Delivery of CR2-fH complement inhibitors using gene therapy as novel treatment for age-related macular degeneration (AMD)

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Technology description

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A group of MUSC researchers have developed a novel gene therapy technique to treat age-related macular degeneration (AMD) pathogeneis by introducing a novel complement inhibitory funsion protein (CR2-fH) via an adeno-associated virus (AAV). Data gathered showed that after subretinal delivery of AAV-VMD2-CR2-fH in C57BL/6J mice, the secretion of CR2-fH was confirmed in the polarized retinal pigment epithelium (RPE) (Figure 1). Further, the reseachers identified a safe dose range where function and morphology of RPE and retinal cells was not altered after delivery. Induction of choroidal neovascularizetion (CNV) was reduced in mice with AAV-VMD2-CR2-fH administration compared to untreated animals (Figure 2). In addition, in a smoke-induced vision loss model of AMD, the CR2-fH AAV group show signifcantly better contrast sensitivty, structure of Bruch’ s membrane and healthier mitochondria (data not shown). Bioavalibility studies showed that the gene-therapy approach delivered similar levels of CR2-fH to RPE as CR2-fH treatment by intravenous injections (Figure 1), indicating that gene therapy provides an alternative to the frequent invasive injections. Overall, this is a needed approach that may halt or reverse progression of AMD, where current treatments are typically ineffecitve and at best will likely only slow progression of the disease.

Overview

Age-related macular degeneration (AMD) is a common eye condition, which is a leading cause of vision loss among people at age 50 and older. Current treatments of advanced neovascular AMD, including injections of anti-VEGF, photodynamic therapy, and laser surgery. While efficacious, not every patients improves with anti_VEGF therapy (25% to 40% has been reported to experience improvements in vision), and long-term treatment may cause adverse effects. Currently no treatment is available for the dry form of advanced AMD (~90% of all patients). The complement system is part of the innate and adaptive immune system, and it functions as an early response system activated at sites of injury either directly or by natural antibody binding to stress and/or injury-exposed antigens. Multiple complement pathway polymorphisms have been linked with an increased risk of developing AMD. Studies have previously shown that injection of the complement inhibitor CD58 into the subretinal space reduced CNV in mice. MUSC researchers conducted safety and efficacy test of subretinal administrations of an AAV vector encoding the CR2-fH complement inhibitor in two mouse models, laser-induced CNV (wet

AMD) and smoke-induced ocular pathology (dry AMD). Inhibition of CNV and vision loss due to smoke was observed throughout the retina even though only a portion (≈60%) of the retina was detached following subretinal injection, suggesting that a targeted complement inhibitor can be used to provide effective complement inhibition throughout the entire eye, reducing complement-dependent lesion progression. Demonstration of efficacy using AAV vectors opens avenues for the development of treatment strategies in AMD and other complement-dependent diseases.

Key Words:Age-related macular degeneration, CR2-fH, Complement Inhibition, Gene Therapy, adeno-associated virus-mediated gene delivery, Choroidal neovascularization, subretinal delivery.
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Application area

Age-related macular degeneration
The gene therapy provides an alternative to the frequent invasive injections to treat AMD. This therapy may also halt or reverse the progression of AMD

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