Chapter 10

The Wound Healing Responses and Corneal Biomechanics after Keratorefractive Surgery

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Abstract

Corneal biomechanics have been concerned recently since it is not only found to play an important role in the wound healing process after corneal refractive surgeries, but also essential to improve the predictability and safety of refractive procedures. Corneal biomechanics and wound healing responses are linked in time and space and may also cause complications of keratectasia, haze formation, and regression. This review focuses on wound healing and biomechanics of the corneal refractive procedures. Identifying corneal wound healing from the biomechanical point of view is mandatory to improve the outcomes and reduce the complications.

Keywords: wound healing, refractive surgery, corneal biomechanics

1. Introduction

Over the past 30 years, corneal refractive surgery has successfully corrected the refractive error for millions of patients. The spread of laser corneal refractive surgery is increasing the interest in the study of the safety and predictability. Many studies showed that the wound healing process influences the predictability and safety. Corneal wound healing is a major contributor to the success of refractive surgeries. Biological differences in wound healing responses are thought to be a major factor limiting the predictability of refractive surgery [1]. In some cases, mechanical instability or an abnormal wound healing process can lead to serious complications such as keratectasia or severe haze.

Hence, it is important to investigate and understand the corneal biomechanics and wound healing process for a better vision after corneal refractive surgery.

2. The wound healing responses and corneal biomechanics after keratorefractive surgery

2.1. Corneal refractive surgery

Corneal refractive surgery changes the corneal curvature to correct the refractive error. The most common laser refractive procedures performed today are small incision lenticule extraction surgery (SMILE) [2, 3], femtosecond laser in situ keratomileusis (FS-LASIK), and surface ablation procedures, i.e., photorefractive keratectomy (PRK), laser epithelial keratomileusis (LASEK), and epi-LASIK [4]. With the development of the femtosecond laser, the SMILE surgery and FS-LASIK have become the most commonly used procedures in China for myopic subjects.

2.2. Corneal structure and biomechanics

The cornea is a highly specialized transparent avascular tissue and is composed of five layers. They are epithelium, stroma, Descemet's membrane, and endothelium. Stroma is the main part of the cornea, and any factor that changes the corneal structure may obviously influence the biomechanical properties of the cornea [5, 6].

2.2.1. Epithelium, Bowman's membrane, and biomechanics

The epithelium's contribution to corneal biomechanics was significantly lower than that of the stroma with respect to the stiffness. Bowman's membrane tissue is a transparent sheet of approximately 12 μm. It is acellular and is composed of densely packed collagen fibrils that are in random direction. The fibrils are continuous with those in the stroma, which is believed to stabilize the corneal curvature [5].

2.2.2. Corneal stroma and biomechanics

The stroma constitutes nearly 90% of the corneal thickness. And its biomechanical properties are influenced by the collagen fibers and extracellular matrix (ECM), which further determine the corneal strength, shape, and transparency [7, 8].

The stroma is a fibrous layer of lamellae made up of connective tissue. Interlamellar branching is more extensive in the anterior stroma than in the posterior stroma. The density of the collagen lamellae is higher, and their arrangement and directionality are more complicated anteriorly than posteriorly. The collagen lamellae in the corneal stroma are organized into a complex, highly intertwined three-dimensional meshwork of transversely oriented fibers, which contributes to the corneal shape and stromal stiffness. Another critical component for corneal stromal biomechanics is the ECM. The ECM is mostly composed of proteoglycans (PGs), which comprise a core protein and are located in the spaces among the collagen fibers in the corneal stroma. PGs play a critical role in collagen fibril assembly and spacing, and their mechanical importance may be greater than currently recognized [9].

2.2.3. Descemet's membrane and biomechanics

Descemet's membrane is approximately 10-nm thick and considered as a secretion of endothelial cells. The membrane is comprised of type IV collagen fibers. It is highly elastic and represents a barrier against punctures. Descemet's membrane serves as an endothelial basement membrane. Bowman's layer and Descemet's membrane accounted for 20% of the bending rigidity of the cornea through the Finite element evaluation [5].

2.2.4. Endothelium and biomechanics

The endothelium is composed of one layer of cells, which adhere to the Descemet's membrane. The endothelium cells cannot regenerate after damage or aging, but can spread and enlarge to maintain the cornea clear and transparent, and further prevent the cornea from becoming hydrated. The corneal endothelium may indirectly affect the corneal stiffness by regulating corneal hydration. The loss of corneal endothelial cells will result in increased water absorption by the corneal stroma [8, 9].

2.3. Corneal biomechanics and corneal wound healing after refractive surgeries

It is noteworthy that the corneal biomechanics and wound healing responses are linked in time and space. Specifically, the corneal biomechanics involves the stromal healing responses; the better stromal healing process will contribute to better corneal biomechanics after surgery and more stable visual results.

2.3.1. Epithelial wound healing

Epithelial wound healing involves three main steps: sliding, proliferation, and stratification of epithelial cells. Specifically, the epithelium cells migrate to the wound surface; then the cells increase and divide; lastly the cells cover the wound area and multiple layers of the epithelium are regenerated [9].

Some studies suggest that many cytokines are involved in the healing process including the epithelial growth factor (EGF), hepatocyte growth factor (HGF), keratinocyte growth factor (KGF), and transforming growth factor β (TGF-β). [9] These changes permit cells to migrate, establishing dynamic adhesion with other epithelial cells and extracellular matrix components. In the epithelial cells surrounding the wound edge, there is an increased expression of CD44. After the migration of epithelial cells, the phase of proliferation begins.

2.3.2. Corneal epithelial and stromal interactions

When the basal membrane is damaged, cytokines, neuropeptides, growth factors, chemokines, and matrix metalloproteinases can diffuse into the stroma and interact with keratocytes. These factors could stimulate the transformation of the keratocytes into myofibroblast cells [9]. One recent study [10] used the exosomes extracted from the epithelial cells, and cultured these exosomes with fibroblast cells; they found that the stroma cells transformed into myofibroblast

cells with higher expression of TGF-β, CD63, and PDGF-B. This study indicates that the epithelial cells are very important for stromal wound healing, and they may use exosomes to transmit the wound healing signals in order to regulate the process [10].

After the epithelial and stromal damage, soluble mediators could be secreted through the epithelium and move to the stroma area. These molecules, like TGF-β and TSP-1, could stimulate the wound healing process and make keratocytes transform into myofibroblasts. The myofibroblasts lay down the ECM and generate alpha-smooth muscle actin (α-SMA) to close the wound. However, abnormal wound healing synthesizes excessive α-SMA, exerts traction forces across the ECM, and causes unorganized tissue architecture, haze, and regression after corneal refractive surgery [11, 12]. Only when the EBM is appropriately re-established, proper stromal levels of TGF-β and PDGF cause myofibroblast apoptosis, keratocyte repopulation, clearing of the abnormal ECM, and restoring of corneal transparency [13]. A delay in the regeneration of the EBM, due to damage, dystrophy, or elevated levels of MMP-2 and MMP-9, causes TGF-β and PDGF to continue entering the corneal stroma.

2.3.3. Stromal wound healing and corneal biomechanics

The wound healing of the stroma is end when the collagen fibrils fully connected the wound edge. Activated cells migrate to the wound area. The keratocytes are changed through the reorganization of the cytoskeleton and the development of stress fibers and focal adhesion structures. Genes that encode fibronectin, metalloproteinases, and integrins are activated. The early matrix consists of fibronectin [14], which was conducive to cell migration and proliferation. Then the matrix is converted to a collagen and proteoglycan matrix that increases the tissue tensile strength and resilience. Growth factors increased stiffness and enhanced mechanical load through enhanced collagen fiber formation and cross-linking. The geometry of the collagen network will determine the mechanical properties of the wound. The collagen fiber diameter increases with time during the wound healing process and is related to tensile strength. Interweaving of collagen bundles between neighboring lamellae provides an important structural foundation for shear resistance and transfer of tensile loads between lamellae.

The transformation of keratocytes into myofibroblasts is curial in the wound healing process. These cells are characterized by the expression of α-smooth muscle actin, stress fibers, and focal adhesion complexes. The microfilament bundles of myofibroblasts form stress fibers, and they contract and remodel the adjacent ECM. Myofibroblasts extend from the anterior stroma to the posterior stroma in a progressive manner. These cells develop fibrotic tissue for repair. Besides that, deposition of the ECM is beneficial for the matrix stiffening and global cellular stress. However, excess myofibroblasts cause the deposition of disorganized collagen and glycosaminoglycan [15]. The underlying mechanism for the interaction between myofibroblast cells and matrix is the focal adhesions. They play the role of a mechanotransduction system, transmitting the force generated by stress fibers to the surrounding ECM and also transducing the extracellular mechanical signals into the intracellular signaling. Further investigations are needed to find whether we could regulate the mechanotransduction system to influence the corneal wound healing process.

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2.4. Complications relevant to the corneal wound healing and biomechanics after laser refractive surgery

Corneal wound healing is important for the predictability and safety of corneal refractive surgery. The refractive outcome and its stability over time are strongly influenced by the corneal biomechanics and wound healing process. And the abnormal healing process or biomechanical instability could cause some complications after corneal refractive surgery.

2.4.1. Regression

Refractive regression is defined as a gradual loss of the attempted correction that limits prediction. Many studies showed loss of surgical outcome and the main cause seems to be the regression. The regression is mainly due to epithelial hyperplasia and stromal remodeling, two processes related to corneal wound healing. Refractive regression is a major challenge for myopia, especially for high levels of correction. Apoptosis, keratocyte proliferation, and myofibroblast cellular density have proved to be more intense following treatment for high myopia compared to treatments for mild myopia. Myofibroblasts are important effectors of regression. The changes of corneal biomechanics also induce the changes of the corneal shape and cause regression.

2.4.1.1. Keratectasia

Corneal ectasia is a rare complication induced by the corneal refractive surgery. It may occur due to an insufficient residual stromal thickness or unidentified subclinical keratoconus. Many advanced examinations have been used clinically to exclude the potential subclinical keratoconus. Moreover, surgeons have also used many ways to preserve as thicker corneal thickness as possible. However, it is still difficult to avoid the onset of keratectasia. It may be because the corneal stiffness or biomechanics is different among individuals [16]. And the postoperative stromal tensile strength is different for each procedure. This indicates that the risk evaluations for ectasia should take the residual stromal bed thickness and corneal biomechanical properties into account. Moreover, biomechanical changes can manifest clinically as changes of the corneal shape and increased sensitivity to shape changes. The role of biomechanics is therefore important to consider in routine refractive procedures and in special cases where the biomechanical status of the cornea is abnormal.

2.4.2. Haze

Corneal haze refers to the cornea opacity. It is commonly seen in surface ablation surgeries. Haze can potentially form in the interface between the LASIK flap and the stromal bed or directly underneath the newly formed epithelium overlying the stromal tissue after PRK surgery [17]. In modern refractive surgery, haze tends to be mild and resolves very quickly. In extremely rare instances, haze can cause decreased visual acuity and increased glare.

Abnormal regulation of the wound healing process can result in the formation of stromal haze with decreased corneal crystalline expression, increased light scattering, and production of a

disorganized extracellular matrix. Myofibroblasts are major contributors to corneal opacity with reduced expression of crystallin, greater secretion of type III collagen, and spread morphology. Over a period of time ranging from several weeks to several months, the myofibroblasts tend to gradually disappear through a series of remodeling processes. This process may be closely related to the expression of matrix metalloproteinases. These proteins are a family of proteolysis enzymes, which could degrade abnormal collagen fibrils. The cytokines, growth factors, and inflammatory mediators could also regulate the synthesis of metalloproteinase [18–20].

3. Conclusions

Laser refractive surgeries are effective for the correction of refractive errors. A better understanding of corneal wound healing from the biomechanical point of view is mandatory if refractive surgery is ever to achieve more predictable and safer refractive results.

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