

DRP1 is Identified as a Promising Therapeutic Target

Impaired energy metabolism has been identified as a major pathology in Huntington's disease. The mitochondria, the cell's energy factories, have not been found to be intrinsically defective but are thought to be mismanaged in some way. A University of Central Florida research team lead by Dr. Ella Bossy-Wetzel has discovered how this occurs. The HD protein interacts abnormally with the mitochondrial fission GTPase dynamin-related protein-1 (DRP1). DRP1 is the protein that is responsible for mitochondria fission in the fission-fusion cycle. DRP1 becomes overactive and upsets the balance in the cycle. The mitochondria fragment, mitochondrial transport becomes impaired, and cells die.



Dr. Ella Bossy-Wetzel

Photo by Jacque Brund

The researchers first examined rat cortical cells. Those with a normal polyglutamine region had healthy mitochondria whereas those with expanded polyglutamine stretches (expanded CAG repeats) had fragmented mitochondria. Those with 97 CAG repeats had more fragmentation than those with 46 CAG repeats. Time lapse imaging showed an increase of fission events compared to fusion events. Fragmentation was correlated with cell death.

Human skin cells were next examined. Fragmentation was also found in cells from people with Huntington's Disease, more so in those with juvenile rather than adult onset.

In addition, the researchers also examined mitochondrial transport and velocity in the rat cortical cells. Transport and velocity were normal when the CAG repeats were normal but decreased with expanded repeats. Again, the impairment was more severe with higher repeats. This is important because decreased transport would likely have a negative effect on energy distribution especially at synapses where demand for energy is high.

The researchers confirmed their findings in the YAC128 mice, finding an increase in mitochondrial fragmentation before the onset of symptoms, neurological deficits, aggregate formation, and cell death.

The researchers next examined the possible role of DRP1 in fragmentation. Examining both the YAC128 mice, and human brain tissue, they found that while the normal huntingtin protein only weakly interacts with DRP1 at best, the HD protein binds to DRP1 and increases its enzymatic activity.

Finally, they found that restoring the normal fission-fusion cycle by replacing DRP1 with a mutant version (DRP1 K38A) which promotes fusion, they were able to rescue the cell from mitochondrial fragmentation, mitochondrial transport impairment, and cell death.

“The next step will be to test the DRP1 function in animals and patients to see whether the protein also protects the brain,” Dr. Bossy-Wetzel said. “This could be done before the onset of disease in patients who have the mutant Huntington gene, but have no neurological symptoms. The hope is that we might be able to delay the onset of disease by improving the energy metabolism of the brain.”

“It is an outstanding piece of work, which further implicates mitochondrial dysfunction in the pathogenesis of Huntington’s disease,” said Dr. Flint Beal, a professor of neurology and neuroscience at the Weill Medical College of Cornell University who specializes in the disease and is a practicing physician. “It opens new therapeutic targets for therapies aimed at disease modification.”

Reference:

Wenjun Song, Jin Chen, Alejandra Petrilli, Geraldine Liot, Eva Klingmayr, Yue Zhou, Patrick Poquiz, Jonathan Tjong, Mahmoud A. Pouladi, Michael R. Hayden, Eliezer Masliah, Mark Ellisman, Isabelle Rouiller, Robert Schwarzenbacher, Blaise Bossy, Guy Perkins, & Ella Bossy-Wetzel. “*Mutant huntingtin binds the mitochondrial fission GTPase dynamin-related protein-1 and increases its enzymatic activity.*” *Nature Medicine* 2011 Feb 20. [Epub ahead of print].

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