Nutrigenetic reprogramming of oxidative stress

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Abstract:
Retinal disorders such as retinitis pigmentosa, age-related retinal degeneration, oxygen-induced retinopathy, and ischemia-reperfusion injury cause debilitating and irreversible vision loss. While the exact mechanisms underlying these conditions remain unclear, there has been a growing body of evidence demonstrating the pathological contributions of oxidative stress across different cell types within the eye. Nuclear factor erythroid-2-related factor (Nrf2), a transcriptional activator of antioxidative genes, and its regulator Kelch-like ECH-associated protein 1 (Keap1) have emerged as promising therapeutic targets. The purpose of this review is to understand the protective role of the Nrf2-Keap1 pathway in different retinal tissues and shed light on the complex mechanisms underlying these processes. In the photoreceptors, we highlight that Nrf2 preserves their survival and function by maintaining oxidation homeostasis. In the retinal pigment epithelium, Nrf2 similarly plays a critical role in oxidative stabilization but also maintains mitochondrial motility and autophagy-related lipid metabolic processes. In endothelial cells, Nrf2 seems to promote proper vascularization and revascularization through concurrent activation of antioxidative and angiogenic factors as well as inhibition of inflammatory cytokines. Finally, Nrf2 protects retinal ganglion cells against apoptotic cell death. Importantly, we show that Nrf2-mediated protection of the various retinal tissues corresponds to a preservation of functional vision. Altogether, this review underscores the potential of the Nrf2-Keap1 pathway as a powerful tool against retinal degeneration. Key insights into this elegant oxidative defense mechanism may ultimately pave the path toward a universal therapy for various inherited and environmental retinal disorders.

Keywords:
Antioxidants, oxidative stress, retinal degeneration

Introduction
Oxidative stress has been studied as part of the pathogenesis of complex retinal disorders such as age-related macular degeneration (AMD), diabetic neuropathy, and glaucoma.1 Reactive oxygen species (ROS) that induce oxidative stress are produced naturally through aerobic metabolism and exposure to environmental influences such as ultraviolet light, smoke, and heavy metals.2 Fortunately, eukaryotic cells have developed protective mechanisms against ROS by promoting cellular production of antioxidant molecules.3

These defensive molecules prevent lipid, DNA, RNA, and mitochondrial damage that can potentially lead to cancer and other diseases.4 Thus, hindrances to the cellular transcription and translation of these essential molecules and chronic oxidative stress pose as serious threats to the proper functioning of organ systems.

The nuclear factor erythroid-2-related factor (NRF2)-Kelch-like ECH-associated protein 1 (KEAP1) pathway is an essential biochemical mechanism that neutralizes the oxidative damage caused by ROS. Nrf2 is a transcription factor that is upregulated in times of oxidative stress, and KEAP1 is a cytosolic inhibitory molecule that associates...
with NRF2 to keep it sequestered in the cytosol for proteasomal degradation. NRF2 is encoded by NF-E2 L2, which belongs to a subfamily of basic leucine zipper transcription factors. It is composed of 605 amino acids and contains 7 conserved regions. Keap1 is encoded by the KEAP1 gene and has four domains that span roughly 611 amino acids. The four domains are called the N-terminal broad complex, Tramtrack, and Bric-a-brac and C-terminal Kelch domain. The collaboration between a double-glycine repeat and the C-terminal region results in the formation of a six-bladed beta-propeller structure that interacts with NRF2.

Under homeostatic cellular conditions, NRF2 levels are kept low via ubiquitination by Keap1; however, under oxidative stressed environments, KEAP1’s inhibitory capacity is diminished. This leads to a sharp increase in cytosolic NRF2 levels, and permits NRF2 to be translocated to the nucleus where it effectively binds to the Phase 2 antioxidant response element (ARE) within a DNA promoter. The transcription of antioxidative enzymes such as superoxide dismutase, catalase, glutathione S-transferase, quinone oxidoreductase, heme oxygenase-1 (HO-1), thioredoxin (TRX) reductase, and glutathione reductase is initiated to neutralize the increased levels of intracellular ROS.

The retina consumes more oxygen than any other tissue in the human body on a per unit weight basis, and its high metabolic state makes it particularly susceptible to oxidative damage. Research has shown that photoreceptors, the retinal pigment epithelium (RPE), retinal ganglion cells (RGCs), and retinal vascular endothelial cells are the specific cellular structures directly impacted by oxidative stress. Here, we present a review of the NRF2-KEAP1 pathway within these cellular structures categorized by different disease models.

**Genetic Model for Retinitis Pigmentosa**

Retinitis pigmentosa (RP) is a diverse group of inherited retinal degenerations that cause progressive vision loss. Affecting 1 in 4000 individuals, RP is caused by over 3100 mutations in >70 genes with varying clinical manifestations depending on the underlying pathogenic mutation. Despite genetic and clinical heterogeneity, RP is characterized by the same pathology: a wave of rod death followed by secondary cone degeneration. More recently, it has been suggested that oxidative stress contributes to secondary cone death in RP. Healthy photoreceptors are metabolically active cells that consume high levels of oxygen. As such, the death of rods, which account for >90% of photoreceptors, leads to a hyperoxidation state that causes lethal oxidative damage on the remaining cones. Given the genetic etiology of RP, genetic manipulation represents a powerful tool to model disease pathogenesis and progression. Here, we provide a summary of studies that have implemented a genetic approach to investigate the functional role of the NRF2-KEAP1 pathway in RP.

A significant number of studies involving preclinical RP models have relied on adeno-associated virus (AAV)-mediated overexpression. Notably, NRF2 upregulation significantly improved cone survival and structure in two distinct mouse models for Pde6-associated RP: Pde6Brd1/rd1 and Pde6Br2/rd2/rd10. Consistent with the observed morphological protection, AAV-NRF2 also drastically delayed the decrease in visual acuity and preserved retinal activity in rd10 mice. Interestingly, AAV-NRF2 was found to significantly reduce lipid peroxidation in rd10 retinas, suggesting that NRF2-mediated rescue of retina function and structure in RP may be related to a reduction in oxidation.

Similar rescue effects were noted in a mouse model for Rho-associated RP: Rho<sup>-/-</sup> mice. AAV-mediated overexpression of NRF2 significantly improved cone viability, which corresponded to preservation of the cone outer segment (OS). This neuroprotective effect was further corroborated in another Rho-associated RP model: Rho<sup>P23H/+</sup>. Importantly, intravitreal injection of protein kinase R-like endoplasmic reticulum kinase (PERK) inhibitor GSK2606414A increased cell viability while reducing NRF2 activation, suggesting that PERK confers protection against photoreceptor death via the NRF2-KEAP1 pathway in RP.

**Age-Related Retinal Degeneration**

AMC is a prevalent eye condition that is characterized by the progressive degeneration of the outer retina. One of the clinical hallmarks of this condition is the presence of drusen, which is thought to cause vision loss via geographic atrophy and choroidal neovascularization. While the mechanism of drusen formation remains unclear, they have been characterized as depositions of lipid and proteins between the basal lamina of the RPE and Bruch’s membrane. Prominent components include byproducts of oxidative modification of fatty acids, implicating the pathological role of oxidative stress in AMD.

Zhao et al. revealed that Nrf2 knockout mice exhibited higher levels of lipofuscin accumulation and increased incidence of choroidal neovascularization. Ocular fundoscopic examination revealed an earlier onset of drusen and atrophic RPE lesions in Nrf2 knockout mice. Interestingly, there was also an accumulation of photoreceptor OS and autophagy-related vacuoles within the RPE in an age-dependent manner, indicating a lysosome-related defect. The buildup of
poly-ubiquitinated proteins underneath the RPE, in turn, suggested an impairment in lysosome-mediated degradation of oxidatively damaged proteins. Altogether, these results indicate that NRF2 may protect the outer retina against age-related degeneration by maintaining oxidation homeostasis via lysosome-dependent degradation [Figure 2A].

It has also been suggested that NRF2 dysregulation may pathologically contribute to AMD by disrupting mitochondrial trafficking and homeostasis. Supporting this model, O’Mealey et al. revealed that NRF2 and KEAP1 form a complex with the mitochondrial outer membrane histidine phosphatase PGAM5 to maintain mitochondrial motility through proteasome-mediated degradation of MIRO2, a mitochondrial GTPase that connects the mitochondria to microtubules. Notably, NRF2 and PGAM5 but not KEAP1 are necessary to facilitate transportation of the mitochondria in RPE-1 cells. While the functional implications remain unclear, studies have demonstrated that the mitochondria undergo retrograde movement toward the centrosome in response to oxidative stress. As such, age-related decline of NRF2 may exacerbate mitochondria-derived ROS in the RPE, ultimately driving retinal degeneration [Figure 2B].

Light-Induced Retinopathy

The exposure of bright light is known to cause photo-oxidative stress, leading to photoreceptor death across various animal models including mice and rats. More specifically, chromophores within photoreceptors and the RPE absorb light and reach an excited state that rapidly interacts with molecular oxygen, leading to a fatal elevation of ROS production. Consistently, there is an increasing body of evidence, indicating that visual light pathologically interacts with oxidative stress and contributes to the development and progression of retinal disorders including AMD and RP. As such, light-induced retinopathy (LR) has received attention as a valuable disease model to investigate the pathological role of oxidative stress in the eye. Here, we provide an overview of how the LR model has been used to elucidate the function and mechanism of the NRF2-KEAP1 pathway in mitigating oxidative stress in photoreceptors and RPE cells.

The cytoprotective effect of the NRF2-KEAP1 pathway on light-induced damage and death in the retina has been well characterized in vitro. Chen et al. found that light damage increased ROS production and cell death in a cultured cone-like 661W cell line in an exposure-dependent manner. This effect was significantly exacerbated following siRNA mediated knockdown of Nrf2, indicating that NRF2 promotes photoreceptor survival by countering light-induced oxidative stress.

To investigate phototoxicity of retinoids in RPE cells, Gao and Talalay treated ARPE19 cells with

![Figure 1: Protective role of the NRF2-KEAP1 pathway in genetic models of RP. (A) Nrf2 overexpression has shown to increase cone survival, preserve outer segment/inner segment structures, improve visual acuity, and enhance retinal activity by inhibiting lipid peroxidation. (B) PERK-mediated activation of NRF2 was found to inhibit photoreceptor degeneration, increase cone viability, and maintain outer segment structures. PERK = protein kinase R-like endoplasmic reticulum kinase, NRF2 = Nuclear factor erythroid-2-related factor, KEAP1 = Kelch-like ECH-associated protein 1, RP = Retinitis pigmentosa](image-url)
varying concentrations of all-trans-retinaldehyde, all-trans-retinol, or all-trans-retinoic acid. Exposure to ultraviolet A (UVA) light induced significant cell death. Sulforaphane activation of NRF2, in turn, offered protection against retinaldehyde-mediated phototoxicity in a dose-dependent fashion as shown by the increase in cell survival. Further investigation using embryonic fibroblast cell lines from transgenic mice revealed that NRF2-mediated protection against UVA exposure was directly correlated with the activities of two NRF2-regulated antioxidant proteins GSH and NAD (P) H quinone dehydrogenase 1 (NQO1). Later, Tanito et al. demonstrated that NRF2 binds to the ARE sequence in the TRX promoter in cultured human K-1034 RPE cells. Altogether, these findings suggest that NRF2 confers cytoprotection against photo-oxidative stress in RPE cells via TRX, GSH, and NQO1 [Figure 3A].

To further characterize NRF2-mediated neuroprotection in vivo, studies have relied on AAV mediated overexpression and pharmacological activators of NRF2 [Figure 3B]. AAV-Nrf2 injection in mice subjected to light damage exhibited full functional recovery and even increased retinal thickness compared to uninjected controls. Consistently, monomethyl fumarate (MMF)-induced upregulation of NRF2 prevented ONL and retinal separation and preserved retinal function in mice. In April 2020, MMF received the Food and Drug Administration approval to treat relapsing forms of multiple sclerosis (MS), supporting the safety and efficacy of NRF2 as a therapeutic target. However, the exact process of MMF-NRF2's neuroprotection remains unclear. There is a growing body of evidence, suggesting that MMF may alleviate neurodegeneration by modulating immune responses and antioxidative pathways. Previous studies have shown that MMF reduces neuronal excitotoxicity by limiting glutamate release from lymphocytes, which is known to play a role in MS. Moreover, MMF-mediated activation of HO-1 and nicotinamide adenine dinucleotide phosphate (NADPH) via NRF2 was found to benefit inflamed human brain endothelial cells by decreasing inflammation and monocyte migration. Further preclinical and clinical studies are warranted to investigate whether these protective mechanisms are conserved within the retinal microenvironment.

More recently, light damage was shown to increase Kitl expression in photoreceptors, triggering Ho1 expression via NRF2 activation. Disruption of KIT signaling worsened light-induced damage to retinal function and structure, while AAV-mediated KIT overexpression partially rescued photoreceptor viability and activity. Altogether, these findings suggest that KIT is necessary and sufficient for NRF2-mediated protection.

**Oxygen-Induced Retinopathy**

The critical role of oxidative stress on the regulation of revascularization within the retina has been well established. A low and transient level of ROS is known to promote angiogenesis in contrast, excessive oxidative stress has been found to negatively impact revascularization in retinal disorders including ischemic...
retinopathy of prematurity, ischemia-reperfusion (I/R)\textsuperscript{[40-42]} and diabetic retinopathy\textsuperscript{[42,43]}

Oxygen-induced retinopathy (OIR) has emerged as a powerful tool to model how oxidative stress contributes to pathological vascularization. Although various OIR protocols have been developed across different species, a protocol by Smith et al. has become established as the golden standard due to its reproducibility and accuracy.\textsuperscript{[44]} Phase I involves subjecting mice to hyperoxia (75%) at postnatal 7 (P7) until Phase II when the mice are returned to normoxia at P12. Aptly described as vaso-obliterative, Phase I causes blood vessels to constrict and die in the central retina. The lack of sufficient vasculature, in turn, induces hypoxia within the central ischemic retina during Phase II.\textsuperscript{[45]} The alternation between hyperoxic and hypoxic states, in turn, drives a dramatic surge in pro-angiogenic factors and ROS,\textsuperscript{[46]} triggering the development of maladaptive pathologic neovascularization. Here, we describe how the OIR model has offered critical insight into the role of the NRF2-KEAP1 pathway in pathological vascularization.

Wild-type (WT) and transgenic Nrf2 knockout mice were subjected to OIR protocols. During Phase I, hyperoxia-treated WT mice exhibited reduced secondary vascular networks compared to mice raised in normoxic conditions.\textsuperscript{[47]} In contrast, there were no secondary or deep capillaries in all the Nrf2 knockout mice irrespective of their oxygen treatment.\textsuperscript{[48]} During Phase II, Nrf2 knockout mice exhibited a larger avascular area in the retina with pathological neovascularization and reduced rod activity.\textsuperscript{[49]} These results collectively show that NRF2 plays a critical role in not only vascularization but also revascularization and functional vision.

Thus far, several mechanisms for NRF2-mediated protection in vascularization have been proposed [Figure 4]. There was a consistent and significant reduction in Nqo1 mRNA expression in Nrf2 knockout mice compared to WT mice throughout Phase II.\textsuperscript{[48]} Interestingly, Nrf2 ablation also elevated protein and mRNA expression of NADPH oxidase 2 (Nox 2), one of the four major NOXs responsible for generating ROS. Pharmacological inhibition of NOX2 rescued vascularization in retinas with Nrf2 ablation. Given that a more recent study has shown that NQO1 may modulate NOX activity,\textsuperscript{[50]} these findings suggest that NRF2-mediated activation of NQO1 inhibits NOX2 to mediate proper revascularization.\textsuperscript{[51]}

Another downstream target impacted during Phase II by Nrf2 ablation was Sema6A, an axon guidance gene.\textsuperscript{[51]} More specifically, SEMA6A protein and mRNA significantly increased in the central ganglion cell layer, which was abrogated by hypoxia inducible factor 1 alpha (HIF-1a) suppression. Notably, Lentivirus-mediated
knockdown of Sema6A in the inner retina of Nrf2 knockout mice significantly reduced the avascular retinal area. Altogether, these results suggest that Nrf2 may promote reparative angiogenesis by inhibiting Sema6A via HIF-1A.

The positive feedback loop between inflammation and angiogenesis has been suggested to prevent proper revascularization. Notably, Nrf2 knockout was found to elevate expression of inflammatory cytokines tumor necrosis factor-alpha and interleukin (IL)-1beta in OIR, suggesting that Nrf2 may normally suppress inflammatory mediators. Interestingly, synthetic triterpenoid 1-[2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oyl]imidazole (CDDO-Imidazolide, CDDO-Im) induced activation of NRF2 attenuated the expression of IL-1B, monocyte chemoattractant protein 1, and intercellular adhesion molecule 1 in Muller glial cell culture. NRF2 deletion in the neuroretina and Muller cells, in turn, significantly decreased revascularization, suggesting that Nrf2 may improve revascularization by inhibiting inflammatory cytokine activation in Muller cells.

Vascular endothelial growth factor (VEGF) is a critical factor in endogenous angiogenesis, and it has been previously suggested that the hyperoxia-induced vaso-obliteration may be caused by the suppression of VEGF expression. Consistently, dh404 treatment restored VEGF mRNA and protein levels in Phase I OIR, which corresponded to reduced vaso-obliteration in Phase I. At the same time, intraperitoneal injection of Nrf2 activator RS9 reduced the avascular area and neovascularization while simultaneously downregulating VEGF and upregulating NRF2 in Phase II. Altogether, these findings suggest that Nrf2 modulation of VEGF has a multifaceted role of both preserving vascularization and inhibiting pathological neovascularization.

**Ischemia-Reperfusion Injury**

I/R injury is another important disease model that is highly relevant to the study of oxidative stress in retinal ischemia and revascularization. Similar to the OIR model, I/R injury is characterized by two distinct phases and leads to severe oxidative stress and inflammatory damage. However, we chose to distinguish between these two models for two reasons. The first is the difference in how ischemia is induced: while OIR relies on hyperoxia, retinal I/R injury is caused by hypoxia by raising the intraocular pressure via an intraperitoneal injection. This causes a halt in the inner retinal blood flow (ischemia), which represents Phase I. After a short, designated period of time, circulation is restored (reperfusion) during Phase II of the protocol. The second reason for separating I/R from OIR lies in its use as a disease model. Beyond its relevance to vascularization-related processes, I/R injury has been widely used to study the effects of neuronal injury in the retina, especially RGC loss. As such, we will provide an overview of how I/R model has been used to understand the role of the NRF2/KEAP1 pathway in ischemia-driven pathology, with particular emphasis on its effect in the inner retina.
Xu et al. demonstrated that Nrf2-deficient mice were found to have an earlier onset of RGC death after I/R.\textsuperscript{[42]} The higher levels of apoptotic DNA cleavage after I/R in these mice suggested that NRF2 mediates protection against apoptotic cell death in RGCs [Figure 5]. The use of pharmacological NRF2 activators further corroborated this relationship. Daily intraperitoneal injections of CDDO-Im and MMF before and after I/R significantly improved ganglion cell layer (GCL) neuronal cell survival in WT but not Nrf2 knockout mice.\textsuperscript{[40,42]} At the same time, NRF2-induced protection of RGC extends beyond I/R injury. More specifically, AAV-NRF2 gene therapy preserves RGCs after optic nerve crush while Nrf2 knockout exacerbates optic neuritis and RGC death in a well-established model of MS.\textsuperscript{[15,57]}

Importantly, the neuroprotective effect of NRF2 correlates to improved retinal function. Cho et al. showed that MMF-mediated activation of Nrf2 significantly enhanced retinal function in WT but not Nrf2 knockout mice after I/R.\textsuperscript{[40]} Consistently, the NRF2-mediated cytoprotection of retinal neurons was conserved in a rat model of I/R. Treatment with CPUY192018 and 18e, two potent NRF2-KEAP1 protein-protein inhibitors improved retinal function as determined by a virtual optomotor system and spatial frequency, respectively.\textsuperscript{[58,59]}

**Conclusion**

Oligogenic retinal disorders including AMD, glaucoma, and diabetic retinopathy are caused by a broad range of factors that lead to the degeneration of different parts of the retina. Despite the clinical and causal heterogeneity, these conditions share a similar pathology that revolves around oxidative stress. The NRF2-KEAP1 pathway is a well-established defense mechanism against oxidative stress, making it an attractive therapeutic target. Here, we provide a review of how different disease models have offered critical insight into the role of the NRF2-KEAP1 pathway in various retinal tissues. More specifically, genetic models of RP and LR models have revealed that the NRF2-KEAP1 pathway offers structural and functional protection for photoreceptors. Age-related degeneration models and LR models, in turn, have been used to elucidate Nrf2-mediated preservation of RPE cells. Finally, OIR and I/R models have demonstrated the cytoprotective role of the NRF2-KEAP1 pathway in vascularization and GCL neuronal cell survival, respectively. Across many of these disease models, NRF2 activators including MMF were used to show the therapeutic benefits of the NRF2-KEAP1 pathway. The ophthalmic applications of pharmacological supplementation of NRF2 activators thus warrant further study. Altogether, the NRF2-KEAP1 pathway represents a promising direction for future therapies, and a deeper understanding of its role will be a critical step toward achieving universal protection against retinal degeneration.

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**Conflicts of interest**

The authors declare that there are no conflicts of interests of this paper.

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**Figure 5:** Protective role of the nuclear factor erythroid-2-related factor-Kelch-like ECH-associated protein 1 pathway in ischemia-reperfusion injury. Nuclear factor erythroid-2-related factor improves retinal function by protecting retinal ganglion cells against apoptotic DNA cleavage.
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