Patient skin- and brain-derived alpha-synuclein strains are distinct and modulate innate immune response in Parkinson's disease

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α-Synuclein (αSyn) aggregates ("strains") can be detected by seed amplification assays such as real-time quaking-induced conversion (RT-QuIC) from the tissues of patients with Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). Previously, we reported that RT-QuIC assay detects αSyn strains from the patient skin. However, whether skin-derived αSyn strains induce disease-specific pathology and trigger immune response is unknown. We generated a Förster resonance energy transfer (FRET)-based αSyn biosensor cell line and biosensor cell-derived neurons carrying the PD-linked A53T mutation. Using FRET-Flow cytometry and high-content confocal imaging, we examined biological activity and morphology of phosphorylated-αSyn inclusions seeded by RT-QuIC-amplified patient skin and brain αSyn strains in cells and neurons. Astrocytoma biosensor cells detected intracellular αSyn aggregation induced by PD, DLB, and MSA skin- and brain-amplified αSyn strains. PD skin-amplified strains induced distinct phosphorylated-αSyn inclusion morphology and conformational changes from PD brain-amplified and DLB skin-amplified strains. Inclusion morphology of DLB and MSA skin and brain-amplified strains were comparable. Skin-amplified strains induced neuronal inclusions and caused neurodegeneration. Biosensor cell-derived PD skin αSyn strains induced higher seeding activity than PD brain and DLB skin αSyn strains. αSyn aggregates triggered an increase in STAT1, which was mainly detected in the detergent insoluble fraction. We report that PD skin-derived αSyn strains are pathologically and conformationally distinct from PD brain-derived αSyn strains and may modulate STAT1 responses. Our results suggest an interplay between distinct αSyn strains and innate immune response in PD pathogenesis.

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