Scientists discover why cornea is transparent, allowing vision

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Scientists at the Harvard Department of Ophthalmology's Schepens Eye Research Institute and Massachusetts Eye and Ear Infirmary (MEEI) are the first to learn why the cornea, the clear window of the eye, is free of blood vessels--a unique phenomenon that makes vision possible.

The key, say the researchers, is the unexpected presence of large amounts of the protein VEGFR-3 (vascular endothelial growth factor receptor-3) on the top epithelial layer of normal healthy corneas. According to their findings, VEGFR-3 halts angiogenesis (blood vessel growth) by acting as a "sink" to bind or neutralize the growth factors sent by the body to stimulate the growth of blood vessels. The cornea has long been known to have the remarkable and unusual property of not having blood vessels, but the exact reasons for this had remained unknown.

These results, published in the July 25, 2006 issue of the *Proceedings of the National Academy of Sciences* and in the July 17 online edition, not only solve a profound scientific mystery, but also hold great promise for preventing and curing blinding eye disease and illnesses such as cancer, in which blood vessels grow abnormally and uncontrollably, since this phenomenon, present in the cornea normally, can be used therapeutically in other tissues.

"This is a very significant discovery," says Dr. Reza Dana, Senior Scientist at the Schepens Eye Research Institute, head of the Cornea Service at the Massachusetts Eye and Ear Infirmary, and an associate

professor at Harvard Medical School, and the senior author and principal investigator of the study. "A clear cornea is essential for vision. Without the ability to maintain a blood-vessel-free cornea, our vision would be significantly impaired," he says, adding that clear, vessel-free corneas are vital to any animal that needs a high level of visual acuity to survive.

The cornea, one of only a few tissues in the body that actively keep themselves vessel-free (the other is cartilage), is the thin transparent tissue that covers the front of the eye. It is the clarity of the cornea that allows light to pass onto the retina and from there to the brain for interpretation. When the cornea is clouded by injury, infection or abnormal blood vessel growth, vision is severely impaired, if not destroyed.

Scientists have been wrestling with the "clarity" puzzle for many decades. And, while some previous studies have revealed small clues, none have pointed to one major mechanism, until this study.

In most other tissues of the body, blood vessel growth or angiogenesis occurs in response to a need for increased blood flow to heal an injured or infected area. The immune system sends in growth factors such as vascular endothelial growth factor (VEGF) to bind with a protein receptor called VEGFR-2 on blood vessels to trigger vessel growth. Three forms of VEGF--A, C, and D--bind with this receptor. Two of them, C and D also bind with VEGFR-3, which is usually found on cells lining lymphatic vessels, to stimulate the growth of lymphatic vessels.

Dana's team began to suspect the involvement of VEGFR-3 in stopping blood growth in corneas when they noticed unexpectedly that large amounts of the protein seemed to exist naturally on healthy corneal epithelium, a previously unknown location for the receptor. Dana and his team were already aware from clinical experience that the epithelium most likely played a role in suppressing blood vessel growth on the

cornea, having witnessed blood vessels develop on corneas stripped of their epithelial layers.

They began to theorize that the large amounts of VEGFR-3, in this new, non-vascular location, might be attracting and sucking up all the C and D VEGF growth factors, thereby blocking them from binding with VEGFR-2. And, because this binding took place in a non-vascular setting, the growth factors were neutralized.

To test their theory, the team conducted a series of experiments.

Using corneal tissue from mice, the team did the following.

They conducted chemical analyses that demonstrated that VEFGR-3 and the gene that expressed it were indeed present on the corneal epithelium. Next, in two separate experiments, they compared corneas with and without epithelial layers that were injured. They found that only the corneas without epithelial layers developed blood vessels, implicating the role of the epithelium in suppressing blood vessel growth To further prove their theory, they added a VEGFR-3 substitute to corneas stripped of their epithelial layers and found that vessel growth continued to be suppressed, replacing the normal anti-angiogenic role of the epithelium. Finally they exposed intact corneas to an agent that blocked VEGFR-3 and found that blood vessels began to grow, formally demonstrating that the corneal epithelium is key to suppression of blood vessels and that the key mechanism is expression of VEGFR-3.

"The results from this series of tests, confirmed our belief that the presence of VEGFR-3 is the major factor in preventing blood vessel formation in the cornea," says Dana, who says that the discovery will have a far reaching impact on the development of new therapies for eye and other diseases.

"Drugs designed to manipulate the levels of this protein could heal corneas that have undergone severe trauma or help shrink tumors fed by rapidly growing abnormal blood vessels," he says. "In fact, the next step in our work is exactly this."

Source: Schepens Eye Research Institute