunction, vascular impairment or abnormal cholesterol affects any one of these parallel pathways, they will induce or facilitate the pathological progression of AD.

In the classical amyloid cascade pathway (Figure 3 Pathway 1, red arrows; see reviews by Karran *et al.*, 2011 and Yoshiyama *et al.*, 2013), toxic A β oligomers increase the phosphorylation of tau by activating protein kinases GSK3 β , CDK5 and ERK; the phosphorylated tau or other toxic tau species may activate multiple cellular events, which eventually lead to synaptic dysfunction and neuronal degeneration (see review by Morris *et al.*, 2011). In addition to increasing the production of A β by modulating r-secretase activity, changes in presenilin may also cause lysosome acidification, ER stress and intracellular calcium dysregulation, which subsequently lead to neuronal death, presynaptic dysfunction and deficits in synaptic plasticity (Figure 3 Pathway 2, blue arrows; Ho & Shen, 2011; Shen, 2013; McBrayer & Nixon, 2013; Endres & Reinhardt, 2013; Fonseca *et al.*, 2013). Many recent studies have emphasized the manifold roles of ER stress in multiple neurodegenerative diseases (see review by Endres & Reinhardt, 2013). In a landmark paper, cellular prion protein (PrP^C) has been identified as a receptor for A β -oligomers and is required for A β -induced inhibition of long-term potentiation (Laurén *et al.*, 2009). Subsequent studies reveal that mGluR5 bridges the association between PrP^C and Fyn, allowing the A β -PrP^C complex to activate Fyn and NMDA receptors, increasing intracellular calcium and inducing synaptic deficits (Figure 3 Pathway 3, purple arrows; Um *et al.*, 2013; Um & Strittmatter, 2013; Larson *et al.*, 2012). Changes in calcium can cause tau hyperphosphorylation by activating calpain and CDK5 (Shukla *et al.*, 2012; Nikkel *et al.*, 2012). By playing a retrograde permissive role, tau hyperphosphorylation in turn allows the A β -PrP^C-Fyn complex to impair postsynaptic function by bringing Fyn to dendritic spines during tau mislocalization; the activated Fyn subsequently increases NMDA receptor activity and enhances A β -mediated neurotoxicity (Figure 3 Pathway 4, dark green arrows; Ittner *et al.*, 2010). Both Pathways 3 and 4 in Figure 3 lead to overt loss of dendritic spines, suggesting that neurotoxicity is already underway at this point. However, our studies indicate that tau mislocalization may induce calcineurin-dependent loss of AMPA receptors before spine loss at a very early stage of the disease through a different parallel mechanism (Figure 3 Pathway 5, orange arrows).

Tau mislocalization to dendritic spines

Some researchers have proposed that the tau-mediated synaptic deficits are presynaptic as tau is typically localized to the axon. Deficits in axonal transport caused by the treatment of cultured neurons with soluble A β oligomers are dependent on the presence of tau (Vossel *et al.*, 2010); however, even a three-fold increase in cellular tau is not sufficient to cause decreases in axonal transport rate implying that tau works in concert with other factor to cause presynaptic deficits (Yuan *et al.*, 2013). A recent line of evidence suggests that tauopathies may originate postsynaptically. Tau is normally found in a gradient along the length of neurons with the highest concentrations of tau found in the axonal compartment of healthy neurons, but mutations in tau or overexpression of human tau cause the gradient to reverse and result in the mislocalization of tau to the somatodendritic compartment (Papasozomenos & Binder, 1987; Götz *et al.*, 1995; Spittaels *et al.*, 1999; Kins *et al.*, 2001; Brandt *et al.*, 2005; Gendron & Petrucelli, 2009). Many models of neurodegeneration demonstrate this pathogenic reversal of the tau protein gradient. A truncation of tau that prevents dendritic tau localization was found to prevent cognitive deficits in an AD transgenic mice without affecting increased A β levels (Ittner *et al.*, 2010). Further research has demonstrated that soluble A β oligomers cause mislocalization of tau to dendrites and that only neurons demonstrating mislocalization display decreased spine density (Zempel *et al.*, 2010).

As a further step, our group has shown that the P301L model of tauopathy demonstrates tau mislocalization not just to the dendritic compartment, but to dendritic spines as well and that this mislocalization is tau-phosphorylation dependent (Hoover *et al.*, 2010). In our

accompanying publication, we extend these findings to a model of AD, showing that A β oligomers cause a similar mislocalization of tau to dendritic spines (Figure 4) (Miller *et al.*, 2014). By blocking tau phosphorylation we were able to inhibit the mislocalization of tau to dendritic spines and restored A β oligomer induced decreases in AMPA glutamate receptor signaling (Miller *et al.*, 2014). This new study provides new evidence of tau as a mediator between A β initiation and final synaptic dysfunction.

Proposed upstream mechanisms of tau mislocalization: GSK3 β and other kinases

Dendritic spines are highly dynamic structures that process the majority of excitatory neurotransmission in the brain (Cingolani & Goda, 2008; Patterson & Yasuda, 2011). Various forms of plasticity, including the most studied forms of LTP result from signaling that occurs in spines (Malenka & Bear, 2004; Matsuzaki *et al.*, 2004; Lee *et al.*, 2009). The signaling that occurs in spines is highly compartmentalized due to long, thin necks that connect the bulbous head of the spine to the dendrite and the variety of protein to protein interactions that occur in spines (Byrne *et al.*, 2011). If tau can become mislocalized to the spine it can interact with the myriad of signaling pathways that control functional and structural plasticity. We will first discuss possible upstream mechanisms that could cause tau to enter spines (Figure 5). Phosphorylation has been shown to be necessary for the entry of tau into dendritic spines and for synaptic deficits; conversely, mutation of those same 14 sites to mimic phosphorylation causes mislocalization to spines and is sufficient to cause synaptic deficits (Hoover *et al.*, 2010). Recent findings indicate that those phosphorylation sites are also necessary for soluble A β oligomers to induce tau mislocalization to dendritic spines, impairing synaptic function (Miller *et al.*, 2014). Therefore, any cellular events that lead to tau hyperphosphorylation may cause tau mislocalization to dendritic spines, impairing synaptic function.

Hyperphosphorylation of tau has been found in tissue from humans with AD and other diseases that demonstrate tau pathology (Grundke-Iqbal *et al.*, 1986; Buée *et al.*, 2000; Avila *et al.*, 2004; Wang *et al.*, 2013). The presence of hyperphosphorylated tau in human CSF has been shown to predict future AD in patients with mild cognitive impairment (Buerger *et al.*, 2005; Hampel *et al.*, 2005; Hansson *et al.*, 2006). These phenomena have been recapitulated in mouse models of AD and tauopathy, often at time points prior to the presence of neurofibrillary tangles (Mucke *et al.*, 2000; Santacruz *et al.*, 2005; Boekhoorn *et al.*, 2006; Schindowski *et al.*, 2006; Roberson *et al.*, 2007; De Felice *et al.*, 2008). Recent evidence has shown that tau hyperphosphorylation is prevalent in the PS1 Δ 9/APP_{Swe} mouse model of AD (Cohen *et al.*, 2013). Using phosphatases to decrease tau phosphorylation has been shown to recover its physiological function (Wang *et al.*, 1996). Tau phosphorylation has been correlated with detrimental effects at synapses in both AD and tauopathy transgenic mice (Steinhilb *et al.*, 2007; Bittner *et al.*, 2010; Hoover *et al.*, 2010; Zempel *et al.*, 2010).

Glycogen synthase kinase-3 (GSK3; especially the isoform GSK3 β) and cyclin dependent kinase 5 (CDK5) are the two most widely-studied protein kinases that phosphorylate tau (reducing its binding affinity to microtubules) although other kinases can phosphorylate tau including PKA, CaMKII, CK1 and ERK (Lovestone *et al.*, 1994; Wagner *et al.*, 1996; Wang *et al.*, 2013; Yoshiyama *et al.*, 2013). Importantly, activation of GSK3 β also increases the production of A β peptides (Ly *et al.*, 2013; Phiel *et al.*, 2003). The dual roles of GSK3 β make its inhibitors strong drug candidates for AD therapy (Yoshiyama *et al.*, 2013; Figure 3, red arrows). There is compelling evidence that GSK3 is highly involved in the abnormal phosphorylation of tau in diseased states (Bhat *et al.*, 2011). GSK3 activity is stimulated by exposure of cultured cells to A β and tau has been shown to be hyperphosphorylated via this pathway (Takashima *et al.*, 1996; Wang *et al.*, 1998; Amadoro *et al.*, 2011). Indeed,

pharmacological inhibition of GSK3 rescues cells from death in AD mice, and A β induced reelin deregulation causes an increase of GSK3 dependent tau phosphorylation (Cuchillo-Ibáñez *et al.*, 2013; Noh *et al.*, 2013). Inhibition of GSK3 blocks the induction of LTD but not LTP or depotentiation although it remains unclear whether tau phosphorylation is involved (Fitzjohn *et al.*, 2008). Proteins involved in other neurodegenerative diseases, including α -synuclein may play a role in promoting the phosphorylation of tau by GSK3, suggesting that this effect may not be specific to AD (Haggerty *et al.*, 2011; Kawakami *et al.*, 2011; Irwin *et al.*, 2013). The upstream causative factors of GSK3 β -mediated tau phosphorylation remain elusive. Receptors for advanced glycation endproducts (RAGEs) have been proposed to activate GSK3 β and aggravate A β -induced cognitive deficits (Li *et al.*, 2012; Chen *et al.*, 2013; Figure 3 Pathway 1). These findings implicate GSK3 as a likely candidate to carry out the hyperphosphorylation of tau found in AD and other neurodegenerative diseases, supporting our hypothetical model in Figure 5.

Several lines of evidence suggest that either A β or tau pathology may result from the misfolding of one or both of the proteins in a prion-like manner (Nussbaum *et al.*, 2013; Zahs & Ashe, 2013). Some researchers have posited that the aggregation of A β that is the initial pathogenic step in the amyloid cascade hypothesis is due to prion-like misfolding (Eisele, 2013). Our research does not address whether A β aggregates are formed through seeding by other misfolded A β peptides, we do have evidence that this effect does not apply to tau phosphorylation induced mislocalization. Unpublished data from our lab indicates that seeding is not involved in tau mislocalization to dendritic spines. We cultured hippocampal neurons from tau^{p301L} mice and then transfected the neurons with wild-type tau tagged with GFP. Wild-type tau did not mislocalize to dendritic spines, even though the neurons also expressed P301L tau (Figure 4C–D).

Several steps in the pathway between A β oligomers and tau-mislocalization are currently unknown. It is well established that there is a mismatch between tau and amyloid beta pathology in patients with AD (Delacourte *et al.*, 2002; van Helmond *et al.*, 2010;). One possible mechanism by which this mismatch may arise is through a signaling pathway whereby A β initiates dysfunction through cell surface receptors on the axons of neurons, resulting in a dendritic (postsynaptic) effect by tau (Figure 5A). A β probable receptor for A β oligomers is PrP^C (Larson & Lesne, 2012; Figure 3 Pathway 3, purple arrows). Furthermore, the precise phosphorylation sites necessary for tau mislocalization and tau-mediated synaptic dysfunction have not been worked out in detail.

Proposed downstream mechanisms: dual roles of tau mislocalization

Our recent study provides a direct link from tau hyperphosphorylation and mislocalization to A β induced synaptic dysfunction (Miller *et al.*, 2014). However, the signaling events occurring between tau mislocalization and synaptic dysfunction remain unknown (Figure 5D). One candidate is calcineurin (aka PP2B), a phosphatase that has been implicated in long-term depression (LTD), which is a weakening of synapses. Calcineurin plays an important role in AMPA glutamate receptor dynamics and spine loss via dephosphorylation of AMPA glutamate receptors (Mulkey *et al.*, 1994; Dell'Acqua *et al.*, 2006; Miller *et al.*, 2012). The similarities between LTD and synaptic deficits associated with AD are notable (Hsieh *et al.*, 2006; Sheng *et al.*, 2012). A correlation between changes in calcineurin activity, A β levels, and cognitive decline in humans was recently discovered (Abdul *et al.*, 2009). Inhibition of calcineurin has been found to ameliorate cognitive deficits and/or neuropathology in AD transgenic mice (Dineley *et al.*, 2007; Taglialetela *et al.*, 2009). Calcineurin has also been implicated in loss of synaptic glutamate receptors in an AD transgenic mice (Wu *et al.*, 2010) and a number of studies using soluble A β oligomers to induce synaptic deficits (Chen *et al.*, 2002; Snyder *et al.*, 2005; Hsieh *et al.*, 2006; Shankar

et al., 2007). Our recent study has shown a correlation between the mislocalization of tau to dendritic spines and the necessity of calcineurin for soluble A β oligomer-induced decreases in AMPA receptor signaling (Miller *et al.*, 2014). A large gap in our understanding of calcineurin's role in AD is the process of its activation. Calcineurin is activated by small increases in the concentration of Ca²⁺. In the case of LTD, low frequency stimulation is sufficient to cause activation of calcineurin and deficits (Dell'Acqua *et al.*, 2006). The role of calcium in AD has been well studied over the years (Green, 2009). Increases of Ca²⁺ and abnormal Ca²⁺ homeostasis due to a disruption of spine calcium compartmentalization in the diseased state have been reported (Kuchibhotla *et al.*, 2008; Wu *et al.*, 2010; Zempel *et al.*, 2010). The NMDA glutamate receptor, a prominent site of Ca²⁺ entry at the synapse, has been implicated in synaptic deficits caused by soluble A β oligomers (Kamenetz *et al.*, 2003; Shankar *et al.*, 2007; Decker *et al.*, 2010; Wu *et al.*, 2010; Li *et al.*, 2011; Kessels *et al.*, 2013). Research indicates that loss of NMDA glutamate receptors can be initiated by increased A β levels (Kamenetz *et al.*, 2003; Snyder *et al.*, 2005; Hsieh *et al.*, 2006; Shankar *et al.*, 2007) and tau mislocalization due to tau mutation (Hoover *et al.*, 2010). Although these results implicate NMDA glutamate receptors in AD, a recent article has suggested that their Ca²⁺-related activity is not necessary for synaptic deficits (Kessels *et al.*, 2013). Calcium dysregulation may also lead to ER and mitochondrial stress, which may initiate various cell death pathways (Fonseca *et al.*, 2013). Other studies hold that increases in intracellular calcium may lead to increases in the presence of A β species due to interaction with APP cleavage, resulting in positive feedback as A β causes more calcium dysregulation (Zeiger *et al.*, 2013).

A variety of other proteins and signaling pathways have been implicated in the synaptic deficits caused by A β . Caspase-3 plays an important role in apoptosis pathways and is elevated in humans with AD (Gervais *et al.*, 1999; Stadelmann *et al.*, 1999). Originally researchers thought that its activity was simply related to cell death found in AD, but recent research has associated caspase-3 with synaptic plasticity in AD. Caspase-3 activity is increased in the dendritic spines of A β transgenic mice and is associated with causing calcineurin-dependent synaptic deficits independently of cell death (D'Amelio *et al.*, 2011). Genetic knockout or inhibition of caspase-3 rescues cognitive and synaptic deficits in an AD model (D'Amelio *et al.*, 2011) and LTP deficits caused by soluble A β oligomers (Jo *et al.*, 2011). This cell death pathway may be mediated by calcium dysregulation due to ER stress resulting in the activation mitochondrial cell death pathways (Endres & Reinhardt, 2013; Fonseca *et al.*, 2013).

Fyn, AMPK and Spastin have been implicated in synaptic deficits found in AD (Ittner *et al.*, 2010; Mairet-Coello *et al.*, 2013; Zempel *et al.*, 2013; Laurén, 2014). In contrast to our studies of tau mutations and A β oligomers, the activation of the aforementioned pathways causes significant loss of dendritic spines. Furthermore, in the study by Ittner *et al.*, PSD95-binding NMDA receptors are increased whereas, in our experimental system, synaptic clustering of NMDA receptors is reduced (Hoover *et al.*, 2010). As illustrated in Figure 3, tau may play dual roles in progressive impairment of synaptic function throughout the long process of AD development. Initially, tau acts in a provocative role, at a very early disease stage, impairing synaptic function directly by causing the loss of glutamate receptors (Hoover *et al.*, 2010). Later in the disease progression, tau takes a permissive role: the abnormal trafficking of tau to dendritic spines may bring Fyn to the spines allowing A β -PrP^C-mediated neurotoxicity to occur (Ittner *et al.*, 2010).

Conclusion

Our understanding of Alzheimer's disease has advanced greatly over the last two decades as the research focus has been shifted from descriptive pathological investigation to functional

and mechanistic studies. Recent studies have emphasized the importance of detecting early functional deficits in AD, the roles of soluble A β oligomers and cellular mechanisms underlying synaptic deficits. Through coordinated efforts by scientists in diverse fields, a consensus has begun to emerge in the support of the concept that A β initiates the onset of AD while tau mediates the subsequent functional deficits at an early stage of the disease. The phosphorylation-dependent mislocalization of tau to the dendritic compartment and to dendritic spines of neurons may play a dual role. At a very early stage, it may directly suppress postsynaptic transmission by inducing calcineurin-mediated AMPA receptor internalization. At a later stage, the missorted tau may bring Fyn to spines, enhancing NMDA receptor activity and allowing A β -PrP^C-mediated neurotoxicity to occur. Interventions focused on abrogating tau mislocalization and hyperphosphorylation in AD may be a more effective strategy for the treatment of AD than present strategies targeting A β oligomers as tau-centered treatments may inhibit multiple parallel pathways that lead to neuronal loss and synaptic deficits long after A β initiation of the toxic cascade.

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Abbreviations

AD	Alzheimer's disease
APP	amyloid precursor protein
Aβ	amyloid beta
GSK3β	glycogen synthase kinase 3 beta
LTD	long-term depression
LTP	long-term potentiation
PS1	presenilin-1
TgNg	transgenic negative

References

- Aarsland D, Beyer MK, Kurz MW. Dementia in Parkinson's disease. *Current Opinion in Neurology*. 2008; 21:676–682. [PubMed: 18989112]
- Abdul HM, Sama MA, Furman JL, Mathis DM, Beckett TL, Weidner AM, Patel ES, Baig I, Murphy MP, LeVine H, Kraner SD, Norris CM. Cognitive decline in Alzheimer's disease is associated with selective changes in calcineurin/NFAT signaling. *Journal of Neuroscience*. 2009; 29:12957–12969. [PubMed: 19828810]
- Alzheimer A. Über eine eigenartige Erkrankung der Hirnrinde. *Allgemeine Zeitschrift Psychiatrie*. 1907; 64:146–148.
- Amadoro G, Corsetti V, Ciotti MT, Florenzano F, Capsoni S, Amato G, Calissano P. Endogenous A β causes cell death via early tau hyperphosphorylation. *Neurobiology of Aging*. 2011; 32:969–990. [PubMed: 19628305]
- Andorfer C, Acker CM, Kress Y, Hof PR, Duff K, Davies P. Cell-cycle reentry and cell death in transgenic mice expressing nonmutant human tau isoforms. *Journal of Neuroscience*. 2005; 25:5446–5454. [PubMed: 15930395]

- Arendt T. Synaptic degeneration in Alzheimer's disease. *Acta Neuropathol.* 2009; 118:167–179. [PubMed: 19390859]
- Arriagada PV, Growdon JH, Hedley-Whyte ET, Hyman BT. Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. *Neurology.* 1992; 42:631–631. [PubMed: 1549228]
- Ashe KH, Zahs KR. Probing the biology of Alzheimer's disease in mice. *Neuron.* 2010; 66:631–645. [PubMed: 20547123]
- Avila J, Lucas JJ, Perez M, Hernandez F. Role of tau protein in both physiological and pathological conditions. *Physiological Reviews.* 2004; 84:361–384. [PubMed: 15044677]
- Bennett DA, Schneider JA, Arvanitakis Z, Kelly JF, Aggarwal NT, Shah RC, Wilson RS. Neuropathology of older persons without cognitive impairment from two community-based studies. *Neurology.* 2006; 66:1837–1844. [PubMed: 16801647]
- Bennett DA, Schneider JA, Wilson RS, Bienias JL, Arnold SE. Neurofibrillary tangles mediate the association of amyloid load with clinical Alzheimer disease and level of cognitive function. *Arch. Neurol.* 2004; 61:378–384. [PubMed: 15023815]
- Bhat RV, Budd Haerberlein SL, Avila J. Glycogen synthase kinase 3: a drug target for CNS therapies. *J Neurochem.* 2004; 89:1313–1317. [PubMed: 15189333]
- Billings LM, Oddo S, Green KN, McGaugh JL, LaFerla FM. Intraneuronal A β causes the onset of early Alzheimer's disease-related cognitive deficits in transgenic mice. *Neuron.* 2005; 45:675–688. [PubMed: 15748844]
- Bittner T, Fuhrmann M, Burgold S, Ochs SM, Hoffmann N, Mitteregger G, Kretzschmar H, LaFerla FM, Herms J. Multiple Events Lead to Dendritic Spine Loss in Triple Transgenic Alzheimer's Disease Mice. *PLoS ONE.* 2010; 5:e15477. [PubMed: 21103384]
- Blennow K, de Leon MJ, Zetterberg H. Alzheimer's disease. *Lancet.* 2006; 368:387–403. [PubMed: 16876668]
- Boekhoorn K, Terwel D, Biemans B, Borghgraef P, Wiegert O, Ramakers GJA, de Vos K, Krugers H, Tomiyama T, Mori H, Joels M, Van Leuven F, Lucassen PJ. Improved long-term potentiation and memory in young tau-P301L transgenic mice before onset of hyperphosphorylation and tauopathy. *Journal of Neuroscience.* 2006; 26:3514–3523. [PubMed: 16571759]
- Bolmont T, Clavaguera F, Meyer-Luehmann M, Herzig MC, Radde R, Staufenbiel M, Lewis J, Hutton M, Tolnay M, Jucker M. Induction of tau pathology by intracerebral infusion of amyloid-beta - containing brain extract and by amyloid-beta deposition in APP $\times$ Tau transgenic mice. *Am. J. Pathol.* 2007; 171:2012–2020. [PubMed: 18055549]
- Bondolfi L, Calhoun M, Ermini F, Kuhn HG, Wiederhold K-H, Walker L, Staufenbiel M, Jucker M. Amyloid-associated neuron loss and gliogenesis in the neocortex of amyloid precursor protein transgenic mice. *Journal of Neuroscience.* 2002; 22:515–522. [PubMed: 11784797]
- Brandt R, Hundelt M, Shahani N. Tau alteration and neuronal degeneration in tauopathies: mechanisms and models. *Biochim. Biophys. Acta.* 2005; 1739:331–354. [PubMed: 15615650]
- Buerger K, Ewers M, Andreasen N, Zinkowski R, Ishiguro K, Vanmechelen E, Teipel SJ, Graz C, Blennow K, Hampel H. Phosphorylated tau predicts rate of cognitive decline in MCI subjects: a comparative CSF study. *Neurology.* 2005; 65:1502–1503. [PubMed: 16275849]
- Buée L, Bussire T, Bue-Scherrer V, Delacourte A, Hof PR. Tau protein isoforms, phosphorylation and role in neurodegenerative disorders. *Brain Res. Brain Res. Rev.* 2000; 33:95–130. [PubMed: 10967355]
- Busche MA, Eichhoff G, Adelsberger H, Abramowski D, Wiederhold KH, Haass C, Staufenbiel M, Konnerth A, Garaschuk O. Clusters of hyperactive neurons near amyloid plaques in a mouse model of Alzheimer's disease. *Science.* 2008; 321:1686–1689. [PubMed: 18802001]
- Byrne MJ, Waxham MN, Kubota Y. The impacts of geometry and binding on CaMKII diffusion and retention in dendritic spines. *J Comput Neurosci.* 2011; 31:1–12. [PubMed: 21104309]
- Castello MA, Soriano S. Rational heterodoxy: cholesterol reformation of the amyloid doctrine. *Ageing Res Rev.* 2013; 12:282–288. [PubMed: 22771381]
- Chapman PF, White GL, Jones MW, Cooper-Blacketer D, Marshall VJ, Irizarry M, Younkin L, Good MA, Bliss TV, Hyman BT, Younkin SG, Hsiao KK. Impaired synaptic plasticity and learning in

- aged amyloid precursor protein transgenic mice. *Nat Neurosci.* 1999; 2:271–276. [PubMed: 10195221]
- Chen C, Li XH, Tu Y, Sun HT, Liang HQ, Cheng SX, Zhang S. A β -AGE aggravates cognitive deficit in rats via RAGE pathway. *Neuroscience.* 2013; 257:1–10. [PubMed: 24188791]
- Chen Q-S, Wei W-Z, Shimahara T, Xie C-W. Alzheimer amyloid beta-peptide inhibits the late phase of long-term potentiation through calcineurin-dependent mechanisms in the hippocampal dentate gyrus. *Neurobiol Learn Mem.* 2002; 77:354–371. [PubMed: 11991763]
- Cheng IH, Searce-Levie K, Legleiter J, Palop JJ, Gerstein H, Bien-Ly N, Puoliväli J, Lesné S, Ashe KH, Muchowski PJ, Mucke L. Accelerating amyloid-beta fibrillization reduces oligomer levels and functional deficits in Alzheimer disease mouse models. *J. Biol. Chem.* 2007; 282:23818–23828. [PubMed: 17548355]
- Cingolani LA, Goda Y. Actin in action: the interplay between the actin cytoskeleton and synaptic efficacy. *Nat Rev Neurosci.* 2008; 9:344–356. [PubMed: 18425089]
- Cohen RM, Rezai-Zadeh K, Weitz TM, Rentsendorj A, Gate D, Spivak I, Bholat Y, Vasilevko V, Glabe CG, Breunig JJ, Rakic P, Davtayan H, Agadjanyan MG, Kepe V, Barrio JR, Bannykh S, Szekely CA, Pechnick RN, Town T. A transgenic Alzheimer rat with plaques, tau pathology, behavioral impairment, oligomeric A β , and frank neuronal loss. *Journal of Neuroscience.* 2013; 33:6245–6256. [PubMed: 23575824]
- Crimins JL, Pooler A, Polydoro M, Luebke JJ, Spires-Jones TL. The intersection of amyloid beta and tau in glutamatergic synaptic dysfunction and collapse in Alzheimer's disease. *Ageing Research Reviews.* 2013
- Citron M, Westaway D, Xia W, Carlson G, Diehl T, Levesque G, Johnson-Wood K, Lee M, Seubert P, Davis A, Kholodenko D, Motter R, Sherrington R, Perry B, Yao H, Strome R, Lieberburg I, Rommens J, Kim S, Schenk D, Fraser P, St George Hyslop P, Selkoe DJ. Mutant presenilins of Alzheimer's disease increase production of 42-residue amyloid β -protein in both transfected cells and transgenic mice. *Nat Med.* 1997; 3:67–72. [PubMed: 8986743]
- Cuchillo-Ibáñez I, Balmaceda V, Botella-López A, Rabano A, Avila J, Sáez-Valero J. Beta-amyloid impairs reelin signaling. *PLoS ONE.* 2013; 8:e72297. [PubMed: 23951306]
- D'Amelio M, Cavallucci V, Middei S, Marchetti C, Pacioni S, Ferri A, Diamantini A, De Zio D, Carrara P, Battistini L, Moreno S, Bacci A, Ammassari-Teule M, Marie H, Cecconi F. Caspase-3 triggers early synaptic dysfunction in a mouse model of Alzheimer's disease. *Nature Publishing Group.* 2011; 14:69–76.
- Davies CA, Mann DM, Sumpter PQ, Yates PO. A quantitative morphometric analysis of the neuronal and synaptic content of the frontal and temporal cortex in patients with Alzheimer's disease. *J. Neurol. Sci.* 1987; 78:151–164. [PubMed: 3572454]
- De Felice FG, Wu D, Lambert MP, Fernandez SJ, Velasco PT, Lacor PN, Bigio EH, Jerecic J, Acton PJ, Shughrue PJ, Chen-Dodson E, Kinney GG, Klein WL. Alzheimer's disease-type neuronal tau hyperphosphorylation induced by A beta oligomers. *Neurobiology of Aging.* 2008; 29:1334–1347. [PubMed: 17403556]
- Decker H, Jürgensen S, Adrover MF, Brito-Moreira J, Bomfim TR, Klein WL, Epstein AL, De Felice FG, Jerusalinsky D, Ferreira ST. N-methyl-D-aspartate receptors are required for synaptic targeting of Alzheimer's toxic amyloid- β peptide oligomers. *J Neurochem.* 2010; 115:1520–1529. [PubMed: 20950339]
- DeKosky ST, Scheff SW. Synapse loss in frontal cortex biopsies in Alzheimer's disease: correlation with cognitive severity. *Ann. Neurol.* 1990; 27:457–464. [PubMed: 2360787]
- Delacourte A, Sergeant N, Champaign D, Wattez A, Maurage C-A, Lebert F, Pasquier F, David J-P. Nonoverlapping but synergetic tau and APP pathologies in sporadic Alzheimer's disease. *Neurology.* 2002; 59:398–407. [PubMed: 12177374]
- Dell'Acqua ML, Smith KE, Gorski JA, Horne EA, Gibson ES, Gomez LL. Regulation of neuronal PKA signaling through AKAP targeting dynamics. *Eur. J. Cell Biol.* 2006; 85:627–633. [PubMed: 16504338]
- DeStrooper B, Saftig P, Craessaerts K, Vanderstichele H, Guhde G, Annaert W, von Figura K, Van Leuven F. Deficiency of presenilin-1 inhibits the normal cleavage. *Nature.* 1998; 391:387–390. [PubMed: 9450754]

- Dineley KT, Hogan D, Zhang W-R, Taglialatela G. Acute inhibition of calcineurin restores associative learning and memory in Tg2576 APP transgenic mice. *Neurobiol Learn Mem.* 2007; 88:217–224. [PubMed: 17521929]
- Eisele YS. From soluble $\text{A}\beta$ to progressive $\text{A}\beta$ aggregation: could prion-like templated misfolding play a role? *Brain Pathol.* 2013; 23:333–341. [PubMed: 23587139]
- Endres K, Reinhardt S. ER-stress in Alzheimer's disease: turning the scale? *Am J Neurodegener Dis.* 2013; 2:247–265. [PubMed: 24319643]
- Fitzjohn SM, Doherty AJ, Collingridge GL. The use of the hippocampal slice preparation in the study of Alzheimer's disease. *Eur. J. Pharmacol.* 2008; 585:50–59. [PubMed: 18423442]
- Fonseca ACRG, Ferreira E, Oliveira CR, Cardoso SM, Pereira CF. Activation of the endoplasmic reticulum stress response by the amyloid-beta 1–40 peptide in brain endothelial cells. *Biochim. Biophys. Acta.* 2013
- Fotuhi M, Hachinski V, Whitehouse PJ. Changing perspectives regarding late-life dementia. *Nat Rev Neurol.* 2009; 5:649–658. [PubMed: 19918254]
- Games D, Adams D, Alessandrini R, Barbour R, Berthelette P, Blackwell C, Carr T, Clemens J, Donaldson T, Gillespie F. Alzheimer-type neuropathology in transgenic mice overexpressing V717F beta-amyloid precursor protein. *Nature.* 1995; 373:523–527. [PubMed: 7845465]
- Gendron TF, Petrucelli L. The role of tau in neurodegeneration. *Mol Neurodegener.* 2009; 4:13. [PubMed: 19284597]
- Gervais FG, Xu D, Robertson GS, Vaillancourt JP, Zhu Y, Huang J, LeBlanc A, Smith D, Rigby M, Shearman MS, Clarke EE, Zheng H, Van Der Ploeg LH, Ruffolo SC, Thornberry NA, Xanthoudakis S, Zamboni RJ, Roy S, Nicholson DW. Involvement of caspases in proteolytic cleavage of Alzheimer's amyloid-beta precursor protein and amyloidogenic A beta peptide formation. *Cell.* 1999; 97:395–406. [PubMed: 10319819]
- Gilman S, Koller M, Black RS, Jenkins L, Griffith SG, Fox NC, Eisner L, Kirby L, Rovira MB, Forette F, Orgogozo J-M, AN1792(QS-21)-201 Study Team. Clinical effects of Abeta immunization (AN1792) in patients with AD in an interrupted trial. *Neurology.* 2005; 64:1553–1562. [PubMed: 15883316]
- Golde TE, Petrucelli L, Lewis J. Targeting Abeta and tau in Alzheimer's disease, an early interim report. *Experimental Neurology.* 2010; 223:252–266. [PubMed: 19716367]
- Gonatas NK, Anderson W, Evangelista I. The contribution of altered synapses in the senile plaque: an electron microscopic study in Alzheimer's dementia. *J. Neuropathol. Exp. Neurol.* 1967; 26:25–39. [PubMed: 6022163]
- Gómez-Isla T, Hollister R, West H, Mui S, Growdon JH, Petersen RC, Parisi JE, Hyman BT. Neuronal loss correlates with but exceeds neurofibrillary tangles in Alzheimer's disease. *Ann. Neurol.* 1997; 41:17–24. [PubMed: 9005861]
- Götz J, Chen F, van Dorpe J, Nitsch RM. Formation of neurofibrillary tangles in P301 tau transgenic mice induced by Abeta 42 fibrils. *Science.* 2001; 293:1491–1495. [PubMed: 11520988]
- Götz J, Probst A, Spillantini MG, Schäfer T, Jakes R, Bürki K, Goedert M. Somatodendritic localization and hyperphosphorylation of tau protein in transgenic mice expressing the longest human brain tau isoform. *EMBO J.* 1995; 14:1304–1313. [PubMed: 7729409]
- Green KN. Calcium in the initiation, progression and as an effector of Alzheimer's disease pathology. *J. Cell. Mol. Med.* 2009; 13:2787–2799. [PubMed: 19650832]
- Green RC, Schneider LS, Amato DA, Beelen AP, Wilcock G, Swabb EA, Zavitz KH, Tarenflurbil Phase 3 Study Group. Effect of tarenflurbil on cognitive decline and activities of daily living in patients with mild Alzheimer disease: a randomized controlled trial. *JAMA.* 2009; 302:2557–2564. [PubMed: 20009055]
- Grundke-Iqbal I, Iqbal K, Tung YC, Quinlan M, Wisniewski HM, Binder LI. Abnormal phosphorylation of the microtubule-associated protein tau (tau) in Alzheimer cytoskeletal pathology. *Proc. Natl. Acad. Sci. U.S.A.* 1986; 83:4913–4917. [PubMed: 3088567]
- Gureviciene I, Ikonen S, Gurevicius K, Sarkaki A, van Groen T, Pussinen R, Ylinen A, Tanila H. Normal induction but accelerated decay of LTP in APP + PS1 transgenic mice. *Neurobiology of Disease.* 2004; 15:188–195. [PubMed: 15006688]

- Haass C, Selkoe DJ. Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid beta-peptide. *Nat. Rev. Mol. Cell Biol.* 2007; 8:101–112. [PubMed: 17245412]
- Haass C, Schlossmacher MG, Hung AY, Vigo-Pelfrey C, Mellon A, Ostaszewski BL, Lieberburg I, Koo EH, Schenk D, Teplow DB. Amyloid beta-peptide is produced by cultured cells during normal metabolism. *Nature.* 1992; 359:322–325. [PubMed: 1383826]
- Haggerty T, Credle J, Rodriguez O, Wills J, Oaks AW, Masliah E, Sidhu A. Hyperphosphorylated Tau in an α -synuclein-overexpressing transgenic model of Parkinson's disease. *European Journal of Neuroscience.* 2011; 33:1598–1610. [PubMed: 21453448]
- Hampel H, Bürger K, Pruessner JC, Zinkowski R, DeBernardis J, Kerkman D, Leinsinger G, Evans AC, Davies P, Möller H-J, Teipel SJ. Correlation of cerebrospinal fluid levels of tau protein phosphorylated at threonine 231 with rates of hippocampal atrophy in Alzheimer disease. *Arch. Neurol.* 2005; 62:770–773. [PubMed: 15883264]
- Hansson O, Zetterberg H, Buchhave P, Londos E, Blennow K, Minthon L. Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study. *Lancet Neurol.* 2006; 5:228–234. [PubMed: 16488378]
- Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science.* 2002; 297:353–356. [PubMed: 12130773]
- Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. *Science.* 1992; 256:184–185. [PubMed: 1566067]
- Heinonen O, Soininen H, Sorvari H, Kosunen O, Paljärvi L, Koivisto E, Riekkinen PJ. Loss of synaptophysin-like immunoreactivity in the hippocampal formation is an early phenomenon in Alzheimer's disease. *Neuroscience.* 1995; 64:375–384. [PubMed: 7700527]
- Herman D, Mezler M, Muller MK, Wicke K, Gross G, Draguhn A, Bruehl C, Nimmrich V. Synthetic A β oligomers (A β (1–42) globulomer) modulate presynaptic calcium currents: prevention of A β -induced synaptic deficits by calcium channel blockers. *European Journal of Pharmacology.* 2013; 702:44–55. [PubMed: 23376566]
- Ho A, Shen J. Presenilins in synaptic function and disease. *Trends Mol Med.* 2011; 17:617–624. [PubMed: 21795114]
- Holmes C, Boche D, Wilkinson D, Yadegarfar G, Hopkins V, Bayer A, Jones RW, Bullock R, Love S, Neal JW, Zotova E, Nicoll JA. Long-term effects of Abeta42 immunisation in Alzheimer's disease: follow-up of a randomised, placebocontrolled phase I trial. *Lancet.* 2008; 372:216–223. [PubMed: 18640458]
- Hoover BR, Reed MN, Su J, Penrod RD, Kotilinek LA, Grant MK, Pitstick R, Carlson GA, Lanier LM, Yuan L-L, Ashe KH, Liao D. Tau Mislocalization to Dendritic Spines Mediates Synaptic Dysfunction Independently of Neurodegeneration. *Neuron.* 2010; 68:1067–1081. [PubMed: 21172610]
- Hsia AY, Masliah E, McConlogue L, Yu GQ, Tatsuno G, Hu K, Kholodenko D, Malenka RC, Nicoll RA, Mucke L. Plaque-independent disruption of neural circuits in Alzheimer's disease mouse models. *Proc. Natl. Acad. Sci. U.S.A.* 1999; 96:3228–3233. [PubMed: 10077666]
- Hsiao K, Chapman P, Nilsen S, Eckman C, Harigaya Y, Younkin S, Yang F, Cole G. Correlative memory deficits, Abeta elevation, and amyloid plaques in transgenic mice. *Science.* 1996; 274:99–102. [PubMed: 8810256]
- Hsieh H, Boehm J, Sato C, Iwatsubo T, Tomita T, Sisodia S, Malinow R. AMPAR removal underlies Abeta-induced synaptic depression and dendritic spine loss. *Neuron.* 2006; 52:831–843. [PubMed: 17145504]
- Huang JK, Ma PL, Ji SY, Zhao XL, Tan JX, Sun XJ, Huang FD. Age-dependent alterations in the presynaptic active zone in a *Drosophila* model of Alzheimer's disease. *Neurobiology of Disease.* 2013; 51:161–167. [PubMed: 23149068]
- Hulette CM, Welsh-Bohmer KA, Murray MG, Saunders AM, Mash DC, McIntyre LM. Neuropathological and Neuropsychological Changes in “Normal” Aging: Evidence for Preclinical Alzheimer Disease in Cognitively Normal Individuals. *J. Neuropathol. Exp. Neurol.* 1998; 57:1168. [PubMed: 9862640]
- Irwin DJ, Lee VMY, Trojanowski JQ. Parkinson's disease dementia: convergence of α -synuclein, tau and amyloid- β pathologies. *Nat Rev Neurosci.* 2013; 14:626–636. [PubMed: 23900411]

- Ishizawa T, Mattila P, Davies P, Wang D, Dickson DW. Colocalization of tau and alpha-synuclein epitopes in Lewy bodies. *J. Neuropathol. Exp. Neurol.* 2003; 62:389–397. [PubMed: 12722831]
- Ittner LM, Ke YD, Delerue F, Bi M, Gladbach A, van Eersel J, Wölfling H, Chieng BC, Christie MJ, Napier IA, Eckert A, Staufenbiel M, Hardeman E, Götz J. Dendritic function of tau mediates amyloid-beta toxicity in Alzheimer's disease mouse models. *Cell.* 2010; 142:387–397. [PubMed: 20655099]
- Jo J, Whitcomb DJ, Olsen KM, Kerrigan TL, Lo S-C, Bru-Mercier G, Dickinson B, Scullion S, Sheng M, Collingridge G, Cho K. A β (1-42) inhibition of LTP is mediated by a signaling pathway involving caspase-3, Akt1 and GSK-3 β . *Nature Publishing Group.* 2011; 14:545–547.
- Kamenetz F, Tomita T, Hsieh H, Seabrook G, Borchelt D, Iwatsubo T, Sisodia S, Malinow R. APP processing and synaptic function. *Neuron.* 2003; 37:925–937. [PubMed: 12670422]
- Karran E, Mercken M, De Strooper B. The amyloid cascade hypothesis for Alzheimer's disease: an appraisal for the development of therapeutics. *Nat Rev Drug Discov.* 2011; 10:698–712. [PubMed: 21852788]
- Kawakami F, Suzuki M, Shimada N, Kagiya G, Ohta E, Tamura K, Maruyama H, Ichikawa T. Stimulatory effect of α -synuclein on the tau-phosphorylation by GSK-3 β . *FEBS J.* 2011; 278:4895–4904. [PubMed: 21985244]
- Kessels HW, Nabavi S, Malinow R. Metabotropic NMDA receptor function is required for β -amyloid-induced synaptic depression. *Proc. Natl. Acad. Sci. U.S.A.* 2013; 110:4033–4038. [PubMed: 23431156]
- Kins S, Cramer A, Evans DR, Hemmings BA, Nitsch RM, Götz J. Reduced protein phosphatase 2A activity induces hyperphosphorylation and altered compartmentalization of tau in transgenic mice. *J. Biol. Chem.* 2001; 276:38193–38200. [PubMed: 11473109]
- Kovacs GG, Alafuzoff I, Al-Sarraj S, Arzberger T, Bogdanovic N, Capellari S, Ferrer I, Gelpi E, Kövari V, Kretschmar H, Nagy Z, Parchi P, Seilhean D, Soininen H, Troakes C, Budka H. Mixed brain pathologies in dementia: the BrainNet Europe consortium experience. *Dement Geriatr Cogn Disord.* 2008; 26:343–350. [PubMed: 18849605]
- Krafft GA, Klein WL. ADDLs and the signaling web that leads to Alzheimer's disease. *Neuropharmacology.* 2010; 59:230–242. [PubMed: 20650286]
- Kuchibhotla KV, Goldman ST, Lattarulo CR, Wu H-Y, Hyman BT, Bacskai BJ. Abeta plaques lead to aberrant regulation of calcium homeostasis in vivo resulting in structural and functional disruption of neuronal networks. *Neuron.* 2008; 59:214–225. [PubMed: 18667150]
- Lacor PN, Buniel MC, Furlow PW, Clemente AS, Velasco PT, Wood M, Viola KL, Klein WL. Abeta oligomer-induced aberrations in synapse composition, shape, and density provide a molecular basis for loss of connectivity in Alzheimer's disease. *Journal of Neuroscience.* 2007; 27:796–807. [PubMed: 17251419]
- Langa KM, Foster NL, Larson EB. Mixed dementia: emerging concepts and therapeutic implications. *JAMA.* 2004; 292:2901–2908. [PubMed: 15598922]
- Lanz TA, Carter DB, Merchant KM. Dendritic spine loss in the hippocampus of young PDAPP and Tg2576 mice and its prevention by the ApoE2 genotype. *Neurobiology of Disease.* 2003; 13:246–253. [PubMed: 12901839]
- Larson ME, Lesné SE. Soluble A β oligomer production and toxicity. *J Neurochem.* 2012; 120(Suppl 1):125–139. [PubMed: 22121920]
- Larson M, Sherman MA, Amar F, Nuvolone M, Schneider JA, Bennett DA, Aguzzi A, Lesné SE. The complex PrP(c)-Fyn couples human oligomeric A β with pathological tau changes in Alzheimer's disease. *J Neurosci.* 2012; 32:16857–16871. [PubMed: 23175838]
- Laurén J. Cellular prion protein as a therapeutic target in Alzheimer's disease. *J Alzheimers Dis.* 2014; 38:227–244. [PubMed: 23948943]
- Laurén J, Gimbel DA, Nygaard HB, Gilbert JW, Strittmatter SM. Cellular prion protein mediates impairment of synaptic plasticity by amyloid-beta oligomers. *Nature.* 2009; 457:1128–1132. [PubMed: 19242475]
- Lee S-JR, Escobedo-Lozoya Y, Szatmari EM, Yasuda R. Activation of CaMKII in single dendritic spines during long-term potentiation. *Nature.* 2009; 458:299–304. [PubMed: 19295602]

- Lei P, Ayton S, Bush AI, Adlard PA. GSK-3 in Neurodegenerative Diseases. *Int J Alzheimers Dis*. 2011; 2011:189246. [PubMed: 21629738]
- Leroy K, Ando K, Laporte V, Dedecker R, Suain V, Authélet M, Heraud C, Pierrot N, Yilmaz Z, Octave J-N, Brion J-P. Lack of tau proteins rescues neuronal cell death and decreases amyloidogenic processing of APP in APP/PS1 mice. *Am. J. Pathol*. 2012; 181:1928–1940. [PubMed: 23026200]
- Lesné S, Koh MT, Kotilinek L, Kaye R, Glabe CG, Yang A, Gallagher M, Ashe KH. A specific amyloid-beta protein assembly in the brain impairs memory. *Nature*. 2006; 440:352–357. [PubMed: 16541076]
- Lewis J, Dickson DW, Lin WL, Chisholm L, Corral A, Jones G, Yen SH, Sahara N, Skipper L, Yager D, Eckman C, Hardy J, Hutton M, McGowan E. Enhanced neurofibrillary degeneration in transgenic mice expressing mutant tau and APP. *Science*. 2001; 293:1487–1491. [PubMed: 11520987]
- Li S, Jin M, Koeglspenger T, Shepardson N, Shankar G, Selkoe D. Soluble A β oligomers inhibit long-term potentiation through a mechanism involving excessive activation of extrasynaptic NR2B-containing NMDA receptors. *Journal of Neuroscience*. 2011; 31:6627–6638. [PubMed: 21543591]
- Li XH, Lv BL, Xie JZ, Liu J, Zhou XW, Wang JZ. AGEs induce Alzheimer-like tau pathology and memory deficit via RAGE-mediated GSK-3 activation. *NBA*. 2011:1–11.
- Lovestone S, Reynolds CH, Latimer D, Davis DR, Anderton BH, Gallo JM, Hanger D, Mulot S, Marquardt B, Stabel S. Alzheimer's disease-like phosphorylation of the microtubule-associated protein tau by glycogen synthase kinase-3 in transfected mammalian cells. *Current Biology*. 1994; 4:1077–1086. [PubMed: 7704571]
- Ly PT, Wu Y, Zou H, Wang R, Zhou W, Kinoshita A, Zhang M, Yang Y, Cai F, Woodgett J, Song W. Inhibition of GSK3 β -mediated BACE1 expression reduces Alzheimer-associated phenotypes. *J Clin Invest*. 2013; 123:224–235. [PubMed: 23202730]
- Malenka RC, Bear MF. LTP and LTD: an embarrassment of riches. *Neuron*. 2004; 44:5–21. [PubMed: 15450156]
- Mairet-Coello G, Courchet J, Pieraut S, Courchet V, Maximov A, Polleux F. The CAMKK2-AMPK kinase pathway mediates the synaptotoxic effects of A β oligomers through Tau phosphorylation. *Neuron*. 2013; 78:94–408. [PubMed: 23583109]
- Masliah E, Terry RD, DeTeresa RM, Hansen LA. Immunohistochemical quantification of the synapse-related protein synaptophysin in Alzheimer disease. *Neurosci. Lett*. 1989; 103:234–239. [PubMed: 2505201]
- Masters CL, Simms G, Weinman NA, Multhaup G, McDonald BL, Beyreuther K. Amyloid plaque core protein in Alzheimer disease and Down syndrome. *Proc. Natl. Acad. Sci. U.S.A.* 1985; 82:4245–4249. [PubMed: 3159021]
- Matsuzaki M, Honkura N, Ellis-Davies GCR, Kasai H. Structural basis of long-term potentiation in single dendritic spines. *Nature*. 2004; 429:761–766. [PubMed: 15190253]
- McBrayer M, Nixon RA. Lysosome and calcium dysregulation in Alzheimer's disease: partners in crime. *Biochem Soc Trans*. 2013; 41:1495–1502. [PubMed: 24256243]
- McLean CA, Cherny RA, Fraser FW, Fuller SJ, Smith MJ, Beyreuther K, Bush AI, Masters CL. Soluble pool of Abeta amyloid as a determinant of severity of neurodegeneration in Alzheimer's disease. *Ann. Neurol*. 1999; 46:860–866. [PubMed: 10589538]
- Miller EC, Teravskis P, Dummer BW, Zhao X, Haganir RL, Ashe KH, Liao D. The role of tau phosphorylation and tau mislocalization in soluble A-beta oligomer-induced deficits in AMPA glutamate receptor signaling. *European Journal of Neuroscience*. 2014
- Miller EC, Zhang L, Dummer BW, Cariveau DR, Loh HH, Law PY, Liao D. Differential Modulation of Drug-Induced Structural and Functional Plasticity of Dendritic Spines. *Molecular Pharmacology*. 2012; 82:333–343. [PubMed: 22596350]
- Mucke L, Masliah E, Yu GQ, Mallory M, Rockenstein EM, Tatsuno G, Hu K, Kholodenko D, Johnson-Wood K, McConlogue L. High-level neuronal expression of abeta 1-42 in wild-type human amyloid protein precursor transgenic mice: synaptotoxicity without plaque formation. *Journal of Neuroscience*. 2000; 20:4050–4058. [PubMed: 10818140]

- Mulkey RM, Endo S, Shenolikar S, Malenka RC. Involvement of a calcineurin/inhibitor-1 phosphatase cascade in hippocampal long-term depression. *Nature*. 1994; 369:486–488. [PubMed: 7515479]
- Näslund J, Haroutunian V, Mohs R, Davis KL, Davies P, Greengard P, Buxbaum JD. Correlation between elevated levels of amyloid beta-peptide in the brain and cognitive decline. *JAMA*. 2000; 283:1571–1577. [PubMed: 10735393]
- Nikkel AL, Martino B, Markosyan S, Brederson JD, Medeiros R, Moeller A, Bitner RS. The novel calpain inhibitor A-705253 prevents stress-induced tau hyperphosphorylation in vitro and in vivo. *Neuropharmacology*. 2012; 63:606–612. [PubMed: 22613839]
- Noh M-Y, Chun K, Kang BY, Kim H, Park J-S, Lee H-C, Kim Y-H, Ku S, Kim SH. Newly developed glycogen synthase kinase-3 (GSK-3) inhibitors protect neuronal cells death in amyloid-beta induced cell model and in a transgenic mouse model of Alzheimer's disease. *Biochemical and Biophysical Research Communications*. 2013; 435:274–281. [PubMed: 23632329]
- Nukina N, Ihara Y. One of the antigenic determinants of paired helical filaments is related to tau protein. *J. Biochem*. 1986; 99:1541–1544. [PubMed: 2423512]
- Nussbaum JM, Seward ME, Bloom GS. Alzheimer disease: a tale of two prions. *Prion*. 2013; 7:14–19. [PubMed: 22965142]
- Oddo S, Billings L, Kesslak JP, Cribbs DH, LaFerla FM. Abeta immunotherapy leads to clearance of early, but not late, hyperphosphorylated tau aggregates via the proteasome. *Neuron*. 2004; 43:321–332. [PubMed: 15294141]
- Oddo S, Caccamo A, Kitazawa M, Tseng BP, LaFerla FM. Amyloid deposition precedes tangle formation in a triple transgenic model of Alzheimer's disease. *NBA*. 2003; 24:1063–1070.
- Oddo S, Vasilevko V, Caccamo A, Kitazawa M, Cribbs DH, LaFerla FM. Reduction of soluble Abeta and tau, but not soluble Abeta alone, ameliorates cognitive decline in transgenic mice with plaques and tangles. *J. Biol. Chem*. 2006; 281:39413–39423. [PubMed: 17056594]
- Østergaard L, Aamand R, Gutiérrez-Jiménez E, Ho YC, Blicher JU, Madsen SM, Nagenthiraja K, Dalby RB, Drasbek KR, Møller A, Brændgaard H, Mouridsen K, Jespersen SN, Jensen MS, West MJ. The capillary dysfunction hypothesis of Alzheimer's disease. *Neurobiol Aging*. 2013; 34:1018–1031. [PubMed: 23084084]
- Papasozomenos SC, Binder LI. Phosphorylation determines two distinct species of Tau in the central nervous system. *Cell Motil. Cytoskeleton*. 1987; 8:210–226. [PubMed: 2446784]
- Patterson M, Yasuda R. Signalling pathways underlying structural plasticity of dendritic spines. *British Journal of Pharmacology*. 2011; 163:1626–1638. [PubMed: 21410464]
- Perez-Cruz C, Nolte MW, van Gaalen MM, Rustay NR, Termont A, Tanghe A, Kirchhoff F, Ebert U. Reduced spine density in specific regions of CA1 pyramidal neurons in two transgenic mouse models of Alzheimer's disease. *Journal of Neuroscience*. 2011; 31:3926–3934. [PubMed: 21389247]
- Phiel CJ, Wilson CA, Lee VM, Klein PS. GSK-3 α regulates production of Alzheimer's disease amyloid-beta peptides. *Nature*. 2003; 423:435–439. [PubMed: 12761548]
- Pimplikar SW. Reassessing the amyloid cascade hypothesis of Alzheimer's disease. *Int. J. Biochem. Cell Biol*. 2009; 41:1261–1268. [PubMed: 19124085]
- Price JL, McKeel DW, Buckles VD, Roe CM, Xiong C, Grundman M, Hansen LA, Petersen RC, Parisi JE, Dickson DW, Smith CD, Davis DG, Schmitt FA, Markesbery WR, Kaye J, Kurlan R, Hulette C, Kurland BF, Higdon R, Kukull W, Morris JC. Neuropathology of nondemented aging: presumptive evidence for preclinical Alzheimer disease. *Neurobiology of Aging*. 2009; 30:1026–1036. [PubMed: 19376612]
- Ramsden M, Kotilinek L, Forster C, Paulson J, McGowan E, SantaCruz K, Guimaraes A, Yue M, Lewis J, Carlson G, Hutton M, Ashe KH. Age-dependent neurofibrillary tangle formation, neuron loss, and memory impairment in a mouse model of human tauopathy (P301L). *Journal of Neuroscience*. 2005; 25:10637–10647. [PubMed: 16291936]
- Reese LC, Taglialetta G. A role for calcineurin in Alzheimer's disease. *Curr Neuropharmacol*. 2011; 9:685–692. [PubMed: 22654726]
- Reichmann H, Schneider C, Löhle M. Non-motor features of Parkinson's disease: depression and dementia. *Parkinsonism Relat. Disord*. 2009; 15(Suppl 3):S87–S92. [PubMed: 20083017]

- Reitz C. Alzheimer's disease and the amyloid cascade hypothesis: a critical review. *Int J Alzheimers Dis.* 2012; 2012:369808. [PubMed: 22506132]
- Roberson ED, Halabisky B, Yoo JW, Yao J, Chin J, Yan F, Wu T, Hamto P, Devidze N, Yu GQ, Palop JJ, Noebels JL, Mucke L. Amyloid- β /Fyn-Induced Synaptic, Network, and Cognitive Impairments Depend on Tau Levels in Multiple Mouse Models of Alzheimer's Disease. *Journal of Neuroscience.* 2011; 31:700–711. [PubMed: 21228179]
- Roberson ED, Scarce-Levie K, Palop JJ, Yan F, Cheng IH, Wu T, Gerstein H, Yu G-Q, Mucke L. Reducing endogenous tau ameliorates amyloid β -induced deficits in an Alzheimer's disease mouse model. *Science.* 2007; 316:750–754. [PubMed: 17478722]
- Rupp NJ, Wegenast-Braun BM, Radde R, Calhoun ME, Jucker M. Early onset amyloid lesions lead to severe neuritic abnormalities and local, but not global neuron loss in APPS1 transgenic mice. *Neurobiology of Aging.* 2011; 32:2324.e1–e6. [PubMed: 20970889]
- Russell CL, Semerdjieva S, Empson RM, Austen BM, Beesley PW, Alifragis P. Amyloid- β acts as a regulator of neurotransmitter release disrupting the interaction between synaptophysin and VAMP2. *PLoS One.* 2012; 7:e403201.
- Santacruz K, Lewis J, Spires T, Paulson J, Kotilinek L, Ingelsson M, Guimaraes A, DeTure M, Ramsden M, McGowan E, Forster C, Yue M, Orne J, Janus C, Mariash A, Kuskowski M, Hyman B, Hutton M, Ashe KH. Tau suppression in a neurodegenerative mouse model improves memory function. *Science.* 2005; 309:476–481. [PubMed: 16020737]
- Schindowski K, Bretteville A, Leroy K, Bégard S, Brion J-P, Hamdane M, Buée L. Alzheimer's disease-like tau neuropathology leads to memory deficits and loss of functional synapses in a novel mutated tau transgenic mouse without any motor deficits. *Am. J. Pathol.* 2006; 169:599–616. [PubMed: 16877359]
- Schneider JA. High blood pressure and microinfarcts: a link between vascular risk factors, dementia, and clinical Alzheimer's disease. *J Am Geriatr Soc.* 2009; 57:2146–2147. [PubMed: 20121957]
- Selkoe DJ. Alzheimer's disease is a synaptic failure. *Science.* 2002; 298:789–791. [PubMed: 12399581]
- Shankar GM, Bloodgood BL, Townsend M, Walsh DM, Selkoe DJ, Sabatini BL. Natural oligomers of the Alzheimer amyloid- β protein induce reversible synapse loss by modulating an NMDA-type glutamate receptor-dependent signaling pathway. *Journal of Neuroscience.* 2007; 27:2866–2875. [PubMed: 17360908]
- Shankar GM, Li S, Mehta TH, Garcia-Munoz A, Shepardson NE, Smith I, Brett FM, Farrell MA, Rowan MJ, Lemere CA, Regan CM, Walsh DM, Sabatini BL, Selkoe DJ. Amyloid- β protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory. *Nat. Med.* 2008; 14:837–842. [PubMed: 18568035]
- Shen J. Function and dysfunction of presenilin. *Neurodegener Dis.* 2013; xx:xxx–xxx.
- Sheng M, Sabatini BL, Sudhof TC. Synapses and Alzheimer's Disease. *Cold Spring Harbor Perspectives in Biology.* 2012; 4:a005777–a005777. [PubMed: 22491782]
- Shrestha BR, Vitolo OV, Joshi P, Lordkipanidze T, Shelanski M, Dunaevsky A. Amyloid β peptide adversely affects spine number and motility in hippocampal neurons. *Mol. Cell. Neurosci.* 2006; 33:274–282. [PubMed: 16962789]
- Shukla V, Skuntz S, Pant HC. Deregulated Cdk5 activity is involved in inducing Alzheimer's disease. *Arch Med Res.* 2012; 43:435–439.
- Snyder EM, Nong Y, Almeida CG, Paul S, Moran T, Choi EY, Nairn AC, Salter MW, Lombroso PJ, Gouras GK, Greengard P. Regulation of NMDA receptor trafficking by amyloid- β . *Nat Neurosci.* 2005; 8:1051–1058. [PubMed: 16025111]
- Spires TL, Orne JD, SantaCruz K, Pitstick R, Carlson GA, Ashe KH, Hyman BT. Region-specific dissociation of neuronal loss and neurofibrillary pathology in a mouse model of tauopathy. *Am. J. Pathol.* 2006; 168:1598–1607. [PubMed: 16651626]
- Spittaels K, Van den Haute C, van Dorpe J, Bruynseels K, Vandezande K, Laenen I, Geerts H, Mercken M, Sciot R, Van Lommel A, Loos R, Van Leuven F. Prominent axonopathy in the brain and spinal cord of transgenic mice overexpressing four-repeat human tau protein. *Am. J. Pathol.* 1999; 155:2153–2165. [PubMed: 10595944]

- Stadelmann C, Deckwerth TL, Srinivasan A, Bancher C, Brück W, Jellinger K, Lassmann H. Activation of caspase-3 in single neurons and autophagic granules of granulovacuolar degeneration in Alzheimer's disease. Evidence for apoptotic cell death. *Am. J. Pathol.* 1999; 155:1459–1466. [PubMed: 10550301]
- Stark DT, Bazan NG. Synaptic and extrasynaptic NMDA receptors differentially modulate neuronal COX-2 function, lipid peroxidation, and neuroprotection. *Journal of Neuroscience.* 2011; 31:13710–13721. [PubMed: 21957234]
- Steinhilb ML, Dias-Santagata D, Mulkearns EE, Shulman JM, Biernat J, Mandelkow E-M, Feany MB. S/P and T/P phosphorylation is critical for tau neurotoxicity in *Drosophila*. *J. Neurosci. Res.* 2007; 85:1271–1278. [PubMed: 17335084]
- Svenningsson P, Westman E, Ballard C, Aarsland D. Cognitive impairment in patients with Parkinson's disease: diagnosis, biomarkers, and treatment. *Lancet Neurol.* 2012; 11:697–707. [PubMed: 22814541]
- Swerdlow, RH.; Burns, JM.; Khan, SM. The Alzheimer's disease mitochondrial cascade hypothesis: Progress and perspectives. *Biochim Biophys Acta.* 2013. <http://dx.doi.org/10.1016/j.bbadis.2013.09.010>
- Sze CI, Troncoso JC, Kawas C, Mouton P, Price DL, Martin LJ. Loss of the presynaptic vesicle protein synaptophysin in hippocampus correlates with cognitive decline in Alzheimer disease. *J. Neuropathol. Exp. Neurol.* 1997; 56:933–944. [PubMed: 9258263]
- Taglialetela G, Hogan D, Zhang W-R, Dineley KT. Intermediate- and long-term recognition memory deficits in Tg2576 mice are reversed with acute calcineurin inhibition. *Behav. Brain Res.* 2009; 200:95–99. [PubMed: 19162087]
- Takashima A, Noguchi K, Michel G, Mercken M, Hoshi M, Ishiguro K, Imahori K. Exposure of rat hippocampal neurons to amyloid beta peptide (25–35) induces the inactivation of phosphatidylinositol-3 kinase and the activation of tau protein kinase I/glycogen synthase kinase-3 beta. *Neurosci. Lett.* 1996; 203:33–36. [PubMed: 8742040]
- Tanzi RE, Bertram L. Twenty years of the Alzheimer's disease amyloid hypothesis: a genetic perspective. *Cell.* 2005; 120:545–555. [PubMed: 15734686]
- Terry RD, Masliah E, Salmon DP, Butters N, DeTeresa R, Hill R, Hansen LA, Katzman R. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. *Ann. Neurol.* 1991; 30:572–580. [PubMed: 1789684]
- Tomiyama T, Matsuyama S, Iso H, Umeda T, Takuma H, Ohnishi K, Ishibashi K, Teraoka R, Sakama N, Yamashita T, Nishitsuji K, Ito K, Shimada H, Lambert MP, Klein WL, Mori H. A mouse model of amyloid beta oligomers: their contribution to synaptic alteration, abnormal tau phosphorylation, glial activation, and neuronal loss in vivo. *Journal of Neuroscience.* 2010; 30:4845–4856. [PubMed: 20371804]
- Um JW, Kaufman AC, Kostylev M, Heiss JK, Stagi M, Takahashi H, Kerrisk ME, Vortmeyer A, Wisniewski T, Koleske AJ, Gunther EC, Nygaard HB, Strittmatter SM. Metabotropic glutamate receptor 5 is a coreceptor for Alzheimer $\text{A}\beta$ oligomer bound to cellular prion protein. *Neuron.* 2013; 79:887–902. [PubMed: 24012003]
- Um JW, Strittmatter SM. Amyloid- β induced signaling by cellular prion protein and Fyn kinase in Alzheimer disease. *Prion.* 2013; 7:37–41. [PubMed: 22987042]
- van Helmond Z, Miners JS, Kehoe PG, Love S. Oligomeric A β in Alzheimer's disease: relationship to plaque and tangle pathology, APOE genotype and cerebral amyloid angiopathy. *Brain Pathol.* 2010; 20:468–480. [PubMed: 19725829]
- Verret L, Mann EO, Hang GB, Barth AM, Cobos I, Ho K, Devidze N, Masliah E, Kreitzer AC, Mody I, Mucke L, Palop JJ. Inhibitory interneuron deficit links altered network activity and cognitive dysfunction in Alzheimer model. *Cell.* 2012; 149:708–721. [PubMed: 22541439]
- Vossel KA, Zhang K, Brodbeck J, Daub AC, Sharma P, Finkbeiner S, Cui B, Mucke L. Tau reduction prevents A β -induced defects in axonal transport. *Science.* 2010; 330:198. [PubMed: 20829454]
- Wagner U, Utton M, Gallo JM, Miller CC. Cellular phosphorylation of tau by GSK-3 beta influences tau binding to microtubules and microtubule organisation. *J. Cell. Sci.* 1996; 109(Pt 6):1537–1543. [PubMed: 8799840]

- Wang J-Z, Xia Y-Y, Grundke-Iqbal I, Iqbal K. Abnormal hyperphosphorylation of tau: sites, regulation, and molecular mechanism of neurofibrillary degeneration. *J. Alzheimers Dis.* 2013; 33(Suppl 1):S123–S139. [PubMed: 22710920]
- Wang JZ, Grundke-Iqbal I, Iqbal K. Restoration of biological activity of Alzheimer abnormally phosphorylated tau by dephosphorylation with protein phosphatase-2A, -2B and -1. *Molecular Brain Research.* 1996; 38:200–208. [PubMed: 8793108]
- Wang JZ, Wu Q, Smith A, Grundke-Iqbal I, Iqbal K. Tau is phosphorylated by GSK-3 at several sites found in Alzheimer disease and its biological activity markedly inhibited only after it is prephosphorylated by A-kinase. *FEBS Lett.* 1998; 436:28–34. [PubMed: 9771888]
- Westerman MA, Cooper-Blacketer D, Mariash A, Kotilinek L, Kawarabayashi T, Younkin LH, Carlson GA, Younkin SG, Ashe KH. The relationship between Abeta and memory in the Tg2576 mouse model of Alzheimer's disease. *Journal of Neuroscience.* 2002; 22:1858–1867. [PubMed: 11880515]
- Wischnik, CM.; Harrington, CR.; Storey, JM. Tau-aggregation inhibitor therapy for Alzheimer's disease. *Biochem Pharmacol.* 2013. <http://dx.doi.org/10.1016/j.bcp.2013.12.008>
- Wu H-Y, Hudry E, Hashimoto T, Kuchibhotla K, Rozkalne A, Fan Z, Spires-Jones T, Xie H, Arbel-Ornath M, Grosskreutz CL, Bacskai BJ, Hyman BT. Amyloid beta induces the morphological neurodegenerative triad of spine loss, dendritic simplification, and neuritic dystrophies through calcineurin activation. *Journal of Neuroscience.* 2010; 30:2636–2649. [PubMed: 20164348]
- Yamada K, Cirrito JR, Stewart FR, Jiang H, Finn MB, Holmes BB, Binder LI, Mandelkow EM, Diamond MI, Lee VM, Holtzman DM. In vivo microdialysis reveals age-dependent decrease of brain interstitial fluid tau levels in P301S human tau transgenic mice. *J Neurosci.* 2011; 31:13110–13117. [PubMed: 21917794]
- Yuan A, Kumar A, Sasaki T, Duff K, Nixon RA. Axonal Transport Rates in vivo are Unaltered in Htau Mice. *J. Alzheimers Dis.* 2013
- Zahs KR, Ashe KH. 'Too much good news' - are Alzheimer mouse models trying to tell us how to prevent, not cure, Alzheimer's disease? *Trends in Neurosciences.* 2010; 33:381–389. [PubMed: 20542579]
- Zahs KR, Ashe KH. β -Amyloid oligomers in aging and Alzheimer's disease. *Front Aging Neurosci.* 2013; 5:28. [PubMed: 23847532]
- Zeiger W, Vetrivel KS, Buggia-Prevot V, Nguyen PD, Wagner SL, Villereal ML, Thinakaran G. Ca^{2+} Influx Through Store-Operated Ca^{2+} Channels Reduces Alzheimer Disease β -Amyloid Peptide Secretion. *Journal of Biological Chemistry.* 2013
- Zempel H, Luedtke J, Kumar Y, Biernat J, Dawson H, Mandelkow E, Mandelkow EM. Amyloid- β oligomers induce synaptic damage via Tau-dependent microtubule severing by TTL6 and spastin. *EMBOJ.* 2013; 32:2920–2937.
- Zempel H, Thies E, Mandelkow E, Mandelkow EM. A Oligomers Cause Localized Ca^{2+} Elevation, Missorting of Endogenous Tau into Dendrites, Tau Phosphorylation, and Destruction of Microtubules and Spines. *Journal of Neuroscience.* 2010; 30:11938–11950. [PubMed: 20826658]
- Zhao W-Q, Santini F, Breese R, Ross D, Zhang XD, Stone DJ, Ferrer M, Townsend M, Wolfe AL, Seager MA, Kinney GG, Shughrue PJ, Ray WJ. Inhibition of calcineurin-mediated endocytosis and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors prevents amyloid beta oligomer-induced synaptic disruption. *Journal of Biological Chemistry.* 2010; 285:7619–7632. [PubMed: 20032460]

Figure 1. Pathological tau and Aβ species may share a common downstream pathway that leads to synaptic dysfunction

A. Representative traces from Hoover *et al.*, 2010. Miniature excitatory postsynaptic currents (mEPSCs) were recorded from 3 week-old cultured rat hippocampal neurons expressing green fluorescent protein (GFP), wild-type tau (WT tau) and mutant P301L tau.

B. Cumulative frequency plots of mEPSC amplitude from the three groups in A.

C. Representative traces from Miller *et al.*, 2014. Un-transfected cultured rat hippocampal neurons were treated with soluble Aβ oligomers for > 3 days and mEPSCs were recorded in both control and treated neurons.

D. Cumulative frequency plots from groups in C. *, p < 0.1; ***, p < 0.001, Kolmogorov-Smirnov test.

Figure 2. Comparison Of The Amyloid Cascade Hypotheses

A and B. The initial amyloid hypothesis introduces the central idea that amyloid pathology precedes tau pathology (Hardy and Allsop 1991; Hardy and Higgins 1992).

C. A more recent version has incorporated synaptic deficits into the cascade, putting synaptic deficits before tau hyperphosphorylation.

D. In our model, tau hyperphosphorylation and tau mislocalization precedes synaptic deficits at a very early stage. However, tau mislocalization may play a permissive role at a later stage (see Figure 3 and Ittner et al., 2010). Tauopathy increases in the amount of extrasynaptic NMDA receptors (Hoover *et al.*, 2010), which may lead to neurodegeneration. Although we only see postsynaptic effects in our experimental system, pre-synaptic deficits may also participate in AD pathogenesis (Hermann *et al.*, 2013; Huang *et al.* 2013; Russell *et al.*, 2012).

Figure 3. Multiple parallel signaling pathways for A β - and tau-mediated neurodegeneration and synaptic deficits

Red arrows denote the classical A β -tau cascade (Pathway 1). GSK3 β affects both tau phosphorylation and A β production. Blue arrows denote additional roles of presenilin (Pathway 2). Purple arrows denote the recently characterized A β -PrP^C-Fyn pathway (Pathway 3). Green and orange arrows denote the dual roles of tau. It may bring Fyn to dendritic spines to allow A β -induced neurotoxicity (Pathway 4) or directly impair synaptic function (Pathway 5). Other cellular events such as ER stress, AMPK activation and spastin activation may also be involved. A β may also affect neuronal circuits by modulating inhibitory synaptic transmission (Verret et al., 2012).

Figure 4. Changes in either Aβ or tau can lead to tau mislocalization to dendritic spines

A. Cultured rat dissociated hippocampal neurons were co-transfected with both DsRed to label dendritic spines and GFP-tagged tau proteins to detect tau mislocalization. Left and middle: overlay images from neurons expressing DsRed and GFP-tagged wild-type tau with or without exposure to Aβ oligomers for 3 days. Right: an untreated neuron co-expressing DsRed and P301L mutant tau proteins.

B. Either Aβ treatment or P301L tau expression significantly increased the abnormal presence of tau proteins in dendritic spines.

C. Neurons were cultured from transgenic negative mice (TgNg), transgenic mice expressing the APP_{Swe} mutation or transgenic mice expressing P301L tau. The neurons were co-transfected with DsRed and GFP-tagged wild-type tau.

D. Only the expression of APP_{Swe} significantly causes tau mislocalization whereas the expression of P301L tau does not drive wild-type tau proteins to dendritic spines. It suggests that Aβ initiates the cascade whereas P301L mutation makes the mutant tau proteins more vulnerable to mislocalization than wild-type tau proteins. This result argues that Aβ is the initiator of a process mediated by tau. ***, $p < 0.01$, ANOVA.

Figure 5. Hypothetical mechanisms for Aβ initiation of tau-mediated synaptic deficits

A. possible initiators of dementia: **A1.** mutation of tau residue 301 from proline to leucine; **A2.** Swedish double mutation of APP at residues 670, lysine to asparagine, and 671, methionine to leucine; **A3.** extracellular soluble Aβ oligomers such as dimers, trimers and higher order species such as Aβ*56 (the mechanism of creation and the crystalline structures of these pathological species remains unknown) may initiate the cascade from the axonal or dendritic compartments; and **A4.** intracellular Aβ.

B. Intracellular Aβ may cause presynaptic dysfunction. However, it is still controversial whether presynaptic release is increased or decreased in AD (Busche *et al.*, 2008; Huang *et al.*, 2013). **C.** initiators A1–A3 result in tau hyperphosphorylation and mislocalization to dendritic spines (*postsynaptic*) possibly mediated by GSK3β activity.

D. Once tau is mislocalized to dendritic spines **D1.** calcineurin activity is increased; **D2.** calcineurin dephosphorylates GluR1 residue S845; **D3.** causing AMPA glutamate receptor internalization resulting in a decrease in excitatory glutamatergic neurotransmission.

E. Interstitial soluble proteins of Tau (ISP-tau) might also be involved (Yamada *et al.*, 2011).