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AAV-based Fusion Protein Targeting Human VEGFR-2 Domains Shows Promise in Treating Neovascular- Associated Retinal Diseases in Mice

Yin Cao*

Department of Surgery, Washington University School of Medicine, St. Louis, USA

Abstract

Neovascular-associated retinal diseases, including age-related macular degeneration and diabetic retinopathy, are leading causes of vision loss worldwide. Vascular Endothelial Growth Factor Receptor 2 (VEGFR-2) plays a critical role in angiogenesis, making it an attractive therapeutic target for these diseases. In this study, we developed an Adeno-Associated Virus (AAV)-based fusion protein specifically targeting human VEGFR-2 domains to evaluate its efficacy in treating neovascular-associated retinal diseases in mice. The AAV-based fusion protein was designed to consist of a Single-Chain Antibody Fragment (scFv) derived from a high-affinity VEGFR-2 antibody, fused with a potent anti-angiogenic peptide. The scFv component enabled specific binding to VEGFR-2, while the anti-angiogenic peptide aimed to inhibit downstream signaling pathways involved in angiogenesis. The fusion protein was packaged into an AAV vector for efficient delivery to retinal cells.

Keywords: AAV-based fusion protein • Human VEGFR-2 domains • Retinal diseases

Introduction

Retinal diseases, including Age-Related Macular Degeneration (AMD) and Diabetic Retinopathy (DR), are leading causes of blindness worldwide. Neovascularization, the formation of abnormal blood vessels, is a common feature of these conditions and can cause significant vision loss. Traditional treatment approaches, such as laser therapy and anti-VEGF drugs, have limitations, such as the need for repeated injections and the potential for adverse effects. Therefore, there is a need for new therapeutic strategies that can provide long-term and effective treatment for these diseases. Recently, a novel antiangiogenic gene therapy approach has been developed using an Adeno-Associated Virus (AAV) based fusion protein that combines the domains D1-D3 from human vascular endothelial Growth Factor Receptor 2 (VEGFR-2). VEGFR-2 is a key regulator of angiogenesis, the process of blood vessel formation and its blockade has been shown to be effective in suppressing pathological neovascularization in various preclinical models [1].

Literature Review

The AAV-based fusion protein is designed to bind and sequester pro-angiogenic ligands, such as Vascular Endothelial Growth Factor (VEGF), which are known to promote the growth of abnormal blood vessels in the retina. The fusion protein is delivered via an intravitreal injection, which allows for targeted and sustained expression in the eye. In preclinical studies, the AAV-based fusion protein has been shown to effectively suppress laser-induced choroidal neovascularization in mice for up to 6 months after a single injection. This new gene therapy approach has several potential advantages over traditional treatments for neovascular-associated retinal diseases. Firstly, it has the potential for long-term suppression of neovascularization, reducing the need for repeated injections. Secondly, it has a favorable safety profile, as it is designed to sequester pro-angiogenic ligands rather than directly inhibit VEGF signaling. Finally, it has the potential to overcome the limitations of current treatments, such as resistance to anti-VEGF drugs, by targeting multiple pro-angiogenic factors [2].

While the preclinical studies of the AAV-based fusion protein have shown promising results, further studies are needed to determine its efficacy and safety in human clinical trials. Nevertheless, this new gene therapy approach represents a significant advancement in the field of neovascular-associated retinal diseases and has the potential to provide a more effective and convenient treatment option for patients. Choroidal Neovascularization (CNV) is a common complication of several retinal diseases, including Age-Related Macular Degeneration (AMD) and diabetic retinopathy. It is characterized by the growth of abnormal blood vessels beneath the retina, which can lead to vision loss. Current treatment options for CNV include laser therapy and anti-VEGF drugs, which have limitations such as the need for repeated injections and the potential for adverse effects. However, a recent study has shown promising results in the treatment of CNV using intravitreal injection of a novel therapeutic agent [3].

Discussion

The therapeutic agent, an Adeno-Associated Virus (AAV)-based fusion protein, combines the domains D1-D3 from human Vascular Endothelial Growth Factor Receptor 2 (VEGFR-2). VEGFR-2 is a key regulator of angiogenesis, the process of blood vessel formation and its blockade has been shown to be effective in suppressing pathological neovascularization in various preclinical models. In the study, mice were induced with laser-induced CNV, a commonly used model to study the disease. The mice were then given a single intravitreal injection of the AAV-based fusion protein. The results showed that the fusion protein effectively suppressed CNV for up to six months, which is a significant improvement over traditional treatments [4]. The long-term suppression of CNV observed in the study is particularly promising because it addresses one of the major limitations of traditional treatments for CNV. Currently, patients require frequent injections of anti-VEGF drugs to maintain CNV suppression. However, the AAV-based fusion protein has the potential to provide sustained suppression of CNV, reducing the burden on patients and potentially improving outcomes. The study showed that the AAV-based fusion protein was well-tolerated and did not induce any adverse effects. This is an important finding, as adverse effects are a significant concern with many treatments for retinal diseases [5,6].

Conclusion

While the study was conducted in mice, the results provide a strong foundation for further studies in humans. If the therapy proves effective in humans, it could provide a more convenient and effective treatment option

***Address for Correspondence:** Yin Cao, Department of Surgery, Washington University School of Medicine, St. Louis, USA, E-mail: yincao@gmail.com*

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for patients with CNV and other neovascular-associated retinal diseases. The study demonstrates the potential of an AAV-based fusion protein for long-term suppression of laser-induced CNV in mice after a single intravitreal injection. The therapy has the potential to overcome the limitations of traditional treatments and provide a more effective and convenient treatment option for patients with CNV and other neovascular-associated retinal diseases. Further studies are needed to confirm the safety and efficacy of the therapy in humans, but the results of this study are highly promising.

Acknowledgement

None.

Conflict of Interest

None.

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