Universität Basel

Research Project

The Time-and Spatially Resolved Aggregation of a-Synuclein and its Relationship to Cell-Cell Transmissibilty

Third-party funded project

Project title The Time-and Spatially Resolved Aggregation of a-Synuclein and its Relationship to Cell-Cell Transmissibilty
Principal Investigator(s) Stahlberg, Henning ;
Co-Investigator(s) Scheiwiller, Marcel ;
Organisation / Research unit
Departement Biozentrum / Structural Biology (Stahlberg)
Department
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The self-association of identical proteins into macroscopic entities with toxic and/or functional activities is an omnipresent process. Some protein aggregates exhibit a cross-β-sheet structure and are associated with several human diseases including Alzheimer's and Parkinson's disease (PD), but may also have a non-pathological function. This interdisciplinary proposal aims to obtain a detailed mechanistic understanding of the structural and cellular basis of the cell-to-cell transmissibility of α-synuclein (α-syn) aggregates, which are associated with PD. In particular it focuses on *in vitro* and in-cell studies of the spatially and time-resolved formation of seeds, the replication of amyloids, the role of the subcellular milieu in these processes, and the elucidation of environment-dependent amyloid polymorphisms and their relationship to transmissibility and toxicity. We propose to study the kinetics and structures of protein aggregation *in vitro* under a plethora of physiologically relevant conditions covering intracellular compartments (**RR**) and beyond, and to correlate these finding with the in-cell aggregation monitored by electron microscopy (EM) (**HS**) and super resolution fluorescence microscopy (SR) (**JR**), accompanied by cell biology studies on the transmissibility and the intracellular route of the infectious material (**LR**). Using this rather unique combination of techniques applied to both *in vitro* and in-cell studies, will give insight into (i) the relationships between the aggregation kinetics of α-syn, its localization to specific intracellular compartments and its cell-to-cell transmissibility and (ii) the relationship between cell toxicity and transmissibility.

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