Steroid eye drops reverse cataracts in mice

More than half of Americans over the age of 70 have cataracts, caused by clumps of proteins collecting in the eye lens. The only way to remove them is surgery, an unavailable or unaffordable option for many of the 20 million people worldwide who are blinded by the condition. Now, a new study in mice suggests eye drops made with a naturally occurring steroid could reverse cataracts by teasing apart the protein clumps.

The proteins that make up the human lens are among the oldest in the body, forming at about 4 weeks after fertilization. The majority are crystallins, a family of proteins that allow the eye to focus and keep the lens clear. Two of the most abundant crystallins, CRYAA and CRYAB, are produced in response to stress or injury. They act as chaperones, identifying and binding to damaged and misfolded proteins in the lens, preventing them from aggregating. But over the years, as damaged proteins accumulate in the lens, these chaperones become overwhelmed. The mutated proteins then clump together, blocking light and producing the tell-tale cloudiness of cataracts.

To treat the condition without surgery, researchers have looked to drug treatments. Although boosting the function of CRYAA and CRYAB seems to be a good target, developing a therapeutic has been challenging. Most drugs that act on disease-related proteins work by changing how the protein functions, something scientists can measure by monitoring the protein’s enzymatic activity. CRYAA, CRYAB, and similar proteins are known as “undruggable” because their activity can’t be measured, says Jason Gestwicki, a biochemist at the University of California (UC), San Francisco, and a senior author of the new study.

Gestwicki’s team decided to use a technology called differential scanning fluorimetry, which allows scientists to measure the temperature at which a target protein begins to melt. They analyzed CRYAA and CRYAB and discovered that in one type of hereditary cataract, CRYAB takes on a mutant form with a much higher melting temperature than its normal version. If they could find a molecule that would bind to the mutant CRYAB protein and lower its melting temperature back to that of a healthy CRYAB, they speculated, CRYAB should function normally and prevent damaged proteins from clumping in the lens. The researchers turned to a bank of 2450 molecules that exhibited similar properties to CRYAA and CRYAB. They added molecules to the mutant CRYAB, looking for one that would stabilize their target. They settled on compound 29, a steroid found naturally in the bloodstream but not in the lens, which has no blood supply. Mice with age-related and hereditary cataracts received drops in the right eye, whereas the left eye went untreated. After just a few weeks, the treated eye was visibly clearer, says Gestwicki, who conducted the work while at the University of Michigan. Cataract severity is measured on a scale of zero to four, with four being the worst case. On average, mice in the study had about a one-grade improvement in cataract severity after 4 weeks of treatment.

This is the second study this year to find that eye drops made from a class of steroids called sterols can successfully reverse cataracts. In July, researchers from UC San Diego reported that lanosterol, a steroid found in the human eye, reversed cataracts in dogs.

There’s still a lot to uncover before either study can move into clinical trials. The lens in the human eye is very different from those in mice or dogs, and neither study explains how the steroids work on cataracts.

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HEALTH SCIENCES LIBRARY

UCSC Genome Browser Training

Save the date! On Thursday Sept 22, the Health Sciences Library will be hosting a day long workshop on how to use the UCSC Genome Browser. Robert Kuhn, PhD Associate Director, UCSC Genome Browser will be presenting genome browser basics, and new features developed in response to the display demands of the ever increasing amount of sequencing and epigenomic data produced in labs everywhere. See the event listing for updates and future registration: http://hslresearch.evanced.info/signup/EventDetails.aspx?EventId=298&lib= (you may need to cut and paste the url into your browser address window)

RESEARCH CORNER

Eric T. Clambey, PhD is an Assistant Professor in the Department of Anesthesiology at UCDenver | Anschutz Medical Campus. Dr. Clambey arrived in 2009, following his postdoctoral research in Immunology on T cell development and differentiation at National Jewish Health. He received his PhD in Immunology from Washington University in St. Louis where he studied the pathogenesis of chronic viral infections.

Eric’s research program focuses on the dynamic interface between the immune system and infection, inflammation and tissue repair. First, his laboratory studies how T cells regulate, and are regulated by, inflammation at mucosal surfaces with emphases on acute lung injury and inflammatory bowel disease. A major theme of these studies is how local microenvironmental factors, such as limiting oxygen availability, serve as tissue-derived instructional cues to modify lymphocyte responses. These studies identified new links between hypoxic environments and the generation of inhibitory T cells, identifying a potential new axis for targeted modulation of T cell function in ischemic diseases. Second, Dr. Clambey’s laboratory studies how acute and chronic virus infections result in mucosal injury, examining the unique contributions of virus and host-derived factors in regulating the balance between disease and recovery. These studies recently identified T cell-mediated regulation of neutrophils as an important pathway that is dysregulated during viral pneumonia. His research program uses molecular analysis of gene regulation, in vitro models of lymphocyte function and whole animal studies. These studies are powered by host and viral genetics, and strengthened by technical innovations in flow cytometric analysis, to study how these processes culminate in either tissue injury or repair. He further collaborates with multiple laboratories studying the cellular and molecular basis of immune responses to infection, injury and tumorigenesis. Dr. Clambey’s research is supported by the Department of Anesthesiology, the American Heart Association, and the Crohn’s and Colitis Foundation of America.

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