Gene therapy for inherited blindness

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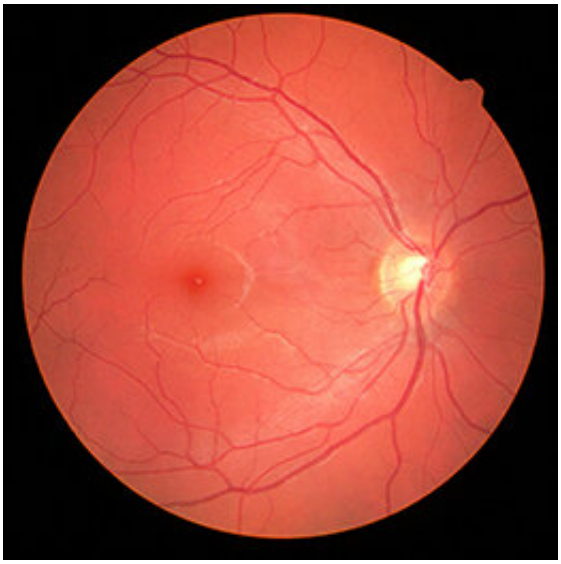

Retinitis pigmentosa is characterized by loss of photoreceptors in the retina

Retinitis pigmentosa is the most prevalent form of congenital blindness. Using a retinitis pigmentosa mouse model, LMU researchers have now shown that targeted activation of genes of similar function can compensate for the primary defect.

As many as 40,000 people in Germany suffer from retinitis pigmentosa. This hereditary disorder is characterized by loss of photoreceptors in the retina, and can be caused by mutations in many different genes. Depending on the nature of the underlying genetic defect, the severity of the condition can vary between night blindness and progressive visual field loss that can ultimately result in total blindness. The first gene

therapies for the disease have recently been approved. However, these approaches have certain disadvantages, which limit their range of application. A research team led by PD Dr. Elvir Becirovic at the Department of Pharmacology of Natural Sciences has developed a new strategy in collaboration with Prof. Dr. Stylianos Michalakis of the Opthalmology Clinic in the LMU Medical Center. This approach is designed to compensate for the causative hereditary defect by activating genes with similar functions that are normally repressed in the affected tissues, and utilizes a variant of the CRISPR/Cas9 technology that was first described in 2015. In the online journal *Science Advances*, the team describes the first successful application of this method in the context of gene therapy.

Currently, two strategies are being used in the development of gene therapies: In the context of gene supplementation, an attempt is made to replace the defective gene with an intact version. However, this is currently only possible for relatively small genes. The second strategy aims to correct disease-causing mutations, but this usually has to be tailored to each individual mutation. In view of the high effort and the associated development costs, a broad application of this strategy is therefore not possible. "To overcome these limitations, we have developed a new strategy," says Becirovic.

Many genes in the human genome fall into families, whose members fulfill similar functions in different cell types, or are activated at different stages during the differentiation of a particular cell type. "Our idea was to compensate for the mutant gene's loss of function by specifically activating genes that have a similar function but are normally not expressed in retinal cells," says Becirovic. "To do so, we delivered a system called Cas9-VPR into the affected retinal cells."

The Cas9-VPR system is a derivative of the CRISPR/Cas9 technology that is widely used for the targeted modification of genes. Akin to the

classical CRISPR/Cas9 system, Cas9-VPR utilizes the same targeting principle to guide an activating protein to the particular gene of interest.

Becirovic and colleagues made use of a mouse model for retinitis pigmentosa to test the activation approach. These mice lack the light-sensitive rhodopsin protein that is normally expressed exclusively in the rod cells of the retina, which are required for dim light and night vision. The researchers delivered the Cas9-VPR system into the rod cells with the aid of a harmless virus. By introducing Cas9-VPR into the rods of the mice, the scientists switched on genes closely related to the rhodopsin gene, which are normally active in the cones responsible for color and daylight vision. "In this way, we were able to compensate for the lack of rhodopsin function in the rod cells, to attenuate the rate of retinal degeneration and improve retinal function without detectable side-effects," says Becirovic.

The authors believe that a similar strategy can be applied to a wide range of genes and genetic diseases, and offers a number of significant advantages over existing strategies. "Given the growing importance of gene therapy and its potential benefits for patients, we are convinced that our approach could soon be used in initial clinical feasibility studies," says Becirovic.

More information: Sybille Böhm et al. A gene therapy for inherited blindness using dCas9-VPR–mediated transcriptional activation, *Science Advances* (2020). DOI: 10.1126/sciadv.aba5614

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