AN UNSTRUCTURED PROTEIN WITH DESTRUCTIVE POTENTIAL: TPPP/P25 IN PARKINSON’S DISEASE

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Tubulin Polymerization Promoting Protein (TPPP/p25) is a prototypical member of a new and unique family of tubulin-binding brain-specific protein that is implicated in the regulation of the microtubule dynamics and enriched in neuronal and glial pathological inclusions characteristic for Parkinson’s disease and other synucleinopathies but not for tauopathies. TPPP/p25 has well-established unstructured motifs: the disordered N- and C-terminal segments straddling the middle highly flexible region. The N-terminal tail can function as a signaling sequence that affects its tubulin polymerization-promoting activity upon specific phosphorylation by its intracellular interacting partners, ERK2. TPPP/p25 occurs predominantly in oligodendrocytes; its expression is extensively enhanced on the course of the differentiation of the progenitor cells which is crucial for the myelinization and ensheatment of axons. Our single cell experiments established with HeLa cells over-expressing TPPP/p25 resulted in aggresome-containing living cells at the centrosome region, which mimic the formation of pathological inclusions. This cell model can be used to analyze the mechanism of action of potential drugs targeting pathological inclusions like Lewy body. Recently we demonstrated the interaction of TPPP/p25 with Ab42 oligomer in vitro system and in living cells leading to protein aggregation. The TPPP/p25-derived microtubule assembly is impeded by the toxic intracellular Ab42 oligomer species due to its direct binding to TPPP/p25. These insights may help to explain the pathomechanism of neurological disorders even in the cases of mixed pathology (simultaneous occurrence of α-synuclein and β42-amyloid), and may contribute to the development of novel therapeutic strategies as well.