

Hunting For The Aggregation Culprits - Individual And Combined Effects Of Post-translational Modifications On Tau Pathology

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Successful site-specific tau modification • Semisynthesis as tool for studying PTMs • Differentiated effects of PTMs *in vitro* • Carbamylation at K311 drives aggregation • Succinylation enhances tubulin polymerization

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	REFERENCES
Fibrillar tau is considered a key driver Alzheimer's onset and progression. Compared to physiological tau, aggregated tau shows a marked increase in post-translational modifications (PTMs), most notably phosphorylation and acetylation. Identifying PTMs emerging at the disease onset could yield biomarker and therapeutic leads. Combining the versatility of solid-phase peptide synthesis with recombinant expression of protein segments, semisynthesis was applied to generate site-specifically modified, full length tau variants in order to map select PTMs.	Defined PTMs were incorporated into synthetic peptides introducing modifications such as acetylation, succinylation and carbamylation. Aggregation and tubulin polymerization for modified variants were characterized through Thioflavin T and intrinsic absorbance measurements. Fibril formation was additionally confirmed by scanning electron microscopy.	Discrete PTMs were introduced into tau employing protein semisynthesis. The examined PTMs have observable effects on aggregation behavior and tubulin polymerization.	The semisynthesis platform enables precise interrogation of individual and combined tau PTMs, addressing the need to analyze modification specific effects. By distinguishing isolated effects of select PTMs, we aim to identify potential disease-driving modifications for biomarker discovery or therapeutic intervention. Prospective biochemical experiments will explore liquid-liquid phase separation and investigate cytotoxicity in SH-SY5Y cells for select tau variants.	Y. Wang, E. Mandelkow, <i>Nat. Rev. Neurosci.</i> 2016, <i>17</i>, 22–35. T. Baldensperger, M. Preissler, C. F. W. Becker, <i>RSC Chemical Biology</i> 2025, <i>6</i>, 129–149. B. N. Dugger, D. W. Dickson, <i>Cold Spring Harb Perspect Biol</i> 2017, <i>9</i>. D. Ellmer, M. Brehs, M. Haj-Yahya, H. A. Lashuel, C. F. W. Becker, <i>Angew. Chem. Int. Ed.</i> 2019, <i>58</i>, 1616–1620. M. Haj-Yahya, H. A. Lashuel, <i>Journal of the American Chemical Society</i> 2018, <i>140</i>, 6611–6621.