Research reveals early steps in Parkinson's pathology

April 6 2010

Although the cause of Parkinson's disease remains a mystery, scientists now have a better understanding of the earliest stages of abnormal aggregation of a key disease-associated protein. The research, published by Cell Press online on April 6th in *Biophysical Journal*, provides new insight into the first steps in the formation of neurotoxic structures called Lewy bodies that are the hallmark of the Parkinson's brain.

Parkinson's disease is a neurodegenerative disorder that impairs movement and has been linked with a pathological accumulation of ?-synuclein protein inside of neurons. ?-Synuclein is a small, abundant protein that is intrinsically present in a disordered or "unfolded" state but displays a remarkable structural versatility. Previous research has shown that large fibrous clumps of ?-synuclein are present in Lewy bodies in the brains of Parkinson's patients.

"?-Synuclein can readily adopt different structures and, prior to formation of the large fibrous form, forms early small intermediates called oligomers," explains senior study author Dr. Yves Engelborghs from the Laboratory of Biomolecular Dynamics at the University of Leuven in Belgium. "Because the potential role of these intermediates in cell death has been established, detection and characterization of early oligomeric species is very important for understanding Parkinson's pathology."

The formation of ?-synuclein oligomers prior to the formation of larger fibrils has been shown before, but the many forms and transient nature

of ?-synuclein oligomers has made identification and characterization of the amount, size and conformation of these early intermediates very difficult. Dr. Engelborghs and colleagues used a sophisticated and sensitive imaging technique called fluorescence correlation spectroscopy to follow the disappearance of individual ?-synuclein molecules (called monomers) and the formation of early oligomers during the aggregation process.

The researchers characterized the kinetics of oligomer formation and demonstrated that the formation of early oligomers was concentration dependent. Using a different technique, they went on to show that oligomer formation was accompanied by a conformational change that preceded formation of higher order structures. Taken together, the results provide new insight into the initial steps of ?-synuclein aggregation.

More information: Engelborghs et al.: "Early aggregation steps in a-synuclein as measured by FCS and FRET. Evidence for a contagious conformational change." The Biophysical Journal, April, 2010. www.biophysics.org/

Provided by Cell Press