Unravelling the Cause of Parkinson's Disease in Molecular Detail

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Project description:

Parkinson's disease (PD) is the second most prevalent neurodegenerative condition after Alzheimer's, affecting millions of people globally. Rapid decline in cognitive function is accompanied by progressive loss of motor function resulting in increasing disability and ultimately death. Currently there is no cure for PD. Autopsy of PD brains reveals extensive tangled deposits, known as Lewy bodies and Lewy neurites which have accumulated in the neurons, resulting is cell death. These deposits are the hallmark of PD and are comprised of twisted fibrils consisting of a protein known as a-Synuclein. This protein has a natural physiological function but under certain conditions can misbehave and form aggregates. There is also strong genetic evidence linking a-Synuclein to PD, consequently this protein has become the subject of intensive research in efforts to find a cure. Early work focussed on the fibrils, however, recent work suggests that this may be a neuro-protective mechanism and that the cell toxic species are small oligomeric aggregates of a-Synuclein. It has been shown that these oligomers can move between cells and can act as seeds promoting the aberrant behaviour, specifically misfolding, of a-Synuclein in healthy cells and this has been postulated as the likely mechanism of spread of the disease. Whilst its true physiological function in the brain is unknown, it is clear that a-Synuclein is able to bind to cell membrane surfaces comprising phospholipids and maybe involved in intercellular signalling. Studies using membrane mimics reveal that aggregation is a thousand fold faster when a-Synuclein interacts with phospholipids. As a result, recent biophysical investigations have concentrated on the mechanism of membrane association, the early stages of oligomer formation and the changes in protein shape that accompany these processes. These studies have been frustrated by the need to work with lipid particles and heterogeneous, dynamic aggregates, such that despite intense conjecture a clear understanding of the aggregation trajectory remains elusive. In this project we seek to address these challenges and apply advanced spectroscopic and biophysical techniques to a series of a-Synuclein molecules engineered specifically to provide information at the molecular level regarding the assembly of single molecules into aggregated species on the surface of homogeneous particles. Using a combination of protein biochemistry and chemical biology approaches we will reveal the precise molecular geometry and alignment of a-Synuclein molecules in the toxic oligomeric species providing new insight on potential axes of therapeutic intervention.