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REGULAR ARTICLE

Antiangiogenic effect of silicate nanoparticles on corneal neo-vascularisation induced by vascular endothelial growth factor

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Abstract Corneal neo-vascularisation (NV) is a major sight-threatening condition and is caused by infections, degenerative disorders, inflammation and long-time contact lens wear. Corneal NV occurs when the balance between angiogenic and antiangiogenic factors is tipped towards angiogenic molecules. The abnormal vessels may decrease corneal clarity and vision, lead to inflammation and corneal scarring and worsen the prognosis of penetrating keratoplasty if needed.

There is no definite therapeutic approach for cornea NV. Medical and surgical therapies used to reduce corneal NV include corticosteroids and non-steroidal anti-inflammatory agents, laser photocoagulation and needle diathermy. Many of these therapies not only have demonstrated limited success but also have associated adverse effects. Therefore, it is very necessary to provide novel therapeutic approaches. Recently, anti-vascular endothelial growth factor (anti-VGEF) therapy has been introduced for the management of corneal NV.

Herein, we hypothesise the use of silicate nanoparticles (SiNPs) as a novel treatment for corneal NV. The penetration rate of SiNPs into the cornea is attributed to the size of nanoparticles. Therefore, different sizes of SiNPs (20–50 nm) would be prepared and loaded onto the tissue to determine corneal permeability towards them. In addition, SiNPs would be administered into the eye by topical, subconjunctival and corneal intrastromal injection and accumulate in newly formed vessels. This hypothesis has been developed by emphasising on the synthesis of SiNPs, characterisation of size-dependent properties and surface modification for the preparation of homogeneous

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nanocomposites, generated by a reverse micro-emulsion method. As the importance of concentration, shape and/or size of SiNPs could be key factors exerting their antiangiogenic effects, we suggest using 20–30-nm SiNPs to enhance their ability to penetrate into the corneal epithelium. We hypothesise that topical, subconjunctival and corneal intrastromal injections of SiNPs may effectively inhibit and treat corneal NV. Controlled experimental studies on rabbits are needed to test whether SiNPs are able to effectively inhibit VEGF-induced angiogenesis in every segment of the eye including anterior, middle (ciliary body and trabecular mesh work) and posterior segments.

Introduction

Nanotechnology has entered the field of medicine in recent decades and is used in different medical fields including diagnosis, biosensors and drug delivery and has thus provided novel nanomedicines and nanodevices [1]. Researchers are exploring nanotechnology as a drug delivery route for both systemic medications and ocular applications. Most of the conditions that affect the eye are treatable through the ocular surface [2–4]. Intravitreal administration of pharmacological agents has been applied for vitreoretinal diseases as drug delivery into the retina or the vitreous body is difficult to achieve through conventional methods in the presence of the blood–aqueous barrier and the inner and outer blood–retinal barriers [5]. For maximising the drug effect, the molecules of the drug need to reach specific locations within the target tissue. Because drug molecules typically cannot reach their site of action, there is a need for a technology that can efficiently deliver the required amount of the drug to its target site. Thus, many research studies on nano-sized drug carriers have been conducted in the field of ophthalmology [6,7]. Nanomedicine uses nanoscale technology for the treatment and prevention of disease that can pave the way for novel ophthalmologic therapeutic applications with an ultimate goal of improving quality of vision and finally the quality of life. Although new drugs have recently been developed within the field of ophthalmology, drugs administered systemically have poor access to the inside of the eye because of the cornea, which is an effective barrier to drug penetration by completely surrounding and effectively sealing the superficial epithelial cells. Conventional systems, such as eye drops, are inefficient, whereas systemic administration requires high doses resulting in significant toxicity. There is a need to develop novel drug delivery carriers capable of increasing ocular bioavailability and decreasing both local and systemic cytotoxicities. Nanotechnology is expected to revolutionise ocular drug delivery. Many nano-structured systems have been employed for ocular drug delivery and yielded some promising results.

The human cornea is normally an avascular, transparent connective tissue that consists of three layers, epithelium, stroma and endothelium, and a mechanical barrier to inhibit transport of exogenous substances into the eye [8]. Each layer possesses a different polarity and a rate-limiting structure for drug permeation. The corneal epithelium is of a lipophilic nature, and tight junctions among cells are formed to restrict paracellular drug permeation from the tear film. The corneal epithelium is almost impermeable to any substance larger than 500 Da [9]. Most of the commonly used topical drugs are larger than that and are not able to cross the cornea. Instead, they permeate throughout the conjunctiva and the underlying sclera, known as 'non-productive passage'. Indeed, $< 5\%$ of topically administered drugs reach intra-ocular tissues [10]. The stroma is composed of an extracellular matrix of a lamellar arrangement of collagen fibrils. Drugs administered systemically because of the blood–aqueous and blood–retinal barriers and annular tight junctions, which make the cornea a major ocular barrier, have poor access to the retina and corneal stroma. Nanoparticle (NP)-mediated delivery not only overcomes the corneal epithelial barrier but can also prolong the resistance time of a drug in the pre-corneal tear-film layer. Therefore, preparing a topical nano-drug which is able to pass through ocular barriers is desirable [11].

New vessels, which sprout from the capillaries and venules of the pericorneal plexus, may block light, compromise visual acuity, worsen the prognosis of penetrating keratoplasty and lead to inflammation, corneal scarring and oedema [12]. In the clinical setting, topical corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) remain the principal primary treatment for corneal vessels [13]. However, in corneas in which vessels have been established, corticosteroid and NSAID treatments are ineffective. Although laser photocoagulation for corneal NV has been reported [14,15], this method achieves an inadequate effect because of the high incidence of recanalisation and thermal damage to adjacent tissue [16]. Other treatments including photodynamic therapy, fine needle diathermy and conjunctival, limbal and amniotic membrane transplantation [17–19] have limited clinical efficacy and also cause a multitude of undesirable side effects. Therapeutic NP technologies have the potential for parenteral, oral, ocular and trans-dermal applications as well as used in sustained release formulations and as a carrier for radionucleotides in nuclear medicine [20]. Sustained drug delivery systems can provide sustained drug levels to a particular tissue, thereby significantly reducing the dosing frequency and the associated complications. Several delivery systems including implants, scleral plugs and microparticles and NPs have been used for this purpose [21–23]. The particulate systems offer several advantages including ease of repeated injections and cellular entry [24]. NPs of various molecules, such as gold and silver, have been reported to have an antiangiogenic effect on pathological NV [25–27]. Silicate NPs (SiNPs) have been used in drug delivery, gene therapy, biolabelling and in combination with other treatment modalities [28–30]. Some characters of nano-sized silica which are size, size distribution and morphology are of great importance to its application. The large size is usually not effective for biomedical applications as cell uptake is limited. Another important requirement in the biomedical application of SiNPs is their aqueous suspensibility. Often, the high-temperature removal of the template poses problems in suspension in solution or destruction of encapsulated agents [31–33]. Many technologies have been explored to fabricate nanostructures and nanomaterials. In most of the preparation