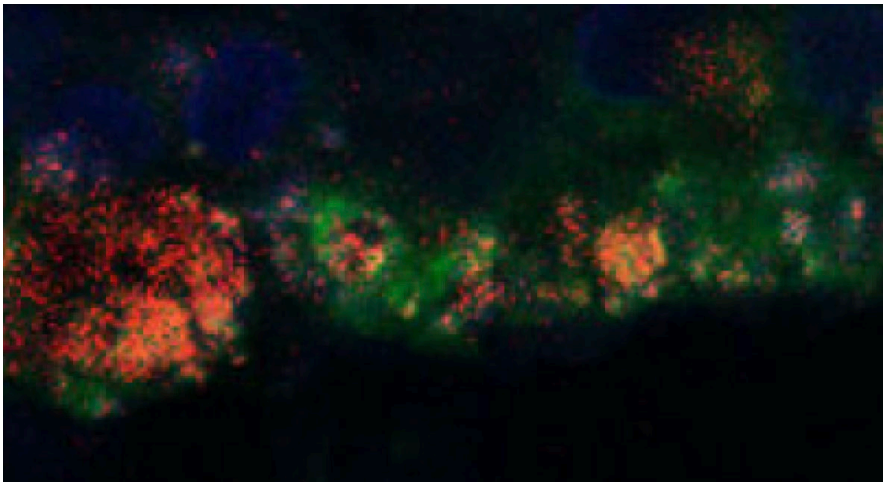


HISTOLOGY. *This image shows the* Alu *cDNA in the RPE at the edge of a GA lesion (red =* Alu *cDNA; blue = DAPI staining of the nucleus; green = autofluorescence of the RPE cells).*

Jayakrishna Ambati, MD

RETINA

Loose DNA Snippets May Fuel Dry AMD

SCIENTISTS AT THE UNIVERSITY OF Virginia have identified "junk" DNA in the cytoplasm of retinal cells as a possible driver of a molecular cascade that leads to geographic atrophy (GA) in patients with age-related macular degeneration (AMD). Furthermore, derivatives of a common anti-AIDS drug, AZT, appear to block the impact of this free-floating DNA and thereby prevent GA lesions from growing, the researchers found.[1,2]

Known as *Alu* cDNA, these molecules were present in retinal pigment epithelium (RPE) cells of donor eyes of patients with GA, the researchers said. The *Alu* cDNA concentrates primarily along the periphery of the GA lesions.

Why RPE cells die. In a series of experiments in rodents, the researchers found that the *Alu* cDNA triggers activation of an inflammasome, *NLRP3,* which then bathes cells in toxic cytokines.[1] This may explain why RPE cells die in patients with dry AMD.

These findings expand on those from an earlier study, in which the researchers published a dogma-toppling conclusion: Contrary to what has long been believed, production of cellular DNA is not always confined inside cell nuclei or mitochondria. Instead, in eyes with GA, small sections of what is usually noncoding *Alu* RNA are released into the cytoplasm, where they cause production of complementary DNA.[2]

It is the extraneous *Alu* cDNA and a consequent release of mitochondrial DNA that trigger an inflammatory response leading to RPE cell degeneration, said study leader Jayakrishna Ambati, MD, at the University of Virginia in Charlottesville. "You have this DNA that's being made in the cytoplasm. It's not supposed to be there. So when our body sees that, it turns on many of the same alarm pathways that it turns on when it sees viruses—that is, the inflammasome," Dr. Ambati said. "What's evolved as a defense mechanism against pathogens has now been hijacked and turned against our own bodies."

The AIDS connection. In a study published in 2014, the researchers found that this inflammatory pathway could be blocked by nucleoside reverse transcription inhibitors (NRTIs), which are used to treat HIV infection.[3] Thus, they hypothesized that NRTIs might be reducing the incidence of dry AMD in patients who take them as AIDS therapy, Dr. Ambati said.

They then analyzed data from four large, longitudinal health insurance databases and found that the use of NRTIs was associated with a 38% lower risk of GA (pooled adjusted hazard ratio, 0.616; 95% confidence interval, 0.493-0.770).[2]

Next steps. If an NRTI were to prove effective against GA, it would need to be in a less toxic formulation that does not have the potential serious side effects of antiretroviral drugs, Dr. Ambati said. "Those drugs are toxic from top to toe. Even the safer ones are not that pleasant. And certainly in an elderly population, you would have to be very careful."

Buoyed by the "natural experiment" they uncovered in the insurance databases, Dr. Ambati said his group hopes to treat GA patients with a modified, less toxic NRTI from the Kamuvudine class in a clinical trial early this year.

—Linda Roach

1 Fukuda S et al. *Sci Adv.* 2021;7(40):eabj3658.
2 Fukuda S et al. *Proc Natl Acad Sci.* 2021;118(6):e2022751118.
3 Fowler BJ et al. *Science.* 2014;346(6212):1000-1003.

Relevant financial disclosures: Dr. Ambati—Inflammasome Therapeutics: O.

CATARACT

Cataract Surgery in RVO Patients

PATIENTS WITH RETINAL VEIN occlusion (RVO) can benefit from cataract surgery, a U.K.-based study has found.[1]

Study rationale. "There is insufficient evidence to inform patients with RVO on their prognosis after cataract surgery," said lead author Ahmed B. Sallam, MD, PhD, FRCOphth, at the Jones Eye Institute in Little Rock, Arkansas. "Very few studies have evaluated the visual outcomes of cataract surgery in these patients." In addition, he said, "there is a lack of studies documenting rates of intraoperative complications such as posterior capsular rupture (PCR) or zonular dialysis" in patients with RVO.

Study specifics. For this retrospective study, researchers pooled data from eight ophthalmology departments affiliated with the U.K. National Health Service, covering a 15-year period from July 2000 to May 2015. All told, 71,449 eyes met inclusion criteria; of these, 563 were in the RVO group, and 70,886 were in the reference group.

Outcomes and complications. Before cataract surgery, eyes with RVO had a visual acuity (VA) of 20/100, compared to 20/70 for those in the reference group. This improved postoperatively to 20/50 for RVO and 20/25 for reference eyes. In addition, at four to 12 weeks postoperatively, 55.1% of eyes with RVO had gained 3 or more Snellen lines in vision, versus 64.55% of reference eyes.

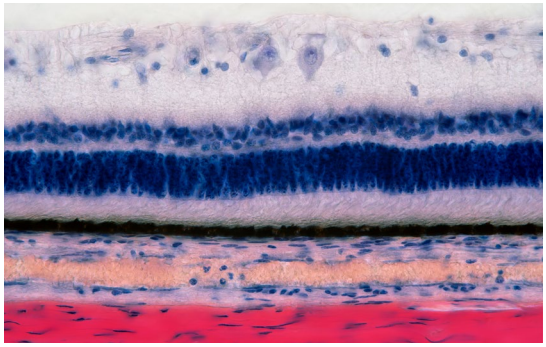
This analysis found no difference in the rate of PCR or dropped lens fragments between the two groups. However, Dr. Sallam said, the RVO group had significantly higher rates of zonular dialysis than did reference eyes (1.06% vs. 0.64%; p = 0.0269). With regard to postoperative cystoid macular edema, the RVO group had a higher rate than did reference eyes (3.02% vs. .87%, respectively; p = .021).

Looking ahead. The researchers believe that their data "will help surgeons more accurately counsel patients on the expected visual outcome and the risks of intraoperative complications in the setting of cataract surgery with RVO," Dr. Sallam said.

He noted that, while the study is limited by its retrospective design, "We provided a large sample size on RVO eyes undergoing cataract surgery from several centers using the same electronic medical records platform, which increases the generalizability of our results." In addition, he noted that, while a prospective randomized controlled study represents the gold standard level of evidence, conducting such a study for cataract surgery in eyes with RVO "is difficult and is unlikely to be feasible." —*Jean Shaw*

1 Ponder CM et al. *J Cataract Refract Surg.* Published online Sept. 27, 2021.

Relevant financial disclosures: Dr. Sallam—None.



RETINAL NUANCES. *Different sets of retinal neurons are sensitive to individual stimuli.*

RESEARCH

How RGCs Encode Visual Space

WITH MORE THAN A MILLION RETINAL ganglion cells (RGCs) in the human eye, all with vast thickets of dendrites, it stands to reason that evolution must have developed ways to organize the electrical signals that these cells gather for sending to the optic nerve. But what are the structural features that enable coordination of all this activity?

Researchers at Duke University in Durham, North Carolina, have published two papers that they believe help answer that question.[1,2] The papers describe the relative arrangements of retinal mosaics, collections of cells that divide up visual space into small regions called receptive fields, one per ganglion cell.

Stacked mosaics. There are roughly 40 types of such mosaics, encoding visual features from motion to contrast, but until recently, it was unclear how the mosaics were arranged.

Last April, the Duke researchers reported that some of these mosaics were carefully positioned with respect to one another.[1] In the group's second paper,[2] they used computational modeling to compare their laboratory observations to the optimized mosaic layouts predicted by an idea called "efficient coding theory." The real-world data and the model's predictions matched.

"The retina is not one mosaic. It's a whole bunch of stacked mosaics. And each of these mosaics encodes something different about the visual field," said coauthor Greg D. Field, PhD. "The depth that the dendrites reach in the retina is kind of an addressing scheme." That is, when the dendrites reach a deeper position, they receive one type of information—and if they are in a shallower position, they receive another.

Subtle organization scheme. The modeling studies also showed that the processing efficiency of the mosaics was affected by the pattern in which they were laid out, said coauthor John Pearson, PhD. "There's a level of organization to the retina that is even greater than what we had thought was there. The very intricate positioning of the mosaics with respect to one another tells us that their various alignments are probably more important [than we realized]." —*Linda Roach*

1 Roy S et al. *Nature.* 2021;592(7854):409-413.

2 Jun NY et al. *Proc Natl Acad Sci.* 2021;118(39):e2105115118.

Relevant financial disclosures: Drs. Field and Pearson—None.

See the financial disclosure key, page 6. **For full disclosures,** including category descriptions, view this News in Review at aao.org/eyenet.