Repositioning of polyubiquitin alters the pathologic tau filament structure

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Structurally diverse tau filaments form proteinaceous aggregates in a heterogeneous group of neurodegenerative diseases called tauopathies1. The factors extrinsic to the highly ordered core structure that influence tau filament stability are not well understood. Here, we found that polyubiquitinated tau filaments from Alzheimer's disease and vacuolar tauopathy human brain tissue exhibit distinct seeding patterns in mice, in association with differences in tau filament ultrastructure determined by cryo-electron microscopy. Interestingly, chemical modulation of the polarity of polyubiquitin adjacent to the tau core with the small molecule ubistatin B resulted in the repositioning of poorly structured densities towards positively charged residues on the highly structured core filament, leading to shifting of the protofilament-protofilament interface of certain vacuolar tauopathy tau filaments. These results suggest that the structure of tau filaments that are associated with different seeding activities in vivo can be influenced by post-translational modifications.

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