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Corneal Basement Membranes and Injury-Related Scarring

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View Technical Abstract

PUBLIC ABSTRACT

The cornea is the clear front wall of the eye that transmits and focuses vision on the retina. Corneal injuries caused by trauma (such as explosions, projectiles, or fists), chemical burns, or infections (with bacteria, fungus, or acanthamoeba) are an important cause of vision loss or blindness in military personnel or non-military individuals. Usually this vision loss or blindness is caused by scarring in the cornea that makes it cloudy. This cloudiness results from the development of cells called "myofibroblasts" that are not normally found in the cornea and produce scarring when they accumulate in the center part of the cornea called the stroma. Pioneering studies in our laboratory have shown that damage to the connective tissue the epithelial cells sit on at the front surface of the cornea (epithelial basement membrane) or the connective tissue the endothelial cells sit on at the back surface of the cornea (Descemet's basement membrane) causes special immune cells to migrate into the cornea from the blood vessels at the edge of the cornea. These cells, called fibrocytes, change into myofibroblasts. Injuries to either one or both of the basement membranes in the cornea are severe because a soluble protein called transforming growth factor beta (TGFbeta) can then gain long-term entry into the center of the cornea from the tears, injured corneal skin (epithelium), or the fluid behind the cornea called the aqueous humor. Our studies have shown the myofibroblasts will stay in the cornea for many months or years unless the damaged basement membrane (or both damaged basement membranes) is repaired or replaced. We have shown in prior studies that if the injured epithelial basement membrane at the front of the eye is repaired by normal corneal cells then the scarring often disappears over time. We believe it is likely this would happen in the back of the cornea if the Descemet's basement membrane is damaged if (1) drugs could block the TGFbeta that causes myofibroblasts to develop, and/or (2) the posterior Descemet's basement membrane and endothelial cells were replaced by surgery.

We have developed a rabbit model in which severe scars occur in the back of the cornea if a large area of the Descemet's basement membrane and attached endothelium (about 80% of the back surface of the cornea) is removed by surgery. We want to use this model to study the development of the abnormal cells called myofibroblasts that cause the corneal scarring. Once we characterize how these cells arise after the injury, we want to study ways to either prevent them from developing or to cause them to die once they develop.

First, we will study the appearance of myofibroblasts in the cornea after removal of the Descemet's basement membrane and endothelium compared to control uninjured corneas to determine if the myofibroblasts come from fibrocytes in the blood or native keratocytes in the cornea. Second, we will study whether an FDA-approved drug called losartan (that is known to block TGFbeta and has been used to block scarring in the heart, muscle, and kidney) can block the development of (1) scars producing myofibroblasts after removal of Descemet's basement membrane and endothelium or (2) scars produced by chemical burns in rabbits. We will test this drug given in drops to the cornea and/or given orally to the rabbit after the injuries that cause scarring and compare this to controls that do not receive losartan. We will also study whether topical corticosteroid drugs have additive effects to losartan in preventing scarring after these injuries. Third, we will study whether surgical replacement of Descemet's basement membrane and endothelium (obtained from donor rabbit eyes) will cause myofibroblasts to die and scarring to resolve after it has already appeared because of a prior injury to Descemet's membrane and the endothelium compared to control animals where the Descemet's membrane and endothelium are not replaced. This surgery is called Descemet's membrane-endothelial keratoplasty (DMEK).

This study will provide a better understanding of scarring that occurs after injuries to Descemet's basement membrane on the back of the cornea. It also could lead to the use of losartan to reduce scarring of the

cornea after trauma (such as explosions, projectiles, or blunt trauma with a weapon or fist), chemical burns (accidental or when these chemicals are used as weapons), or infections that sometimes occur after even mild injuries to the cornea such as contact lens wear. Finally, it will help us to understand whether surgical replacement of Descemet's basement membrane and attached endothelium leads to the death of myofibroblasts in scarred corneas and, therefore, could help corneal scarring improve or disappear.

Back to Search Results

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