Editorial

Special issue on retinal remodeling

This special issue of Experimental Eye Research was developed with two motivations: 1) to solicit manuscripts from our colleagues around the world that would give broad, yet substantial insight into the various disorders associated with retinal degeneration and 2) to focus discussion in the vision research community into the negative plasticity now known as retinal remodeling that is associated with blinding diseases.

Evidence in the literature over the past decade has accelerated our understanding into mechanisms of initial retinal degeneration and, increasingly informed our understanding into the subsequent remodeling events in the neural retina that occur post-retinal degeneration. Retinal remodeling associated with retinal degeneration is intimately linked with insults that cause photoreceptor stress and eventually photoreceptor cell death. These phenomena result in progressive neural degenerative disease involving both neuronal and glial classes.

Retinal degenerative diseases manifest themselves in numerous forms from age-related macular degeneration (AMD) to glaucoma to retinitis pigmentosa (RP) and the Usher's Syndromes among others. Investigations into how each of these diseases progress, and ultimately impact visual function has been an ongoing process. Aside from a more complete understanding of the basic science behind retinal function and dysfunction, the natural extension of all this work becomes crafting interventions in human disease to arrest or recover vision that has been lost. However, until we understand the precise mechanisms that impact anatomy and physiology that accompany retinal degenerative disease, we do not have any hope of long lasting interventions.

1. Glia

Glia are becoming an increasingly studied class of cells in both intact neural systems and in various diseases and disease models, so it should be no surprise that given their central role in metabolism and maintaining homeostasis in normal tissues, they become deranged in pathological tissues.

The first article in this issue, "Astrocyte Structural Reactivity and Plasticity in Models of Retinal Detachment (Luna et al., 2016)" demonstrates astrocytes as a participant in the photoreceptor degeneration cascade, post retinal detachment with heterogeneous cells that send processes coursing along retinal blood vessels. This paper demonstrates that not only are neurons modified and remodeled after photoreceptors become compromised, but astrocytes also respond by altering their morphology.

The next paper is one of two in this special issue that address

plasticity in glaucoma using the DBA/2J mouse model. "Early Astrocyte Redistribution in the Optic Nerve Precedes Axonopathy in the DBA/2J Mouse Model of Glaucoma (Cooper et al., 2016)" describes early and novel pathogenic findings in the optic nerve of DBA/2J mice demonstrating that the optic nerve expands with age as do the axons prior to degeneration. While axons expand, glial retraction occurs as the numbers of mitochondria in them are diminished.

The next paper by Alejandra Bosco et al., "Glial Coverage in the Optic Nerve Expands in Proportion to Optic Axon Loss in Chronic Mouse Glaucoma (Bosco et al., 2016)" explores glial reactivity through explorations of gene expression, anatomy and function in a mouse model of chronic, age-related glaucoma. This manuscript uses conventional anatomical approaches to quantify axonal loss as well as explores glial elements and the distribution of dystrophic retinal ganglion cell axons. The ultimate conclusions of this paper are that gliosis can be used as a quantitative readout of axonal loss and as an index of the severity of glaucomatous involvement.

The fourth paper, "Idiopathic Preretinal Glia in Aging and Age-Related Macular Degeneration (Edwards et al., 2016)" focuses on the pre-retinal glia as it progresses through aging and in AMD. There is some debate in the literature on the origins and formation of pre-retinal membranes and this manuscript demonstrates glial cells extending through the inner limiting membrane and onto the vitro retinal surface as the retina ages. Furthermore, Müller glia extend from the retina into the vitreal space ahead of astrocytes and in retinas with choroidal neovascularization, pre-retinal glial membranes increase in number. The pre-retinal membranes observed in this study are likely subclinical, but likely are the precursors to formation of larger epiretinal membranes.

Muller cells are the most prominent macroglia in the retina and play a critical role in retinal metabolism. They are among the first cells in the retina to respond to stress and disease, however, the timing, mechanism, and impact are still an active area of research. In the next paper, "Müller Cell Metabolic Chaos During Retinal Degeneration (Pfeiffer et al., 2016)", the authors explore the metabolic alterations in degeneration and subsequent remodeling through computational molecular phenotyping. This study revealed that Muller cells drastically alter their phenotypes, not only in their relationship to the robust normal Muller cell signature, but also in respect to one another. These results demonstrate the tumultuous processes of remodeling that are initiated by retinal degeneration.

2. Neurons

The next section of this special issue focuses on neuronal alterations to the retina in the course of retinal degenerative disease. It is perhaps awkward to try and separate glia from neurons in the study of retinal disease given the complex interrelated biochemical relationships between them. But experimentally, segmentation of cell types allows the study of each participating component of the network. That said, it is important to realize that both neurons and glia are intimately involved not just in normal neuronal function, but as this special issue shows, are particularly dependent upon each other in the remodeling process.

The first paper in this second section is a comprehensive review by Bales and Gross, "Aberrant Protein Trafficking in Retinal Degenerations: The Initial Phase of Retinal Remodeling (Bales and Gross, 2016)" explores how proteins are trafficked and involved in the genesis of retinal degenerations induced by mistrafficking of proteins involved in visual function. This work is critically important because it summarizes the first steps in many of the degenerative forms of RP and allied diseases, and reveals that regardless of initial insult, photoreceptor degeneration is a final common pathway.

We then have a paper exploring neuronal activity in the degenerate retina. The manuscript "Aberrant Activity in Retinal Degeneration Impairs Central Visual Processing and Relies on Cx36-Containing Gap Junctions (Ivanova et al., 2016)" shows with clever use of genetic manipulation and electrophysiological exploration, that spontaneous activity, originating in AII amacrine cells increases in the degenerate retina. Ivoanova et al., eliminated Cx36-containing gap junctions and found that the aberrant activity was reduced compared with rd10 controls showing not only that cells expressing Cx36 are important for aberrant activity, but also revealing the fundamental importance of gap junctions in retinal circuitry.

The next manuscript summarizes what we know about an exciting model of retinal degeneration that shows promise for revealing a path forward in neural regeneration, "Seasonal And Post-Trauma Remodeling of the Ground Squirrel Retina (Merriman et al., 2016)". This manuscript reviews what is known about ground squirrel visual systems, with comparisons to traditional rodent models and human retina. This manuscript then presents what is known about hibernation in ground squirrels and the rapidly-reversible, neural plasticity found in retina associated with hibernation and plasticity associated with retinal detachment.

The next paper, "Functional and Anatomical Retinal Remodeling in Retinitis Pigmentosa (Kalloniatis et al., 2016)" reviews what we know about the clinical presentation of human RP and discusses our understanding of anatomical and functional remodeling in human RP through the use of the rd1 mouse. Finally, implications for carriers of RP mutations are discussed in response to retinal stress.

The future of retinal degenerative disease tracking and therapies will depend upon non-invasive imaging of retinal degenerative processes. Therefore, correlating tools like fundus autofluorescence (FAF), Optical Coherence Tomography (OCT) and immunohistochemistry is going to be a critical step. While this work has been demonstrated by other groups at single time points before, the paper "Long Time Remodeling During Retinal Degeneration Evaluated by Optical Coherence Tomography, Immunocytochemistry and Fundus Autofluorescence (Pinilla et al., 2016)" comprehensively demonstrates progression of retinal degeneration using Scanning Last Ophthalmoscopy, OCT, angiography, FAF and immunohistochemistry with histology to correlate at cellular resolution, the changes retinas undergo in degenerative disease.

Comprehensive analysis of retinas in normal and degenerative states requires tools to uniquely identify individual cell types. The human retina with nominally 70 cell types is a complex, yet compact tissue to explore and retinal disease and the inherent retinal remodeling complicates interpretation of specific cell classes. The manuscript, "Macromolecular Markers in Normal Human Retina and Applications to Human Retinal Disease (de Souza et al., 2016)" uses macromolecular markers to reveal cell types in human retina, shows that there are species specific differences in labeling patterns and illustrates macromolecular applications in tracking retinal disease progression.

While many studies of retinal degeneration and the remodeling process have been published over the years using animal models, examples using human tissues are more infrequent. The last chapter in this special issue, "Retinal Remodeling in Human Retinitis Pigmentosa (Jones et al., 2016)" describes more completely than ever before, what happens in the late stage human retina. This study demonstrates that no cell class in the retina is spared from the effects of retinal remodeling. The earliest cell classes involved in remodeling are bipolar and Müller cells and the Müller glia are the last cell class left in the remodeling retina. Fundamentally important, this paper demonstrates that neuronal circuit topologies are altered in human RP which has substantial implications for the success of interventions designed to provide retinal rescues.

We believe this special issue presents a coherent and comprehensive view of where the field of retinal remodeling currently stands. This collection of works highlights some of the labs behind retinal remodeling work, their approaches, insights and discoveries, and reveals future directions for where the field of retinal remodeling needs to go if we are to intervene with therapies for vision loss. We are hopeful that this body of work will highlight the efforts of these investigators as well as stimulate additional discussion in the community.

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Bryan William Jones, Ph.D.[*]

University of Utah, Moran Eye Center, Ophthalmology & Visual Neurosciences, USA

E-mail address: bryan.jones@m.cc.utah.edu (B.W. Jones)

Geoffrey P. Lewis, Ph.D.[*]

University California, Santa Barbara, Neuroscience Research Institute, Santa Barbara, CA, USA

E-mail address: g_lewis@lifesci.ucsb.edu (G.P. Lewis)

[*] Corresponding authors.