Antibody-binding differences in alpha-synuclein from Parkinson’s disease and multiple system atrophy

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Objective: Determine whether biochemical differences exist in alpha-synuclein found in Parkinson's disease (PD) and multiple system atrophy (MSA).

Background: In synucleinopathies such as PD and MSA there is growing support for the idea that different conformations of alpha-synuclein exist. In prior studies we found alpha-synuclein seeding ability present in both PD and MSA brain extracts using a cell-based FRET assay (Holmes and Furman, PNAS 2013). Here we test biochemical properties and antibody-binding of alpha-synuclein in these two diseases.

Methods: Brain tissue was serially extracted from patients with PD (n=3) and MSA (n=3) to yield detergent- insoluble fractions. We used commercial and novel antibodies generated to alpha-synuclein fibril and monomer to test MSA and PD fractions for binding of alpha-synuclein by immunoprecipitation. The forms of alpha-synuclein bound to the antibodies were assessed by fluorescence microscopy for ability to induce alpha-synuclein aggregation in the cell-based FRET assay.

Results: There were distinct differences in the ability of various antibodies to bind to alpha-synuclein from PD vs MSA. Both commercial and novel antibodies were able to bind a form of alpha-synuclein which was capable of seeding synuclein aggregation in the cell-based assay from MSA samples, but only minimally from PD samples. Investigation of species bound by Western blot is in progress.

Conclusion: Biochemical differences in pathologic alpha-synuclein in PD and MSA support the idea of conformational differences in the aggregated state and may underlie the diverse clinical and pathologic characteristics seen in these two synucleinopathies.