# Biology of Native Alpha-Synuclein Tetramers in Parkinsons Disease

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Biology of Native Alpha-Synuclein Tetramers in Parkinsons Disease

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Parkinson's disease & PD-related disorders

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alpha synuclein, Parkinson Disease, monomer, Biology, Lewy Body Dementia

**Research Abstract**
DESCRIPTION (provided by applicant): Pathogenic aggregation of alpha-synuclein (alphaSyn) is increasingly implicated in familial and sporadic Parkinson’s disease (PD) and other human synucleinopathies. Based largely on studies of the recombinant protein, alphaSyn has long

been defined as a “”natively unfolded”” monomer of 14 kD that is believed to acquire secondary (alpha- helical) structure only upon binding to certain lipid vesicles. In contrast, our lab discovered in 2011 that endogenous alphaSyn isolated under non-denaturing conditions from living human cells and neuronal lines occurs principally as a helically-folded tetramer of ~60 kD. Multiple methods, including sedimentation equilibrium analysis by analytical ultracentrifugation, scanning transmission electron microscopy, mass spectrometry and circular dichroism, established the existence of an alpha-helically folded tetramer. Not unexpectedly, this discovery engendered controversy, but we have recently completed an extensive analysis of living cells (including neurons) using in vivo crosslinking that has confirmed that the principa form of native alphaSyn in intact cells is a 60 kD tetramer. Also, 3 other labs recently provided evidence for the occurrence of alpha-helical oligomeric structures based on certain methods of preparing alphaSyn. If this finding that endogenous alphaSyn exists as a helically-folded tetramer can be further extended, it will have major implications for the biology of alphaSyn in health and disease, as the reviewers of our first version of this application recognized. A central concept of human neurodegenerative diseases — that normally soluble proteins (alphaSyn, tau, Abeta, etc.) can misfold and aggregate into neurotoxic species – depends on understanding the normal state of the protein and what “”misfolding”” and “”aggregation”” actually mean. Accordingly, we propose an integrated series of entirely novel Specific Aims to characterize the dynamic relationship of the metastable alphaSyn tetramers to the unfolded monomer believed to be the native structure of alphaSyn since its description 20 years ago. Aim 1 Raise conformation-specific monoclonal antibodies to purified alphaSyn tetramers as key tools for all Aims. Aim 2 Examine the effects of four PD-causing missense mutations and certain structure-altering artificial mutations on the kinetic equilibrium of tetramers and monomers in intact cells. Aim 3 Study the biochemical mechanism and dynamics of the assembly of freshly synthesized monomers into tetramers (and other oligomers), their stability in the cell, and their subsequent disassembly. Aim 4 Purify endogenous human ?Syn from normal and diseased (DLB) brains to establish its structure and assembly state in the most disease-relevant organ; then, systematically analyze its biochemical properties. We have made major progress towards these Aims since our first submission (see Preliminary Data). Our work elucidates the dynamic relationship between metastable physiological (alpha-helical) oligomers, unfolded monomers, and abnormally folded (beta-sheet-rich) oligomers of ?Syn in human cells and brain, with attendant mechanistic and therapeutic implications for PD.

**Lay Summary**

PUBLIC HEALTH RELEVANCE: Many brain diseases are characterized by “”misfolding”” and progressive aggregation of otherwise soluble proteins. To decipher the molecular basis of such a disease and devise effective therapies, one should know the normal biology of the responsible protein. In Parkinson’s disease (PD) and certain related disorders, ?-synuclein accumulates in neurons. Since its discovery 20 years ago, ?Syn has been defined as a “”naturally unfolded”” protein. In contrast, we discovered in 2011 that the major cellular form of alphaSyn is a helically-folded tetramer. Here, we propose many novel experiments to elucidate the complex relationship between the newly discovered helical tetramer, the unfolded monomer, and misfolded aggregates that are neurotoxic in PD.

**Further information available at:**

**Types:**

Investments > €500k

**Member States:**
United States of America

**Diseases:**
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2016

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