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

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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 a-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 a-Syn pathology and are generated by different intracellular milieus