GENE THERAPY APPROACHES TO TREAT UVEITIS

Uveitis is also known as inflammation of the eye where the vascularized middle layer of the eye becomes inflamed resulting in tissue damage and in some cases vision loss. Uveitis is estimated to have a prevalence of 1 in 1000 people and most of the cases have inflammation in the anterior or front of the eye1. Anterior uveitis is treatable with corticosteroid eye drops such as prednisolone, which is typically the first line of therapy. However, there are some side effects associated with sustained steroid use including increased incidence of glaucoma or carcinogenesis[1]. However, patients with posterior uveitis that is deeper in the eye may not benefit from topical steroid eye drops as it is estimated that only about 5% of an eye drop medication penetrates eye tissues[2]. Systemic steroid therapies are an option but are known to have side effects including metabolic disruptions, disrupted wound healing etc. Therefore, there is a clear need for more targeted uveitis treatments that can penetrate ocular tissues and have limited side effects.

More targeted therapies for uveitis will depend on a deeper understanding of the underlying inflammation mechanisms. The eye is considered to be immune-privileged and this is due, in part, to the expression of IL-27, an anti-inflammatory cytokine in retinal cells[1]. Environmental triggers, infections or other stimuli can trigger the expression of pro-inflammatory cytokines such as IFN-gamma that trigger a strong inflammatory response and recruitment of specific T-cells. The timing of cytokine expression is also critical to manage the balance of pro- and anti-inflammatory cytokine expression. Given the growing body of information on the immune mechanisms associated with uveitis, several investigators are developing immunomodulatory therapies that can delivered directly to the eye.

Viral and non-viral gene therapies are being developed to treat non-infectious uveitis. Researchers at Eyevensys, a biotech based in France, that is working on ocular therapies delivered via electroporation, developed a non-viral gene therapy plasmid that encoded a fusion protein of the TNF-alpha extracellular domain and the human IgG1 Fc domain[3]. The plasmid was delivered to the ciliary muscle in the eye via electroporation and was shown to reduce inflammation in two rat models of uveitis – an endotoxin-induced model and an autoimmune model. The plasmid therapy (called pEYS606) is currently in phase I/II clinical trials for safety and dose escalation studies[4]. A group at North Carolina State University reported the development of an adeno-associated virus (AAV) gene therapy to deliver an immunosuppressive gene (HLA-G or IL-10) via intravitreal injection into the eye[5]. HLA-G is known to have an immunomodulatory and anti-inflammatory effect and is implicated in protecting the fetus from the maternal immune system. IL-10 is a widely studied anti-inflammatory cytokine that inhibits the function of Th1 cells, natural killer (NK) cells and macrophages. The researchers tested the AAV therapy in a rat model of autoimmune uveitis and showed that there was significant reduction in inflammation over 2 weeks post injection. Importantly, the AAV remained largely in the eye and did not spread systemically resulting in a low neutralizing antibody response[5].

These data suggest that gene therapies can be delivered directly to the eye carrying anti-inflammatory payloads and have the potential to be novel and effective treatments for non-infectious uveitis. However, the long-term impact of immunomodulatory gene expression in the eye tissues will need to be evaluated along with any long-term toxicity issues due to viral gene delivery. For now, these therapeutic approaches offer a viable alternative to systemic or topical steroids that are less than ideal to treat non-infectious uveitis.

References:

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