1. Introduction

Retinal pigment epithelium (RPE) is a single layer of epithelial cells lined between the neurosensory retina and choriocapillaris. It is part of the blood-retinal barrier and is a central component of the visual phototransduction pathway. RPE cells regenerate 11-cis-retinal by RPE65 isomerase and its related enzymes and chaperones (Moiseyev et al., 2006; Xue et al., 2004). They are professional phagocytes and are responsible for the clearance of daily shed photoreceptor outer segments (POS) (Young, 1967; Young & Bok, 1969). The multi-step process of phagocytosis includes receptor-mediated binding of POS to the RPE (Finnemann et al., 1997), internalization (Feng et al., 2002; Finnemann & Silverstein, 2001), transport to lysosome and degradation. The importance of RPE phagocytosis has been clearly illustrated by the Royal College of Surgeons (RCS) rats, which carry a mutation in \textit{Mertk} gene (D'Cruz et al., 2000). MERTK is a membrane-associated receptor tyrosine kinase and is activated upon binding of POS to the RPE (Feng et al. 2002). In RCS rats, loss-of-function mutation of \textit{Mertk} causes defects in phagocytosis and consequently these animals develop inherited retinal dystrophy and photoreceptor apoptosis (Tso et al., 1994). In addition to their roles in the visual cycle, RPE cells provide vital support for the structure and function of the outer retina. They transport ions, water and nutrients between choroidal blood supply and the retina, and synthesize melanin which absorbs light and shields the retina. RPE-produced growth factors, such as vascular endothelial growth factor (VEGF), are indispensable for the choroidal vasculature (Saint-Geniez et al., 2009).

Degeneration of the RPE with aging is an initiating event in age-related macular degeneration (AMD), a major cause of blindness in elderly people. Approximately 11% of persons between ages 65 and 74 have AMD, with prevalence rates rising to 30% in individuals at age 75 or older (Lee et al., 2003). Vision loss in AMD occurs through photoreceptor loss in the macula, the central area of the retina, and results either from a gradual “geographic atrophy” of the RPE (dry or atrophic disease) or from leakage and/or bleeding from choroidal neovascularization (CNV) (wet or neovascular disease). During CNV, blood vessels break through Bruch’s membrane, leading to rapid loss of central vision in many cases. In recent years anti-VEGF agents have achieved unprecedented success in preserving visual acuity in patients with CNV (Brown et al., 2006; Rosenfeld et al., 2006; Galbinur et al., 2009). Detailed clinical aspects of wet AMD and anti-VEGF therapy are covered by other chapters of this book.
The genetic and biochemical mechanisms of RPE degeneration in dry AMD, however, remain largely unknown. Several hypothetical models have been proposed, including accumulation of lipofuscin and its bisretinoid fluorophore (Sparrow et al., 2003; Zhou et al., 2006), iron overload (Dunaief, 2006; Hahn et al., 2004), autoimmune response (Hollyfield et al., 2008) and exposure to double strand RNA (Ambati, 2011; Kaneko et al., 2011). All of them have suggested clinical associations with AMD and their causal relationships to the disease have been demonstrated by respective animal models (Ramkumar et al., 2010).

Oxidative stress is a common mechanism underlying these diversified pathological processes. Photooxidation of the bisretinoids can produce singlet oxygen and release methylglyoxal to form advanced glycation end product (Wu et al., 2010). Iron overload increased isoprostane, a marker of lipid peroxidation, in the RPE/choroid (Hadziahmetovic et al., 2008). Mice immunized with serum albumin conjugated with carboxyethylpyrrole, an oxidation product of docosahexaenoic acid, developed signs of RPE degeneration and deposition of complement proteins in the Bruch’s membrane (Hollyfield et al., 2008). Oxidative stress can downregulate DICER1, a RNA processing enzyme whose deficiency was shown to cause Alu RNA-induced cytotoxicity and RPE apoptosis (Kaneko et al., 2011).

Results from earlier clinical and laboratory studies also support the contributing roles of oxidative stress to AMD. Smoking is the strongest environmental risk factor of AMD (Cano et al., 2010; Smith et al., 2001) and has been clearly associated with oxidative stress (DeBlack, 2003; Mitchell et al., 2002; Pryor et al., 1983; Smith et al., 2001). A number of interventional studies showed that antioxidant supplementation had protective effects against development of AMD or limiting its progression. Experimental animals fed with diets supplemented with antioxidants demonstrated an increased resistance to retinal degeneration (Ham et al., 1984; Organisciak et al., 1985; Tso et al., 1984). Results from the Age-Related Eye Disease Study (AREDS) showed that supplemental antioxidants (vitamin C, vitamin E and beta carotene) and zinc can decrease the risk of progression from intermediate AMD to advanced AMD by 25% (AREDS 2000 & 2001). Taken together, the findings from the research of the past two decades suggest that AMD is a multifactorial disease, with oxidative stress viewed as a common mechanism involved in the gene-environmental interaction of its etiology.

Oxidative stress is due to an imbalance between the generation of reactive oxygen species and their clearance by antioxidant systems. The RPE has powerful endogenous antioxidant capacity to overcome the high level of oxidative stress, which is caused by both focal light exposure and high metabolic rate of the retina. In addition to utilizing direct radical scavengers such as β-carotene, ascorbic acid and α-tocopherol, RPE cells have an elaborate enzymatic antioxidant system that can prevent and repair oxidative injury. Nuclear factor erythroid 2-related factor 2 (NRF2) is a master regulator of cellular antioxidant and detoxification responses (Kensler et al., 2007). We and others have shown previously that elevating the transcriptional activity of NRF2 can protect against oxidative injury to the RPE; while mice that are deficient of NRF2 developed pathological features similar to human AMD (Zhao et al., 2011; Cano et al., 2010). Oral zinc supplementation, which was used in the AREDS to slow AMD progression, can activate NRF2-dependent antioxidant system in the RPE (Ha et al., 2006). More recently, a newer class of NRF2 inducers, which are based on synthetic triterpenoid 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO) and its
derivatives, have achieved potent protection in various models of retinal damage (Pitha-Rowe et al. 2009). In this chapter we will review past and recent literature reports, based on cell culture, animal models and human clinical studies, to address how NRF2 regulates RPE function both in vitro and in vivo.

2. NRF2-dependent antioxidant defense

NRF2 is a transcription factor that controls the expression of phase 2 detoxification genes. It heterodimerizes with members of the Maf family of transcription factors and binds to the cis-acting antioxidant response element in the promoter regions of various phase 2 genes (Katsuoka et al., 2005; Motohashi et al., 2004). The latter encode a group of enzymes, such as glutamate-cysteine ligase, glutathione S-transferase, glutathione peroxidase, heme oxygenase, NAD(P)H:quinone reductase and glutamate-cysteine exchanger, which are essential for detoxification of xenobiotics and endogenous reactive intermediates (Kensler et al., 2007; Wakabayashi et al. 2010). NRF2-deficient mice showed increased sensitivity to a variety of pharmacological and environmental toxicants (Kensler et al., 2007; Rangasamy et al., 2004). The protective effects of NRF2 inducers have been tested in a number of models of human diseases, including cancer, neurodegeneration, cardiovascular disease, and liver and lung injury (Kensler et al., 2007; Wakabayashi et al., 2010).

Activation of NRF2 is subjected to multiple levels of regulation. Under basal conditions, NRF2 is sequestered by its inhibitor protein, Keap1, and is targeted for Cullin 3/Rbx1-mediated ubiquitination and degradation (Cullinan et al., 2004; Furukawa & Xiong, 2005; Kobayashi et al., 2004). Upon conditions of oxidative stress or exposure to electrophilic compounds, NRF2 protein can be liberated from Keap1 and will translocate into nucleus to mediate gene transcription. As illustrated in Fig. 1, there are six Neh (NRF2 ECH homology) domains that are responsible for most of the functions of NRF2. The Neh domains show amino acid sequence homology conserved between different species including human, rodents and chicken (McMahon et al., 2004; Zhang et al., 2007).

Fig. 1. Illustration of the Neh domains of the NRF2 protein. Human NRF2 is a polypeptide of 605 amino acids and contains 6 Neh domains. The relative positions of each domain and their putative functions are listed. Neh1 contains the signature cap-n-collar motif which is a highly conserved basic leucine zipper domain for DNA binding. The nuclear localization and export signals are present in both Neh6 and Neh1.

3. NRF2-mediated protection in cultured RPE cells

Compounds that promote the nuclear translocation of Nrf2 and elevate its transcriptional activity can protect against oxidative injury in cultured RPE cells. In 2001, Talalay and
colleagues first reported that sulforaphane could prevent RPE cell death caused by treatments with menadione, t-butyl hydroperoxide, 4-hydroxynonenal and peroxynitrite (Gao et al., 2001). Since then numerous other studies reported the protective effects of a wide range of structurally-different NRF2 inducers including isothiocyanates (sulforaphane) (Gao & Talalay, 2004), polyphenols (curcumin, resveratrol and flavonoids) (Alex et al., 2010; Johnson et al., 2009; Mandal et al., 2009), 1,2-dithiole-3-thiones (oltipraz) (Nelson et al., 2002), zinc (Ha et al., 2006) or triterpenoids (Pitha-Rowe et al., 2009). Many of them are naturally occurring compounds present in fruits and vegetables, making them ideal for dietary supplementation. Some of the compounds have either gone through human clinical trials or are currently used for other applications. For instance, zinc was used in the AREDS supplementation either alone or with antioxidant vitamins. Oltipraz, a dithiole derivate, is used in treating schistosomiasis and cancer chemoprevention (Jacobson et al., 1997). A common mechanism underlying the antioxidant and detoxification functions of NRF2 is to increase cellular glutathione (GSH) synthesis.

Fig. 2. Structure of glutathione. The $\gamma$-glutamylcysteine is formed by a peptide bond between the carboxylate group of glutamate and amino group of cysteine. The sulfhydryl group of cysteine is responsible for the antioxidant function of the tripeptide.

GSH is a tripeptide consisted of glutamate, cysteine and glycine. It contains a unique peptide bond between the amine group of cysteine and the carboxyl group of the glutamate side chain so that it is much more resistant to degradation by peptidase (Fig. 2). The sulfhydryl group of cysteine of GSH can be used by glutathione S-transferase to conjugate electrophilic centers on a wide variety of substrates (Pool-Zobel et al., 2005). GSH is also used by glutathione peroxidase to reduce lipid hydroperoxides and hydrogen peroxide to alcohols and water, respectively. The glutamate cysteine ligase (GCL) is the rate-limiting enzyme of GSH synthesis. It generates $\gamma$-glutamylcysteine from glutamate and cysteine. NRF2 inducers can elevate the mRNA levels of the catalytic and modulatory subunits of GCL. Cystine uptake by the RPE is mediated by a sodium independent, cystine/glutamate exchanger (Bridges et al., 2001; Ishii et al., 1992). The transporter is consisted of two subunits, xCT as the light chain and 4F2hc as the heavy chain (Wagner et al., 2001). NRF2 controls the expression of xCT gene (Sato et al., 1999). In xCT knock out mice, the plasma cystine concentration almost doubled, resulted from decreased tissue uptake (Sasaki et al., 2002). The xCT$^{-/-}$ mice showed more severe renal injury caused by ischemia-reperfusion (Shibasaki et al., 2009). Thus, NRF2 inducers can increase both the rate of GSH synthesis and cellular concentration of its amino acid precursor.
Monitoring the RPE glutathione content is a reliable assay for initial screening of model compounds designed to activate NRF2. For instance, RPE cells pretreated with oltipraz showed increased total and mitochondrial GSH. At 50 μM, oltipraz increased total cellular GSH by 18% and mitochondrial GSH by 50%, and achieved significant protection against tert-butylhydroperoxide-induced RPE cell death (Nelson et al., 2002). Similar results were obtained from cells pretreated with dimethylfumarate (DMF) for 24 hours (Nelson et al., 1999). However, when the time course of the DMF was evaluated, a transient decrease in GSH levels was found that preceded the increase noted at later time points. Compared to vehicle-treated control cells, cells pretreated with DMF for 3 hours showed a significant reduction in viability when further challenged by peroxide (Nelson et al., 1999). Thus, the initial decrease of GSH after DMF treatment rendered the RPE cells more sensitive to oxidative injury, although it can subsequently lead to a feedback increase of GSH synthesis and a more robust antioxidant response (Nelson et al., 1999). Many of the NRF2 inducers are thiol-reacting compounds and may cause a similar initial depletion of cellular GSH. Therefore, although the in vitro culture system does not present the complexity of the retinal microenvironment and cell-cell interaction in vivo, it is a valuable tool for assessing both the pharmacological properties of new NRF2 inducers and their potential toxicities. For treatment of a chronic disease like AMD, the RPE cells are already stressed by oxidative burden and may not tolerate transient GSH depletion after repeated administration of agents that react with cellular thiols with low selectivity.

4. Ocular pathology of Nrf2 knockout mice

Nrf2 knockout mice have normal embryonic development (Chan et al., 1996) and their basal level of antioxidant status in many tissues is not different from age-matched wild type mice. However, the Nrf2 null mice show increased sensitivity to a variety of pharmacological and environmental toxicants (Cano et al., 2010; Kensler et al., 2007; Osburn & Kensler, 2008). Depending upon the stimuli, injuries occur in different organs and tissues. The phenotypes vary, but commonly involve oxidative and inflammatory stress. For ocular pathology, neonatal Nrf2 knockout mice develop more severe retinal vaso-obliteration at early phase after hyperoxia exposure (Uno et al., 2010). NRF2 also modulates the innate immune response in the retina and iris-ciliary body in a mouse model of uveitis induced by intraperitoneal injection of lipopolysaccharide (Nagai et al., 2009).

Aging and smoking are the major demographic and environmental risk factor of AMD, respectively. Cano and colleagues (2010) reported that NRF2-deficient mice were more susceptible to smoking-induced retinal injury. At 8 months, Nrf2 null mice showed a mild degree of ultrastructural change in the RPE. Comparing to age-matched wild type mice, RPE of the knockout mice exposed to cigarette smoking for 6 months (starting at 2 months) displayed markedly increased staining of 8-hydroxydeoxyguanosine, an indicator of accumulated oxidative DNA damage (Cano et al., 2010). On electron microscopy, Nrf2-/- smoking mice displayed abnormal RPE basal infoldings and vacuoles, without apparent changes of the choroidal endothelium or sub-RPE deposit formation (Cano et al., 2010). Thickening and deposits in the outer collagenous layer of Bruch’s membrane were often observed in smoking mice. The data suggest that NRF2-mediated protection to the RPE is important against chronic environmental toxicities associated with AMD.
Fig. 3. Accelerated aging in Nrf2−/− mice. (A) and (B) Growth curves of male and female Nrf2−/− mice and their age-matched littermates. Knockout animals showed a lower body weight after the first year. (C) and (D) Hair loss in Nrf2−/− mice. A representative picture of a 12-month-old alopecic Nrf2−/− mouse is shown in (C). Hair loss was often first observed between 5 to 6 months of age (D).

We recently reported that Nrf2−/− mice developed age-related RPE and choroidal degeneration resembling cardinal features of human AMD (Zhao et al., 2011). The Nrf2−/− mice have accelerated aging. Some of the animals exhibited extensive hair loss (alopecia), which began as early as 4 months and peaked at 8 months (Fig. 3). Interestingly, more female Nrf2−/− mice suffered from hair loss than male ones; this could possibly be attributed to the higher susceptibility of female mice to autoimmune diseases as reported by Takahashi and colleagues (Yoh et al., 2001). After 12 months, the Nrf2−/− mice started to show lower body weight than the age-matched wild type littermates (Fig. 3). The life expectancy of Nrf2−/− mice is about 20 months which is only 60% of wild type mice with the same genetic background (Pearson et al., 2008).
Fig. 4. Fundus examinations of Nrf2-/- mice. (A) Normal fundus image taken from a 12-month-old wild type mouse. (B) Drusen like deposits developed in the peripheral retina of an 8-month-old Nrf2-/- mouse. (C) Yellowish patchy lesions found in a 14-month-old Nrf2-/- mouse. (D-F) A 16-month-old knockout mouse developed extensive RPE lesions (D), one of which showed hyperfluorescence in both early (E) and late (F) phase of fluorescein angiography. Arrowheads in D and E indicate the same lesion.

Drusen-like deposits were noted in around 70% of eyes from Nrf2-/- mice, as examined by funduscopy between 8 to 11 months (Fig. 4B). With aging, these small, dome-shaped whitish spots in the fundus tended to become confluent yellowish lesions, gradually increasing in area (Fig. 4C). Atrophic RPE lesions were frequently seen in Nrf2-/- mice after the first year (Fig 4C and 4D). Some of these lesions would eventually develop into sites of CNV, which were identified by both fundus fluorescein angiography (Fig 4E and 4F) and histopathology (Zhao et al., 2011). Moderate but statistically significant decreases in both a- and b-wave amplitudes on ERG were observed between the Nrf2-/- and wild-type mice at 12 months of age (Zhao et al., 2011), indicating compromised visual function in knockout mice.
The fundus phenotype in aged Nrf2-/- mice was further confirmed by histology (Fig. 5 and Zhao et al., 2011), which showed drusen formation, extensive RPE atrophy with numerous vacuoles, increased autofluorescence inside the RPE layer and CNV. Thickening of the Bruch’s membrane with age and basal laminar and basal linear deposit were found exclusively in Nrf2-/- mice by electron microscopy (Zhao et al., 2011). Immunostaining of eye sections revealed increased deposition of proteins that are related to innate immunity (i.e., C3d, vitronectin and serum amyloid P) and marker of oxidative injury (nitrotyrosine) between the RPE and Bruch’s membrane in Nrf2-/- mice (Zhao et al., 2011). The same proteins have been found in drusen and Bruch’s membrane of human AMD eyes (Crabb et al., 2002; Mullins et al., 2000).

Fig. 5. Histology examination of retina of Nrf2-/- mice. (A) A 14-month-old wild type mouse showed normal structure of the outer retina. (B) Representative image of RPE degeneration with big vacuoles, taken from a 14-month-old Nrf2-/- mouse. (C-D) Semi-thin sections from a 12-month-old wild-type mouse (C) and an age-matched Nrf2-/- mouse (D). Bruch’s membranes of the two were aligned at the same level (red line). Note that the RPE layer was elevated due to heterogeneous deposits (under the dotted line) in the sub-RPE space. (A and B: Paraffin section with hematoxylin and eosin staining. C and D: Plastic section with toluidine blue staining. ONL: outer nuclear layer; POS: photoreceptor outer segment; CC: choriocapillaris)

The accelerated degeneration after middle age and the typical pathology of the RPE/choroid indicate that the Nrf2-/- model shares many features of human AMD. At advanced age, the retinal pathology progressed from atrophic form to neovascularization and about 15% of the Nrf2-/- mice developed spontaneous CNV (Zhao et al., 2011). Photoreceptor degeneration was moderate and was probably secondary to RPE dysfunction. Rodents do not have macula and, therefore, cannot be used to generate ideal models of AMD. On the other hand, mechanistic studies exploring the molecular and biochemical mechanisms of age-related RPE degeneration and CNV can greatly benefit from animal models that at least partially reproduce representative lesions commonly seen in human AMD eyes. Animal models, such as the Nrf2-/- mice, will display the dynamic process of the disease and offer windows of intervention that can either slow down or accelerate the progression. Similar experiments will be difficult if not impossible to perform with human eyes mainly at late stages of AMD.
5. Pharmacological interventions that activate NRF2 in vivo

A number of in vivo studies have investigated the protective roles of NRF2 inducers in models of retinal injury and inflammation. A study by Yodoi and colleagues (Tanito et al., 2005) showed that sulforaphane, a prototypic NRF2 inducer, could upregulate thioredoxin in both the RPE and neural retina, and was effective in protecting photoreceptors from photo-oxidative damage. Compared to vehicle-treated controls, mice received sulforaphane showed fewer apoptotic cells in the outer nuclear layer and RPE, and had moderate but statistically significant improvement of both a- and b-wave amplitudes. At four days after light exposure, the ONL was significantly thicker in sulforaphane-treated mice (Tanito et al., 2005). Sulforaphane also delayed photoreceptor cell death in tubby mouse, a model of Usher syndrome (Kong et al., 2007). Homozygous tubby mice develop progressive photoreceptor degeneration shortly after birth. Sulforaphane-treated tub/tub mice showed significantly increased ONL thickness and b-wave amplitude at P28 and P34, as compared to vehicle-treated animals (Kong et al., 2007).

For human clinical studies, AREDS reported (2001) that supplementation with zinc alone, or antioxidants plus zinc, decreased the risk of progression towards advanced AMD by 20%. We showed that zinc could activate NRF2 both in cultured RPE cells and in RPE of NRF2 reporter mice (Chen et al., data not shown). In an ancillary study of AREDS, we analyzed the effects of long-term zinc supplementation on plasma thiol metabolites and their redox status (Moriarty-Craige et al., 2007). There was a significant decrease in plasma cystine concentration in the zinc-supplemented group. The systemic effects may be due to increased tissue uptake of cystine, as NRF2 regulates the transporter protein xCT (Sasaki et al., 2002). These results prove the concept that long term dietary supplementation of an NRF2 inducer is a feasible approach for treating early stage AMD patients.

A new class of synthetic triterpenoids derivatives of oleanolic acid have been tested both in cultured RPE cells and in vivo. These agents exerted highly potent activity at concentration as low as 10 nM. They reacted with a broad range of accessible protein thiols and activate NRF2 about 10 times more potently (by the ARE reporter assay) than previously used compounds (Pitha-Rowe et al., 2009). The in vivo protection against light-induced retinal toxicity has been demonstrated. Mice receiving 200 mg/kg CDDO-trifluoroethylamidine (-TFEA) showed significantly increased ONL thickness after light-induced retinal degeneration (Pitha-Rowe et al., 2009). CDDO-imidazolide decreased mouse leukocyte adherence to retinal vasculature after lipopolysaccaride treatment, and reduced expression of inflammatory mediators including ICAM-1, IL-6, COX-2, TNF-α and MCP-1 (Nagai et al., 2009; Cano et al., 2010). CDDO-methyl ester inhibited neutrophil infiltration in vitreous and internal limiting membrane after retinal ischemia-reperfusion induced by high intraocular pressure, and inhibited degeneration of retinal capillary (Wei et al., 2011). The CDDO compounds are currently under clinical trials for chronic kidney disease and type 2 diabetes. Their potential applications in treating dry AMD can be explored in human studies in the near future.

6. Signaling pathways that regulate NRF2 activation

The interaction between Keap1 and NRF2 is considered as a major determinant of the stability and function of NRF2 (Dinkova-Kostova et al., 2002; Hong et al., 2005). Electrophilic compounds, such as sulforaphane, can directly react with various cysteine residues of Keap1 and consequently cause dissociation and activation of NRF2 (Eggler et al., 2005). Keap1-
deficient hepatocytes had increased NRF2 activity and were more resistant to acetaminophen (Okawa et al., 2006). In addition to thiol modification and redox regulation, it is well established that there are cross-talk between the protein kinase pathways and NRF2-dependent antioxidant system (Sherratt et al., 2004).

Several phosphorylation sites of NRF2 protein have been mapped out and associated to its activity (Fig. 6). Phosphorylation of NRF2 at Serine 40 by protein kinase C promotes its dissociation from Keap1 and translocation into the nucleus (Bloom and Jaiswal, 2003; Huang et al., 2002). Phosphorylation at Tyrosine 568 by a Src subfamily kinase Fyn controls the export and inactivation of NRF2 at the late phase of induction (Jain and Jaiswal, 2006; Salazar et al., 2006). Other Src subfamily kinases, Src, Yes and Fgr, can also function as negative regulators of NRF2 by phosphorylating the protein at Tyr568 (Niture et al., 2011). A recent study by Rada et al (2011) demonstrated that a serine cluster in the Neh6 domain (Ser335, 338, 342, 347, 351, and 355) (Fig. 1) of NRF2 can be phosphorylated by glycogen synthase kinase-3β (GSK-3β). The phosphorylation enhanced the association between Nrf2 and SCF/β-TrCP, which is an adaptor protein for ubiquitin ligase and targets NRF2 for cullin-1/Rbx1-mediated degradation (Rada et al., 2011). Thus, phosphorylation of NRF2 by GSK-3β will facilitate its proteosomal degradation and inhibit its transactivation function. GSK-3β may also act upstream of Src family kinases (Jain and Jaiswal, 2006; Kaspar and Jaiswal, 2011). It remains elusive whether those two mechanisms work independently or additively. Mitogen-activated protein kinases (MAPKs) have been shown to phosphorylate NRF2 at Ser215, 408, 558, 577 and Tyr559; however, impacts on NRF2 location and activity were marginal after phosphorylation at those residues (Sun et al., 2009).

Results from the functional studies consistently showed that inhibition of the PI3K/Akt pathway decreased NRF2 activation induced by a variety of stimuli in different cell lines, while expression of a constitutive active mutant of Akt increased NRF2 activity, indicating that PI3K/Akt signalling is a positive regulator of NRF2 (Chen et al., 2009; Jain and Jaiswal, 2006; Kang et al., 2000; Lee et al., 2001; Wang et al., 2008). PI3K/Akt controls NRF2 via multiple indirect mechanisms. They can facilitate translocation of NRF2 into the nucleus via rearrangement of cytoskeletal actin (Kang et al., 2002). They are upstream kinases of GSK-3β. Akt phosphorylates GSK-3β at Ser9 and inhibits its kinase activity, which in turn will potentiate NRF2 activation because GSK-3β is its negative regulator (Jain and Jaiswal, 2006; Niture et al., 2011; Rada et al., 2011; Salazar et al., 2006).

There are other kinases that can be positive regulators of NRF2. PKR-like endoplasmic reticulum kinase phosphorylates and activates NRF2 under conditions of ER stress (Cullinan and Diehl, 2004; Cullinan et al., 2003). Casein kinase 2 phosphorylates endogenous NRF2 and regulates its activity and degradation (Pi et al., 2007). MAPK family proteins, extracellular signal-regulated protein kinases (ERKs) and the c-Jun N-terminal kinases (JNK), also play positive roles in NRF2-signaling pathway (Shen et al., 2004; Yu et al., 2000a; Zipper and Mulcahy, 2003). However, the positive regulation by ERKs and JNK may not through direct phosphorylation of NRF2 (Shen et al., 2004; Zipper and Mulcahy, 2003). Instead, they may upregulate NRF2 activity by phosphorylating and activating Nrf2 binding partner, such as the nuclear transcriptional coactivator CBP (Shen et al., 2004; Yu et al., 2000a). The p38 kinase may either stimulate or inhibit NRF2 activity, depending on the different type of cells and the pharmacological agents used for the studies (Yu et al., 2000b; Zipper and Mulcahy, 2000).
Because of the multiple putative phosphorylation sites of NRF2, and its dual regulation by cellular redox status and protein phosphorylation, it is difficult to clearly define its upstream signalling network both at basal level and in response to oxidative stress. Identification of authentic phosphorylation sites and development of antibodies specific for phosphorylated NRF2 can greatly advance our knowledge in this area. More importantly, most of the works on signal transduction of NRF2 have been performed in transformed cancer cells, which harbour genetic and biochemical variations and function quite differently from the RPE. Future mechanistic studies of NRF2 will be needed to address cell type-specific signalling mechanisms involved in RPE aging and degeneration.

7. Potential mechanisms linking NRF2 to AMD

A unique pathology of AMD is that RPE degeneration occurs before severe loss of photoreceptors, a retinal phenotype also seen in NRF2-deficient mice. In contrast, in model systems of retinal toxicities, animals exposed to excessive levels of oxidative stress often showed much more severe retinal degeneration than the RPE damage. Compared to epithelial cells, neurons are less efficiently protected by the endogenous antioxidant system. The outer segments of rods and cones have very low GSH (Winkler 2008). As shown in both the SOD1- and SOD2-deficient mice, severe loss of neurons occurred before or at the same time of RPE degeneration (Imamura et al. 2006; Justilien et al., 2007). In Vldlr⁻/⁻ mice, antioxidant supplementation protected retinal degeneration and improved the retinal electrophysiology (Dorrell et al., 2009). The fact that Nrf2⁻/⁻ mice showed preferential loss of RPE suggests that NRF2 can have functions other than antioxidant protection.
It is noteworthy that the retinal ultrastructure of aged Nrf2-/- mice showed signs of dysregulated autophagy (Zhao et al., 2011). Autophagy is a major self-renewal process which is essential for organelle turnover and removal of aggregated proteins that cannot be processed by proteasome (Klionsky 2007). During autophagy, unwanted proteins and organelles are sorted to double-membrane autophagosomes, which are further delivered to and fused with lysosomes to degrade the sequestered cargos. The accumulation of various intermediate forms of autophagic vacuoles and multivesicular bodies in the RPE and Bruch’s membrane was evident on EM images of aged Nrf2-/- mice (Zhao et al. 2011). This can be caused by either increased autophagic flux or decreased final degradation by lysosome. Similar findings of dysregulated autophagy were reported in another study using human AMD eyes (Wang et al., 2009).

Autophagy is of particular importance in non-dividing cells like neurons and RPE which, unlike proliferating cells, are incapable of diluting the waste products by mitosis. Dysregulated autophagy is considered as pathogenic in various neurodegenerative diseases; and the underlying mechanisms are disease-specific. In Alzheimer’s disease, mutations in presenilin-1 impairs lysosomal targeting of v-ATPase V0a1, which is essential for lysosome acidification and protease activation (Lee et al., 2010). In Parkinson’s disease, mutated α-synuclein cannot be efficiently degraded by autophagy (Cuervo et al., 2004). In Huntington’s disease, mutant huntingtin may impair the initial cargo assembly of autophagic vesicles (Martinez-Vicente et al., 2010). It has been hypothesized that dysregulated autophagy is also involved in AMD (Wang et al., 2009; Kaarniranta 2010).

NRF2 can be an important regulator of RPE autophagy via multiple mechanisms. In normal RPE cells, autophagy is responsible for the removal of ubiquitinated and/or aggregated proteins. Cargos inside autophagosomes will be delivered to lysosome for degradation and recycled for catabolism. NRF2 is likely involved in autophagosome formation. Several previous studies reported that p62, which is a receptor protein of ubiquitinated proteins and essential for the initial assembly of autophagosome, is transcriptionally regulated by NRF2 (Komatsu et al., 2010). Whether NRF2 controls other specific molecular components of the autophagy pathway remains to be characterized by future studies. Accelerated accumulation of lipofuscin was observed in Nrf2-/- RPE (Zhao et al., 2011). Reactive metabolites from bisretinoids inhibit lysosome-mediated autophagic degradation. NRF2-dependent detoxification can be protective in both formation and elimination of lipofuscin-related metabolic waste products. Thus, compromised NRF2 signalling can impact both the early and late stages of RPE autophagy.

NRF2 may also be involved in the innate immune response that amplifies the initial RPE lesions in AMD. As shown in the uveitis model, NRF2-deficient retina had higher number of infiltrated leukocytes and increased production of pro-inflammatory cytokines (Cano et al., 2010). Thioredoxin 1, a downstream protein of NRF2, can interact with complement factor H and regulate its activation (Inomata et al., 2008). Autophagy can be a possible mechanistic link between oxidative stress and inflammation (Levine et al., 2011). Elevated cellular stress will cause increased damage to proteins and organelles and overwhelm the degradation capacity of RPE autophagy. Consequently, the undigested wastes could be exported into Bruch’s membrane via exocytosis and deposited in the sub-RPE space (Wang et al., 2009). The exported proteins, possibly in oxidatively modified forms, may further promote drusen formation and cause local inflammation mediated by complement proteins and
macrophages. Loss of endothelial fenestration was observed in choriocapillaris of aged \textit{Nrf2-/-} mice (Zhao et al., 2011). In human AMD eyes, choroidal vascular degeneration occurs in areas of geographic atrophy (McLeod et al., 2009; Mullins et al. 2011). Decreased transport function of choroidal vessels can facilitate the accumulation of damaged proteins in the sub-RPE space and Bruch’s membrane.

Single nucleotide polymorphisms (SNPs) in the coding region of \textit{NRF2} gene have been detected in human cancerous tissues (Shibata et al. 2008). Functional polymorphisms in the promoter region of \textit{NRF2} have been reported (Marzec et al., 2007). However, according to the GWAS data (Chen et al., 2010), \textit{NRF2} is not a major risk allele of AMD and SNPs of \textit{NRF2} are unlikely to be a major genetic factor. A recent study showed that age-dependent decline of \textit{NRF2} function could be caused by upstream regulatory mechanisms, such as GSK-3\(^\beta\), that control its localization and activity (Tomobe et al., 2011). Defining these mechanisms will open up new revenues of intervention to prevent oxidative injury and RPE loss during dry AMD. Unlike the inherited genetic variations, the biochemical changes associated with RPE aging are likely treatable.

8. Conclusion

\textit{NRF2} is a protein that has been extensively studied in cancer and other chronic human diseases. Accumulating evidence suggests that \textit{NRF2}-mediated signalling pathways have central roles in protecting the RPE cells from aging and age-related degeneration. The \textit{Nrf2-/-} mice represent a new model for translational and mechanistic studies of AMD. Agents that activate \textit{Nrf2} are potential candidates for treating AMD and other retinal diseases involving oxidative and inflammatory stress.

9. Acknowledgment

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10. References

AREDS (2000). The Age-Related Eye Disease Study: a clinical trial of zinc and antioxidants--AREDS Report No. 2. \textit{Journal of Nutrition} Vol.130, No.5S (Suppl), (May 2000), pp. 1516S-1519S, ISSN 0022-3166

AREDS (2001). A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. \textit{Archives of Ophthalmology} Vol.119, No.10, (October 2001), pp. 1417-1436, ISSN 0003-9950

Alex, A.F., Spitznas, M., Tittel, A.P., Kurts, C., & Eter, N. (2010). Inhibitory effect of epigallocatechin gallate (EGCG), resveratrol, and curcumin on proliferation of human retinal pigment epithelial cells in vitro. \textit{Current Eye Research} Vol.35, No.11, (November 2010), pp. 1021-1033, ISSN 1460-2202

Ambati, J. (2011). Age-related macular degeneration and the other double helix. The Cogan Lecture. \textit{Investigative Ophthalmology & Visual Science} Vol.52, No.5, (April 2011), pp. 2165-2169, ISSN 0146-0404
Bloom, D.A., & Jaiswal, A.K. (2003). Phosphorylation of Nrf2 at Ser40 by protein kinase C in response to antioxidants leads to the release of Nrf2 from IκB, but is not required for Nrf2 stabilization/accumulation in the nucleus and transcriptional activation of antioxidant response element-mediated NAD(P)H:quinone oxidoreductase-1 gene expression. *Journal of Biological Chemistry* Vol.278, No.45, (November 2003), pp. 44675-44682, ISSN 0021-9258

Bridges, C.C., Kekuda, R., Wang, H., Prasad, P.D., Mehta, P., Huang, W., Smith, S.B., & Ganapathy, V. (2001). Structure, function, and regulation of human cystine/glutamate transporter in retinal pigment epithelial cells. *Investigative Ophthalmology & Visual Science* Vol.42, No.1, (January 2001), pp. 47-54, ISSN 0146-0404

Brown, D.M., Kaiser, P.K., Michels, M., Soubrane, G., Heier, J.S., Kim, R.Y., Sy, J.P., & Schneider, S. (2006). Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *New England Journal of Medicine* Vol.355, No.14, (October 2006), pp. 1432-1444, ISSN 0028-4793

Cano, M., Thimmalappula, R., Fujihara, M., Nagai, N., Sporn, M., Wang, A.L., Neufeld, A.H., Biswal, S., & Handa, J.T. (2010). Cigarette smoking, oxidative stress, the antioxidant response through Nrf2 signaling, and Age-related Macular Degeneration. *Vision Research* Vol.50, No.7, (March 2010), pp. 652-664, ISSN 0042-6989

Chan, K., Lu, R., Change, J.C. & Kan, Y.W. (1996) NRF2, a member of the NFE2 family of transcription factors, is not essential for murin erythropoiesis, growth, and development. *Proceedings of the National Academy of Sciences of the United States of America* Vol.93, No.24, (November 1996), pp. 13943-13948, ISSN 1091-6490

Chen, J. B., Wang, L., Chen, Y., Sternberg, P., & Cai, J. (2009). Phosphatidylinositol 3 Kinase Pathway and 4-Hydroxy-2-Nonenal-Induced Oxidative Injury in the RPE. *Investigative Ophthalmology & Visual Science* Vol.50, No.2, (February 2009), pp. 936-942, ISSN 0146-0404

Chen, W., Stambolian, D., Edwards, A.O., Branhman, K.E., Othman, M., et al. (2010) Genetic variants near TIMP3 and high-density lipoprotein-associated loci influence susceptibility to age-related macular degeneration. *Proceedings of the National Academy of Sciences of the United States of America* Vol.107, No.16, (April 2010), pp. 7401-7406, ISSN 1091-6490

Crabb, J.W., Miyagi, M., Gu, X., Shadrach, K., West, K.A., Sakaguchi, H., Kamei, M., Hasan, A., Yan, L., Rayborn, M.E., et al. (2002). Drusen proteome analysis: an approach to the etiology of age-related macular degeneration. *Proceedings of the National Academy of Sciences of the United States of America* Vol.99, No.23, (November 2002), pp. 14682-14687, ISSN 1091-6490

Cullinan, S.B., & Diehl, J.A. (2004). PERK-dependent activation of Nrf2 contributes to redox homeostasis and cell survival following endoplasmic reticulum stress. *Journal of Biological Chemistry* Vol.279, No.19, (May 2004), pp. 20108-20117, ISSN 0021-9258

Cullinan, S.B., Gordian, J.D., Jin, J., Harper, J.W., & Diehl, J.A. (2004). The Keap1-BTB protein is an adaptor that bridges Nrf2 to a Cul3-based E3 ligase: oxidative stress sensing by a Cul3-Keap1 ligase. *Molecular and Cell Biology* Vol.24, No.19, (October 2004), pp. 8477-8486, ISSN 0270-7306

Cullinan, S. B., Zhang, D., Hannink, M., Arvisais, E., Kaufman, R. J., & Diehl, J. A. (2003). Nrf2 is a direct PERK substrate and effector of PERK-dependent cell survival.

www.intechopen.com
Molecular and Cellular Biology Vol.23, No.20, (October 2003), pp. 7198-7209, ISSN 0270-7306

Cuervo, A.M., Stefanis, L., Fredenburg, R., Lansbury, P.T. & Sulzer, D. (2004) Impaired degradation of mutant α-synuclein by chaperone-mediated autophagy. Science Vol.305, No.5688, (August 2004), pp. 1292-1295, ISSN 0036-8075

DCruz, P.M., Yasumura, D., Weir, J., Matthes, M.T., Abderrahim, H., LaVail, M.M., & Vollrath, D. (2000). Mutation of the receptor tyrosine kinase gene Mertk in the retinal dystrophic RCS rat. Human Molecular Genetics Vol.9, No.4, (March 2000), pp. 645-651, ISSN 0964-6906

DeBlack, S.S. (2003). Cigarette smoking as a risk factor for cataract and age-related macular degeneration: a review of the literature. Optometry Vol.74, No.2, (February 2003), pp. 99-110, ISSN 1558-1527

Dinkova-Kostova, A.T., Holtzclaw, W.D., Cole, R.N., Itoh, K., Wakabayashi, N., Katoh, Y., Yamamoto, M., & Talalay, P. (2002). Direct evidence that sulfhydryl groups of Keap1 are the sensors regulating induction of phase 2 enzymes that protect against carcinogens and oxidants. Proceedings of the National Academy of Sciences of the United States of America Vol.99, No.18, (September 2002), pp. 11908-11913, ISSN 1091-6490

Dorrell, M.I., Aguilar, E., Jacobson, R., Yanes, O., Gariano, R., Heckenlively, J., Banin, E., Ramirez, G.A., Gasmi, M., Bird, A., Siu, Z. G. & Friedlander, M. Antioxidant or neurotrophic factor treatment preserves function in a mouse model of neovascularization-associated oxidative stress. Journal of Clinical Investigation Vol.119, No.3, (March 2009), pp. 611-623, ISSN 0021-9738

Dunaief, J.L. (2006). Iron induced oxidative damage as a potential factor in age-related macular degeneration: the Cogan Lecture. Investigative Ophthalmology & Visual Science Vol.47, No.11, (November 2006), pp. 4660-4664, ISSN 0146-0404

Eggler, A.L., Liu, G., Pezzuto, J.M., van Breemen, R.B., & Mesecar, A.D. (2005). Modifying specific cysteines of the electrophile-sensing human Keap1 protein is insufficient to disrupt binding to the Nrf2 domain Neh2. Proceedings of the National Academy of Sciences of the United States of America Vol.102, No.29, (July 2005), pp. 10070-10075, ISSN 1091-6490

Feng, W., Yasumura, D., Matthes, M.T., LaVail, M.M., and Vollrath, D. (2002). Mertk triggers uptake of photoreceptor outer segments during phagocytosis by cultured retinal pigment epithelial cells. Journal of Biological Chemistry Vol.277, No.19, (May 2002), pp. 17016-17022, ISSN 0021-9258

Finnemann, S.C., Bonilha, V.L., Marmorstein, A.D., & Rodriguez-Boulan, E. (1997). Phagocytosis of rod outer segments by retinal pigment epithelial cells requires alpha(v)beta5 integrin for binding but not for internalization. Proceedings of the National Academy of Sciences of the United States of America Vol.94, No.24, (November 1997), pp. 12932-12937, ISSN 1091-6490

Finnemann, S.C., & Silverstein, R.L. (2001). Differential roles of CD36 and alphavbeta5 integrin in photoreceptor phagocytosis by the retinal pigment epithelium. Journal of Experimental Medicine Vol.194, No.9, (November 2001), pp. 1289-1298, ISSN 0022-1007
Furukawa, M., & Xiong, Y. (2005). BTB protein Keap1 targets antioxidant transcription factor Nrf2 for ubiquitination by the Cullin 3-Roc1 ligase. *Molecular and Cell Biology* Vol.25, No.1, (January 2005), pp. 162-171, ISSN 0270-7306

Galbinur, T., Averbukh, E., Banin, E., Hemo, I., & Chowers, I. (2009). Intravitreal bevacizumab therapy for neovascular age-related macular degeneration associated with poor initial visual acuity. *British Journal of Ophthalmology* Vol.93, No.10, (October 2009), pp. 1351-1352, ISSN 0007-1161

Gao, X., Dinkova-Kostova, A.T., & Talalay, P. (2001). Powerful and prolonged protection of human retinal pigment epithelial cells, keratinocytes, and mouse leukemia cells against oxidative damage: the indirect antioxidant effects of sulforaphane. *Proceedings of the National Academy of Sciences of the United States of America* Vol.98, No.26, (December 2001), pp. 15221-15226, ISSN 0027-8424

Gao, X., & Talalay, P. (2004). Induction of phase 2 genes by sulforaphane protects retinal pigment epithelial cells against photooxidative damage. *Proceedings of the National Academy of Sciences of the United States of America* Vol.101, No.28, (July 2004), pp. 10446-10451, ISSN 0027-8424

Ha, K.N., Chen, Y., Cai, J., & Sternberg, P., Jr. (2006). Increased glutathione synthesis through an ARE-Nrf2-dependent pathway by zinc in the RPE: implication for protection against oxidative stress. *Investigative Ophthalmology & Visual Science* Vol.47, No.6, (June 2006), pp. 2709-2715, ISSN 0146-0404

Hadziahmetovic, M., Dentchev, T., Song, Y., Haddad, N., He, X., Hahn, P., Pratico, D., Wen, R., Harris, Z.L., Lambris, J.D., et al. (2008). Ceruloplasmin/hephaestin knockout mice model morphologic and molecular features of AMD. *Investigative Ophthalmology & Visual Science* Vol.49, No.6, (June 2008), pp. 2728-2736, ISSN 0146-0404

Hahn, P., Qian, Y., Dentchev, T., Chen, L., Beard, J., Harris, Z.L., & Dunaief, J.L. (2004). Disruption of ceruloplasmin and hephaestin in mice causes retinal iron overload and retinal degeneration with features of age-related macular degeneration. *Proceedings of the National Academy of Sciences of the United States of America* Vol.101, No.38, (September 2004), pp. 13850-13855, ISSN 0027-8424

Ham, W.T., Jr., Mueller, H.A., Ruffolo, J.J., Jr., Millen, J.E., Cleary, S.F., Guerry, R.K., and Guerry, D., 3rd (1984). Basic mechanisms underlying the production of photochemical lesions in the mammalian retina. *Current Eye Research* Vol.3, No.1, (January 1984), pp. 165-174, ISSN 0271-3683

Hollyfield, J.G., Bonilha, V.L., Rayborn, M.E., Yang, X., Shadrach, K.G., Lu, L., Ufret, R.L., Salomon, R.G., and Perez, V.L. (2008). Oxidative damage-induced inflammation initiates age-related macular degeneration. *Nature Medicine* Vol.14, No.2, (February 2008), pp. 194-198, ISSN 1078-8956

Hong, F., Sekhar, K.R., Freeman, M.L., & Liebler, D.C. (2005). Specific patterns of electrophile adduction trigger Keap1 ubiquitination and Nrf2 activation. *Journal of Biological Chemistry* Vol.280, No.36, (September 2005), pp. 31768-31775, ISSN 0021-9258

Huang, H.C., Nguyen, T., & Pickett, C.B. (2002). Phosphorylation of Nrf2 at Ser-40 by protein kinase C regulates antioxidant response element-mediated transcription. *Journal of Biological Chemistry* Vol.277, No.45, (November 2002), pp. 42769-42774, ISSN 0021-9258
Imamura, Y., Noda, S., Hashizume, K., Shinoda, K., Yamaguchi, M., Uchlyama, S., Shimizu, T., Mizushima, Y., Shirasawa, T. & Tsubota, K. Drusen, choroidal neovascularization, and retinal pigment epithelium dysfunction in SOD1-deficient mice: a model of age-related macular degeneration. Proceedings of the National Academy of Sciences of the United States of America Vol.103, No.30, (July 2006), pp. 11282-11287, ISSN 0027-8424

Imomata, Y., Tanibara, H., Tanito, M., Okyama, H., Hoshino, Y., Kinumi, T., Kawaji, T., Kondo, N., Yodoi, J & Nakamura H. Suppression of choroidal neovascularization by thioredoxin-1 via interaction with complement factor H. Investigative Ophthalmology & Visual Science Vol.49, No.11, (November 2008), pp. 5118-5125, ISSN 0146-0404

Ishii, T., Sato, H., Miura, K., Sagara, J., & Bannai, S. (1992). Induction of cystine transport activity by stress. Annals of the New York Academy of Sciences Vol.663, (November 1992), pp. 497-498, ISSN 0077-8923

Jacobson, L.P., Zhang, B.C., Zhu, Y.R., Wang, J.B., Wu, Y., Zhang, Q.N., Yu, L.Y., Qian, G.S., Kuang, S.Y., Li, Y.F., et al. (1997). Oltipraz chemoprevention trial in Qidong, People’s Republic of China: study design and clinical outcomes. Cancer Epidemiology, Biomarkers & Prevention Vol.6, No.4, (April 1997), pp. 257-265, ISSN 1055-9965

Jain, A. K., & Jaiswal, A.K. (2006). Phosphorylation of tyrosine 568 controls nuclear export of Nrf2. Journal of Biological Chemistry Vol.281, No.17, (April 2006), pp. 12132-12142, ISSN 0021-9258

Johnson, J., Maher, P., and Hanneken, A. (2009). The flavonoid, eriodictyol, induces long-term protection in ARPE-19 cells through its effects on Nrf2 activation and phase 2 gene expression. Investigative Ophthalmology & Visual Science Vol.50, No.5, (May 2009), pp. 2398-2406, ISSN 0146-0404

Justilien, V., Pang, J.J., Renganathan, K., Zhan, X., Crabb, J.W., Kim, S.R., Sparrow, J.R., Hauswirth, W.W. & Lewin, A.S. SOD2 knockdown mouse model of early AMD. Investigative Ophthalmology & Visual Science Vol.48, No.10, (October 2007), pp. 4407-4420, ISSN 0146-0404

Kaarniranta, K. (2010) Autophagy-hot topic in AMD. Acta Ophthalmologica Vol.88, No.4, (June 2010), pp. 387-388, ISSN 1755-3768

Kaneko, H., Dridi, S., Tarallo, V., Gelfand, B.D., Fowler, B.J., Cho, W.G., Kleinman, M.E., Ponicsan, S.L., Hauswirth, W.W., Chiido, V.A., et al. (2011). DICER1 deficit induces Alu RNA toxicity in age-related macular degeneration. Nature Vol.471, No.7338, (March 2011), pp. 325-330, ISSN 0028-0836

Kang, K. W., Lee, S. J., Park, J. W., & Kim, S. G. (2002). Phosphatidylinositol 3-kinase regulates nuclear translocation of NF-E2-related factor 2 through actin rearrangement in response to oxidative stress. Molecular pharmacology Vol.62, No.5, (November 2002), pp. 1001-1010, ISSN 0026-895X

Kang, K. W., Ryu, J. H., & Kim, S. G. (2000). The essential role of phosphatidylinositol 3-kinase and of p38 mitogen-activated protein kinase activation in the antioxidant response element-mediated rGSTA2 induction by decreased glutathione in H4IE hepatoma cells. Molecular pharmacology Vol.58, No.5, (November 2000), pp. 1017-1025, ISSN 0026-895X
Kaspar, J.W. & Jaiswal, A.K. (2011) Tyrosine phosphorylation control nuclear export of Fyn, allowing Nrf2 activation of cytoprotective gene expression. *FASEB Journal* (March 2011), pp 1076-1087, ISSN 0892-6638.

Katsuoka, F., Motohashi, H., Ishii, T., Aburatani, H., Engel, J.D., & Yamamoto, M. (2005). Genetic evidence that smallmaf proteins are essential for the activation of antioxidant response element-dependent genes. *Molecular and Cell Biology* Vol.25, No.18, (September 2005), pp. 8044-8051, ISSN 0270-7306

Kensler, T.W., Wakabayashi, N., & Biswal, S. (2007). Cell survival responses to environmental stresses via the Keap1-Nrf2-ARE pathway. *Annual Review of Pharmacology and Toxicology* Vol.47, (2007), pp. 89-116, ISSN 0362-1642

Klionsky, D.J. (2007) Autophagy: from phenomenology to molecular understanding in less than a decade. *Nature Review Molecular &Cell Biology* Vol.8, (November 2007), pp. 931-937, ISSN 1471-0072

Kobayashi, A., Kang, M.I., Okawa, H., Ohtsuki, M., Zenke, Y., Chiba, T., Igarashi, K., and Yamamoto, M. (2004). Oxidative stress sensor Keap1 functions as an adaptor for Cul3-based E3 ligase to regulate proteasomal degradation of Nrf2. *Molecular and Cell Biology* Vol.24, No.16, (August 2004), pp. 7130-7139, ISSN 0270-7306

Komatsu, M., Kurokawa, H., Waguri, S., Taguchi, K., Kobayashi, A., et al. (2010) The selective autophagy substrate p62 activates the stress responsive transcription factor Nrf2 through inactivation of Keap1. *Nature Cell Biology* Vol.12, No.3, (March 2010), pp. 213-224, ISSN 1465-7392

Kong, L., Tanito, M., Huang, Z., Li, F., Zhou, X., Zaharia, A., Yodoi, J., McGinnis, J.F., & Cao, W. (2007). Delay of photoreceptor degeneration in tubby mouse by sulforaphane. *Journal of Neurochemistry* Vol.101, No.4, (May 2007), pp. 1041-1052, ISSN 0022-3042

Lee, J. M., Hanson, J. M., Chu, W. A., & Johnson, J. A. (2001). Phosphatidylinositol 3-kinase, not extracellular signal-regulated kinase, regulates activation of the antioxidant-responsive element in IMR-32 human neuroblastoma cells. *Journal of biological chemistry* Vol.276, No.23, (June 2001), pp. 20011-20016, ISSN 0021-9258

Lee, J.-H., Yu, W.H, Kuma A., Lee, S., Mohan, P.S., Peterhoff, C.M., Wolfe, D.M., Martinez-Vicente, M., Massey, A.C., Sovak, G., Uchiyama, Y., Westaway, D., Cuervo, A.M. & Nixon, R.A. (2010) Lysosomal proteolysis and autophagy require presenilin 1 and are disrupted by Alzheimer-related PS1 mutations. *Cell* Vol.141, No.7, (June 2010), pp 1146-1158, ISSN 0092-8674

Lee, P. P., Feldman, Z. W., Ostermann, J., Brown, D. S., & Sloan, F. A. (2003). Longitudinal prevalence of major eye diseases. *Archives of Ophthalmology* Vol.121, No.9, (September 2003), pp. 1303-1310, ISSN 0003-9950

Levine, B., Mizushima, N. & Virgin, H.W. (2011) Autophagy in immunity and inflammation. *Nature* Vol.469, (January 2011), pp. 323-335, ISSN 0028-0836

Mandal, M. N. A., Patlolla, J. M. R., Zheng, L., Agbaga, M. P., Tran, J. T. A., Wicker, L., Asus-Jacobi, A., Elliott, M. H., Rao, C. V., & Anderson, R. E. (2009). Curcumin protects retinal cells from light-and oxidant stress-induced cell death. *Free Radical Biology and Medicine* Vol.46, No.5, (March 2009), pp. 672-679, ISSN 0891-5849

Marzec, J. M., Christie, J. D., Reddy, S. P., Jedlicka, A. E., Vuong, H., Lanken, P. N., Aplenc, R., Yamamoto, T., Yamamoto, M., Cho, H. Y., & Kleeberger, S. R. (2007). Functional polymorphisms in the transcription factor NRF2 in humans increase the risk of
acute lung injury. *Faseb Journal* Vol.21, No.9, (July 2007), pp. 2237-2246, ISSN 0892-6638 1546-1726

Martinez-Vicente, M., Talloczy, Z., Wong, E., Tang, G., Koga, H., et al. (2010) Cargo recognition failure is responsible for inefficient autophagy in Huntington’s disease. *Nature Neuroscience* Vol.13, (April 2010), pp. 567-576, ISSN

McLeod, D. S., Grebe, R., Bhutto, J., Merges, C., Baba, T., & Lutty, G. A. (2009) Relationship between RPE and choriocapillaris in age-related macular degeneration. *Investigative Ophthalmology & Visual Science* Vol.50, No. 10, (October 2009), pp 4982-4991, ISSN 0146-0404

McMahon, M., Thomas, N., Itoh, K., Yamamoto, M., & Hayes, J. D. (2004). Redox-regulated turnover of Nrf2 is determined by at least two separate protein domains, the redox-sensitive Neh2 degron and the redox-insensitive Neh6 degron. *Journal of Biological Chemistry* Vol.279, No.30, (July 2004), pp. 31556-31567, ISSN 0021-9258

Mitchell, P., Wang, J. J., Smith, W., & Leeder, S. R. (2002). Smoking and the 5-year incidence of age-related maculopathy - The Blue Mountains Eye Study. *Archives of Ophthalmology* Vol.120, No.10, (October 2002), pp. 1357-1363, ISSN 0003-9950

Moiseyev, G., Takahashi, Y., Chen, Y., Gentleman, S., Redmond, T. M., Crouch, R. K., & Ma, J. X. (2006). RPE65 is an iron(II)-dependent isomerohydrolase in the retinoid visual cycle. *Journal of Biological Chemistry* Vol.281, No.5, (February 2006), pp. 2835-2840, ISSN 0021-9258

Moriarty-Craige, S.E., Ha, K.N., Sternberg, P. Jr., Lynn, M., Bressler, S., Gensler, G. & Jones, D.P. (2007) Effects off long-term zinc supplementation on plasma thiol metabolites and redox status in patients with age-related macular degeneration. *American Journal of Ophthalmology* Vo.143, No.2, (February 2007), pp. 206-211, ISSN 0002-9394

Motohashi, H., Katsuoka, F., Engel, J. D., & Yamamoto, M. (2004). Small Maf proteins serve as transcriptional cofactors for keratinocyte differentiation in the Keap1-Nrf2 regulatory pathway. *Proceedings of the National Academy of Sciences of the United States of America* Vol.101, No.17, (April 2004), pp. 6379-6384, ISSN 0027-8424

Mullins, R. F., Johnson, M. N., Faidley, E. A., Skeie, J. M., & Huang, J. (2011) Choriocapillaris vascular dropout related to density of drusen in human eyes with early age-related macular degeneration. *Investigative Ophthalmology & Visual Science* Vol.52, No. 3, (March 2011), pp 1606-1612, ISSN 0146-0404

Mullins, R. F., Russell, S. R., Anderson, D. H., & Hageman, G. S. (2000). Drusen associated with aging and age-related macular degeneration contain proteins common to extracellular deposits associated with atherosclerosis, elastosis, amyloidosis, and dense deposit disease. *Faseb Journal* Vol.14, No.7, (May 2000), pp. 835-846, ISSN 0892-6638

Nagai, N., Thimmulappa, R. K., Cano, M., Fujihara, M., Izumi-Nagai, K., Kong, X. O., Sporn, M. B., Kensler, T. W., Biswal, S., & Handa, J. I. (2009). Nrf2 is a critical modulator of the innate immune response in a model of uveitis. *Free Radical Biology and Medicine* Vol.47, No.3, (August 2009), pp. 300-306, ISSN 0891-5849

Nelson, K. C., Armstrong, J. S., Moriarty, S., Cai, J. Y., Wu, M. W. H., Sternberg, P., & Jones, D. P. (2002). Protection of retinal pigment epithelial cells from oxidative damage by olitpraz, a cancer chemopreventive agent. *Investigative Ophthalmology & Visual Science* Vol.43, No.11, (November 2002), pp. 3550-3554, ISSN 0146-0404
Nelson, K.C., Carlson, J, Newman, M.L., Sternberg, P. Jr., Jones, D.P., Kavanagh, T.J., Diaz, D., Cai, J. & Wu M. (1999) Effect of dietary inducer dimethylfumarate on glutathione in cultured human retinal pigment epithelial cells. *Investigative Ophthalmology & Visual Science* Vol.40, No. 9, (August 1999), pp 1927-1935, ISSN 0146-0404

Niture, S.K., Jain, A.K., Shelton, P.M. & Jaiswal, A.K. (2011) Src subfamily kinases regulate nuclear export and degradation of the transcription factor Nrf2 to switch off Nrf2-mediated antioxidant activation of cytoprotective gene expression. *Journal of Biological Chemistry*. in press, (June 2011), ISSN 0006-291X

Okawa, H., Motohashi, H., Kobayashi, A., Aburatani, H., Kensler, T. W., & Yamamoto, M. (2006). Hepatocyte-specific deletion of the keap1 gene activates Nrf2 and confers potent resistance against acute drug toxicity. *Biochemical and Biophysical Research Communications* Vol.339, No.1, (January 2006), pp. 79-88, ISSN 0006-291X

Organisciak, D. T., Wang, H. M., Li, Z. Y., & Tso, M. O. M. (1985). The Protective Effect of Ascorbate in Retinal Light Damage of Rats. *Investigative Ophthalmology & Visual Science* Vol.26, No.11, (November 1985), pp. 1580-1588, ISSN 0146-0404

Osburn, W. O., & Kensler, T. W. (2008). Nrf2 signaling: An adaptive response pathway for protection against environmental toxic insults. *Mutation Research-Reviews in Mutation Research* Vol.659, No.1-2, (July-August 2008), pp. 31-39, ISSN 1383-5742

Pearson, K.J., Lewis, K.N., Price, N.L., et al. (2008) Nrf2 mediates cancer protection but not longevity induced by caloric restriction. *Proceedings of the National Academy of Sciences of the United States of America* Vol.105, No.7, (February 2008), pp. 2325-2330, ISSN 0027-8424

Pi, J., Bai, Y., Reece, J. M., Williams, J., Liu, D., Freeman, M. L., Fahl, W. E., Shugar, D., Liu, J., Qu, W., Collins, S., & Waalkes, M. P. (2007). Molecular mechanism of human Nrf2 activation and degradation: role of sequential phosphorylation by protein kinase CK2. *Free Radical Biology & Medicine* Vol.42, No.12, (June 15 2007), pp. 1797-1806, ISSN 0891-5849

Pitha-Rowe, I., Liby, K., Royce, D., & Sporn, M. (2009). Synthetic Triterpenoids Attenuate Cytotoxic Retinal Injury: Cross-talk between Nrf2 and PI3K/AKT Signaling through Inhibition of the Lipid Phosphatase PTEN. *Investigative Ophthalmology & Visual Science* Vol.50, No.11, (November 2009), pp. 5339-5347, ISSN 0146-0404

Pool-Zobel, B., Veeriah, S., & Bohmer, F. D. (2005). Modulation of xenobiotic metabolising enzymes by anticarcinogens - focus on glutathione S-transferases and their role as targets of dietary chemoprevention in colorectal carcinogenesis. *Mutation Research-Fundamental and Molecular Mechanisms of Mutagenesis* Vol.591, No.1-2, (December 2005), pp. 74-92, ISSN 0027-5107

Pryor, W. A., Prier, D. G., & Church, D. F. (1983). Electron-Spin Resonance Study of Mainstream and Sidestream Cigarette-Smoke - Nature of the Free-Radicals in Gas-Phase Smoke and in Cigarette Tar. *Environmental Health Perspectives* Vol.47, (January 1983), pp. 345-355, ISSN 0091-6765

Rada, P., Rojo, A. I., Chowdhry, S., McMahon, M., Hayes, J. D., & Cuadrado, A. (2011). SCF/[beta]-TrCP promotes glycogen synthase kinase 3-dependent degradation of the Nrf2 transcription factor in a Keap1-independent manner. *Molecular and Cellular Biology* Vol.31, No.6, (March 2011), pp. 1121-1133, ISSN 1098-5549
Ramkumar, H. L., Chan, C. C., & Zhang, J. (2010). Retinal ultrastructure of murine models of dry age-related macular degeneration (AMD). *Progress in Retinal and Eye Research* Vol.29, No.3, (May 2010), pp. 169-190, ISSN 1350-9462

Rangasamy, T., Cho, C. Y., Thimmulappa, R. K., Zhen, L. J., Srirama, S. S., Kensler, T. W., Yamamoto, M., Petracek, I., Tudor, R. M., & Biswal, S. (2004). Genetic ablation of Nrf2 enhances susceptibility to cigarette smoke-induced emphysema in mice. *Journal of Clinical Investigation* Vol.114, No.9, (November 2004), pp. 1248-1259, ISSN 0021-9738

Rosenfeld, P. J., Brown, D. M., Heier, J. S., Boyer, D. S., Kaiser, P. K., Chung, C. Y., & Kim, R. Y. (2006). Ranibizumab for neovascular age-related macular degeneration. *New England Journal of Medicine* Vol.355, No.14, (October 2006), pp. 1419-1431, ISSN 0028-4793

Saint-Geniez, M., Kurihara, T., Sekiyama, E., Maldonado, A. E., & D’Amore, P. A. (2009). An essential role for RPE-derived soluble VEGF in the maintenance of the choriocapillaris. *Proceedings of the National Academy of Sciences of the United States of America* Vol.106, No.44, (November 2009), pp. 18751-18756, ISSN 0027-8424

Salazar, M., Rojo, A. L., Velasco, D., de Sagarra, R. M., & Cuadrado, A. (2006). Glycogen synthase kinase-3beta inhibits the xenobiotic and antioxidant cell response by direct phosphorylation and nuclear exclusion of the transcription factor Nrf2. *Journal of Biological Chemistry* Vol.281, No.21, (May 2006), pp. 14841-14851, ISSN 0021-9258

Sasaki, H., Sato, H., Kuriyama-Matsumura, K., Sato, K., Maebara, K., Wang, H. Y., Tamba, M., Itoh, K., Yamamoto, M., & Bannai, S. (2002). Electrophile response element-mediated induction of the cystine/glutamate exchange transporter gene expression. *Journal of Biological Chemistry* Vol.277, No.47, (November 2002), pp. 44765-44771, ISSN 0021-9258

Shibata, T., Iuchi, Y., Okada, F., Kuwata, K., Yamanobe, T., Bannai, S., Tomita, Y., Tomita, Y. & Fujii J. (2009) Aggravation of ischemia-reperfusion-triggered acute renal failure in xCT-deficient mice. *Archives of Biochemistry and Biophysics* Vol.490, No.1, (October 2009), pp. 63-69, ISSN 0003-9861

Shibata, T., Ohta, T., Tong, K.I., Kokubu, A., Odogawa, R., Tsuta, K., Asamura, H., Yamamoto, M. & Hirohashi S. (2008). Cancer related mutations in NRF2 impair its recognition by Keap1-Cul3 E3 ligase and promote malignancy. *Proceedings of the
Smith, W., Assink, J., Klein, R., Mitchell, P., Klaver, C. C. W., Klein, B. E. K., Hofman, A., Jensen, S., Wang, J. J., & de Jong, P. T. V. M. (2001). Risk factors for age related macular degeneration - Pooled findings from three continents. *Ophthalmology* Vol.108, No.4, (April 2001), pp. 697-704, ISSN 0161-6420

Sparrow, J. R., Fishkin, N., Zhou, J. L., Cai, B. L., Jang, Y. P., Krane, S., Itagaki, Y., & Nakanishi, K. (2003). A2E, a byproduct of the visual cycle. *Vision Research* Vol.43, No.28, (December 2003), pp. 2983-2990, ISSN 0042-6989

Sun, Z., Huang, Z., & Zhang, D. D. (2009). Phosphorylation of Nrf2 at multiple sites by MAP kinases has a limited contribution in modulating the Nrf2-dependent antioxidant response. *PLoS One* Vol.4, No.8, (August 2009), pp. e6588, ISSN 1932-6203

Tanito, M., Masutani, H., Kim, Y. C., Nishikawa, M., Ohira, A., & Yodoi, J. (2005). Sulforaphane induces thioredoxin through the antioxidant-responsive element and attenuates retinal light damage in mice. *Investigative Ophthalmology & Visual Science* Vol.46, No.3, (March 2005), pp. 979-987, ISSN 0146-0404

Tomobe, K., Shinozuka, T., Kuroiwa, M. & Nomura Y. (2011) Age-related changes of Nrf2 and phosphorylated GSH-3β in a mouse model of accelerated aging (SAMP8). *Archives of Gerontology and Geriatrics* Article in Press, ISSN 0167-4943

Tso, M. O. M., Woodford, B. J., & Lam, K. W. (1984). Distribution of Ascorbate in Normal Primate Retina and after Photic Injury - a Biochemical, Morphological Correlated Study. *Current Eye Research* Vol.3, No.1, (January 1984), pp. 181-191, ISSN 0271-3683

Tso, M. O. M., Zhang, C., Abler, A. S., Chang, C. J., Wong, F., Chang, G. Q., & Lam, T. T. (1994). Apoptosis Leads to Photoreceptor Degeneration in Inherited Retinal Dystrophy of Rcs Rats. *Investigative Ophthalmology & Visual Science* Vol.35, No.6, (May 1994), pp. 2693-2699, ISSN 0146-0404

Uno, K., Prow, T. W., Bhutto, I. A., Yerrapureddy, A., McLeod, D. S., Yamamoto, M., Reddy, S. P., & Lutty, G. A. (2010). Role of Nrf2 in retinal vascular development and the vaso-obliterative phase of oxygen-induced retinopathy. *Experimental Eye Research* Vol.90, No.4, (April 2010), pp. 493-500, ISSN 0014-4835

Wagner, C. A., Lang, F., & Broer, S. (2001). Function and structure of heterodimeric amino acid transporters. *American Journal of Physiology-Cell Physiology* Vol.281, No.4, (October 2001), pp. C1077-C1093, ISSN 0363-6143

Wakabayashi, N., Slocum, S. L., Skoko, J. J., Shin, S., & Kensler, T. W. (2010). When NRF2 Talks, Who’s Listening? *Antioxidants & Redox Signaling* Vol.13, No.11, (December 2010), pp. 1649-1663, ISSN 1523-0864

Wang, A. L., Lukas, T. J., Yuan, M., Du, N., Tso, M. O., & Neufeld, A. H. (2009). Autophagy and Exosomes in the Aged Retinal Pigment Epithelium: Possible Relevance to Drusen Formation and Age-Related Macular Degeneration. *PLoS One* Vol.4, No.1, (January 8 2009), pp. e4160, ISSN 1932-6203

Wang, L., Chen, Y., Sternberg, P., & Cai, J. (2008). Essential roles of the PI3 kinase/Akt pathway in regulating Nrf2-dependent antioxidant functions in the RPE. *Investigative Ophthalmology & Visual Science* Vol.49, No.4, (April 2008), pp. 1671-1678, ISSN 0146-0404
Wei, Y., Gong, J., Yoshida, T., Eberhart, C.G., Xu, Z., Kombairaju P., Spron, M.B., Handa, J.T. & Duh, E.J. (2011) Nrf2 has a protective role against neuronal and capillary degeneration in retinal ischemia-reperfusion injury. *Free Radical Biology & Medicine* Vol.51, No.1 (July 2011), pp 216-224, ISSN 0891-5849

Winkler, B.S. (2008) An hypothesis to account for the renewal of outer segments in rod and cone photoreceptor cells: renewal as a surrogate antioxidant. *Investigative Ophthalmology & Visual Science* Vol.49, No.8, (August 2008), pp. 3259-3261, ISSN 0146-0404

Wu, Y. L., Yanase, E., Feng, X. D., Siegel, M. M., & Sparrow, J. R. (2010). Structural characterization of bisretinoid A2E photocleavage products and implications for age-related macular degeneration. *Proceedings of the National Academy of Sciences of the United States of America* Vol.107, No.16, (April 2010), pp. 7275-7280, ISSN 0027-8424

Xue, L. L., Gollapalli, D. R., Maiti, P., Jahng, W. J., & Rando, R. R. (2004). A palmitoylation switch mechanism in the regulation of the visual cycle. *Cell* Vol.117, No.6, (June 11 2004), pp. 761-771, ISSN 0092-8674

Yoh, K., Itoh, K., Enomoto, A., Hirayama, A., Yamaguchi, N., Kobayashi, M., Morito, N., Koyama, A., Yamamoto, M., & Takahashi, S. (2001). Nrf2-deficient female mice develop lupus-like autoimmune nephritis. *Kidney International* Vol.60, No.4, (October 2001), pp. 1343-1353, ISSN 0085-2538

Young, R. W. (1967). The renewal of photoreceptor cell outer segments. *The Journal of Cell Biology* Vol.33, No.1, (April 1967), pp. 61-72, ISSN 0021-9525

Young, R. W., & Bok, D. (1969). Participation of the retinal pigment epithelium in the rod outer segment renewal process. *The Journal of Cell Biology* Vol.42, No.2, (August 1969), pp. 392-403, ISSN 0021-9525

Yu, R., Chen, C., Mo, Y. Y., Hebbar, V., Owwor, E. D., Tann, T. H., & Kong, A. N. T. (2000). Activation of mitogen-activated protein kinase pathways induces antioxidant response element-mediated gene expression via a Nrf2-dependent mechanism. *Journal of Biological Chemistry* Vol.275, No.51, (December 2000), pp. 39907-39913, ISSN 0021-9258

Yu, R., Mandlekar, S., Lei, W., Fahl, W. E., Tan, T. H., & Kong, A. N. (2000). p38 mitogen-activated protein kinase negatively regulates the induction of phase II drug-metabolizing enzymes that detoxify carcinogens. *Journal of Biological Chemistry* Vol.275, No.4, (January 2000c), pp. 2322-2327, ISSN 0021-9258

Zhang, J., Hosoya, T., Maruyama, A., Nishikawa, K., Maher, J. M., Ohta, T., Motohashi, H., Fukamizu, A., Shibahara, S., Yamamoto, M., & Itoh, K. (2007). Nrf2 Neh5 domain is differentially utilized in the transactivation of cytoprotective genes. *Biochemical Journal* Vol.404, (June 2007), pp. 459-466, ISSN 0264-6021

Zhao, Z. Y., Chen, Y., Wang, J., Sternberg, P., Freeman, M. L., Grossniklaus, H. E., & Cai, J. Y. (2011). Age-Related Retinopathy in NRF2-Deficient Mice. *PLoS One* Vol.6, No.4, (April 2011), pp. e19456 ISSN 1932-6203

Zhou, J. L., Jang, Y. P., Kim, S. R., & Sparrow, J. R. (2006). Complement activation by photooxidation products of A2E, a lipofuscin constituent of the retinal pigment epithelium. *Proceedings of the National Academy of Sciences of the United States of America* Vol.103, No.44, (October 2006), pp. 16182-16187, ISSN 0027-8424
Zipper, L. M., & Mulcahy, R. T. (2000). Inhibition of ERK and p38 MAP kinases inhibits binding of Nrf2 and induction of GCS genes. *Biochemical and Biophysical Research Communications* Vol.278, No.2, (November 2000), pp. 484-492, ISSN 0006-291X
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