Light in sight: A step towards a potential therapy for acquired blindness

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Hereditary blindness caused by a progressive degeneration of the light-sensing cells in the eye, the photoreceptors, affects millions of people

worldwide. Although the light-sensing cells are lost, cells in deeper layers of the retina, which normally cannot sense light, remain intact. A promising new therapeutic approach based on a technology termed "optogenetics" is to introduce light-sensing proteins into these surviving retinal cells, turning them into "replacement photoreceptors" and thereby restoring vision. However, several factors limit the feasibility of a clinical optogenetic therapy using traditional light-sensitive proteins, as they require unnaturally high and potentially harmful light intensities and employ a foreign signaling mechanism within the target retinal cells.

New research publishing May 7th in the Open Access journal *PLOS Biology* from van Wyk and colleagues demonstrates how optogenetic proteins can be tailored to bring this promising technology closer to medical application. "We were asking the question, 'Can we design light-activatable proteins that gate specific signaling pathways in specific cells?', in other words, can the natural signaling pathways of the target cells be retained and just modified in a way to be turned on by light instead of a neurotransmitter released from a preceding neuron?" says Dr. Sonja Kleinlogel, corresponding author of the paper (whose research group is based at the University of Berne, Switzerland). The aim of molecular engineering was to achieve maximal compatibility with native signaling whilst retaining all the advantages of traditional optogenetic proteins, such as fast kinetics and resistance to bleaching by light.

The novel light-sensing protein, termed Opto-mGluR6, is a chimeric protein composed of the light-sensing domains of the retinal photopigment melanopsin and the ON-bipolar cell-specific metabotropic glutamate receptor mGluR6, which is naturally activated by glutamate released from the photoreceptors and amplifies the incoming signal through a coupled intracellular enzymatic pathway. Unlike rhodopsin, for example, the "light antenna" of melanopsin is resistant to bleaching. In other words, the response strength of Opto-mGluR6 never attenuates, no matter how often and hard the protein is hit by light. Moreover, since

Opto-mGluR6 is a chimeric protein consisting of two "local" retinal proteins it is also likely to be "invisible" to the immune system, another improvement over traditional optogenetic proteins.

In their study van Wyk and colleagues targeted the retinal ON-bipolar cells, which naturally receive direct input from the photoreceptors. Targeting the surviving cells at the top end of the visual cascade has the advantage that signal computation of the retina is maximally utilized. Turning the native chemical receptor (mGluR6) into a light-activated receptor ensures conservation of native signaling within the ON-bipolar cells, conferring high light-sensitivity and fast "normal" responsiveness. In their study they show proof-of-principle that mice suffering from Retinitis pigmentosa can be treated to regain daylight vision. "The new therapy can potentially restore sight in patients suffering from any kind of photoreceptor degeneration" says Dr. Kleinlogel, "for example also those suffering from severe forms of age-related macular degeneration, a very common disease that affects to some degree about one in every 10 people over the age of 65".

"The major improvement of the new approach is that patients will be able to see under normal daylight conditions without the need for light intensifiers or image converter goggles" Dr. Kleinlogel further notes "and retaining the integrity of the intracellular enzymatic cascade through which native mGluR6 acts ensures consistency of the visual signal, as the enzymatic cascade is intricately modulated at multiple levels". The mGluR6 receptor of ON-bipolar cells belongs to the large family of so-called G-protein-coupled transmembrane receptors (GPCRs). The novel principle of engineering bleach-resistant chimeric Opto-GPCRs opens a whole palette of new possibilities. For example, as GPCRs are prime targets for pharmaceutical interventions, Opto-GPCRs could potentially be used to treat conditions such as pain, depression and epilepsy.

More information: van Wyk M, Pielecka-Fortuna J, Löwel S, Kleinlogel S (2015) Restoring the ON Switch in Blind Retinas: Opto-mGluR6, a Next-Generation, Cell-Tailored Optogenetic Tool. *PLoS Biol* 13(5): e1002143. DOI: 10.1371/journal.pbio.1002143