Transcription factor clears protein clumps in Huntington's mice models

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Over expressing a transcription factor that promotes the increase in number of mitochondria greatly improves the neurological function of transgenic mice models for Huntington's disease (HD), researchers today told the American Society of Cell Biology's 50th Annual Meeting in Philadelphia.

Albert La Spada, M.D., Ph.D., and colleagues at the UC San Diego (UCSD) explained that over expression of the transcription factor results in a substantial clearing of the mutant protein aggregates in the brains of the mice models for HD.

The misfolded huntingtin (htt) proteins responsible for the aggregate formation in the mice also characterize human HD sufferers.

La Spada said that the over-expressed transcription factor, PGC-1α, may work by reducing oxidative stress that builds up toxic by-products from mitochondrial energy production in HD-impaired neurons.

Genetic studies have tied HD to a distinctive genetic repeat, a CAG trinucleotide in the htt gene that, if copied more than 35 times, results in the disease.

The mutated htt protein carries an expanded polyglutamine (polyQ) tract that misfolds and forms aggregates in neurons. HD affects many cell functions, but recently, researchers investigating the impact of toxins on mitochondrial function in rodents and nonhuman primates reported

similarities to the progression of HD.

Studies on HD transgenic mice and human HD patient material in the La Spada laboratory reinforced these recent findings.

The researchers took a closer look at a nuclear receptor activator, PPARg, and its coactivator, PGC-1α, which promotes the transcription of genes involved in mitochondrial biogenesis and energy production.

Their HD mouse models revealed that the mutant htt protein impaired PGC-1α function.

To test the connection, the researchers over-expressed PGC-1α in the HD-model transgenic mice.

An overabundance of PGC-1α significantly improved neurological function. It also markedly decreased htt protein aggregation in the animals' brains, which may account for the improved neurological phenotype, according to La Spada.

Indeed, the overexpression of PGC-1α virtually eliminated aggregated htt protein in the brains of the HD mice, he added.

La Spade said he attributes this unexpected result to the abilities of PCG-1α to reduce oxidative stress in the beleaguered mitochondria, the powerhouses of the cell that generate the energy needed to fuel cellular functions.

La Spada said that he hopes that this discovery could lead to therapies aimed at restoring PGC-1α function as a viable treatment for HD and perhaps for related neurological disorders such as Alzheimer's disease and Parkinson's disease.

HD, an inherited progressive neurodegenerative disorder, affects roughly 40,000 Americans. HD can vary considerably, but in its most severe form in adults, it takes an average of 20 years from the first onset of symptoms involving muscle control to severe cognitive decline and death, often from pneumonia. The disease currently has no cure.

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