Nano-Scale Structural Characterization of Parkinson's Disease

Henning Stahlberg, Thomas Braun, Paula Perez Navarro, Andreij Bieri, Rosmarie Sütterlin, Stefan Arnold, and Sarah Shamoradian

C-CINA, Biozentrum, University of Basel, Mattenstrasse 26, CH-4058 Basel, Switzerland
Henning.Stahlberg@unibas.ch

Abstract

Parkinson's Disease (PD) is the second most common neurodegenerative disease. PD affects ~2% of individuals over 60 years of age. The primary hallmark of PD is a loss of neurons in a central region of the human brain, called *substantia nigra*, which then leads to tremor and other neuromotor deficits. The affected brain regions show so-called Lewy-bodies, which are dense "blobs" of several tens of micrometers in size that are found in the affected neurons. These Lewy-bodies are commonly associated with the presence of the protein alpha-synuclein, which is a protein that otherwise is involved in normal neuronal function.

In order to understand the biological processes behind the formation of Lewy bodies, we study the protein alpha-synuclein and its consequences on neurons, using nano-scale tools.

Alpha-synuclein (a-syn) is a small, 14kDa protein, which can be monomeric, form higher-order oligomers, or aggregate into fibrils of various shapes and sizes. Interestingly, the fibril formation is a transmissive process: A certain type of fibril can "seed" the growth of other fibrils of the same type, in a prion-like process. Even though the presence of a-syn fibrils is correlated with PD, it was previously not known, how these fibrils lead to neuronal death. A-syn can also interact with membranes in various forms, such as coating membranes, disrupting membranes, forming pores in membranes, or assisting membrane fusion.

We used biochemical and biophysical methods to produce and characterise a-syn [1], and developed nano-technology tools to study its biophysical behaviour and impact on neurons. We also developed microfluidics-based tools to seed a-syn fibrils into neurons, and then analyse the cytosol of single neurons by microfluidics and transmission electron microscopy [2-3]. We further study human brain samples from deceased PD patients who donated their brain to research. Here, we analyse the cellular ultrastructure of the affected brain tissue [4], and characterize in 3D at the nanometer scale the different processes and mechanisms of disease progression, and their impact on neuronal function.

References

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