The RCAN1-1l gene and HD

As basic research into Huntington's Disease continues, more and more is being learned about what goes wrong in the cell and the brain. The challenge is to understand which pathologies are both significant and targetable for treatment.

Researchers at the University of Southern California have discovered that the RCAN1-1l protein is dramatically reduced – by 70 percent - in the brains of HD patients after death as compared to controls who died of other causes.

This is not a surprising finding. It is known that the HD protein causes the dysregulation of gene transcription with the result that some proteins are downregulated while others are upregulated. However, the researchers feel that the downregulation of this particular gene may play a major role in HD pathology.

In a cell model of HD, they used a viral vector to add the RCAN1-1l gene. The cells were rescued from toxicity by this overexpression of the gene.

"Our findings allow for the possibility that controlled over-expression of RCAN1-1l might in the future be a viable avenue for therapeutic intervention in Huntington disease patients," said Kelvin J. A. Davies, professor of gerontology in the USC Davis School of Gerontology and professor of biological sciences in the USC College of Letters, Arts and Sciences.

The researchers suggested that the mechanism by which upregulating RCAN1-1l exerts its positive effect is through inhibiting calcineuron. The gene is known to down regulate calcineurin, an enzyme which modifies proteins by removing phosphates. Earlier research has shown that phosphorylating the HD protein at a particular serine is neuroprotective. The decrease of RCAN1-1l may allow calcineurin to operate unchecked and make the HD protein more toxic.

However, other researchers found that inhibiting calcineurin actually accelerated the disease in an R6/2 mouse. What accounts for these different findings? It may be that what works in a cell model does not work in a living organism or the findings might be reconcilable in that either too much or too little calcineurin is damaging. Clearly more work needs to be done but the current findings are intriguing and need to be explored further in the HD mice.

"It is important to keep in mind that these protective findings are in-vitro, meaning in cell cultures. Further proof of protection by RCAN1-1L will be required in-vivo, or in actual Huntington disease patients," said lead author Gennady Ermak, research associate professor at the USC Davis School of Gerontology.

References:

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- Marsha L. Miller, Ph.D., July 8, 2009