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Teaser: Nucleic acid therapeutics have come a long way since their advent with aptamers being the latest brainchild – this article deals with the past, present and future of aptamer-based therapeutics from the perspective of the eye.

Aptamer-based therapeutics of the past, present and future: from the perspective of eye-related diseases

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Aptamers have emerged as a novel and powerful class of biomolecules with an immense untapped potential. The ability to synthesise highly specific aptamers against any molecular target make them a vital cog in the design of effective therapeutics for the future. However, only a minutia of the enormous potential of this dynamic class of molecule has been exploited. Several aptamers have been studied for the treatment of eye-related disorders, and one such strategy has been successful in therapy. This review gives an account of several eye diseases and their regulatory biomolecules where other nucleic acid therapeutics have been attempted with limited success and how aptamers, with their exceptional flexibility to chemical modifications, can overcome those inherent shortcomings.

Introduction

The eye is one of the major organs of the human body in terms of its complexity as well as its function. Owing to its peculiar architecture and its sensitivity, the types of diseases that occur in the eye are vast and there are many causes. One such cause is angiogenesis in the eye leading to irreversible vision loss in developing and developed countries. Previous studies have shown that vascular endothelial growth factor (VEGF), a 40 kDa dimeric glycoprotein, is responsible for angiogenesis in most of the diseased conditions in the eye making it a significant therapeutic target. Neovascularisation in the eye is associated with various disease conditions like diabetic retinopathy and age-related macular degeneration (AMD). Laser photocoagulation is often performed to destroy the new blood vessels and stop further vascularisation or to decrease the vascular leakage. However, laser treatments are painful and can cause irreversible damage to the retina. Hence, VEGF and its signalling pathways can be a better option to target in many neovascularising diseases occurring in the eye. Administration of antiangiogenic drugs could be in the form of eye drops or through local intraocular injection. However, owing to the pleiotropic spectrum of actions performed by VEGF including cell proliferation, cell migration, cell survival and vessel permeability under normal conditions, anti-VEGF therapies currently available on the market have to be well validated. Another strategy for antiangiogenic treatment

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1359-6446/06/$ - see front matter © 2014 Published by Elsevier Ltd. http://dx.doi.org/10.1016/j.drudis.2014.02.009

Please cite this article in press as: J.R. Kanwar, et al., Aptamer-based therapeutics of the past, present and future: from the perspective of eye-related diseases, Drug Discov Today (2014), http://dx.doi.org/10.1016/j.drudis.2014.02.009

is the inhibition of endothelial cell adhesion proteins called integrins. Integrins aid the interaction of endothelial cells with the extracellular matrix to form new blood vessels. Vitaxin®, an inhibitor of integrin $\alpha v\beta_3$, is currently under clinical trials that have proved it induces endothelial cell apoptosis and decreases neovascularisation. The major disadvantage of Vitaxin® is high immunogenicity with the host and the need for intravenous administration. In addition to the above mentioned strategies, other therapies that have been used against age-related maculopathy are thalidomide, tetracyclines, non-steroidal anti-inflammatory drugs, spironolactone, captopril, furosemide, bumetanide and paclitaxel. However, the use of these drugs has to be further validated to achieve high therapeutic efficacy with reduced side effects. Use of nucleic acid therapeutics is one of the key upcoming strategies to combat eye-related disorders because of the lower dosages required and the promise of a long-term cure. Gene expression and silencing strategies have been highly explored with limited clinical translation and success. In this review the possibilities provided by aptamers, a novel and emerging class of nucleic-acid-based target-specific therapeutics in the field of eye-related disorders, are explored.

Eye-related disorders with a potential to be cured by nucleic acid therapeutics

Glaucoma

Glaucoma is one of the leading causes of blindness second only to cataract [1]. Glaucoma is caused by chronic elevated levels of intraocular pressure (IOP) above normal physiological limits leading to ocular tissue destruction. Blindness in glaucoma is caused by degeneration of the retina and optic nerve. It includes loss of cells as well as the deposition and accumulation of extracellular debris including a protein plaque-like material, but is functionally associated with impairments in the balance between aqueous humour secretion and outflow [2]. The aim of therapeutics against glaucoma is to reduce the intraocular pressure and the medicines administered include beta blockers, prostaglandins, alpha-2 adrenergic receptor antagonists and carbonic anhydrase inhibitors but all these medications have their inherent disadvantages [3]. Several nucleic-acid-based therapeutics have been conceptualised and designed targeting several aspects of glaucoma. The most notable among them include SYL040012 (Sylentis), a siRNA-based drug, currently in Phase II clinical trials, that can target and inhibit beta adrenergic receptors and has showed very promising results [4]. Also QPI-1007 (Quark Pharmaceuticals) is a chemically modified siRNA against caspase-2 the application of which in glaucoma is currently being tested [5].

Age-related macular degeneration

AMD is the leading cause of severe vision loss among individuals over 50 years of age in the Western world and it is caused by various issues ranging from genetic to environmental factors [6]. This disease is usually associated with the accumulation of undegraded waste around the retinal pigment epithelium, which is produced as a result of the repair and regeneration process of the eye [6]. There are two forms of AMD, namely wet and dry AMD, leading to the central loss of vision. Wet AMD is characterised by the presence of leaky and fragile blood vessels leading to the accumulation of fluids. This results in scars to the macula. In dry AMD there is a loss of photoreceptors and the pigmentation in the retinal epithelium [7]. Dry AMD is the more difficult form to treat and drugs targeting the pathophysiology of the disease progression have been designed, although only one of them is an oligonucleotide-based aptamer that shall be discussed in detail in the coming sections. More successful drugs have been demonstrated for the treatment of wet AMD, among which pegaptanib (Macugen®) is the most notable oligonucleotide-based drug. There have also been other oligonucleotide-based drugs for wet AMD treatments especially the ones that target VEGF. Bevasiranib was developed by OPKO Health as an RNA interference strategy towards VEGF [8], unfortunately the trials for this have been terminated. Another notable siRNA-based strategy is siRNA-027 designed by Sirna Therapeutics against VEGF-R1 [9]. PF-655 is a synthetic siRNA designed by Quark and Pfizer against a novel target, RTP801, which works with VEGF in close association to reduce neovascularisation. This drug is still in Phase II trials [10].

Diabetic retinopathy

Diabetic retinopathy (DR) is currently the leading cause of vision loss among working age individuals–predominantly in developed countries. It is a secondary complication of diabetes mellitus. The primary cause of this is the thickening of the capillary basement wall due to hyperglycaemia, which leads to microaneurysms in the vasculature. The occlusion of the blood vessels leads to ischemia and hypoxia, triggering the neovascularisation response. This in turn leads to leaky blood vessels and accumulation of fluid causing vision loss [11]. All the therapeutics that target VEGF activity should also be effective in diabetic retinopathy along with the most prominent therapeutic strategy such as laser photocoagulation. Apart from the ones mentioned earlier, there are a few other oligonucleotide-based drugs, such as iC0-007 (iCo Therapeutics) that targets c-Raf and ATL1103 (Antisense Therapeutics) that targets growth hormone receptors, in clinical trials [12].

Infections of the eye

Like most of the other parts of the body, the eye is susceptible to various infections and especially those caused by viruses. Because viral disease progression depends on the incorporation of the viral gene into the host genome, oligonucleotide-based gene therapy forms an important line of therapeutics against these diseases. Herpes simplex virus (HSV), cytomegalovirus (CMV), varicella zoster virus (VZV), enterovirus (EV70) and cocxackievirus (CVA24) are a few viruses that have been commonly involved in eye-related infections. Several antisense therapeutics have been designed against these viral infections in addition to the commercially available antiviral drugs. Acute retinal necrosis is a disease in healthy as well as immune-compromised individuals caused by HSV-1, CMV and VZV. Tumour necrosis factor (TNF)α-targeted antisense oligonucleotides have shown promising results against this infection [13], and so have the phosphorodiamidate morpholino oligomers (PMO) designed against HSV-1 genes [14]. HSV-1 also causes herpetic stromal keratitis (HSK), an immune-mediated blinding corneal disease in which antisense therapeutics against TNFα or interferon (IFN)γ demonstrated effective recovery [15,16]. CMV-induced retinitis is also a common infection in AIDS patients for which the first FDA-approved antisense oligonucleotide drug fomivirsen was developed by Isis [17].

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