editorial

Lipids and lipid metabolism in the eye

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The vertebrate eye is a complex sensory organ consisting of multiple, distinct tissues, each having its own unique biochemical composition, structure, and physiological function. Key among these are the retina, lens, and cornea, working in concert to bring photons of light into the eye, focus them correctly on the retina, and convert their energy into electrochemical signals that are conveyed to the brain where, ultimately, they are processed into a coherent visual image. Defects in any or all of these tissues, whether inborn or acquired, whether through a disease process or by traumatic injury, can compromise vision and, eventually, may result in complete and irreversible blindness.

The study of lipids and lipid metabolism in relation to ocular tissues has not been reviewed heretofore in any single text or organized collection of monographs or review articles. Such discussions are usually relegated to a relatively small subsection of a review article or text that more broadly addresses the biochemistry of the eye or one of its constituent tissues. Yet, lipids and lipid-soluble compounds are essential constituents of the cells and tissues that comprise the eye, and defects in their synthesis, intracellular and extracellular transport, and turnover underlie a variety of significant, common, and often severely debilitating eye diseases. Classical "grind and find" lipid composition analyses have given way more recently to detailed lipidomic, metabolomic, and lipid-dependent signaling studies, linking a detailed, quantitative knowledge of lipids and bioactive, lipid-derived molecules to a more comprehensive understanding of the structure, function, and pathophysiology of ocular tissues. Starting in January 2010, a series of 11 monthly review articles will appear in the *Journal of Lipid Research* that will provide an overview of topics relevant to lipids and lipid metabolism in the retina, lens, and cornea of the vertebrate eye.

The retina is a complex neurosensory tissue comprised of at least six neuronal cell types that are organized into distinct cell layers, in addition to glia (e.g., Müller cells) and astrocytes. It is nourished by two distinct blood supplies, the choroid and the inner retinal vasculature. Historically, much of what we know about lipids and lipid metabolism in the retina has been obtained within the context of studies that have addressed membrane assembly and turnover in the rod and (to a lesser extent) cone photoreceptor cells. However, more recently, studies of lipids and lipid metabolism in the retina have focused on disease processes caused by either an over-abundance or, in some instances, a deficiency of specific lipid species within retinal cells or their surrounding extracellular environment, often resulting in toxic insult to these cells and ensuing retinal dysfunction, cell death, and progressive retinal degeneration. The majority of this thematic series will address topics pertinent to lipid composition and metabolism and lipid-mediated signaling in the retina.

Dr. Raju Rajala will lead off this series with an overview of phosphoinositide 3-kinase (PI3K) signaling in the vertebrate retina. The foundation for research in this area was provided by the seminal studies of Lowell and Mabel Hokin in the early 1950s, extended over subsequent decades by the work of many other investigators (e.g., Yasutomi Nishizuka, Michael Berridge, Robert Michell, and others). Rajala and coworkers were the first to show that the PI3K-dependent pathway is regulated by light in retinal rod photoreceptors. Their work and that of others has suggested that PI3K inactivation leads to cell death, whereas PI3K activation promotes cell survival (neuroprotection). Diabetic retinopathy, a highly prevalent blinding disorder, has been linked to dysregulation of PI3K, and there is great potential for development of therapeutic interventions in a variety of ocular diseases that target phosphoinositide metabolism.

In a thematically related article, Dr. Norma Giusto and coworkers will review lipid "second messengers" and related enzymes specifically localized to retinal rod outer segments, the compartment of rod photoreceptor cells where rhodopsin-mediated visual transduction takes place. The levels of products derived from the lipids phosphatidylcholine (PC) and phosphatidic acid (PA), as well as diacylglyerol (DAG), are modulated differentially by exposure of the retina to light, as are the enzymatic activities of related enzymes (e.g., phospholipase D, lipid phosphate phosphatase, diacylglyceride kinase, diacylglyceride lipase)

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that generate lipid second messengers. There appears to be an integral relationship between such lipid-dependent signaling events and light/dark-dependent translocation and membrane association-disassociation of proteins involved in the phototransduction cascade, but the details of this relationship remain to be elucidated.

Phosphatidylethanolamine (PE) is one of two dominant glycerophospholipid classes in both the vertebrate retina as a whole as well as in retinal rod outer segment membranes (the other being PC). When it combines with two molecules of the all-*trans* retinaldehyde that is generated by photoisomerization of the 11-*cis* retinaldehyde chromophore of the visual pigment, rhodopsin, and subsequent hydrolytic release from the protein, fluorescent *bis*-retinoid PE adducts such as A2E form. Although initial formation of such products starts in the photoreceptor outer segments, they end up accumulating with age in the adjacent cell layer known as the retinal pigment epithelium (RPE), constituting the major fluorescent components of lipofuscin (also called "age pigment"). Dr. Janet Sparrow and coauthors will review the current state of knowledge concerning the formation, physical properties, and possible physiological functions of *bis*-retinoids in the retina, including their implication in RPE cell death and retinal degenerative diseases such as age-related macular degeneration (ARMD).

The saga of life and death in the retina will continue with two additional articles in this series. One, by Nora Rotstein and coauthors, will review the role of sphingolipids–specifically, sphingosine, ceramide, and sphingosine-1-phosphate–in the regulation of growth arrest and cellular differentiation in the developing retina and induction of apoptosis in the developing and mature retina, the latter within the context of animal models of human hereditary retinal degenerations. The other, by Drs. Jorgelina Calandria and Nicolas G. Bazan, will focus on the synthesis and potential biological functions of neuroprotectin D1 (NPD1). A series of studies, largely emanating from the Bazan laboratory over the past several years, have shown that the RPE synthesizes NPD1 from docosahexaenoic acid (DHA), the most prevalent fatty acid present in photoreceptor outer segment membranes. This "docosanoid" product not only may protect RPE cells from oxidative stress (to which they are continually exposed, due to their juxtaposition to the adjacent choroidal capillary network), but also is thought to bolster survival of the photoreceptor cells. There is a symbiotic relationship between RPE and photoreceptor cells that promotes the survival of both. RPE cells phagocytize the shed tips of the photoreceptor outer segments and subsequently degrade them in their lysosomes, whereupon photoreceptor-derived DHA is made available for, among other things, NPD1 synthesis. The mechanisms by which NPD1 exerts its biological effects is not yet clear, but seems to involve (as the authors say) "tipping the balance" between pro- versus anti-inflammatory signaling events as well as pro- versus anti-apoptotic signaling.

Three articles in this series will deal with different aspects of cholesterol and cholesterol-containing lipoprotein metabolism and transport in the retina. In the first, Dr. Christine Curcio and coauthors will address the dynamics of apolipoprotein-B lipoproteins in the retina, with particular emphasis on their role in normal aging of the retina as well as in the formation of extracellular lipid deposits known as "drusen" and "basal linear deposits" that are molecular signatures associated with ARMD. These authors review the evidence that such deposits arise largely, if not totally, as a result of formation and subsequent export of lipoproteins by the RPE cells, and draw parallels between the pathophysiology of ARMD and the more intensively studied processes underlying the formation of atherosclerotic lesions (in particular, the "response to retention" hypothesis of Tabas and coworkers). Subsequently, in a topically related article, Drs. Ignacio Rodriguez and Ignacio Larrayoz will present an overview of cholesterol oxidation in the retina, focusing on the formation and biological properties of 7-ketocholesterol, a highly potent oxysterol, with particular emphasis on its potential involvement in the induction of pro-inflammatory molecules (e.g., IL-6, IL-8) and in the etiology of ARMD. In the third of these retina-related review articles concerning cholesterol (and the last of the 11 articles in this thematic series), Dr. Lionel Bretillon and I will present an overview of how cholesterol arises in the retina in the first place, how it is transported into and out of the retina, and also consider the balance between de novo synthesis versus uptake from extra-retinal sources. In addition, we will address the consequences of cholesterol deficiency in the retina, such as occurs in the Smith-Lemli-Opitz syndrome and other allied anabolic defects in cholesterol biosynthesis.

Dr. Martin-Paul Agbaga and coauthors will review the occurrence, formation, and physiological function of very long chain polyunsaturated fatty acids (VLC-PUFAs) in the retina, particularly *omega*-3 PUFAs of the C28-C38 series (which are highly enriched in, and possibly unique to, retina and brain as well as sperm). These authors recently have provided compelling evidence for the role of ELOVL4, a presumed fatty acid elongase, in the formation of C28 and C30 saturated fatty acids and of C28-C38 VLC-PUFAs. Notably, mutations in ELOVL4 have been shown to cause Stargardt-like macular dystrophy (STGD3), a juvenile onset, autosomal dominant form of macular degeneration. Evidence from the authors' laboratory as well as from others suggests that preventing the formation of these VLC-PUFAs causes photoreceptor cell death; hence, VLC-PUFAs appear to serve some critical function in photoreceptors.

The ocular lens is a unique tissue in the body: it is completely avascular, it lacks innervation, and the vast majority of its constituent cells (called lens fiber cells) are devoid of organelles, essentially consisting of a plasma membrane encapsulating cytoplasm. Hence, the lens faces some significant challenges with regard to nutrient supply, waste exchange, and replacement of worn out or damaged molecular constituents. The lens is the second refractive element of the visual system (the first being the cornea), and maintaining the optical transparency of the lens is essential for normal, undistorted vision. When that

transparency is disrupted, such as occurs during cataract formation, vision becomes compromised. Drs. Douglas Borchman and Marta Yappert will review the current state of knowledge concerning lipids in the ocular lens, including changes in lipid composition with aging and disease states (e.g., cataract formation), and the relationship of lipid composition to the structure and function of lens cell membranes.

The cornea is the external-most tissue of the eye and serves as a protective barrier for the more delicate internal tissues of the eye, such as the retina. About two-thirds of the total refractive power of the eye is due to the cornea, and the physical integrity, optical clarity, and correct curvature of the cornea are essential for normal vision. Drs. Sachidananda Kenchgowda and Haydee Bazan will present an overview of lipid mediators involved in both injury and repair mechanisms in the cornea. The former include molecules such as platelet-activating factor (PAF) and various products derived from the action of cycooxygenase-2 (COX-2), whereas the latter encompass molecules such as lipoxygenase-derived eicosanoids (e.g., 12- and 15-HETE), lipoxin A4 (LxA4), and the DHA metabolite NPD1. A better understanding of these lipid-derived molecules and the mechanisms that regulate their formation and turnover may provide useful clues for the development of better pharmaceutical compounds that will minimize inflammation and augment wound healing in the cornea.

It is hoped that this thematic review series will be informative to the reader and will stimulate the interest of lipid biochemists and others to consider both the unique aspects as well as the potential overlaps in ocular tissues versus other organs and tissues (e.g., brain, heart, liver) that historically have been more conventional targets of investigations involving lipid structure-function relationships, lipid metabolism, and lipid-mediated signaling. With the advent of technologies that afford improved resolution, ultra-sensitive detection, and quantification of lipids and lipid-derived molecules as well as nonradioactive approaches for studying lipid metabolism in cultured cells, cell-free systems, and in vivo in intact experimental animals as well as human patients, our capabilities to answer the remaining fundamental questions in this field, as articulated in each of the review articles in this thematic series, have never been better. It is anticipated that those answers will lead to new, efficacious treatments for a variety of blinding disorders that involve defects in the formation or turnover of lipids and bioactive, lipid-derived metabolites.