Study marks breakthrough in IOP regulation in fight against glaucoma

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A six-year collaboration between two faculty members of Bascom Palmer Eye Institute of the University of Miami Miller School of Medicine has yielded new insight regarding the regulation of intraocular pressure (IOP) in glaucoma - an irreversible blinding disease that causes progressive visual impairment due to optic nerve damage and is the leading cause of blindness worldwide.

The key finding by associate professors of ophthalmology Richard K. Lee, M.D., Ph.D. and Sanjoy Bhattacharya, M. Tech., Ph, D. validates their hypothesis that the response of aqueous humor (fluid produced in the eye) to mechanical stimuli at the cellular level (mechanosensing) impacts the regulation of IOP through cells converting that stimuli into chemical activity (mechanotransduction). At the center of this breakthrough lies the protein cochlin, which was discovered in the trabecular meshwork (TM) seven years ago using highly sensitive mass spectrometry. The TM refers to tissue located around the base of the cornea that is responsible for filtering and draining aqueous humor from the eye and controlling the IOP. Mass spectrometry is a technique used to identify proteins and to determine their amino acid sequence with great precision and can also ascertain if a protein has been modified. Bascom Palmer Eye Institute is one of only a few eye centers in the nation to have its own mass spectrometer. In fact, two such cutting edge machines are now part of Bascom Palmer Eye Institute's Adrienne Arsht Hope for Vision Retinal Degeneration Research Laboratory, which was established with a $1 million gift from philanthropist Adrienne Arsht, given in 2008.

"With elevated IOP being the primary modifiable risk factor affecting the development and progression of glaucoma," said Lee, "This advancement opens up potential avenues for effective and innovative manipulation of the pathway of aqueous outflow using mechanosensors and mechanotransducers. In turn, it could lead to meaningful intervention strategies." Currently, the primary treatment for glaucoma is to lower IOP through the topical use of medications or eye surgery.

Additionally, Bhattacharya and Lee found that mechanosensing of fluid flow is transduced, or converted into chemical signals, by TREK-1 mechanotransducers on the cell surface. TREK -1 is a protein in the TM, but how it affects IOP was previously unknown. Also missing was an understanding of how cochlin works in mechanosensing. Lee and Bhattacharya's extensive research demonstrated that TREK 1 functions in conjunction with cochlin to regulate IOP.

Furthermore, Lee and Bhattacharya determined that aberrant levels of secreted cochlin disrupt aqueous outflow, thus allowing for a rise in IOP. "Fluctuations of IOP can alter cells of the trabecular meshwork," explained Bhattacharya. "This results in dysfunction of aqueous flow. Presently, there are over 2 million known proteins and 46,000 lipids that can be tested to determine their impact upon IOP."

Bhattacharya and Lee are already working on next steps using advanced mass spectrometry techniques. They hope to uncover endogenous and exogenous molecules that regulate aqueous humor outflow by modulating mechanosensors and mechanotransducers, "The success of this research is based on a strong, ongoing collaboration between Dr. Lee and myself, as well as hard work by postdoctoral fellows and graduate students," summarized Bhattacharya. "We are also fortunate that Bascom Palmer Eye Institute is one of the few vision research centers in the country to have two mass spectrometers. " Both Bhattacharya and Lee agree that without a mass spectrometer, and faculty members who have

the expertise to use it to its full potential, this discovery would not have been possible. Funding for their research was received through the National Institutes of Health via two grants totaling $3.4 million.

Mass spectrometers are currently being used by other researchers at Bascom Palmer to identify mechanistic aspects of retinal degeneration and for unraveling mechanistic details of glaucoma pathology. "We continually learn from one another how mass spectrometry can lead to more exciting discoveries," said Bhattacharya. "It is a very valuable tool in the work to combat eye diseases."

On April 4, 2012, *PLoS ONE*, an open-access peer-reviewed scientific journal, produced by the Public Library of Science, published an article by Drs. Bhattacharya and Lee about this recent breakthrough. Click here to read the article.

Provided by Bascom Palmer Eye Institute

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