Visual Electrophysiology

Director: Neal S. Peachey, Ph.D.
Staff, Department of Ophthalmic Research
Cole Eye Institute
9500 Euclid Avenue, i31
Office: 216.445.1942
Laboratory: 216.445.1941
Fax: 216.445.3670
Email: peachen@ccf.org

Goals and projects

Congenital Stationary Night Blindness

Congenital stationary night blindness (CSNB) is a family of inherited conditions which severely limit visual sensitivity. Three classes of CSNB can be distinguished, based on their impact on rod phototransduction (Riggs CSNB), the release of neurotransmitter by rods and cones (incomplete CNSB) or signal transduction in depolarizing bipolar cells (DBCs; complete CSNB). We focus on the complete form of CSNB, and use mouse models to understand how defects in the 5 known genes (*GPR179, GRM6, LRIT3, NYX, TRMP1*), impact retinal function and structure. Current studies examine how these proteins interact with one another and with other proteins required for normal DBC function, and the impact of mutations in these genes on visual function in mouse models and human subjects.

Non-Neuronal Cells Support of Retinal Function

Müller glial and retinal pigment epithelium (RPE) cells support many aspects of photoreceptor physiology. We use mouse models to understand this relationship, and thus retinal conditions which involve Müller or RPE dysfunction. Current studies focus on (a) the pathways by which lactate and glutamate are delivered to rod and cone photoreceptors as well as cells of the inner retina; and (b) the role of specific ion channels or transporters in normal RPE function. In addition, we collaborate with laboratories across the country to evaluate Müller and/or RPE function in mouse models of interest.

Research and Innovations

Congenital Stationary Night Blindness

Personnel: Neal S. Peachey, Minzhong Yu

(a) **Identification of *GPR179* as a human disease gene.** This project was initiated when a mouse that lacks DBC function was identified. We named this mouse '*nob5*' and used the functional defect to identify the gene involved as GPR179, a previously unstudied orphan G-protein receptor. GPR179 is normally expressed at the tips of DBC dendrites which form synapses with rod and cone photoreceptor terminals, but is missing in the *nob5* retina. We collaborated with a large international group to identify *GPR179* mutations in a series of patients with complete CSNB. Like other models of complete CSNB, the *nob5* retina has a generally normal appearance indicating that the loss of DBC function does not cause cellular degeneration, and supporting the potential of gene replacement to restore normal visual function to patients with complete CSNB.

(b) **TRPM1.** Mutations in *TRPM1*, encoding Transient Receptor Potential subfamily M member 1, have been identified in patients with complete CSNB. TRPM1 is the cation channel used in DBC signaling. We have developed two *Trpm1* mouse mutants, with distinct genetic defects. TRPM1 is completely absent in one model while the other has normal levels of TRPM1, but the channel does not function due to a point mutation. In homozygous mice, the mutations lead to a similar loss of DBC function. In heterozygotes, however, the point mutant has a very different impact on DBC function, which we interpret as reflecting the incorporation of non-functional components into the signaling complex used by these cells. These observations indicate that an allelic series of mouse mutants can provide important information regarding how DBCs function, an avenue which we are currently pursuing with respect to other members of the DBC signal transduction cascade.

Non-Neuronal Cells Support of Retinal Function

RPE Electrophysiology. We have established a noninvasive procedure for analyzing the electrical response of the RPE to light. The RPE generates a series of slow potentials, which can be recorded from the corneal surface. To understand the cellular origins of these potentials, we have examined their response properties in a series of mouse models involving ion channels and other proteins expressed in the RPE. This has allowed us to develop a more complete understanding of what these potentials represent and what changes identified in other mouse models reflect. This novel approach will allow us to understand the interplay between the RPE and rod and cone photoreceptors.

Lab staff members

- Neal S. Peachey, Ph.D., *Director*
- Ivy Samuels, *Post-doctoral Fellow*
- Minzhong Yu, *Research Associate*