Super-resolution microscopy informs on the molecular architecture of alpha-synuclein inclusions in model systems and in the human brain

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Abstract
Lewy bodies (LBs) and Lewy neurites are pathological hallmarks of Parkinson’s disease and other progressive neurodegenerative disorders known as Lewy body diseases (LBD). These proteinaceous depositions are immunopositive for alpha-synuclein (aSyn) and several other proteins, as neurofilament components. The structural organization and composition of aSyn inclusions is still unclear and needs to be addressed in greater detail, as this may open novel avenues for our understanding the disease-relevant pathological events.

In this study, we investigated the molecular architecture of aSyn, both in cell models and in human brain tissue, using state-of-art super resolution X10 Expansion microscopy (ExM). This approach physically expands specimens embedded into a swellable gel, preserving their biological information. Then, the specimen can be analyzed using standard epifluorescence microscopes, thereby obtaining nanoscale information.

The combination of different cell models, and human brain tissue enabled us to distinguish different types aSyn assemblies (e.g. ring shape or tubular structures), and a conserved pattern of aSyn inclusions surrounded/encaged by intermediate filament proteins. Overall, X10 ExM enabled us to gain insight into the architecture and biology of aSyn inclusions, and constitutes a powerful tool in the quest to understanding underlying disease mechanisms in synucleinopathies.