Toxicity mechanism identified for Parkinson's disease

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Neurologists have observed for decades that Lewy bodies, clumps of aggregated proteins inside cells, appear in the brains of patients with Parkinson's disease and other neurodegenerative diseases.

The presence of Lewy bodies suggests underlying problems in protein recycling and waste disposal, leading to the puzzle: how does disrupting those processes kill brain cells?

One possible answer: by breaking a survival circuit called MEF2D. Researchers at Emory University School of Medicine have discovered that MEF2D is sensitive to the main component of Lewy bodies, a protein called alpha-synuclein.

In cell cultures and animal models of Parkinson's, an accumulation of alpha-synuclein interferes with the cell's recycling of MEF2D, leading to cell death. MEF2D is especially abundant in the brains of people with Parkinson's, the researchers found.

The results are scheduled for publication in the Jan. 2, 2009 issue of *Science*.

"We've identified what could be an important pathway for controlling cell loss and survival in Parkinson's disease," says senior author Zixu Mao, PhD, associate professor of pharmacology at Emory University School of Medicine.

Further research could identify drugs that could regulate MEF2D, allowing brain cells to survive toxic stresses that impair protein recycling, he suggests.

Most cases of Parkinson's disease are termed sporadic, meaning that there is no obvious genetic cause, but there are inherited forms of Parkinson's. Some of these can be linked to mutations in the gene for alpha-synuclein or triplications of the gene. The mutations and triplications cause the brain to produce either a toxic form of alpha-synuclein or more alpha-synuclein than normal.

"Somehow it's toxic, but alpha-synuclein isn't part of the cell's machinery of death and survival," Mao says.

He and his colleagues began examining how alpha-synuclein influenced MEF2D after a report from another laboratory on disposal of alpha-synuclein by chaperone-mediated autophagy (CMA).

During CMA, certain selected proteins are funneled into lysosomes, compartments of the cell devoted to chewing up discarded proteins. Mao and colleagues found that lysosomes isolated from cells will absorb MEF2D protein, and interfering with CMA chemically causes MEF2D levels to rise.

MEF2D is a transcription factor, a protein that controls whether several genes are turned on or off. Previous studies have shown MEF2D is needed for proper development and survival of brain cells. To function, MEF2D must be able to bind DNA.

The authors found that when CMA is disrupted, most of the accumulated MEF2D can't bind DNA. This may indicate that the protein is improperly folded or otherwise modified.

"Even though there's a lot of it, something is making the MEF2D protein inactive," Mao says.

Mao and his colleagues found that mice that artificially overproduce alpha-synuclein (a model of Parkinson's disease) have elevated levels of apparently inactive MEF2D in their brains. In addition, MEF2D protein levels were higher in the brains of Parkinson's patients than in controls.

Following the influence of alpha-synuclein on MEF2D may be a way to connect the various genetic and environmental risk factors for Parkinson's, even if CMA is not the sole mechanism, Mao says.

"It may be that various stresses impact MEF2D in different ways," he says. "We think this work provides an explanation that ties several important observations together."

Reference: Yang Q., et al., Regulation of Neuronal Survival Factor MEF2D by Chaperone-Mediated Autophagy, *Science*, Jan 2, 2009.

Source: Emory University