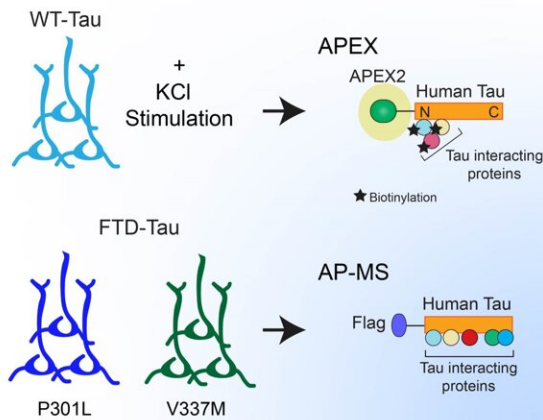


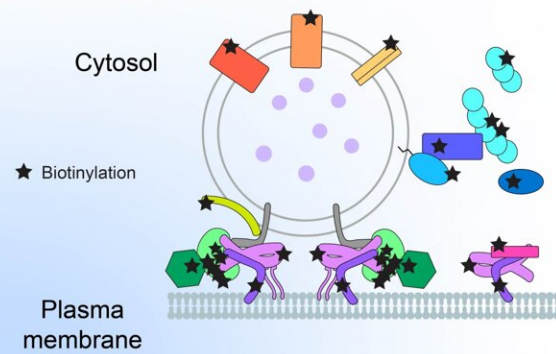
New findings for the function of tau in neurodegenerative disease

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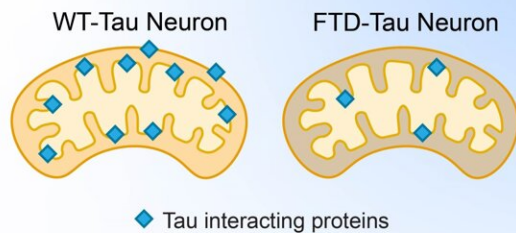
Human iPSC-derived neuron Tau interactome platform



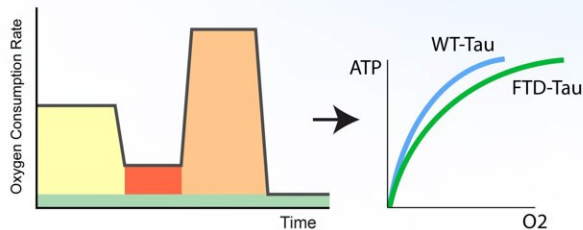
Activity-dependent binding of Tau to synaptic vesicle proteins during Tau secretion



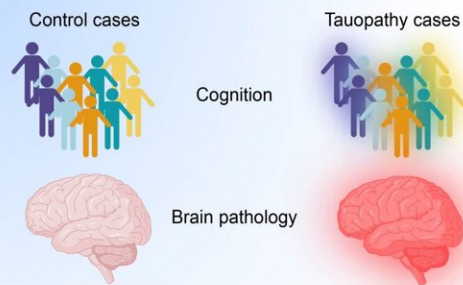
FTD mutations reduce Tau interaction with mitochondrial proteins



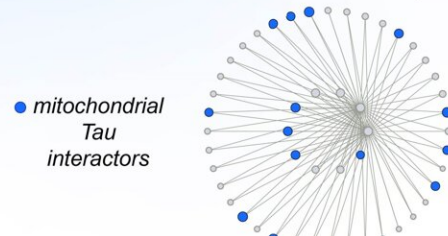
FTD mutations impair bioenergetics



Tau interacting proteins downregulated in human tauopathy



Mitochondrial Tau interactors downregulated



Tau interactome maps synaptic and mitochondrial processes associated with neurodegeneration. Credit: The Buck Institute for Research on Aging

Utilizing cutting-edge proteomics, researchers at the Buck Institute and elsewhere have mapped the "tau interactome" uncovering new findings about the role of tau in neurodegenerative disease. Publishing in *Cell*, scientists found that mutant tau impacts the function of mitochondria in human neurons. They also suggest a mechanism for how tau gets released from neurons and spreads throughout the brain, a pathological process that is strongly correlated with disease progression.

"Understanding the mechanisms of what is happening within cells during disease is key to discovering new ways to treat [neurodegenerative diseases](#) including Alzheimer's, which is the most common tauopathy," said Buck Institute assistant professor Tara Tracy, Ph.D., lead author of the paper. "We hope that other researchers take advantage of our 'tau interactome' which is a broad and unbiased survey of tau interacting proteins in the cell that could be contributing to disease."

The properties of tau

Normal tau is well-known for its role in binding to microtubules which maintain the cytoskeleton of the cell. In disease, abnormal chemical changes cause tau to detach from the microtubules and stick to other tau proteins forming threads that eventually join to become tangles inside of neurons. The presence of tau tangles are one of the hallmarks of Alzheimer's disease and related tauopathies.

Tracy says over the last decade researchers realized that, in disease, tau is doing a lot more than just impacting the cytoskeleton of the cell. "Tau interactions are more complex than what was initially thought. There's

been a lot of attention in the field to the fact that tau can be secreted from neurons and spread across connected [cells](#)—but there hasn't been an understanding of how this occurs and the cellular machinery involved," she said. "The methods used in this paper provide an unprecedented dynamic map of the tau interactome to shed light on the interactions that occur during tau secretion and on tau's role in neuronal function and disease."

New insights

Working in neurons derived from human induced [pluripotent stem cells](#), researchers show that when tau is secreted during increased neuronal activity it interacts with proteins on the outside, rather than inside, of [synaptic vesicles](#). These vesicles store neurotransmitters which are released at the junction between neurons. Tracy said this is surprising when it comes to tau, adding that the release likely happens through an association with the SNARE complex, proteins that exist at the presynaptic terminal and that are necessary for the fusion vesicles with the plasma membrane to release neurotransmitters. "Showing a potential mechanism for how tau gets released can inform future studies into how we can prevent diseased tau from getting out of neurons and spreading throughout the brain," said Tracy.

Researchers also show that tau binds to mitochondrial proteins in [neurons](#). Tracy says the binding appears to be beneficial when tau is normal, but when diseased tau impairs neuronal bioenergetics it may be due to tau's diminishing interaction with mitochondrial proteins. These tau interacting proteins in mitochondria were downregulated in brain tissue from multiple human cohorts and the downregulation correlated with disease severity.

Important for Alzheimer's and much more

Tauopathies encompass several clinical-pathological entities including Alzheimer's disease, [progressive supranuclear palsy](#), Pick's disease, [chronic traumatic encephalopathy](#), frontotemporal dementia, corticobasal degeneration, and post-encephalitic parkinsonism. "Millions of people worldwide are currently living with the burden of tauopathy-associated neurological diseases," said Tracy. "This provides an urgency to those of us working to develop treatments for these diseases. It is our hope that this paper helps move the field forward in a major way."

More information: Li Gan, Tau interactome maps synaptic and mitochondrial processes associated with neurodegeneration, *Cell* (2022). [DOI: 10.1016/j.cell.2021.12.041](https://doi.org/10.1016/j.cell.2021.12.041).
[www.cell.com/cell/fulltext/S0092-8674\(21\)01563-4](https://www.cell.com/cell/fulltext/S0092-8674(21)01563-4)

Provided by Buck Institute for Research on Aging

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