

News in Review

COMMENTARY AND PERSPECTIVE

Cellular Secrets of Exfoliation Syndrome

A TEAM OF RESEARCHERS FROM Mount Sinai in New York City is the first to demonstrate a cellular defect in exfoliation syndrome (XFS)—an age-related systemic disorder that leads to a disorderly buildup of protein aggregates in multiple organs. Among its many pathologic effects, XFS is linked with hearing loss, as well as cardiovascular and cerebrovascular disease. For ophthalmologists, the most familiar manifestation is exfoliation glaucoma, in which the material clogs the trabecular meshwork and hinders outflow.¹ XFS has also been linked with increased risks of cataract and retinal vein occlusion.

Broadening the field of XFS study. The team delving into this poorly understood disorder includes Audrey Bernstein, PhD, associate professor of ophthalmology and cell biology, and J. Mario Wolosin, PhD, professor of ophthalmology—both at Icahn School of Medicine at Mount Sinai—collaborating with Robert Ritch, MD, the Shelley and Steven Einhorn Distinguished Chair in Ophthalmology, at New York Eye and Ear Infirmary. They are taking a cell biology approach to uncover the mechanisms of XFS.

“In recent years, XFS researchers have focused their study on a gene called lysyl oxidase-like 1 (*LOXLI*), which cross-links elastin in the eye,” said Dr. Bernstein. “XFS develops almost exclusively when the *LOXLI*

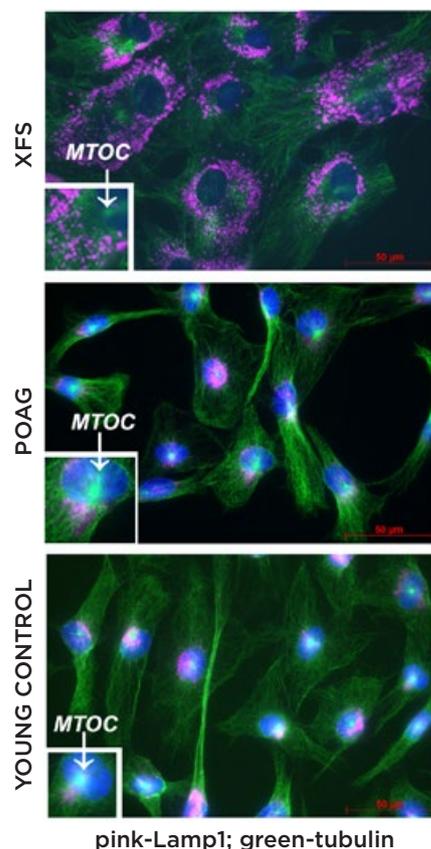
genotype includes certain single amino acid *LOXLI* variants. However, these variants are also found in many people without the disease,” said Dr. Bernstein, “which means that *LOXLI* is only a part of the story.”

For this reason, Bernstein and colleagues turned their attention to what unites all age-related diseases such as XFS: a problem with proteolysis and autophagy. Normally, certain cells degrade unnecessary or toxic cellular components in a process somewhat similar to the recycling role of sharks and buzzards in the natural world.

Major findings. The researchers grew and compared cells from tissue samples normally discarded during surgery from patients with XFS, primary open-angle glaucoma (POAG), and strabismus. “We found that lysosomal function and autophagy were significantly dysfunctional in the exfoliation cells,” said Dr. Bernstein.

The exfoliation cells showed the following key characteristics: They were much larger than normal cells, proliferated slowly, and contained many disorganized vesicles. Under “starvation conditions” induced by removal of serum, the lysosomes and many vesicles in XFS cells did not relocate to the correct area and, therefore, failed to carry out their function of clearing cellular waste. In addition, a buildup of dead mitochondria—thought to cause oxidative stress—was likely due to an autophagy defect, said Dr. Bernstein.

Links with neurodegeneration research. “Our findings suggest that XFS is similar to diseases such as



CELLULAR IMPAIRMENT. Lysosomes in XFS—tenon fibroblasts (TFs) cannot relocate to the perinuclear area under starvation conditions. TFs were seeded on collagen in a serum-free medium and immunostained for lysosomal-associated membrane protein 1 (Lamp1; pink) and β -tubulin (green). MTOC (microtubule organizing center), which organizes vesicular traffic, is absent in XFS. Bar = 50 μ m.

Alzheimer’s and Parkinson’s,” said Dr. Bernstein. “This is exciting because we can leverage what has been learned from thousands of studies conducted in the field of neurodegeneration.” In addition, she said, the accessibility of the eye provides a unique opportunity for testing therapies to reverse XFS pathology.

Ongoing research. Drs. Bernstein and Wolosin are now investigating the mechanisms underlying the autophagy failure. They are currently exploring whether there is a problem with *LOXLI* folding that might directly cause XFS pathology. Further, is *LOXLI* secreted into the extracellular space because waste-degrading processes inside the cell are dysfunctional?

Although these and other questions remain, Dr. Bernstein said, the findings from this research provide a basis for studying the mechanisms of this puzzling degenerative disease and, further, may suggest possible therapeutic approaches. —Annie Stuart

1 Want A et al. *PLoS One*. 2016;11(7):e0157404. doi:10.1371/journal.pone.0157404.

Relevant financial disclosures—Dr. Bernstein: Bright Focus Foundation: S; Glaucoma Foundation: S; Research to Prevent Blindness: S; The MYS Family U.S. Charitable Foundation: S.

NOVEL DRUG DELIVERY

Eye Drop Alternative Tested in Monkeys

A LATANOPROST-ELUTING CONTACT lens is showing early promise of being a controlled-release drug delivery system that could help ophthalmologists overcome the problem of their glaucoma patients' nonadherence to eye drop regimens. The device consists of a translucent latanoprost-polymer film, cut into a ring shape and encapsulated inside a contact lens lathed from methafilcon, a poly-HEMA based hydrogel.

Sustained IOP reductions. In a rare preclinical study published by *Ophthalmology*,¹ researchers reported that cynomolgus monkeys with experimentally induced glaucoma who wore the contact lenses for 7 days at a time showed sustained reductions in intraocular pressure (IOP) throughout the test periods.

Moreover, the researchers found statistically significant evidence that a higher-dose contact lens was more effective than either a low-dose lens or standard topical therapy, said coauthor

Joseph B. Ciolino, MD, a cornea subspecialist at Massachusetts Eye and Ear, in Boston. Specific results included the following:

- After 5 days of topical dosing with 0.005% latanoprost solution (50 μ L once daily), the maximum IOP reduction from baseline was 6.6 ± 1.3 mm Hg.
- With the low-dose contact lens, the maximum reduction was 7.8 ± 3.8 mm Hg, recorded on day 8 as the lenses were removed.
- With the high-dose lens, the reductions in IOP compared with baseline were 10.5 ± 1.4 mm Hg lower on day 3; 11.1 ± 4.0 mm Hg lower on day 5; and 10.0 ± 2.5 mm Hg lower on day 8.

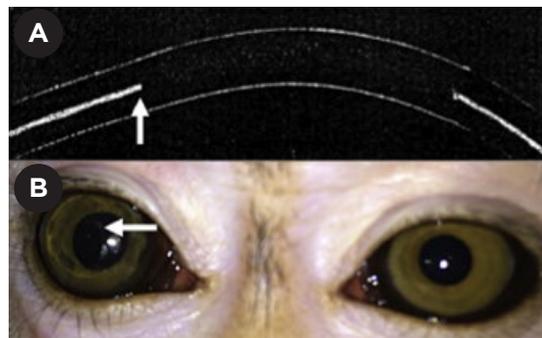
Apparent dose-response relationship. These findings are in contrast to observations from clinical use of latanoprost. "Our results are surprising because with latanoprost drops, more frequent applications or higher concentrations do not necessarily result in better IOP reduction. Whereas with our study we found what appeared to be a dose-response relationship," Dr. Ciolino said. "We'll have to do more studies to determine this, though, because this is a small study in monkeys."

Possible uses beyond glaucoma therapy. According to Daniel S. Kohane, MD, PhD, a Boston Children's Hospital anesthesiologist and biomaterials researcher who partnered with Dr. Ciolino to invent the drug-eluting contact lens, the device might be adaptable to other ocular medications.

"Although glaucoma is the disease we studied here, this is in fact a platform technology," Dr. Kohane said. "So it could be used for disease states where the contact lens wear would be much shorter—perhaps steroids for uveitis or postop applications for antibiotics and pain medications." —Linda Roach

1 Ciolino JB et al. *Ophthalmology*. 2016;123(10):2085-2092.

Relevant financial disclosures—Dr. Ciolino and Dr. Kahane are inventors on a patent for the drug-eluting contact lens.



DRUG-ELUTING LENS. (A) Optical coherence tomography cross-section of lens. Arrow points to the inner edge of the drug-polymer film within the hydrogel. (B) Lens in place in the monkey's right eye. The clear central aperture is surrounded by a translucent ring of drug-polymer film. Arrow indicates the inner margin of the drug-polymer film.

GLAUCOMA RISK FACTORS

Oral Health and POAG

NUMEROUS STUDIES HAVE LINKED tooth loss resulting from periodontal disease to systemic conditions including diabetes, cardiovascular disease, rheumatoid arthritis, certain cancers, and neurodegenerative diseases. Now, we may consider adding primary open-angle glaucoma (POAG) to that list. A large prospective cohort study has found that recent tooth loss was associated with an increased risk of POAG.¹

Tooth loss + gum disease = increased risk. Findings were based on data from the ongoing Health Professionals Follow-up Study, in which 40,536 men answered questions biennially about their health, including ocular and oral health status. Over a 26-year period, the researchers confirmed 485 cases of POAG through review of medical records. At each 2-year period within that span, they identified participants 40 years and older who reported eye examinations and were free of POAG.

Periodontal disease by itself was not associated with POAG, said Jae H. Kang, ScD, associate epidemiologist at Brigham and Women's Hospital and assistant professor of medicine at Harvard Medical School. However,

tooth loss in the past 2 years was associated with a 1.45-fold increased risk of POAG. And tooth loss accompanied by prevalent periodontal disease showed the strongest association: a 1.85-fold increased risk of POAG.

What's the connection? The researchers theorize that oral infections, particularly those implicated in periodontal disease, trigger a cascade of events in which inflammatory microbes and their attendant cytokines origi-

nating in the vascular bed at the base of the tooth ultimately reach the optic nerve head microcirculatory system. The result: endothelial cell dysfunction that may compromise retinal ganglion cell axons.

Although the study looked only at men, Dr. Kang said that the findings likely would hold for women, since periodontal disease has been associated with systemic diseases in both sexes.

Dr. Kang urged caution in interpret-

ing the results, saying that further study is needed. "One epidemiologic study cannot establish causal relations," she said. "Nevertheless, this study's findings raise the possibility that systemic adverse effects of poor oral health may also impact eye health."

—Miriam Karmel

1 Pasquale LR et al. *Ophthalmology*. 2016; 123(11):2318-2327.

Relevant financial disclosures—Dr. Kang: None.

FEMTOSECOND VS. MANUAL

Largest Meta-analysis Compares Cataract Sx

WHEN IT COMES TO WHAT MATTERS MOST TO

patients, it may matter little which type of cataract surgery they choose. Screening 2,802 articles published from 2007 to March 2016, Canadian researchers compared the efficacy and safety of femtosecond laser-assisted cataract surgery (FLACS) with manual cataract surgery. The articles selected for inclusion involved 14,567 eyes from 15 randomized controlled trials and 22 observational cohort studies in the largest meta-analysis to date on this topic.¹

Key outcomes comparable. The researchers found no significant differences in overall, pupillary, and corneal complications, nor in visual and refractive outcomes, including uncorrected distance visual acuity, corrected distance visual acuity, and mean absolute error.

There may be specific cases in which laser surgery is clearly preferable, such as when it is very difficult to do a manual continuous capsulorrhexis, said coauthor Iqbal K. Ahmed, MD, FRCSC, at the University of Toronto. "But our goal was to focus on outcomes for routine cases."

FLACS pluses. Laser-assisted surgery did excel in several secondary surgical end points, such as phacoemulsification time, absolute mean deviation from intended capsule diameter, horizontal intraocular lens centration, and postoperative central corneal thickness. "However, for many of these surrogates," said Dr. Ahmed, "we have not found corresponding positive clinical outcomes."

Reduced energy in the eye from FLACS has often been posited as potentially reducing collateral damage in the eye, but this did not translate into many obvious benefits. "Less energy does appear to be linked to reduced endothelial cell loss," said Dr. Ahmed. "However, this may be tied to how femtosecond laser is used.

A previous study by Abell et al.² found that making incisions with femtosecond laser actually led to greater endothelial cell loss."

FLACS minuses. FLACS was associated with higher intraocular prostaglandin concentrations and higher rates of posterior capsular tears. "Higher levels of prostaglandin raises questions about increased inflammation," said Dr. Ahmed, "indicating that there are remaining questions about the impact of femtosecond laser in the eye."

The higher rates of posterior capsular tears came as a surprise, said Dr. Ahmed. "This may well be due to early learning curves with the femtosecond laser," he said, explaining that the meta-analysis included records from the period of its inception. "Over time, complications rates may have become comparable." In fact, a recent study in the *Journal of Cataract and Refractive Surgery* found higher complication rates in the manual surgery group, which may support this hypothesis.³

High-quality data needed. Although the study benefits from a large sample size, Dr. Ahmed cautioned that not all the data are of the highest quality. Observational studies, in particular, introduce confounders and selection bias, and that poses a challenge when interpreting results.

"That's why we encourage investigators to design trials that are randomized and prospective in nature, producing the highest level of evidence possible," he said. "However, despite confounders present in our study, we are reassured by findings from a large study presented at ESCRS,⁴ which recently reported outcomes consistent with ours."

—Annie Stuart

1 Popovic M et al. *Ophthalmology*. 2016;123(10):2113-2126.

2 Abell RG et al. *J Cataract Refract Surg*. 2014;40(11):1777-1783.

3 Scott WJ et al. *J Cataract Refract Surg*. 2016;42(7):1003-1008.

4 Barry P. ESCRS FLACS Study. Paper presented at: 33rd Congress of the ESCRS; Sept. 5-9, 2015; Barcelona.

Relevant financial disclosures—Dr. Ahmed: Alcon, AMO, Bausch & Lomb, and Zeiss: C.