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Challenging drug target for moonlighting and chameleon proteins

The conformational diseases such as Parkinson's disease (PD) and Multiple System Atrophy (MSA) represent an important group of neurodegenerative disorders. The hallmarks of these diseases are the α-synuclein (SYN) and the recently discovered Tubulin Polymerization Promoting Protein (TPPP/p25). Both proteins are disordered with chameleon characteristics and expressed distinctly in neurons and oligodendrocytes (OLGs), respectively; notwithstanding they are co-enriched and co-localized in pathological inclusions in the case of PD and MSA. TPPP/p25 is the prototype of the Neomorphic Moonlighting Proteins by displaying both physiological and pathological functions due to their interactions with distinct partners. At physiological conditions TPPP/p25 modulates the dynamics and stability of the microtubule system; its expression is crucial for the differentiation of OLGs, the major constituents of the myelin sheath. The assembly of TPPP/p25 and SYN, as fatal initiative, of the etiology of PD and MSA has been established. Due to the unique structural and functional features of TPPP/p25, a new innovative strategy has to be evaluated to inhibit and/or destruct specifically the interaction of TPPP/p25 with SYN; this could be fulfill by targeting of the interface of the pathological complex without affecting the physiological one. Our studies underline that targeting multifunctional proteins is a challenging task; nevertheless, the validation of a drug target can be achieved by identifying the interface of complexes of the partner proteins existing at the given pathological conditions.

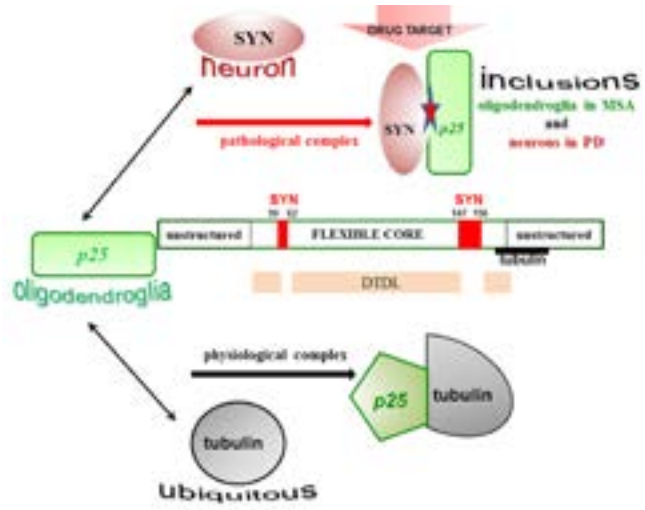

Figure 1: Distinct interfaces of TPPP/p25 are involved in its hetero-association with tubulin and SYN as physiological and pathological partners. The interaction of the disordered TPPP/p25 with tubulin results in significant conformational changes; this effect does not manifest itself in the case of its association with SYN. Although the deletions within the middle CORE segments do not abolish the binding of TPPP/p25 mutants to SYN, except in the case of the double truncated double loop mutant (DTDL), due to its chameleon feature; however, a potential segments (marked red) were identified as potential drug target.

Biography

Judit Ovádi has expertise in Biochemistry, Enzymology and Molecular Biology. She defined the metabolic channeling at microscopic and macroscopic levels as a powerful mechanism to control and direct metabolic pathway at crossroads. Her research team showed the sensing potency of the microtubule network at system level that can regulate signaling pathways due to its decoration by interacting partners. They discovered a unique brain-specific protein denoted Tubulin Polymerization Promoting Protein (TPPP/p25) that displays two exciting characteristics: Intrinsically unstructured and enriched in brain inclusion in the case of Parkinson disease and other synucleinopathies. The structural and functional features of this protein have been characterized at different levels of organizations under physiological and pathological conditions. She has supervised several DSc and PhD dissertations. She was an invited Visiting Professor in USA, Spain and Italy; Invited Speaker in international congresses in the last few years in Tokyo, San Francisco, Jerusalem, Orleans, Nice. At present, she is a Professor Emerita, Laureata Academiae of the Research Center of Hungarian Academy of Sciences.

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