More than a synuclein story

Moors, T.E.

2020

document version
Publisher's PDF, also known as Version of record

Parkinson's disease is a devastating neurological disease. The development of urgently needed disease-modifying therapies requires thorough understanding of mechanisms involved in the initial stages and progression of this disease. A pathological hallmark in Parkinson's disease is the presence of cellular inclusions in the brain, called Lewy bodies and Lewy neurites, containing the accumulated protein alpha-synuclein. A substantial part of alpha-synuclein in Lewy inclusions is phosphorylated or truncated, indicating a role for these variants in Parkinson's disease. The accumulation of alpha-synuclein may be related to impaired functioning of pathways responsible for protein degradation in cells, including the autophagy-lysosomal system. In the past decades, different genetic risk factors for Parkinson's disease were found in genes related to this system.

In the present thesis, we aimed to obtain more insight into key determinants for alpha-synuclein aggregation and degradation in the Parkinson's disease brain using various biochemical and advanced microscopy techniques. Together, our studies confirm that truncated and mainly phosphorylated alpha-synuclein are important markers for pathology in Parkinson's disease, and demonstrate differences in their biochemical manifestations and (sub)cellular localizations in the brain. However, we also present evidence that impaired protein degradation is intimately linked with alpha-synuclein pathology, while our super-resolution microscopy observations suggested that the orchestration of alpha-synuclein in Lewy bodies is regulated by structural proteins. These findings highlight that alpha-synuclein aggregation and inclusion formation in Parkinson's disease are not isolated processes, but part of the dynamic and complex cellular environment in which they take place, thus more than solely *a synuclein story*.