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# Tau aggregates possibly compromise neuronal health in the *C. elegans* model of Alzheimer's disease

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## Abstract

Alzheimer's disease (AD) is the most common degenerative brain disease in the aged population [1]. By 2050, AD prevalence is expected to increase from 4.7 million (based on 2010 census) to 13.8 million people [2]. It is characterized by the progressive decline of cognition and memory, as well as changes in behavior and personality [1]. Pathological hallmarks of AD include mainly formation of senile plaques consisting of amyloid-beta (Aβ) peptide in the intercellular space and neurofibrillary tangles (NFTs) in the cell bodies, which are primarily composed of abnormally modified tau protein [3]. Tau isolated from AD brain exhibits a number of post-translational modifications (PTMs), including increase in phosphorylation and acetylation at specific epitopes that likely impair its function and conformation [4,5]. Interestingly, research over the years has primarily focused on amyloid plaques, whereas less importance has been given to tau and its PTMs which leads to change in structural moiety of the protein and drive its neurotoxicity.

## Background

Previous studies have demonstrated that soluble tau oligomers accumulate at synapses in the AD brain, block synaptic connection among neurons, causing neurodegeneration and eventually neuronal death [6]. But the precise mechanism of what leads to the toxicity of tau, causing severe cortical and hippocampal shrinkage and ultimately affecting nearly all functions of the brain, still remains elusive! A major bottleneck in understanding the mechanisms behind the neurotoxicity of pathological forms of Tau is the lack of genetically tractable models that can recapitulate the effects of Tau PTMs in a short time frame without artifacts associated with Tau overexpression. In our lab, human 0N4R wild type isoform of tau (TauT4) was expressed in touch receptor neurons of the genetic model organism *C. elegans* through single-copy gene insertion [7]. Defined mutations were then introduced into the single-copy tau transgene through CRISPR-Cas9 genome editing. These mutations included T231E (Threonine substituted to Glutamic Acid) and T231A (Threonine substituted to Alanine), to mimic phosphorylation and phosphoablation of a commonly observed pathological epitope, respectively, and K274/281Q (Lysine substituted to Glutamine), to mimic disease-associated acetylation. Our study demonstrated that unlike existing tau overexpression models, *C. elegans* single-copy expression of tau did not elicit overt pathological phenotypes at baseline. However, strains expressing disease associated PTM-mimetics (T231E and K274/281Q) exhibited reduced touch sensation and neuronal morphological abnormalities that increased with age, whereas the phospho-ablation mimetic (T231A) which prevents phosphorylation at that disease epitope, acted like a wild type strain (TauT4). The question still remains

what is the mechanism behind such a beneficial protein like tau to become toxic, and to cause neurodegeneration phenotypes as demonstrated by both functional decline of the neurons, indicative of neuronal health, as well as altered neuronal morphology.

## Major Findings

The concept of insoluble fibrillary structures in AD and other tauopathies being the principal mediators of neuronal toxicity has been gradually ruled out [8], and the mechanism by which specific tau PTMs contribute to the toxicity of soluble tau forms is still unclear. I hypothesize, that presence of soluble tau aggregates can be the backbone behind the neurodegeneration, as demonstrated in the previous papers [9][10]. To confirm that, I imaged the same *C. elegans* transgenic strains (as listed in table 1) under confocal laser scanning biological microscope FV1000 Fluoview (Olympus 1X61) at two different days of their life cycle (day 3 and day 10 of adulthood).

| Site-specific AD-relevant Tau PTMs | Transgenic strains |
|---|---|
| *TauT4* | Wild type Tau (single copy) |
| *TauT4 (T231A)* | Phospho-ablation |
| *TauT4 T231E))* | Phospho-mimetic |
| *TauT4 (K274/281Q)* | Acetyl-mimetic |

Table 1. List of the different *C. elegans* strains used for the neuronal aggregation assay.

Interestingly, at day 3 stage of their adulthood I didn't observe any presence of aggregates either in the neuronal soma or in the axon, in none of the transgenic strains. However, as the worms were aged a week more, at day 10 of their adulthood, I observed that the cell bodies of both the tau-mimetic strains (T231E and K274/281Q) have aggregates, whereas interestingly, the cell body of the negative control strain (T231A), phosphoablation, lacks any of them (Figure 1). Another observation was that the aggregates of the T231E are mostly concentrated within the soma itself, however the aggregates of the K274/281Q seem to be localized in the axon initiation segment (AIS). Interestingly, in cell culture and mouse models of AD, as demonstrated by pioneering groups, missorting of pathologic tau and accumulation in the AIS, led to destruction of the cytoskeletal network in the dendrites, coinciding with the synapse loss and functional impairments [9][10]. Thus, it is astonishing to observe that our single copy tau worm model also can successfully replicate this pathological missorting of tau phenomenon.

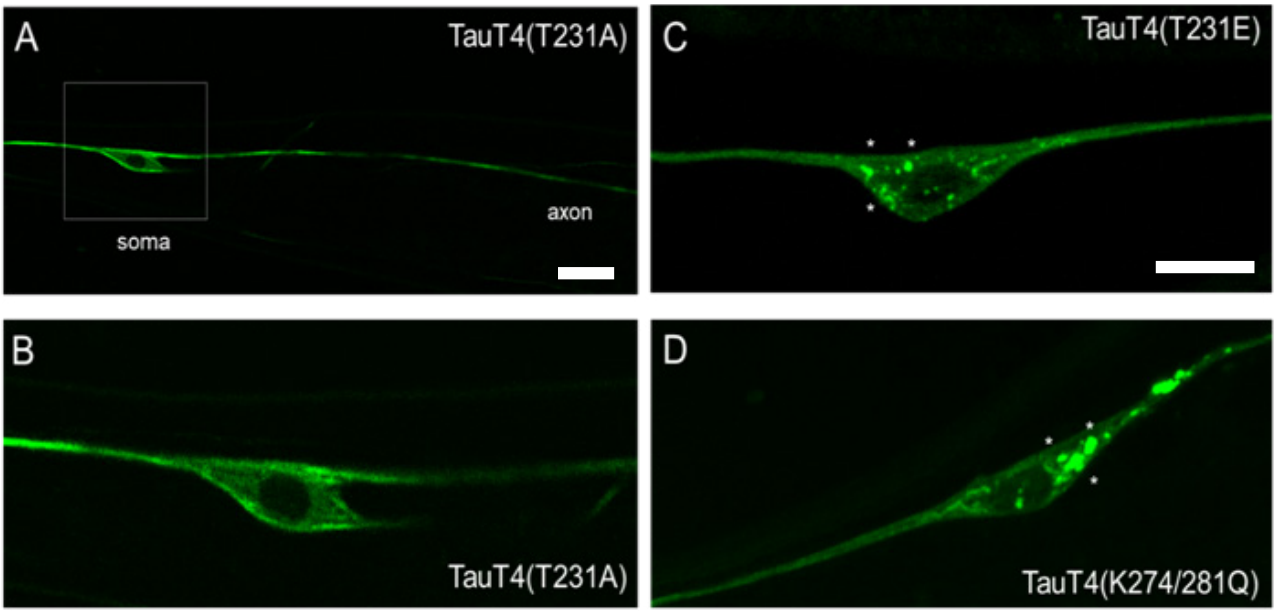


**Figure 1. A) Representative image of the sensory neuron as viewed under 100X objective in the Olympus Confocal microscope. B) 2X zoom image of the cell body (lacking any aggregates) of the T231A strain. C and D) 2X images of the cell bodies of the T231E and K274/281Q strains. White asterisks indicate the presence of aggregates.**



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## Discussion

Tau is a major microtubule associated protein which promotes microtubule assembly and stabilization, and thus helps in outgrowth of neuronal processes and development of neuronal polarity [3]. *C. elegans* model containing single-copy expression cassettes coding for tau and tau with disease-associated PTM-mimetic mutations impairs neuron function and alters neuronal morphology [7]. Intriguingly, I observed that day 10 worms expressing T231E and K274/281Q showed presence of severe aggregates in and around the neuronal soma respectively. However, wild type tau strain (TauT4) didn't show presence of aggregates at that same age. Thus, functional decline of the neurons due to tau modifications can be correlated with presence of these tau aggregates providing hints towards commonalities with the aging mammalian brain and suggesting conserved mechaninsms which can be operative in neuronal decline across phyla. Previous studies have demonstrated that tau interacts with the microtubules in a "kiss and hop" mechanism, where tau dwells on a single microtubule in the range of milliseconds before it hops onto the neighboring one, residing only transiently on each of them. Importantly, it explained why tau, when its gets modified due to various PTMs cannot effectively bind with the microtubule anymore. Thus, in pathophysiological conditions, presence of free floating tau aggregates can be detected, which destabilizes microtubules due to decreased binding, causes disintegration of microtubules, disruption of neuronal communication, synaptic failure and ultimately neuronal death. It will be of interest to determine that if I can get rid off these tau aggregates either genetically or pharmacologically, whether the neuronal structral ingetrity restores or not. Another interesting observation was that the aggregates of the K274/281Q seemed bigger and brighter than that of the T231E mutant, and also they tend to concentrate on the AIS perimeter, rather than the soma itself. Whether it causes any exacerbated neurodegeneration in the older K274/281Q *C. elegans* model need to be determined, and whether this specific tau modification is more sensitive to exposure to toxic substances such as paraquat, arsenic, lead, etc.

## Conclusion

In conclusion, this study clearly demonstrate that single-copy expression of tau with disease-associated PTM mimetics-mutations that mimic pathologic PTMs of tau have presence of tau aggregates in the neuron. Concerning novel therapeutic approaches, natural small molecules can possibly be tested in the near future as they have a good rationale for being beneficial for AD patients at any age. Since, *C. elegans* is a great genetic model organism for drug screening owing to its short life span and ease of growing in a plate, this novel *C. elegans* AD model can be used as a platform for therapeutic drug screening. Small molecules can be screened at a rapid pace which can reduce or remove the accumulating tau aggregates and simultaneously improve neuronal health. If promising, those compunds can be tested in neuronal cell lines, and applied in higher model organisms, such as rats and mice and eventually can undergo clinical trials.

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