Hypoxia Inducible Factor-1 (HIF-1) as a Target for Ocular Drug Delivery

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Received date: January 20, 2017; Accepted date: January 23, 2017; Published date: January 26, 2017

The human eye is the most important sensory organ within the body due to its ability to give us sight to perceive the world around us as well as maintain balance. During embryological development, the eye is derived from the fore-brain giving it a blood-retina barrier that is structurally similar to the blood-brain barrier [1]. Although treatment to diseases affecting the anterior segment of the eye are administered through topical application, the posterior segment of the eye consists of several barriers as well as mechanisms of clearance that inhibit therapeutic access and show poor bioavailability due to systemic absorption [2].

Ocular diseases

The posterior segment of the eye is composed of the vitreous humour, retina, and choroid (Figure 1) [2]. Ocular disease in this segment has been found to be the most predominant causes of visual damage and/or deficiency today and affects an estimated 1.75 million people in the United States today [3,4]. This number is expected to reach ~3 million people by 2020 [4]. Current treatments for posterior segment diseases, such as neovascular Age-related Macular Degeneration (AMD), proliferative diabetic retinopathy, and diabetic macular edema, consist of a variety of steroids and oligonucleotides. It has been demonstrated that Vascular Endothelial Growth Factor (VEGF) is the dominant stimulator of angiogenesis in the process of each of the fore-mentioned ocular diseases. Therefore, most therapies utilize VEGF inhibitors in combination with a variety of therapeutic agents to combat these diseases [5]. However, these treatments invasive administration through intravitreal and subtenon injections, which when continually repeated, may cause a variety of complications, such as vitreous hemorrhages, retinal detachment, and cataracts. In order to minimize these complications, researchers must develop a means to control and sustain the release of therapeutic agents [6]. In addition to side effect reduction, current anti-angiogenic therapies utilizing VEGF inhibitors have shown only minimal success in clinical trials, necessitating the need to further understand ocular disease mediators that regulate VEGF, such as hypoxia inducible factor-1 (HIF-1) [7].

Hypoxia inducible factor-1 (HIF-1)

Oxygen must be constantly supplied to ocular tissues in order to maintain both environmental homeostasis as well as proper eye function. The transcriptional regulator (HIF-1) mediates the cells’ response to reduced levels of oxygen [8]. Specifically, HIF-1 activates the transcription of the gene that codes for angiogenic growth factors, such as VEGF, through the binding of hypoxia response elements...
HIF-1α to HIF-1β. Upon the activation of VEGF in response to the binding of these hypoxia response elements there is a breakdown of the blood-retinal barrier as well as neovascularization within the posterior segment of the eye (Figure 2) [9]. This has been demonstrated through examination of VEGF 5′-flanking sequences, which contain two HIF-1 binding sites allowing for mediation in hypoxic environmental conditions. Once binding sites were discovered, researchers forced the expression of hypoxia response elements HIF-1α and HIF-1β to demonstrate an increase of VEGF expression while cells were exposed to 20% O₂ in a manner which was dose-dependent [10].

Conclusion and Future Considerations

HIF-1 has been studied and observed for years in its effect on both protective and pathogenic responses in cancer, stroke, lung disease, and heart disease due to its angiogenic growth factor coating [9]. The impact of HIF-1 on angiogenic growth factors, such as VEGF, has opened the door for researchers to take a more novel approach at the treatment of ocular diseases and a novel targeted for the ocular drug delivery.

References