

# New Insight into Alzheimer's Disease via Caspase 3-cleaved Tau: Pathogenic Role in Tau Oligomer Formation and Memory Deficits

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## Abstract

Alzheimer's disease (AD) is the most common and leading cause of dementia. AD has two different pathological hallmarks, extracellular amyloid beta plaques and intracellular neurofibrillary tangles (NFT). NFTs consist of abnormally modified tau protein that forms protein aggregates. Tau protein aggregates are prevalently observed as disease progresses and are believed to cause neuronal dysfunction. The caspase-3 cleaved form of tau, TauC3, is generated in cultured neurons under stress and is found in the brains of patients with AD in the early stages of disease when patients are asymptomatic. TauC3 accelerates tau oligomerization in vitro and in vivo, and induces neuronal degeneration. Moreover, the neuronal expression of TauC3 in transgenic mice causes memory deficits at a young age, which is concomitant with the appearance of tau oligomers. The removal of TauC3-containing oligomers and aggregates using drug treatment improves both memory and synaptic function. These findings demonstrate that TauC3 is critical for the formation of tau oligomers and small aggregates and may ultimately play a role in the rapid memory impairments observed in AD. Overall, TauC3 may represent a new therapeutic target for the prevention of AD.

**Keywords:** Alzheimer's disease; Memory deficit; Neurofibrillary tangle; Tau aggregate; Tau oligomer; TauC3

## Introduction

Alzheimer's disease (AD) accounts for 70% of all dementias and the number of patients with AD is increasing every year [1]. Some medications are available to improve the symptoms of AD; however, disease-modifying medicine is not adequately developed and studies on the pathogenesis of AD are urgently required. AD has two major pathological hallmarks: One is the extracellular amyloid beta (A $\beta$ ) plaque [2], and the other is the intracellular neurofibrillary tangles (NFT) that consists of tau protein [3]. NFTs are primarily found in the entorhinal cortex and hippocampus, the primary brain regions that show functional deficits and degeneration in patients with AD in early stages of the disease, and spread to the cortex and other parts of the brain as disease progresses [4]. Nonetheless, it is under discussion whether NFTs themselves are toxic [5,6].

While turning off tau protein expression mitigates neuronal cell death and results in the recovery of memory [7], overexpression of normal full-length tau does not induce either memory deficits or tau oligomers in most cases [8]. In general, it is accepted that conformers between monomer and large tangle level aggregates, such as intermediate tau oligomers/small aggregates, may be the cause of the disease. Compared to normal tau, genetic mutation in or post-translational modification of tau facilitates the formation of tau aggregates. Similar intracellular protein oligomer and aggregate conformers found in other neurodegenerative diseases, such as mutant Huntingtin in Huntington's disease [9,10], Spinocerebellar ataxia type 1 (SCA) in spinocerebellar ataxia [11], alpha-synuclein in Parkinson's disease [12], and TAR DNA-binding protein-43 (TDP-43) in amyotrophic lateral sclerosis [13] are also thought to induce the respective diseases [14]. Therefore, it is important to study the tau species between oligomers and aggregates found in Alzheimer's disease, with particular attention to their role in memory impairment and the loss of synaptic function.

## Tau Oligomers and Aggregates in Tau Pathology

How can tau proteins form oligomers or small aggregates? There are two species of tau protein that can readily assemble into oligomers; abnormally phosphorylated tau [15] and the caspase-cleaved form

of tau (TauC3) [16]. Although no genetic tau mutation has been uncovered in AD, other neurodegenerative diseases, such as FTD with Parkinsonism linked to chromosome 17 (FTDP-17), have several tau mutants (TauP301S, TauP301L, or TauR406W) that are likely to become highly phosphorylated [17]. Overexpression of these mutants in neuronal cells or mouse brain results in hyperphosphorylation of tau protein, and the formation of tau oligomers and aggregates in the late stages of disease in mice.

However, the tau pathologies that result from these genetic mutations do not lead to memory deficits in many in vivo mouse models. The induction of TauR406W expression in the mouse brain fails to induce memory deficits until the end of the life span of the mouse [18]. Moreover, overexpression of TauP301S in mice does not induce significant memory deficits, although the brains display massive neuronal loss [19]. Other mice expressing human TauV337M, THY-Tau22 or hTau40/ $\Delta$ K280 show memory deficits. However, the memory loss observed in these mouse models appears in the late stages of disease (>9 months), after significant neuronal loss, which differs from the events occurring in the brains of patients with AD where neuronal loss occurs after memory loss [20-22]. On the other hand, an AD mouse model expressing mutant TauP301L at an extremely high level (>13 times the normal tau level in mice) exhibits tau aggregation and tangles, and early memory deficits (<3 months) that occur before neuronal loss (>6 months) [7]. Interestingly, this transgenic tau model shows caspase activation and rapid aggregation of tau together with TauC3 at the early stages of memory deficits, and only the cells in which TauC3 is present show electron microscopy-detectible or Thioflavin S-positive

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tau aggregates, indicating a potential link between tau pathology and TauC3 generation [23,24].

## A Role of TauC3 in Tau Oligomer Formation and Aggregate-based Memory Impairments

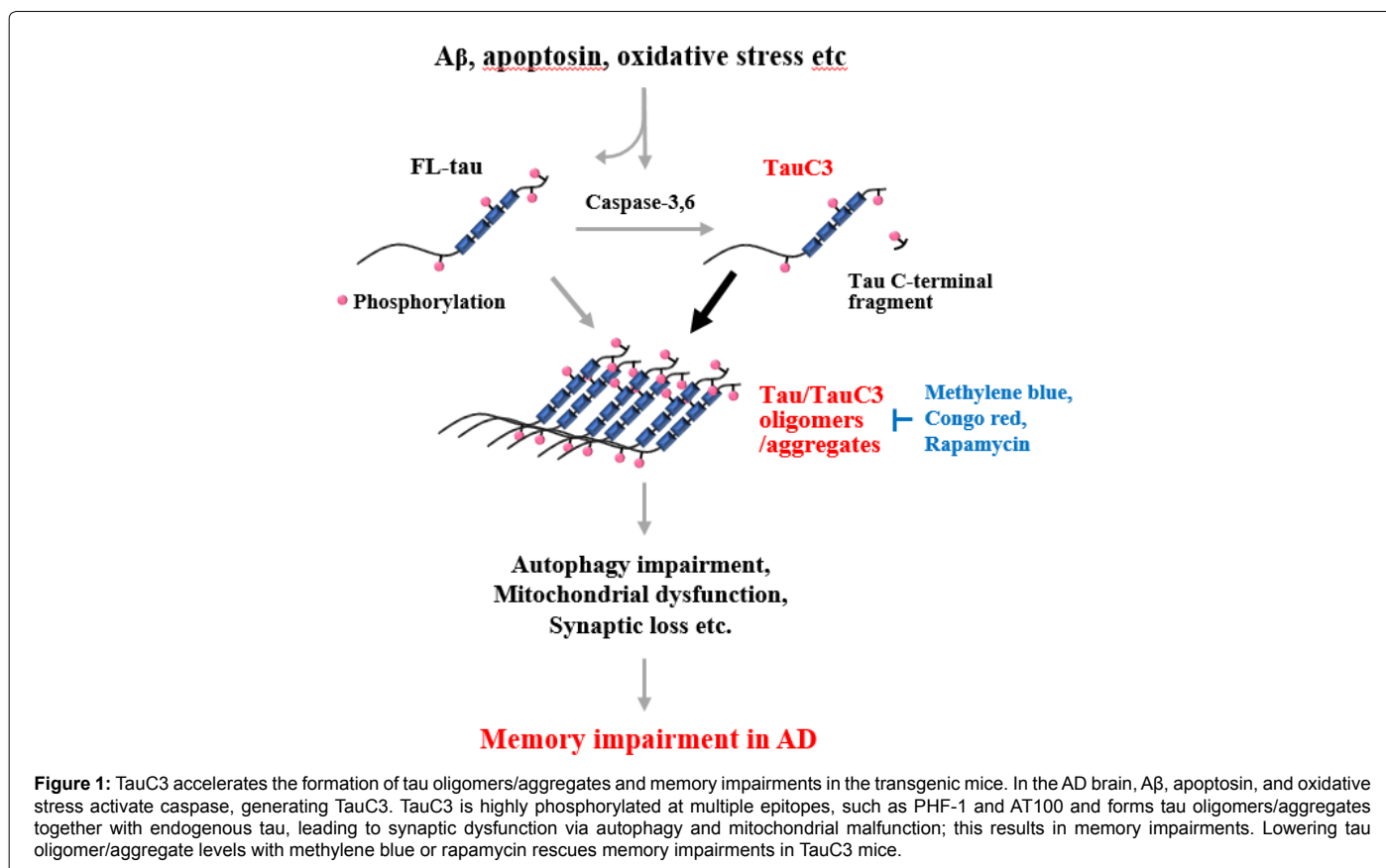
It had been assumed that caspase activation is limited to cell death only. However, today, many proteins essential for cell function are known to be activated by caspase cleavage [25]. For example, low-level activation of caspase can regulate the  $\alpha$ -amino-3-hydroxy-5-methyl-4-isooxazolepropionic acid (AMPA) receptor in the synapses of neurons and mediate synaptic transmission [26].  $A\beta$  and multiple stressors appear to induce aberrant activation of caspases in neurons [27]. Tau is also known to be a substrate for multiple caspases: at least three caspases have been shown to participate in tau cleavage and the major form of caspase-cleaved tau found in AD brains is the caspase-3-cleaved tau, TauC3 [16]. TauC3 is also found in the brains of patients with AD with mild cognitive impairment [28], indicating that caspase-cleavage of tau is an early event in AD tangle pathology.

Tau contains a caspase-3 cleavage motif (DMVD) located in the 20th amino acid (421th Asp) from the C-terminus [16,28], and cleavage at this site can generate TauC3. TauC3 tends to form TauC3 self-oligomers or acts as a seed to produce oligomers with full-length tau *in vitro* [29]. Moreover, neurite regression and neuronal loss were observed with TauC3/tau aggregates in cultured primary neurons [16,30] and *in vivo* in a TauC3 drosophila model [31], respectively. Interestingly, expression of TauC3 in a transgenic mouse (similar level as endogenous mouse tau expression) results in learning and memory deficits, with synaptic dysfunction occurring as early as two months after birth [32]. Notably, tau oligomers appear in the brains of TauC3 mice showing

memory deficits. Similar to TauC3 mice, a Tau35 transgenic mouse model expressing another truncated form of tau (Tau187-441) at a relatively low level (<10% of endogenous mouse tau expression) also shows memory deficits [33]. It will be interesting to determine whether tau oligomers or aggregates also appear together with tau pathology in this Tau35 mouse model.

Then, an important question remains; how does TauC3 cause rapid memory deficits in the mouse model? As seen in an *in vitro* aggregation assay and in a fly model [31], TauC3 seems to be critical for the formation of both low-n tau oligomers and detergent-insoluble tau aggregates, and thereby for memory impairments in the mouse brain. TauC3 is found only in tau oligomers in the brains of mice showing memory deficits. In addition, soluble oligomers and detergent-insoluble small aggregates of tau can be detected in TauC3 mouse brains at a similar time point to that of the start of the memory deficits [32]. Moreover, when tau oligomers and aggregates are removed by treatment with aggregation blockers, such as methylene blue and Congo-red [32] or an autophagy inducer, such as rapamycin and pimozone memory [34] and synaptic function can be rescued (Figure 1). Similar data are also observed in an apoptosin-induced caspase-cleaved tau transgenic mouse model. Caspase-cleaved tau boosts the rapid formation of tau aggregates and synaptic protein loss [35]. These observations suggest a critical role of TauC3 in the formation of tau oligomers and aggregates, which leads to tau pathology, synaptic dysfunction and memory deficits.

Of course, other roles of TauC3 in neuronal degeneration are possible. FKBP52 (52-kDa FK506 binding protein) and mitochondria are essential factors for axonal growth and synaptic function, respectively [36,37]. Recently it was shown that TauC3 and its oligomers might deplete FKBP52, an autophagy regulator, leading to



lysosomal malfunction [38]. Given that mitochondria are critical for high energy demand fast protein turn-over in synapses [39], TauC3 might impair mitochondrial dynamics in neuronal cells [40]. Even in these situations, it might be the TauC3-harboring oligomers and small aggregates that affect axonal growth and mitochondrial dynamics, although this requires further clarification. Finally, propagation of disease-inducing protein oligomers has emerged as one of the causes of neurodegenerative diseases [41]. Propagation of pathogenic tau protein is a key issue for AD and other tauopathy progression, and the major form of tau conformers responsible for disease is the soluble low-n tau oligomers [42]. A recent report also suggested that transmitting tau oligomers also build up with TauC3: Treatment with a TauC3 monoclonal antibody effectively blocked tau transmission *in vitro* [43], highlighting the crucial role of TauC3 in disease propagation.

In summary, the TauC3 mouse might be a disease-relevant model of AD and TauC3 is an important therapeutic target for the prevention or treatment of AD. In the preclinical study by a biopharmaceutical company, TauC3 monoclonal antibody, which binds uniquely to Asp421 at the C-terminus of TauC3, reduces certain phosphorylated forms of Tau [44]. This kind of therapeutic approach targeting TauC3 might be useful to treat Alzheimer's disease and other tauopathies in the near future.

## Conclusion

Disease-related protein aggregation is indicated as the critical source of neurotoxicity in many neurodegenerative diseases. Many forms of wild-type and mutant tau proteins, including TauC3, are prone to form tau oligomers and aggregates both *in vitro* and *in vivo*. Of these, TauC3 is known to induce the formation of tau oligomers and aggregates in a transgenic mouse model, and this event appears to play a role in early and rapid memory impairments. Thus, TauC3 mice may be useful for investigating the role of tau in the pathogenesis of AD, and for testing drug candidates that interfere or block with the formation of tau oligomers and aggregates. To conclude, it is now more important than before to better understand tau-based memory loss in AD, in particular that related to TauC3.

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