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Einstein researchers discover important clue to the cause of Parkinson's disease

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A glitch in the mechanism by which cells recycle damaged components may trigger Parkinson's disease, according to a study by scientists at the Albert Einstein College of Medicine of Yeshiva University. The research, which appears in the January 2 advance online issue of The Journal of Clinical Investigation, could lead to new strategies for treating Parkinson's and other neurodegenerative diseases.

All cells depend on a surveillance system known as autophagy (which literally means "self eating") to digest and recycle the damaged molecules that arise as cells age. In autophagy, defective proteins and other molecules are transported to membrane-bound sacs called lysosomes. After attaching to the lysosomal membrane, the molecules enter the lysosome, where they are digested by enzymes. This cleanup process may be particularly important for nerve cells, which generate defective molecules more rapidly than most other types of cells. When autophagy is impaired, toxic compounds can accumulate and cause cell death.

"It is widely suspected that accumulation of a particular protein, known as alpha-synuclein, within affected nerve cells of Parkinson's disease patients contributes to the death of these cells," says Dr. Ana Maria Cuervo, senior author of the article and associate professor of anatomy & structural biology at Einstein.

Dr. Cuervo previously showed that mutant forms of alpha-synuclein—found in the five to 10 percent of patients who have familial

Parkinson's disease—are poorly digested via autophagy and also block the breakdown of other substances. While these alpha-synuclein mutations are rare, other modifications of alpha-synuclein—phosphorylated and oxidized forms, for example—can be found in the brains of all Parkinson's disease patients.

In this study, Dr. Cuervo and her colleagues looked at how several different modified forms of alpha-synuclein affected autophagy in vitro and in tissue culture. One particular modification of alpha-synuclein was found to interfere with autophagy: the compound created by the interaction of alpha-synuclein with dopamine, the main neurotransmitter produced by the nerve cells damaged in Parkinson's disease.

"Alpha-synuclein molecules modified by dopamine bound tightly to the lysosomal membrane, but they got stuck there and weren't effectively transported into the lysosome," says Dr. Cuervo. As a result, the alpha-synuclein molecules altered by dopamine were poorly degraded, and the presence of these molecules on the lysosomal membranes interfered with autophagic digestion of other compounds as well.

"We propose that inhibition of autophagy caused by dopamine's alteration of alpha-synuclein could explain the selective death of dopamine-producing nerve cells in Parkinson's disease," says Dr. Cuervo, who notes that interference with autophagy has also been implicated in other neurodegenerative diseases including Alzheimer's.

"By devising strategies for boosting autophagy in nerve cells or suppressing the chemical reactions that interfere with the autophagy—by lowering alpha synuclein expression, for example--we may be able to treat patients afflicted with these conditions," she says.

Source: Albert Einstein College of Medicine