Synergistic interaction enhances pathogenesis of Parkinson's disease

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Scientists have identified a synergistic interaction that disrupts normal intracellular transport mechanisms and leads to the accumulation of neuron-damaging clumps of protein associated with Parkinson's disease (PD), a neurodegenerative disorder that is characterized by a specific loss of neurons in the midbrain and brainstem. The research, published by Cell Press in the December 24 issue of the journal Neuron, identifies a new potential therapeutic option for preventing PD-associated neuropathology.

Mutations in the α-synuclein (α-syn) and Leucine-rich repeat kinase (LRRK2) genes have been linked with inherited and sporadic forms of PD and previous research has shown that accumulation of cytotoxic α-syn protein inside of neurons represents a key step in the pathogenesis of PD. "Although earlier studies have suggested interplay between α-syn and LRRK2, a synergistic interaction in the pathogenesis of PD has not been established," explains senior study author Dr. Huaibin Cai from the Laboratory of Neurogenetics at the National Institutes of Health in Bethesda, Maryland.

In order to systematically investigate whether LRRK2 and α-syn act synergistically to potentiate PD, Dr. Cai and colleagues generated and characterized several types of transgenic mice that overexpressed different combinations of a PD-related α-syn mutation along with various forms of normal and PD-associated LRRK2. The researchers found that although overexpression of LRRK2 alone did not cause neurodegeneration, excess LRRK2 significantly accelerated the

progression of neuropathological abnormalities in transgenic mice expressing PD-related α-syn.

Overexpression of LRRK2 disrupted key structures and mechanism that play a role in transporting proteins inside of the neurons. Importantly, genetic disruption of LRRK2 maintained normal intracellular transport and reduced the accumulation of α-syn, thereby significantly delaying the progression of PD pathology in the PD α-syn transgenic mice. These findings suggest that LRRK2 exacerbates the abnormal intracellular accumulation of α-syn.

"We have uncovered a novel function for LRRK2 in regulating the intracellular trafficking and accumulation of α-syn in neurons and our results suggest that excessive amounts of LRRK2 or its mutants may result in abnormal neuron-damaging accumulation of α-syn protein," concludes Dr. Cai. "It is possible that inhibition of LRRK2 expression may provide an applicable therapeutic strategy to ameliorate α-syn-induced neurodegeneration in PD or other related neurodegenerative diseases."

More information: "Leucine-Rich Repeat Kinase 2 Regulates the Progression of Neuropathology Induced by Parkinson's-Disease-Related Mutant α-synuclein." Publishing in Neuron 64, 807-827, December 24, 2009. DOI 10.1016/j.neuron.2009.11.006 www.neuron.org

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