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Transport of alpha-synuclein fibril aggregates in an in vivo mouse model of Parkinson's disease.

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Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder for which there are currently no treatments to slow, halt, or reverse the disease process. The disease is defined by the accumulation of the protein alpha-synuclein into aggregates known as Lewy inclusions, but how these aggregates initiate and propagate to various locations throughout the brain is unknown. To develop targeted disease modifying therapies, it is important to understand how aggregated forms of alpha-synuclein are transported throughout the nervous system and to determine the effect aggregation of alpha-synuclein has on specific cell types and specific behaviors. The hypotheses of this research are that alpha-synuclein aggregates propagate through neuroanatomically connected pathways and that induction of Lewy pathology results in behavioral deficits. Current results support these hypotheses. In a new transgenic mouse model of PD we see direct evidence for axonal transport of aggregated alpha-synuclein using in vivo multiphoton and correlative light and electron microscopy (CLEM) imaging approaches. We also extend the findings of previous work and show that intramuscular injection of aggregated alpha-synuclein into the hind limb musculature not only leads to the formation of Lewy pathology in the cortico-spinal tract and brainstem motor system, but also to higher parts of the motor system, including primary motor cortex, strongly suggesting retrograde trans-synaptic spread through neuroanatomically connected pathways. Additional analyses also show differences in several behavioral assays including ultrasonic vocalizations, gross motor tasks, and cognitive behaviors following injection of aggregated vs monomeric forms of alpha-synuclein. Future work will target perturbation of possible mechanisms of transport to halt or reverse the accumulation of abnormal alpha-synuclein and reduce the resulting behavioral deficits in this mouse model of PD.