Chaperone protein subverts removal of glaucoma-causing protein

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The chaperone protein Grp94 can interfere with the clearance of another protein known to cause the glaucoma when mutated, a new study led by researchers at the University of South Florida has found. Using a cell model, the researchers also demonstrated that a new specific inhibitor of Grp94 facilitates clearance of the genetically-defective protein, called myocilin, from cells.

Reported online this month in *JBC* (The Journal of Biological Chemistry), the discoveries could lead to a new treatment for some hereditary cases of glaucoma, an eye disease that is a leading cause of blindness, said principal investigator Chad Dickey, PhD, associate professor of molecular medicine at the USF Health Byrd Alzheimer's Institute.

"When mutated, the glaucoma-causing protein becomes toxic to a cell network known as the trabecular meshwork cells that regulate pressure within the eye," Dickey said. "Once these cells die, the ocular pressure increases, causing glaucoma."

Genetic defects of myocilin account for approximately 8 to 36 percent of hereditary juvenile-onset glaucoma and 5 to 10 percent of adult-onset hereditary glaucoma.

The researchers suggest that mutant myocilin, triggered by an interaction with the chaperone Grp94, is highly resistant to degradation, thus clogging the protein quality control pathway and subverting efficient removal of the glaucoma-causing protein. So, the development of

targeted therapies to inhibit Grp94 may be beneficial for patients suffering from myocilin glaucoma.

More information: "Grp94 triage of mutant myocilin through ERAD subverts a more efficient autophagic clearance mechanism;" Amirthaa Suntharalingam, Jose F. Abisambra, John C. O'Leary III, John Koren III, Bo Zhang, Myung Kuk Joe, Laura J. Blair, Shannon E. Hill, Umesh K. Jinwal, Matthew Cockman, Adam S. Duerfeldt, Stanislav Tomarev, Brian S.J. Blagg, Raquel L. Lieberman, and Chad A. Dickey; JBC: *The Journal of Biological Chemistry*; published Oct. 3, 2012 as manuscript M112.384800

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