NEURODEGENERATIVE DISEASE

Mitochondria, huntingtin and HD

New research links mutant huntingtin protein with mitochondrial abnormalities—and subsequent impaired mitochondrial function and dynamics—that could ultimately lead to neuronal damage and degeneration in affected brain regions of patients with Huntington disease (HD).

HD is an incurable genetic disorder in which symptoms—such as chorea, dystonia and cognitive decline—typically manifest between the ages of 35 and 55 years. HD symptoms then progress for the next 10–20 years until affected individuals eventually die, usually from complications such as pneumonia. “Several lines of evidence suggest that defective mitochondrial bioenergetics are present in patients with HD and mouse models of HD,” explains lead researcher Hemachandra Reddy from Oregon Health & Science University, USA. “However, the precise link between mitochondrial structure or function and mutant huntingtin aggregates was unclear.”

Reddy and his colleagues analyzed postmortem brain samples from six patients with HD (three with grade III HD, three with grade IV HD) and three age-matched healthy controls. The researchers measured the expression of several mitochondrial structural and electron transport genes, and quantified the amount of mutant huntingtin and mitochondrial structural proteins in the striatum and frontal cortex of HD patients as well as investigating levels of mitochondrial function and oxidative damage.

Mitochondrial dynamics were abnormal in patients with HD compared with healthy controls. The investigators found increased expression (at both the messenger RNA and protein level) of mitochondrial fission proteins (Drp1 and Fis1) and decreased levels of mitochondrial fusion proteins (Mfn1, Mfn2, Opa1 and Tomm40) in patients with HD. Moreover, expression of the mitochondrial matrix protein CypD was increased in HD patients, and levels of this protein increased with HD progression. Evidence of oxidative DNA damage (increased levels of the oxidative stress biomarker 8-hydroxy-guanosine) and loss of mitochondrial function (reduced levels of the electron transport proteins cytochrome b and cytochrome c oxidase 1) were found in individuals with HD, and these patients also exhibited markedly increased levels of mutant huntingtin oligomers in the cortex. Importantly, immunolabelling of brain samples revealed the presence of mutant huntingtin oligomers in the nuclei of neurons and mitochondria of patients with HD.

The study authors propose that mutant huntingtin oligomers associated with mitochondria could be the missing link between mitochondrial dysfunction and HD progression and pathogenesis. These new insights could lead to therapies for HD—a condition for which no cure is currently available. “Inhibiting mutant huntingtin oligomer association with mitochondria may be a therapeutic approach to treat patients with HD,” says Reddy. “Alternatively, treating presymptomatic individuals who carry the HD mutation with mitochondria-targeted antioxidants is another approach to delay HD progression.” Reddy now plans further work to understand the biology of mutant huntingtin oligomers and mitochondria and to investigate the effects of mitochondria-targeted antioxidants in HD mouse models.

Katrina Ray

Original article Shirendeb, U. *et al.* Abnormal mitochondrial dynamics, mitochondrial loss and mutant huntingtin oligomers in Huntington's disease: implications for selective neuronal damage. *Hum. Mol. Genet.* doi: 10.1093/hmg/ddr024