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Cellular Milieu Imparts Distinct Pathological α -Synuclein Strains in α -Synucleinopathies

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Ronald Gathagan
SKMC Class of 2021
SI CTR Abstract
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Cellular milieu imparts distinct pathological α -synuclein strains in α -synucleinopathies.

Peng C, Gathagan RJ, Covell DJ, Medellin C, Stieber A, Robinson JL, Zhang B, Pitkin RM, Olufemi MF, Luk KC, Trojanowski JQ, Lee VM.

Introduction: In Lewy body diseases-including Parkinson's disease, without or with dementia, dementia with Lewy bodies, and Alzheimer's disease with Lewy body co-pathology - α -synuclein (α -Syn) aggregates in neurons as Lewy bodies and Lewy neurites. By contrast, in multiple system atrophy α -Syn accumulates mainly in oligodendrocytes as glial cytoplasmic inclusions (GCIs)

Objective: Our objective was to determine the conformational and biological profiles of α -Syn strains.

Methods: The following methods were used to collect and analyze data: Recombinant α -Syn purification and in vitro fibrillization. Preparation of sarkosyl-insoluble fractions from disease and control brains. Sandwich ELISA. Cell cultures. Stereotaxic injection of sarkosyl-insoluble fraction of pathological α -Syn and α -Syn PFFs. Immunohistochemistry. Purification and depletion of α -Syn from the sarkosyl-insoluble fraction by immunoprecipitation.

Results: GCI- α -Syn forms structures that are more compact and it is about 1,000-fold more potent than LB- α -Syn in seeding α -Syn aggregation, consistent with the highly aggressive nature of multiple system atrophy. We found that oligodendrocytes but not neurons transform misfolded α -Syn into a GCI-like strain. Moreover, GCI- α -Syn maintains its high seeding activity

when propagated in neurons. Thus, α -Syn strains are determined by both misfolded seeds and intracellular environments.

Discussion: Here we report that pathological α -Syn in GCIs and Lewy bodies (GCI- α -Syn and LB- α -Syn, respectively) is conformationally and biologically distinct. Furthermore, we showed that distinct α -Syn strains had no cell type preference in seeding α -Syn pathology and are generated by different intracellular milieus