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Review Article

Applications of biomaterials in corneal wound healing

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Abstract

Disease affecting the cornea is a common cause of blindness worldwide. To date, the amniotic membrane (AM) is the most widely used clinical method for cornea regeneration. However, donor-dependent differences in the AM may result in variable clinical outcomes. To overcome this issue, biomaterials are currently under investigation for corneal regeneration *in vitro* and *in vivo*. In this article, we highlight the recent advances in hydrogels, bioengineered prosthetic devices, contact lenses, and drug delivery systems for corneal regeneration. In clinical studies, the therapeutic effects of biomaterials, including fibrin and collagen-based hydrogels and silicone contact lenses, have been demonstrated in damaged cornea. The combination of cells and biomaterials may provide potential treatment in corneal wound healing in the future.

Keywords: bioengineered prosthetic devices; biomaterials; contact lenses; corneal regeneration; hydrogels

1. Introduction to the ocular surface and corneal diseases

As a sense organ of light perception, the ocular surface is the outermost part of the eyes, interacting with the outside environment during most of the daytime and protecting the intraocular tissues. The ocular surface is guarded by the eyelid when the eye is closed and comprises transparent cornea centrally with surrounding conjunctival tissues. The conjunctiva is mainly composed of bulbar, palpebral conjunctiva to cover the sclera and the tarsus. The conjunctiva reflects to form a fornix on three sides and a semilunar fold medially. The epithelium of the conjunctiva is continuous with the cornea at the limbus, where it is viewed as the major niche of corneal stem cells for regeneration of epithelial cells.[1–3] The cornea is the most vital refractive medium in the anterior part of the eye, and it is responsible for two-thirds of the total ocular refractive power. From the outer surface to the innermost cellular layer, the cornea consists of the epithelium, Bowman's layer, stroma, Descemet's membrane, and endothelium.[4]

Ocular surface diseases may be induced by extrinsic infectious pathogens, chemical burn, an intrinsic autoimmune reaction, dysregulation of the tear film, and corneal decompensation. A disrupted ocular surface not only leads to severe irritation but also can result in severe visual loss. Here, we introduce some important diseases of the ocular surface and the cornea.

Infectious corneal diseases are mainly derived from bacteria, fungi, viruses, and other rare pathogen invaginations,

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such as acanthamoeba and microsporidia.[5,6] Even with proper treatment, the complications that follow corneal infection, such as scar formation, corneal thinning, and corneal decompensation, may require surgical intervention in order to restore vision. Penetrating keratoplasty, partial layer corneal graft (lamellar keratoplasty), or endothelial keratoplasty can be performed, depending on which part of the cornea tissue is damaged.[7–9]

Chemical injury to the eye may range from mild irritation to complete destruction of the ocular surface and even loss of the eye. Depending on the offending agent, chemical injury can be divided into acidic or alkaline damage, which have different consequences. When acid come in contact with the eye, the proteins of the conjunctival and corneal tissues will become denatured and precipitated to prevent further intraocular penetration of chemical agents. Thus, it will localize the damage in the superficial layer. By contrast, strong alkalis will cause saponification of fatty acids in the cell membrane and result in cellular disruption. They easily penetrate the corneal stroma and rapidly destroy the proteoglycan ground substance and collagen fibers of the matrix. They may also infiltrate the anterior chamber and induce intense intraocular inflammation and tissue destruction. Both acid and alkaline injury to the ocular surface will possibly cause severe tissue necrosis and inflammation. The extensive conjunctival and corneal limbal epithelial damage will result in poor epithelial healing, neovascularization, scar formation, and fornix shortage. The management of complications after chemical injury aims to restore the normal physiological condition of the ocular surface and vision. Several methods can be performed in the reconstruction of the ocular surface, including autologous conjunctival transplantation, limbal stem cell transplantation (LSCT), autologous cultivated oral mucosal epithelial transplantation, and amniotic membrane (AM) transplantation.[10–12] Penetrating keratoplasty or keratoprosthesis can be considered after the inflammation has been controlled.

Graft-versus-host disease (GVHD) is one of the most severe complications after allogenic hematopoietic stem cell transplantation (HSCT) in patients with mainly hematopoietic dysfunction or hematologic and lymphoid malignancies.[13] In the pathogenesis of GVHD, it is supposed that grafted cells attack the recipient's tissues, such as the skin, lungs, liver, gastrointestinal tract, and eyes. If the intervention of immunemodulators or steroid therapy is inadequate or delayed, inflammatory conjunctiva with or without fibrosis, keratoconjunctivitis sicca from the destroyed lacrimal gland, and corneal scarring due to limbal stem cell deficiency (LSCD) will occur. Some studies demonstrated that cytokines in tear film, such as interleukin-6 (IL-6) and interferon-gamma (IFN-γ), are strongly correlated to the severity of dry eye in GVHD patients.[14] Thus, anti-inflammatory agents may help in the treatment of ocular GVHD. Topical cyclosporine has recently been proposed as an effective agent to control ocular inflammation and dryness in patients with severe dry eyes and chronic GVHD.[15] After stabilization of GVHD treated with anti-inflammatory agents and frequent lubricants, corneal or limbal transplantation with reconstruction of the ocular surface are necessary to rescue vision.[16]

Although the detailed etiology of ocular cicatricial pemphigoid (OCP) or mucous membrane pemphigoid remains unknown, autoantibodies with activated complements are believed to mediate cytotoxic (type II sensitivity) effects on the basement membrane and the subsequent breakdown of the conjunctiva. Some proinflammatory cytokine imbalances have been detected in patients with OCP, such as elevated macrophage migration inhibitory factor and macrophage colony stimulating factor in tear film,[17,18] increasing tumor necrosis factor-α and decreasing IL-6 levels in serum.[19] OCP is clinically characterized to involve the mucous membrane, including the mouth, oropharynx, kidney, gastroenteric tract, and genital tract. Based on the severity of OCP, subepithelial fibrosis (Stage I), loss of goblet cells, fornice shortening (Stage II), symblepharon (Stage III), and surface keratinization and extensive adhesion of the lid to the globe (Stage IV) will occur sequentially. In addition to conventional therapy with topical steroids and lubricants, biotherapies with interferons, immunoglobulins, monoclonal antibodies, rituximab, and mycophenolate mofetil are generally investigated.[20–22]

Erythema multiforme major, the so-called Stevens–Johnson syndrome (SJS), is induced by several medications, including sulfonamides, anticonvulsants, salicylates, penicillin, ampicillin, and isoniazid; or pathogens such as herpes simplex virus, mycoplasma, streptococcus, and adenovirus. The pathogenesis of SJS is the deposition of immune-complex in the dermis and conjunctival stroma, leading to severe desquamation of the skin, subepithelial bullae, fibrosis, and scarring of the conjunctiva. Symblepharon is a severe complication because the necrotic conjunctivas adhere to each other. The main treatment for SJS is supportive care using lubricant, ointment, and prophylactic antibiotic drops along with selective steroid administration to reduce inflammation and protect the cornea and the conjunctiva from drying out or becoming infected.[23] Treatment outcomes of late sequelae with cicatricial changes and severe dry eye have been disappointing. Therefore, early topical treatment in the acute stage is the main goal to reduce the risk of late complications.[24–26]

LSCD may result from congenital diseases, such as congenital aniridia, ectodermal dysplasia, and sclerocornea; or acquired injuries, including chemical burn, thermal injury, chronic contact lens wearing, ocular surgery, and chronic cicatricial conjunctivitis. The re-epithelialization of cornea is based on the availability of healthy LSCs to renew the corneal epithelium and, at the same time, to prevent pannus formation across the cornea from conjunctival vascular intrusion. Maintaining a healthy corneal surface requires 25–33% intact limbus; accordingly, transplantation with autologous, allogenic, and even cadaveric limbal tissue provides convincing effects in restoring the corneal surface.[27,28]

2. The AM and LSCs

The limbus is a unique structure that serves as a barrier between the cornea and the conjunctiva. Cumulated evidence