Scientists uncover role of Alzheimer's-linked APOE gene in glaucoma protection and identify promising treatment

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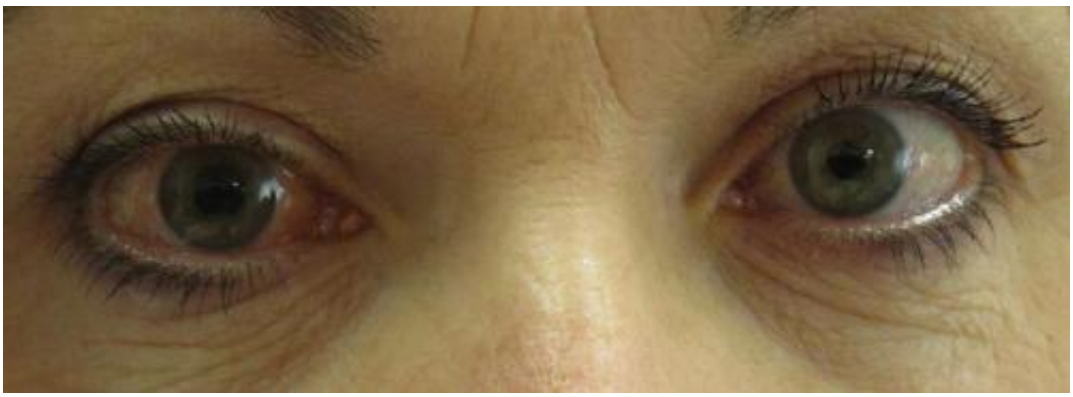

Acute angle closure glaucoma of the right eye (intraocular pressure was 42 in the right eye). Credit: James Heilman, MD/Wikipedia

New research led by scientists at Mass Eye and Ear and Brigham and Women's Hospital, member hospitals of Mass General Brigham, reveals the role that a genetic variant associated with Alzheimer's disease, APOE4, plays in protecting against glaucoma. In the new study, published August 16 in *Immunity*, the researchers also used a pharmacologic treatment to successfully prevent the destruction of neurons in the eyes of mice with glaucoma by targeting the APOE signaling pathway.

Specifically, the scientists demonstrated that the APOE4 gene variant,

which increases risk for Alzheimer's but decreases risk of glaucoma in humans, blocks a disease cascade that leads to the destruction of retinal ganglion cells in glaucoma. Additionally, they showed in separate mouse models that the death of retinal ganglion cells—the cause of vision loss in glaucoma—can be prevented by using medications to inhibit a molecule called Galectin-3, which is regulated by the APOE gene. These findings taken together emphasize the critical role of APOE in glaucoma and suggest that Galectin-3 inhibitors hold promise as a glaucoma treatment, according to the authors.

"Our research provides greater understanding of the genetic pathway that leads to irreversible blindness in glaucoma, and importantly, points to a possible treatment to address the root cause of the vision loss," said lead study author Milica Margeta, MD, Ph.D., a glaucoma specialist and scientist at Mass Eye and Ear, and assistant professor of ophthalmology at Harvard Medical School. "This study shows that the APOE-mediated disease cascade is clearly harmful in glaucoma, and that when you interfere with it genetically or pharmacologically, you can actually stop the disease."

Understanding and halting the cause of vision loss in glaucoma

Glaucoma is a leading cause of blindness, affecting an estimated 80 million people worldwide. Despite how common the disease is, little is known about the underlying mechanisms that lead to the loss of retinal ganglion cells, which ultimately results in vision loss. Accordingly, there is no treatment to directly promote survival of these cells; current treatments, including medications, laser therapies and surgeries are aimed at lowering eye pressure, the only modifiable risk factor for glaucoma. However, the disease often progresses despite these interventions and can result in complete blindness.

Scientists have suspected that glaucoma may be the result of a microscopic inflammatory process in the eyes. Previous studies by this research team and others, showed that this inflammatory process occurs in the optic nerve of glaucoma patients, as indicated by the presence of activated microglia, which are cells that act as first-line immune responders in the eye and brain. Microglia can be beneficial in healthy tissue; however, in eye diseases and neurodegenerative conditions like Alzheimer's and Parkinson's disease, microglia can produce toxic molecules, destroy living neurons, and make neighboring cells become inflammatory.

A seminal 2017 *Immunity* study led by research principal investigator, Oleg Butovsky, Ph.D., in the Department of Neurology at Brigham and Women's Hospital, found that in neurodegenerative diseases, including Alzheimer's, amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS), microglia switch to a microglial neurodegenerative phenotype (MGnD), which is mediated by the APOE (Apolipoprotein E) gene. It is well established in neurological research that one variant of this gene, called APOE4, is linked to an increased risk for late-onset Alzheimer's disease. Interestingly, an earlier *Investigative Opthalmology & Visual Science* study led by Dr. Margeta found APOE4 is associated with a decreased risk of developing glaucoma, but it was not understood why.

The new study led by Drs. Margeta and Butovsky, sheds light on this mechanism. The scientists used RNA sequencing to provide an unbiased look at which genes were turned on and off in microglia in different mouse models with glaucoma. They identified a disease cascade in which APOE controls the microglial transition from a healthy cell to a toxic neurodegenerative cell by regulating another molecule called Galectin-3.

When researchers attempted to induce glaucoma in a mouse with the APOE4 variant, they found despite the expected elevated eye pressure,

the microglia were unable to turn on this toxic cascade and did not produce Galectin-3, instead remaining in a homeostatic state with preservation of retinal ganglion cells. The same findings were observed in mice without APOE: the toxic signaling cascade was not turned on, Galectin-3 was not produced, and neurons were protected. The scientists also analyzed human eye tissue samples provided by Duke University Medical Center and confirmed that Galectin-3 was increased in the retina of glaucoma patients with the common APOE3 variant but was almost undetectable in patients with APOE4 variant.

"This was a striking finding and led to testing whether a pharmacologic intervention could block Galectin-3, which could potentially treat glaucoma," explained senior study author Dr. Butovsky, who is also an associate professor of neurology at Harvard Medical School.

The scientists used Galactin-3 inhibitors, which can be derived from natural sources and are currently in clinical trials for the lung disease pulmonary fibrosis. They found that injecting these inhibitors blocked the disease cascade in mice with glaucoma, and the retinal ganglion cells were protected despite elevated eye pressure.

"Our findings provide an explanation as to why APOE4 is associated with a decreased risk of glaucoma and show that the APOE signaling pathway is a promising target for neuroprotective treatments for this blinding disease. However, why the same allele is deleterious in Alzheimer's disease but protective in eye neurodegenerative diseases has yet to be addressed", said Dr. Butovsky.

Paving the way for clinical trials

This study is the first to examine the role of Galectin-3 in the development of glaucoma and to show the value of inhibiting this molecule in order to prevent retinal ganglion cell death.

Future studies by this research team will look more closely at Galectin-3 inhibitors as treatments for glaucoma, testing them in additional animal models as well as looking at more minimally invasive approaches of inhibitor delivery, such as oral administration or in a slow-release gel.

Ongoing studies are also examining eye fluid and serum samples collected from patients during glaucoma surgery to better understand the patient population in which Galectin-3 inhibition would be a potential therapeutic approach. For example, if Galectin-3 is found to be elevated in the biofluids of a patient, it could suggest that he/she could be a candidate for treatment with the inhibitor medication. Such studies can pave the way to translate this research into human clinical trials, according to the authors.

"Glaucoma remains a blinding disease for millions of people around the world, and these exciting findings by Drs. Margeta and Butovsky and team provide insight into the role of genetic variants, and the promise of translation to a treatment for patients," said Joan W. Miller, MD, Chief of Ophthalmology at Mass Eye and Ear, Massachusetts General Hospital and Brigham and Women's Hospital, and Chair of Ophthalmology and the David Glendenning Cogan Professor of Ophthalmology at Harvard Medical School.

Dr. Butovsky and his lab are conducting research examining the APOE microglial cascade and the role of APOE4 variant in microglial regulation in Alzheimer's disease.

More information: Milica A. Margeta et al, Apolipoprotein E4 impairs the response of neurodegenerative retinal microglia and prevents neuronal loss in glaucoma, *Immunity* (2022). DOI: 10.1016/j.immuni.2022.07.014

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Provided by Massachusetts Eye and Ear Infirmary

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