Medical Xpress

# Scientists identify new Huntington disease pathway

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(Medical Xpress)—An international group of researchers has identified a major new pathway thought to be involved in the development of Huntington disease. The findings, published in the *Proceedings of the National Academy of Sciences* journal, could eventually lead to new treatments for the disease, which currently has no cure.

Scientists at the BC Cancer Agency Research Centre and the Centre for Molecular Medicine and Therapeutics in Vancouver, Canada, and the MRC Toxicology Unit in Leicester, UK, studied mice and human tissue and found that the HACE1 gene is essential for mopping up toxic molecules during periods of oxidative stress, where harmful 'reactive oxygen species' build up in the cell.

Oxidative stress is thought to be involved in the development of a number of diseases including cancer and neurodegenerative disorders like Alzheimer's and Parkinson's disease. Therefore finding out how this process occurs in the body is important for understanding the course of disease.

The body has evolved highly effective defence mechanisms that sense and respond to oxidative stress to protect the cells from damage. One of these protective mechanisms is controlled by a molecule called NRF2 which springs into action and switches on the production of proteins and enzymes that detoxify the cell.

In this study, scientists found that the HACE1 also plays a vital role in

this detoxification process, by activating NRF2. The authors believe that this mechanism goes wrong in Huntington's disease, leading to gradual destruction of nerve cells in the brain.

Lead author Dr Barak Rotblat, of the MRC Toxicology Unit, said:

"One of the early observations was that enhanced HACE1 expression rescued cells from mutant Huntingtin (the mutant protein that is responsible for Huntington disease) toxicity. We knew then that we had to figure out how HACE1 can protect these cells.

"Our evidence points towards a previously unknown role of HACE1 in Huntington disease and possibly other forms of neurodegeneration. It's very early days, but if we were able to find a way to boost this pathway, we might be able to develop a treatment that halts, or even reverses progression of Huntington disease."

HACE1 is already known to play a protective role against tumour formation, but its role in neurodegeneration has not been investigated before.

Dr Poul Sorensen, the senior author of the work from the BC Cancer Agency Research Centre and a Professor at the University of British Columbia, said:

"This is a glowing example of how work in one field, namely childhood cancers, where we first identified the HACE1 gene, has applications to a completely different disease, Huntington disease".

In this study, researchers looked at mice with and without the HACE1 gene and found that those without the gene had more oxidative stress in the brain, and their response to this was impaired. Depleting HACE1 in cells also resulted in reduced NRF2 activity, leading to lower tolerance

against oxidative stress triggers.

The scientists also looked at human brain samples from Huntington disease patients and found a striking reduction of HACE1 levels in the striatum – the area of the brain where the disease develops and is most damaged.

Finally, they looked at HACE1 in a cellular model of Huntington disease. They found that upping expression of the gene in nerve precursor cells protected them against oxidative stress.

**More information:** Barak Rotblat, Amber L. Southwell, Dagmar E. Ehrnhoefer, Niels H. Skotte, Martina Metzler, Sonia Franciosi, Gabriel Leprivier, Syam Prakash Somasekharan, Adi Barokas, Yu Deng, Tiffany Tang, Joan Mathers, Naniye Cetinbas, Mads Daugaard, Brian Kwok, Liheng Li, Christopher J. Carnie, Dieter Fink, Roberto Nitsch, Jason D. Galpin, Christopher A. Ahern, Gerry Melino, Josef M. Penninger, Michael R. Hayden, and Poul H. Sorensen. "HACE1 reduces oxidative stress and mutant Huntingtin toxicity by promoting the NRF2 response." *PNAS* 2014 ; published ahead of print February 10, 2014, DOI: 10.1073/pnas.1314421111

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