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Study first to link mitochondrial dysfunction and alpha-Synuclein multiplication in human fibroblasts

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A new study in the *Journal of Parkinson's Disease* shows for the first time the effects of α-Synuclein (α-syn) gene multiplication on mitochondrial function and susceptibility to oxidative stress in human tissue. Mitochondrial dysfunction has been frequently implicated in the neurodegenerative process that underlies Parkinson's disease, but the basis for this has not been fully understood.

Investigators from The Parkinson's Institute in Sunnyvale, CA, evaluated skin fibroblasts from a patient with parkinsonism carrying a triplication in the α-syn gene (SNCA). The cells showed a significant decrease in cell growth compared with healthy controls. "Our results in patient-derived fibroblasts were remarkably similar to overexpression experiments in cell lines and animal models. We detected a decrease in ATP production, a reduction in mitochondrial membrane potential, and a reduction in complex I activity," commented Birgitt Schüle, MD, Assistant Professor, The Parkinson's Institute. Furthermore, these fibroblasts proved to be more sensitive to the effects of the neurotoxin and herbicide paraquat compared to controls.

Mitochondrial function and cellular damage were partially rescued after siRNA knockdown of α-synuclein in fibroblasts after paraquat treatment. "We observed a significant increase in membrane potential and cellular ATP synthesis as well as a decrease in LDH release, supporting the hypothesis that α-synuclein expression levels are directly

related to mitochondrial dysfunction," said Dr. Schüle.

According to Dr. William Langston, the Scientific Director and CEO of The Parkinson's Institute, and a co-author on the paper, these results are particularly exciting because they directly link a-syn over-expression and mitochondrial dysfunction in tissue from a parkinsonian patient. "One of the keys to unraveling this incurable and progressive disease is to solve the relationship between a-syn and mitochondrial dysfunction. In these results, we may have the first such link in human tissue," Langston said.

More information: The article is "Mitochondrial Dysfunction in Skin Fibroblasts from a Parkinson's Disease Patient with an alpha-Synuclein Triplication" by Sally K. Mak, Deepika Tewari, James W. Tetrud, William J. Langston, and Birgitt Schüle. *Journal of Parkinson's Disease*. 1(2). DOI:10.3233/JPD-2011-11205

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