Improved vectors for ocular gene therapy

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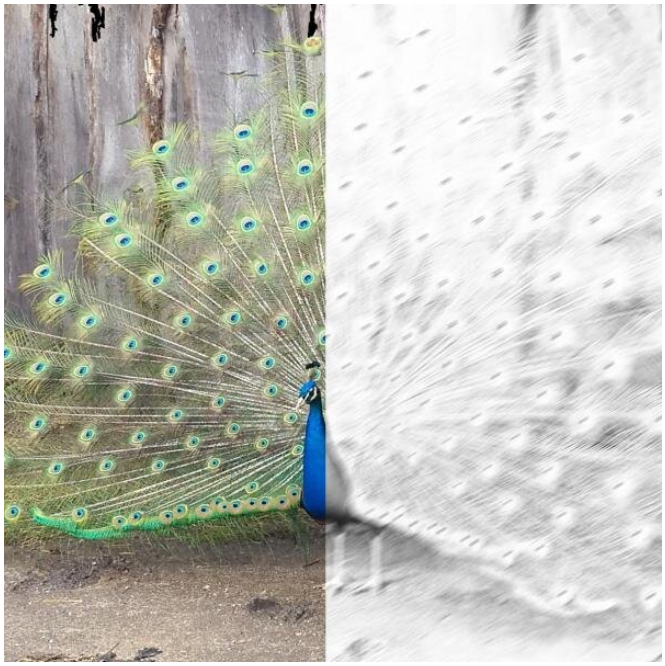

atients with achromatopsia are completely color blind. The cause of the disease is a gene defect. Credit: S. Michalakis

Strategies based on the use of gene therapy to mitigate the effects of mutations that cause blindness are undergoing rapid development. Novel gene vectors now achieve widespread gene delivery and reduce the risks associated with these approaches.

The incidence of genetic mutations that result in rapid deterioration of the ability to see is larger than is generally supposed. For example, on the order of five million people around the world suffer from congenital retinal dystrophies, which often lead to blindness at an early age. These diseases are caused by defects in specific genes, which direct the production of proteins that play an essential role in the visual process. Many of these errors alter only a single element of the blueprint, but they can nevertheless lead to loss of function of the photoreceptors or the cells that form the retinal pigmented epithelium. Approximately 150 such defects have been identified. Up until quite recently, there was no way to treat these conditions. However, thanks to the development of dedicated gene-delivery vehicles based on harmless viruses, this picture has begun to change. These 'vectors' can be used to transport functional copies of the relevant gene into the retinal cells. Since these intact copies can direct the synthesis of a functional version of the defective protein, they should be able to supplement the missing function, at least in part. In the case of one specific form of retinal dystrophy, this approach is already in clinical use.

Stylianos Michalakis (Professor of the Gene Therapy of Ocular Diseases at the Department of Ophthalmology at LMU Medical Center) has been working on the design of gene vectors for this purpose over the past several years. These efforts have focused on vectors that are based on the genomes of adeno-associated viruses (AAVs). In collaboration with Hildegard Büning (Professor of the Infection Biology of Gene Transfer at Hannover Medical School (MHH)) and an international team of researchers, Michalakis has now succeeded in constructing vectors that can be more easily and effectively introduced into retinal cells. Up to now, it was necessary to inject the viral vectors directly under the retina. This is a technique that requires highly skilled experts and facilities that are available only at specialized hospitals, and there is always a risk of damage to the fragile retinal tissue itself. Another drawback of this method is that each injection reaches only a relatively small fraction of the target cells.

Using animal models, as well as human retinal cells cultured in the laboratory, Michalakis and colleagues injected their AAV constructs directly into the jelly-like material that fills the eyeball. Known as the vitreous humor, this substance directly overlies the retina at the back of the eye. These experiments confirmed that the novel vectors could be transported into the light-sensitive photoreceptors in the retinal tissue. This delivery

method entails less risk than those employed hitherto. Indeed, the technique is already used in clinical practice for the treatment of macular degeneration. "And it can be performed by any ophthalmologist," Michalakis adds.

Further studies on three animal models confirmed the efficacy of the procedure, and experiments on human retinal tissue grown in culture confirmed that the vectors can infect photoreceptors and other retinal cells. Finally, initial results of experiments on a mouse model of achromatopsia (complete lack of color vision) suggested that the procedure is capable of restoring some degree of daylight vision.

More information: Marina Pavlou et al. Novel AAV capsids for intravitreal gene therapy of photoreceptor disorders, *EMBO Molecular Medicine* (2021). DOI: 10.15252/emmm.202013392

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