The role of a-synuclein accumulation in lysosomal hydrolase trafficking and function

https://neurodegenerationresearch.eu/survey/the-role-of-a-synuclein-accumulation-in-lysosomal-hydrolase-trafficking-and-function/

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The role of a-synuclein accumulation in lysosomal hydrolase trafficking and function

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NIH (NINDS)

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01/08/2015

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4

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

Hydrolase, alpha synuclein, trafficking, Parkinson Disease, Endoplasmic Reticulum

Research Abstract

? DESCRIPTION (provided by applicant): Protein accumulation is a soundly documented feature of all age-related neurodegenerative disorders, however the initiating events that lead to

their formation, as well as their relationship to disease, remains unknown. Parkinson’s disease (PD) is characterized by the conversion of a normally soluble synaptic protein called a-synuclein into insoluble amyloid fibrils that comprise Lewy body inclusions within Parkinson’s brain. Our recent data indicated that disruption of cellular degradation capacity through mutations in the lysosomal gene GBA1 contribute to the aggregation of a-synuclein. This suggested that disruption of lysosomal function contributes to the formation of Lewy bodies. Interestingly, we found that when a-synuclein accumulates, it can in turn feedback to inhibit the lysosomal system, thus causing a self-propagating cycle that promotes amyloid formation and growth within neurons. Our preliminary data indicate that a-synuclein inhibits the trafficking of hydrolases and prevents them from reaching the lysosomal compartment; however the molecular mechanism is not known. Experiments outlined in this application aim to delineate how a-syn disrupts lysosomes using cell lines, PD patient-derived induced pluripotent stem cell models, transgenic mice, and PD brain. Our goals are to 1) define the relationship between distinct a-syn aggregated assemblies and lysosomal dysfunction / neurotoxicity, 2) determine how a-syn affects protein trafficking of lysosomal hydrolases, 3) discover new rescue pathways in PD centered around promoting hydrolase folding and trafficking to the lysosome. These studies will provide new insight into the mechanism of how amyloid aggregates disrupt cellular processes, and identify novel therapeutic pathways for synucleinopathies centered on enhancement of the lysosomal clearance pathway.

Lay Summary
PUBLIC HEALTH RELEVANCE: Project Narrative Protein aggregates are found in all age-related neurodegenerative diseases, however the relationship of the aggregation process to cellular toxicity is not understood. This proposal aims to elucidate pathogenic cellular pathways responsible for promoting the formation of aggregates and define the downstream toxic action within cells. Our studies will advance our understanding of how neurons die in these diseases, and identify new cellular pathways for therapeutic intervention.

Further information available at:

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