DANDRITE
Danish Research Institute of Translational Neuroscience
Nordic EMBL Partnership for Molecular Medicine

DANDRITE Seminar

by visitor Mia Pöhler

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11.15 – 12.00

Small Anatomy Auditorium (building 1231-424)
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The autophagy-lysosomal pathway in aggregation, release, and toxicity of alpha-synuclein

Alpha-synuclein (aSyn) aggregation plays a crucial role in synucleinopathies such as Parkinson's disease and dementia with Lewy bodies. Aggregating and non-aggregating aSyn species are degraded by the autophagy-lysosomal pathway (ALP). In a previous study we have shown that the ALP is not only responsible for aSyn degradation but is also involved in the intracellular aggregation process of aSyn. Here, inhibition of lysosomal degradation at a late stage by bafilomycin A1 (BafA1) led to a substantial induction of cellular toxicity which was paralleled by a dichotomous effect on aSyn aggregation resulting in a reduction of large intracellular aSyn aggregates but an increase of smaller punctuate structures further supporting a protective role of intracellular aSyn aggregation.

An additional role of extracellular aSyn in the pathology of synucleinopathies substantiating a prion-like cell-to-cell propagation hypothesis has been suggested since released aSyn species and spreading of aSyn pathology throughout neural cells have been observed. However, the molecular interplay between intracellular pathways, aSyn aggregation, release, and response of the local microenvironment remains unknown. In our current study we attributed aSyn-induced toxicity mainly to secreted species in a cell culture model of aSyn aggregation and in aSyn transgenic mice: We showed that ALP inhibition by BafA1 reduced intracellular aSyn aggregation but increased secretion of smaller oligomers that exacerbated microenvironmental response including uptake, inflammation and cellular damage. Low-aggregated aSyn was predominantly released by exosomes and Rab11-associated pathways whereas high-aggregated aSyn was secreted by membrane shedding. The novel role of ALP connecting degradation and secretion of aSyn directly underline the importance of extracellular toxic action of aSyn. Thus, impaired ALP in the diseased brain not only limits intracellular degradation of misfolded proteins, but also leads to a detrimental microenvironmental response due to enhanced aSyn secretion. Balancing the protein homeostasis by supporting intracellular degradation systems and modulating secretion pathways facilitate new therapeutic strategies to overcome protein aggregation in age-related chronic diseases.

Host: Group leader Mark Denham, DANDRITE