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Review

Corneal regenerative medicine

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ABSTRACT

Recently, regenerative medicine has become a highlighted field because it has great potential to induce a paradigm shift of supportive conventional therapy into definitive treatment. The cornea is the avascular, transparent, dome-shaped outermost layer of the eyeball, and it consists of three layers: epithelium, stroma, and endothelium. Conventional corneal transplantation, known as keratoplasty, has two main problems, a donor shortage and immunological rejection. Therefore, regenerative medicine has been applied to overcome these challenges. Regenerative medicine involving the corneal epithelium has been clinically applied, along with an understanding of corneal epithelial stem cell biology, earlier than that of the corneal stroma or endothelium. Thus, the effectiveness and safety of cultivated corneal or oral mucosal epithelial cell sheet transplantation have been reported by many researchers. Clinical studies on regenerative medicine for corneal stroma or endothelium have begun after basic and nonclinical study. Translational research has been performed to make corneal regenerative medicine a universal therapy. This article reviews corneal regenerative medicine.

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Contents

1. Structure of the cornea

The cornea is the avascular, transparent, dome-shaped outermost layer of the eyeball. The main optical function of the cornea, together with the lens, is the refraction of light to focus on the retina. Thus, the cornea and lens in the eye function similarly to the lens in a camera, while the retina functions analogously to film in a camera (Fig. 1). The cornea consists of three layers: corneal

Abbreviations: LEC, limbal epithelial crypts; LSCD, limbal stem-cell deficiency; COMET, cultivated oral mucosal epithelial cell sheet transplantation; iPS, induced pluripotent stem; GAG, glycosaminoglycan; PMD Act, Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (PMD Act).

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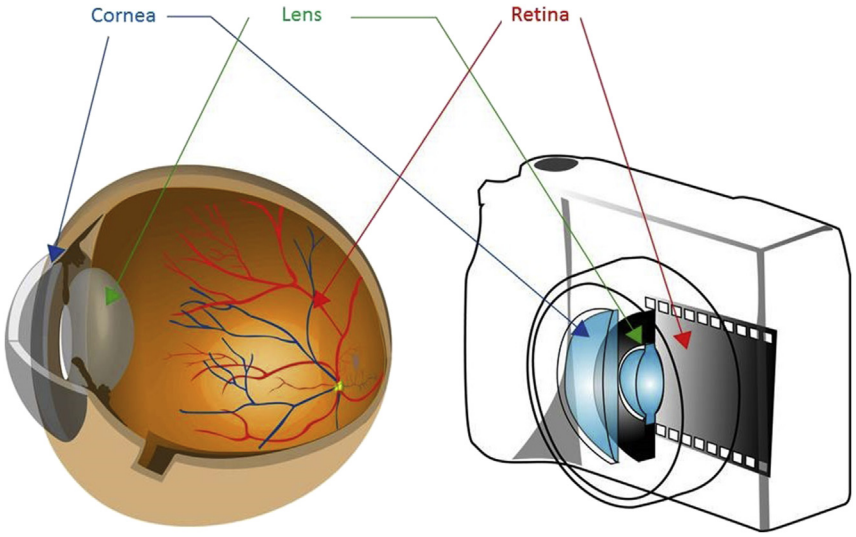

Fig. 1. Structure of the eyeball. The structure of the eyeball is similar to that of a camera. The cornea and lens in the eyeball function similarly to the lens in a camera. The retina in the eyeball functions similarly to film in a camera.

epithelium, stroma, and endothelium (Fig. 2). All of the layers play important roles to maintain corneal homeostasis. The corneal epithelium blocks the passage of foreign materials, including bacteria, fungi, and dust into the eye and provides a smooth surface that absorbs oxygen from the tear film. The corneal stroma is the middle connective tissue, and it consists of three main groups of proteins, collagens, proteoglycans, glycoproteins, and a small amount of stromal cells known as keratocytes. Regular alignment and the consistent diameter of collagen fibers are crucial for the maintenance of transparency and the strength of the cornea. The corneal endothelium is a single cell layer that forms a boundary between the cornea and the anterior chamber. Proteoglycans are associated with stromal collagens that bind to water and produce a pressure gradient. A major function of the corneal endothelium is to maintain corneal transparency using Na/K ATPase pump function, which regulates corneal hydration [1]. In addition, the endothelium forms leaky tight junctions by permitting a paracellular pathway of aqueous humor into the cornea.

2. Regenerative medicine for corneal epithelium

2.1. Corneal epithelium and limbal stem cells

The corneal epithelium is stratified squamous nonkeratinized epithelium. The thickness of the corneal epithelium has been reported to be 48–53 μm [2–7]. This layer is five to seven cells thick, and consists of small basal cells, flattened middle cells (wing cells), and polygonal flattened superficial cells.

It has been proposed that corneal epithelial stem cells are located in the basal layer of the limbus, the transitional zone

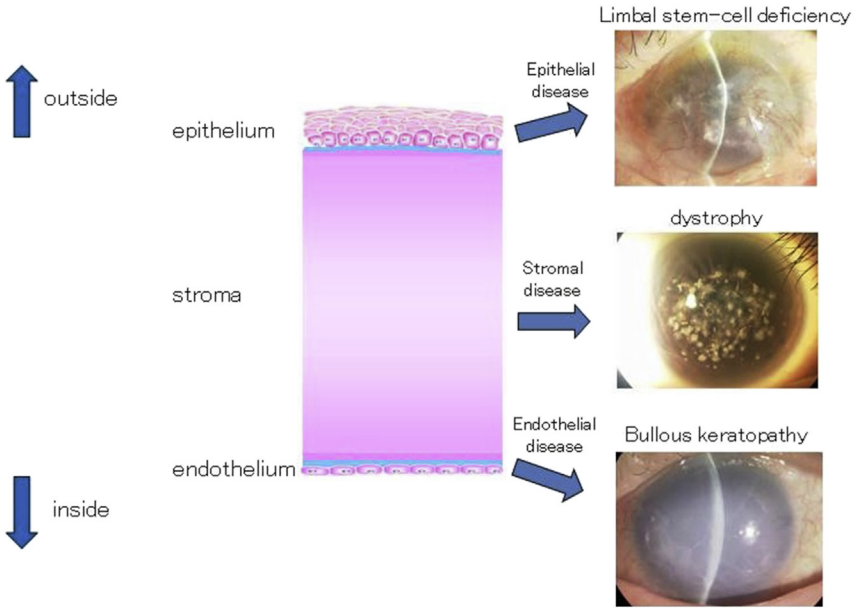

Fig. 2. Structure of the cornea and corneal disease. The cornea consists of three layers: epithelium, stroma, and endothelium. Vision can deteriorate due to disease in any layer: epithelial disease (e.g., limbal stem-cell deficiency), stromal disease (e.g., dystrophy), and endothelial disease (e.g., bullous keratopathy).

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