How the Pathology of Parkinson's Disease Spreads

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Neuron-to-neuron transmission of a-synuclein may cause α-synuclein aggregates *to propagate*

Accumulation of the synaptic protein α-synuclein, resulting in the formation of aggregates called Lewy bodies in the brain, is a hallmark of Parkinson's and other related neurodegenerative diseases. This pathology appears to spread throughout the brain as the disease progresses. Now, researchers at the University of California, San Diego School of Medicine and Konkuk University in Seoul, South Korea, have described how this mechanism works. Their findings – the first to show neuron-to-neuron transmission of α-synuclein – will appear in the *Proceedings of the National Academy of Sciences (PNAS)* on July 29.

"The discovery of cell-to-cell transmission of this protein may explain how α-synuclein aggregates can pass to new, healthy cells," said first author Paula Desplats, project scientist in UC San Diego's Department of Neurosciences. "We demonstrated how α-synuclein is taken up by neighboring cells, including grafted neuronal precursor cells, a mechanism that may cause Lewy bodies to spread to different brain structures."

Eliezer Masliah, MD, and Paula Desplats, PhD.

This insight will impact research into stem cell therapy for Parkinson's disease. "Our findings indicate that the stem cells used to replace lost or damaged cells in the brains of Parkinson's

disease patients are also susceptible to degeneration," said Eliezer Masliah, MD, professor of neurosciences and pathology at UC San Diego School of Medicine. "Knowledge of the molecular basis of the intercellular transmission of α-synuclein may result in improved stem-cell based therapies with long-lasting benefits, by preventing the grafted cells to uptake α-synuclein or by making them more efficient in clearing the accumulated α-synuclein."

In a large proportion of Parkinson's disease cases, the aggregation of α-synuclein progresses in a predictable pattern – from the lower brainstem, into the limbic system and eventually to the neocortex, the part of the brain responsible for higher level cognitive functions. The hypothesis of disease progression by neuron-to-neuron transmission of α-synuclein that encouraged this study was supported by findings of two separate reports in 2008. In these studies, autopsies of deceased Parkinson's patients who had received implants of therapeutic fetal neurons 11 to 16 years prior revealed that α-synuclein had propagated to the transplanted neurons.

Collaborating with South Korean researcher Seung-Jae Lee, the UC San Diego researchers first looked at neural precursor cells in culture, co-culturing them with neuronal cells expressing α-synuclein. After 24 to 48 hours, the aggregated α-synuclein was evident in the precursor cells – results suggesting cell-to-cell transmission.

Using specific inhibitors, the research team also discovered that α-synuclein is transmitted via endocytosis, the normal process by which cells absorb proteins from the extracellular media by engulfing them within their cell membrane. Blockage of the endocytic pathway resulted in lesser accumulation of α-synuclein.

Additionally, the researchers found that failure of the quality-control systems of the cell contributes to the observed accumulation of α-synuclein in recipient cells. This is due to inhibited activity of cell particles called lysosomes, which would usually degrade and remove aggregates – resulting in their increased formation.

Next, the team tested to determine if α-synuclein could be transmitted directly from host to grafted cells in a mouse model of Parkinson's disease. Brains of the mouse model were grafted with fresh, healthy stem cells. Within four weeks, cells containing Lewy body-like masses were quite common, supporting the cell-to cell transmission mechanism.

Contributors to the study included co-first author He-Jin Lee and Eun-Jin Bae of Konkuk University in Seoul, South Korea; and Christina Patrick, Edward Rockenstein, Leslie Crews and Brian Spencer of the UC San Diego School of Medicine. The research was supported by the Brain Research Center of the 21st Century Frontier Research Program, funded by the Ministry of Education, Science and Technology; the Diseases Network Research Program of the Ministry of Education, Science and Technology; the Korea Science and Engineering Foundation, funded by the Korean government, and grants from the U.S. National Institutes of Health.

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