Anomalous Acute Inflammatory Response in Rabbit Corneal Stroma

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PURPOSE. To investigate the nature and cause of an acute, anomalous stromal edema after epithelial debridement in the rabbit cornea.

METHODS. Series I: Adult New Zealand White rabbit corneas were mounted in perfusion chambers. The endothelium was bathed with Ringer's fluid, and the outer surface was covered with silicone oil. The epithelium of one eye was debrided with a scalpel before mounting, and the cornea of the fellow eye was debrided with a rotating brush after stabilization in the perfusion chamber. Using specular microscopy tracking software, it was possible to measure total swelling and local swelling within the cornea. Series II: Diclofenac sodium ophthalmic solution 0.1% or a placebo was applied topically, 1 drop per 45 minutes for 3 hours before animals were euthanatized.

RESULTS. Series I: Corneas with their epithelium scraped with a scalpel before mounting were 37.5 ± 17.5 μm (n = 6; P < 0.001) thicker in vitro than the stromas of perfused, intact fellow corneas. Epithelial debridement with a rotating brush after mounting resulted in an immediate (within 8 minutes) stromal swelling that plateaued in 1 hour at 31.0 ± 5.3 μm (n = 6; P < 0.001). Curiously, in six of six corneas, the anterior stroma swelled more than the posterior stroma. In four of six corneas, the posterior stroma thinned. Analysis showed this pattern to be consistent with a sudden increase in anterior swelling pressure or osmotic pressure and to be inconsistent with a change in endothelial transport properties. Series II: Placebo-treated corneas swelled 30.6 ± 7.7 μm (n = 5) 1 hour after debridement, whereas corneas pretreated with diclofenac sodium swelled only 19.2 ± 3.1 μm (n = 6; P < 0.008).

CONCLUSIONS. The anterior stromal swelling occurs rapidly and near the site of epithelial injury suggesting messenger and/or enzymatic involvement with an effect parallel to apoptosis. Reduction of the swelling response with nonsteroidal anti-inflammatory drugs (NSAIDs) implicates the cyclooxygenase pathway. The swelling is similar to the unexplained acute edema that occurs during inflammation in the rat paw edema model, and may represent a general mechanism for mobilization of inflammatory cells. (Invest Ophthalmol Vis Sci. 2000;41:2523–2530)

The general mechanisms by which the cornea maintains its hydration, and therefore its transparency against the tendency for the stromal connective tissue to imbibe fluid and swell, are thought to be well understood.1 The collagen fibers in the stroma are surrounded by a relatively amorphous ground substance rich in glycosaminoglycans (GAGs) that impart the properties of polyelectrolyte gels.2 This type of biomatric, common to all connective tissue, is very hydrophilic and provides the driving force for fluid accumulation in edema. Current dogma argues that the swelling properties of the corneal stroma are fixed for a given hydration; in the absence of disease, it is not expected that the swelling mechanisms of the stroma can be rapidly or locally modified. For rabbits, normal hydration is 3.45 (dimensionless ratio = [wet weight − dry weight]/dry weight) with an associated swelling pressure of approximately 55 mm Hg.3,4 Variations in these parameters and their relationship to stromal fluid flow have been described by carefully determined empirical equations.5 Finally, it is generally agreed that the ion permeability properties and ion transport processes of the bounding membranes provide conditions necessary to maintain normal hydration in spite of the tendency for the stroma to swell.6–19

During attempts to isolate the corneal endothelium and stromal tissue for membrane transport experiments, we observed that the stroma appeared to swell after debridement of the epithelium with a scalpel blade.20 This was unexpected because silicone oil was used to block fluid movements across the debrided surface of the tissue. For this reason, it was surmised that fluid from the anterior chamber perfusate must have been drawn into the stroma through the endothelium to produce such swelling. Because corneal epithelial debridement is used routinely not only in animal investigations, but as

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a commonplace method to prepare the human cornea for excimer laser photorefractive keratectomy (PRK), we explored this anomalous swelling in the isolated cornea of the rabbit.

METHODS

Definition of Total and Local Stromal Thickness

In this article, total stromal thickness refers to the distance between the anterior stromal surface and the endothelium, along a line through the central stroma. Local stromal thickness refers to the distance between internal markers in the stroma (e.g., keratocyte nuclei) that occur fortuitously along the same line and are detected by our automatic scanning specular microscope.

Experimental Series

There were two experimental series conducted to investigate anomalous stromal swelling after epithelial débridement. In series I, the magnitude, location within the stroma, and time course of the swelling response to débridement was investigated. Both the total and local stromal thicknesses were tracked continuously in corneas after débridement with a bristle brush. For comparison, the total thickness of corneas that had been scraped with a scalpel before mounting was compared at relevant time points. In series II, the effect of a general nonsteroidal anti-inflammatory drug (NSAID) on the total stromal swelling response was investigated. In these eyes, diclofenac sodium ophthalmic solution 0.1% (sterile, unpreserved formulation, 0.3 ml single dose unit; CIBA Vision Ophthalmics, Atlanta, GA) or the vehicle alone as a placebo control (CIBA) was applied topically 1 drop per 45 minutes for 3 hours before the animals were euthanatized.

Animals

Our procedures conformed to the Louisiana State University Medical Center Institute Animal Care and Use Committee (IACUC) standards, which are in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. New Zealand White rabbits of either sex and of 1.5 to 4.0 kg in body weight were deeply anesthetized with an intramuscular injection of a ketamine-xylazine mixture (40.0 mg/kg and 5.0 mg/kg, respectively). Subsequently they were euthanatized with a lethal dose of pentobarbital sodium (100 mg/kg) administered intravenously through the marginal ear vein.

Corneal Perfusion

Excised rabbit corneas for both series of experiments were mounted in thermally controlled perfusion chambers using the method of Dickstein and Maurice.19 The two chambers were attached to the base of an automatic specular tracking microscope and could be alternately rotated under the objective. The endothelial perfusion solution was the glutathione-bicarbonate Ringer’s solution used by Klyce and Russell10 with the antibiotic gentamicin omitted. Successful preparations maintain a steady thickness under these conditions for 7 to 8 hours. As is customary to prevent anterior surface (epithelial) fluid movements, a layer of silicone oil (Dow Corning, Midland, MI) was applied to the epithelium or to the bare anterior stromal surface if the epithelium had been removed before mounting.

Epithelial Débridement Protocol

For series I, before enucleation, the cornea of one eye was débrided with a scalpel and swabbed with silicone oil, and the fellow eye was left intact under the eyelid. The débrided eye was then enucleated, and its cornea was excised and mounted in one perfusion chamber. Without undue delay, the intact, undebrided companion cornea was enucleated, excised, and mounted in the second chamber. After completion of both mounting procedures (approximately 35 minutes) and after a brief period for acclimation of the newly mounted intact cornea (approximately 10 minutes), the total stromal thicknesses of both corneas were recorded. The total time from cardiac cessation to these initial thickness measurements was approximately 55 minutes. The undebrided cornea remained under the microscope, and its total thickness was tracked briefly to establish the stability of the preparation. Then, to facilitate observation of the time course of any rapid swelling response to epithelial débridement, the intact perfused cornea was débrided in the chamber. To accomplish this, the perfusion chamber was rotated from under the microscope, most of the silicone oil was aspirated from the anterior surface, and the epithelium was removed. Because the cornea was in a recess, débridement was performed with a rotating bristle brush (405; Dremel, Racine, WI) with the motor speed reduced by hand-braking instead of with a scalpel. The epithelial debris and remaining silicone oil were aspirated. The exposed anterior stroma was then covered with a fresh layer of silicone oil, and the chamber was returned to its previous location. After determining with the microscope that the central epithelium and basement membrane were removed completely, the total and local stromal thicknesses were tracked continuously for 1 hour. At the end of the hour, the chamber containing the perfused scalpel-débrided cornea was rotated back under the microscope objective, and its total stromal thickness was recorded for comparison. In series II, both the control and experimental corneas were mounted sequentially in the perfusion chamber; the order of mounting was randomized. The stabilized, intact cornea of one of the eyes (experimental or placebo control; also randomized) was débrided with a bristle brush, and its total stromal thickness was tracked for 1 hour. The procedure was then repeated in the second chamber on the waiting, perfused fellow cornea. The Pallikaris débride ment brush (designed by Ioannis Pallikaris, Heraklion, Crete21), specifically for use in corneal refractive surgery, was used.

Total and Local Stromal Thickness Measurements

For series I, the total stromal thickness of a scalpel-débrided cornea was compared with its perfused, intact fellow cornea before and at 1 hour after débridement with a bristle brush. In addition, the time course of both the total and local stromal swelling of the bristle brush-débrided cornea was continuously tracked with the automatic specular microscope for 1 hour. For series II, the total stromal thickness changes of topical NSAID- and placebo-treated corneas, after débridement with a bristle brush, were tracked continuously for an hour. The time resolution, accuracy, and sensitivity of the scanning specular microscope22 were enhanced by the addition of an analog-to-digital (A/D) data acquisition board (DT2831; Data Translation, Marlboro, MA) and custom digital signal processing software. The signal processor treated the output (optical scans made bidirectionally across the perfused central cornea) from
the specular microscope’s photomultiplier tube in the following manner: A 7-point gaussian filter smoothed the original signal, first derivatives were calculated, a second gaussian filter was applied to the first derivative output curve, and the second derivatives were calculated. Reflective structures that produced peaks of light intensity in the optical scans could then be identified automatically by detecting where the first derivative was zero, whereas the second derivative was negative and larger than an adjustable threshold. Wherever the tracking system recorded a peak in light intensity, it was assumed that a reflective structure was found. Surface peaks correlate with the epithelial surface (when present) or the anterior stromal surface and the endothelial surface. Light peaks within the stroma were identified as keratocyte nuclei on visual inspection; many of these appeared consistent enough in the measuring system to be used as reference sites. During the observation period, changes in the relative positions of keratocytes must be caused by fluid shifts within and between the lamellae. Thus, local and total stromal thickness changes can be tracked with this instrument.

Anterior versus Posterior Stromal Swelling Estimates

To characterize local swelling, thickness measurements were taken from the anterior and posterior stroma. The thickness of each half (defined by bounding keratocyte tracks) was calculated immediately after the debriding procedure and again after 15 minutes.

Computational Modeling

During corneal swelling, merely tracking the total stromal thickness provides no information about where in the central stroma (whether anterior, posterior, or uniform) dimensional changes occur. With both corneal cell layers intact and exposed to fluid, it is impossible to deduce whether fluid enters from the anterior or the posterior boundaries. Further, because of the ability of the stroma to sustain significant hydration gradients, it is also possible that the tissue is simultaneously swelling and thinning at different locations across its thickness. Such phenomena have been predicted by a corneal numerical model and verified by experiment. The ability to track keratocyte motions within the stroma provides information about the magnitude and location of local swelling (and thinning). These data were combined with the Klyce and Russell computational model in an attempt to characterize the nature of the forces that drive the observed swelling response.

To simulate the total and local swelling patterns observed in this study, the baseline endothelial transport parameters for hydraulic conductivity \([Lp = 42.0 \times 10^{-12} \text{ cm}^2/(\text{dyne sec})], \text{ reflection coefficient } (\sigma_{\text{NaCl}} = 0.45), \text{ and permeability } (\theta_{\text{NaCl}} = 8.0 \times 10^{-5} \text{ cm/sec})\) were set to those determined by Klyce and Russell. The corresponding epithelial transport parameters were set to values \([0.0 \text{ cm}^2/(\text{dyne sec}), 1.0, \text{ and } 0.0 \text{ cm/sec, respectively}], \text{ that generate zero flux to simulate the effect of silicone oil blocking fluid movement across the bare stromal surface.}\)

RESULTS

Low-noise optical scans through the cornea were obtained with the aid of the digital filter, and the peak detection algorithm provided accurate position sensing of the peaks of light intensity within the corneal scans (Fig. 1). With the improved detection methods described, the corneal surfaces, as well as keratocytes, could be tracked with the automatic specular microscope for hours. In this study, dynamic changes in local stromal volume could be quantified and local thickness changes could be modeled accurately with the Klyce and Russell formulation.

Series 1

A troubling finding in our earlier work was that removal of the epithelium by debriding caused corneal swelling, which, although limited in time and amount, was repeatable. The results of the current investigation, which examines this phenomenon more closely, demonstrate that the total stromal swelling is statistically significant. Corneas with their epithelium scraped with a scalpel before isolation in the chamber stabilized at 37.5 ± 17.5 \(\mu\text{m}\) (\(n = 6; P < 0.001\)) thicker than the stromas of incubated intact fellow corneas. When the epithelia of the previously intact fellow corneas were debrided with a bristle brush, stromas swelled 31.0 ± 5.3 \(\mu\text{m}\) (\(n = 6; P = 0.001\)) in a 1-hour period. The time course of swelling in bristle brush-debrided corneas is shown in Figure 2. Corneas approached an apparent new steady state thickness within 1 hour. At the end of the experiment (1 hour after bristle brush:

**FIGURE 1.** Two scans with the specular microscope across an intact, incubated rabbit cornea. Scanning a slit beam of visible light at approximately 8 \(\mu\text{m/sec}\) back and forth across the thickness of the tissue, the photomultiplier signal indicates the position of the endothelium (e), reflections from keratocyte nuclei (stromal fibroblasts), and reflections from the epithelium (E). A digital analyzer detects peaks (□□) and correlates them with the position of the microscope objective to permit tracking of surfaces and internal reflections for thickness calculations.
debrided) the total stromal thickness of the bristle brush-debrided corneas was not significantly different from that of their companion scalpel-debrided corneas ($P = 0.7$). Of interest, the final and initial total thicknesses of the scalpel-debrided corneas were not significantly different ($P = 0.9$), indicating that the swelling in the scalpel-debrided eye occurred before the first measurement.

When keratocyte tracks in the bristle brush-debrided corneas were examined during the swelling phase, we observed what appeared to be anomalous anterior stromal swelling in the absence of posterior stromal edema (Fig. 3). In six of six corneas, the anterior stroma swelled more than the posterior, whereas in four of the six corneas keratocytes could not be tracked and were therefore not analyzable. For the placebo group, four corneas exhibited the swelling pattern, and one was not analyzable. Therefore, pretreatment of the corneas in vivo with diclofenac sodium did not alter the characteristic swelling pattern seen after epithelial débridement.

However, pretreatment of the corneas in vivo with diclofenac sodium was found to reduce the total stromal edema purely physical reason for the observed swelling (e.g., rapid dilution of the anterior stromal fluid could evoke such a response). We hypothesized that if this swelling response was related to inflammation, a nonspecific cyclooxygenase inhibitor might reduce it.

After the 3 hours of treatment with drug or placebo in vivo, followed by perfusion of the intact corneas in the perfusion chambers, stromal thicknesses stabilized at $405.0 \pm 19.3 \mu m$ for the diclofenac sodium-treated corneas compared with $404.6 \pm 11.9 \mu m$ for those treated with placebo. The difference between these values was not statistically significant ($P = 0.969$) indicating that NSAID treatment by itself did not alter the swelling properties of the stroma.

The pattern observed in series I, consisting of anterior swelling and posterior thinning (the swelling pattern) after epithelial débridement, also occurred in series II. For the diclofenac sodium-treated corneas, three corneas exhibited the swelling pattern, whereas in three corneas keratocytes could not be tracked and were therefore not analyzable. For the placebo group, four corneas exhibited the swelling pattern, and one was not analyzable. Therefore, pretreatment of the corneas in vivo with diclofenac sodium did not alter the characteristic swelling pattern seen after epithelial débridement.

Series II

In a second series of experiments, we sought to provide evidence to differentiate between biochemical reactions and a

![Figure 2](http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/933219/)  
**Figure 2.** Total stromal swelling after epithelial débridement. In series I the average swelling at 1 hour after the procedure was $31.0 \pm 5.3 \mu m$ ($n = 6; P = 0.001$).

![Figure 3](http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/933219/)  
**Figure 3.** Localization of stromal swelling. The *upper trace* plots the position of the reflected light intensity peaks representing the anterior stromal face, taken as the reference surface at $0 \mu m$, and the *lower trace* represents the position of the corneal endothelium. The remaining peaks result from reflections of keratocyte nuclei within the stroma. The 18-minute gap in the record represents the time taken to remove the epithelium and re-cover the bare stromal surface with silicone oil to prevent fluid movement. Local swelling and thinning before and after epithelial removal is revealed by changes in the separation of the peaks. After débridement, the local thickness of the anterior (*hatched*) and posterior stroma are indicated by the bars (*white*, thickness immediately after débridement; *gray*, approximately 15 minutes later). The box to the *right* places the bars in close apposition to contrast the swelling of the anterior stroma with the thinning of the posterior stroma 15 minutes after débridement.
The unexpected stromal edema was an inflammatory response. This finding strengthened the hypothesis that fellow eyes treated with the placebo (vehicle) alone ($P < 0.008$; Fig. 6). This result suggested that the unexpected stromal edema was an inflammatory response.

**DISCUSSION**

The results of these experiments raise significant questions about our understanding of how the cornea (and perhaps connective tissue in general) responds to damage in the short term. We observed both a total corneal swelling and a local swelling of the anterior stroma after removal of the epithelium. In some cases, the drive for fluid movement to the anterior stroma was so strong that the posterior stroma actually thinned.

Numerical simulation of edema. The results of two different numerical simulations are compared with the data from Figure 3 (large dots). (A) Mechanical debridement of the corneal epithelium could well damage the inner sensitive monolayer of cells. In this simulation (light dotted lines: calculated internal stromal compartment interfaces), the endothelial permeability was increased three times normal at arrow. Doing so would cause the posterior stroma to swell more rapidly than the anterior stroma, particularly in that fluid movement across the outer surface was blocked. Although the total thickness change was fit well, the initial transients within the stroma were not. (B) Testing the hypothesis that an increase in the number of osmotic particles in the anterior stroma is responsible for the edema, we simulated the addition of 3.75 mOsm (equivalent to a swelling pressure increase of 72.5 mm Hg) at the arrow. The swelling characteristics are well described by this maneuver.
explosions of these potential mechanisms began to clarify the origin of the initial phase of the acute edema response to local burn injury and application of irritants, including carrageenan.29–32 Using Lund’s third hypothesis, coupled with the supposition that the dermal cells provide the mechanism to alter the local extracellular matrix in the short term,33,34 Reed et al.35 re-examined the onset of local edema and found that there was a cell–matrix interaction mediated by β1 integrins. This result led to the proposal that the hydration of the dermal interstitium is maintained, in part, by the local fibroblasts, and that these cells can modulate matrix properties in the relatively short term.33 In subsequent investigations, the same laboratory found that α-trinositol mitigates the extent of interstitial pressure increase after disruption of the β1-integrin system and that proteoglycans may also mediate cellular control of local hydration.36–37 Thus, a plausible theory for cellular control and a potential pathway to modulation of acute edema and local hydration has been advanced for connective tissue.

Similar to the dermis, the normal corneal stromal imbibition pressure is negative relative to the atmosphere. At normal hydration, the in vivo imbibition pressure is −40 mm Hg and the in vitro value is −60 mm Hg, the difference being the in vivo presence of the 20-mm Hg intraocular pressure.4,38 The classic concept of the maintenance of corneal hydration and transparency implies that this stromal swelling tendency provided by the imbibition pressure is balanced by the combination of active transport of HCO₃⁻ into the aqueous humor by the endothelium6,12 and the barrier properties of the bounding membranes. These factors act in concert to limit the passive stromal absorption of fluid.10 However, stromal swelling properties generally had been thought to remain constant (for a given hydration) in response to environmental stress (osmotic challenges, hypoxia, and inflammation). The current findings challenge this assumption.

The well-known ability of the corneal stroma to imbibe fluid during impairment of ion transport or after membrane barrier compromise has been attributed to the osmotic properties and the repulsion of the fixed negative charges of the stromal GAGs.3 Our results indicate that after epithelial débridement, the stromal swelling pressure has locally increased negativity. Lund’s third hypothesis, which would require keratocyte-mediated structural control of corneal hydration, is not likely to apply to the cornea, because corneal swelling in the anterior to posterior direction is observed to proceed virtually unrestricted under a variety of stimuli. This suggests that, at least in the cornea, local edema of the stromal tissue after injury does not appear to be immediately controlled by the connective tissue cells.

It is clear from our results that the behavior of the stromal tissue after injury is not consistent with the traditional paradigms that define corneal hydration control, nor is it consistent with the new cellular-based theories of connective tissue edema modulation. Thus, the traditional models of corneal hydration maintenance must be modified to include a mechanism that rapidly alters local stromal swelling pressure. We postulate that a local increase in the osmotic pressure is responsible for the observed anterior stromal edema (cf. Figs. 3, 4, 5). However, the constituent molecules that are responsible for the increase in osmotic pressure have not yet been identified. It is possible that some of the increased osmolarity is due to the proteolytic action of enzymes on the macromolecular constituents of the tissue’s extracellular matrix. This suggested cause is similar to Lund’s second hypothesis, which holds that local matrix constituents are modified or damaged to produce higher oncotic pressures.28 Indeed, proteases specific for stromal core protein-GAG linkage molecules (serine) have been identified in the anterior keratocytes and in the tears after injury.39,40 However, lysis of GAG molecules from their protein cores is not expected to significantly increase their oncotic pressure contribution. Urban et al.41 demonstrated that most of the oncotic pressure associated with GAG molecules depends primarily on the concentration of their fixed negative charges (Donnan effects) and not on their molecular weight or aggregation state. Because lysis of the GAG from its core protein changes only the latter two quantities, we cannot attribute the observed large change in swelling pressure in such a short time to lysis of these particular molecules. Another possible mechanism explaining the swelling is that local stromal keratocytes release hyperosmotic products of proteolysis as they undergo apoptosis.42 Unfortunately, the paucity of available biochemical data with regard to the process of keratocyte apoptosis requires acknowledgment that the cause of anterior stromal swelling is not fully understood at this time.

The significance of an alteration in stromal swelling characteristics in response to débridement is of paramount importance to both experimental corneal transport physiology and corneal surgery. In these disciplines, the epithelium is removed or damaged routinely with the traditional assumption that the underlying tissue remains stable. However, it has been known for some time that epithelial débridement or trauma can induce apoptosis in the anterior stromal keratocytes43 on a time...
scale similar to the swelling response reported in this article (Steve E. Wilson, personal communication, May 1999). In wound-healing studies it has been shown that subepithelial keratocytes undergo apoptosis as quickly as the tissue can be processed after traumatic débridement. Of particular concern, epithelial débridement is typically used in PRK to expose the stromal surface (Bowman’s layer) to the excimer laser for reshaping. Surgeons have used manual débridement with a scalpel or blunt spatula as well as a rotating bristle brush. Damaged epithelial cells remain in contact with the stromal surface from 30 seconds to several minutes with these procedures. During this time, cytokines are released to the anterior stroma where they initiate keratocyte apoptosis that can involve the anterior half or more of the stroma. Apoptosis is greatly attenuated when the epithelium is removed cleanly (without crushing) with the excimer laser. This has particular relevance to our investigation, in that it suggests a potentially less traumatic approach to the anterior stroma than using a scalpel or a spatula.

PRK ablations after manual débridement of the epithelium are not nearly as accurate as ablations of inert materials and are prone to generating central islands of unablated tissue. We believe that excess fluid in the central anterior cornea arising from the acute inflammatory response could be a contributing factor in the formation of central islands. With this scheme, fluid is drawn anteriorly as shown in the experiments reported here, resulting in extra laser energy’s being spent in its removal rather than tissue ablation. Because the cornea swells preferentially in the center under a variety of uniformly applied stimuli, energy absorption is likely to be exacerbated in that region. In addition to the increase in anterior hydration, fluid may collect on the bare stromal surface further reducing ablation efficiency through absorption and reflection of the incident laser energy.

The success of refractive surgery depends on the management of inflammation and wound healing, without which tissue remodeling and stromal scarring can occur. Although topical prednisolone has been used for this purpose, NSAIDs, used before and after surgery, have the additional benefit of ameliorating postoperative pain. We have shown that the edema produced by corneal epithelial débridement can be diminished using pretreatment of the cornea with the NSAID diclofenac sodium, a nonspecific cyclooxygenase inhibitor. We suspect that this acute edema may have a cause similar to that of the inflammatory response seen in the rat paw model, as noted earlier. If this is the case, we may have uncovered a basic early process in the response of tissues to injury that leads to a swelling and loosening of the connective tissue that may provide an avenue through which migrating inflammatory cells may respond. Until we learn more, it may be prudent to minimize contact between the scraped epithelium and the underlying stroma during surgical procedures to reduce hydration-related complications.

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