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The self-assembly of alpha-synuclein amyloid fibrils into higher order aggregates

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The formation of α-synuclein (aS) amyloid aggregates, called Lewy bodies (LBs), is a hallmark of Parkinson's disease (PD). The role of LBs in PD is however still unclear; they have been associated with both neuroprotection and toxicity. In an attempt to resolve this contradiction, we studied the aggregation of aS in cell model systems and in the test tube. We induced the formation of aS inclusions, using three different methods in SH-SY5Y cells and rat-derived primary neuronal cells. Using confocal and STED microscopy we observed method dependent differences in aS inclusion morphology, location and function. The aggregation of aS in functionally different compartments correlates with the toxicity of the induction method measured in viability assays. The most cytotoxic treatment largely correlates with the formation of proteasome associated juxta-nuclear inclusions. Cytosolic deposits formed by less toxic methods are not associated with the proteasome and are more prevalent. The formation of inclusions is however not necessarily an active process governed by the cells biochemical machinery. In the test tube, we observed that, under physiological salt conditions aS spontaneously self-assembles into micrometer-sized suprafibrillar aggregates (SFAs) that are reminiscent of LBs. The assembly of these SFA is very sensitive to physicochemical conditions such as ionic strength. This sensitivity leads to the formation of anisotropic SFAs *in vitro* and may also be the cause of the anisotropy observed in their *in vivo* counterparts. The onset of disease may trigger changes in the physicochemical conditions within the cell which are reflected in the architecture of LBs.

Biography

Mireille Claessens has obtained her PhD training from Wageningen University, Netherlands. After receiving her PhD degree in 2003, she did her Post-doctoral studies from the Technical University of Munich, where she investigated the physical properties of cytoskeletal networks. In 2008, she joined the Nanobiophysics Group at the University of Twente, Netherlands as an Assistant Professor and in 2013 she became the Chair of the Nanobiophysics group.

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