Molecular basis of Parkinson’s Disease: the fate of cytotoxic oligomers under cell-like conditions

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Research Abstract

The protein a-synuclein (aSN) is a critical component in the development of Parkinson’s Disease (PD) due to its ability to aggregate. While aSN ultimately forms amyloid fibrils, oligomers corresponding to 30mers of aSN are increasingly identified as the cytotoxic species which kill neurons and lead to PD. The groups of the two main applicants have recently made great progress in elucidating how oligomers form and turn over in vitro, showing that different oligomers co-exist and the major species inhibits fibril formation and is exceedingly stable,

though cytotoxicity can be impeded by small molecules which prevent or reduce interactions with cell membranes. However, it is unclear to what extent this insight can be transferred to in vivo conditions. The present application will address this. We will exploit the fact that hydrogen-deuterium exchange monitored by mass spectrometry (HDX-MS) both allows us to distinguish different oligomers and to characterize how molecular interactions affect their dynamics and stability. Accordingly, we will (1) develop techniques to separate different oligomeric species using MIPs (Molecularly Imprinted Polymers) and/or SEDUPS (Selective Degradation of Unstable Protein Species) and exploit this to selectively extract aSN oligomers from complex mixtures and then (2) investigate how the distribution and stability of the different species respond to physiologically relevant conditions such as oxidative stress, changes in pH, small molecules modulating aggregation, molecular crowding and vesicles mimicking membranes. This will culminate in (3) analysis of the fate of the different oligomers in neuronal cell extracts which will also allow us to test the in vivo effects of small molecule aggregation modulators. Overall we expect this to lead to a very significant advance in our understanding of how aSN oligomers exert their effects in vivo and how these effects may be controlled and reduced by juidicious use of small molecule compounds.

Further information available at:

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