Mechanisms of the Interplay of Tau and Alpha-Synuclein on Tubulin Polymerization Promoting Protein (TPPP/p25)

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In neurodegenerative diseases such Parkinson’s disease (PD), the misfolding and deposition of proteins a-synuclein and tau is hallmark. Conformational changes in native unfolded proteins, tau and a-synuclein lead to abnormal proteinaceous deposits called Lewy bodies (LBs) and neurofibrillary tangles (NFTs) respectively. An intermediate structure (oligomers) in route to large fibrillar deposit is consider responsible for neuronal loss in PD. Although a crosstalk between, tau and a-synuclein oligomers have been suggested, the mechanism of toxicity remain unclear. TPPP/p25, an unfolded protein found in the oligodendrocytes of the normal brain, appear within the neurons in PD cases. Evidence has shown that a-synuclein induce the misfolding of TPPP/p25. Whether tau oligomers can induce the misfolding of TPPP/p25 remains unclear. To further study the mechanism by which tau and a -synuclein induce the misfolding and aggregation of TPPP/p25, we performed a set of experiments in vitro. Here, we generated a stable cell line overexpressing TPPP/p25 fused with GFP protein. Cells were exposed to tau and a-synuclein monomers, oligomers, and fibrils. Our immunostaining and toxicity assays suggest that tau oligomers can induce the misfolding and aggregation of TPPP/p25. To our knowledge, this is the first evidence showing the role of tau oligomers into TPPP/p25 aggregation pathway. Furthermore, we confirmed that the oligomeric structure of a-synuclein triggers the misfolding of TPPP/25 in vitro. With these results, it can be concluded that both tau oligomers and a-synuclein oligomers likely play a vital role in the progression of Parkinson’s disease.

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