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Huntington's disease takes protein prisoners

RIKEN researchers uncover how a protein that controls the expression of genes is hijacked in Huntington's disease.

Huntington's disease (HD) remains incurable mostly due to our limited understanding of the specific mechanisms of HD progression. Some advancement in this arena is now apparent in the Feb. 21, 2008, issue of *The EMBO Journal*, the journal of the European Molecular Biology Organization, in which researchers from RIKEN's Brain Science Institute describe how a specific protein responsible for regulating the expression of many other proteins is itself targeted and effectively inactivated in HD, leading to damaging knock-on effects.

HD, one of the few genetic diseases in which the pathology can be traced to mutant forms of a single gene, is a rare neurological disorder in which the responsible gene encodes the protein Huntingtin (Htt). Genes comprise specific sequences of key chemical units, called nucleotides, designated A, C, G, and T, aligned along the length of DNA strands. HD is one of a number of so-called 'CAG repeat disorders' in which this same sequence of three successive nucleotides, CAG, is repeated many more times within the protein-coding portion of the mutant gene than it is in a normal gene. CAG codes for the amino acid glutamine and mutant Htt proteins have expanded 'poly-glutamine' stretches but it remains unclear how this alters normal Htt activity to the point that it somehow promotes toxic protein accumulations that ultimately kill only susceptible brain cells.

There is accumulating evidence that gene expression - during which a gene's specific nucleotide sequences are used to create a genetic template for proteins in a process termed 'transcription' - is disrupted in HD, and that important components of the transcription machinery, transcription factors (TFs), are implicated. TFs are DNA-binding proteins that regulate gene expression by attaching to key gene activation control sites called 'promoters.' Mutant Htt is known to interact with several TFs and even to incorporate such proteins into aggregates but the results of such sequestrations do not always correlate tightly with HD pathology. The evidence linking mutant Htt

sequestration of TF with neurodegeneration is largely inconclusive. The BSI group demonstrated that mutant Htt sequesters several components of an important TF, NF-Y. The researchers then investigated how this sequestration, which reduces NF-Y functional levels, could be linked to the HD pathological process.

The scientists focused on ubiquitous 'housekeeping' players called 'heat shock proteins' (HSPs), because the expression of several such HSPs is inhibited in mouse HD models and these 'molecular chaperones' protect cells by preventing undesirable protein aggregation. Accordingly, HSPs should suppress progression of HD pathology - and there is evidence of this, in the form of inhibition of mutant Htt aggregation, observed in laboratory experiments - but these protective activities of HSPs are in some way dysregulated in the HD brain. HSP70, which decreases progressively in mouse HD models, and which is regulated by NF-Y, was particularly intriguing.

NF-Y controls HSP70 gene expression by first binding to the gene's promoter. To examine this, the group used a special assay technique called EMSA that allowed them to directly visualize and quantify DNA-protein binding. Using brain tissue samples from several distinct mice strains that model HD, the team found that there were marked reductions in levels of NF-Y binding to *HSP70* promoter, and that this was associated with reduced *HSP70* expression. They confirmed these results with a separate assay method involving cultured brain cells. The authors have used this strong evidence to posit a model that links mutant Htt sequestration of NF-Y, and subsequent downstream suppression of *HSP70*, with neurodegeneration.

The RIKEN team's findings on how specific protein-to-protein interactions in HD can be dramatically derailed and can lead to a domino effect should pave the way for new potential therapeutic modalities.

Original work:

Yamanaka, T., Miyazaki, H., Oyama, F., Kurosawa, M., Washizu, C., Doi, H., Nukina, N. Mutant Huntingtin reduces HSP70 expression through the sequestration of NF-Y transcription factor, *The EMBO Journal*, published online on Feb.21, 2008

For more information, please contact:

RIKEN Public Relations Office
Email: koho@riken.jp