Decoding tau: signatures of aging and neurodegeneration

Jui-Heng (Henry) Tseng

The physiological relevance of protein modification in neurodegenerative diseases is now generally well accepted, as the tau protein, one of the hallmark features of Alzheimer's disease (AD), is heavily modified in disease. Previously, we identified a distinct form of tau termed "aged tau" that accumulates in wild-type mice during aging. This aged tau is defined by its specific modification profile and localization pattern, and could be a prelude to the development of tau pathology in AD. Furthermore, this aged tau formation can be accelerated by AD-related stresses including neuroinflammation. These findings led us to explore unique tau modifications in a subsequent study, where we showed that unique pathogenic tau conformations can occur in neurons exposed to transmissible tau seeds. Moreover, this pathogenic tau species drives hallmark pathogenic mechanisms in AD. Lastly, we suspected that age-related stress could impact tau's conformation and began identifying stress-regulated pathways that may converge onto tau. We unexpectedly observed that oxidative stress impacts the global acetylated protein profile (acetylome) in neurons, and among these factors that were impacted, tau is one of them, but many others exist that are poorly studied. We hypothesize that these stress-induced alterations lead to neuronal vulnerability in many biological aspects. How age-related stress alters neuronal function will be a major topic of investigation in the future.