How the pathology of Parkinson's disease spreads

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Eliezer Masliah, MD & Paula Desplats, PhD

(PhysOrg.com) -- Accumulation of the synaptic protein alpha-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 alpha-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 alpha-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 alpha-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."

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 alpha-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 alpha-synuclein ."

In a large proportion of Parkinson's disease cases, the aggregation of alpha-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 alpha-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 alpha-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 alpha-synuclein . After 24

to 48 hours, the aggregated alpha-synuclein was evident in the precursor cells - results suggesting cell-to-cell transmission.
Using specific inhibitors, the research team also discovered that alpha-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 alpha-synuclein

Additionally, the researchers found that failure of the quality-control systems of the cell contributes to the observed accumulation of alpha-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 alpha-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.

Source: University of California - San Diego (news : web)