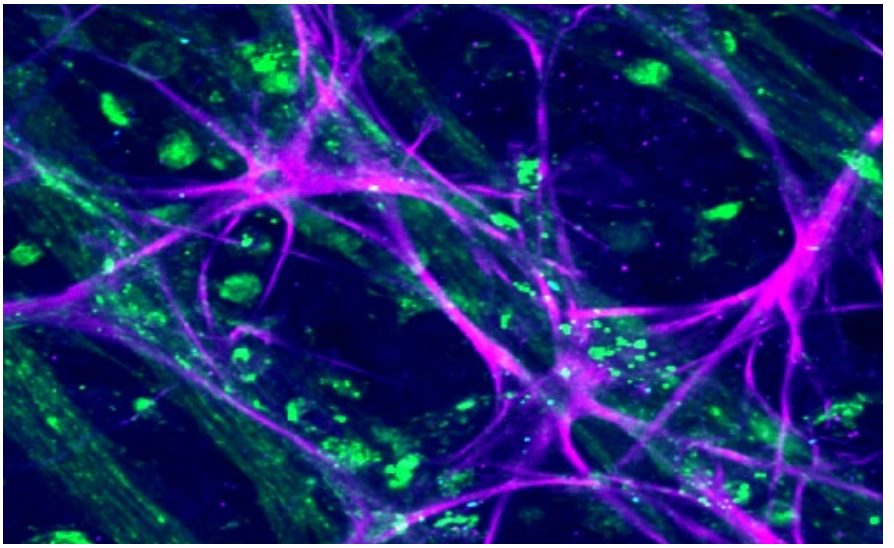
GLAUCOMA

Astrocytes Try to Rescue Fellow Eye's Optic Nerve



Courtesy of Melissa L. Cooper, PhD

ENERGY TRANSFER. *Astrocytes (purple) in the mouse retina interconnect via gap junctions to form a plexus that covers retinal ganglion cells and their axons (green), which form the optic nerve to the brain.*

AS STOREHOUSES FOR GLYCOGEN, astrocytes are known to nourish optic nerves by funneling large amounts of metabolic energy (for example, lactose) to the retinal ganglion cell axons, which transfer visual signals to the brain. But new research has revealed that the astrocytes in a healthy optic nerve play a key role in responding to neurodegenerative signals from the contralateral, glaucomatous eye: The astrocytes begin donating some of the healthy optic nerve's metabolic resources to the nerve from the eye with glaucoma.[1]

Ironically, this redistribution of available energy weakens the healthy optic nerve and may explain why glaucoma that begins in one eye often "spreads" to the other eye, said senior author David J. Calkins, PhD, at the Vanderbilt Vision Research Center in Nashville, Tennessee.

Novel finding. "This is the first time anyone has demonstrated the sharing of energy resources between the two eyes and nerves," Dr. Calkins said. "But unfortunately, because these resources are limited, the nerve that donates the resources becomes more susceptible to intraocular pressure–related stress in glaucoma." Thus, he said, "Over time the pathology in the two optic projections to the brain equilibrates, endangering both optic nerves."

Murine model. Working with a mouse model of glaucoma, the scientists found that astrocytes used gap junctions to transport metabolites along the long distance from one optic nerve, through the optic chasm, to the other optic nerve. (In a human, this would correspond to several centimeters, Dr. Calkins said.)

The movement was facilitated by connexin 43 (Cx43), an essential protein, the researchers reported. In the absence of Cx43, this protective response to oxidative and metabolic stress did not occur.

Dr. Calkins said the group's next step is to build a viral vector modified to upregulate the astrocytes' capacity to store glycogen and exchange energy. "Basically what we're trying to do is build and bootstrap energy depots large enough to keep both optic nerves healthy," he said.

A role in other neurodegenerative diseases? It is possible that a similar astrocyte-mediated rescue mechanism is at work in other neurodegenerative conditions, Dr. Calkins said. For instance, in patients with Leber hereditary optic neuropathy who have undergone gene therapy and in patients with the Argus II retinal implant (Second Sight), there have been reports that the untreated eyes show unexplained visual improvement, he said. And Alzheimer disease lesions in one brain hemisphere commonly appear in the other hemisphere over time, he said.

Call for research. "I think we need to put more research into understanding how the two optic projections can talk to one another," Dr. Calkins said. "The gap junctions between astrocytes are large enough to pass different kinds of molecules." He added, "This is exciting because it opens up entire new avenues for understanding how pathology spreads between the two eyes." *—Linda Roach*

1 Cooper ML et al. *Proc Natl Acad Sci U S A.* 2020;117(31):18810-18821.

Relevant financial disclosures—Dr. Calkins: None.

CORNEA

Newly Discovered Genes Linked to Corneal Structure

RESEARCHERS HAVE IDENTIFIED OVER 200 genes that influence the viscoelastic properties of the cornea.[1] The genes—all but eight of which are novel—are significantly associated with two corneal biomechanical properties: corneal hysteresis (CH) and corneal resistance factor (CRF).

The discovery was made in a genome-wide association study (GWAS) that was designed to explore the genetic architecture of CH and CRF and to clarify their genetic correlation with eye and systemic disease. "Understanding the underlying genetics of these traits allows us to understand the mechanisms that might be involved in the variation of viscoelastic properties of the cornea," said Christopher J. Hammond, FRCOphth, MD, at King's College London in the United Kingdom.

Study findings. The study involved over 100,000 participants drawn from UK Biobank, a population-based cohort between the ages of 40 and 69. An analysis of their CH and CRF measures found a significant association for expression of 86 genes with CH and 107 with CRF. Most were expressed in corneal tissue.

The study also identified 21 genetic loci implicated in keratoconus, 22 loci associated with Fuchs dystrophy, and many novel associations, including a component in collagen-related pathways that influences corneal biomechanical properties.

The GWAS also identified, for the first time, traits such as lung function and height that have shared genetic variants in the cornea. This finding possibly relates to elasticity of tissues, Dr. Hammond said.

UVEITIS

MUST Trial Confirms Advantages of Systemic Uveitis Tx

A NEW ANALYSIS FROM THE MULTICENTER UVEITIS Steroid Treatment (MUST) Trial Follow-Up Study found that long-term risk and poor outcomes of glaucoma in uveitic eyes were significantly higher in patients receiving a fluocinolone acetonide implant (Retisert) compared to systemic therapy.[1]

Although eyes in both treatment groups did well in terms of inflammation control, 79 of 196 implant-treated eyes (40%) developed glaucoma, compared to 17 of 209 eyes (8%) that received systemic treatment during follow-up (median, 6.9 years). Most cases of uveitic glaucoma were successfully managed with intraocular pressure (IOP)–lowering treatment, yet despite close monitoring, a minority experienced a worsening of visual field defects and/or cup-to-disc ratios.

"Because IOP-lowering treatment worked for avoiding further worsening of glaucoma in most cases, uveitic eyes should be monitored indefinitely for IOP elevation and glaucoma," said John H. Kempen, MD, MPH, MHS, PhD, at Massachusetts Eye and Ear in Boston. "The risk of IOP elevation and glaucoma never goes away completely, at least through seven to 10 years of follow-up."

Elevated IOP. This prospective follow-up of 405 uveitic eyes (232 patients) found that implant therapy offered excellent inflammation control for the first few years. However, it was associated with IOPs of ≥30 mm Hg more often than systemic treatment, often leading to glaucoma.[2] At two years, the MUST Trial data showed no difference between the groups in best-corrected visual acuity outcomes. But at seven years, eyes randomized to systemic therapy fared better than the implant cohort by 1.4 lines on average.

Surprise finding. "We generally think that optic nerve injury from glaucoma is due to very high IOPs, so it was surprising that use of implant treatment was a slightly a stronger predictor of glaucoma than IOP measurements," Dr. Kempen said. "That makes me wonder if there was more to glaucoma incidence than just IOP elevation. Could there be some structural effect of very long-lasting intraocular corticosteroids affecting glaucoma risk?"

Keep monitoring patients. Dr. Kempen monitors all uveitis patients for IOP elevation and glaucoma at least every three months. For implant patients, he prefers every six weeks for the first two years.

Also, the findings suggest value for early filtering surgery in implant eyes that appear to be developing substantially elevated IOP. In an earlier analysis from the MUST Trial, 45.3% of cases in the implant group required incisional surgery to lower IOP within seven years.[3]

Given these findings, and an economic analysis favoring systemic therapy, the researchers concluded that systemic therapy should be first line for average cases. "It is not yet known whether newer implants with lower doses of corticosteroid might compare to systemic therapy more favorably," Dr. Kempen said. "But initial systemic therapy did rather well in the MUST Trial, providing a high bar for new treatments to surpass to achieve first-line status for average cases. Implants are indicated when systemic therapy is not feasible or fails and for selected severe cases." *—Miriam Karmel*

1 Kempen JH et al. *Am J Ophthalmol.* Published online July 3, 2020.
2 Friedman DS et al. *Ophthalmology*. 2013;120(8):1571-1579.
3 Kempen JH et al., for the Writing Committee for the MUST Trial and Follow-Up Study Group. *JAMA*. 2017;317(9):1993-2005.
Relevant financial disclosures—Dr. Kempen: The MUST trial received a donation of fluocinolone acetonide intraocular implants from Bausch + Lomb for patients who would be unable to enroll in the trial without a donated implant.

A weak IOP correlation. It has been suggested that CH and CRF may be predictors of glaucoma, independent of elevated IOP. However, in this study, CH was negatively correlated with applanation pressures. CRF was positively correlated with applanation pressures, but only to a small degree. Dr. Hammond said the analyses show that IOP alters CH and CRF, rather than the other way around.

Looking ahead. "This study shows the complexity of the eye and its traits and [points out] that different genetic traits are related to each other in the eye," Dr. Hammond said. "Knowledge gained might improve future treatments for corneal diseases that are associated with abnormal corneal elasticity, such as keratoconus." —*Miriam Karmel*

1 Simcoe MJ et al. *Hum Mol Genet.* Published online July 27, 2020.

Relevant financial disclosures—Dr. Hammond: None.

RETINA

Adding PDT Improves Outcomes in PCV

IN PATIENTS WITH POLYPOIDAL choroidal vasculopathy (PCV), a subtype of age-related macular degeneration, combining anti-VEGF injections with photodynamic therapy (PDT) has been found to improve visual outcomes compared to ranibizumab monotherapy at 24 months.[1]

The EVEREST II study was a follow-up to an earlier trial (EVEREST) that found similar results after following patients for 12 months, said lead author Tock H. Lim, MBBS, FRCSEd, at the National Healthcare Group Eye Institute in Singapore. "The EVEREST studies' 12-month and now 24-month data have shown that if you treat PCV with combination therapy you get a very good outcome."

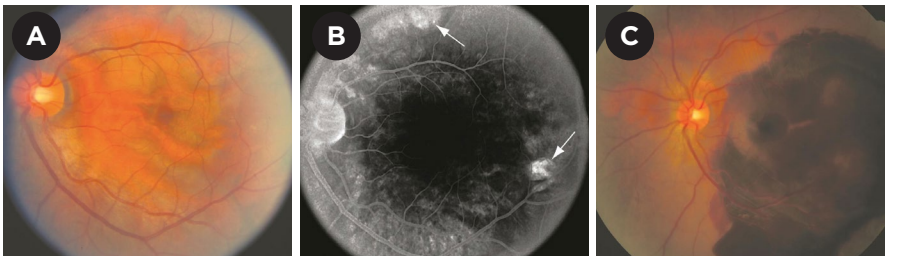
Overview of EVEREST II. Of 322 participants randomized to receive combination therapy or monotherapy in EVEREST II, 274 completed the 24-month study. Those in the monotherapy group (n = 154) received ranibizumab 0.5% intravitreal therapy. Combination therapy patients (n = 168) received intravitreal injections of ranibizumab 0.5% and standard verteporfin PDT.

With regard to the study's outcomes, Dr. Lim said, "Specifically, if you combine verteporfin PDT with ranibizumab injections you get a 9.6-letter gain," compared to 5.5 letters in the monotherapy group. Moreover, he said, "You get that visual acuity gain when your baseline is already quite high at 61 letters. And you will use half the median number of injections of ranibizumab that you would use with monotherapy, with no increased risk."

PCV in East Asia . . . The EVEREST trials gathered subjects from ophthalmic institutions throughout East Asia, Dr. Lim said. About a third of neovascular AMD patients in East Asian countries have PCV, he said.

"The PCV subtype consists of two lesion components, which are intertwined. In the center, there is often a branching vascular network, similar to the pattern seen in type 1 choroidal neovascularization," Dr. Lim said. "At the perimeter of the vascular area are aneurysmal dilatations known as polypoidal lesions. Leakage and bleeding can either come from the lesions or from the branching vascular network."

. . . and elsewhere. Now that the diagnostic protocol used in the EVEREST trials has been published, researchers in other countries are beginning to find PCV cases in other ethnic groups,[2] which might previously have remained unsuspected, Dr. Lim said.



PCV. *In this patient with polypoidal choroidal vasculopathy, (A) red-orange nodular and tubular lesions are evident in the peripapillary and macular regions. (B) Hyperfluorescent polypoidal lesions (arrows) without apparent leakage on fluorescein angiography. (C) A dense subretinal hemorrhage has occurred.*

Advice to clinicians. The PCV imaging and diagnostic methods used in the EVEREST trials already are commonly used by ophthalmologists in referral centers in Asia, based on earlier study reports, Dr. Lim said. The protocol is based on confocal scanning laser ophthalmoscopy indocyanine green angiography (ICGA) in tandem with other imaging techniques.

Typically, identification of PCV begins with a fundus examination aided by optical coherence tomography (OCT). "The key is that, if you see round-shaped hyperreflective lesions between the retinal pigment epithelium and Bruch's membrane in a good set of OCT images, consider ICGA to confirm the diagnosis of PCV," Dr. Lim said.

He added, "If a person receives anti-VEGF monotherapy and you don't seem to see the same response that you would expect in a standard case, it's important to go through the OCT sections and determine whether you see any suspicious polypoidal lesions. And if in doubt, then you should do ICGA or send the patient to a colleague who does this procedure."

He added, "That's important, because once you find that the disease is PCV, you now have an additional treatment method that can give the patient a better outcome." —*Linda Roach*

1 Lim TH et al. *JAMA Ophthalmol.* Published online July 16, 2020.
2 Sohraab Yadav et al. *Br J Ophthalmol.* 2017;101 (10):1377-1380.

Relevant financial disclosures—Dr. Lim: Heidelberg Engineering: L; Novartis: C.

See the financial disclosure key, page 8. **For full disclosures,** including category descriptions, view this News in Review at aao.org/eyenet.