Using Mass Spectrometry to Decipher Diagnose and Drug Dementia

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Protein aggregation in the brain is central to neuronal death in neurodegenerative diseases, and in Alzheimer's Disease, Tau aggregation directly correlates with cognitive decline. Recently, Tau oligomers were shown to have prion-like seeding activity that propagate Tau aggregation throughout the brain. However, the biophysical mechanisms by which Tau forms prion-like seeds are unknown. While Tau biochemistry has been studied for over 30 years in vitro and in vivo, animal models, large-scale molecular human studies that interface clinical and pathological data have not been performed. We carried out an in-depth qualitative and quantitative characterization of Tau and its associated proteins in post-mortem human brain tissue from over 100 human tauopathy patients, Alzheimer's Disease patients, and control subjects. We identified 90 post-translational modifications (PTMs). To understand which modifications are crucial to prion formation and pathology, we analyzed the quantitative data obtained. These analyses reveal high occupancy and patient frequency for specific PTMs associated with pathology. Studies of size-resolved Tau suggest a temporal processivity of modification that leads to protein aggregation. In Alzheimer's disease, the ordered and progressive accumulation of PTMs in these human subjects correlates with disease progression. We further defined specific structural features that are associated with soluble tau oligomers which have been proposed as the tau prion in cell-based aggregation as well fibrilization assays. Once these features were defined, synthetic forms of these molecules were made and found to cause protein aggregation in cell-based and fibrilization studies. Together these data provide a mechanism for fibril formation and identify key modifications that promote aggregation in and around the core of the protofilament structure. These detailed analyses of Tau allow us to define the chemical nature of Tau that is associated with its aggregation in human disease and the means to prevent the prion-like spread of aggregation.

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