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AAVHSCs Target Multiple Cell Types in the Eye and have Potential to Treat Rare Retinal Diseases

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Purpose

Inherited retinal diseases (IRDs) are a group of rare blinding conditions originating from mutations in genes critical for vision. Gene therapy has emerged as a viable strategy for treatment of IRDs. Adeno-associated viruses (AAVs) show promise as delivery vehicles for gene therapy due to their stable transgene expression in post-mitotic cells, low risk of insertional mutagenesis and diminished immune response. We have recently reported the discovery of novel naturally occurring AAVs derived from human hematopoietic stem cells (HSCs). These 15 novel AAVHSCs are Clade F members, alongside AAV9. We have previously described the biodistribution of three AAVHSCs in the central nervous system of male cynomolgus macaques following a single intravenous dose. Here, we extend this study to the retinas of three mammalian species (mice, minipigs and macaques) and demonstrate the feasibility of using AAVHSCs to target cell types most frequently affected in inherited retinal diseases.

Methods

Biodistributions of AAVHSCs, packaging a self-complementary enhanced green fluorescent protein (sc-eGFP) transgene driven by the chicken beta actin (CBA) promoter, were investigated via 3 routes of administration. Capsid tropism was first evaluated via intravenous administration in non-human primate retinas (prescreened for anti-AAVHSC neutralizing antibodies), followed by an evaluation of more therapeutically compatible dosing routes in smaller mammals: C57B6/J mice (subretinal and intravitreous) and Gottingen minipigs (subretinal). In all species, biodistribution of scAAVHSC7/-15 and/or -17.eGFP was assessed by anti-eGFP immunostaining.

Results

Following a single IV administration in macaques, retinal tropism of the AAVHSCs was confirmed in the inner retina and ganglion cell layers. Subretinal injections of AAVHSCs in mice and minipigs readily transduced photoreceptors and retinal pigment epithelial (RPE) cells, cell types most commonly affected in inherited retinal diseases. Both neuronal cell bodies and their processes (axons & dendrites) were anti-eGFP positive. Furthermore, intravitreal delivery of a subset of AAVHSCs in mice resulted in the transduction of photoreceptors and RPE.

Conclusions

These data demonstrate that AAVHSCs transduce clinically relevant neurons of the mammalian retina via multiple dosing routes, opening the door for therapeutic applications in treating inherited retinal diseases.