Review Article

Role of reactive oxygen species and oxidative stress in the pathomechanism of glaucoma

Nicholas T. H. Chan [1] , Ushasree Pattamatta [1, 2] and Andrew White [1, 2, 3]

[1] *Faculty of Medicine and Health, University of Sydney, NSW, Australia*
[2] *Centre for Vision Research, Westmead Institute for Medical Research, NSW, Australia*
[3] *School of Optometry and Vision Science, University of New South Wales, NSW, Australia*

ABSTRACT

Background: Glaucoma is a major cause of vision impairment and blindness, characterized by damage to retinal ganglion cells (RGC) at the optic nerve head (ONH). The pathomechanism underlying glaucoma is heterogeneous and theories explaining the pathomechanism can be categorized as mechanical, vascular, or immunological. This mini-review explores the involvement of reactive oxygen species (ROS) and oxidative stress in these established mechanisms of glaucoma.

Methods: A review of literature was conducted using PubMed/MEDLINE, with the query including the following keywords: "antioxidants", "glaucoma", "glaucoma pathomechanism", "immunological", "intraocular pressure", "mechanical", "reactive oxygen species", "ocular hypertension", "oxidative stress", and "vascular". The date filter was set from January 2010 to September 2025. Papers that were relevant to ROS or oxidative stress in the glaucoma pathomechanism were thoroughly reviewed. Their reference lists were also reviewed for relevant papers of any date.

Results: Following a comprehensive literature search, 67 journal articles were selected for review. They revealed the role of ROS and oxidative stress in the mechanical, vascular, and immunological pathomechanism theories of glaucoma. In the mechanical theory, oxidative stress mediates RGC apoptosis and trabecular meshwork damage. In vascular processes, retinal ischemia causes oxidative stress and vice versa, thus causing RGC death and ONH damage. With the immunological theory, ROS is implicated in glial cell and inflammasome activity that causes RGC injury. Key players in the generation of oxidative stress include NADP oxidase 2, dynamin-related protein 1, mitofusin 2, nuclear factor (erythroid-derived 2)-like 2, and nitric oxide. Conversely, various antioxidant factors are also implicated in glaucoma, yet in oxidative stress conditions their effects are outweighed by those of ROS.

Conclusions: ROS and oxidative stress are important mediators in the glaucoma pathomechanism. They contribute to and unify the existing theories of mechanical, vascular, and immunological injury in glaucoma. Investigating specific oxidative stress players in the pathomechanism may reveal new therapeutic targets in the treatment of glaucoma.

KEYWORDS

antioxidants; glaucoma; ocular disease; ocular hypertension; optic nerve head; oxidative stress; reactive oxygen species; retinal ganglion cells

Correspondence: Nicholas T. H. Chan, Faculty of Medicine and Health, The University of Sydney, Camperdown, NSW 2050, Australia. Email: ncha0289@uni.sydney.edu.au, ORCID iD: https://orcid.org/0009-0004-3367-0083.

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INTRODUCTION

Glaucoma is a group of optic neuropathies that represent a leading cause of irreversible blindness worldwide. It was estimated that nearly 70 million individuals had glaucoma in 2020, with increasing prevalence yearly [1]. Every year, glaucoma leads to blindness in 3.61 million individuals and to the development of moderate-to-severe vision impairment in a further 4.14 million [2]. The defining feature of glaucoma is damage to retinal ganglion cells (RGC) at the optic nerve head (ONH) as the RGC traverse through pores in the lamina cribrosa. As neural tissue is lost, patients experience a loss of visual field of varying patterns. Elevated intraocular pressure (IOP), or ocular hypertension (OHT), is regarded as the main and only modifiable risk factor in glaucoma, thus the majority of current treatments are aimed at lowering IOP [3].

The pathomechanism underlying glaucoma is heterogeneous, incompletely characterized, and most likely attributable to multiple mechanisms. Prevailing theories can be broadly categorized into one of three groups: mechanical, vascular, and immunological. The mechanical theory of glaucoma pathogenesis is perhaps the most elaborated on, as it relates to the mechanical strain by OHT. Ahmad [4] divides mechanical damage into pre-laminar, laminar, and post-laminar. Pre-laminar damage includes RGC apoptosis and remodeling of pre-laminar tissue [5, 6]. Laminar damage involves changes to the collagen meshwork, extracellular matrix, astrocytes, and axonal transport [6–8]. Lastly, post-laminar damage refers to mechanical shear stress from fluid pressure gradients that cause axonal damage and optic disc cupping [7, 9]. Vascular mechanisms propose that retinal blood vessels inadequately perfuse RGC at the ONH, leading to ischemia and RGC death. Chan et al. [10] describe the main factors behind vascular pathogenesis as either impaired vessel autoregulation or vasospasm, resulting in constricted vessels with altered paths in the retina. The converse relationship has also been described, whereby glaucoma is the cause of vascular changes [11]. Both directions are likely implicated in the diverse glaucoma pathomechanism, considering that different studies demonstrate each relationship [12–15]. The immunological theory suggests that immune cells near the ONH, notably glial cells, cause RGC damage by mediating neuroinflammation [16–18]. It is even suggested that glaucoma is an autoimmune condition, given the potential involvement of autoimmune cells and autoantibodies in the disease process [19].

The role of reactive oxygen species (ROS) and oxidative stress in glaucoma is increasingly being investigated. In physiology, ROS are mainly produced by mitochondrial enzymes and NADPH oxidase (NOX) [20, 21]. The best-characterized ROS species are hydrogen peroxide (H_2O_2) and superoxide ($O2^{\bullet-}$), though numerous other radical and non-radical ROS have been identified [22]. Homeostasis is maintained when ROS are subsequently degraded by scavenger enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, or scavenger molecules including glutathione and vitamins [20, 21]. Zuo et al. [21] summarized the physiological roles of ROS in immune responses, synaptic plasticity, and cellular responses to stress. Elevated ROS levels can disrupt homeostasis, creating oxidative stress which is associated with disease-causing macromolecular damage [20, 21].

Unsurprisingly, ROS are also generated in the eye where oxidative stress is implicated in ocular pathologies like glaucoma. A multicenter study by Engin et al. [23] showed that glaucoma patients have elevated serum oxidative stress biomarkers. Nucci et al. [24] also measured elevated ROS and decreased antioxidant capacity in the aqueous humor of glaucoma patients. This mini review will explore specific mechanisms by which ROS and oxidative stress are associated with glaucoma. They complement the established theories of mechanical, vascular, and immunological damage, providing more details into their mechanisms. ROS and oxidative stress may also unify these mechanisms. Throughout, there is also new input on targeting ROS and oxidative stress, as this offers a new avenue into developing effective glaucoma therapies.

METHODS

A comprehensive review of literature related to ROS and oxidative stress in glaucoma was conducted. PubMed/MEDLINE was used, with the query including the following keywords: “antioxidants”, “glaucoma”, “glaucoma pathomechanism”, “immunological”, “intraocular pressure”, “mechanical”, “reactive oxygen species”, “ocular hypertension”, “oxidative stress”, “vascular”. The date filter was set for papers published between January 2010 and September 2025. Papers that explained the role of ROS or oxidative stress in the glaucoma pathomechanism were thoroughly analyzed. The reference lists of these studies were also examined, including studies of any date.

Table 1. Summary of primary studies on ROS and oxidative stress in glaucoma.

Author (Year)	Model	Key findings
Mechanical pathomechanism		
Jung et al. (2015) [5]	Human	Prelaminar tissue is thinner in primary OAG than NTG
Zhang et al. (2020) [6]	Human	Prelaminar shear moduli are higher in OHT
Piao et al. (2024) [25]	Mouse	*Drp1* knockout and inhibition reduces cardiac tissue damage following I/R injury by improving cardiac mitochondrial homeostasis [a]
Zeng et al. (2023) [26]	Mouse	Inhibiting the ERK1/2-Drp1-ROS pathway decreases PANoptosis in elevated IOP
Cheng et al. (2017) [27]	Human	*Nrf2* reduces apoptosis in TM cells
Xu et al. (2025) [28]	Human	Multiple hub genes are associated with oxidative stress in glaucomatous TM (*TNFRSF1A*, *CXCL1*, *CCL3*, *NFKBIA*, *VCAM1*, *LCN2*, and *HP*)
Zhang et al. (2022) [29]	Rat	Mdivi-1, a *Drp1* inhibitor, reduces mitochondrial fission in a diabetic retinopathy model [a]
Nivison et al. (2017) [30]	Mouse	With age, *Mfn2* levels decrease, and mitochondrial dysfunction increases
Vascular pathomechanism		
Mann et al. (2019) [12]	Rat	Vessels in the optic nerve have lower caliber and area in glaucoma
Mitchell et al. (2005) [13]	Human	Retinal arteriolar diameter is narrower in glaucoma
Tan et al. (2017) [14]	Rat	Total retinal blood flow and blood vessel size are lower when IOP is elevated
Zheng et al. (2010) [15]	Human	Low diastolic blood pressure, mean ocular perfusion pressure, and diastolic perfusion pressure are associated with OAG
Braunersreuther et al. (2013) [31]	Mouse	*NOX1* and *NOX2* contribute to I/R damage in myocardial infarction [a]
Liao et al. (2024) [32]	Mouse	Setanixib inhibits *NOX1* and *NOX4* expression, thus reducing I/R injury
McCann et al. (2014) [33]	Mouse	*NOX2* deletion delays but does not prevent neuronal loss in strokes [a]
Yokota et al. (2011) [34]	Mouse	*NOX2* and ROS increase in I/R injury
Chidlow et al. (2017) [35]	Rat	Reduced ONH blood flow in OHT upregulates *NOX2*
Karim et al. (2015) [36]	Mouse	*NOX2* modulates IR injury following kidney transplantation [a]
Gericke et al. (2019) [37]	Mouse	In elevated IOP, NOX2 levels increase but not hypoxic markers
Wang et al. (2022) [38]	Mouse	Oxidative stress causes endothelial dysfunction in OHT
Immunological pathomechanism		
Howell et al. (2012) [16]	Mouse	Endothelin-2, a monocyte-derived mediator, contributes to optic nerve damage under glaucomatous stress conditions.
Margeta et al. (2022) [18]	Mouse	APOE4 microglia are involved in RGC loss, independently of IOP
Shi et al. (2024) [39]	Mouse	*NOX2* mediates the activation of pro-inflammatory, M1-like microglia
Pronin et al. (2019) [40]	Mouse	NLRP1 and NLRP3 inflammasomes contribute directly to OHT injury
Feng et al. (2024) [41]	Rat	The NLRP3 inflammasome pathway contributes directly to TM injury
Munoz et al. (2020) [42]	Mouse	P2X7 receptor activation activates ROS production, possibly involving NOX enzymes, in spinal astrocytes[a]
Krishnan et al. (2019) [43]	Mouse	ONL1204, a Fas receptor inhibitor, reduces RGC death in OHT
Kumar et al. (2016) [44]	Mouse	*NOX2* increases markers of M1-like microglial activity
Jung et al. (2025) [45]	Mouse	The NLRP3 inflammasome mediates neuroinflammation [a]
Martin & Harry (2022) [46]	Mouse	Inflammasomes are found in microglia [a]
Park et al. (2020) [47]	Rat	FM101, an A3 adenosine receptor modulator used against glaucomatous inflammation, is safe

Note: [a] These studies were not conducted using glaucoma models, yet are mechanistically related to oxidative stress pathways that are described in glaucoma. They were therefore included as they reveal plausible oxidative stress mechanisms of pathology or treatment in glaucoma too. Abbreviations: APOE4, apolipoprotein E4; Drp1, dynamin-related protein 1; IOP, intraocular pressure; I/R, ischemia-reperfusion; Mfn2, mitofusin 2; NLRP, NOD-like receptor family, pyrin domain-containing protein; NOX, NADPH oxidase; Nrf2, nuclear factor (erythroid-derived 2)-like 2; NTG, normal tension glaucoma; OAG, primary open-angle glaucoma; OHT, ocular hypertension; ONH, optic nerve head; RGC, retinal ganglion cell; ROS, reactive oxygen species; TM, trabecular meshwork.

RESULTS

Following a comprehensive search for literature related to ROS, oxidative stress, and glaucoma, 67 relevant articles were analyzed in-depth for this review. These articles explained the roles of ROS and oxidative stress in relation the mechanical, vascular, and immunological theories of the glaucoma pathomechanism, or were related to other relevant disease models. Of these articles, 31 reported on primary studies related to the pathomechanism and are summarized in Table 1 [5, 6, 12–16, 18, 25–47]. Several papers also examined the potential to target these elements of the pathomechanism using antioxidant drugs [8, 11, 17–20, 25–28, 31–33, 39–43, 48–54].

DISCUSSION

Glaucoma has a heterogeneous pathomechanism. It is thus most likely for numerous changes in the eye to result in the RGC damage that characterizes glaucoma. Broadly, the theories explaining glaucoma are categorized as either mechanical, vascular, or immunological, with ROS and oxidative stress being increasingly understood as contributors to these mechanisms [4, 10, 17]. These roles are summarized in Figure 1 according to studies that are discussed in this review.

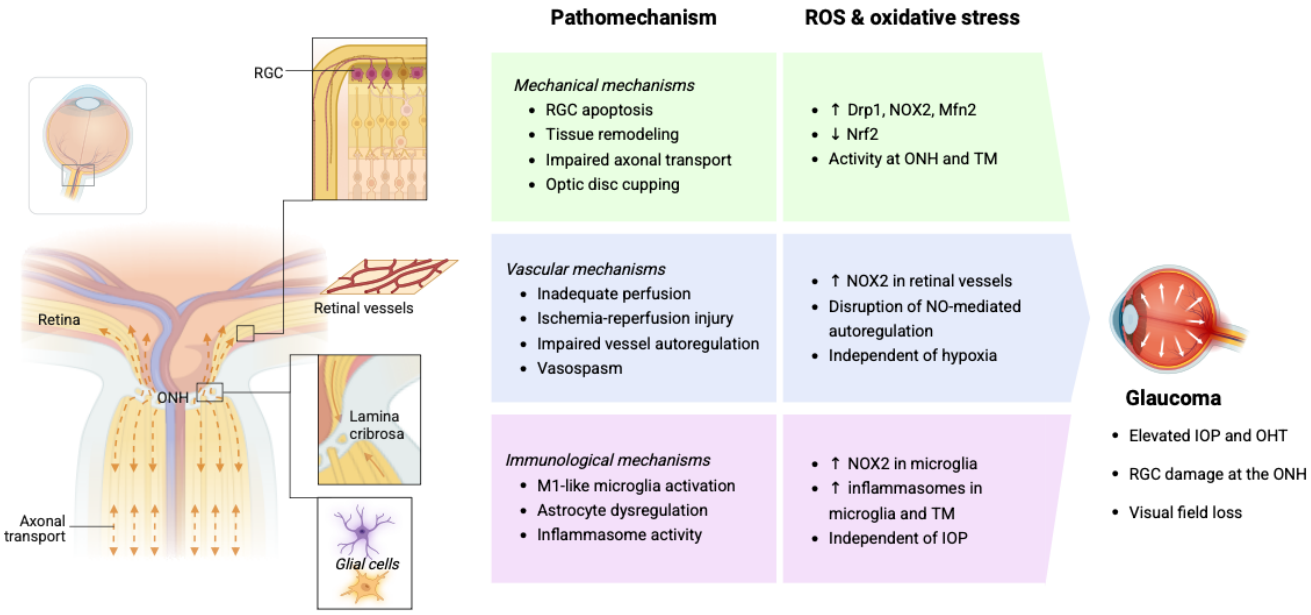

Figure 1. The involvement of ROS and oxidative stress in the pathomechanism of glaucoma. They are implicated in the mechanical, vascular, and immunological mechanism theories of glaucoma that are described in this review. The mechanical mechanisms involve Drp1 [25, 26, 29], NOX2 [20, 30], Mfn2 [20, 30], and Nrf2 [27, 28, 55]. The vascular mechanisms also involve NOX2 [20, 31–37], along with NO [11, 50]. The immunological mechanisms involve *NOX2* [8, 39, 56] and inflammasomes [40, 41, 45, 46, 57]. Created in BioRender. Chan, N. (2025) https://BioRender.com/i3gzc5q.

Mechanical pathomechanism

The mechanical theory explains the pathomechanism of glaucoma in relation to posterior pressure on the ONH that deforms the lamina cribrosa. This compresses RGC axons that pass through it, limiting axoplasmic flow and resulting in RGC apoptosis. With prolonged injury to the axons, there is cupping of the optic disc accompanied by visual field loss [4].

Oxidative stress mediates RGC apoptosis: IOP is said to induce RGC apoptosis. This is understood to result from the impaired transport of cellular components from the RGC cell body where they are produced to distal regions along the RGC axon. Importantly, mitochondria and metabolic substrates are inadequately delivered to the distal regions [7]. With fewer mitochondria and fewer metabolic substrates for energy production, there is metabolic stress and mitochondrial dysfunction. Dynamin-related protein 1 (Drp1) has been particularly studied in this pathomechanism as it is upregulated in elevated IOP, causing mitochondrial fission and increased ROS production [26]. The oxidative stress then triggers RGC death through PANoptosis—a term that amalgamates pyroptosis, apoptosis, and necroptosis [26]. Conversely, understanding the role of Drp1 has led to studies on its inhibition in non-glaucoma models. The use of Mdivi-1 to inhibit Drp1 was shown to restore mitochondrial integrity and homeostatic function in both *in vitro* and *in vivo* models of diabetic retinopathy. Following the injection of Mdivi-1 (150 ng) into the limbus of 80 male Sprague-Dawley rats, Western Blot and immunohistochemistry analyses showed reduced mitochondrial fission. Correspondingly, clinical measures of diabetic retinopathy improved [29]. Piao et al. also identified Drp1 as an important protein in oxidative stress following ischemia-reperfusion injury in cardiac tissue, along with the protective effect of a Drp1 inhibitor, Drpitor1a [25]. This reveals the potential relevance of Drp1 in oxidative stress damage and potential treatment through Drp1 inhibition across different tissue types. In the context of glaucoma, this highlights the importance of the Drp1-ROS-mediated pathomechanism as a potential target for glaucoma therapy too. Drp1 is implicated in oxidative stress injury in glaucoma [26], diabetic retinopathy [29], and cardiac ischemia [25]. Since Drp1 inhibitors have positive outcomes in the latter two conditions [25, 29], it is plausible that targeting Drp1 in glaucoma will also be efficacious.

Other proteins of relevance to ROS pathways have been identified in relation to IOP and axonal transport, including NADPH oxidase 2 (NOX2) and mitofusin 2 (Mfn2) [20, 30]. NOX2 produces ROS that then disrupt axonal transport [20]. Similarly to Mfn2, its loss of function in RGC axons is associated with the glaucoma pathomechanism. This is because the protein is associated with mitochondrial transport along the axons, while impairment of axonal transport is pathological [30]. Though Nivison et al. [30] primarily attributed decreased Mfn2 and mitochondrial dysfunction to age, they noted that the DBA mouse model used in the study spontaneously developed OHT as they aged. All considered, there are various

sources of oxidative stress that may contribute to IOP-mediated RGC damage in the glaucoma pathomechanism, including Drp1, NOX2, and Mfn2 [20, 26, 30].

Oxidative stress damages the trabecular meshwork: The trabecular meshwork (TM) enables aqueous humor outflow, thus helping limit IOP. Oxidative stress damages the TM, impairing outflow and raising IOP [57]. In this manner, ROS not only contributes to direct RGC damage but also mediates other ocular damage that indirectly causes glaucoma. In an analysis of TM cells from glaucoma patients and controls, Cheng et al. [27] measured the expression of nuclear factor (erythroid-derived 2)-like 2 (Nrf2), a transcription factor for antioxidant production to reduce oxidative stress. Western blotting and RT-qPCR to quantify Nrf2 expression revealed a significant decrease in expression in glaucoma TM cells ($P < 0.05$). Cell viability assays further demonstrated that this might increase apoptosis of TM cells. Following this, there may be fibrosis from increased extracellular meshwork molecules, increasing outflow resistance [55]. These results demonstrate how ROS can contribute to TM failure, OHT, and ultimately glaucoma. While *Nrf2* is only one example, a bioinformatics analysis by Xu et al. [28] identified numerous other genes that modulate oxidative stress damage in the TM and thus may have similar roles in glaucoma. Further analyses on the effects of these other components in TM cells and animal models may confirm their relevance in the pathomechanism.

Vascular pathomechanism

While there is a strong link between mechanical stress and the pathomechanism of glaucoma, it is not the sole contributor to the disease. In patients with normal-tension glaucoma, for example, IOP is not elevated, and yet there is RGC damage and vision loss [3, 5]. The vascular theory has been proposed as another explanation, describing the relationship between reduced blood flow and ischemia, and RGC damage in glaucoma [5].

Retinal ischemia results in oxidative stress: A prominent explanation in the vascular theory is that in glaucoma there can be ischemia to the retina. In this process, increased ROS are produced and may damage the RGC as also described in the mechanical theory. This has been exhibited in studies whereby ischemia and reperfusion injury are induced in animal models to study the mechanism of injury. Yokota et al. [34] provided convincing evidence of this by comparing ischemia-reperfusion injury in mice with a NOX2 deletion to wild-type mice. They induced ischemia-reperfusion to mimic the vascular mechanism in glaucoma. In NOX2-deficient mice, retinal cell death was less significant compared to wild-type mice [34]. They then measured biomarkers to compare vascular activity and ROS production in the retinas of healthy versus glaucomatous eyes. Retinal neuron damage was more significant in wild-type mice, whereby NOX2 expression was also upregulated [34]. As NOX are ROS-generating enzymes in the eye [20], this highlights the key role of ROS and oxidative stress in the vascular pathomechanism. Other studies in glaucoma models also evidence the involvement of NOX in ischemia-reperfusion injury [32, 35]. Meanwhile, the causative role of NOX2 in ischemic injury is also observed in other organs like the heart, brain, and kidneys [31, 33, 36]. In glaucoma models, the longest post-procedural period was only 7 days [32, 34], so it may be that the production of ROS in ischemic conditions is only implicated in the early pathomechanism.

In fact, Gericke et al. [37] conducted similar investigations but with a longer, 2-week follow-up period. They noted that ischemia does not lead to ROS generation, but rather that IOP is a confounder that causes both. IOP increased in rats with induced ischemic damage. ROS concentrations were also higher in RGC and blood vessels, along with NOX2 in the vessels and ganglion cells of the retina, with mRNA expression being 7 times greater in glaucomatous retinas versus healthy ones. However, the levels of the hypoxic factors HIF-1α and VEGF-A, along with their respective mRNA expressions, were not markedly elevated. Since IOP, NOX2, and ROS increased independently of ischemic hypoxia markers, the results suggested the direct causative factor was IOP and not ischemia. The authors proposed that ROS may be produced in the vessels where NOX2 enzyme expression was elevated, and generated ROS would be transported nearer to RGC via the vessels [37]. In that sense, this investigation turned out to better support the mechanical theory of glaucoma.

Oxidative stress results in ischemia: That said, Gericke et al. [37] did not rule out the potential involvement of hypoxia in later stages of the condition. This is because retinal arteriole autoregulation was measured to be abnormal in glaucomatous eyes with sham-treated eye arterioles responding to increased perfusion pressure with vasoconstriction as expected, whereas glaucomatous eyes responded with vasodilation (decrease or increase in vessel diameter of 15.83 μm ± 3.270% at 80 mmHg, respectively). This may imply that ROS can impair vessel autoregulation, which causes ischemia and hypoxia, and ultimately RGC death. Wang et al. [38] arrived at a similar conclusion, evidencing that oxidative stress triggers vascular autoregulatory dysfunction but not the other way around. Another explanation involves nitric oxide (NO), which is a potent vasodilator in vessel autoregulation but also contributes to oxidative stress itself. In ocular pathologies, ROS disrupts NO levels, which may in turn affect vascular diameter, mitochondrial metabolite supply, and thus ROS production [50]. The interplay between ROS and ischemia in glaucoma is therefore unlikely to be unidirectional. Perhaps ROS and the

vascular theory are only implicated in very early stages of the glaucoma pathomechanism [32, 34, 35], then again during later stages of the disease [37, 38]. Further studies involving NOX knockout models—or those for other oxidative stress enzymes—with longer follow-up periods can help elucidate the exact role of ROS in ischemia-reperfusion damage across glaucoma progression.

Immunological pathomechanism

The immunological theory of glaucoma refers to the roles of neuroinflammatory responses that cause RGC death. Greater understanding of ROS and oxidative stress in inflammation and other inflammatory diseases more generally make it clear that they play central roles in the inflammatory pathomechanism of glaucoma too [16–18].

ROS stimulate glial cells: Glial cells including microglia and astrocytes are involved in the homeostasis of RGC. In health they secrete metabolites, growth factors, and anti-inflammatory compounds. Conversely, in disease states such as glaucoma they are found to secrete pro-inflammatory products that mediate RGC damage [49]. A study of microglial cells in OHT elucidated the mechanism behind the shift in functions as a shift in microglial subtype expression [39]. In the study, NOX2 and ROS production upregulated the neuroinflammatory subtype of microglia, M1-like, instead of the anti-inflammatory and wound-healing subtype, M2-like. In their analysis of mice retinas, wild-type mice had significantly elevated levels of M1-like microglia compared to NOX2-deficient mice. Correspondingly, wild-type mice displayed more aggressive RGC and ONH decline by two weeks post-induction of OHT. Subsequent administration of the NOX2 inhibitor gp91ds-tat in wild-type mice improved RGC survival by up to 95% at a 300 μM dose [39]. This underscored ROS-activated microglial inflammation as a promising target for reversing glaucomatous damage. While studies on the anti-inflammatory effects of NOX2 inhibition in glaucoma models are limited, turning to non-glaucoma models offers further evidence to support this mechanism of treatment [44]. In traumatic brain injury, for example, NOX2 activates microglial inflammation in the cortex accompanied by cognitive decline. As with glaucomatous damage, the extent of traumatic brain damage is reduced with gp91ds-tat [44].

Astrocytes are another type of glial cell that may be relevant to the glaucoma pathomechanism. Like other glial cells, they are diverse and serve physiological functions that support RGC, but in disease they become activated and change in morphology and gene expression [8, 56]. Such changes are diverse. For example, astrocytes around the ONH in early glaucoma are said to have decreased expression of intermediate filaments like glial fibrillary acidic protein, along with smaller and retracted astrocyte processes [8]. ONH astrocytes are also purported to cause oxidative stress in glaucoma through increased oxidative phosphorylation when activated [56]. Overall, the supportive roles of the astrocytes are lost and they instead predispose axons at the ONH to damage. Studies focusing on astrocytes and ROS in glaucoma are limited, so firm conclusions on their role in the condition cannot be made. Further studies into the specific relevance of ROS and astrocytic inflammation to glaucoma are required to determine if their role in the disease is significant.

ROS stimulate inflammasomes: Inflammasomes are mediators of inflammatory responses, and ROS signaling is one means by which inflammasomes are activated and cause damage [58]. Though this is broadly extrapolated from systemic immune studies, inflammasomes may also be highly relevant in glaucoma. For example, inflammasomes are found in microglia [45, 46] and may explain the mechanism of microglial inflammatory damage. Pronin et al. [40] created glaucoma models by inducing ischemia-reperfusion injury to raise IOP, followed by inflammasome activation via agonist injections. At 24 hours post-injury, the activities of inflammasomes NLRP1, NLRP3, and Aim2 were determined to be robust based on pyroptotic pore formation. Besides their activity in microglia, inflammasomes also have activity in RGC themselves, and thus also play a direct role in RGC pyroptosis. Pronin et al. [40] also found that markers of pyroptotic pore formation were stronger in RGC than microglia at 12- and 24-hours post-injury, meaning inflammasome injury was more significant in RGC than microglia at this early timepoint. Based on this temporal analysis, they propose that microglial activation only occurs later in the pathogenesis and therefore plays a supplementary rather than a primary role in glaucomatous neuroinflammatory damage. Additionally, inflammasomes mediate TM damage where glial cells are not present [57]. ROS is found to activate NLRP3 inflammasomes, activating caspase-1 and triggering TM cell death via pyroptosis [41]. This complements the mechanical pathomechanism of glaucoma as the pro-inflammatory activities of ROS provide an additional mechanism behind OHT at the level of the TM. Importantly again, this inflammasome process occurs without microglial involvement.

Inflammation in a positive feedback cycle: Glial cells themselves produce ROS once activated, which may trigger a positive feedback cycle of inflammatory damage at the RGC. Here, astrocyte-mediated inflammation may be more confidently said to play a role in the disease. Munoz et al. [42] investigated astrocytes in the spine, concluding that activation

of the P2X7 receptor on astrocytes activates NOX and hence ROS production. They also found that ROS are important in the pathway of secreting IL-6, a pro-inflammatory cytokine. Considering the heterogeneity of astrocyte subtypes, this mechanism may or may not apply to astrocytes found in the retina [59]. Nonetheless, this raises the possibility that inflammation occurs in a vicious cycle, with inflammatory cells producing ROS and ROS activating even more inflammatory cells. All the while, this injures the RGC and contributes to the progression of glaucoma. Immunomodulatory therapies can therefore be effective agents against glaucoma progression. The Fas ligand receptor antagonist ONL1204 was shown to protect against murine glaucoma even after its onset [43], while the A_3 adenosine receptor modulator FM101 underwent a safety evaluation in rats and demonstrated a high, "no observed adverse effect" dose of 1000 mg/kg/day [47].

Upregulation of antioxidant factors in glaucoma

While there is significant and increasing attention to the role of dietary antioxidants in protecting against glaucoma, antioxidants in the glaucoma pathomechanism are infrequently evaluated. Mitochondrial uncoupling protein 2 (Ucp2) was shown to protect RGC against cell death in a murine glaucoma model [60]. Ucp2 expression increased proportionally to IOP ($r^2 = 0.8$, $P = 0.0001$), and transgenic mice overexpressing Ucp2 experienced an attenuated reduction in RGC loss compared to wild-type mice (reduction of 10 ± 4%, vs 19 ± 3% respectively) [60]. Conversely, in the TM of human neovascular glaucoma (NVG) patients Ucp2 expression was determined to have decreased, hence contributing to the mechanical theory of glaucoma [61]. Note that NVG represents one of the secondary glaucoma subtypes, so caution should be exercised when extending these results to primary or other subtypes [61]. This may provide evidence that ROS has nuanced, tissue-specific roles in glaucoma, causing mechanical dysfunction at the TM to elevate IOP but being compensated against at the RGC. Another antioxidant mechanism is the KEAP1-Nrf2 stress response, which is considered the primary defense against mechanism oxidative and electrophilic stresses [48]. In glaucoma, there seems to be an early increase in this pathway even prior to the loss of RGC that helps delay the onset of pathology [62]. While Naguib et al. [62] propose that the KEAP1-Nrf2 response slows axonal degeneration in glaucoma, none of the studies discussed suggest that endogenous antioxidant activity is sufficient to fully prevent glaucoma [60–62]. However, the significance of relevant antioxidants should not be overlooked as they may be germane to glaucoma therapies.

Leveraging antioxidants for therapy: Dietary interventions are commonly discussed, and extensive research has revealed potential options. Dziedziak et al. [63] provided a comprehensive review of numerous food and drink options plus their respective antioxidant activities in relation to glaucoma. There may also be antioxidative pharmacotherapeutic options, including geranylgeranylacetone and edaravone [54]. The latter had ROS-scavenging activities that limited RGC death in various glaucoma models [52, 53]. Even if they do not live up to be effective treatments, studying antioxidant activity provides insights into ROS imbalance in the glaucoma pathomechanism, helping us further understand the nature of oxidative stress in glaucoma.

Risk factors, ROS, and glaucoma

Besides increased IOP, several risk factors of glaucoma are potentially explained by their increasing of oxidative stress. Ageing is one of the major risk factors for glaucoma, with one systematic review showing that the incidence rate of primary open-angle glaucoma increases progressively with age in adults aged 40 years and older [64]. An accumulation of ROS and oxidative stress due to senescence offers a compelling explanation as to why the incidence of glaucoma rises with age. Analyses of oxidative stress biomarkers across age groups has proven that oxidative stress increases with age. Furthermore, senescent cells are understood to accumulate in regions of the eye associated with the glaucoma pathomechanism, including RGC, retinal vessels, and the TM [51]. Systemic hypertension is also understood as a risk factor in open-angle glaucoma. This is likely related to hypertension creating mechanical injury, which as discussed in this review may increase oxidative stress [65]. Additionally, environmental risk factors such as exposure to pollutants and occupational hazards can also be explained by their roles in generating more ROS and oxidative stress [22, 66]. Lastly, behaviors that affect the IOP, ranging from eye rubbing to the use of eye muscles and even postural changes, may induce oxidative stress in the mechanical and vascular pathomechanism theories [67]. All considered, the role of oxidative stress may offer an explanation behind these diverse risk factors. This raises the potential for efficacious therapies once again, since the targeting of oxidative stress may help counter glaucoma from multiple etiologies.

This review has incorporated a variety of evidence regarding the role of ROS and oxidative stress in glaucoma. It includes a detailed exploration of ROS and oxidative stress in all three mechanicals, vascular, and immunological theories of glaucoma. Furthermore, there is a focus on the therapeutic opportunities within each pathomechanism. As for limitations, this is a narrative review, therefore papers included are neither exhaustive nor free from selection bias. This limits the

generalizability of the findings. The inclusion of non-human and/or non-glaucoma models further limits the extrapolation of findings to what occurs in glaucoma patients. Nonetheless, opportunities are revealed for future studies. Glaucoma models could be utilized to confirm the precise roles of key ROS like NOX2, Drp1, Mfn2, Nrf2, NO, and inflammasomes in glaucoma. In particular, the use of knockout models can elucidate the individual roles of ROS. Studies should likewise examine these roles in different subtypes of glaucoma, as pathomechanisms may differ. Having a clearer understanding of individual ROS in different subtypes of glaucoma can support the development of targeted, efficacious therapies.

CONCLUSIONS

Recent insights into the roles of ROS and oxidative stress in the various mechanisms of glaucoma reveal a unifying factor underlying the disease pathomechanism. In relation to the mechanical theory of glaucoma, oxidative stress mediates RGC death both directly and indirectly by damaging the TM. In the vascular theory, ischemia-reperfusion injury leads to the production of ROS that proceeds to damage RGC, and vice versa. In the immunological theory, ROS stimulates neuroinflammatory responses from microglial and astrocyte cells in a positive feedback cycle. Key players in oxidative stress include NOX2, Drp1, Mfn2, Nrf2, NO, and inflammasomes. By exploring key ROS mechanisms in the glaucoma pathomechanism along with related therapeutic developments, this review identifies potential gaps in research on glaucoma. It also highlights potential spaces for further research into developing glaucoma treatments.

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None.

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