MEDICAL SCIENCE MONITOR

REVIEW ARTICLES

e-ISSN 1643-3750
© Med Sci Monit, 2020; 26: e921514
DOI: 10.12659/MSM.921514

Received: 2019.11.19
Accepted: 2020.01.02
Published: 2020.01.17

The Potential Role of Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2) in Glaucoma: A Review

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF Mingxuan Wang
E Jia Li
AE Yajuan Zheng

Department of Ophthalmology, The Second Hospital of Jilin University, Changchun, Jilin, P.R. China

Corresponding Author: Yajuan Zheng, e-mail: zhengyajuan124@126.com
Source of support: Departmental sources

Nuclear factor erythroid 2-related factor 2 (Nrf2) acts as a regulator of many biological processes and plays an essential role in preventing oxidation, inflammation, and fibrosis. In the past 20 years, there has been increasing research on the role of Nrf2 and oxidative stress in human glaucoma, including the roles of inflammation, trabecular meshwork cells, retinal ganglion cells, Tenon's capsule, antioxidants, fibrosis, and noncoding RNAs. Studies have shown that the upregulation of Nrf2 can reduce damage from oxidative stress in the trabecular meshwork cells and the retinal ganglion cells, reduce fibrosis in Tenon's capsule fibroblasts, which may reduce the progression of fibrosis after surgery for glaucoma. The regulatory roles of Nrf2, microRNAs (miRNAs), long noncoding RNAs (lncRNAs), and exogenous compounds on trabecular meshwork cells (TMCs) and retinal ganglion cells have also been studied. The use of Nrf2 agonists, including noncoding RNAs, control the expression of Nrf2 through signaling pathways that continue to be investigated to identify effective treatments to improve clinical outcome following surgery for glaucoma. This review of publications between 1999 and 2019 aims to focus on the potential mechanisms of Nrf2 in the occurrence and development of glaucoma and the prognosis following surgical treatment. Also, several factors that induce the expression of Nrf2 in trabecular meshwork cells, retinal ganglion cells, and human Tenon's capsule fibroblasts are discussed.

MeSH Keywords: Fibrosis • Glaucoma • NF-E2-Related Factor 2 • Optic Nerve • Oxidative Stress

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/921514

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Background

Worldwide, glaucoma results in irreversible blindness in humans, especially in elderly individuals, and is associated with oxidative stress [1]. One of the critical risk factors of primary open-angle glaucoma (POAG) is ocular hypertension [1]. Recent studies have shown that oxidative stress is involved in the occurrence and development of POAG [2,3]. In conditions of oxidative stress, the biological defense system comes across dysfunctions and will cause an imbalance between the production and elimination of reactive oxygen species (ROS) [4,5]. Increased accumulation of ROS leads to damages to genes, proteins, and lipids [6]. These effects of oxidative stress have also been reported in corneal disease [7], cataract [8], retinal disease [9], and glaucoma [10].

According to the mechanical theory of glaucoma, studies have shown that outflow of the aqueous humor may be partially blocked by dysfunction induced by oxidative stress of trabecular meshwork cells, which results in ocular hypertension [11]. Pathologically high intraocular pressure (IOP) can further cause retinal ganglion cell mitochondrial dysfunction and apoptosis and contributes to loss of vision in patients with glaucoma [12].

Recently, the roles of nuclear factor erythroid 2-related factor 2 (Nrf2) and the associated signaling pathways in the regulation of oxidative stress responses have been studied [13,14]. Nrf2 is an important regulator of protective antioxidant and anti-inflammatory responses, which regulates the expression of many genes [15]. Nrf2 regulates not only responsive antioxidant enzymes but also a series of genes involved in processes that include inflammation, tissue remodeling, and fibrosis [16]. The Nrf2 signaling system, together with its regulatory molecules and interacting proteins, performs a critical antioxidant and anti-inflammatory function in cells. In normal conditions, Nrf2 is located in the cytoplasm and mediates proteasome degradation by binding to Kelch-like erythroid cell-derived protein with CNC homology-associated protein 1 (Keap1).

Following the initiation of cellular oxidative stress on exposure to electrophiles, including hydrogen peroxide (H_2O_2) superoxide anion (O_2^-), hydroxyl radical (–OH), and ROS, Keap1 undergoes conformational changes. These changes allow Nrf2 to be transported into the cell nucleus to bind to the antioxidant response element (ARE) regions. Then, transcription of antioxidant enzymes and phase II detoxification enzymes occurs, including heme oxygenase-1 (HO-1), NAD(P)H: quinone oxidoreductase 1 (NQO1) [17]. Also, γ-glutamyl cysteine ligase catalytic subunit (GCLC), glutathione peroxidase [13], glutathione-S-transferase (GST), catalase, superoxide dismutase, and thioredoxin uridine 5'-diphospho-glucuronosyltransferase) (UDP)-glucuronosyltransferase occurs [18–21]. However, Nrf2 may be dissociated from the cytoplasmic Nrf2-keap1-cul3 complex by p62, which is a marker of cell autophagy [22].

Some compounds, primarily exogenous compounds, including polyphenols [23], flavonoids [24], terpenoids [25], or noncoding RNAs [26] have been reported to be Nrf2 activators or inducers. These compounds may have key roles in protecting ocular cells from oxidative stress, inflammation, and fibrosis [27,28]. The participation in the mechanism and antioxidative capacity of Nrf2 occurs in several systemic diseases, including respiratory disease [29], cardiovascular, and cerebrovascular disease [30], degenerative disease, tumors [31], and ocular disease.

This review aims to focus on the specific role and potential mechanism of Nrf2-mediated defense in glaucoma, including the prevention of oxidation and fibrosis in glaucoma. Publications have been reviewed from the past 20 years, between 1999 and 2019, with a focus on the potential mechanisms of Nrf2 in the occurrence and development of glaucoma and the prognosis following surgical treatment. Also, several factors that induce the expression of Nrf2 in trabecular meshwork cells, retinal ganglion cells, and Tenon's capsule fibroblasts are discussed.

Oxidative Stress, Glaucoma, Trabecular Meshwork Cells, and Nrf2

The trabecular meshwork is an avascular, complex connective tissue component that can effectively regulate the outflow of aqueous humor [32]. The sources of trabecular meshwork oxidative stress include ultraviolet (UV)-based byproducts of the anterior chamber, excess ROS accumulation [33], and the imbalance between oxidants and antioxidants [6,34]. Studies have shown that in patients with POAG, the trabecular meshwork is exposed to ROS in aqueous humor, which suggests that ROS may have a causative role in glaucoma at the level of trabecular meshwork cells [35,36]. As one of the most sensitive ocular cells, the trabecular meshwork cell is a primary cell type that occupies and forms the proximal portion of the aqueous humor outflow pathway. Trabecular meshwork cells under oxidative stress show changes that are typical for POAG. These changes include the accumulation of extracellular matrix (ECM), cell apoptosis, cell necrosis, changes in the structure and function of the cytoplasm and lysosomes [37], and disruption of the cytoskeletal disruption [38]. These changes may be significantly reduced using prostaglandin analogs [39], antioxidants, beta-blockers [40], or the local use of carbonic anhydrase inhibitors [41,42].

The reduction of total reactive antioxidant capacity in patients with POAG is reduced by 60–70%, which indicates that these patients might be more susceptible to damage from oxidative stress [6,43]. In 2017, Cheng et al. found that compared with normal human trabecular meshwork cells, Nrf2 expression was down-regulated in glaucomatous trabecular meshwork cells,

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

and in both cell types, the overexpression of Nrf2 promoted cell viability and reduced cell apoptosis [44]. Also, in 2016, Wang et al. showed that microRNA- 93 (miRNA-93) inhibited the cell viability and induced apoptosis of the glaucomatous trabecular meshwork cells via the suppression of Nrf2 [45]. These findings support the role of Nrf2 in protecting trabecular meshwork cells from oxidative stress.

Oxidative Stress, Glaucoma, Retinal Ganglion Cells, and Nrf2

Retinal ganglion cells are specialized neurons that receive visual information from photoreceptor cells [46]. Retinal ganglion cells transmit visual information to the brain in the form of retinal action potentials [9]. In many ocular diseases, including glaucoma, age-related macular degeneration, and diabetic retinopathy, oxidative stress results in cell death of retinal ganglion cells [9,27].

The potential mechanisms involved in cell death of retinal ganglion cells in glaucoma and disorders of optic nerve blood flow have been studied [47]. These mechanisms include excitatory glutamate toxicity [48], and injury due to the effects of nitric oxide [49]. Recently, studies have shown that vascular and mechanical processes that include pro-apoptotic factors can result from oxidative stress leading to oxidative mitochondrial dysfunction in retinal ganglion cells and apoptosis during acute glaucoma [50–52].

Based on the vascular theory of glaucoma, reactive oxygen species (ROS) are produced by ischemia. The mechanical theory of glaucoma proposes that ROS formation results from increased intraocular pressure (IOP) and inhibition of axons of retinal ganglion cells [53]. Chronic hypertensive glaucoma and retinal ischemia caused by a sudden increase in IOP stimulate the production of ROS and dysregulate essential autophagy [50]. With a chronic retinal injury or a sudden and severe increase in IOP, cell autophagy increases that result in retinal ganglion cell death in a relatively short time [50]. Also, in the retina of humans with ocular hypertension, several proteins are involved in redox homeostasis in cells, and oxidative stress responses are upregulated [54].

In 2015, Xu et al. reported that Nrf2 had a role in retinal neuroprotection from ischemia-reperfusion injury [55]. These investigators developed and studied an Nrf2 knockout mouse retinal ischemia-reperfusion model [55]. When compared with wild-type mice, the loss of neurons in the retinal ganglion cell layer in the Nrf2 knockout mice was increased, and the retinal ganglion cell activity of Nrf2 knockout mice was reduced, indicating that Nrf2 had an inherent protective effect on retinal ganglion cells [55]. In 1999, Lam et al. showed that, in a rat model, repeated mild retinal reperfusion resulted in chronic oxidative stress, especially in cell mitochondria [56]. Virus-mediated delivery of Nrf2 can effectively protect retinal ganglion cells from damage due to oxidative stress after acute nerve damage [57]. Therefore, pharmacologic and physiological induction of Nrf2 has potential as a new therapeutic strategy for retinal ischemia-reperfusion damage, and possibly for other retinal diseases, including glaucoma.

Fibrosis, Nrf2, and Tenon's Capsule Cells

Fibrosis is part of the healing process that follows inflammation in many diseases, including lung disease, liver fibrosis [58], systemic sclerosis [59], and diabetic renal fibrosis [60]. The mechanisms leading to fibrosis can involve stress responses involving the endoplasmic reticulum (ER) [61], oxidative stress [62], and inflammation [63]. Trabeculectomy, a traditional method of glaucoma filtration surgery, is regarded as one of the most effective strategies to achieve a sustained reduction in IOP in patients with glaucoma [64]. Glaucoma filtration surgery destroys the structure of the conjunctiva and subconjunctival tissue, activates the immune system, and results in the release of inflammatory cytokines [65]. Platelet activation and inflammatory cytokines activate downstream vascular endothelial growth factor-α(VEGF-α), transforming growth factor-β (TGF-β), and platelet-derived growth factor (PDGF) [65]. Inflammatory cytokines and growth factors induce cell proliferation, cell migration, the accumulation of extracellular matrix (ECM), and results in the contraction of collagen to promote scar formation, which results in impaired surgical outcomes in patients with glaucoma [66].

TGF-β1 causes cell apoptosis [67], the expression of genes associated with fibrosis, and myofibroblast differentiation following the production of ROS [68]. TGF-β1 also inhibits the glutathione antioxidant system [69]. The miRNA-29 family is closely associated with TGF-β-mediated fibrosis [70,71]. In patients with glaucoma, TGF-β2 was shown to stimulate fibroblast proliferation in Tenon's capsule by the suppression of miR-29b expression regulated by Nrf2 [72]. These findings indicate that Nrf2 may protect cells from the effects of TGFβ and fibrosis by upregulating miR-29b. Long noncoding RNA (lncRNA)-MEG3 upregulates the expression of Nrf2 and controls the proliferation of ECM [73]. These findings support that Nrf2 might be a potential therapeutic target to prevent fibroblast proliferation in Tenon's capsule after glaucoma filtration surgery.

Novel Strategies for Activating Nrf2: Noncoding RNAs

MicroRNAs (miRNAs) are small noncoding RNAs of between 19–25 nucleotides in length that regulate a wide range of

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 1. The regulatory roles of nuclear factor erythroid 2-related factor 2 (Nrf2), microRNAs (miRNAs), and long noncoding RNAs (lncRNAs).

miRNA	Cell type	Functions
miR-29b	Tenon's capsule fibroblasts	TGF-β2 stimulates fibroblast proliferation by suppression of miR-29b expression regulated by Nrf2 [89]
miR-93	Trabecular meshwork cells	Inhibits the viability and induces apoptosis of the trabecular meshwork cells by the inhibition of Nrf2 [43,45]
miR-141	Retinal ganglion cells	Reduces ultraviolet (UV) light-induced oxidative stress via the activation of Keap1-Nrf2 signaling [90,91]
lncRNA-MEG3	Tenon's capsule fibroblasts	TGF-β2 induces proliferation by binding MEG3 to Nrf2 [73,92]

Table 2. The regulatory role of nuclear factor erythroid 2-related factor 2 (Nrf2) and exogenous compounds on trabecular meshwork cells (TMCs) and retinal ganglion cells (RGCs).

Name	Target	Type of study	Functions
Quercetin	TMCs	Fruit, vegetables, and dietary sources, using conventional doses or nanodoses	Upregulates antioxidant peroxiredoxins through the Nrf2 pathway [93]
Lipoic acid	RGCs	A disulfide compound found both naturally in mitochondria or in pharmaceutical form	Induces HO-1 by promoting the translocation of Nrf2 to the cell nucleus [94–96]
Sulforaphane (SFN)	TMCs & RGCs	Broccoli sprouts, other cruciferous vegetables, or food supplements	reduces H2O2-induced oxidative stress via PI3K/Akt-mediated Nrf2 signaling activation [97,98]
CDDO-Im	661W cells	A synthetic triterpenoid compound	Inhibits ROS and increases neuronal cell survival after ischemia-reperfusion injury [55]
1R-iso Propyloxy genipin (IPRG001)	RGCs	A long-acting synthetic compound.	The protective action depends on NO induction and the Nrf2/HO-1 antioxidant response element pathway by S-nitrosylation [99].
Resveratrol	RGCs	Grapes, peanuts, red wine, cocoa, berries, or pharmaceutical form	Upregulates the expression of Nrf2, HO-1, and NQO1 [100,101]
L-carnitine (LC)	RGCs	Endogenous biosynthesis and dietary sources, or in pharmaceutical form	Increases levels of Nrf2, ho-1, and γ-GCS, and decreases expression of Keap1 protein [9]
SNJ-1945 – an exogenous calpain inhibitor	RGCs	In pharmaceutical form	Protects RGCs against OS induced by high glucose [102]
Monomethyl fumarate (MMF)	Ganglion cell layer	In pharmaceutical form.	Protects neuronal function via Nrf2 modulation [103].
Trimetazidine	RGCs	In pharmaceutical form	Confers protection against RGC apoptosis via Nrf2/Ho-1 signaling [104]
Hydrogen sulfide (H_2S) donor drugs	RGCs	In pharmaceutical form	Increases the levels of Nrf2, HO-1, and inhibits oxidative stress-induced cell death [105].
5α-and rost-3β, 5α, 6β-triol (TRIOL)	RGCs	A synthetic compound	Activates and upregulates Nrf2, HO-1, by negative regulation of Keap1 [106]

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 2 continued. The regulatory role of nuclear factor erythroid 2-related factor 2 (Nrf2) and exogenous compounds on trabecular meshwork cells (TMCs) and retinal ganglion cells (RGCs).

Name	Target	Type of study	Functions
Nipradilol	RGCs	In pharmaceutical form	Protects RGCs through S-nitrosylation of Keap1 and HO-1 induction [107].
Flavonoids	RGCs	Fruits, vegetables or food supplements	Induces Nrf2 and HO-1 [108].
Sulbutiamine	RGCs	Sulbutiamine (Arcalion 200®)	Stimulates catalase and increases Nrf2 and HO-1 levels [109]
L2H17, a chalcone analog	RGCs	A synthetic compound	L2H17 exhibits antioxidative effects by activating the Nrf2 pathway [110]
Chlorogenic acid	RGCs	In food or food supplements	Reduces oxidative injury through lncRNA-TUG1/Nrf2 [111]

TMCs – trabecular meshwork cells; RGCs – retinal ganglion cells; HO1 – heme oxygenase-1; ROS – reactive oxygen species; NO – nitric oxide.

processes by targeting genes [6]. Long noncoding RNAs (lncRNAs) are >200 nucleotides in length that regulate transcription (cis or trans), the organization of nuclear domains, and RNA or protein formation through several different mechanisms [6,74,75]. Recently, noncoding RNAs have become a focus of glaucoma research, as shown in Table.1. Noncoding RNAs provide a potential therapeutic approach for defense against oxidative stress and fibrosis in glaucoma.

Novel Strategies for Activating Nrf2: Exogenous Compounds

There are several compounds that have anti-inflammatory, antioxidant, and properties that prevent fibrosis by directly targeting the Nrf2 and Nrf2 inhibitors that include Keap1, Bach1, c-Myc, with the potential for preventing ocular disease [76–78]. There has been increasing interest in studies on the role of exogenous compounds to prevent oxidative stress. Compounds that include chalcones, flavonoids, and terpenoids can suppress Nrf2 ubiquitination and induce ARE-mediated antioxidative and cytoprotective enzymes [79]. These proteins react with the cysteine thiolate groups in Keap1, which are typical Nrf2 inducers [79]. Also, phenols and quinones, such as t-BHQ [80], polyphenolic flavonoids, including quercetin [81], stilbenoid, and nonflavonoid polyphenolics, including resveratrol [82] have been studied. Other compounds include sulforaphane (SFN), sphaeropsidin A (SA), CDDO-Im, long-acting (1R)-isopropyloxygenipin (IPRG001), omaveloxolone, astaxanthin [83], and lycopene [84], which also show activation of Nrf2 and upregulation of some downstream Nrf2 genes. Table 2 summarizes the studies on Nrf2 activators associated with glaucoma and neuroprotection.

The Negative Effects of Nrf2 in Glaucoma

Although Nrf2 has many protective effects in oxidative stress, studies have shown that Nrf2 can have harmful effects, including as a carcinogen, as cancer-associated mutations activate Nrf2 [85–87]. Also, when ROS exceeds the critical threshold, Nrf2 upregulates the expression of Klf9. However, Klf9 inhibits Trx reductase expression, amplifying the ROS cascade, which ultimately leads to cell death [88]. Therefore, it is important to consider the beneficial effects of Nrf2 as well as the harmful effects.

Conclusions

In the past 20 years, studies have shown that Nrf2 has a role in the occurrence and development of glaucoma and the prognosis following surgical treatment. Also, several factors that induce the expression of Nrf2 in trabecular meshwork cells, retinal ganglion cells, and human Tenon's capsule fibroblasts. Nrf2 plays a specific role in the occurrence and development of glaucoma. Oxidative stress accounts for some of the main mechanisms of trabecular meshwork cell injury, apoptosis, aqueous humor outflow disorders, and the loss of structure and function of retinal ganglion cells. Also, Nrf2 has a role in preventing fibrosis after glaucoma filtration surgery. Therefore, Nrf2 might be a potential therapeutic target to protect ocular cells from oxidative stress.

Conflict of interest

None.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

References:

1. Aslan M, Dogan S, Kucuksayan E: Oxidative stress and potential applications of free radical scavengers in glaucoma. Redox Rep, 2013; 18(2): 76–87
2. Tanito M, Kaidzu S, Takai Y, Ohira A: Association between systemic oxidative stress and visual field damage in open-angle glaucoma. Sci Rep, 2016; 6: 25792
3. Sacca SC, Izzotti A: Oxidative stress and glaucoma: Injury in the anterior segment of the eye. Prog Brain Res, 2008; 173: 385–407
4. Christman LM, Dean LL, Allen JC et al: Peanut skin phenolic extract attenuates hyperglycemic responses *in vivo* and *in vitro*. PLoS One, 2019; 14(3): e0214591
5. Zhang Z, Ma JM, Wang NL: [Is glaucoma a mitochondrial neurodegenerative disease.] Zhonghua Yan Ke Za Zhi, 2016; 52(9): 714–17 [in Chinese]
6. Wang M, Zheng Y: Oxidative stress and antioxidants in the trabecular meshwork. Peer J, 2019; 7: e8121
7. Cejka C, Cejkova J: Oxidative stress to the cornea, changes in corneal optical properties, and advances in treatment of corneal oxidative injuries. Oxid Med Cell Longev, 2015; 2015: 591530
8. Babizhayev MA, Yegorov YE: Reactive oxygen species and the aging eye: Specific role of metabolically active mitochondria in maintaining lens function and in the initiation of the oxidation-induced maturity onset cataract – a novel platform of mitochondria-targeted antioxidants with broad therapeutic potential for redox regulation and detoxification of oxidants in eye diseases. Am J Ther, 2016; 23(1): e98–117
9. Cao Y, Li X, Wang CJ et al: Role of NF-E2-related factor 2 in neuroprotective effect of l-carnitine against high glucose-induced oxidative stress in the retinal ganglion cells. Biomed Pharmacother, 2015; 69: 345–48
10. Kimura A, Namekata K, Guo X et al: Targeting oxidative stress for treatment of glaucoma and optic neuritis. Oxid Med Cell Longev, 2017; 2017: 2817252
11. Grant MW: Experimental aqueous perfusion in enucleated human eyes. Arch Ophthalmol, 1963; 69(69): 783–801
12. Chrysostomou V, Rezania F, Trounce IA, Crowston JG: Oxidative stress and mitochondrial dysfunction in glaucoma. Curr Opin Pharmacol, 2013; 13(1): 12–15
13. Wild AC, Moinova HR, Mulcahy RT: Regulation of gamma-glutamylcysteine synthetase subunit gene expression by the transcription factor Nrf2. J Biol Chem, 1999; 274(47): 33627–36
14. Cao Z, Zhu H, Zhang L et al: Antioxidants and phase 2 enzymes in cardiomyocytes: Chemical inducibility and chemoprotection against oxidant and simulated ischemia-reperfusion injury. Exp Biol Med (Maywood), 2006; 231(8): 1353–64
15. Ahmed SM, Luo L, Namani A et al: Nrf2 signaling pathway: Pivotal roles in inflammation. Biochim Biophys Acta Mol Basis Dis, 2017; 1863(2): 585–97
16. Hybertson BM, Gao B, Bose SK, McCord JM: Oxidative stress in health and disease: The therapeutic potential of Nrf2 activation. Mol Aspects Med, 2011; 32(4–6): 234–46
17. Kurutas EB: The importance of antioxidants which play the role in cellular response against oxidative/nitrosative stress: Current state. Nutr J, 2016; 15(1): 71
18. Liu XF, Zhou DD, Xie TvThe Nrf2 signaling in retinal ganglion cells under oxidative stress in ocular neurodegenerative diseases. Int J Biol Sci, 2018; 14(9): 1090–98
19. Zhang H, Davies KJA, Forman HJ: Oxidative stress response and Nrf2 signaling in aging. Free Radic Biol Med, 2015; 88(Pt B): 314–36
20. Suzuki T, Yamamoto M: Molecular basis of the Keap1-Nrf2 system. Free Radic Biol Med, 2015; 88(Pt B): 93–100
21. Ruiz S, Pergola PE, Zager RA, Vaziri ND: Targeting the transcription factor Nrf2 to ameliorate oxidative stress and inflammation in chronic kidney disease. Kidney Int, 2013; 83(6): 1029–41
22. Reinisalo M, Karlund A, Koskela A et al: Polyphenol stilbenes: Molecular mechanisms of defence against oxidative stress and aging-related diseases. Oxid Med Cell Longev, 2015; 2015: 340520
23. Pawlowska E, Szczepanska J, Koskela A et al: Dietary polyphenols in age-related macular degeneration: Protection against oxidative stress and beyond. Oxid Med Cell Longev, 2019; 2019: 9682318
24. Pallauf K, Duckstein N, Hasler M et al: Flavonoids as putative inducers of the transcription factors Nrf2, FoxO, and PPARgamma. Oxid Med Cell Longev, 2017; 2017: 4397340
25. Liby K, Hock T, Yore MM et al: The synthetic triterpenoids, CDDO and CDDO-imidazolide, are potent inducers of heme oxygenase-1 and Nrf2/ARE signaling. Cancer Res, 2005; 65(11): 4789–98
26. Silva-Palacios A, Ostolga-Chavarria M, Zazueta C, Konigsberg M: Nrf2: Molecular and epigenetic regulation during aging. Ageing Res Rev, 2018; 47: 31–40
27. Liu XF, Zhou DD, Xie T et al: The Nrf2 signaling in retinal ganglion cells under oxidative stress in ocular neurodegenerative diseases. Int J Biol Sci, 2018; 14(9): 1090–98
28. Hyttinen JMT, Kannan R, Felszeghy S et al: The regulation of NFE2L2 (NRF2) signalling and epithelial-to-mesenchymal transition in age-related macular degeneration pathology. Int J Mol Sci, 2019; 20(22): pii: E5800
29. Tu W, Wang H, Li S et al: The anti-inflammatory and anti-oxidant mechanisms of the Keap1/Nrf2/ARE signaling pathway in chronic diseases. Aging Dis, 2019; 10(3): 637–51
30. Chen QM, Maltagliati AJ: Nrf2 at the heart of oxidative stress and cardiac protection. Physiol Genomics, 2018; 50(2): 77–97
31. Geismann C, Arlt A, Sebens S, Schafer H: Cytoprotection "gone astray": Nrf2 and its role in cancer. Onco Targets Ther, 2014; 7: 1497–518
32. Stamer WD, Clark AF: The many faces of the trabecular meshwork cell. Exp Eye Res, 2017; 158: 112–23
33. Stamer WD, Clark AF: The many faces of the trabecular meshwork cell. Exp Eye Res, 2017; 158: 112–23
34. Aydin Yaz Y, Yildirim N et al: Role of oxidative stress in pseudoexfoliation syndrome and pseudoexfoliation glaucoma. Turk J Ophthalmol, 2019; 49(2): 61–67
35. Zhao J, Du X, Wang M et al: Salidroside mitigates hydrogen peroxide-induced injury by enhancement of microRNA-27a in human trabecular meshwork cells. Artif Cells Nanomed Biotechnol, 2019; 47(1): 1758–65
36. Lin C, Wu X: Curcumin protects trabecular meshwork cells from oxidative stress. Invest Ophthalmol Vis Sci, 2016; 57(10): 4327–32
37. Gabelt BT, Kaufman PL: Changes in aqueous humor dynamics with age and glaucoma. Prog Retin Eye Res, 2005; 24(5): 612–37
38. Babizhayev MA, Yegorov YE: Senescent phenotype of trabecular meshwork cells displays biomarkers in primary open-angle glaucoma. Curr Mol Med, 2011; 11(7): 528–52
39. Kim EJ, Kwon KJ, Park JY et al: Neuroprotective effects of prostaglandin E2 or cAMP against microglial and neuronal free radical mediated toxicity associated with inflammation. J Neurosci Res, 2002; 70(1): 97–107
40. Miyamoto N, Izumi H, Miyamoto R et al: Nipradilol and timolol induce Foxo3a and peroxiredoxin 2 expression and protect trabecular meshwork cells from oxidative stress. Invest Ophthalmol Vis Sci, 2009; 50(6): 2777–84
41. Welge-Lussen U, Birke K: [Oxidative stress in the trabecular meshwork of POAG]. Klin Monbl Augenheilkd, 2010; 227(2): 99–107 [in German]
42. Zanon-Moreno V, Garcia-Medina JJ, Gallego-Pinazo R et al: Antioxidant status modifications by topical administration of dorzolamide in primary open-angle glaucoma. Eur J Ophthalmol, 2009; 19(4): 565–71
43. Ferreira SM, Lerner SF, Brunzini R et al: Oxidative stress markers in aqueous humor of glaucoma patients. Am J Ophthalmol, 2004; 137(1): 62–69
44. Cheng J, Liang J, Qi J: Role of nuclear factor (erythroid-derived 2)-like 2 in the age-resistant properties of the glaucoma trabecular meshwork. Exp Ther Med, 2017; 14(1): 791–96
45. Wang Y, Li F, Wang S: MicroRNA93 is overexpressed and induces apoptosis in glaucoma trabecular meshwork cells. Mol Med Rep, 2016; 14(6): 5746–50
46. Sanes JR, Masland RH: The types of retinal ganglion cells: Current status and implications for neuronal classification. Ann Rev Neurosci, 2015; 38(1): 221
47. Aoki Y, Sato H, Nishimura N et al: Accelerated DNA adduct formation in the lung of the Nrf2 knockout mouse exposed to diesel exhaust. Toxicol Appl Pharmacol, 2001; 173(3): 154–60
48. Sullivan RKP, Elizabeth W, Lauren M et al: Evoked expression of the glutamate transporter GLT-1c in retinal ganglion cells in human glaucoma and in a rat model. Invest Ophthalmol Vis Sci, 2006; 47(9): 3853
49. Neufeld AH, Sawada A, Becker B: Inhibition of nitric oxide synthase 2 by aminoguanidine provides neuroprotection of retinal ganglion cells in a rat model of chronic glaucoma. Proc Natl Acad Sci USA, 1999; 96(17): 9944–48

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

50. Nita M, Grzybowski A: The role of the reactive oxygen species and oxidative stress in the pathomechanism of the age-related ocular diseases and other pathologies of the anterior and posterior eye segments in adults. Oxid Med Cell Longev, 2016; 2016(12): 3164734
51. Osborne NN, Casson RJ, Wood JP et al: Retinal ischemia: Mechanisms of damage and potential therapeutic strategies. Prog Retin Eye Res, 2004; 23(1): 91–147
52. Gupta VK, You Y, Li JC et al: Protective effects of 7,8-dihydroxyflavone on retinal ganglion and RGC-5 cells against excitotoxic and oxidative stress. J Mol Neurosci, 2013; 49(1): 96–104
53. McMonnies C: Reactive oxygen species, oxidative stress, glaucoma and hyperbaric oxygen therapy. J Optom, 2018; 11(1): 3–9
54. Yang X, Hondur G, Li M et al: Proteomics analysis of molecular risk factors in the ocular hypertensive human retina. Invest Ophthalmol Vis Sci, 2015; 56(10): 5816–30
55. Xu Z, Cho H, Hartsock MJ et al: Neuroprotective role of Nrf2 for retinal ganglion cells in ischemia-reperfusion. J Neurochem, 2015; 133(2): 233–41
56. Lam TT, Abler AS, Tso MO: Apoptosis and caspases after ischemia-reperfusion injury in rat retina. Invest Ophthalmol Vis Sci, 1999; 40(5): 967–75
57. Wenjun X, Garfinkel MC, Yiqing L et al: NRF2 promotes neuronal survival in neurodegeneration and acute nerve damage. J Clin Invest, 2015; 125(4): 1433–45
58. Sharma RS, Harrison DJ, Kisielewski D et al: Experimental nonalcoholic steatohepatitis and liver fibrosis areameliorated by pharmacologic activation of Nrf2 (NF-E2-related factor 2). Cell Mol Gastroenterol Hepatol, 2017; 5(3): 367–98
59. Kavian N, Mehlal S, Jeljeli M et al: The Nrf2-antioxidant response element signaling pathway controls fibrosis and autoimmunity in scleroderma. Front Immunol, 2018; 9: 1896
60. Zhang L, Chen Z, Gong W et al: Paeonol ameliorates diabetic renal fibrosis through promoting the activation of the Nrf2/ARE pathway via upregulating Sirt1. Front Pharmacol, 2018; 9: 512
61. Burman A, Tanjore H, Blackwell TS: Endoplasmic reticulum stress in pulmonary fibrosis. Matrix Biol, 2018; 68–69: 355–65
62. Su H, Wan C, Song A et al: Oxidative stress and renal fibrosis: mechanisms and therapies. Adv Exp Med Biol, 2019; 1165: 585–604
63. Mack M: Inflammation and fibrosis. Matrix Biol, 2018; 68–69: 106–21
64. Schlunck G, Meyer-ter-Vehn T, Klink T, Grehn F: Conjunctival fibrosis following filtering glaucoma surgery. Exp Eye Res, 2016; 142: 76–82
65. Eren K, Turgut B, Akin MM, Demir T: The suppression of wound healing response with sirolimus and sunitinib following experimental trabeculectomy in a rabbit model. Current Eye Res, 2015; 41(3): 367
66. Yang L, Kazuhiro K, Tomoko O et al: Inhibition by all-trans-retinoic acid of transforming growth factor-β-induced collagen gel contraction mediated by human tenon fibroblasts. Invest Ophthalmol Vis Sci, 2014; 55(7): 4199–205
67. Albright CD, Salganik RI, Craciunescu CN et al: Mitochondrial and microsomal derived reactive oxygen species mediate apoptosis induced by transforming growth factor-beta1 in immortalized rat hepatocytes. J Cell Biochem, 2003; 89(2): 254–61
68. Bracey NA, Benjamin G, Justin C et al: Mitochondrial NLRP3 protein induces reactive oxygen species to promote Smad protein signaling and fibrosis independent from the inflammasome. J Biol Chem, 2014; 289(28): 19571–84
69. Rui-Ming L, Desai LP: Reciprocal regulation of TGF-β and reactive oxygen species: A perverse cycle for fibrosis. Redox Biol, 2015; 6: 565–77
70. Roderburg C, Urban GW, Bettermann K et al: Micro-RNA profiling reveals a role for miR-29 in human and murine liver fibrosis. Hepatology, 2011; 53(1): 209–18
71. Cushing L, Kuang PP, Qian J et al: miR-29 is a major regulator of genes associated with pulmonary fibrosis. Am J Respir Cell Mol Biol, 2011; 45(2): 287–94
72. Ran W, Zhu D, Feng Q: TGF-β2 stimulates Tenon's capsule fibroblast proliferation in patients with glaucoma via suppression of miR-29b expression regulated by Nrf2. Int J Clin Exp Pathol, 2015; 8(5): 4799
73. Wang Y, Wang J, Wei LJ et al: Biological function and mechanism of lncRNA-MEG3 in Tenon's capsule fibroblasts proliferation: By MEG3-Nrf2 protein interaction. Biomed Pharmacother, 2017; 87: 548–54
74. Wawrzyniak O, Zarebska Z, Rolle K, Gotz-Wieckowska A: Circular and long noncoding RNAs and their role in ophthalmologic diseases. Acta Biochim Pol, 2018; 65(4): 497–508
75. Ulitsky I, Bartel D: lincRNAs: Genomics, evolution, and mechanisms. Cell, 2013; 154(1): 26–46
76. Itoh K, Wakabayashi N, Katoh Y et al: Keap1 represses nuclear activation of antioxidant responsive elements by Nrf2 through binding to the amino-terminal Neh2 domain. Genes Dev, 1999; 13(1): 76–86
77. Ying S, Lambrecht RW, Donohue SE, Bonkovsky HL: Role of Bach1 and Nrf2 in upregulation of the heme oxygenase-1 gene by cobalt protoporphyrin. FASEB J, 2006; 20(14): 2651–53
78. Levy S, Forman HJ: C-Myc is a Nrf2-interacting protein that negatively regulates phase II genes through their electrophile responsive elements. IUBMB Life, 2010; 62(3): 237–46
79. Sadagopan M, Yu C, Longqin H: Small molecule modulators of Keap1-Nrf2-ARE pathway as potential preventive and therapeutic agents. Med Res Rev, 2012; 32(4): 687–726
80. Prochaska HJ, Bregman HS, Long MJD, Talalay P" Specificity of induction of cancer protective enzymes by analogues of tert-butyl-4-hydroxyanisole (BHA). Biochem Pharmacol, 1985; 34(21): 3909–14
81. Tanigawa S, Fujii M, Hou DX: Action of Nrf2 and Keap1 in ARE-mediated expression by quercetin. Free Radic Biol Med, 2007; 42(11): 1690–703
82. Kode A, Rajendrasozhan S, Caito S et al: Resveratrol induces glutathione synthesis by activation of Nrf2 and protects against cigarette smoke-mediated oxidative stress in human lung epithelial cells. Am J Physiol Lung Cell Mol Physiol, 2008; 294(3): L478–88
83. Kim JH, Nam SW, Kim BW et al: Astaxanthin improves stem cell potency via an increase in the proliferation of neural progenitor cells. Int J Mol Sci, 2010; 11(12): 5109–19
84. Lei X, Lei L, Zhang Z, Cheng Y: Neuroprotective effects of lycopene pretreatment on transient global cerebral ischemiareperfusion in rats: The role of the Nrf2/HO1 signaling pathway. Mol Med Rep, 2016; 13(1): 412–18
85. Nioi P, Nguyen T: A mutation of Keap1 found in breast cancer impairs its ability to repress Nrf2 activity. Biochem Biophys Res Commun, 2007; 362(4): 816–21
86. Shibata T, Ohta T, Tong KI et al: Cancer related mutations in NRF2 impair its recognition by Keap1-Cul3 E3 ligase and promote malignancy. Proc Natl Acad Sci USA, 2008; 105(36): 13568–73
87. Solis LM, Carmen B, Wenli D et al: Nrf2 and Keap1 abnormalities in non-small cell lung carcinoma and association with clinicopathologic features. Clin Cancer Res, 2010; 16(14): 3743
88. Zucker SN, Fink EE, Bagati A et al: Nrf2 amplifies oxidative stress via induction of Klf9. Mol Cell, 2014; 53(6): 916–28
89. Ran W, Zhu D, Feng Q: TGF-beta2 stimulates Tenon's capsule fibroblast proliferation in patients with glaucoma via suppression of miR-29b expression regulated by Nrf2. Int J Clin Exp Pathol, 2015; 8(5): 4799–806
90. Cheng LB, Li K-r, Yi N et al: miRNA-141 attenuates UV-induced oxidative stress via activating Keap1-Nrf2 signaling in human retinal pigment epithelium cells and retinal ganglion cells. Oncotarget, 2017; 8(8): 13186
91. Cheng LB, Li KR, Yi N et al: miRNA-141 attenuates UV-induced oxidative stress via activating Keap1-Nrf2 signaling in human retinal pigment epithelium cells and retinal ganglion cells. Oncotarget, 2017; 8(8): 13186–94
92. Wang Y, Wang J, Wei LJ et al: Biological function and mechanism of lncRNA-MEG3 in Tenon's capsule fibroblasts proliferation: By MEG3-Nrf2 protein interaction. Biomed Pharmacother, 2017; 87: 548–54
93. Miyamoto N, Izumi H, Miyamoto R et al: Quercetin induces the expression of peroxiredoxins 3 and 5 via the Nrf2/NRF1 transcription pathway. Invest Ophthalmol Vis Sci, 2011; 52(2): 1055–63
94. Koriyama Y, Nakayama Y, Matsugo S, Kato S: Protective effect of lipoic acid against oxidative stress is mediated by Keap1/Nrf2-dependent heme oxygenase-1 induction in the RGC-5 cell line. Brain Res, 2013; 1499(4): 145–57
95. Inman DM, Lambert WS, Calkins DJ, Horner PJ: α-Lipoic acid antioxidant treatment limits glaucoma-related retinal ganglion cell death and dysfunction. PLoS One, 2013; 8(6): e65389
96. Chen B, Lu Y, Chen Y, Cheng J: The role of Nrf2 in oxidative stress-induced endothelial injuries J Endocrinol, 2015; 225(3): R83–99
97. Liu Y, Liu P, Wang Q et al: Sulforaphane attenuates H_2O_2-induced oxidant stress in human trabecular meshwork cells (HTMCs) via the phosphatidylinositol 3-kinase (PI3K)/serine/threonine kinase (Akt)-mediated factor-E2-related factor 2 (Nrf2) signaling activation. Med Sci Monit, 2019; 25: 811–18
98. Pan H, He M, Liu R et al: Sulforaphane protects rodent retinas against ischemia-reperfusion injury through the activation of the Nrf2/HO-1 antioxidant pathway. PLoS One, 2014; 9(12): e114186

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

99. Koriyama Y, Chiba K, Yamazaki M et al: Long-acting genipin derivative protects retinal ganglion cells from oxidative stress models *in vitro* and *in vivo* through the Nrf2/antioxidant response element signaling pathway. J Neurochem, 2010; 115(1): 79–91
100. Shen C, Cheng W, Yu P et al: Resveratrol pretreatment attenuates injury and promotes proliferation of neural stem cells following oxygen-glucose deprivation/reoxygenation by upregulating the expression of Nrf2, HO-1 and NQO1 *in vitro*. Mol Med Rep, 2016; 14(4): 3646–54
101. Wang G, Song X, Zhao L et al: Resveratrol prevents diabetic cardiomyopathy by increasing Nrf2 expression and transcriptional activity. BioMed Res Int, 2018; 2018(107): 2150218
102. Shanab AY, Nakazawa T, Ryu M et al: Metabolic stress response implicated in diabetic retinopathy: The role of calpain, and the therapeutic impact of calpain inhibitor. Neurobiol Dis, 2012; 48(3): 556–67
103. Cho H, Hartsock MJ, Xu Z et al: Monomethyl fumarate promotes Nrf2-dependent neuroprotection in retinal ischemia-reperfusion. J Neuroinflammation, 2015; 12(1): 239
104. Wan P, Su W, Zhang Y et al: Trimetazidine protects retinal ganglion cells from acute glaucoma via the Nrf2/Ho-1 pathway. Clin Sci (Lond), 2017; 131(18): 2363–75
105. Majid AS, Majid AM, Yin ZQ, Ji D: Slow regulated release of H2S inhibits oxidative stress induced cell death by influencing certain key signaling molecules. Neurochem Res, 2013; 38(7): 1375–93
106. Sheng L, Lu B, Chen H et al: Marine-steroid derivative 5alpha-Androst-3beta, 5alpha, 6beta-triol protects retinal ganglion cells from ischemia-reperfusion injury by activating Nrf2 pathway. Mar Drugs, 2019; 17(5): pii: E267
107. Koriyama Y, Kamiya M, Takadera T et al: Protective action of nipradilol mediated through S-nitrosylation of Keap1 and HO-1 induction in retinal ganglion cells. Neurochem Int, 2012; 61(7): 1242–53
108. Maher P, Hanneken A: Flavonoids protect retinal ganglion cells from oxidative stress-induced death. Invest Ophthalmol Vis Sci, 2005; 46(12): 4796–803
109. Majid AS, Yin ZQ, Ji D: Sulphur antioxidants inhibit oxidative stress induced retinal ganglion cell death by scavenging reactive oxygen species but influence nuclear factor (erythroid-derived 2)-like 2 signalling pathway differently. Biol Pharm Bull, 2013; 36(7): 1095–110
110. Wang L, Chen HC, Yang X et al: The novel chalcone analog L2H17 protects retinal ganglion cells from oxidative stress-induced apoptosis. Neural Regen Res, 2018; 13(9): 1665–72
111. Gong W, Li J, Zhu G et al: Chlorogenic acid relieved oxidative stress injury in retinal ganglion cells through lncRNA-TUG1/Nrf2. Cell Cycle, 2019; 18(14): 1549–59

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]