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Review Article

Nanotechnology-based drug delivery treatments and specific targeting therapy for age-related macular degeneration

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Abstract

Nanoparticles combined with cells, drugs, and specially designed genes provide improved therapeutic efficacy in studies and clinical setting, demonstrating a new era of treatment strategy, especially in retinal diseases. Nanotechnology-based drugs can provide an essential platform for sustaining, releasing and a specific targeting design to treat retinal diseases. Poly-lactic-co-glycolic acid is the most widely used biocompatible and biodegradable polymer approved by the Food and Drug Administration. Many studies have attempted to develop special devices for delivering small-molecule drugs, proteins, and other macromolecules consistently and slowly. In this article, we first review current progress in the treatment of age-related macular degeneration. Then, we discuss the function of vascular endothelial growth factor (VEGF) and the pharmacological effects of anti-VEGF-A antibodies and soluble or modified VEGF receptors. Lastly, we summarize the combination of anti-angiogenic therapy and nanomedicines, and review current potential targeting therapy in age-related macular degeneration.

Keywords: age-related macular degeneration; choroidal neovascularization; nanotechnology; target therapy; vascular endothelial growth factor

1. Introduction

Age-related macular degeneration (AMD) is a common degeneration of retina in aging people, characterized by a yellowish deposit in the macula in dry type and choroidal neovascularization (CNV) in wet type. Wet AMD, also named neovascular AMD, is the leading cause of visual impairment in the elderly in industrialized countries, and results in blurred central vision due to macular edema from vascular hyperpermeability and abnormal blood vessel growth behind the macula.[1] Vascular endothelial growth factor (VEGF), a protein essential in angiogenesis and vascular hyperpermeability, is highly associated with wet AMD. According to the severity of wet AMD, several treatment choices are available nowadays, including intravitreal injection of therapeutic agents, argon

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laser photocoagulation of abnormal vessels, photodynamic therapy with verteporfin, and vitreoretinal surgery as a final resolution. Argon laser photocoagulation has been used to directly destroy the abnormal CNV membrane since the 1970s,[2] playing an important role in the treatment of wet AMD before we knew the importance of VEGF. Photocoagulation is now used as a supplement to treat extrafoveal neovascularization and polypoidal choroidal vasculopathy, a variant of AMD, due to its tissue-destroying effect. Photodynamic therapy is targeted at the subfoveal CNV to prevent traditional laser burn in the macula.[3] It is performed with the assistance of an intravenously injected photosensitive agent, followed by exposure to light of a specific wavelength (689 nm). However, its clinical application is limited due to its high cost and possible choroidal ischemia after treatment.[4]

Considering the pathophysiology of wet AMD, it is believed that the causes of neovascularization are increased intraocular concentration of VEGF and macrophage-induced inflammation within retinal tissues. Thus, intravitreal injection of anti-VEGF agents and/or anti-inflammatory drugs (mainly steroids) monthly for at least three times has become a consensus in the treatment of patients with fresh and recurrent wet AMD.[5] Since intraocular delivery of a steroid may lead to elevated intraocular pressure or cataract formation, this treatment should be used selectively, especially in young patients.[6] In patients with refractory wet AMD presenting severe vitreous hemorrhage and epiretinal CNV membrane,[7] vitreoretinal surgery should be considered to remove the blood and restore the integrity of the retinal structure.

2. VEGF, anti-VEGF-A antibodies, and soluble or modified VEGF receptors

VEGF belongs to a growth factor family, which includes VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor.[8] VEGF-A induces hemangiogenesis through VEGF receptor-2 (VEGFR-2), and VEGF-C/VEGF-D stimulates lymphangiogenesis through VEGFR-2 and VEGFR-3.[9–12] Currently, anti-VEGF agents such as bevacizumab (Avastin, Genentech, CA, USA), ranibizumab (Lucentis, Genentech, CA, USA), and aflibercept (Eylea, Regeneron Pharmaceuticals, NY, USA) are available in the market. Bevacizumab is a whole anti-VEGF-A immunoglobulin, while ranibizumab is a fab fragment of an antibody against VEGF-A. By contrast, aflibercept is a new recombinant fusion protein that is composed of two main components, the VEGF binding portions from the extracellular domains of human VEGFR-1 and VEGFR-2, which is then fused to the Fc portion of human immunoglobulin G1.[13] Aflibercept has the ability to bind VEGF-A, VEGF-B, or placental growth factor and to inhibit angiogenesis. Currently, many studies are comparing the efficacy and safety of these three drugs.

By contrast, studies have found a common expression of soluble VEGFRs on the corneal surface. These truncated forms of VEGFR are formed by alternative splicing or proteolytic shedding, and can block the effect of VEGF ligand by VEGF trapping, further preventing their binding at membrane-bound VEGFRs. This mechanism helps inhibit angiogenesis and further maintains avascularity of cornea.[14–18] The soluble truncated form of VEGFR-1 (Flt-1), called fms-like tyrosine kinase (sFlt-1, sVEGFR-1), has high affinity for VEGF-A.[14] VEGFR-2 and VEGFR-3 both have their soluble forms, sVEGFR-2 and sVEGFR-3, respectively, and can block the function of VEGF-C.[16,18]

VEGFR intraceptor can also block VEGF. Lys-Asp-Glu-Leu (KDEL) is a quadripeptide retention signal that binds endoplasmic reticulum retention receptors. Thus, proteins coupled with KDEL cannot be secreted from the endoplasmic reticulum.[19] When domains 2 and 3 of VEGFR-1 are coupled to KDEL, the recombinant construct can bind VEGF intracellularly and block the function of VEGF. Flt23k (coupled domains 2–3 of Flt-1 with KDEL) was found to be a potential therapeutic agent for CNV in primate and murine AMD models.[20]

3. Nanotechnology-based drug delivery treatment

Most of the developing intraocular therapies are aiming at the reduction of macular edema or suppression of CNV resulting from elevated vitreous VEGF under several conditions, including not only AMD, but also diabetic retinopathy and retinal venous occlusion. Recently, naturally biodegradable or synthetic nanoparticulated drug delivery systems have been proposed as promising and alternative drug carriers in the treatment of retinal diseases. Nanotechnology can create and combine materials or devices with drugs and specially designed genes at a size of < 100 nm and, with advantages such as slow release, better tissue penetration, and higher drug packing, can help monitor, control, and cure diseases.[21] Fig. 1 shows the current applications of nanotechnology in ocular diseases, and the following section presents the details of current development of intraocular therapy with the use of nanomedicines.

3.1. Intraocular therapy by intravitreal injection

Current nanotechnology-based applications in intraocular therapy are summarized in Table 1 and described as follows.

3.2. VEGF-associated products

Nowadays, patients with neovascular AMD can reach better visual outcomes by the administration of different types of VEGF antagonists.[22] However, these treatments require frequent injections on a long-term basis, which may lead to patient noncompliance and increased risks of iatrogenic injury, such as bleeding, retinal detachment, and even endophthalmitis.[23] Therefore, a formulation with a stable, efficient, yet sustained releasing profile is necessary for the development of future therapeutics against AMD.

Poly-lactic acid (PLA) and poly-lactic-co-glycolic acid (PLGA) are biocompatible and biodegradable polymers, which have been approved by the Food and Drug Administration for use in drug products and widely studied for delivery