Nrf2 responsive genes are activated in HD

Researchers in the Netherlands found that Nrf2 responsive genes are activated in a cell model of Huntington's Disease. This new study adds to our knowledge of how gene transcription is altered in Huntington's Disease.

While we focus on keeping you abreast of the most exciting breakthroughs regarding potential therapies that are working their way through the HDSA drug pipeline, there is still very groundbreaking work being done in the area of basic research. This work is vitally important as it may hold the key to fine-tuning approaches that are close to or in clinical trials or to open up new targets for potential therapies.

One critical area in which basic research is continuing is gene transcription. As identified by Coalition for the Cure researcher Dr. Jang-Ho Cha, the dysregulation of gene transcription is a major pathology in Huntington's Disease. DNA is the blueprint for life, a set of instructions for making an organism. The DNA blueprint has to be 'read' (gene transcription) and then transcribed (proteins made). The presence of the HD protein causes some genes to be abnormally up-regulated (more of the protein is expressed than is normal) and others to be down-regulated.

Studies of gene expression have been done in mouse models and human brain tissue. The value of the cell model however, is that it's possible to look at the earliest changes as well as changes over time. The researchers used an inducible PC-12 cell model derived from rats with exon 1 of the HD gene (the sequence where the polyglutamine expansion occurs). In this model, the HD gene is activated by the administration of doxycycline.

Early on, before the aggregates that are a hallmark of HD appeared in the cell, most of the genes with changed levels of expression were up-regulated. Over time, more changes in gene expression occurred and after the aggregates appeared, as much down-regulation occurred as up-regulation.

The researchers found that Nrf2 responsive genes were up-regulated. Nrf2 is a protein, which, if added to the cell, stimulates sets of genes that boost the cell's neuroprotective responses to both oxidative stress and the presence of toxins. These genes were activated, leading the authors to hypothesize that this is a compensatory measure given that oxidative stress is known to be a problem in the disease.

This reminds us that the changes that are found in the Huntington's Disease brain through basic research need to be evaluated for their role in the disease. Some changes may be compensatory, some may be pathological, and some may have no effect either way. The activation of the Nrf2 responsive genes may be compensatory response rather than a consequence of the pathological dysregulation known to occur.

Other changes in gene expression were found which were dysfunctional, however. They found changes that are likely to increase oxidative stress. In addition, genes that control the biosynthesis of dopamine were down-regulated.

HDAC inhibitors that partially ameliorate gene transcription problems are already in the pipeline, but the more we learn about gene transcription in HD, the more likely we are to discover or develop a highly effective drug with minimal side effects.

The authors suggest that Nrf2-Antioxidant Response Element pathway might be a good target for the development of a treatment.

Reference

Willeke M.C. van Roon-Mom, Barry A. Pepers, Peter A.C. 't Hoen, Carola A.C.M. Verwijmeren, Johan T. den Dunnen, Josephine C. Dorsman, and GertJan B. van Ommen. **"Mutant huntingtin activates Nrf2-responsive genes and impairs dopamine synthesis in a PC12 model of Huntington's disease."** BMC Molecular Biology 2008 Oct 9;9(1):84.

- *Marsha L Miller, Ph.D., October 27, 2008*