An early step in Parkinson's disease: Problems with mitochondria

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For the last several years, neurologists have been probing a connection between Parkinson's disease and problems with mitochondria, the miniature power plants of the cell.

Toxins that mimic Parkinson's effects act specifically to poison mitochondria, and mitochondria appear to be damaged in the brain cells that are endangered in the disease. But one unresolved question has been: are mitochondria simply the vulnerable "canaries in the coal mine" or is their deterioration a key step on the way to neurodegeneration?

Now researchers at Emory University School of Medicine have found that a protein called MEF2D, which helps brain cells withstand stress and toxins, also plays an unexpected role inside mitochondria. MEF2D's ability to keep mitochondria well tuned appears to be especially sensitive to impairment in Parkinson's disease, the research team found.

The results will be published online in the Journal of Clinical Investigation.

"Our data suggest that problems with MEF2D in mitochondria could represent one of the earlier steps in the progress of the disease," says senior author Zixu Mao, PhD, associate professor of pharmacology and neurology at Emory University School of Medicine. Postdoctoral researcher Hua She, PhD, was the first author.

The Emory team showed that MEF2D binds one particular

mitochondrial gene, ND6, which is necessary for assembly of complex I. Complex I begins the electron transport process that is necessary for mitochondria to function.

Mitochondria are thought to have evolved from bacteria that once lived independently, but were engulfed and harnessed by a primitive cell millions of years ago. Mao and his colleagues found an example of how this symbiosis has extended to having proteins like MEF2D turn on genes inside mitochondria.

"Our findings make a convincing and very intriguing case that dysregulation of mitochondrial DNA gene expression contributes to Parkinson's," Mao says.

Genes in the nucleus (that is, outside mitochondria) now encode most of the proteins that go into mitochondria. However, mitochondria still make a few of their own proteins, such as ND6.

In addition to showing how MEF2D functions in mitochondria, the team showed that toxins such as MPTP and the natural pesticide rotenone, which interfere with complex I and bring on Parkinson's in animals, also block MEF2D from working in mitochondria.

Mao's laboratory's previous research found that in Parkinson's, MEF2D levels are increased in the cell because of defects in a recycling process called autophagy. Now, they show that in the brains of Parkinson's patients, even when MEF2D levels are increased in the cell as a whole, they are reduced in mitochondria.

Because disruptions in mitochondria have been linked to other neurodegenerative diseases and heart disease as well, Mao says probing MEF2D's involvement in those disease processes may yield new insights.

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More information: H. She, Q. Yang, K. Shepherd, Y. Smith, G. Miller, C. Testa and Z. Mao. Direct regulation of complex I by mitochondrial MEF2D is disrupted in a mouse model of Parkinson disease and in human patients. *J. Clin. Invest.* 121, (2011)

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