

Seeds of destruction in Parkinson's disease: Spread of diseased proteins kills neurons

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New research suggests that small "seed" amounts of diseased brain proteins can be taken up by healthy neurons and propagated within them to cause neurodegeneration. The research, published by Cell Press in the October 6 issue of the journal *Neuron*, sheds light on the mechanisms associated with Parkinson's disease (PD) and provides a model for discovering early intervention therapeutics that can prevent or slow the devastating loss of neurons that underlies PD.

Alpha-synuclein (α -syn) is a brain protein that forms abnormal, neuron-damaging intracellular clumps called "Lewy bodies." These clumps are the hallmark lesions of PD and other neurodegenerative disorders known as α -synucleinopathies. Strikingly, even healthy fetal nerve cells transplanted into the brains of PD patients for therapeutic purposes can develop Lewy bodies, suggesting that α -syn pathology spreads through the nervous system. However, it is not clear whether these Lewy bodies are formed by the spread of abnormal α -syn between cells or if the neighboring diseased neurons exert a toxic influence that causes the normal grafted neurons to produce Lewy bodies.

"We examined whether exposure of neurons to α -syn fibrils recruited normal α -syn in these neurons to form Lewy bodies," explains senior author, Dr. Virginia M.-Y. Lee, from the Perelman School of Medicine at the University of Pennsylvania. "We performed our experiments using synthetic α -syn fibrils and normal neurons, similar to the physiological conditions seen in the majority of sporadic PD patients."

Dr. Lee and colleagues found that the α -syn fibrils were taken up by the neurons and acted as "seeds" that induced normal α -syn to aggregate into PD-like Lewy bodies. The fibrils were taken up by a nerve cell process and then spread to the cell body where the PD-like Lewy bodies formed and impaired neuronal function, ultimately leading to death of the neuron. This suggests that abnormal extracellular α -syn can amplify and propagate PD-like Lewy bodies throughout the nervous system.

"We have developed a novel neuronal model of PD-like α -syn inclusions that enables dissection of mechanisms leading to Lewy body formation, as well as understanding how these inclusions affect the function and viability of affected neurons," concludes Dr. Lee. "These findings open up new avenues of research into understanding mechanisms of α -synuclein pathology, its impact on neuronal function, and discovering therapies for PD and other α -synucleinopathies." The research may lead to new therapies that can prevent the diseased protein from spreading to healthy [neurons](#) and causing irreversible damage.

Provided by Cell Press

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