News in Review

A LOOK AT TODAY'S IDEAS AND TRENDS

Keeping Cornea Transplants Clear

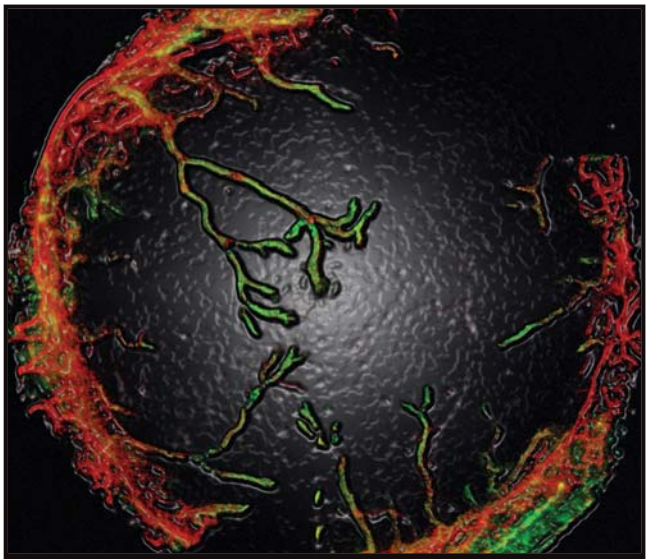
Why do lymph vessels begin growing in some transplanted corneas but not others? Blame the lack of a molecule that, when present, blocks the "C" form of VEGF from causing lymphangiogenesis, according to an international team of researchers.

The group reports discovering a shortened, free-floating version of VEGF Receptor-2 that blocks lymph vessel growth.[1] It does so by preventing molecules of VEGF-C from binding to receptor sites on the cell membrane.

"This work answers the long-standing question of why the cornea is alymphatic, and at the same time it provides a new way to prevent corneal transplant rejection," said the study's senior author, Jayakrishna Ambati, MD, professor and vice chairman of ophthalmology and visual sciences at the University of Kentucky in Lexington. (The research team also included members from Germany, Japan and, in the United States, Utah and Louisiana.)

"Until now, there was no endogenous molecule that we knew selectively stops lymph vessels from growing," Dr. Ambati said.

The antilymphangiogenesis molecule is a soluble splicing variant of VEGF Receptor-2 (sVEGFR-2). Splicing variants occur when the cell's genetic machinery "snips" a gene's protein product prematurely.



CORNEAL LYMPHANGIOGENESIS. A plastic wrapper rendering of a flat mount of a mouse cornea in which sVEGFR-2 has been deleted showing invasion of LYVE-1+ lymphatic (green) vessels but not CD31+ blood (red) vessels.

The truncated receptor keeps the cornea clear of lymphatics by making it impossible for VEGF-C to attach to normal, membrane-bound receptors, the scientists report. In a series of experiments with gene-knockout mice, they showed that the unbound sVEGFR-2 molecules trap VEGF-C, preventing it from triggering lymph vessel growth. In control mice, the ratio of sVEGFR-2 to VEGF-C was more than 35 to 1. But the corneas of mice without sVEGFR-2 were covered with lymphatics at birth.

Furthermore—and contrary to ophthalmic dogma—the experiments suggest that blood vessels in a transplanted cornea are not responsible for rejection. Corneal transplant survival more than doubled

JAYAKRISHNA AMBATI, MD

in mice after intracorneal administration of dimeric sVEGFR-2, despite blood vessels in the interface.

"We have shown in mice that we can almost eliminate transplant rejection—but only if there are no lymphatics in the transplant," Dr. Ambati said.

If the group's conclusions about sVEGFR-2 are confirmed, modulating local levels of the molecule eventually might give physicians a new way to:

- Prevent rejection of transplanted organs, especially kidneys, whose rejection is associated with lymphangiogenesis.
- Treat congenital diseases of the lymphatic system such as lymphangioma, a disfiguring disease which affects one in 50 children. In vitro tests of endothelial cells taken from two infants showed that sVEGFR-2 halted abnormal cell proliferation.
- Block metastasis of cancer cells, by preventing lymph vessel growth near tumors.
- Reduce lymphedema by using an sVEGFR-2 antagonist to nurture new lymph vessels.

Steven A. Stacker, PhD, an Australian researcher who has published many studies on the molecular control of lymphatic metastasis, said he would want to study the data before assessing the potential of sVEGFR-2. But each new step in understanding the VEGF system is important, he said. Dr. Stacker is cochief of the Angiogenesis Laboratory at the Ludwig Institute for Cancer Research in Melbourne.

"Any new insight into the regulation of the factors that control the vascular system, both lymphatic and blood vessels, is interesting," Dr. Stacker said. "That the VEGF pathway is seen to be such a significant player in developmental and pathological angiogenesis makes it important for us to understand the impact of any additional variant of the receptor." —*Linda Roach*

1 Albuquerque, R. J. C. et al. Alternatively spliced VEGF receptor-2 is an essential endogenous inhibitor of lymphatic vessel growth. *Nature Medicine* Published online August 9, 2009.

Glaucoma Update

Study Supports OAG/ Alzheimer's Connection

A diagnosis of glaucoma may be a red flag for the future onset of Alzheimer's disease, according to Duke University researchers, who explored a connection between the two diseases in a longitudinal study involving the Medicare claims data of more than 100,000 patients.[1]

The study also has implications for the development of novel therapeutics aimed at neuroprotection, said Yvonne Ou, MD, a glaucoma fellow at Duke University, who headed the study.

The researchers reported that patients with newly diagnosed open-angle glaucoma had a statistically significant increased risk of a diagnosis of Alzheimer's over a 12-year period (1994 to 2006) compared with those without glaucoma. A similar risk existed for other kinds of dementia. What's more, the time to diagnosis of Alzheimer's or other dementia was shorter in the OAG patients than in the controls.

According to Dr. Ou, these findings support the growing body of evidence that glaucoma and Alzheimer's disease, both age-related neurodegenerative diseases, may share a relationship, though the exact nature of that relationship is still not known.

Previous clinical studies have demonstrated an increased prevalence of glaucoma in patients with Alzheimer's disease, she said. Uniting all of these studies is the theory that both OAG and Alzheimer's share a common underlying pathogenic substance—beta amyloid. Extracellular beta amyloid plaques found in Alzheimer's patients' brains is one hallmark of the disease. And structural studies of the optic nerves of Alzheimer's patients have shown loss of retinal ganglion cells, similar to that of glaucoma. Beta amyloid has also been implicated in retinal ganglion cell death in a rodent model of glaucoma, said Dr. Ou. But the details of these shared underlying mechanisms are still unknown, she said.

The clinical implications of these findings are twofold. First, said Dr. Ou, "Clinicians should be aware of this possible relationship so that patients with glaucoma can be monitored for signs of dementia and referred to the appropriate specialists."

Second, the underlying relationship between these two neurodegenerative diseases supports the possibility that neuroprotective therapies may have a role in treating both diseases, she said.

Next up, said Dr. Ou: "We would like to test the hypothesis that Alzheimer's patients taking medications with possible neuroprotective effects have a lower risk of diagnosis of glaucoma or less severe glaucoma."

—*Miriam Karmel*

1 Ou, Y. et al. Assessing the relationship between open-angle glaucoma and Alzheimer's disease in the Health Retirement Survey. Presented at ARVO, May 6, 2009.

Alzheimer's Talk

As part of the Academy Seniors Special Program and Reception, Andrew G. Lee, MD, will discuss lifestyle modifications that may keep Alzheimer's at bay. Monday, Oct. 26 from 2:30 to 5 p.m. West, Room 3001. Free. All are welcome.

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Cornea News

Contacts With Stem Cells May Clear Up Cornea

Australian researchers have discovered a method for using a hydrogel contact lens not just to bandage the cornea but also to grow autologous epithelial stem cells and transport them into the eye for repairing the ocular surface.

In a three-person pilot study, the scientists found that corneas covered for two or three weeks with the cell-laden contact lenses developed a stable, transparent corneal epithelium, and their visual acuity improved. The healed surfaces persisted for up to 13 months without conjunctivization or corneal neovascularization, the study reported.[1] The ophthalmologist who performed the procedure, Stephanie L. Watson, MBBS, PhD, a senior lecturer in ophthalmology at the University of New South Wales, said the patients also had relief from debilitating pain.

Ivan R. Schwab, MD, professor of ophthalmology and director of the cornea and external disease service at University of California, Davis, called the results exciting, plausible findings by a respected research group but cautioned that they are very preliminary. The study's design prevented the team from showing directly whether cultured limbal stem cells migrated onto the cornea, or perhaps secreted biochemical messengers that reactivated almost-normal corneal epithelial stem cells, Dr. Schwab said.

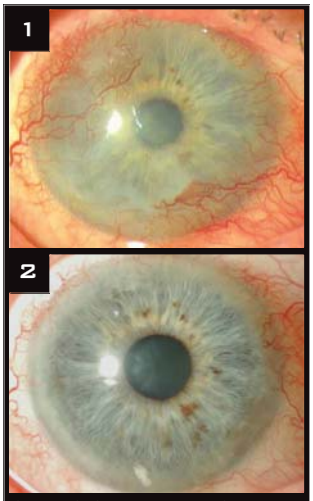
"It might not make a difference, and it might be the extracellular matrix that is more important. The newly secreted extracellular matrix may activate the corneal fibroblasts or neurons or alter them to promote proper healing. In other words, these cells may 'right' the listing ship," he said.

Two patients in the study had unilateral limbal stem cell deficiency caused by surgery for ocular melanoma, and limbal cells were harvested from the fellow eye. But the third had a bilateral deficiency, from aniridia. Relying on the idea of functional plasticity in conjunctival and corneal cells, the researchers prepared this therapeutic contact lens with superior forniceal conjunctiva taken from the fellow eye.

At 13 months after treatment, the aniridic patient's eye had transparent corneal epithelium, with less central irregularity. A mild subepithelial opacity persisted, and BCVA had improved from 10/200 to 20/200. The other two patients also had transparent epithelium. BCVA improved from 20/120 to 20/40 at 13 months in one patient, and from count fingers to 20/200 at eight months in the other.

It will be difficult to sort out what is really going on underneath the therapeutic contact lens especially if conjunctival cells are used, Dr. Schwab said. "It is possible and plausible that oligopotent stem cells are distributed throughout the mammalian ocular surface," he said. "It is also plausible that these are conjunctival stem cells and under certain conditions can strongly resemble the corneal epithelial stem cells. They may even produce characteristic extracellular matrix."

—Linda Roach



SEEING CLEARLY. Before treatment with a contact lens covered in stem cells, this patient had 20/120 vision (1). Afterward, her vision was 20/40 (2).

1 Di Girolamo, N. et al. *Transplantation* 2009;87(10):1571–1578.

Community Service

Dogs for Blinded Veterans

One of the most devastating injuries for soldiers in the Iraq and Afghanistan wars is ocular trauma from roadside bombs, mortars and grenades. In many instances their vision cannot be saved, and hundreds of veterans are coming home sightless. Yet, with a guide dog, the quality of life of these veterans can be improved.

In a June ceremony in Washington, D.C., four dogs were given to triple-amputee veterans, thanks to the fundraising efforts of the not-for-profit Veterans Helping Today's Returning Heroes. This organization is headed by veterans and an ophthalmologist and was founded two years ago to solicit and provide funds for a charitable organization called America's VetDogs, which provides specially trained dogs to help veterans who are blind or visually impaired.

"These dogs allow blinded veterans to interact with their environment, while also providing emotional support. This is such an important program, yet it receives no government funding," said Sam Bierstock, MD, a retired ophthalmologist in Delray Beach, Fla., and a board member of Veterans Helping Today's Returning Heroes.

For more information, visit www.vetshelpingheroes.com.

—Lori Baker Schena