New hope for treatment of neurodegenerative disorder

April 20 2009

Researchers from the University of Southern California have taken an important first step toward protecting against Huntington disease using gene therapy.

Huntington Disease is an incurable neurological disorder characterized by uncontrolled movements, emotional instability and loss of intellectual faculties. It affects about 30,000 people in the United States, and children of parents with the disease have a 50 percent chance of inheriting it themselves.

"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.

In a paper in the June 2009 issue of Journal of Biological Chemistry, now available online, Davies and his coauthors use cell culture findings to show that a form of the gene RCAN1, known as RCAN1-1L, is dramatically decreased in human brains affected by Huntington disease. RCAN1-1L was first discovered in Davies' lab.

The investigators also show that increasing levels of RCAN1-1L rescues cells from the toxic effects of Huntington disease, a result that could someday lead to new avenues of treatment, according to Davies.

"Our discovery offers real hope and may even have wide-ranging implications for a variety of other important CAG repeat-related diseases," Davies said.

While the Huntington gene, which makes the normal Huntington protein, is an essential component to healthy nerve cells, the mutant Huntington gene makes a toxic mutant Huntington protein. Mutant Huntington contains increased levels of the amino acid glutamine, which is generated by a repetition of the DNA triplet CAG.

A normal Huntington gene has a sequence of between six and 34 CAG repeats. Any strand of DNA possessing more than 40 CAG repeats indicates the carrier will develop Huntington disease, according to the researchers.

Indeed, the more repeats of CAG, the earlier the disease manifests itself and the more devastating the disease becomes. Currently available drugs do little more than help control erratic movements associated with the condition.

"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.

Previous in-vitro research has revealed that adding the phosphate PO4, an inorganic chemical, to the mutant Huntington protein can protect against the mutant gene. This process is called phosphorylation, and can be achieved by either inhibiting an enzyme (calcineurin) or by activating an enzyme (Akt).

"Our findings point to increased phosphorylation of mutant Huntington

through calcineurin inhibition as the likely mechanism by which RCAN1-1L may be protective against the mutant Huntington," Ermak said.

As Davies explained: "RCAN1-1L may actually play a role in the cause of Huntington disease."

"The gene is required to down-regulate the activity of calcineurin. We have previously linked too much RCAN1-1L expression to Alzheimer's disease," Davies said. "Thus, Alzheimer's disease and Huntington disease appear to involve opposite problems with RCAN1 expression and calcineurin activity."

In cases of Huntington disease, too little RCAN1-1L may allow calcineurin to act unopposed and remove too many phosphates from the mutant Huntington protein.

"We observed complete protection against the mutant Huntington by RCAN1-1L," Ermak said, but he reiterated the need for further research with Huntington disease patients.

The results offer a new direction for further research, Davies added.

Source: University of Southern California (news : web)