

# Foreword

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The sensory modality that we call vision is initiated in the “outer retina”, a site that lies at the interface between the pigmented, vascular layer of the eye named the choroid, and the retina. The cellular components of the outer retina include a cell monolayer called the retinal pigment epithelium (RPE) and the light-sensing rod and cone photoreceptor cells (photoreceptors). Franz Boll in 1877, recognized that the photochemical event that we refer to as “photopigment bleaching” involves rhodopsin, which he called visual purple. Willy Kühne, in 1878, taught us that the regeneration of rhodopsin requires an intact RPE. Thus, these investigators introduced us to the concept of photoreceptor/RPE interactions, the subject of this book.

The study of photoreceptor/RPE interactions was accelerated by the advent of tissue autoradiography. This allowed us for the first time to study the dynamics of rod photoreceptor outer segment components and the involvement of the RPE in the daily disposal of discarded outer segment fragments. Likewise, tissue autoradiography was used to study the catastrophic effect that disruption of the disposal phase has upon photoreceptor cells. However, insights into mechanisms underlying these interesting phenomena did not evolve at a rapid pace until we gained access to recombinant DNA methods. This rapidly led to the development of modern gene discovery techniques and the ability to produce transgenic animal models. The outstanding collection of reviews in this book is

eloquent testimony to the progress that has been made toward our understanding of photoreceptor/RPE interactions in health and disease.

The cytoarchitecture of the retina is dependent upon a cohort of molecules that bind the cellular components into functional layers, arranging the strata into a pattern that optimizes photoexcitation. Chapter 2 describes how mutations in a human homologue of *crumbs* disrupts this architecture by compromising the integrity of an array of adherens junctions that form the outer limiting membrane of the retina. Proper cytoarchitecture aligns the photoreceptors with respect to the incident light and places them in appropriate contact with the RPE, their source of nutrients and general caregiver.

Tissue autoradiographic studies identified the inner segment of rods and cones as the biosynthetic center, whereas the light-sensitive outer segment was shown to be silent in this regard. Molecules synthesized in the inner segment must therefore be transported to their sites of utilization in the outer segment. Chapters 3 and 4 describe current evidence for some of the targeted delivery mechanisms that serve this essential process. Photoreceptor cells appear to use conventional methods in this regard, namely encoded targeting signals, molecular motors and microtubule-based tracks, whose polarity is appropriately established for movement of cargo from the trans Golgi network toward the negative microtubule ends via cytoplasmic dyneins. The photoreceptor provides a unique challenge however at the junction between outer and inner segment, which consists of the equivalent of the transitional zone of a non-motile cilium, followed by the outer segment itself, which represents a highly modified cilium. Additionally, the microtubules of the ciliary axoneme exhibit a polarity that is the reverse of those in the inner segment, calling for a “change of horses” for completion of the journey, at least for those cargoes that have been brought to this location by dyneins. The presence of filamentous actin within the cilium also suggests a role for non-conventional myosins (chapters 7 and 15). The cargo destined for the outer segment consists of a mixture of integral membrane proteins (rhodopsin etc.) plus soluble and lipid-anchored membrane proteins. The potential division of labor for the motors that effect the transport of these components is discussed in chapters 6 to 10 and 15. This process also

includes components of the classical intraflagellar transport (IFT) complex, which is conserved from *Chlamydomonas* to photoreceptor cells plus a class of potential gatekeeping molecules named centrins that are found in the “bore” of the cilium. Complicating the matter of IFT even further is the fact that some of the soluble proteins such as arrestin and transducin involved in phototransduction activation and attenuation, are not permanent residents of the outer segment. Instead, they move back and forth between inner and outer segment as a function of ambient light levels (chapter 8). The connecting cilium, a mere 0.2  $\mu\text{m}$  in diameter, is the only thoroughfare for all components moving to and from the outer segments.

Once situated within the outer segment, the components that serve outer segment disc assembly, phototransduction, retinoid cycling and other metabolic processes are maintained in an extraordinary degree of order (chapter 11). Although most, if not all of the components of the phototransduction machinery have been identified and characterized in terms of their primary structure, the players that are responsible for the highly ordered maintenance of outer segment architecture and the mechanisms responsible for outer segment morphogenesis are ill-defined. Interestingly, the outer segment is itself a highly labile structure as demonstrated by early autoradiographic studies. Laboratory rodents, and probably humans, renew this entire sensory organelle approximately every 10 days through a process of constitutive assembly at the transition zone (proximal end) of the cilium and intermittent shedding at the distal end. Shedding is accompanied by phagocytosis by the RPE (chapters 13 and 14). Shedding and phagocytosis involve a coordinated process that takes place between the RPE and photoreceptors, the details of which are just beginning to unfold. The mechanisms thus far appear to be akin to those observed in the phagocytosis of apoptotic cells by macrophages. This involves integrins, various co-receptors and MerTK, a receptor tyrosine kinase, whose disease-causing alleles are responsible for phagocytic failure in the RCS (*rdy*<sup>-/-</sup>) rat (chapter 13). Finally, hearkening back to Franz Boll and Willy Kühne, chapter 12 lays out our current understanding of the retinoid cycle, the unusual process whereby Vitamin A (retinol) is converted to the chromophore essential for vision (11-*cis* retinal) in the RPE, shuttled to the photoreceptors for utilization in phototransduction,

and returned to the RPE for regeneration to 11-*cis* retinal. This is a fascinating story that has received a great deal of attention and enhancement over the past two decades.

One might question why the RPE and photoreceptors engage in the process of outer segment renewal and retinoid cycling. The likely answer is that the photoreceptor outer segment, with its high degree of organization, specialization and sensitivity to light, resides in a highly toxic environment featuring maximal oxygen tension, high photon flux and significant free radical formation. This, coupled with the fact that photoreceptors are postmitotic and must last a lifetime, requires mechanisms that strive toward a high rate of repair. Outer segment renewal would achieve this. Unfortunately, photoreceptors and RPE are also susceptible to the ravages of gene mutations. This results in disease families that include retinitis pigmentosa, macular degeneration and Usher Syndrome, a combination of sight loss and deafness. Gene therapies for some of the inherited retinal diseases have been performed successfully in animal models of human disease and a small number of phase I clinical trials in humans are currently in progress. Those of us working in the fascinating field of retinal cell biology have the profound hope that individuals affected with these blinding diseases may someday benefit from the efforts outlined in this volume.

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