Post-translational Modifications in Parkinson's disease and Synucleinopathies: From mechanisms to novel targets and therapeutic opportunities

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The misfolding and aggregation of the presynaptic protein alpha-synuclein (aSyn) play central roles in the development and progression of Parkinson's disease (PD) and several other neurodegenerative diseases, collectively referred to as Synuclieopathies. However, what triggers aSyn aggregation in the first place remains a mystery, and our knowledge about the molecular determinants of aSyn pathology and how it spreads in the brain remains incomplete. Although aSyn in pathological aggregates is subjected to extensive post-translational modifications (PTMs), whether these PTMs represent makers or drivers of pathology formation was not clear.

In this lecture, I will present work from our group that illustrates how using integrative chemical biology approaches and novel neuronal models of pathology formation enabled addressing this knowledge gap, deciphering the aSyn PTM code, and uncovering new therapeutic opportunities for the treatment of PD. Collectively, our work shows that targeting PTMs presents unique opportunities to 1) stabilize the native state of aSyn; 2) lower aSyn protein levels, or 3) neutralize the activity of pathogenic aSyn species and prevent their propagation in the brain. I will close by discussing the implications of our findings for ongoing efforts to develop aSyn targeting therapies and biomarkers.