Corneal Wound Healing and the Future of Refractive Surgery

Since the cornea provides the principal focal power of the eye, ophthalmologists have attempted to alter its curvature to improve uncorrected visual acuity. Unfortunately, any manipulation of the cornea—even the presence of a contact lens—evokes an ocular response.

The vagaries of refractive surgery have caused us to abandon the simplistic notion that the cornea is composed only of lamellar stacks of collagen. The true syncytial nature of the keratocytes in the corneal stroma has been recently demonstrated using confocal tandem microscopy. The role of proteoglycans in maintaining the regular spacing of collagen fibrils is being elucidated. We now know that it is impossible to perform a true lamellar stromal dissection, since some keratocytes will inevitably be sacrificed and the lamellae will be disrupted. Hence, any intrastromal implant (regardless of whether it is an allograft or a synthetic lens) must inevitably create an interface and incite a tissue response. Surgical intrusion into the cornea triggers myriad biological responses that account for some of the unpredictability of refractive surgery, especially since scar tissue is critical to the success of refractive surgery; it is required to anchor lenticles, to flatten corneas, and to repair damaged tissue. Furthermore, wound healing is a prolonged evolutionary process that contributes to weakness of the cornea and to instability of refraction after surgical procedures. Binder's extensive review of wound healing after refractive surgery in this issue of Refractive & Corneal Surgery (pages 98-120) emphasizes the practical consequences of these events.

Any type of incision into the cornea damages the epithelium, transects collagen fibrils, and disrupts the ground substance, inducing activation of keratocytes and their transformation into fibroblasts. Both epithelial and stromal wound healing response must be modulated to give a predictable refractive result. The concept of "corneal mortar" used after radial keratotomy is an excellent theoretical example. The mortar has numerous components: collagens (eg, type I), proteoglycans (eg, chondroitin sulphate), glycoproteins (eg, fibronectin), growth promoting peptides (eg, recombinant human epidermal growth factor), and others. It can serve numerous functions: maintaining the separation of the wound to enhance (and maybe titrate) the mechanical effect of a keratotomy, keeping the epithelial plug out to promote more rapid stromal wound healing, and providing a microscopic scaffold along which fibroblasts can migrate and lay down new extracellular matrix in a more orderly structure to create a cleaner scar. Ideally, if the new collagen fibrils had a normal diameter and periodicity, and if the new proteoglycans held them in a normal array, nearly "scarless" wound healing would be possible. Presently, no such "mortar" is available for clinical use, but research continues in many laboratories.

Genetic engineering has now provided human growth factors that make pharmacologic manipulation of wound healing possible. The corneal epithelium, stroma, and endothelium are all responsive to these polypeptide hormones, but the optimal formulation, dosing, and form of delivery have not been determined. Indeed, early clinical trials with human epidermal growth factor have demonstrated the need for meticulous formulations of the drug to be useful for topical application.

Approximately a quarter of a century has elapsed since growth factors were first discovered, and we are still struggling to discover their role as a clinically useful drug in the management of corneal wound healing; diligent dogged research continues to hold out the hope that we may develop these drugs for clinical use. But we must be realistic, even if we can use drugs to modulate corneal stromal wound healing, we will still face the twin challenges of eliminating light scattering by scar tissue and of creating scar tissue that has tensile strength similar to that of the undisturbed cornea—tall orders, indeed, as Binder emphasizes in pointing out these complications of wound healing in numerous clinical circumstances.

Recently, a novel approach to refractive surgery has been taken by surgeons using an excimer laser to photoablate the cornea with sub-micron accuracy. One of the hopeful premises of this new type of sur-
surgery was that the tissue might be ablated gently enough, with so little disruption of the remaining adjacent tissue that the wound healing response of the epithelium and stroma would be minimal—as if the cornea had not known it had been hit. This would allow linear keratectomies or surface reprofiling to proceed with minimal wound healing and presumably maximal control over the refractive effect. Unfortunately, the cornea does not remain unaffected after excimer laser refractive surgery. Most published reports of surface area ablation relate some amount of subepithelial scarring and epithelial hyperplasia, with their “auto-leveling” effect that would diminish the refractive change induced by the laser. Reports of linear keratectomy in humans have related persistence of a broad epithelial plug for many months. These responses will probably persist for years following excimer laser refractive surgical procedures. Further refinements in laser and delivery system technology and the possible use of pharmacologic agents to modify this type of wound healing still hold forth the hope of developing truly controllable refractive surgical procedures.

Another area of corneal wound healing that is extremely important but about which we have little practical information is the interaction between the epithelium and the stroma. Do healing epithelial cells communicate to the underlying fibroblasts the need for secretion of more extracellular matrix in the form of a scar? Does the epithelial basement membrane provide an important barrier between these tissues? What is the role of the attachment complexes from the epithelium as they extend into the underlying stroma by way of type VII collagen anchoring fibrils? Does the epithelium remain in a low grade of chronic metabolic activity with a continued called for subepithelial stromal proteolysis and remodeling? Fundamental questions such as these about corneal wound healing need to be answered if surgery as subtle as refractive corneal surgery is ultimately to be successful.

As Dr Binder emphasizes in his review, until we better understand the dynamics of normal wound healing, refractive corneal surgery will be unreliable and unpredictable. If we can regulate the amount of tissue that is either added to or subtracted from the cornea and control the biological response, we may then be able to optimize refractive surgery.

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