Researchers discover possible key to degenerative nerve diseases

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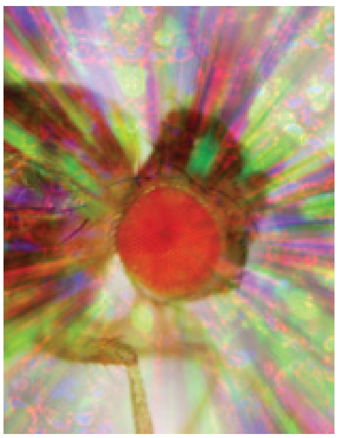

Fruit fly eye.

(Medical Xpress) -- Researchers at the University of Wisconsin-Madison and collaborators have discovered a powerful new protein in the eye of the fruit fly that may shed light on blinding diseases and other sensory problems in humans.

Reporting in the Nov. 16, 2011, issue of *Neuron*, the scientists note that similar but yet- to-be-identified proteins in the eye and brain could help explain age-related macular degeneration and retinitis pigmentosa, as well as Huntington's, Parkinson's, Alzheimer's and prion diseases.

The protein, which the scientists have named XPORT, serves as a molecular chaperone for two important proteins that are key to sensory activities in the eye. One protein, rhodopsin, is responsible for absorbing light, and the other protein, TRP, is a channel that plays a role in calcium influx into cells. XPORT guides the two proteins from the place where they are made in the cell to the location where they do their jobs.

This intricate process of chaperoning includes synthesis, folding, assembly, quality control, transport and targeting of proteins to their appropriate locations, explains senior author Dr. Nansi Jo Colley of the UW School of Medicine and Public Health. The complex process is prone to error, and a malfunction in any of the steps can have dire consequences in tissues.

"Accumulation of misfolded proteins often leads to severe pathology and cell death, producing blinding diseases and other neurodegenerative diseases," says Colley, a professor in the Department of Ophthalmology and Visual Sciences, the Department of Genetics and the Eye Research Institute. "Molecular chaperones are one of the first lines of defense in these fundamental processes."

Colley and her team discovered XPORT as a result of screening a collection of 900 fruit-fly mutants that undergo retinal degeneration. The XPORT mutant displayed retinal degeneration and defects in rhodopsin and TRP.

"TRP channels play a vital role as biological sensors, regulating calcium entering cells involved in vision, taste, olfaction, hearing and touch," says Colley, adding that the channels are found in many organisms and tissues. "Defective TRP channels can cause night blindness in certain people."

The first author on the paper, Erica Rosenbaum, a doctoral student in the UW Neuroscience Training Program where Colley is a faculty member, joined with Colley and UW collaborators Kimberly S. Brehm and Eva

Vasilijevic, as well as Che-Hsiung Liu and Roger C. Hardie at Cambridge University. Together they identified the mutation and discovered a small novel gene never described before.

They named the protein XPORT, for exit protein of rhodopsin and TRP.

In their experiments, the scientists showed that XPORT forms a complex with rhodopsin and TRP, and is required to successfully transport the two proteins to a specific location on the cell surface. They also determined that XPORT is essential for cell survival-mutations in XPORT prevented the two proteins from moving through the trafficking pathway, and this ended in retinal degeneration and blindness in the fly.

XPORT was also found to interact closely with another family of molecular chaperones called heat shock proteins, which are indispensable in the folding of newly synthesized proteins.

"Heat shock proteins have also been implicated as agents that protect nerve cells from degeneration," Colley says, "so XPORT or XPORT-like proteins might have therapeutic potential as well."

While XPORT is an eye-specific protein that is expressed in flies and other insects, Colley expects that a protein very similar to XPORT exists in humans.

The lab works on fruit flies because, as Colley says, "It is an invaluable model system for unraveling the complexity of many neurodegenerative diseases stemming from protein misfolding and aggregation. Studies using molecular genetics in the fruit fly are already greatly improving our ability to treat and perhaps even prevent these diseases."

Provided by University of Wisconsin-Madison