

Parkinson's mutation stunts neurons

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Mutations in a key brain protein known to underlie a form of Parkinson's disease wreaks its damage by stunting the normal growth and branching of neurons, researchers have found. They have pinpointed the malfunction of the protein made by mutant forms of the gene called LRRK2 and how it affects neurons, ultimately leading to their death.

The researchers, Asa Abeliovich and colleagues at Columbia University, said their findings could lead to animal models for studying the form of PD and ultimately to new treatments for the disease. They reported their findings in the November 22, 2006, issue of the journal *Neuron*, published by Cell Press.

The researchers launched their study of LRRK2 because other scientists had identified mutations in the gene in an inherited form of PD that mimics the clinical and pathological features of the common sporadic form of the disease. LRRK2 stands for "leucine-rich repeat kinase-2," which means that the LRRK2 protein is an enzyme called a kinase--a biochemical switch that activates other proteins by attaching a molecule called a phosphate to them.

In their experiments, when the researchers generated mutant forms of the enzyme, they discovered that the mutants showed higher-than-normal enzymatic kinase activity compared to the normal version. When they introduced the mutant forms into cultures of neurons, they saw a reduction in the growth and branching of the neurons. Such growth is critical for the neurons to establish and maintain connections with one another in the brain's neural circuitry. The researchers also found that cultured neurons with mutant LRRK2 enzymes showed reduced survival.

The researchers analyzed the function of the mutant proteins, establishing that it was the "triggering" kinase segment of the protein that was central to the enzyme's defective function.

The pathology of PD caused by mutated LRRK2 also includes formation of abnormal deposits, or

"inclusions," in the neurons. Similarly, Abeliovich and his colleagues found that the mutant LRRK2 proteins they created also caused such inclusions in the brain cell cultures.

What's more, when the researchers introduced the mutant form of LRRK2 into the adult rat brain, they saw the same stunting of growth of dopamine-producing neurons and production of abnormal inclusions. Finally, when they introduced the mutant LRRK2 into embryonic rat brain, they saw a reduction of length and branching of neuronal wiring during brain development.

The researchers wrote that their findings offer "a useful animal model for early LRRK2-associated disease." They concluded that their techniques of introducing the mutated gene could lead to a primate model for the form of PD. "These cellular and animal models may promote the discovery of effective therapeutics for LRRK2-associated disease," they wrote.

Source: Cell Press

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