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Review Article

The Role of Nanofibers in the Treatment of Corneal Defects: A Review

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Abstract

Severe damage of the ocular surface is still one of the leading causes of impaired vision. Next to widely used treatment methods, such as keratoplasty and usage of amniotic membrane, a new approach has been in the focus of the research for the past few years. This review presents possibilities for using nanofibrous materials in the treatment of corneal defects. There is a broad spectrum of natural and synthetic polymers suitable for this purpose. Thanks to their mechanical strength, nanofibrous scaffolds are durable, and due to their high porosity, they promote optimal cell growth and proliferation conditions. Those three-dimensional, thread-like structures can also be used as a drug delivery system for different substances, such as antibiotics or stem cells.

Keywords: Electrospun nanofibers; Corneal defects; Regenerative medicine; Stem cells

Introduction

Damage of the ocular surface represents one of the most common causes of impaired vision and can lead to blindness [1]. Inflammation, infections, trauma, chemical burns, and systemic diseases are the most common causes of ocular surface damage [2]. For severe defects, allogenic tissue transplantation by penetrating keratoplasty is the last resort [3]. Although keratoplasty may offer visual improvement, it can fail due to non-optimal fixation or tissue rejection [4]. Nevertheless, damage to corneal innervations or limbal cells, as is often seen in trauma, chemical burns, or infections, can lead to limited transplantation possibilities [5]. Amniotic membrane, a widely used material for ocular surface reconstruction, demonstrates supportive function in epithelial cell growth [6] and reduces inflammatory response and scarring [7]. The search for non-biologic materials in corneal reconstruction and wound healing led to the recent and extensive research on nanofibers. Recent studies suggested that nanofibers are a promising alternative for treating various corneal pathologies. By definition, they are elongated, thread-like structures with at least one diameter in a range less than 100 nm [8]. Vital features such as optical transparency, mechanical strength, permeability to glucose and other nutrients, and the capacity to integrate into the host tissue are essential to overcome specific ocular tissue challenges [4,9]. In addition, nanofibers have unique advantages. Previous studies suggested they have a vital role in reducing the inflammatory response, enhancing cell adhesion and growth, direct cell migration, and offering superior storage and transport capacity [9-11]. Electrospinning is the leading method for generating nanofibers that can be broadly divided into two groups: natural and synthetic polymers [8]. Natural polymers include elastin, silk, fibrinogen, and collagen; synthetic polymers include poly(e-caprolactone), poly(lactic-co-glycolic) acid, Poly(ethylene oxide), poly(L-lactic) acid, and Polyvinyl-alcohol [12], all must be biocompatible and biodegradable [10].

Methods

We performed article research in PubMed using a combination of keywords cornea and nanofiber with 66 results, ranging between the years 2007 and 2021. Those articles were reviewed and sorted out original research papers concerning corneal defects treatment using nanofibrous scaffolds. Finally, we used 30 articles concerning our target topic. We divided them into subtopic groups – Materials suitable for an artificial cornea development, Nanofiber scaffold for cell growth, Nanofiber scaffold enriched by cultivated cells used for cornea defect reparation, nanofiber as drug delivery system in vitro, and nanofiber as a drug delivery system in vivo.

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Results

Materials Suitable for an Artificial Cornea Development

A shortage of good-quality donor cornea is still a severe public health problem worldwide [13]. In the last decades, the development of tissue engineering brings an excellent opportunity for better alternatives to donor cornea. An ideal material must be transparent, biocompatible, and have optimal mechanical properties [14]. The scaffold should act as a template to promote tissue growth in three dimensions. Eventually, it should be replaced with new regenerated corneal tissue that integrates naturally into the host [15].

Cross-Linking Stabilization

The stability of the used material is usually supported by cross-linking. Arabpour et al. stabilized their three-layered nanofibrous scaffold by cross-linking using 1-ethyl-3-(3 dimethyl aminopropyl) carbodiimide hydrochloride and glutaraldehyde. It led to slower degradation but also better cell attachment a proliferation [16]. Sahi et al. used ethanol vapor to cross-link their silk fibroin nanofibers enriched by gelatin in a more recent study. On the other hand, even though the ethanol cross-linking improved the mechanical properties, it also significantly reduced the transparency of the nanofibrous scaffold, which is one of the essential properties of the artificial cornea [14].

Materials Combination

Recent studies show that it is convenient to combine more materials to achieve optimal properties. Aslan et al. compared three different materials potentially suitable for corneal regeneration - collagen foam, Poly(L-Lactic Acid) (PLLA) nanofiber mesh, and decellularized matrices. The aligned PLLA scaffold was found to be the best candidate as a corneal regeneration substituent among the constructs prepared in this study with its slow degradation profile, good biocompatibility, and decent transparency. When considering the cell morphology and original ECM organization features, a bovine-sourced decellularized cornea was an optimal matrix, but transparency wasn't optimal. On the other hand, the collagen foam scaffolds showed effective cell proliferation and the best light transmittance but a fast degradation rate [17].

Tonsomboon and Oyen also used a combination of materials. They developed fiber-reinforced hydrogels that show great promise as mechanically robust scaffolds for corneal tissue engineering applications. Electrospun gelatin nanofibers were infiltrated with alginate hydrogels. This structure is transparent with significant water content similar to the natural cornea, but thanks to electrospun and cross-linked gelatin nanofibers also mechanically stable [13].

Even though most of the studies present a combination of materials as a blend or a layered scaffold, Bakhshandeh et al. showed a different approach. The team fabricated a 2-part artificial cornea as a substitute for penetrating keratoplasty. The peripheral part consisted of plasma-treated electrospun poly (ε-caprolactone) nanofibers attached to a hydrogel disc of polyvinyl alcohol as a central optical part. Whereas the peripheral part showed high porosity that enhanced limbal stem cell attachment and proliferation, the central part showed light transparency of more than 85%, similar to the natural human cornea [18].

Nanofiber Scaffold for Cell Growth

In recent years, nanofibers have been investigated as an alternative carrier for cell growth, aiming to replace the widespread use of human amniotic membrane. Although many studies use amniotic membrane as a carrier for stem cells in ophthalmology, its biological origin has an inherent risk of infection transmission. In addition, low availability, transport, and storage pose a burden in many countries, especially third-world countries. For this reason, most research on ocular tissue engineering aims to compare nanofibers to a human amniotic membrane in several main aspects.

Biocompatibility

The first aspect is the ability of cells to attach, grow and maintain normal phenotypic appearance on the polymer media, thus indicating the extent of biocompatibility of the nanofibers. Sharma et al. used in their research PCL nanofibers and Limbal Stem Cells (LCS). Results suggest the favorable ability of the cells to attach and proliferate on the polymer surface, suggesting high biocompatibility. Scanning electron microscope proves normal phenotype [19].

Results of a study by Baradaran-Rafii et al. support the findings of Sharma et al. In this study, poly (3-hydroxybutyrate-co-3-hydroxy valerate) was used as a substrate for LSC. Using the scanning electron microscope and immunohistochemistry, they showed that LSC grown on were able to attach firmly, exhibited increased proliferation, and retain normal phenotype [20].

Salehi et al. used PCL nanofibers and blended PCL nanofibers with other materials such as Chitosan or Poly (glycerol sebacate) that are both random and aligned. They examine the adherence and metabolic activity of human corneal keratocytes and human corneal epithelial cells. Their results suggest that cells adhere better to hydrophilic nanofibers. However, all matrices show good performance as a substrate for cell adherence [21]. The results of all studies support the potential use of nanofibers to serve as a media for ocular surface engineering.

Growth Pattern

The growth pattern is a vital interest when exploring nanofibers as scaffolds. Sharma et al. used immunofluorescence and real-time polymerase chain reaction to show that there is no difference in growth profile between cells grown on nanofibers and amniotic membrane. The study demonstrates the ability of the stem cells to grow three-dimensional corneal epithelium, thus serving as an alternative substrate for HAM [19]. The work of Salehi et al. emphasize the importance of nanofibers orientation in promoting cell growth. Their results suggest that human corneal keratocytes and human corneal epithelial cells had unstructured growth on random fibers while elongated growth on aligned fibers [21].

Nanofiber Scaffold Enriched by Cultivated Cells used for Corneal Defect Reparation

The defect can lead to limbal stem cell deficiency if the corneal damage is extensive and the limbal region is affected [22]. In those cases, penetrating keratoplasty is not a sufficient treatment method. It is necessary to perform transplantation of limbal tissue or limbal epithelial stem cells. Limbal tissue

transplantation is usually used when only one eye is affected due to a strong immune response to a limbal allograft – the autotransplantation from the fellow eye is performed. Therefore, a more promising treatment method is LSC transplantation [1]. The obstacle is that LSC represents a relatively small population of cells, so it is necessary to look for other alternatives.

Limbal Stem Cells Alternatives

Holan et al. used as stem cells source Mesenchymal Stem Cells (MSC) obtained from bone marrow. In vitro expansion, those cells can differentiate into cells expressing corneal epithelial cell markers [23]. They compared the healing effect of MSC to tissue-specific LSC using alkali-burned rabbit corneas. Nanofibrous scaffolds were used for cells transportation. Their study proved that bone marrow-MSC could be used as a convenient source of stem cells to support the healing of the wounded cornea. Moreover, they suggest that more important than differentiation of MSC into corneal epithelial cells is their production of numerous trophic and growth factors. They support the growth of residual corneal epithelial cells and LSC and suppress the local inflammatory reaction [1].

Another study concerns using nanofibrous scaffolds enriched by MSC to treat alkali-injured rabbit cornea. Čejková et al. proved that bone marrow-derived MSC effectively decreases alkali-induced oxidative stress. MSC reduced apoptotic cell death and decreased metalloproteinase levels, and proinflammatory cytokines induction. This resulted in suppressed corneal inflammation and neovascularization, and accelerated corneal healing [24].

Zajícová et al. studied the growth, proliferation, and immunosuppressive activity of MSC and LSC isolated from mice corneal limbus and bone marrow. They cultivated those stem cells on electrospun copolymer polyamide. Cells were labeled by a fluorescent dye for their detection after transfer on the damaged ocular surface.

A corneal debridement and limbus excision were performed on an animal model (mouse). The corneal and limbal region was covered with nanofibre enriched by MSC and LSC, which led to inhibition of local inflammatory reaction and support of the healing process. The local inflammatory reaction was monitored by producing genes for Interleukine-2, Interferon –γ, and inducible nitric oxide synthase [25].

Stroma Regeneration

Uzunalli et al. focused on stroma regeneration in their study. They developed a liquid bioactive peptide nanofiber scaffold system. These nanofibers are formed by self-assembling peptide amphiphile molecules containing laminin and fibronectin-inspired sequences. In in vivo experiments, corneal stromal pockets were made by lamellar dissection of rabbit cornea with a fine corneal spatula, and nanofibre solutions were injected into corneal stromal pockets.

Anti-vimentin staining was used as a keratocyte marker to visualize the cells that migrated to the corneal dissection site. Results showed that laminin-mimetic substrate was the driving factor for inducing cellular migration to the stromal defect. However, no cell migration to the lesion was observed in the negative control group and fibronectin-mimetic substrate. It shows that this laminin-mimetic peptide nanofiber system presents a promising scaffold for corneal stroma regeneration [26].

Nanofiber Drug Delivery System – In Vitro Studies

In the last years, several studies proved that nanofibers could also be used as a carrier for different types of substances reducing infection or enhancing tissue regeneration. Göttel et al. showed promising results in ocular drug delivery research. The paper published in 2019 presents a new in situ gelling nanofibrous, 3D-printed lens as a new drug-delivery system. In this case, fluorescein sodium eye drops were used. The lens was fabricated via electrospinning from a pullulan-gellan gum solution, a natural polysaccharide. Göttel and his team developed an artificial 3D-printed moistening chamber that enabled experiments with porcine eyes under physiological conditions. In those conditions, the fluorescein signal of dye-loaded fibers was compared to the fluorescence of conventional fluorescein sodium eye drops. Results showed prolonged in-vitro residence time caused by the higher viscosity of the fiber-formed gel in comparison to eye drops. In addition, compared to the eye drops, the fluorescein was much more homogenously distributed on the ocular surface because of the fibers' lens structure [27].

Anti-Infectives Loaded Nanofibers

Another paper presented by Göttel et al. concerns the development of Amphotericin B-loaded (AmpB) in situ gelling nanofibers to treat keratomycosis. The dry fibers were applied to the ocular surface and formed a gel immediately after administration. This AmpB polyelectrolyte complex was very effective against the fungal strain Candida crusei in vitro. In the disk diffusion test, the complex-loaded fibers showed a clear and homogenous zone of inhibition. Subsequently, in comparison with the conventionally used eye drop formulation, the new AmpB-complex loaded nanofibers in the same concentration were less toxic to cornea cells in vitro (the bile salts used for solubilization of the AmpB in aqueous eye drops as well as the drug itself are characterized by high cytotoxicity). When using conventional eye drops, the viability of cornea cells in vitro was 19%, whereas using the complex loaded fibers led to viability of 32.5% [27].

Polat et al. developed Besifloxacin HCl (BH) loaded nanofibrous ocular inserts to treat bacterial keratitis. These inserts were coated with mucoadhesive polymers such as sodium alginate, which increased the bioadhesion of the formulations. After seven days of incubation, the final product was not achieving acidic pH values, which generally irritates the eye. Insert formulations (tested in vitro in phosphate-buffered saline medium) showed a burst release in the first two days, followed by a slow-release profile. They were capable of delivering the drug at an effective concentration throughout the treatment period (seven days). Subsequently, antibacterial activities of the BH inserts (the BH concentration was arranged to 40 μg for a 1 cm^2 fiber insert) were measured against Pseudomonas Aeruginosa by disk diffusion method. Similar zone inhibition diameters were observed for developed insert formulations and commercial drug disc [28].

Vitamin C Loaded Scaffold

Moghanizadeh-Ashkezari et al. based their study on the fact that vitamin C positively affects keratocyte growth and proliferation. Their work aimed to find a suitable polymeric substrate for the regeneration of corneal stroma tissue. They designed nanofibrous scaffolds enriched by Zinc–Aluminium layered nanoparticles loaded with vitamin C. Via in vitro cell culture,

the viability of the corneal keratocytes on the scaffolds was evaluated. After 24h, the vitamin C-enriched scaffold induced higher cell viability than the control group without vitamin C. After one week, keratocytes completely covered the vitamin C-enriched scaffold, unlike the control group. His findings showed that their product is a promising candidate for corneal stromal tissue regeneration applications [29]. Another recent study by Farasatkia et al. also focused on stroma regeneration by using vitamin C-enriched nanofibers. They proved that a controlled release of vitamin C has a positive role in the improvement of stroma cells proliferation and stimulating their collagen secretion [30].

Nanofiber Drug Delivery System – In Vivo Studies

Čejková et al. studied an anti-inflammatory and immunosuppressive effect of Cyclosporine-A (CsA)-loaded nanofibers to treat alkali burns. Alkali burns were introduced on living rabbits' corneas using NaKOH. They then were divided into the following groups: untreated (control), CsA eye drops, drug-free nanofibers, and CsA-loaded nanofibers (that were sutured to the conjunctiva). After 12 days, results showed subtle signs of inflammation (such as lower numbers of T-lymphocytes and proinflammatory molecules) and less evidence of neovascularization in the CsA-loaded nanofibers groups compared to control. Furthermore, the expression of Caspase-3, a reliable marker of apoptosis, was markedly reduced in the CsA-loaded group. Results prove the continued release of CsA-loaded nanofibers and the beneficial healing effect [31].

Ye et al. studied nanofibers' potential effect in alkali burn corneas on rats' model. Although the nanofibers were not saturated with antibiotics in this study, it has several important conclusions. Results suggest the high performance of mechanical and biological properties of the Chitosan-modified, collagen-based nanofibers, mainly transparency, tensile strength, and significant promotion of cell growth such as human corneal epithelial cells, conjunctival epithelial cells, and dermal fibroblast. Results of in vivo studies demonstrated the superior effect of collagen-hyaluronate saturated nanofibers in cellular adhesion and significant re-epithelization in acute alkali burn rat model, similar to HAM. Since possible transmission of infectious disease is the main disadvantage of HAM, nanofibers may have a growing role in cornea's wound healing in the future [32].

Polat et al. used insert into the cul-de-sac made of nanofibers loaded with besifloxacin to treat infectious keratitis in 18 rabbits. They created four groups: insert with Besifloxacin, insert without Besifloxacin, topical treatment, and a control group. Study results showed that clinical scores regarding discharge, corneal edema, conjunctival chemosis were significantly lower in the inset loaded group compared to the other groups [28].

Conclusion

Recent studies mentioned in this review show that nanofibers are a very promising material in the modern treatment of corneal defects. They can be widely used due to their mechanical strength, high porosity, and biocompatibility for different approaches in regenerative medicine, such as material for artificial cornea, scaffold for stem cell growth, or a delivery system of various types of drugs and cells.

Conflict of Interests

The authors declare that they have no conflict of interests.

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Authorship Confirmation/Contribution Statement

Katerina Senkova: Writing – original draft, Conceptualization. Hadas Elbaz: Writing – original draft. Adela Klezlova: Writing – review & editing. Magdalena Netukova: Supervision, Resources. Pavel Studeny: Supervision, Funding aquisition

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