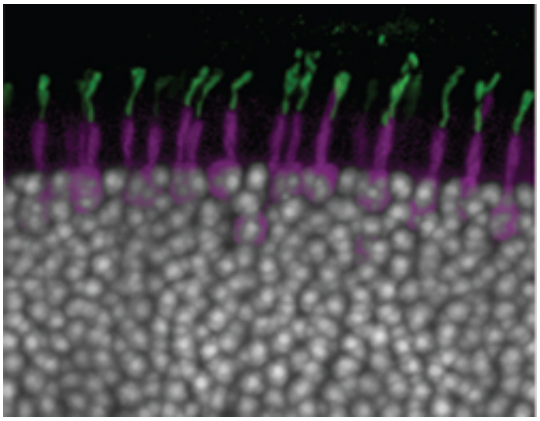
Inducing visual function

July 2 2014



Scientists from the groups of Botond Roska and Witold Filipowicz at the Friedrich Miescher Institute for Biomedical Research have resolved the mechanism controlling the maintenance of the light sensitive "antennas" of photoreceptors in the retina. With this knowledge, they have been able to induce the formation of light sensitive photoreceptors in cultured retinas derived from embryonic stem cells. This opens exciting new avenues for the study of blindness and its treatment.

In about a third of the cases, loss of vision is caused by the loss of function of photoreceptors. Age-related macular degeneration (AMD) is the most prevalent disease in this class leading to the loss of vision in a growing population of older adults. Other disease in this class, such as Retinitis pigmentosa or Startgardt's disease, affect fewer but younger

patients.

In recent years, therapeutic approaches using stem cells for retinal diseases such as AMD have gained a lot of attention. However, progress has been hampered by the lack of understanding of the molecular processes controlling the maintenance of the light sensitive antennas of photoreceptors, the so called outer segments, and the inability to grow light sensitive retinas with functional photoreceptors from stem cells.

Botond Roska, Group Leader at the FMI, and his team in collaboration Witold Filipowicz, FMI emeritus Group Leader, and his scientists have now successfully identified two small RNAs—both only approximately 20 nucleotides in length—necessary for the dynamic maintenance of the outer segment of cone photoreceptors in mice. In the absence of these microRNAs, called miR-182 and miR-183, cone outer segments and cone vision is lost. Cone cells are one of the two types of photoreceptors present in the retina. They are responsible for color vision and fine detail. The microRNAs control thus the maintenance of the structures in the retina, which are absolutely necessary for the majority of our visual tasks. Research described in Neuron started more than 5 years ago and was driven by two very dedicated postdoctoral fellows, Volker Busskamp and Jacek Krol, co-first authors on the paper.

Most excitingly, miR-182 and miR-183 induced the formation of the outer segment of photoreceptors in cultured retinas derived from embryonic stem cells, and rendered these retinas light sensitive.

"The understanding of the mechanisms leading to the formation and maintenance of outer segments and therefore functional photoreceptors is highly valuable, because we can now derive functional retinas from stem cells under clearly defined conditions," comments Roska, "The next step is to study the processes leading to the loss of outer segments in retinas built from skin cells of patients, and to find compounds that have

an effect on these processes."

Stem cells in retinal diseases

Scientists have tried to obtain functional retinas through the culture of induced pluripotent stem cells, iPSCs. These iPSCs have been generated from fully differentiated patient cells by forcing them to express a set of "stem cell" transcription factors. Thus reprogrammed and dedifferentiated, they exhibit pluripotent qualities and can then differentiate into many different cell types, also retinal cells. Up until this publication in Neuron the molecules and mechanisms controlling the differentiation process to a functioning photoreceptor have been largely unknown.
iPSC-based cellular therapies hold promise in many areas of regenerative medicine.

More information: Busskamp V, Krol J, Nelidova D, Daum J, Szikra T, Tsuda B, Juettner F, Farrow K, Gross Scherf B, Patino Alvarez PP, Genoud C, Sothilingam V, Tanimoto N, Stadler M, Seeliger M, Stoffel M, Filipowicz W, Roska B (2014) "MiRNAs 182 and 183 are necessary to maintain adult cone photoreceptor outer segments and visual function." *Neuron*

Provided by Friedrich Miescher Institute for Biomedical Research