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Anne-Marie Lambeir*

University of Antwerp, Belgium

The prolyl oligopeptidase and α -synuclein connection: context, insights and hypotheses

More than a decade after the discovery that prolyl oligopeptidase (PREP) influences α -synuclein (aSyn) aggregation by a process that does not rely on its peptidase activity, the molecular basis of this phenomenon is still largely unknown. We revisit the connection between PREP and aSyn and review old and new experimental data in a contemporary setting. In vitro the interaction between PREP and aSyn is weak and transient, mostly promoting early phases of aggregation without affecting the rate of β -fibril formation. Moreover, this interaction is not dependent upon the C-terminal prolines of aSyn but is affected by PREP inhibitors and it inhibits PREPs peptidase activity. There is evidence for a binding site for peptides much longer than the usual PREP substrates. In cellular aggregation models PREP colocalizes with aSyn in the cell periphery and neurites but not with aggresomes and stress markers. The modular assembly of molecular machines and the observation that PREP's protein-protein interactions are tuneable by active site inhibitors, lead to the hypothesis that this binding site features in the crosstalk between autophagy and neuron-specific pathways involving vesicle transport and protein secretion.

Keywords: Prolyl oligopeptidase, α -synuclein, autophagy, peptidase inhibitor, Parkinson's Disease

Biography

Professor Anne-Marie Lambeir is Emerita Professor of Medical Biochemistry in the Department of Pharmaceutical Sciences at the University of Antwerp, where she has built a distinguished career in research and higher education. Her academic work centers on enzymology, with particular expertise in enzyme kinetics, structure-function relationships, and the biochemical mechanisms that regulate enzyme activity. Throughout her career, she has been dedicated to advancing pharmaceutical sciences while mentoring students and researchers in the fields of biochemistry and molecular medicine.

Professor Lambeir is widely recognized for her contributions to the study of enzymes as therapeutic targets, particularly in the context of neurodegenerative diseases and other disorders with significant unmet medical needs. Her research has enhanced the understanding of enzyme function and inhibition, supporting the development of novel drug discovery strategies. Through her extensive scientific publications, collaborative research, and commitment to education, she has made lasting contributions to biomedical science and pharmaceutical research.