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Review

Biomaterials in ophthalmology: human cornea bioengineering

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Abstract: Medical engineering, as an auspicious conjunction between healthcare practice, biotechnology and materials science, has emerged over time with the aim to improve human's health. Cornea, an essential part of the eye responsible for most of its optical power, suffers every day due to accidents or various diseases. To avoid complications and overcome limitations of conventional transplantation and other surgical procedures, biomaterials and bioprinting proved beneficial can be used to design optimal devices for corneal implantation. During medical evolution, biopolymers have been used especially in tissue engineering applications, due to their high elasticity and flexibility, adaptable optical properties and tunable microstructure. Natural polymers are well accepted by the body, their offer support for tissue regeneration and, in most cases, they are easy to obtain. Beside natural-derived biopolymers, synthetic polymers can be used in bioprinting to develop performance-enhanced platforms for corneal bioengineering. Bioprinting represents an innovative method to obtain a corneal implant and has the advantage to enable the facile control over some specific properties, such as thickness, color, elasticity or shape.

Keywords: corneal bioengineering, biomaterials, polymers, bioprinting

1. Introduction

Ophthalmology, the main domain responsible for the proper functioning of eyes, involves the diagnosis, prevention and treatment of ocular-orbital conditions [1]. Even if the eye is an organ which can be easily observed, accessed and manipulated, it possesses an intrinsic physiological complexity, compared to other internal organs. Corneal allografts represent the first and most successful solid organ transplantation of tissue from a human donor [2]. Besides transplantation, biomaterials have significantly gained the attention of worldwide scientific communities, as an alternative in ocular diseases therapy. An essential aspect of biomaterials considered for ocular devices consists in their transparency, which should not alter the visual acuity and should to offer comfort over time [3, 4].

Cornea, the anterior part of the eye, represents one of the most sensitive human tissues, with high importance in the optimal function and main responsibility in the refractive power of the eye. The health and intrinsic functions (refraction and transparency) of cornea are essential requirements for the protection of physiology of inner structures in ocular systems. For various reasons, including traumas or specific

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inflammatory, infectious or degenerative conditions, the damage of cornea occur. In such specific conditions, human vision is drastically impaired, since the damaged cornea inhibit the passing of light [5].

Anatomically, cornea is an avascular transparent and protective tissue situated in the anterior part of the eye, consisting in three cellular layers (epithelium, stroma and endothelium), respectively separated by Bowman's and Descemet's membranes. The inner part of cornea is composed of collagen networks (type I, V and VI collagen) which offer transparency due to uniform interfibrillar spacing and lamellar distribution of collagen fibrils [6, 7].

2. Polymeric biomaterials in corneal bioengineering

In the last years, biocompatible natural and synthetic polymers have occupied a new and progressive domain in clinical medicine. They are considered an important part in tissue engineering and prosthetic devices, being present in various biomaterials and medical fields: artificial organs, vascular grafts, skin grafts, artificial lenses, dentistry, orthopedics, etc.

In particular, ophthalmic polymeric biomaterials, especially those used in corneal engineering, should have optimal tribological characteristics and mechanical strength, transparency and porosity, liquid semi-permeability and compatibility with the amphiphilic tear film inside the eye [8, 9].

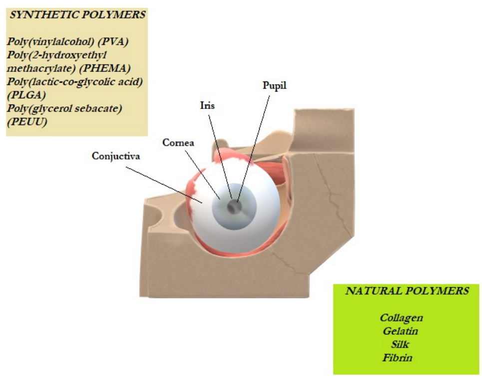

Figure 1. Schematic representation of the human eye and examples of biopolymers used in corneal engineering

2.1. Natural Polymers

2.1.1. Collagen

Collagen, an important protein of all living organisms, is found in a huge percentage through almost all biological systems. It is a protein which offers stability and strength for body tissues, supporting the formation of networks along the cellular structures. It was established that collagen molecules represent ideal candidates for genuine therapeutic alternatives in modern biomedical and biotechnological applications, thanks to their low immunogenicity, superior biodegradability and excellent biocompatibility [10]. For these reasons, collagen is nowadays one of the most studied biopolymer in the medical field. Being accepted by the human host, not inducing a negative reaction and supporting tissue regeneration, collagen proved a promising potential in corneal bioengineering [11, 12].

In human cornea, type I collagen is found in the highest amount. Therefore, most materials and devices developed for corneal tissue engineering and regenerative medicine are based on this particular fibrillar protein. To improve the mechanical strength of collagen-based materials designed for corneal bioengineering applications, glutaraldehyde or carbodiimides were proposed as chemical cross-linking agents [13]. According to experimental data, collagen-based graft cross-linked with a water-soluble carbodiimide proved efficient for corneal substitution, in comparison with human corneal transplant. The healing time was significantly different in the case of patients who received artificial corneal substitutes, since the entire epithelium regeneration was reported within 1 to 3 months. The as-treated patients didn't present any infection or rejection, so these clinical results strongly encourage the use of biomaterials based on collagen for corneal implantation [13, 14].

2.1.2. Silk fibroin

Silk fibroin, another biopolymer used in corneal bioengineering, is a natural-derived protein obtained from silkworm cocoons. Silk is used in tissue engineering due to the superior and safe biodegradation and to the remarkable biocompatibility. It offers mechanical support to tissues and sustains a fast epithelium regeneration in corneal implantation [15, 16].

Many biomaterials based on silk fibroin were successfully assessed for treatment for cornea disease. Among them, a membrane based on silk fibroin, with the aim of regenerating the epithelium tissue which is found in cornea, was proposed [17]. According to a recent study, the fabrication of a silk film developed in a 3D architecture model allowed a faster functionality of corneal tissue. The use of 3D cultures is an attractive and successful approach which induces a lot of benefits for corneal stroma regeneration, such as cell organization, transparency and extracellular matrix production. In comparison with native cornea, such a biomaterial acts with good mechanical and optical properties. Cell maturation and tissue regeneration are sustained, while cornea stroma can be developed in cell cultures in few weeks [18].

2.2. Synthetic Polymers

Beside natural materials, synthetic polymers are beneficial for tissue engineering and regenerative medicine. Synthetic biopolymers can be obtained throughout a wide variety of chemical reactions and can be used in many biomedical and biotechnological applications due to their facile fabrication and tunable physicochemical features and biofunctionality. They are flexible, able to offer a better support, easy tunable and cheaper (which is an important aspect in biomedical applications). The best reason related to the selection of synthetic biopolymers relies on the lack of immunological concerns. Even if the biocompatibility of natural-derived polymers is high, side effects could appear. So, in order to balance this situation, mixing the two types of biopolymers could represent an optimal situation for tissue restorative and regenerative applications [19-21].

2.2.1. Poly(lactic-co-glycolic acid) (PLGA)

PLGA is the most biomedical-relevant representative of polyester family, which particularly represents a proper choice for tissue engineering thanks to its intrinsic functional versatility, excellent biological behavior and high biodegradability. In ophthalmology, the biocompatibility and beneficial tissue integration of PLGA-based materials can be increased by combining *in vitro* the synthetic polymer and its derivatives with isolated cells [22, 23].

In the last few years, tissue engineering has been successfully involved in the design of artificial corneal tissue able to simulate the native cornea. In order to mimic the specific architecture of the natural tissue, researchers focused on the development of polymeric corneal constructs consisting in epithelial layers and adjacent nervous networks. The need of alternative therapeutic strategies for severe cornea impairment became a real concern of healthcare and scientific communities, as to overcome the limitations and possible negative reactions reported in the case of conventional cornea transplant from human donors [24, 25].

In cornea tissue engineering, many methods were successfully addressed in the scaffold's fabrication. Electrospinning and bioprinting [26] or chemical reactions are promising solutions for designing a specific biomaterial-based structure suitable for tissue restoration and regeneration. According to a recent study, corneal blindness can be controlled by using biomedical constructs designed to improve the quality of vision. The sandwich-like materials based on plastic compressed collagen and electrospun PLGA, exhibited strong mechanical character (without performing cross-linking reactions) and suitable porosity (responsible for beneficial cellular interactions). The combination of natural and synthetic polymers induced a better integrity of the resulted hybrid biomaterial within the human host, while the mechanical and physical properties were maintained for a long-time use. Given the good adhesion and proliferation of corneal cells in the presence of hybrid constructs based on PLGA and collagen, the results of this study strongly encouraged the use of such artificial architectures for corneal tissue engineering [27].

2.2.2. Poly(vinyl-alcohol) (PVA)

PVA is another synthetic polymer optimal for cornea reconstruction, especially due to intrinsic high hydrophilicity and superior biocompatibility. To obtain PVA, a two-step chemical method is involved and consists in the free-radical polymerization of vinyl acetate in an alcoholic solution, followed by the partial hydrolysis of poly(vinyl acetate).. In biomedical engineering, PVA is used thanks to its good biocompatibility and optimal behavior in biological systems [28].

PVA is a suitable choice for printing techniques. In the case of printed biomaterials, the most important properties which must be considered include printability, good mechanical and structural properties and biocompatibility. Furthermore, for real success following implantantion, the printed biomaterial should encourage beneficial interactions with endogamous tissues and surrounding organs [29].

In a recent research study, a highly elastic hydrogel based on PVA and nanocellulose whiskers was designed for contact lenses and corneal implants [30]. The composite biomaterials showed viscoelastic character, good oxygen permeability, superior biocompatibility, and encouraged the proper development of corneal cells. The integration of cellulose induced a high water content in comparison with commercial products, but the mechanical behavior of such composite hydrogel can be successfully compared to other devices for ophthalmology applications [30, 31].

3. Bioprinting

Bioprinting is a modern and promising technique for the design of complex three-dimensional structures, which have similar microstructure and architecture with original tissues. In bioprinting, the end-result consists in acellular scaffolds with tunable features (such as roughness, porosity, flexibility) for tissue engineering and regenerative medicine. This additive manufacturing technique allows defining and controlling the geometry of a tissue or organ, with or without cell-biomaterial interactions (depending on the needs). It has many advantages, as described in *Table 1*, but the biggest issue is related to the inaccurate mechanism by which corneal cells can be placed within the artificial construct [26]

Table 1. Advantages/Disadvantages of bioprinting in cornea tissue engineering

Advantages	Disadvantages
Fast method	Expensive equipment
Good chemical properties	Depending on the method, the mechanical properties can suffer
Diversity in polymeric materials	Trained personnel
Possibility to incorporate cells and biological molecules	Rough surface in most cases
Easy to obtain	Special properties of used materials

Bioprinting enables the fabrication of complex biomaterial-based constructs, which can be chemically associated with living cells through the layer-by-layer method in order to create cornea-mimicking tissue constructs [32, 33].

Bioprinting can include many methods, such as inkjet, extrusion or laser-assisted printing. In corneal implants fabrication and corneal tissue engineering, significant attention was oriented toward the highly efficient inkjet and extrusion techniques. For corneal tissue reconstruction, small polymeric droplets are deposited in a specific location within a precise shape during the inkjet procedure. The extruder system is based on two components, operating at different temperatures, namely the cold end which introduce the material into the printer and the hot end which melts the material that is subsequently concentrated though a nozzle. In this case, the material adheres to a surface in a precise matrix-form. According to literature, even if the extrusion is a faster method, the cell viability seems to be significantly increased in case of inkjet systems [34, 35].

A recent study proposed a collagen-based scaffold obtained by drop-on-demand bioprinting method and seeded with human corneal stroma keratinocytes as a suitable platform for corneal regeneration. The final product consisted in collagen and agarose, the last material being included to reinforce the scaffold's stability. Both materials present similar optical density as native cornea. The results of this study showed that the drop-on-demand method can be used for the obtaining of translucent cornea tissue. The biological tests evidenced the promising used of the bioprinted scaffold in corneal tissue engineering, by pursuing an increased and prolonged viability of corneal stroma keratinocytes [36].

4. Conclusions and future perspectives

Cornea diseases can alter the quality of human life, regardless the age of the patient. Bioprinted materials designed for cornea tissue engineering represent a promising, tunable and easy alternative to increase the quality vision.

The bioprinting technique is an attractive method that enables the fabrication of high quality and complex constructs for restorative and regenerative applications.

Natural and synthetic polymers represent the most suitable choice in corneal tissue reconstruction, due to their flexibility, adjustable degradability and biocompatibility.

In order to increase the efficiency and versatility of this technique, future perspectives include to promote stronger interactions between human cells and biomaterials and to develop specific systems that allow the targeted location of cells within the material.

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Conflicts of Interest

The authors declare no conflict of interest.

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