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Stem Cell Research 2017-Corneal Stromal Remodelling Using Stem Cells-Advances and Potential Application: A Literature Review- Beibei Wu- Shenzhen People's Hospital

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Introduction

Cornea stromal anatomy

The human corneal layers can be classified into five layers; three cellular layers (epithelium, stroma, and endothelium) and two interface membranes (Descemet membrane and Bowman membrane) (Figure 1). The main bulk of the structural framework of the cornea is provided by corneal stroma that constitutes up to 85% of the thickness of the cornea. In the seventh week of gestation, and due to the neural crest migration, the stroma is formed after the establishment of the primitive endothelium. Histologically, it's considered as a cellular collagenous structure; however, it di□ers from other collagenous structures in many aspects as transparency, the organization of collagen fibrils, and extracellular matrix (ECM). The corneal stroma is formed of three parts; collagens, proteoglycans, and cells. Moreover, it has specialized glycoproteins and ions that responsible for organizing the collagen fibrils to maintain transparency. The collagen fibrils of the stroma are arranged in parallel bundles called fibrils, which are laid down within layers or lamellae, which have a variable thickness (300-500 lamellae); increases peripherally at the limbus and decreases centrally, with higher packing density in the anterior lamella than in the posterior ones. These organized fibrils work on reducing forward light scatter and have a significant role in the transparency of the stroma. It was found that the stromal collagen fibrils are composed of type I and a large amount of type V collagens. Type I collagen is found in a heterodimeric complex with variable diameters, while type V provides a unique and small diameter. These structures are surrounded by a kind of matrix gel contains mucopolysaccharides, keratan sulphate, chondroitin sulphate, and dermatan sulphate. This gel is defined as glycosaminoglycans (GAGs) which are attached to a core protein, they called the whole molecule a proteoglycan. These sulfate groups are very important for the function of proteoglycans; dermatan sulfate binds water at the hydration level, while the keratan sulfate are not and this suggests that the keratan sulfate acts as a reserve for hydration. Furthermore, the whole size of the proteoglycans is small enough to fit the spaces between the collagen fibrils. The proteoglycan has an important role in the regulation of stromal hydration and corneal transparency. There are four types of core proteins of major proteoglycans in the adult corneal stromal ECM: mimecan, decorin, keratocan and lumican. The core proteins have a similar size ranged between 35-40 kD. In terms of stromal cells, the major cell type is keratocytes that have a significant contribution in maintaining the ECM environment and synthesizing the collagen molecules and GAGs. The corneal stroma performs numerous critical roles within the eye. Optically, it is the main refracting lens and thus has to combine almost perfect transmission of visible light with precise shape, to focus incoming light. Besides, mechanically it has to be very firm to preserve the inner contents of the eye. Its structure at all hierarchical levels governs these functions.

Wound Healing Events and e Role of Growth Factors:

Regeneration of the ocular tissues in order to the healing of the wounds required many complex processes as migration, mitosis, and di□erentiation of epithelial cells and stromal fibroblast. After a few hours of injury, the epithelial cells begin to interact with the ECM and migrate from the edge of a wound. A new layer of stratified squamous epithelial cells is formed from repeated mitosis of the surrounding cells to replace the migrating cells and resurface the defect. These processes are regulated by many peptide growth factors as a Keratinocyte Growth Factor (KGF),

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Epidermal Growth Factor (EGF), Platelet-Derived Growth Factor (PDGF), Hepatocyte Growth Factor (HGF), and Transforming Growth Factor (TGF)-b . It was observed that the tear film contains some molecules of EGF that can penetrate the injured epithelial layer to stimulate the epithelial cells. This mechanism can occur through an autocrine pathway; the epithelial cells contain EGF mRNA that can be synthesized into EGF to stimulate the healing processes. The central corneal cells have very sensitive HGF receptors that rapidly expressed to the released HGF from the fibroblast after the epithelial injury to re-epithelialize the wound. Moreover, HGF works on inducing the motility of the cells through transactivation of the EGF receptor. In human corneal epithelial cells, the binding of HGF to c-Met activates mitogenactivated protein kinase (MAPK) pathways through the receptorGrb2/Sos complex to the Ras pathway or through protein kinase C (PKC). Many biological factors are required for the epithelial cell survival as a phosphatidylinositol-3 kinase (PI3K) and p70 S6 kinase (S6K) that are regulated by PKC and protein kinase B.

In case of a corneal stromal wound, an increased expression of actin was observed, which lead to di□erentiate the keratocytes into spindleshaped fibroblasts (a migratory phenotype) to proliferate and migrate towards the injured area. During this di□erentiation, some keratocyte proteins such as keratan sulfate proteoglycans and corneal crystallins are down-regulated to remodel the wounded ECM. The corneal wound bed is formed as a product of these processes. Furthermore, the fibroblasts di□erentiate into myofibroblasts, which are characterized by the expression of α-smooth muscle actin (α-SMA) that has a significant role in corneal wound contraction. All of these di□erentiation, proliferation, and transformation processes of Keratocyte-Fibroblast-Myofibroblast (KFM) are regulated by TGF-β1 and PDGF. Carrington and his colleague investigated the e□ects of HGF and KGF on early corneal epithelium and stromal wound healing. They reported that the KGF accelerated the epithelial coverage of the wound, while the HGF did the opposite. However, the presence of HGF enhanced the keratocyte repopulation of the denuded area under the wound, while it decreased in response to KGF. Therefore, they recommended inhibiting HGF in case of persistent epithelial defects. Pastor and Calonge conducted an RCT multicenter study to investigate the e□ect of EGF on corneal wound healing. They randomly assigned 47 patients to topical EGF and 57 patients to placebo. At the end of the trial, they found that the EGF significantly ($p<0.01$) decreased the time of healing in the group of EGF (44.17 h) compared with the placebo group (61.05 h). In contrast, Dellaert et al. showed that there is no significant acceleration of corneal re-epithelialization in the topical EGF group when compared with the placebo group [28]. They explained this by the possible down-regulation of the receptor sites after the keratoplasty. However, this finding was confirmed by Cohen et al. who reported that the topical application of epidermal growth factor onto partial-thickness wounds in human volunteers does not enhance re-epithelialization [29]. Regarding the fibroblast growth factor, Meduri et al. showed that the combination of basic fibroblast growth factor and cysteine was significantly accelerated the corneal re-epithelialization after keratectomy in patients with myopia.

Conclusion

In conclusion, the currently published experimental studies support the beneficial impact of corneal stromal stem cells on repairing corneal damage, corneal scarring, and blindness, in addition to their utility in bioengineering stromal tissue. Future studies could assess the utility of pluripotent stem cells or other adult stem cells to restore the corneal stroma, with guaranteeing safety measures before transplantation. Cell treatments for each corneal layer will focus on a specific disorder, instead of a full or partial thickness corneal transplant, which is the present therapy

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