



Editorial

Free radicals are metabolic byproducts of reduction-oxidation reactions in all living cells. Accumulation of these causes partially reduced oxygen (ROS) and nitrogen (RNS) species. These forms are highly reactive and must be scavenged and rapidly metabolized by exogenous or endogenous antioxidant systems aiming to keep their level below a critical threshold. However, they are also signaling molecules; thus, these molecules' basal level is needed for cellular homeostasis [1]. These ROS/RNS can be removed from the cell by antioxidant enzymes (such as superoxide dismutases (SODs), catalase, and glutathione peroxidase), and low molecular weight antioxidants (such as minerals, vitamin C, vitamin E, carotenoids, and glutathione). Oxidative stress occurs when there is excessive ROS/RNS production or insufficient antioxidant activity; it has been shown to contribute to several diseases' pathogenesis.

The retina and retinal pigment epithelium (RPE) are exposed to chronic oxidative stress [2–4]. Light exposure induces high oxygen consumption, oxidation of the photoreceptor's highly abundant polyunsaturated fatty acids (PUFAs), phagocytosis, and digestion of photoreceptor outer segments by the RPE that result in high levels of free radicals. Failure or dysregulation in any of these processes leads to the accumulation of excessive oxidative stress and inflammation and can ultimately induce deleterious changes resulting in visual impairment. The high oxygen tension in the retina, together with high levels of light exposure, and high levels of various lipid compounds, specifically the enrichment of PUFAs in photoreceptor disk membranes, promotes the production of free radicals leading to oxidative stress, and makes the retina particularly susceptible to damage by ROS and by lipid-derived oxidative protein modifications (Fig. 1). In this Special Issue entitled "Oxidative stress in Retina," manuscript submissions of original research or reviews related to this subject were gathered. We included the work from 15 different leading research groups dealing with the main topics in this area.

In the eye, oxidative stress has been linked to the pathogenesis of lens cataracts, glaucoma, diabetic retinopathy, retinitis pigmentosa, and age-related macular degeneration (AMD) [5–9]. The progressive loss of retinal ganglion cell (RGC) neurons due to oxidative stress causes vision loss in glaucoma and other optic neuropathy. Dr. Zack and colleagues report differences on oxidative stress-degradation pathways in hPSC-derived RGCs (hRGCs) and differentiated RGC states. In another glaucoma-related study, Dr. Rex and colleagues analyze Nrf2 pathway activation early in glaucoma due to phosphorylation of Nrf2 by the PI3K/AKT pathway. Ocular vascular dysfunction is another major factor associated with the pathogenesis of glaucoma. Dr. Manicam and colleagues elucidate the integrated cellular response to acute Angiotensin II (Ang II)-elicited oxidative insult on two major ocular vascular beds comprising the ophthalmic artery and retina using a comprehensive

proteomics approach.

Oxidative stress is also reported as a critical contributor to the pathogenesis of diabetic retinopathy, a microvascular complication of diabetes, which is the primary cause of acquired blindness in diabetic patients. Dr. Yang's review describes how oxidative stress can contribute to and result from the metabolic abnormalities induced by hyperglycemia. Specifically, the increased flux of the polyol and hexosamine pathways, the hyperactivation of protein kinase C (PKC) isoforms, and the accumulation of advanced glycation end products (AGEs) are discussed. The review also describes how the antioxidant defense system's repression by hyperglycemia-mediated epigenetic modification also leads to the imbalance between the scavenging and production of ROS through mitochondrial damage, cellular inflammation, and structural and functional alterations in the retina.

Dr. Bonilha and colleagues examine sensitivity to exogenous oxidative stress in mice's retinas displaying inactivation of the antioxidant gene *PARK7* (DJ-1) during aging.

The retina and RPE are affected continuously by light-induced oxidative stress [3,4]. The review by Dr. Ozawa discusses the multiple pathways of light-induced oxidative stress and retinal neurodegeneration and introduces the concept of a recent novel potential therapeutic approach for combatting the influence of oxidative stress.

Iron accumulation has been implicated in the pathogenesis of retinal degenerative diseases [10]. However, the mechanisms of iron-induced retinal toxicity are not fully understood. Dr. Dunaief and colleagues investigate the mechanisms of acute intravitreal Fe^{2+} -induced retinal toxicity, shedding light on the pathobiology of several chronic retinal iron overload/degeneration models.

Mitochondrial damage in the RPE is involved in AMD pathology, the leading cause of blindness among the elderly [11]. Dr. Ferrington and colleagues use primary cultures of RPE isolated from human donors with or without AMD to evaluate compounds designed to protect mitochondria from oxidative damage, remove damaged mitochondria, increase mitochondrial biogenesis, and improve oxidative phosphorylation. Dr. Finnemann and colleagues analyze mice displaying inactivation of the antioxidant methionine sulfoxide reductase A (MsrA) gene, abundantly expressed in the retina and RPE cells. Dr. Kannan's review summarizes the multiple effects of mitochondrial-derived peptides (MDPs) such as humanin (HN) and its analogs, SHLP2 and MOTSc in oxidatively stressed human RPE and the regulatory pathways of signaling, mitochondrial function, senescence, and inter-organelle crosstalk. Emphasis is given to the mitochondrial functions in RPE undergoing oxidative stress, and the therapeutic potential of HN and its analogs in the prevention of AMD is also presented.

PPAR β/δ (peroxisome-proliferator-activated receptor β/δ) is a

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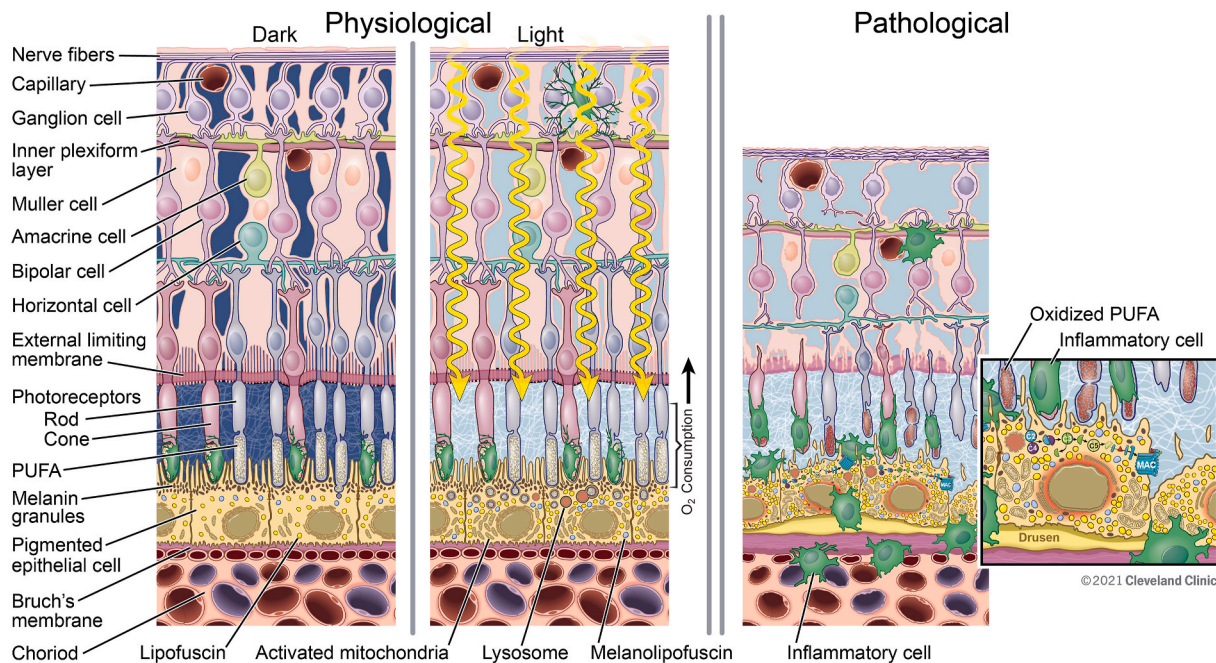


Fig. 1. Schematic model of the retina and RPE in physiological and pathological conditions. In physiological conditions, light exposure induces high oxygen consumption, oxidation of highly abundant polyunsaturated fatty acids (PUFAs), phagocytosis, and digestion of photoreceptor outer segments resulting in high levels of free radicals. In pathological conditions, excess free radicals damage cells and results in degeneration.

transcription factor known to regulate lipid metabolism, extracellular matrix remodeling, angiogenesis, and inflammation [12]. Here, Dr. Ash and colleagues analyze mice retinas displaying inactivation of PPAR δ .

Polymorphisms in genes that regulate complement activation and cholesterol metabolism are strongly associated with AMD [13], but the biology underlying disease-associated variants is not well understood. Dr. Lakkaraju and colleagues review a proposed pathway involving the bisretinoid-mediated accumulation of cholesterol and ceramide as the initiating events for AMD pathogenesis, which then triggers ceramide production complement deposition and mitochondria adverse effects on RPE cells.

Additional manuscripts investigate two diseases with pathophysiology similar to AMD, namely Stargardt macular dystrophy (STGD) and Sorsby Fundus Dystrophy (SFD). Mutations in the *ABCA4* gene cause STGD, a blinding disease that result in abnormal accumulation of toxic lipofuscin granules in the RPE and loss of the photoreceptor cells. Dr. Radu and colleagues evaluate oxidative stress and complement deposition on the RPE cells of STGD donor eyes of patients clinically diagnosed with STGD. Mutations in the *TIMP3* gene cause SFD, a rare inherited autosomal dominant macular degeneration. Dr. Anand-Apte and colleagues evaluate sensitivity to exogenous oxidative stress in mice carrying the S179C-Timp3 mutation, a variant commonly observed in SFD patients.

To sum up, the reader has here an excellent summary of contemporary contributions in the field of redox regulation of retina function. I hope that this special issue will stimulate further efforts to understand retinal diseases to both senior and younger researchers interested in the fascinating area of retinal redox biology. I thank the contributing authors for their efforts and the reviewers for their expert reports and assistance in preparing this Special Issue for Redox Biology.

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Vera L. Bonilha

E-mail address: bonilhav@ccf.org.