Apoptosis in glaucoma: A new direction for the treatment of glaucoma (Review)

QIONGRONG XIA[1,2] and DINGDING ZHANG[3]

[1]Department of Medical Laboratory, Xindu District People's Hospital of Chengdu, Chengdu, Sichuan 610500; [2]College of Medical Technology, Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan 610036; [3]Sichuan Provincial Key Laboratory for Genetic Disease, Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu, Sichuan 610072, P.R. China

Received October 20, 2023; Accepted March 4, 2024

DOI: 10.3892/mmr.2024.13207

Abstract. Glaucoma is a group of progressive optic nerve disorders characterized by the loss of retinal ganglion cells, a thinner retinal nerve fibre layer and cupping of the optic disk. Apoptosis is a physiological cell death process regulated by genes and plays a crucial role in maintaining tissue homeostasis, ensuring the natural development and immune defence of organisms. Apoptosis has been associated with glaucoma and inhibiting apoptosis by activating phosphatidylinositol 3-kinase-protein kinase B or other medicines can rescue pathological changes in glaucoma. Due to the complex crosstalk of apoptosis pathways, the pathophysiological mechanism of apoptosis in glaucoma needs to be fully elucidated. The present review aimed to discuss the mechanism of cell apoptosis in glaucoma, improve the understanding of the pathophysiology of glaucoma, summarize new directions for the treatment of glaucoma and lay the foundation for new treatment strategies for glaucoma.

Contents

Correspondence to: Dr Qiongrong Xia, Department of Medical Laboratory, Xindu District People's Hospital of Chengdu, 199 South Section of Yuying Road, Xindu, Chengdu, Sichuan 610500, P.R. China
E-mail: xiaqr@stu.cdutcm.edu.cn

Key words: glaucoma, apoptosis, PI3K/Akt, inhibitors of apoptosis, polymorphism of the p53, therapy

1. Introduction

Globally, glaucoma is the primary cause of blindness in individuals with eye diseases other than cataracts (1). An estimated 111.8 million people worldwide will suffer from glaucoma by 2040, leading to unilateral or bilateral vision loss if not diagnosed and treated promptly (2). Glaucoma is now recognized as a group of progressive optic neuropathies characterized by excavation or cupping of the optic disc and corresponding visual field loss (3,4). Elevated intraocular pressure (IOP), a major risk factor for the development and progression of glaucoma, is considered to impair the lamina cribrosa, resulting in a loss of normal structural and metabolic support for retinal ganglion cell (RGC) axon and impaired axoplasmic transport (5-7) (Fig. 1). In addition, meta-analyses have shown that individuals with myopia, especially those with high myopia, have an increased risk of suffering from primary open-angle glaucoma (POAG) (8,9). On the one hand, the increased axial length of the myopic eye appears to result in greater deformability of the lamina cribrosa, which may contribute to a greater susceptibility to optic disc changes in glaucoma (10,11). On the other hand, in patients with glaucoma, a longer axial length disrupts the IOP-microvascular autoregulation relationship and decreases the thickness of the lamina cribrosa, increasing the susceptibility of eyes with longer axial length to IOP-induced blood flow reduction (12,13). However, for individuals with normal tension glaucoma (NTG), even when the IOP is <21 mm Hg, there are also symptoms of optic neuropathy, manifested as optic disc excavation and loss of vision (14). Comprehensive reviews indicated that the mechanisms of the pathophysiology of NTG are related to the following factors: i) Lower tolerance of normal IOP results in mechanical damage and generates stress on the axons in the lamina cribrosa; ii) vascular dysregulation and perfusion deficit; iii) greater than normal pressure gradient across the lamina cribrosa; iv) impaired cerebrospinal fluid circulation in the subarachnoid space of the optic nerve which results in a toxic damage to the nerve; v) genetic predisposition (15,16) and vi) abnormal function of neuroserpin (17). Upregulation of neural serine proteases may protect the function of RGCs and restore the function of biochemical networks related to autophagy, microglia and synaptic function in glaucoma (17).

Antioxidant defence weakens with age, which is also associated with an increased risk of glaucoma (18-20) (Fig. 1). Thus, a number of studies suggested that IOP-independent factors in NTG, such as vasoconstriction, gliosis, glutamate toxicity and oxidative stress, activate an apoptosis signalling pathway similar to that involved in glaucoma with elevated IOP, resulting in the loss of RGCs (21,22).

Apoptosis, first described by Kerr *et al* (23) in the 1970s, has become a vital part of exploring the pathogenesis of diseases. Apoptosis plays a crucial role in maintaining tissue homeostasis, ensuring the natural development of the organisms and protecting the immune defence of the body (24,25). Apoptosis, which occurs in normal cells or severely damaged cells, is triggered by various stimuli, such as reactive oxygen species (ROS), endoplasmic reticulum stress (ERS), calcium ions (Ca^{2+}), inflammation and impaired DNA (26-30). Typical morphological signs of apoptosis include crumpling of the cell membrane to form budding protrusions, cytoplasmic dehydration and condensation, nuclear consolidation, nucleolar lysis, chromatin condensation, formation of apoptotic bodies and degradation by phagocytosis (31). Morphological changes in apoptosis are accompanied by complex biochemical processes, including DNA fragmentation, activated caspases, increased mitochondrial permeability, a marked increase in cytoplasmic free Ca^{2+} and phosphatidylserine ectopia (31,32). Apoptosis is executed through a cascade of intrinsic and extrinsic apoptotic pathways that activate the cysteine protease family and the cleavage of multiple substrates.

Although significant progress has been made in understanding the pathogenic mechanism of glaucoma in recent years, the pathogenesis of this disease has yet to be explored. Baleriola *et al* (33) detected apoptotic cells in the trabecular meshwork (TM) of patients with glaucoma by TdT-mediated dUTP nick end labelling (TUNEL) staining. Moreover, RGC apoptosis is also regarded as the earliest form of cell loss in glaucoma (34). In recent years, a number of studies have shown that apoptotic signals, such as Fas signalling, contribute to the pathogenesis of glaucoma by activating apoptosis signalling pathway and inflammatory cytokines, suggesting that surgical injury and global trauma also lead to rapid retinal inflammation and RGC apoptosis (35,36). In glaucomatous mice after surgery or corneal trauma, tumour necrosis factor-alpha (TNF-α) and other inflammatory cytokines are produced in the anterior segment (37). These inflammatory cytokines rapidly spread to the retina, where they cause RGC apoptosis, which is known to lead to glaucoma optic neuropathy (37). The long-term administration of antiglaucoma therapy may lead to TM cell apoptosis, so the onset, development and prognosis of glaucoma appear to be associated with apoptosis (33,37-39). Lowering IOP with ocular hypotensive drops and surgery are effective treatments for glaucoma, but these treatments simply delay disease progression and preserve partial eye-sight. Besides, some medications, such as anticholinergics and adrenergic agents, are known to increase the risk of glaucoma, while benzalkonium-containing beta-blockers and prostaglandin analogues have been reported to trigger mild expression of apoptotic molecules (40,41). Moreover, surgical treatments for glaucoma depend on traditional filtering surgery, such as trabeculectomy, which also has side effects. In more challenging cases of glaucoma, tubes or antifibrotic agents are also needed to improve the surgical success rate (42,43). However, antifibrotic agents are associated with a higher incidence of complications, some of which may be vision-threatening (44). Thus, identifying apoptotic signals in glaucoma is essential for understanding the pathogenesis of this disease and is also fundamental for developing new therapeutic approaches. The present study reviewed the apoptosis and survival pathways of patients with glaucoma and the progress of research on apoptosis as a targeted therapy for glaucoma.

2. Apoptosis and glaucoma

Apoptosis is involved in the pathological and physiological processes of glaucoma. Clinical and experimental evidence has revealed a rapidly initiated, inflammatory (TNF-α-mediated RGC apoptosis) and IOP-independent glaucoma pathway induced by acute anterior segment trauma or surgery, suggesting that cell apoptosis promotes the development of glaucoma (36,37). Administration of infliximab (a TNF-α antibody) or a TNF-α inhibitor has been revealed to protect against cell apoptosis, ameliorating neuroglial remodelling and inhibiting monocyte infiltration (36,37,45,46). Fas signalling reportedly contributes to the pathogenesis of glaucoma by activating both apoptotic and inflammatory pathways and the small peptide inhibitor of the Fas receptor, ONL1204, provides potent neuroprotection (35,47). In addition, several studies have shown that the apoptosis pathway is an essential mediator of RGC death in glaucoma (48-52). Moreover, in glaucoma, TM cells also undergo death through apoptotic pathway, such as the Fas/Fas ligand (FasL) pathway and ERS (51,53-55). Notably, benzalkonium chloride, the most common preservative used in glaucoma treatment also induces toxic changes in the TM and cell apoptosis, which further leads to impaired function of the TM and may worsen any glaucomatous process within the TM if used for a long time (38,56,57). Glaucoma-related cell death typically occurs through apoptosis, triggered by oxidative stress through mitochondrial damage, inflammation, endothelial dysregulation and dysfunction, hypoxia and other factors (39,58).

Molecular basis of apoptosis in the anterior chamber. TM cell apoptosis in the anterior chamber is the most significant concern in glaucoma. It has been suggested that mechanical stress, oxidative stress and intense phagocytic activity of TM cells likely cause cell apoptosis (59). The extent of mechanical stress on the TM depends on the IOP. Thus, glaucoma itself can also induce TM cell apoptosis via mechanical stress or trabecular hypoperfusion (59,60). TM cells die due to apoptosis, loss of barrier function, alteration of aqueous humour outflow and increased IOP (61,62) (Fig. 1).

Programmed cell death can be detected in the TM of patients with glaucoma by using TUNEL (33). Moreover, the experimental results regarding Fas monoclonal antibody-induced apoptosis in cultured human TM cells demonstrated that human TM cells were stimulated to undergo apoptosis through the Fas/FasL pathway (63). Upregulation of activating transcription factor-4 (ATF4) and C/EBP homologous protein (CHOP) and colocalization of ATF4 with endothelial leukocyte adhesion molecule (ELAM-1) were found in the TM of patients with POAG and

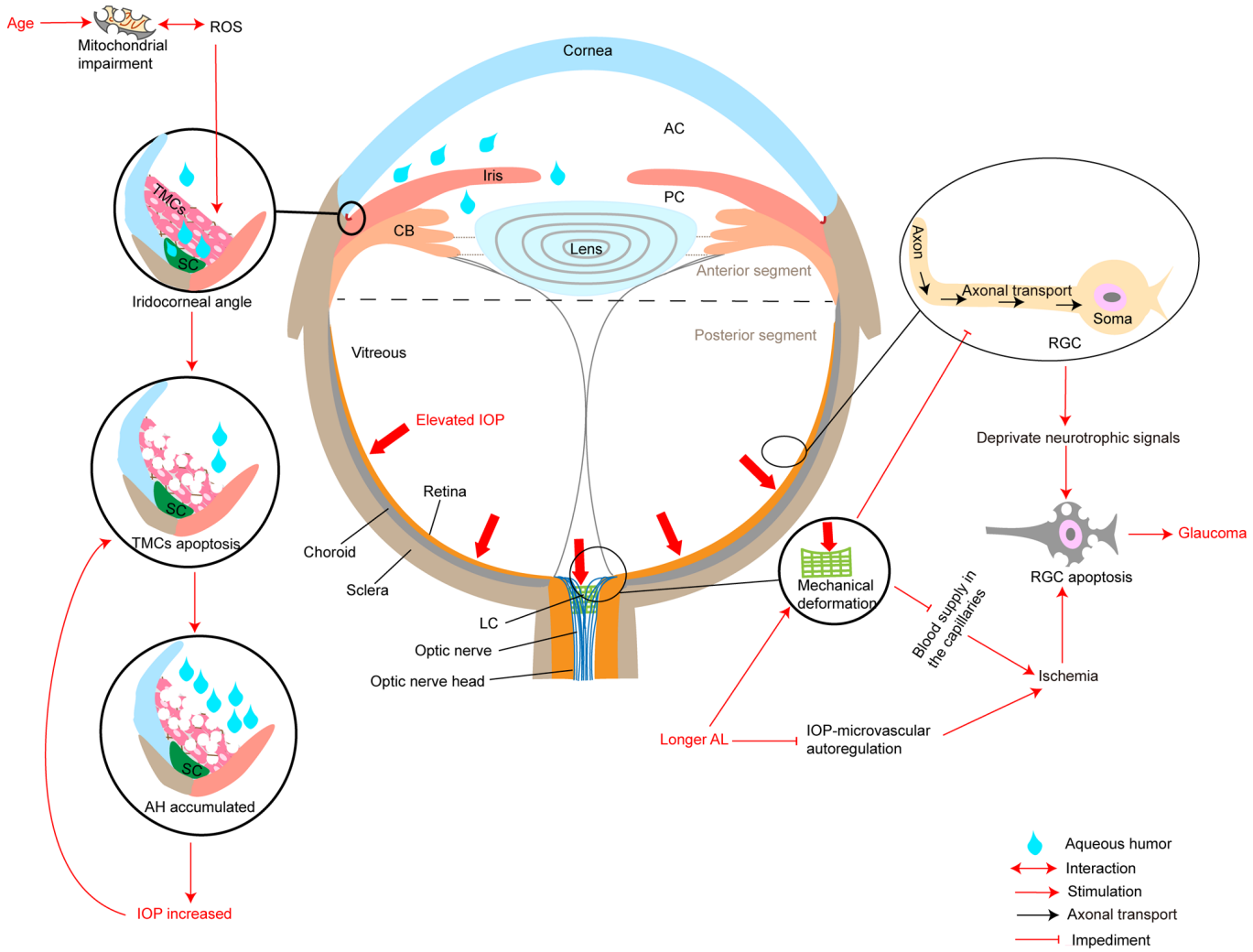

Figure 1. Elevated IOP, age and myopia play important roles in glaucoma. As age increases, the production of mitochondrial ROS increases, which may exacerbate mitochondrial damage and induce oxidative stress-induced apoptosis of TMCs, leading to the accumulation of AH and ultimately an increase in IOP. Elevated IOP further causes TM cell death. In addition, an increase in IOP in glaucoma is considered to cause mechanical deformation of LC, thereby hindering the flow of axoplasm in RGC axons and blood supply in capillaries, leading to the loss of normal structural and metabolic support of RGC, resulting in RGC apoptosis due to ischemia and hypoxia damage and deprivation of neurotrophic signals, leading to symptoms of glaucoma. Furthermore, longer AL in myopic patients disrupts the automatic regulation of IOP-microvascular, aggravates the mechanical deformation of LC and makes the eyes with longer AL more susceptible to the reduced blood flow induced by IOP, leading to RGC apoptosis due to ischemia. IOP, intraocular pressure; ROS, reactive oxygen species; TMCs, trabecular meshwork cells; AH, aqueous humour; LC, lamina cribrosa; RGCs, retinal ganglion cells; AL, axial length; AC, anterior chamber; CB, ciliary body; PC, posterior chamber; SC, Schlemm's canal.

inhibition of ATF4 reduced tunicamycin-induced caspase-3 activation, ROS production, ELAM-1 expression and human TM cell phagocytosis impairment (53). An *in vivo* study in mice revealed that overexpression of ATF4 in the TM induces CHOP expression and TM cell apoptosis, leading to the production of inflammatory cytokines and possibly increased IOP (53). The aforementioned study demonstrated that the eukaryotic initiation factor 2 alpha (eIF2α)/ATF4/CHOP branch of the unfolded protein response (UPR) was activated in human TM cells from patients with glaucoma patients following tert-butyl hydroperoxide exposure (53). In addition, alteration of the TM cell extracellular matrix (ECM) is also considered to be one of the mechanisms that induces IOP elevation by increasing TM resistance. Furthermore, the effects of oxidative stress and latent transforming growth factor beta-binding protein 2 knockdown on ECM and TM cell apoptosis may be mediated by activation of the transforming growth factor-beta (TGF-β)/bone morphogenetic protein signalling pathway (64). CD9 was found to be involved in a wide range of biological processes, such as cell migration and differentiation and cell adhesion and motility, by regulating the phosphatidylinositol 3-kinase (PI3K)-protein kinase B (Akt) signalling pathway (65,66). Yan *et al* (67) reported that CD9 was downregulated in glaucoma and the overexpression of CD9 could activate integrin α4 (ITGA4), PI3K and Akt, leading to reduced TM cell apoptosis and alleviating glaucoma (Fig. 2). MicroRNAs (miRNAs) are single-stranded noncoding RNAs that regulate cellular processes in human TM cells and the effect of miRNAs on TM cell apoptosis in glaucoma has been reported in previous studies. The expression of miR-93 was significantly upregulated in human TM cells in glaucoma and miR-93 induced human TM cells and inhibited their viability by suppressing the expression of nuclear factor erythroid 2-like 2, thus indicating that miR-93

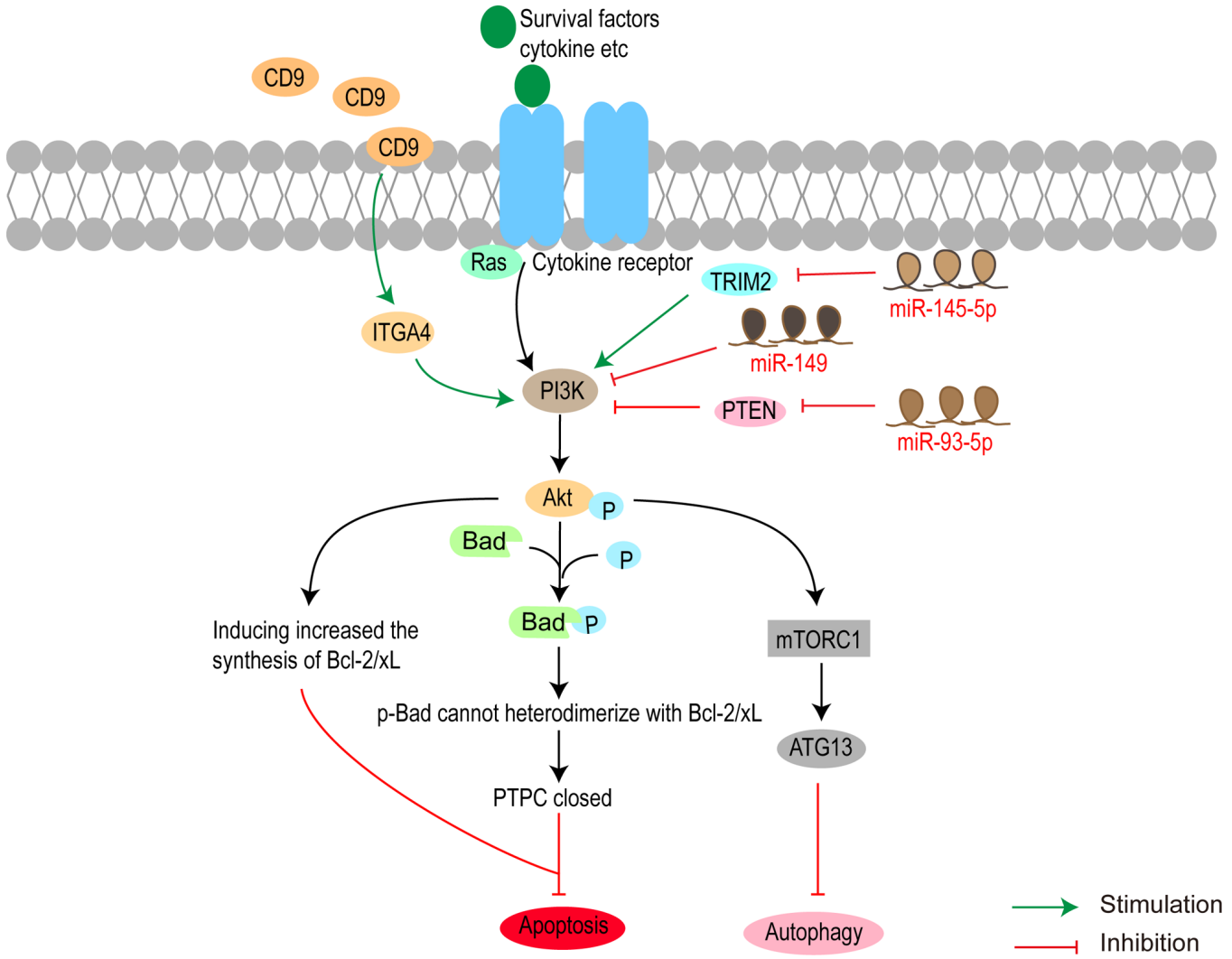

Figure 2. PI3K/Akt pathway in glaucoma. Upregulation of CD9 or Ras integrating survival and other factors, can activate PI3K and induce Akt phosphorylation. Phosphorylated Akt induces an increase in new synthesis of Bcl-2/xL and phosphorylates Bad, preventing heterodimerization of Bad/Bcl-2, thereby facilitating the closure of the permeability transition pore complex and inhibiting cell apoptosis. On the other hand, miR-93-5p negatively regulates phosphatase and tensin homolog, an inhibitor in the PI3K/Akt pathway, inhibiting the autophagy through the PI3K/Akt/mTOR pathway. miR-145-5p induces cell apoptosis by downregulating TRIM2 to inhibit the PI3K/Akt pathway. miR-149 induces cell apoptosis by directly inhibiting the PI3K/Akt pathway. PI3K, phosphatidylinositol 3-kinase; Akt, protein kinase B; Bcl-2, B-cell lymphoma 2; xL, extra-large; mTOR, mammalian target of rapamycin; TRIM2, tripartite motif-containing 2; miR, microRNA.

is a vital regulator in glaucoma (68). However, the effect of miR-200c-3p on TM cell is opposite to that of miR-93. A different study revealed that overexpression of miR-200c-3p negatively regulates the expression of phosphatase and tensin homologue (PTEN) to inhibit cleaved caspase-3, reduce Bax expression and activate the PTEN/Akt/mammalian target of rapamycin (mTOR) signalling pathway, thereby promoting cell proliferation and inhibiting TM cell apoptosis (69). Furthermore, the effects of miR-17-5p on the human TM cell apoptosis and proliferation are similar to those of miR-200c-3p (70). Moreover, miR-181a enhances the survival rate of TM cells by blocking the nuclear factor kappa-B and c-Jun amino-terminal kinase (JNK) signalling pathway (71).

In addition, increased TM stiffness leads to increased IOP (72). TM stiffness is affected by lysophospholipids, rho-associated kinase inhibitors (ROCKis), cytoskeletal disrupting agents, dexamethasone (DEX), TGF-β2, nitric oxide and cellular senescence (72-74).

Therefore, elevated IOP resulting from TM dysfunction caused by the apoptosis signalling pathway and changes in stiffness, inflammation and oxidative stress, aggravates TM cell damage and causes TM cell death. Moreover, TM-derived molecules from damaged TM cells and harmful signals released from stressed TM cells act as apoptotic stimulators, such as neuronal-like cell apoptosis (55,75) (Fig. 1).

Molecular basis of apoptosis in the posterior chamber. The exact mechanisms of RGC apoptosis are not fully understood and increasing evidence suggests that RGC apoptosis may involve blocking anterograde and retrograde axonal transport resulting in the deprivation of neurotrophic signals (4). Moreover, this process, which is accompanied by microglial activation, neuroinflammation and ECM remodelling, was enhanced by high IOP (76-79).

Microglia are activated before RGC loss, and early changes in the retina and optic nerve were detected in the

DBA/2J mouse model of glaucoma (80,81). Moreover, the degree of microglial activation in the optic nerve head (ONH) is proportional to the severity of optic nerve degeneration (81). Numerous studies have revealed that microglia may be essential modulators involved in peripheral monocyte infiltration and retinal pigment epithelial migration (36,45,82,83). The depletion of these proteins leads to abnormal neuroglial remodelling, exacerbating neuroretinal tissue damage (45). Furthermore, infiltrating monocytes may amplify the inflammatory cascade response and contribute to the activation of retinal microglia (36). Inflammatory cytokines, such as TNF-α, lead to permanent changes in the immune function of the retina, called 'permanent neuroglial remodelling' and the anti-inflammatory agents have significant neuroprotective effects on RGCs (36,37).

Furthermore, RGC apoptosis is associated with the level of IOP. Elevated IOP causes axonal degeneration at the ONH in the region of lamina cribriform, a process that occurs in parallel to RGC apoptosis (84). Elevated IOP is considered to damage the lamina cribrosa by mechanical stress, resulting in loss of normal structural and metabolic support of RGC axons and impaired axoplasmic transport. A reduction in neurotrophic signals in RGCs may lead to the initiation of apoptosis and ultimately to the RGC death (5,39). Another novel mechanism of IOP-induced RGC apoptosis is that IOP-induced changes in specific ECM components or cytokines in the retina may increase the activity of matrix metalloproteinases (MMPs), such as MMP-9 (79). One of the reasons for the increase in MMP-9 may be that the mechanical effects of elevated IOP may lead to the RGC axonal damage in the ONH region, which further results in retrograde damage to the RGC body and, in turn, may induce increased MMP-9 activity, causing changes in the ECM (79). Another explanation for the MMP-9 increase induced by elevated IOP is an indirect effect mediated by glutamate (79). Glutamate is a major excitatory neurotransmitter that is increased by stimuli, such as IOP, ischaemia and injury (85). Glutamate excitotoxicity has been reported to be one of the critical pathophysiological causes of RGC injury in glaucoma (86). Thus, glutamate-mediated activation of MMP-9 may lead to RGC apoptosis.

An increase in MMP-9 activity during RGC apoptosis parallels to a decrease in deposition of laminin in the RGC layer, which may lead to disruption of the cell-ECM and cell-cell interactions, increasing susceptibility to apoptosis (79). Tissue inhibitors of matrix metalloproteinase-1 (TIMP-1) are generally considered to be inhibitors of MMPs, particularly MMP-9, that maintain ECM homeostasis (87). TIMP-1 activity in the RGC layer increases with increasing MMP-9 activity and is correlated with IOP exposure (79). An increase in retinal TIMP-1 may contribute to its neuroprotective effects on RGCs by inhibiting MMP-9 and antiapoptotic effects. This finding is consistent with the theory that the ECM is continually remodelled after retinal exposure to elevated IOP.

Molecules associated with ECM changes at the glaucoma ONH site, such as TGF-β2 and collagen 1, are also involved in glaucomatous RGC loss. The experimental results revealed that TGF-β2 and collagen 1 deposition was significantly associated with increased IOP at the ONH (73,79,88). A possible mechanism for increased TGF-β expression in the ONH is the stress response to elevated IOP, as TGF-β is a crucial molecule stimulated by mechanical stress (89,90). However, with increased IOP exposure, TGF-β2 deposition in the retina significantly decreases, whereas MMP-9 increases. TGF-β1 regulates the mRNA and protein levels of MMP-9, similar to its inhibitor TIMP-2 (91). Furthermore, the effect of TGF-β2 depends on its concentration and specificity in targeting cells (92). The biphasic behaviour of TGF-β explains why both the low levels of TGF-β2 found in the RGC layer and the high levels of TGF-β2 in the ONH may be involved in RGC apoptosis (79).

3. The mechanism of apoptosis in glaucoma

The intrinsic (or mitochondrial) and extrinsic (or death receptor) pathways of apoptosis are two commonly described pathways. Both pathways eventually lead to a common pathway or the executive phase of apoptosis. The third pathway is an ERS-induced pathway (28,93-95) (Fig. 3).

The extrinsic death receptor (DR) pathway. Although several extrinsic DR pathways have been described, the best-known pathway is triggered by death signals including TNF-α and FasL (Fig. 3). A previous study has shown that Fas signal contributes to glaucoma pathogenesis by activating apoptotic and inflammatory pathways (35). At the same time, a marginal single nucleotide polymorphism association of TNF-α was also found in human glaucoma and the assessment of the expression levels of TNF-α may serve as a promising biomarker for POAG in African Americans (96). In this pathway, corresponding DRs of TNFα and FasL are TNF receptorl (TNFR1) and Fas, respectively, which help transmit death signals from the cell surface to intracellular pathways through their death domain (DD). DD recruits adaptor proteins, such as Fas-associated DD proteins (FADD), TNFR1-associated DD protein and cysteine proteases such as caspase-8 (97). Subsequently, the death-inducing signalling complex (DISC), a ligand-receptor-adaptor protein complex, is formed by a sequential process. The death ligand of DISC binds to DR to recruit an adaptor protein in order (98,99). The DISC activates caspase-8, which initiates apoptosis through cleavage of the downstream caspases (97).

The intrinsic pathway of apoptosis. Previous studies have revealed that stimuli (toxic substances, ROS and aging) and inherent DNA deficiencies can impair mitochondrial structure and function, triggering the intrinsic mitochondrial pathway in glaucoma (Fig. 3) (100,101). Meanwhile, these stimuli induce the opening of the mitochondrial permeability transition pore and hinder the mitochondrial transmembrane potential, thus accelerating the release of proapoptotic proteins, such as cytochrome c (Cytc) and apoptosis-inducing factors, such as apoptosis-inducing factor (AIF) from mitochondria into the cytoplasm (102,103). Apoptotic protease activating factor 1 (Apaf-1, homologous to cell death protein 4) with an N-terminal caspase recruitment domain (CARD) consists of a six-helix bundle, is an activator of procaspase-9 and is considered to be a junction protein of the mitochondrial pathway (104). Apaf-1 oligomerizes in response to the release of Cytc and forms a disc-shaped heptamer $(Cytc\text{-}Apaf\text{-}1)_7$ called apoptosome (104).

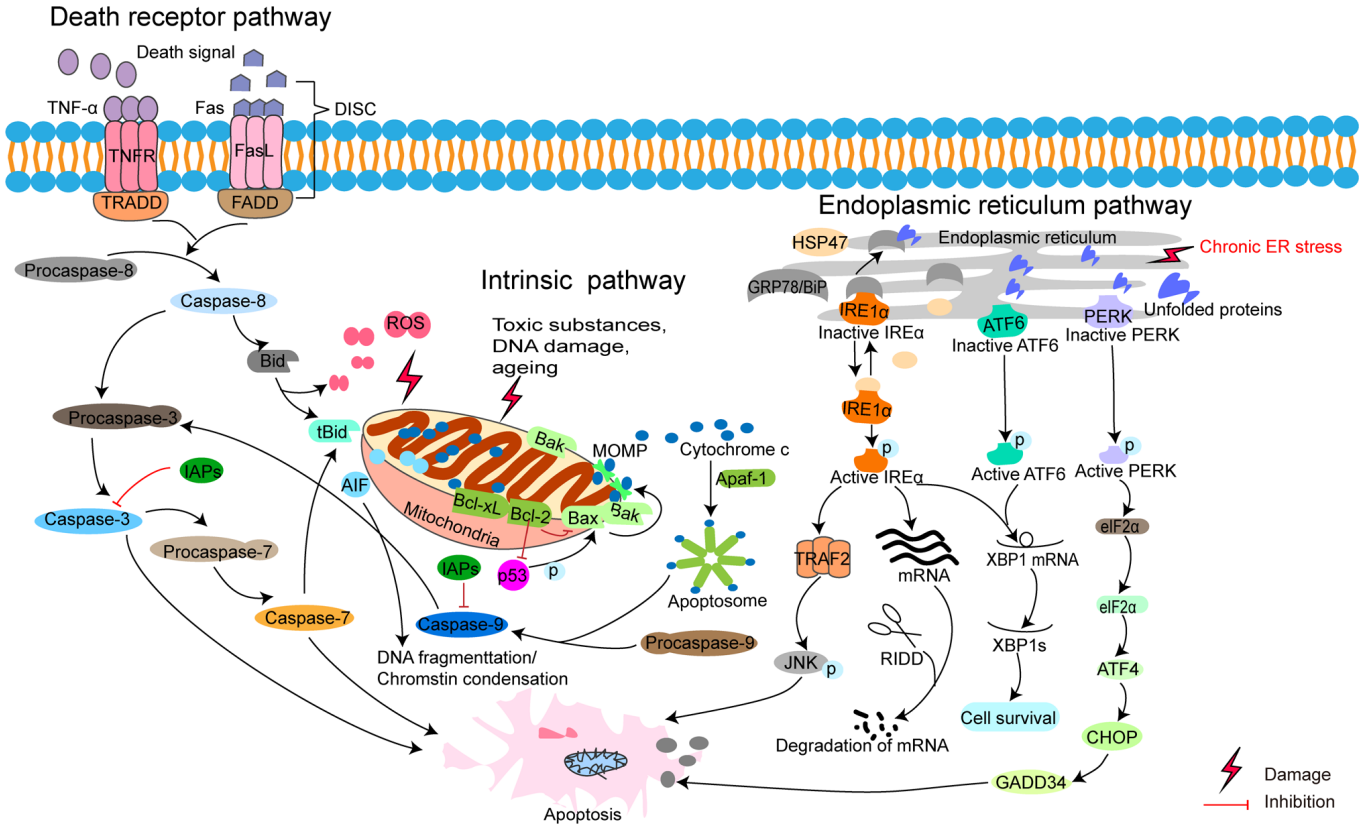

Figure 3. The mechanism of apoptosis in glaucoma. In the death receptor pathway, death signals, death receptors and death domain adaptors such as FADD and TRADD form the DISC to activate caspase-8. The latter activates the latter effector to execute apoptosis. The intrinsic pathway is initiated by internal damage including toxic substances, DNA damage, aging and ROS. Bax/Bak induces the MOMP and releases Cytc to initiate cell apoptosis. The unfolded protein response begins with signalling cascades through three different pathways, including ATF6, inositol-requiring enzyme 1α (IRE1α) and PERK. FADD, Fas-associated death domain proteins; TRADD, tumour necrosis factor receptor type 1-associated DEATH domain protein; DISC, death-inducing signalling complex; ROS, reactive oxygen species; MOMP, mitochondrial outer membrane permeabilization; Cytc, cytochrome c; ATF6, activating transcription factor 6; IRE1α, inositol-requiring enzyme 1α; PERK, PKR-like endoplasmic reticulum kinase.

Subsequently, the apoptosome recruits and activates procaspase-9, an initiator of caspase in the mitochondrial pathway, leading to downstream caspase-3 processing (105).

Mitochondrial-initiated processes are mediated by B-cell lymphoma 2 (Bcl-2) family proteins. Bcl-2 family proteins are in the outer mitochondrial membrane that regulates mitochondrial outer membrane permeabilization (MOMP) and the release of the Cytc. The conformations of members of the Bcl-2 family all have one to four homology BH domains (BH1 to BH4), of which the homology BH3 domain of the proapoptotic proteins (Bax, Bak) is required for MOMP and the execution of intrinsic apoptosis (106). Based on their function in regulating MOMP and their domains, members of the Bcl-2 family are classified into three categories. The first category is anti-apoptotic members, including Bcl-2, Bcl-extra-large, induced myeloid leukemia cell differentiation protein Mcl-1, Bcl-w and Bcl-2 related protein A1, characterized by all having four BH domains (107). These proteins inhibit Bax homo-oligomerization in MOMP by competing with Bax to bind to the BH3 helix of Bax through the groove BH1-3 (108). The second category is proapoptotic proteins comprising Bax, Bak and Bok, containing four BH domains (107). Activated by interaction with the BH3 domain of Bim or BH3 interacting-domain death agonist (Bid), oligomerization of Bak and Bax results in the formation of MOMP and induces Cytc release into the cytoplasm (107,109). The BH3-only proteins are the third subfamily, comprised of Bid, Bim, Bcl-2-interacting killer, Bcl2 modifying factor, p53-upregulated modulator of apoptosis and Noxa. Compared with the sequence homology of other subfamily members, these proteins only have the BH3 domain (107,110). BH-3 only proteins act as apoptotic signal receptors and Bax-like proteins contribute to MOMP, which results in the release of proapoptotic proteins (Cytc, AIF) from mitochondria (110). In the late stages of apoptosis, AIF nuclear translocation induces chromatin condensation or DNA fragmentation in a caspase-independent manner (111). In the apoptosis signalling pathway, Bcl-2 and Bax with negative or positive p53 response elements are located downstream of p53 (112). Oxidative stress-induced DNA damage upregulates Bax by phosphorylating p53 (113). Moreover, Bcl-2 inhibits p53-mediated apoptosis and transcriptional activation (114,115).

ER pathway. The third apoptosis pathway is mediated by ERS, which is critical for cell survival (Fig. 3). ERS is a condition in which some physiological and pathological impairments impede the ability of the cell to properly fold and post-translationally modify secretory and transmembrane proteins in the ER, resulting in the accumulation of misfolded proteins in the ER lumen (116). When protein misfolding persists or

is excessive, ERS triggers cell death, usually apoptosis. ER proteostasis surveillance is sensed by the UPR, the highly conserved signal transduction pathway in the ER lumen that senses the fidelity of protein folding and determines cell fate in response to ERS (117).

UPR is activated by three transmembrane ER proteins, namely ATF6, inositol-requiring enzyme 1α (IRE1α) and protein kinase RNA-like ER kinase (PERK) (118,119). These ERS sensors have a common domain, namely the ER-luminal domain, which senses high concentrations of misfolded proteins to alter the oligomerization state of each senor and activates their downstream molecular signal (116). The phosphorylated form of IRE1α (p-IRE1α) activates chaperone genes and also activates JNK by binding to TNF receptor associated factor-2 (TRAF2) (120). In a rat model of experimental glaucoma, p-JNK is increased and may play a role in RGC death (121). Thus, it is assumed that IRE1α-JNK signalling pathway is involved in ERS of glaucoma. Besides, p-IRE1α initiates mRNA splicing of the X-box binding protein (XBP1) to produce a frameshift that code encodes a potent transcription factor, XBP1s. XBP1s enters the nucleus and initiates the transcription of a subset of UPR-related genes associated with protein folding, secretion, ER-associated degradation and lipid synthesis (122). In addition, p-IRE1α is involved in the regulated IRE1-dependent decay process to promote the degradation of mRNA and slow down the synthesis of new polypeptide chains, thereby alleviating ERS (123). Thus, IRE1α is a crucial protein that regulates cell survival or induces apoptosis in response to surrounding ERS.

PERK is activated in a similar way to IRE1α. Activation of PERK induces translational attenuation of p-eIF2α. Under excessive or prolonged ERS, p-eIF2α translates the transcription factor ATF4, which further induces the expression of other transcription factors, CHOP and ATF3, thus participating in the proapoptotic process (124,125). The expression of ATF4 and CHOP significantly increased in human glaucomatous TM cells (126). However, in the DBA/2J mouse model of glaucoma, an age-related, naturally occurring ocular hypertensive mouse model of glaucoma, though CHOP plays a minor role in contributing to RGC somal apoptosis, it does not lead to axonal degeneration (127). Additional studies have confirmed that the eIF2α/ATF4/CHOP pathway induces TM cell apoptosis in experimental glaucoma (53,128,129).

Similarly, ATF6 activates the target transcription factor, XBP1, to perform a pro-survival effect. XBP1 mRNA is induced by ATF6 and spliced by IRE1α to form the spliced form of XBP1 (130). TM cells treated with DEX showed that IRE1, ATF6 and GRP78 were downregulated (131). A recent study suggested that loss of ATF6 exacerbates retinal degeneration (132). However, the specific mechanism of ATF6-associated ERS in glaucoma has not been revealed.

The executor of apoptosis. The cysteine protease family is the core of the caspase-dependent apoptosis pathway. A total of 13 caspases encoded by the human genome belong to the peptidase C14A family and are orthologous to CED-3 in *C. elegans* (133,134). Caspases are divided into apoptotic and inflammatory caspases based on their biological function; apoptotic caspase includes initiator caspase (caspase-2, -8, -9 and -10) and effector caspase (caspase-3, -6 and -7). The initial caspase is the first caspase to be activated by induced self-cleavage. The primary structure of the initial caspase is characterized by the presence of a long N-terminal propeptide and two death effector domains (DED) or CARD and it mainly activates the effector caspases (135). The effector caspase, characterized by a short N-terminal propeptide without DED and CARD, performs apoptosis by shearing various target proteins (136). Cell pyroptosis is a form of inflammatory programmed cell death pathway activated by human and mouse caspase-1, human caspase-4 and caspase-5, or mouse caspase-11 (137). Inflammatory caspases (caspase-1, -4, -5, or caspase-11) with CARD followed by the catalytic domain mediate cell pyroptosis by the effector protein gasdermin D (137). A recent study reported that melatonin reduced the expression of cleaved caspase-1, cleaved gasdermin D and decreased the number of IL-1β-positive RGC cells after acute ocular hypertension injury (138).

The initiator caspase of the intrinsic pathway is caspase-9, while the extrinsic pathway is caspase-8 and both converge to caspase-3. In the caspase-8/-9 cleavage process of Bid in tBid to remodel mitochondria, favourable conditions are created for ROS production, inhibited by caspase-3 and enhanced by caspase-7 (105). Moreover, caspase-3 is the primary executor of apoptosis.

Survival pathway. In a rat model of chronic hypertensive glaucoma induced by episcleral vein cauterization, activation of the PI3K/Akt/mTOR pathway was shown to be neuroprotective against glaucoma (139). Apoptosis crosstalk with autophagy remains limited in glaucoma and the balance between autophagy and apoptosis is crucial for the survival of glaucoma cells (22). In recent years, additional regulators have been found to be involved in the development of glaucoma through the PI3K/Akt pathway. For example, overexpression of CD9 decreases human TM cell apoptosis and attenuates symptoms of human glaucoma by activating ITGA4, PI3K and Akt (67). miR-145-5p induces RGC apoptosis by suppressing tripartite motif-containing 2 (TRIM2)-mediated activation of the PI3K/Akt signalling pathway in a rat model of glaucoma induced by intraocular injection of N-methyl-D-aspartate (NMDA) (140). Using the same animal model of glaucoma, miR-93-5p was revealed to negatively regulate phosphatase and PTEN to promote the survival of RGCs by activating the Akt/mTOR pathway (141). Moreover, p21/Ras integrates survival signals and induces the activation of PI3K to phosphorylate Akt (p-Akt) (142). p-Akt increases Bcl-2/Bcl-xL synthesis and phosphorylates Bad, preventing the heterodimerization of Bad with Bcl-2/Bcl-xL (142). Subsequently, it facilitates the closure of the permeability transition pore complex and prevents the release of mitochondrial factors into the cytoplasm (142). In addition, Yan *et al* (62) reported that accumulation of the Asn450Tyr mutant myocilin gene (Myoc-N450Y) promotes apoptosis of primary human TM cell through the ERS-induced apoptosis pathway, with the PI3K/Akt signalling pathway playing a crucial role. This evidence suggested that survival signals promote cell survival through the PI3K/Akt signalling pathway in glaucoma (Fig. 2).

Table I. Summary of the relationship between apoptotic molecules and glaucoma.

Apoptotic molecule	The role in glaucoma	Mechanism	(Refs.)
mFasL	Proapoptotic	Neurotoxic effect	(150)
sFasL	As a mFasL antagonist	Blocking FasL-induced apoptosis and inflammation	(145-148)
sTNFα	Proapoptotic	Binding to TNFR1 to promote inflammation and induce RGC death	(159,160)
		Glia-derived sTNFα modulates neuronal death	(161)
tTNFα	Survival signalling	Binding to TNFR2 to activate the PI3K/Akt signalling pathway	(159,162,163)
DR	Transmit signal	Increased expression level of TNF-α and TNFR1 cause RGC apoptosis, involving in caspases	(97,163)
Caspases	Proapoptotic	Mediating the apoptotic pathway	(181,183)
Bcl-2/Bcl-xL	Antiapoptotic	Inhibiting Bax/Bak homo-oligomerization in the MOMP	(108)
Bax, Bak	Proapoptotic	Inducing the formation of MOMP to release Cytc into the cytoplasm	(107,109)
IAPs	Antiapoptotic	Inhibiting the activity of the caspase	(202)
p53	Increase individual susceptibility to glaucoma	*p53* polymorphism reduces the ability of p53 to induce the cell cycle arrest and DNA damage	(213,214)

RGC, retinal ganglion cell; DR, death receptor; MOMP, mitochondrial outer membrane permeabilization; IAP, inhibitor of apoptosis proteins.

4. Regulators of apoptotic pathway in glaucoma

In the 1990s, Quigley *et al* (48) linked apoptosis to RGC death after axotomy injury in experimental glaucoma. Subsequent studies have reported that apoptosis plays a crucial role in the development and prognosis of glaucoma (Table I).

Disrupted balance between membrane-bound FasL and soluble FasL. Microglial activation is an early change in the retina and optic nerve in the DBA/2J mouse model of chronic inherited glaucoma and may contribute to the onset or progression of glaucoma (80,81). Detection of microglial activation may be valuable for early glaucoma diagnosis, while modulation of microglial responses may change disease progression (80). Increased Fas/FasL immunoreactivity was found in microglia and FADD immunoreactivity was found in Müller glial cells and RGCs (47). FasL (CD95-L/APO-1L) is a signal membrane-bound type II transmembrane protein that belongs to the TNF family, a central pathway in the regulation of apoptosis by the immune system (143,144). Membrane-bound FasL (mFasL) induces apoptosis and promotes inflammation upon binding to Fas. By contrast, the soluble Fas-ligand (sFasL), which is formed by cleavage of the 103-137 amino acid region of mFasL by MMPs, blocks the apoptosis and inhibits inflammation (145-148). Previous research has revealed that the sFas concentration in the aqueous humour is lower in patients with POAG than in control individuals, suggesting that a low level of sFas may provide an appropriate microenvironment for increased apoptosis of TM cells in glaucoma (149).

In the C57BL/6J $^{\Delta CS}$ mouse model of glaucoma, a mouse model of a membrane-only FasL gene-targeted mouse in which the FasL metalloproteinase cleavage site was mutated in exon two, mFasL, which is expressed mainly in retinal microglia, had a neurotoxic effect on the retina, causing retinal degeneration and inducing RGC death (150). Injection of exogenous sFasL into a mouse model of glaucoma induced by intravitreal TNF-α led to a reduction in RGC loss (150). O'Reilly *et al* (151) also confirmed that mFasL toxicity induces apoptosis, while sFasL is non-apoptotic. In addition, a different study reported that heat shock protein-induced RGC apoptosis results in microglial activation and upregulation of Fas and suggested that RGC apoptosis is mediated by the inflammatory cytokine FasL (152).

Currently, for the antagonistic effect of mFasL and sFasL in glaucoma, Gregory-Ksande and Marshak-Rothstein (148) suggested that sFasL competes with mFasL for binding to Fas, resulting in steric hindrance. However, except for the Met12 small-molecule inhibitor, the steric hindrance mechanism by which Met12 binds to Fas results in fewer receptors available for FasL binding, directly interfering with FasL binding to Fas (153). There is no better answer to how the sFasL monomer effectively blocks the binding of mFasL multimers to Fas. Nevertheless, other studies have reported that the proapoptotic activity of trimeric sFasL in the ciliary body is enhanced when sFasL binds to corneal ECM proteins (154). A specific cytokine in the ECM, such as TGF-β, increases the local concentration of sFasL (154). Thus, the antagonistic effects of mFasL/sFasL may be a treatment target in glaucoma in the future.

Disrupted balance of transmembrane TNFα and soluble TNFα. Full-length tropomyosin receptor kinase C (TrkC) is the primary receptor for neurotrophin-3. TrkCT1 is a truncated receptor isoform of TrkC, that lacks the kinase domain and has a unique short intracellular domain. TrkCT1 has been reported to control the production of TNF-α in glial cells, leading to the death of RGCs (155). TNFα is a type II single-transmembrane

protein (N-terminal at the cytoplasmic face), that is expressed mainly by macrophages, natural killer cells, T and B cells and plays a role in inflammation, cell proliferation, apoptosis and morphology (155-157). TNFα binds to two types of TNF-α receptors (TNFR1 and TNFR2) to perform its multiple biological functions (158,159). Soluble TNF-α (sTNFα) preferentially binds to TNFR1, which results in neuroinflammation and cell death (160). In addition, Cueva Vargas *et al* (161) reported that glia-derived sTNFα modulates neuronal death in glaucoma via calcium-permeable AMPA receptor activation. Conversely, transmembrane TNF-α (tTNFα) mainly binds to TNFR2 by activating the prosurvival PI3K-Akt/PKB signalling pathway which mediates neuroprotective effects (159,162,163). A reduction in the number of activated microglia shifts the balance towards antiapoptotic effects in glaucoma (164). A mouse model of glaucoma generated by ocular surgery or trauma has demonstrated that rapid inhibition of TNFα or IL-1β significantly inhibits monocyte infiltration and RGC apoptosis caused by surgical injury and global trauma (36). Additionally, the expression levels of IL-1β and TNFα in the TM of patients with POAG were significantly greater than those in the control group and TNFα induced TM cell death (165,166). TNFα stimulates mitochondria to form a stress response, which sequentially releases ROS, Cytc and Bax to activate caspase-9 and a downstream caspase cascade to initiate apoptosis (167). Moreover, neutralizing the action of TNFα and IL-1β prevents the loss of RGCs induced by elevated hydrostatic pressure or lipopolysaccharide (168). Previous studies demonstrated that patients with the TNFα-308 G/A polymorphism may have increased susceptibility to glaucoma (169,170). However, the relationship between the TNFα-308 G/A polymorphism and glaucoma has not yet been verified.

Overexpression of DR. DR, which belongs to the TNFR superfamily, is a type I signal transmembrane receptor (97). All members of the DR family are characterized by the presence of a DD consisting of an ~80 amino-acid-long motif (171). DD recruits various junction proteins to form a DR platform to mediate cell death. In addition to TNFR1 (known as DR1) and Fas (known as DR2, CD95, or APO-1), DR includes DR-3 (APO-3), DR4, known as TNF-related apoptosis-inducing ligand receptor1 (TRAIL-R1), DR5 (TRAIL-R2), DR6 (CD358), nerve growth factor receptor and ectodysplasin A receptor (172). However, death ligands bind to decoy receptors without DDs, such as TRAIL-R3, which cannot transform apoptotic signals, thus producing antiapoptotic effect (172). The level of DR plays a role in transmitting an apoptotic signal to balance cell life or die. Regardless of the mechanism underlying the upregulation of DR or enhancement of DR function, cell death occurs.

For example, upregulation of the Fas receptor is a marker of human glaucomatous neuropathy (173). In glaucoma, inhibiting Fas expression via an inhibitor provides protection to the retinal nerve (35,174). The glial production of TNFα is increased in the glaucomatous retina and ONH which caused RGCs death through its direct or indirect neurotoxicity (175). Increased immunostaining for TNFα and TNFR1 is observed mainly in glial cells and in glial cells processed around axons and blood vessels in the ONH (176). Under normal circumstances, only TNFR1 is constitutively expressed in the vasculature of the ONH. In human glaucoma, the expression of TNFα and TNFR1 in astrocytes and microglia is increased (177). In severe glaucomatous damage, RGC axons expresses TNFR1, which may be a direct target for TNFα mediated optic nerve degeneration (177). The mRNA and protein expression levels of TNFα and TNFR1 are greater in the inner retinal layers in glaucomatous eyes and TNFR1 is expressed at high levels in RGCs, whereas TNFα, is expressed mainly in glial cells (178). In rat model of experimental glaucoma, TNFα strengthened the excitability of RGCs by activating TNFR1 to upregulate the current density of Nav1.6, namely, the voltage-gated Na^+ channel, thereby promoting RGC apoptosis, while choosing a suitable sodium channel blocker to block Nav1.6 may be a useful strategy for treating glaucoma (179). An explanation for the cause of TNFR2-mediated RGC death, was that TNFα simulated ocular hypertension, leading to the release of cytotoxic agents followed by the activation of microglia and the loss of oligodendrocytes that encapsulate RGCs, which in turn led to slow RGC death (180).

Activation of the caspase family. The caspase family plays a significant role in the execution of cell apoptosis. Hence, caspase activation is likely related to cell apoptosis in glaucoma.

Activation of caspase-9, an initiator of the intrinsic caspase cascade, was found to be involved in RGC death in a rat model of experimental glaucoma (181). In addition, the downregulation of caspase-8 significantly alleviated RGC death in a mouse model of acute glaucoma by inhibiting the processing of IL-1β (182). Caspase-8 has various functions in both RGCs and astroglia in glaucoma. In the C57BL/6J mouse model of experimental glaucoma, caspase-$8^{-/-}$ astroglia protected RGCs from glial-driven inflammatory impairment, while an inhibitor of caspase-8 cleavage rescued RGCs against from apoptosis, as Yang *et al* (183) reported that caspase-8 plays a crucial role in RGC apoptosis and astroglia-induced neuroinflammation in glaucoma. Additionally, in caspase-$7^{-/-}$ mice, caspase-$7^{-/-}$ ameliorated RGC death in optic nerve crush (ONC) injury and improved the functional response of RGCs (184).

Combined inhibition of caspase activity contributes to the survival of RGCs (185). In a mouse model of glaucoma induced by ischaemia/reperfusion injury, RGC death was reduced by the downregulation of caspase-8 and caspase-3 following resveratrol treatment (186). Inflammatory pyroptotic death, a non-apoptotic process that involves caspases, is essential in death of RGCs (187).

Imbalance of Bcl-2 family proteins. The *Bcl-2* gene encodes Bcl-2, which has antiapoptotic effects. *Bcl-2*, the proto-oncogene of chromosomal t(14;18) in mammalian B-cell lymphomas, has been implicated in apoptosis (188). The Bcl-2 family of proteins comprises proapoptotic and antiapoptotic proteins that regulate MOMP formation and RGC apoptosis after optic nerve injury (189). The imbalance between the proapoptotic and antiapoptotic effects of Bcl-2 family proteins in health and disease determines the fate of cell death or survival (190). Dysregulation of Bcl-2 family members results in an imbalance in the ratio of antiapoptotic (Bcl-2) to proapoptotic (Bax) proteins (191). Other findings suggested that Bak and Bax were highly expressed, while Bcl-2

was expressed at low levels in glaucomatous optic axons in primary angle-closure glaucoma (PACG) (192). Bcl-2 overexpression protects mitochondria from oxidative stress-induced pH acidification, whereas the physiological pH is normal (193). Additionally, high-level Bcl-2 decreases MOMP to reduce mitochondrial-dependent apoptosis by binding to the megapore to facilitate megapore closure, which improves RGC survival in glaucoma (142,194,195). Moreover, high-level Bcl-xL protects neurons from death in the absence of trophic factors, preventing the degeneration of somas and proximal axon segments after degenerating after axotomy (196-198). In the DBA/2J mouse model of inherited glaucoma, *Bcl-xL* gene therapy prevents Bax translocation and RGC degeneration and reduces cell loss in the RGC layer after ONC (199). Moreover, overexpression of Bim and Bax promoted the RGC death, whereas elevation of Bcl-2 contributed to slowing RGC apoptosis (200). By contrast, decreasing the concentration of Bax in RGCs had a neuroprotective effect after ONC, which indicated that damaged RGCs in a quiescent state did not respond to apoptotic stimulation (201). These findings are consistent with the results of Libby *et al* (49), who reported that Bax ablation prevents RGC death.

Dysregulated inhibitor of apoptosis proteins (IAP). IAPs regulate the cell cycle, signal transduction, cell apoptosis, cytokinesis and are composed of a group of proteins similar in structure and function. IAPs are characterized by the baculovirus IAP repeat (BIR) protein domain at the N-terminus; some possess a new, interesting gene finger domain at the C-terminus (202). To date, eight human IAPs have been identified, including X-chromosome-linked IAP (XIAP/BIRC4), cellular IAP1 (c-IAP1/BIRC2), cellular IAP2 (c-IAP2/BIRC3), IAP-like protein 2 (BIRC8), melanoma IAP (Livin/BIRC7), neuronal apoptosis inhibitory protein (BIRC1), survivin (BIRC5) and the BIR repeat-containing ubiquitin-conjugating enzyme system (BIRC6, Apollo) (202). Although not all proteins with a BIR domain antiapoptotic functions, the BIR domain is necessary for the antiapoptotic effects of IAP family proteins.

As an endogenous inhibitor, IAP inhibits caspase activity by binding its conserved BIR domain to the active sites of caspases (202). By promoting the degradation of caspases or separating caspases from their substrates, IAPs inhibit caspases (202). Recently, dysregulated expression of IAPs has attracted increased amounts of attention in eye disease research. c-IAP1 is upregulated early in experimental glaucoma, as part of the intrinsic neuroprotective mechanism (203). A reduction in the level of c-IAP1 and XIAP secreted by RGCs and the accumulation of TRAF2 result in increased susceptibility to death in cells in the mature RGC layer being more susceptible to death (204,205). Previous studies concluded that ageing impaired the endogenous neuroprotective mechanism of RGCs evoked by elevated IOP in glaucoma patients, namely, a reduction in survival signals mediated by IAPs and TRAF (204,205).

Another IAP, the T allele of rs2754511 in the *BIRC6* gene, reportedly protects against glaucoma by alleviating ERS (206,207). On the other hand, overexpression of XIAP and survivin can protect TM cells and ONH astrocytes from apoptosis induced by oxidative stress (208). Besides, a number of studies have identified that Rho/ROCK is involved in the pathogenesis of glaucoma (74,209). In patients with glaucoma, Rho/ROCK activation alters the cytoskeleton and increases TM cell adhesion, reducing aqueous humour outflow and increasing IOP (74). Additionally, Liu *et al* (209) reported that the long non-coding RNA small nucleolar RNA host gene 11 regulates Wnt/β-catenin signalling through Rho/ROCK via β-catenin phosphorylation at Ser675 or through GSK-3β-mediated phosphorylation at Ser33/37/Thr41, affecting TM cell proliferation, migration, apoptosis and autophagy. Therefore, the absence of activation of prosurvival genes in patients with glaucoma is a potential explanation for the increased vulnerability of the optic nerve to elevated IOP (210).

Polymorphism of p53. The tumour suppressor gene *p53* encodes the p53 protein. *p53*, located on chromosome 17p13.1, is a crucial transcription factor with a wide range of target gene repertoires. *p53* with one promoter and three mRNA splice variants encodes full-length *p53* and different isoforms of the p53 protein, respectively (211). The structure of the p53 protein contains transcriptional activation, DNA binding and oligomerization domains, the molecular weight of *p53* is 53 kDa (211). The p53 protein responds to DNA damage or directs damaged cells to the apoptotic pathway to protect the organism from abnormal development (212). The functional polymorphism of the *p53* gene that affects the activity of the p53 protein may be related to the induction of apoptosis and the reduction in the ability to induce cell cycle arrest and DNA repair (213,214). Thus, *p53* activation is one of the critical steps of apoptosis and upregulates the expression of the proapoptotic gene *Bax* and downregulates the expression of the antiapoptotic gene *Bcl-2* (112,215).

There is a link between polymorphisms in the *p53* gene and POAG and PACG in some ethnic populations (216). The *p53* codon 72 polymorphism has recently attracted widespread attention in glaucomatous neuropathy in patients with POAG. Due to the change in CGC to CCC, amino acid residue 72 (the fourth exon) was changed from arginine (Arg) to proline (Pro) (217). Lin *et al* (214) reported that the homozygous Pro/Pro form of *p53* codon 72 led to an increased risk of POAG in the Chinese population. Fan *et al* (218) confirmed the role of *p53* variants in POAG, at least in the Chinese population. Several studies have indicated that *p53* codon 72 (Pro/Pro vs. Arg/Pro + Pro/Pro) polymorphisms and the introductions of three 16-bp insertions (insertion vs. deletion) possibly contribute to individual susceptibility to POAG, at least in Spain and Iran, and to an increased risk of developing PACG in North India (219-223). Additionally, Wiggs *et al* (224) demonstrated that the *p53* codon 72 Pro/Pro genotype was a potential risk factor for early paracentral visual field defects in Caucasians with POAG. The pro-form of *p53* codon 72 results in RGC instability but does not protect RGCs from apoptosis in glaucoma (214). More *in vitro* studies have revealed that the apoptotic activity of p32-Arg greater than that of p53-Pro due to the p53 inhibitor, which inhibits the activity of p53-Pro and that the apoptotic activity of p53-Pro may be enhanced by certain conditions (low oxygen tension) (224,225).

However, there are conflicting studies about *p53* codon 72 polymorphisms increasing the risk of POAG.

Dimasi *et al* (226) noted out that the Arg/Pro polymorphism of *p53* codon 72 was irrelevant to the age of onset or severity of glaucoma in Australia. In addition, *p53* polymorphisms were not related to POAG in the Japanese, Turkish, or Brazilian populations (227-229). Whether p53 increases individual susceptibility to POAG appears to vary by ethnic subgroup.

5. Targeting apoptosis inhibition: A new hope for treating glaucoma?

Although lowering IOP with ocular hypotensive drops and surgery are effective treatments for glaucoma, the disease continues to progress. Thus, therapeutic strategies targeting the activation of intrinsic and extrinsic apoptotic signalling pathways for further investigation into the study of the pathogenesis of glaucoma may provide a novel and practical neuroprotective approach (230). Specific blockade or interference with apoptosis is a potential new therapy for the treatment of glaucoma (Table II).

Targeting the caspase family. Blocking caspase activation is one of the targets for the treatment of glaucoma. Tahzib *et al* (231) proposed that if caspase activation results in prolonged apoptosis in RGCs, then the use of caspase inhibitors (such as XIAP) to inhibit apoptosis extends the therapeutic window. The pharmacological inhibitor Z-VDVAD-fmk (Z-VDVAD) is a small molecular inhibitor and an available agent that will enter clinical trials. Vigneswara *et al* (232) reported that Z-VDVAD protected RGCs from apoptosis after ONC by specifically inhibiting caspase-2 activation but did not promote regeneration of RGC axons. Moreover, these results resemble those reported by Monnier *et al* (233), who used Z-VEID-FMK, a selective inhibitor of caspase-6, to achieve similar effects on RGC survival at 14 days after axotomy and promoted axonal regeneration after ONC. In addition, the caspase-3 inhibitor, Z-DEVD-FMK has neuroprotective effects and significantly promotes visual recovery by inhibiting RGC apoptosis when injected 30 min after optic nerve injury (234). Similarly, the loss of RGCs was delayed by brain-derived neurotrophic factor, an inhibitor of caspase-3 (235,236).

More RGCs were retained in caspase-$7^{-/-}$ mice than in wild-type mice after ONC, suggesting that blocking caspases may have neuroprotective effects (184). Small interfering RNAs (siRNAs) against caspases have been used in several studies. Tawfik *et al* (237) reported that non-viral gene therapy with siRNA-nanoparticles selectively silenced the expression of caspase-3 and blocked apoptosis in post-mitotic neurons. Furthermore, in a rat model of optic nerve transection, siRNA inhibited the expression of caspase-2 and provided neuroprotection to RGCs for at least 30 days (238).

Targeting the Bcl-2 family of proteins. Minocycline, which has anti-inflammatory and antiapoptotic properties is a second-generation tetracycline with protease inhibitory properties (239). It is considered a candidate neuroprotective drug for experimental glaucoma and other neurodegenerative diseases (239). Minocycline has been reported to reduce the number of activated microglia and improve RGC axon transport in glaucoma (240). Minocycline upregulates *Bcl-2* expression and downregulates *Bax* and *Tp53bp2* expression, shifting the balance to the antiapoptotic direction in experimental glaucoma, and is ready for clinical trials of acute neurological injury (164,239). A similar drug, Asiatic acid, ameliorates retinal dysfunction and protects RGCs from ocular hypertension (241). The antiapoptotic effect of a small molecule inhibitor [2,6-diaminopyridine-3,5-bis(thiocyanate) (PR-619)] on RGCs is mediated by modulation of parkin function and interaction with Bax and Bcl-2 (242). PR-619 protects RGCs from glutamate excitotoxicity-induced apoptosis by increasing the levels of Bcl-2 in RGCs (242). PR-619 regulates neurodegeneration-related stress by stabilizing the mitochondrial membrane potential of RGCs, reducing cytotoxicity and apoptosis, as well as *Bax* expression. Thus, PR-619 protects RGCs from glutamate excitotoxicity by enhancing parkin-mediated mitochondrial autophagy rather than the apoptotic pathway.

Injection of Szeto-Schiller peptide 31 (SS-31) into a Sprague Dawley rat model of experimental glaucoma had neuroprotective effects. SS-31 improved the a-wave and b-wave amplitudes of the ERG and F-VEP amplitude in the eye, upregulated the level of Bcl-2, downregulated the level of Bax, and inhibited the release of Cytc (243). Numerous experimental drugs have demonstrated that upregulating the expression of Bcl-2 and downregulating the expression of Bax and caspase-3 are potential methods for protecting RGCs (195,241,244).

Targeting the IAPs. IAPs, especially XIAP, are potent caspase inhibitors and are attractive molecular targets. IAPs significantly inhibit apoptosis by inhibiting the activity of caspase-9, -3 and -7 (245). A number of novel treatments include gene therapy, such as with *XIAP*, which offers a new direction in glaucoma treatment. In a rat model of glaucoma, recombinant adeno-associated viral (AAV) loaded with *XIAP* promoted the survival of optic nerve axons (246). Moreover, the expression of the *XIAP* prevents IOP elevation by regulating the production of aqueous humour (246). Other findings indicated that AAV-loaded *XIAP* protected both the structure and function of the axons of RGCs and decreased glial cell infiltration in a mouse model of glaucoma (247).

In addition, it has been revealed that tacrolimus inhibits the expression of survivin to reduce cell proliferation and induce cell apoptosis (248). A small-molecule survivin inhibitor decreased TGF-β-induced cell proliferation and migration during the epithelial mesenchymal transition (249). Thus, survivin depletion results in TGF-β1 induced cell cycle arrest and apoptosis and reduces the phosphorylation of retinoblastoma proteins (249). Therefore, a strategy to improve survivin expression may be a useful for treating glaucoma. Recently, ROCK inhibitors have been identified as a new class of drugs that directly target TM cells to reduce IOP (250,251). In a transgenic mouse model, ROCKi was reported to reduce IOP by promoting cell proliferation and phagocytosis of TM cell, reducing actin cross-linking and cell adhesion interactions (74,250,252). Currently, two types of ROCKis, namely, ripasudil (K-115) in Japan and netarsudil (known as AR-13324z), are approved for the clinical treatment of glaucoma in the United States (253-256). These findings indicated that the ROCKi may be a new first-line drug for glaucoma treatment.

Table II. Summary of the agents between apoptotic molecules and glaucoma.

Target	Agent	Mechanism	Experimental model	(Refs.)
Caspases	BDNF	Activating the PI3K/Akt pathway	Optic nerve crush or transection in mice	(235,236)
	Inhibitors	BIRC4 inhibits of retinal caspase-3 activity	A chronic intraocular hypertension rat model of glaucoma induced by hypertonic saline	(231)
		Z-DEVD-FMK, the specific caspase-3 inhibitor	A rabbit model of fluid percussion injury	(234)
		Z-VDVAD suppresses level of cleaved caspase-2	Crushing the optic nerve in adult rats	(232)
		Z-VEID-FMK, an inhibitor of caspase-6	Organotypic retinal cultures and axotomy in rats	(233)
	siRNA	Selectively silence caspace-3 expression to block apoptosis in post-mitotic neurons	A preclinical glaucoma model of optic nerve crush in adult rats	(237)
	siRNA	Elicit RNAi-mediated cleavage of caspase-2 mRNA	Optic nerve crush injury in rat	(238)
Bcl-2 family	Minocycline	Neuroprotective by upregulating expression of Bcl-2 and downregulating expression of Bax, Tp53bp2 and TRAF4; reducing the number of activated microglia in glaucoma	Mice model of glaucoma induced by limbal photocoagulation laser	(164,239)
	AA	Neuroprotection by upregulating the expression of Bcl-2 and downregulating the expression of Bax and caspase-3	Rat model of glaucoma induced by microspheres injection	(241)
	PR-619	Neuroprotection by promoting parkin-mediated mitophagy	Excitotoxicity model	(242)
	SS-31	Neuroprotection by upregulating expression of Bcl-2, downregulating expression of Bax and reducing Cytc release	A rat experimental glaucoma model induced by injection of polystyrene microspheres	(243)
p53	PP-1	Dephosphorylate p53 at Ser-15 and Ser-37, negatively modulates its transcriptional and apoptotic activity	Cultured human lens epithelial cells	(257)
IAPs	Gene therapy	p53 induces p21WAF-1/Cip1 expression, leading to p21WAF1 dependent inhibition of cyclin-dependent kinase and proliferating cell nuclear antigen mediates DNA replication without inducing cell apoptosis	Cultured Human Tenon's capsule fibroblasts Rabbit model of glaucoma surgery Primate model of glaucoma surgery	(259,264,265)
		Direct or indirect inhibition of caspase-8 and caspase-3	A chronic intraocular hypertension rat model of glaucoma induced by hypertonic saline	(246)
		Caspase-dependent and caspase-independent mechanism (such as NF-kB)	A magnetic microbead mouse model of induced ocular hypertension	(247)
Survival signals	SNC-121	Activating the PI3K/Akt pathway	A chronic intraocular hypertension rat model of glaucoma induced by hypertonic saline	(260)
	Baicalin	Activating the PI3K/Akt pathway and inhibit autophagy	A mouse model of glaucoma induced by episcleral venous occlusion with cauterization	(261)
	Ligustrazine	Inhibiting autophagy by activating PI3K/Akt/mTOR pathway	A rat chronic hypertensive glaucoma model induced by episcleral vein cauterization	(139)
	Acteoside	Activating the PI3K/Akt pathway by upregulating caveolin 1	A rat model of glaucoma induced by episcleral venous occlusion with cauterization	(262)

siRNA, small interfering RNA; AA, Asiatic acid; IAP, inhibitor of apoptosis proteins.

Targeting p53. The use of p53 as a therapeutic target has been studied in glaucoma. The function the transcription factor *p53* depends on its phosphorylation and dephosphorylation. Serine/threonine-protein phosphatase-1 has been reported to directly dephosphorylate *p53* to negatively regulate its transcriptional and apoptotic activities, thus promoting cell survival (257). Vitamin B1 has been revealed to significantly reduce *p53* expression (258). Johnson *et al* (259) demonstrated that the adenoviral *p53* gene replaced the role of mitomycin C and 5-fluorouracil in glaucoma surgery due to its antiproliferative properties.

Activation of the PI3K/Akt pathway. The PI3K/Akt pathway is a pivotal intracellular signalling pathway that promotes cell proliferation, inhibits apoptosis and induces angiogenesis by activating multiple downstream regulatory elements. A sustained decrease in Akt activation was observed in the ocular-hypertensive retina and optic nerve of a rat model of glaucoma induced by injecting hypertonic saline into the limbal veins (260). Factors that activate the PI3K/Akt pathway constitute a novel molecular therapy for glaucoma (Fig. 2). Yan *et al* (67) demonstrated that CD9-knockdown significantly reduced the expression of ITGA4, p-PI3K and p-Akt and increased the apoptotic activity of TM cells, which was increased dramatically in the CD9-overexpressing group. Knockdown of ITGA4 rescued p-PI3K and Akt expression, suggesting that overexpression of CD9 activates the ITGA4/PI3K/Akt axis to attenuate TM cell apoptosis in human glaucoma (67).

Moreover, several traditional Chinese medicines may suppress glaucoma pathogenesis by activating PI3K/Akt signalling both *in vitro* and *in vivo*. Husain *et al* (260) reported that the δ-opioid receptor agonist SNC-121 significantly increased the ERG amplitude and RGC number in a rat model of chronic glaucoma by activating the PI3K/Akt pathway. Moreover, baicalein inhibits NMDA-induced apoptosis, autophagy and oxidative stress in RGCs by activating the PI3K/Akt signalling pathway *in vitro* and *in vivo* (261). A mouse model of glaucoma induced by injection of NMDA confirmed that baicalin inhibited autophagy and subsequently attenuated pathological changes in retinal tissues by activating PI3K/Akt signalling (261). Furthermore, ligustrazine increased protein levels of p-PI3K, p-Akt and p-mTOR in a rat model of chronic hypertensive glaucoma, while rapamycin or Ly294002 attenuated these changes (139). A recent study revealed that acteoside may be a potential protective drug for maintaining RGC homeostasis and preventing glaucoma-related blindness because of its therapeutic effects, such as antioxidative stress, anti-inflammatory, anti-aging and proliferative effects (262).

In addition to drugs, several microRNAs mediate apoptosis in glaucoma through the PI3K/Akt pathway. miR-145-5p suppresses TRIM2 expression by targeting the 3'-untranslated region of TRIM2. Inhibition of miR-145-5p promotes cell survival and suppresses RGCs apoptosis by activating the TRIM2/PI3K/Akt signalling pathway (140). miR-149 inhibition also promoted the viability of RGCs and inhibited RGC apoptosis in a mouse model of glaucoma by increasing the levels of BTC, p-PI3K and p-Akt (263).

6. Conclusions and future perspectives

Glaucoma is a complex group of eye diseases that involve degeneration of the retinal nerve. The clinical symptoms of glaucoma are aggravated with age, resulting in partial blindness or lifelong blindness in patients with glaucoma and severely influencing quality of life. In the early stages of glaucoma, patients are usually treated with eye-drop drugs, such as prostaglandin analogues or β-adrenergic antagonists. Although drugs reduce IOP to some extent, they cannot maintain long-term effectiveness or avoid producing side effects. Currently, the most promising treatment for glaucoma is surgical intervention as the primary treatment and medication as an adjunct. However, some surgical treatments, including filtration surgery, still have drawbacks, as visual function damage continues to progress.

There has been significant progress in understanding the pathogenesis of glaucoma in the recent years and several genes such as *MYOC* and *CYP1B1*, and epigenetic regulators, have been found to be involved in this disease. Additionally, an abundance of literature indicated that apoptosis plays a vital role in glaucoma onset, development and prognosis and that novel apoptosis-targeted strategies are promising approaches for treating glaucoma. Furthermore, survival signals that activate the PI3K/Akt pathway may lead to novel treatment options for glaucoma. Among drugs and gene therapies, targeting apoptosis is feasible in animal models and preclinical experiments. However, further proof of the feasibility of treatment is needed.

Thus, there are several remaining problems to be solved, for example: i) How can specific mechanisms and molecular changes involved in glaucoma apoptosis be further explained? ii) Identification of specific apoptotic genes or pathways that inhibit apoptosis is essential. iii) How can the effect of existing drugs or gene therapy on the inhibition of apoptosis last longer and be more stable? iv) How can the balance between proapoptotic and antiapoptotic signals be addressed? Future research will combine mechanism-based assays with improved detection methods to further explore changes in apoptotic proteins and their interrelationships and identify targets for inhibiting cell apoptosis. Furthermore, the necessary combination of interventions to maintain a subtly inclined balance while preventing apoptosis may achieve long-term and effective protection in the treatment of glaucoma.

Acknowledgements

Not applicable.

Funding

The present study was supported by the National Natural Science Foundation of China (grant no. 81470667), the Department of Science and Technology of Sichuan (grant no. 2020YFS0435), the Health Care of Sichuan Provincial cadres (grant no. 2020-227) and the Science & Technology Bureau of Chengdu (grant nos. YF05-00198-SN and YF05-00060-SN).

Availability of data and materials

Not applicable.

Authors' contributions

QX designed and completed the editing of the manuscript and created the figures and tables. QX and DZ revised the manuscript. Both authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Authors' information

Qiongrong Xia, ORCID: 0000-0001-8642-9139.

References

1. GBD 2019 Blindness and Vision Impairment Collaborators; Vision Loss Expert Group of the Global Burden of Disease Study: Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to VISION 2020: The right to sight: An analysis for the global burden of disease study. Lancet Glob Health 9: e144-e160, 2021.
2. Tham YC, Li X, Wong TY, Quigley HA, Aung T and Cheng CY: Global prevalence of glaucoma and projections of glaucoma burden through 2040: A systematic review and meta-analysis. Ophthalmology 121: 2081-2090, 2014.
3. Kang JM and Tanna AP: Glaucoma. Med Clin North Am 105: 493-510, 2021.
4. Quigley HA: Glaucoma. Lancet 377: 1367-1377, 2011.
5. Burgoyne CF, Downs JC, Bellezza AJ, Suh JK and Hart RT: The optic nerve head as a biomechanical structure: A new paradigm for understanding the role of IOP-related stress and strain in the pathophysiology of glaucomatous optic nerve head damage. Prog Retin Eye Res 24: 39-73, 2005.
6. Weinreb RN, Aung T and Medeiros FA: The pathophysiology and treatment of glaucoma: A review. JAMA 311: 1901-1911, 2014.
7. Li L and Song F: Biomechanical research into lamina cribrosa in glaucoma. Natl Sci Rev 7: 1277-1279, 2020.
8. Marcus MW, de Vries MM, Junoy Montolio FG and Jansonius NM: Myopia as a risk factor for open-angle glaucoma: A systematic review and meta-analysis. Ophthalmology 118: 1989-1994.e2, 2011.
9. Ha A, Kim CY, Shim SR, Chang IB and Kim YK: Degree of myopia and glaucoma risk: A dose-response meta-analysis. Am J Ophthalmol 236: 107-119, 2022.
10. Fong DS, Epstein DL and Allingham RR: Glaucoma and myopia: Are they related? Int Ophthalmol Clin 30: 215-218, 1990.
11. Saw SM, Gazzard G, Shih-Yen EC and Chua WH: Myopia and associated pathological complications. Ophthalmic Physiol Opt 25: 381-391, 2005.
12. Juliano J, Burkemper B, Lee J, Nelson A, LeTran V, Chu Z, Zhou G, Jiang X, Wang RK, Varma R and Richter GM: Longer axial length potentiates relationship of intraocular pressure and peripapillary vessel density in glaucoma patients. Invest Ophthalmol Vis Sci 62: 37, 2021.
13. Ren R, Wang N, Li B, Li L, Gao F, Xu X and Jonas JB: Lamina cribrosa and peripapillary sclera histomorphometry in normal and advanced glaucomatous Chinese eyes with various axial length. Invest Ophthalmol Vis Sci 50: 2175-2184, 2009.
14. Kim KE and Park KH: Update on the prevalence, etiology, diagnosis, and monitoring of normal-tension glaucoma. Asia Pac J Ophthalmol (Phila) 5: 23-31, 2016.
15. Killer HE and Pircher A: Normal tension glaucoma: Review of current understanding and mechanisms of the pathogenesis. Eye (Lond) 32: 924-930, 2018.
16. Mi XS, Yuan TF and So KF: The current research status of normal tension glaucoma. Clin Interv Aging 9: 1563-1571, 2014.
17. Chitranshi N, Rajput R, Godinez A, Pushpitha K, Mirzaei M, Basavarajappa D, Gupta V, Sharma S, You Y, Galliciotti G, *et al*: Neuroserpin gene therapy inhibits retinal ganglion cell apoptosis and promotes functional preservation in glaucoma. Mol Ther 31: 2056-2076, 2023.
18. Miglior S, Torri V, Zeyen T, Pfeiffer N, Vaz JC and Adamsons I; EGPS Group: Intercurrent factors associated with the development of open-angle glaucoma in the European glaucoma prevention study. Am J Ophthalmol 144: 266-275, 2007.
19. Suzuki Y, Iwase A, Araie M, Yamamoto T, Abe H, Shirato S, Kuwayama Y, Mishima HK, Shimizu H, Tomita G, *et al*: Risk factors for open-angle glaucoma in a Japanese population: The Tajimi study. Ophthalmology 113: 1613-1617, 2006.
20. Saccà SC and Izzotti A: Oxidative stress and glaucoma: Injury in the anterior segment of the eye. Prog Brain Res 173: 385-407, 2008.
21. Flammer J and Mozaffarieh M: What is the present pathogenetic concept of glaucomatous optic neuropathy? Surv Ophthalmol 52 (Suppl 2): S162-S173, 2007.
22. Shen WC, Huang BQ and Yang J: Regulatory mechanisms of retinal ganglion cell death in normal tension glaucoma and potential therapies. Neural Regen Res 18: 87-93, 2023.
23. Kerr JF, Wyllie AH and Currie AR: Apoptosis: A basic biological phenomenon with wide-ranging implications in tissue kinetics. Br J Cancer 26: 239-257, 1972.
24. Fleisher TA: Apoptosis. Ann Allergy Asthma Immunol 78: 245-250, 1997.
25. Elmore S: Apoptosis: A review of programmed cell death. Toxicol Pathol 35: 495-516, 2007.
26. Li C, Liu W, Wang F, Hayashi T, Mizuno K, Hattori S, Fujisaki H and Ikejima T: DNA damage-triggered activation of cGAS-STING pathway induces apoptosis in human keratinocyte HaCaT cells. Mol Immunol 131: 180-190, 2021.
27. Yu J, Sun W, Song Y, Liu J, Xue F, Gong K, Yang X and Kang Q: SIRT6 protects retinal ganglion cells against hydrogen peroxide-induced apoptosis and oxidative stress by promoting Nrf2/ARE signaling via inhibition of Bach1. Chem Biol Interact 300: 151-158, 2019.
28. Wang Y, Osakue D, Yang E, Zhou Y, Gong H, Xia X and Du Y: Endoplasmic reticulum stress response of trabecular meshwork stem cells and trabecular meshwork cells and protective effects of activated PERK pathway. Invest Ophthalmol Vis Sci 60: 265-273, 2019.
29. Wang M, Tan J, Miao Y, Li M and Zhang Q: Role of Ca^{2+} and ion channels in the regulation of apoptosis under hypoxia. Histol Histopathol 33: 237-246, 2018.
30. Liu Z, Fu G and Liu A: The relationship between inflammatory mediator expression in the aqueous humor and secondary glaucoma incidence after silicone oil tamponade. Exp Ther Med 14: 5833-5836, 2017.
31. Saraste A and Pulkki K: Morphologic and biochemical hallmarks of apoptosis. Cardiovasc Res 45: 528-537, 2000.
32. Geske FJ and Gerschenson LE: The biology of apoptosis. Hum Pathol 32: 1029-1038, 2001.
33. Baleriola J, García-Feijoo J, Martínez-de-la-Casa JM, Fernández-Cruz A, de la Rosa EJ and Fernández-Durango R: Apoptosis in the trabecular meshwork of glaucomatous patients. Mol Vis 14: 1513-1516, 2008.
34. Galvao J, Davis BM and Cordeiro MF: In vivo imaging of retinal ganglion cell apoptosis. Curr Opin Pharmacol 13: 123-127, 2013.
35. Krishnan A, Kocab AJ, Zacks DN, Marshak-Rothstein A and Gregory-Ksander M: A small peptide antagonist of the Fas receptor inhibits neuroinflammation and prevents axon degeneration and retinal ganglion cell death in an inducible mouse model of glaucoma. J Neuroinflammation 16: 184, 2019.
36. Chen X, Lei F, Zhou C, Chodosh J, Wang L, Huang Y, Dohlman CH and Paschalis EI: Glaucoma after ocular surgery or trauma: The role of infiltrating monocytes and their response to cytokine inhibitors. Am J Pathol 190: 2056-2066, 2020.

37. Dohlman CH, Zhou C, Lei F, Cade F, Regatieri CV, Črnej A, Dohlman JG, Shen LQ and Paschalis EI: Glaucoma after corneal trauma or surgery-A rapid, inflammatory, IOP-independent pathway. Cornea 38: 1589-1594, 2019.
38. Rasmussen CA, Kaufman PL and Kiland JA: Benzalkonium chloride and glaucoma. J Ocul Pharmacol Ther 30: 163-169, 2014.
39. Almasieh M, Wilson AM, Morquette B, Cueva Vargas JL and Di Polo A: The molecular basis of retinal ganglion cell death in glaucoma. Prog Retin Eye Res 31: 152-181, 2012.
40. Wu A, Khawaja AP, Pasquale LR and Stein JD: A review of systemic medications that may modulate the risk of glaucoma. Eye (Lond) 34: 12-28, 2020.
41. Hamard P, Blondin C, Debbasch C, Warnet JM, Baudouin C and Brignole F: In vitro effects of preserved and unpreserved antiglaucoma drugs on apoptotic marker expression by human trabecular cells. Graefes Arch Clin Exp Ophthalmol 241: 1037-1043, 2003.
42. Gedde SJ, Schiffman JC, Feuer WJ, Herndon LW, Brandt JD and Budenz DL; Tube versus Trabeculectomy Study Group: Treatment outcomes in the tube versus trabeculectomy (TVT) study after five years of follow-up. Am J Ophthalmol 153: 789-803.e2, 2012.
43. Javaid U, Ali MH, Jamal S and Butt NH: Pathophysiology, diagnosis, and management of glaucoma associated with Sturge-Weber syndrome. Int Ophthalmol 38: 409-416, 2018.
44. Yoon PS and Singh K: Update on antifibrotic use in glaucoma surgery, including use in trabeculectomy and glaucoma drainage implants and combined cataract and glaucoma surgery. Curr Opin Ophthalmol 15: 141-146, 2004.
45. Paschalis EI, Lei F, Zhou C, Chen XN, Kapoulea V, Hui PC, Dana R, Chodosh J, Vavvas DG and Dohlman CH: Microglia regulate neuroglia remodeling in various ocular and retinal injuries. J Immunol 202: 539-549, 2019.
46. Cade F, Paschalis EI, Regatieri CV, Vavvas DG, Dana R and Dohlman CH: Alkali burn to the eye: Protection using TNF-α inhibition. Cornea 33: 382-389, 2014.
47. Ju KR, Kim HS, Kim JH, Lee NY and Park CK: Retinal glial cell responses and Fas/FasL activation in rats with chronic ocular hypertension. Brain Res 1122: 209-221, 2006.
48. Quigley HA, Nickells RW, Kerrigan LA, Pease ME, Thibault DJ and Zack DJ: Retinal ganglion cell death in experimental glaucoma and after axotomy occurs by apoptosis. Invest Ophthalmol Vis Sci 36: 774-786, 1995.
49. Libby RT, Li Y, Savinova OV, Barter J, Smith RS, Nickells RW and John SW: Susceptibility to neurodegeneration in a glaucoma is modified by Bax gene dosage. PLoS Genet 1: 17-26, 2005.
50. Kerrigan LA, Zack DJ, Quigley HA, Smith SD and Pease ME: TUNEL-positive ganglion cells in human primary open-angle glaucoma. Arch Ophthalmol 115: 1031-1035, 1997.
51. Tök L, Nazıroğlu M, Uğuz AC and Tök O: Elevated hydrostatic pressures induce apoptosis and oxidative stress through mitochondrial membrane depolarization in PC12 neuronal cells: A cell culture model of glaucomaz: A cell culture model of glaucoma. J Recept Signal Transduct Res 34: 410-416, 2014.
52. Erisgin Z, Ozer MA, Tosun M, Ozen S and Takir S: The effects of intravitreal H_2 S application on apoptosis in the retina and cornea in experimental glaucoma model. Int J Exp Pathol 100: 330-336, 2019.
53. Ying Y, Xue R, Yang Y, Zhang SX, Xiao H, Zhu H, Li J, Chen G, Ye Y, Yu M, *et al*: Activation of ATF4 triggers trabecular meshwork cell dysfunction and apoptosis in POAG. Aging (Albany NY) 13: 8628-8642, 2021.
54. Saccà SC, Pulliero A and Izzotti A: The dysfunction of the trabecular meshwork during glaucoma course. J Cell Physiol 230: 510-525, 2015.
55. Saccà SC, Gandolfi S, Bagnis A, Manni G, Damonte G, Traverso CE and Izzotti A: From DNA damage to functional changes of the trabecular meshwork in aging and glaucoma. Ageing Res Rev 29: 26-41, 2016.
56. Ammar DA and Kahook MY: Effects of benzalkonium chloride- or polyquad-preserved fixed combination glaucoma medications on human trabecular meshwork cells. Mol Vis 17: 1806-1813, 2011.
57. Goldstein MH, Silva FQ, Blender N, Tran T and Vantipalli S: Ocular benzalkonium chloride exposure: Problems and solutions. Eye (Lond) 36: 361-368, 2022.
58. Baudouin C, Kolko M, Melik-Parsadaniantz S and Messmer EM: Inflammation in glaucoma: From the back to the front of the eye, and beyond. Prog Retin Eye Res 83: 100916, 2021.
59. Liton PB and Gonzalez P: Stress response of the trabecular meshwork. J Glaucoma 17: 378-385, 2008.
60. Rohen JW, Lütjen-Drecoll E, Flügel C, Meyer M and Grierson I: Ultrastructure of the trabecular meshwork in untreated cases of primary open-angle glaucoma (POAG). Exp Eye Res 56: 683-692, 1993.
61. Stamer WD and Acott TS: Current understanding of conventional outflow dysfunction in glaucoma. Curr Opin Ophthalmol 23: 135-143, 2012.
62. Yan X, Wu S, Liu Q, Li Y, Zhu W and Zhang J: Accumulation of Asn450Tyr mutant myocilin in ER promotes apoptosis of human trabecular meshwork cells. Mol Vis 26: 563-573, 2020.
63. Agarwal R, Talati M, Lambert W, Clark AF, Wilson SE, Agarwal N and Wordinger RJ: Fas-activated apoptosis and apoptosis mediators in human trabecular meshwork cells. Exp Eye Res 68: 583-590, 1999.
64. Suri F, Yazdani S and Elahi E: LTBP2 knockdown and oxidative stress affect glaucoma features including TGFβ pathways, ECM genes expression and apoptosis in trabecular meshwork cells. Gene 673: 70-81, 2018.
65. Oritani K, Aoyama K, Tomiyama Y, Kincade PW and Matsuzawa Y: Stromal cell CD9 and the differentiation of hematopoietic stem/progenitor cells. Leuk Lymphoma 38: 147-152, 2000.
66. Jiang X, Teng M, Ji R, Zhang D, Zhang Z, Lv Y, Zhang Q, Zhang J and Huang Y: CD9 regulates keratinocyte differentiation and motility by recruiting E-cadherin to the plasma membrane and activating the PI3K/Akt pathway. Biochim Biophys Acta Mol Cell Res 1867: 118574, 2020.
67. Yan J, Yang X, Jiao X, Yang X, Guo M, Chen Y, Zhan L and Chen W: Integrative transcriptomic and proteomic analysis reveals CD9/ITGA4/PI3K-Akt axis mediates trabecular meshwork cell apoptosis in human glaucoma. J Cell Mol Med 24: 814-829, 2020.
68. Wang Y, Li F and Wang S: MicroRNA-93 is overexpressed and induces apoptosis in glaucoma trabecular meshwork cells. Mol Med Rep 14: 5746-5750, 2016.
69. Shen Y, Zhu Y and Rong F: miR-200c-3p regulates the proliferation and apoptosis of human trabecular meshwork cells by targeting PTEN. Mol Med Rep 22: 1605-1612, 2020.
70. Wang X, Li Z, Bai J, Song W and Zhang F: miR-17-5p regulates the proliferation and apoptosis of human trabecular meshwork cells by targeting phosphatase and tensin homolog. Mol Med Rep 19: 3132-3138, 2019.
71. Wang Y, Zhou H, Liu X, Han Y, Pan S and Wang Y: MiR-181a inhibits human trabecular meshwork cell apoptosis induced by H_2O_2 through the suppression of NF-κB and JNK pathways. Adv Clin Exp Med 27: 577-582, 2018.
72. Wang K, Read AT, Sulchek T and Ethier CR: Trabecular meshwork stiffness in glaucoma. Exp Eye Res 158: 3-12, 2017.
73. Fuchshofer R and Tamm ER: The role of TGF-β in the pathogenesis of primary open-angle glaucoma. Cell Tissue Res 347: 279-290, 2012.
74. Wang J, Liu X and Zhong Y: Rho/Rho-associated kinase pathway in glaucoma (review). Int J Oncol 43: 1357-1367, 2013.
75. Vernazza S, Tirendi S, Passalacqua M, Piacente F, Scarfì S, Oddone F and Bassi AM: An innovative in vitro open-angle glaucoma model (IVOM) shows changes induced by increased ocular pressure and oxidative stress. Int J Mol Sci 22: 12129, 2021.
76. Soto I and Howell GR: The complex role of neuroinflammation in glaucoma. Cold Spring Harb Perspect Med 4: a017269, 2014.
77. Ebneter A, Casson RJ, Wood JP and Chidlow G: Microglial activation in the visual pathway in experimental glaucoma: Spatiotemporal characterization and correlation with axonal injury. Invest Ophthalmol Vis Sci 51: 6448-6460, 2010.
78. Bordone MP, González Fleitas MF, Pasquini LA, Bosco A, Sande PH, Rosenstein RE and Dorfman D: Involvement of microglia in early axoglial alterations of the optic nerve induced by experimental glaucoma. J Neurochem 142: 323-337, 2017.
79. Guo L, Moss SE, Alexander RA, Ali RR, Fitzke FW and Cordeiro MF: Retinal ganglion cell apoptosis in glaucoma is related to intraocular pressure and IOP-induced effects on extracellular matrix. Invest Ophthalmol Vis Sci 46: 175-182, 2005.
80. Bosco A, Steele MR and Vetter ML: Early microglia activation in a mouse model of chronic glaucoma. J Comp Neurol 519: 599-620, 2011.
81. Bosco A, Romero CO, Breen KT, Chagovetz AA, Steele MR, Ambati BK and Vetter ML: Neurodegeneration severity can be predicted from early microglia alterations monitored in vivo in a mouse model of chronic glaucoma. Dis Model Mech 8: 443-455, 2015.

82. Williams PA, Marsh-Armstrong N and Howell GR; Lasker/IRRF Initiative on Astrocytes and Glaucomatous Neurodegeneration Participants: Neuroinflammation in glaucoma: A new opportunity. Exp Eye Res 157: 20-27, 2017.
83. Tribble JR, Kokkali E, Otmani A, Plastino F, Lardner E, Vohra R, Kolko M, André H, Morgan JE and Williams PA: When is a control not a control? Reactive microglia occur throughout the control contralateral pathway of retinal ganglion cell projections in experimental glaucoma. Transl Vis Sci Technol 10: 22, 2021.
84. Unlu M, Aktas Z, Gocun PU, Ilhan SO, Hasanreisoglu M and Hasanreisoglu B: Neuroprotective effect of systemic and/or intravitreal rosuvastatin administration in rat glaucoma model. Int J Ophthalmol 9: 340-347, 2016.
85. Dyka FM, May CA and Enz R: Metabotropic glutamate receptors are differentially regulated under elevated intraocular pressure. J Neurochem 90: 190-202, 2004.
86. Wu X, Dou YN, Fei Z and Fei F: Parkin prevents glutamate excitotoxicity through inhibiting NLRP3 inflammasome in retinal ganglion cells. Neuroscience 478: 1-10, 2021.
87. Murphy G, Knäuper V, Lee MH, Amour A, Worley JR, Hutton M, Atkinson S, Rapti M and Williamson R: Role of TIMPs (tissue inhibitors of metalloproteinases) in pericellular proteolysis: The specificity is in the detail. Biochem Soc Symp: 65-80, 2003.
88. Mathew DJ, Livne-Bar I and Sivak JM: An inducible rodent glaucoma model that exhibits gradual sustained increase in intraocular pressure with distinct inner retina and optic nerve inflammation. Sci Rep 11: 22880, 2021.
89. Sakata R, Ueno T, Nakamura T, Ueno H and Sata M: Mechanical stretch induces TGF-beta synthesis in hepatic stellate cells. Eur J Clin Invest 34: 129-136, 2004.
90. Kirwan RP, Crean JK, Fenerty CH, Clark AF and O'Brien CJ: Effect of cyclical mechanical stretch and exogenous transforming growth factor-beta1 on matrix metalloproteinase-2 activity in lamina cribrosa cells from the human optic nerve head. J Glaucoma 13: 327-334, 2004.
91. Gomes LR, Terra LF, Wailemann RA, Labriola L and Sogayar MC: TGF-β1 modulates the homeostasis between MMPs and MMP inhibitors through p38 MAPK and ERK1/2 in highly invasive breast cancer cells. BMC Cancer 12: 26, 2012.
92. Cordeiro MF, Bhattacharya SS, Schultz GS and Khaw PT: TGF-beta1, -beta2, and -beta3 in vitro: Biphasic effects on Tenon's fibroblast contraction, proliferation, and migration. Invest Ophthalmol Vis Sci 41: 756-763, 2000.
93. Nguyen TTM, Gillet G and Popgeorgiev N: Caspases in the developing central nervous system: Apoptosis and beyond. Front Cell Dev Biol 9: 702404, 2021.
94. Cohen GM: Caspases: The executioners of apoptosis. Biochem J 326: 1-16, 1997.
95. Abate M, Festa A, Falco M, Lombardi A, Luce A, Grimaldi A, Zappavigna S, Sperlongano P, Irace C, Caraglia M and Misso G: Mitochondria as playmakers of apoptosis, autophagy and senescence. Semin Cell Dev Biol 98: 139-153, 2020.
96. Alapati T, Sagal KM, Gudiseva HV, Pistilli M, Pyfer M, Chavali VRM and O'Brien JM: Evaluating TNF-α and interleukin-2 (IL-2) levels in African American primary open-angle glaucoma patients. Genes (Basel) 13: 54, 2021.
97. Wilson NS, Dixit V and Ashkenazi A: Death receptor signal transducers: Nodes of coordination in immune signaling networks. Nat Immunol 10: 348-355, 2009.
98. Mahdizadeh SJ, Thomas M and Eriksson LA: Reconstruction of the Fas-based death-inducing signaling complex (DISC) using a protein-protein docking meta-approach. J Chem Inf Model 61: 3543-3558, 2021.
99. Hillert-Richter LK and Lavrik IN: Measuring composition of CD95 death-inducing signaling complex and processing of procaspase-8 in this complex. J Vis Exp, 2021.
100. Yang XJ, Ge J and Zhuo YH: Role of mitochondria in the pathogenesis and treatment of glaucoma. Chin Med J (Engl) 126: 4358-4365, 2013.
101. Zeng Z, You M, Fan C, Rong R, Li H and Xia X: Pathologically high intraocular pressure induces mitochondrial dysfunction through Drp1 and leads to retinal ganglion cell PANoptosis in glaucoma. Redox Biol 62: 102687, 2023.
102. Bock FJ and Tait SWG: Mitochondria as multifaceted regulators of cell death. Nat Rev Mol Cell Biol 21: 85-100, 2020.
103. Saelens X, Festjens N, Vande Walle L, van Gurp M, van Loo G and Vandenabeele P: Toxic proteins released from mitochondria in cell death. Oncogene 23: 2861-2874, 2004.
104. Shakeri R, Kheirollahi A and Davoodi J: Apaf-1: Regulation and function in cell death. Biochimie 135: 111-125, 2017.
105. Brentnall M, Rodriguez-Menocal L, De Guevara RL, Cepero E and Boise LH: Caspase-9, caspase-3 and caspase-7 have distinct roles during intrinsic apoptosis. BMC Cell Biol 14: 32, 2013.
106. Kale J, Osterlund EJ and Andrews DW: BCL-2 family proteins: Changing partners in the dance towards death. Cell Death Differ 25: 65-80, 2018.
107. Leibowitz B and Yu J: Mitochondrial signaling in cell death via the Bcl-2 family. Cancer Biol Ther 9: 417-422, 2010.
108. Ding J, Mooers BHM, Zhang Z, Kale J, Falcone D, McNichol J, Huang B, Zhang XC, Xing C, Andrews DW and Lin J: After embedding in membranes antiapoptotic Bcl-XL protein binds both Bcl-2 homology region 3 and helix 1 of proapoptotic Bax protein to inhibit apoptotic mitochondrial permeabilization. J Biol Chem 289: 11873-11896, 2014.
109. Luna-Vargas MPA and Chipuk JE: The deadly landscape of pro-apoptotic BCL-2 proteins in the outer mitochondrial membrane. FEBS J 283: 2676-2689, 2016.
110. Huang DC and Strasser A: BH3-Only proteins-essential initiators of apoptotic cell death. Cell 103: 839-842, 2000.
111. Bano D and Prehn JHM: Apoptosis-inducing factor (AIF) in physiology and disease: The tale of a repented natural born killer. EBioMedicine 30: 29-37, 2018.
112. Porat S and Simantov R: Bcl-2 and p53: Role in dopamine-induced apoptosis and differentiation. Ann N Y Acad Sci 893: 372-375, 1999.
113. Sawada O, Perusek L, Kohno H, Howell SJ, Maeda A, Matsuyama S and Maeda T: All-trans-retinal induces Bax activation via DNA damage to mediate retinal cell apoptosis. Exp Eye Res 123: 27-36, 2014.
114. Wang Y, Okan I, Szekely L, Klein G and Wiman KG: bcl-2 inhibits wild-type p53-triggered apoptosis but not G1 cell cycle arrest and transactivation of WAF1 and bax. Cell Growth Differ 6: 1071-1075, 1995.
115. Chylicki K, Ehinger M, Svedberg H and Gullberg U: Characterization of the molecular mechanisms for p53-mediated differentiation. Cell Growth Differ 11: 561-571, 2000.
116. Oakes SA and Papa FR: The role of endoplasmic reticulum stress in human pathology. Annu Rev Pathol 10: 173-194, 2015.
117. Hetz C, Zhang K and Kaufman RJ: Mechanisms, regulation and functions of the unfolded protein response. Nat Rev Mol Cell Biol 21: 421-438, 2020.
118. Ron D and Walter P: Signal integration in the endoplasmic reticulum unfolded protein response. Nat Rev Mol Cell Biol 8: 519-529, 2007.
119. Lafleur MA, Stevens JL and Lawrence JW: Xenobiotic perturbation of ER stress and the unfolded protein response. Toxicol Pathol 41: 235-262, 2013.
120. Urano F, Wang X, Bertolotti A, Zhang Y, Chung P, Harding HP and Ron D: Coupling of stress in the ER to activation of JNK protein kinases by transmembrane protein kinase IRE1. Science 287: 664-666, 2000.
121. Kwong JMK and Caprioli J: Expression of phosphorylated c-Jun N-terminal protein kinase (JNK) in experimental glaucoma in rats. Exp Eye Res 82: 576-582, 2006.
122. Hwang J and Qi L: Quality control in the endoplasmic reticulum: Crosstalk between ERAD and UPR pathways. Trends Biochem Sci 43: 593-605, 2018.
123. Maurel M, Chevet E, Tavernier J and Gerlo S: Getting RIDD of RNA: IRE1 in cell fate regulation. Trends Biochem Sci 39: 245-254, 2014.
124. Hayashi T, Saito A, Okuno S, Ferrand-Drake M, Dodd RL and Chan PH: Oxidative injury to the endoplasmic reticulum in mouse brains after transient focal ischemia. Neurobiol Dis 15: 229-239, 2004.
125. Wek RC, Jiang HY and Anthony TG: Coping with stress: eIF2 kinases and translational control. Biochem Soc Trans 34: 7-11, 2006.
126. Peters JC, Bhattacharya S, Clark AF and Zode GS: Increased endoplasmic reticulum stress in human glaucomatous trabecular meshwork cells and tissues. Invest Ophthalmol Vis Sci 56: 3860-3868, 2015.
127. Marola OJ, Syc-Mazurek SB and Libby RT: DDIT3 (CHOP) contributes to retinal ganglion cell somal loss but not axonal degeneration in DBA/2J mice. Cell Death Discov 5: 140, 2019.
128. Kasetti RB, Patel PD, Maddineni P, Patil S, Kiehlbauch C, Millar JC, Searby CC, Raghunathan V, Sheffield VC and Zode GS: ATF4 leads to glaucoma by promoting protein synthesis and ER client protein load. Nat Commun 11: 5594, 2020.

129. Doh SH, Kim JH, Lee KM, Park HY and Park CK: Retinal ganglion cell death induced by endoplasmic reticulum stress in a chronic glaucoma model. Brain Res 1308: 158-166, 2010.
130. Yoshida H, Matsui T, Yamamoto A, Okada T and Mori K: XBP1 mRNA is induced by ATF6 and spliced by IRE1 in response to ER stress to produce a highly active transcription factor. Cell 107: 881-891, 2001.
131. Watanabe M, Ida Y, Furuhashi M, Tsugeno Y, Ohguro H and Hikage F: Screening of the drug-induced effects of prostaglandin EP2 and FP agonists on 3D cultures of dexamethasone-treated human trabecular meshwork cells. Biomedicines 9: 930, 2021.
132. Lee EJ, Chan P, Chea L, Kim K, Kaufman RJ and Lin JH: ATF6 is required for efficient rhodopsin clearance and retinal homeostasis in the P23H rho retinitis pigmentosa mouse model. Sci Rep 11: 16356, 2021.
133. Julien O and Wells JA: Caspases and their substrates. Cell Death Differ 24: 1380-1389, 2017.
134. Yuan J, Shaham S, Ledoux S, Ellis HM and Horvitz HR: The C. elegans cell death gene ced-3 encodes a protein similar to mammalian interleukin-1 beta-converting enzyme. Cell 75: 641-652, 1993.
135. Van Opdenbosch N and Lamkanfi M: Caspases in cell death, inflammation, and disease. Immunity 50: 1352-1364, 2019.
136. Ramirez MLG and Salvesen GS: A primer on caspase mechanisms. Semin Cell Dev Biol 82: 79-85, 2018.
137. Man SM, Karki R and Kanneganti TD: Molecular mechanisms and functions of pyroptosis, inflammatory caspases and inflammasomes in infectious diseases. Immunol Rev 277: 61-75, 2017.
138. Ye D, Xu Y, Shi Y, Fan M, Lu P, Bai X, Feng Y, Hu C, Cui K, Tang X, *et al*: Anti-PANoptosis is involved in neuroprotective effects of melatonin in acute ocular hypertension model. J Pineal Res 73: e12828, 2022.
139. Du HY, Wang R, Li JL, Luo H, Xie XY, Yan R, Jian YL and Cai JY: Ligustrazine protects against chronic hypertensive glaucoma in rats by inhibiting autophagy via the PI3K-Akt/mTOR pathway. Mol Vis 27: 725-733, 2021.
140. Xu K, Li S, Yang Q, Zhou Z, Fu M, Yang X, Hao K, Liu Y and Ji H: MicroRNA-145-5p targeting of TRIM2 mediates the apoptosis of retinal ganglion cells via the PI3K/AKT signaling pathway in glaucoma. J Gene Med 23: e3378, 2021.
141. Li R, Jin Y, Li Q, Sun X, Zhu H and Cui H: MiR-93-5p targeting PTEN regulates the NMDA-induced autophagy of retinal ganglion cells via AKT/mTOR pathway in glaucoma. Biomed Pharmacother 100: 1-7, 2018.
142. Tatton WG, Chalmers-Redman RM, Sud A, Podos SM and Mittag TW: Maintaining mitochondrial membrane impermeability. An opportunity for new therapy in glaucoma? Surv Ophthalmol 45 (Suppl 3): S277-S283, S295-S296, 2001.
143. Miano M, Madeo A, Cappelli E, Lanza F, Lanza T, Stroppiano M, Terranova P, Venè R, Bleesing JJH and Di Rocco M: Defective FAS-mediated apoptosis and immune dysregulation in gaucher disease. J Allergy Clin Immunol Pract 8: 3535-3542, 2020.
144. Li-Weber M and Krammer PH: Function and regulation of the CD95 (APO-1/Fas) ligand in the immune system. Semin Immunol 15: 145-157, 2003.
145. Levoin N, Jean M and Legembre P: CD95 structure, aggregation and cell signaling. Front Cell Dev Biol 8: 314, 2020.
146. Guégan JP and Legembre P: Nonapoptotic functions of Fas/CD95 in the immune response. FEBS J 285: 809-827, 2018.
147. Krishnan A, Fei F, Jones A, Busto P, Marshak-Rothstein A, Ksander BR and Gregory-Ksander M: Overexpression of soluble fas ligand following adeno-associated virus gene therapy prevents retinal ganglion cell death in chronic and acute murine models of glaucoma. J Immunol 197: 4626-4638, 2016.
148. Gregory-Ksander M and Marshak-Rothstein A: The FasLane to ocular pathology-metalloproteinase cleavage of membrane-bound FasL determines FasL function. J Leukoc Biol 110: 965-977, 2021.
149. Razeghinejad MR and Kamali-Sarvestani E: Aqueous humor levels of soluble Fas and Fas-ligand in patients with primary open angle and pseudoexfoliation glaucoma. Iran J Immunol 4: 215-219, 2007.
150. Gregory MS, Hackett CG, Abernathy EF, Lee KS, Saff RR, Hohlbaum AM, Moody KS, Hobson MW, Jones A, Kolovou P, *et al*: Opposing roles for membrane bound and soluble Fas ligand in glaucoma-associated retinal ganglion cell death. PLoS One 6: e17659, 2011.
151. O' Reilly LA, Tai L, Lee L, Kruse EA, Grabow S, Fairlie WD, Haynes NM, Tarlinton DM, Zhang JG, Belz GT, *et al*: Membrane-bound Fas ligand only is essential for Fas-induced apoptosis. Nature 461: 659-663, 2009.
152. Wax MB, Tezel G, Yang J, Peng G, Patil RV, Agarwal N, Sappington RM and Calkins DJ: Induced autoimmunity to heat shock proteins elicits glaucomatous loss of retinal ganglion cell neurons via activated T-cell-derived fas-ligand. J Neurosci 28: 12085-12096, 2008.
153. Besirli CG, Chinskey ND, Zheng QD and Zacks DN: Inhibition of retinal detachment-induced apoptosis in photoreceptors by a small peptide inhibitor of the fas receptor. Invest Ophthalmol Vis Sci 51: 2177-2184, 2010.
154. Aoki K, Kurooka M, Chen JJ, Petryniak J, Nabel EG and Nabel GJ: Extracellular matrix interacts with soluble CD95L: Retention and enhancement of cytotoxicity. Nat Immunol 2: 333-337, 2001.
155. Bai Y, Shi Z, Zhuo Y, Liu J, Malakhov A, Ko E, Burgess K, Schaefer H, Esteban PF, Tessarollo L and Saragovi HU: In glaucoma the upregulated truncated TrkC.T1 receptor isoform in glia causes increased TNF-alpha production, leading to retinal ganglion cell death. Invest Ophthalmol Vis Sci 51: 6639-6651, 2010.
156. Aggarwal BB, Gupta SC and Kim JH: Historical perspectives on tumor necrosis factor and its superfamily: 25 Years later, a golden journey. Blood 119: 651-665, 2012.
157. Kelker HC, Oppenheim JD, Stone-Wolff D, Henriksen-DeStefano D, Aggarwal BB, Stevenson HC and Vilcek J: Characterization of human tumor necrosis factor produced by peripheral blood monocytes and its separation from lymphotoxin. Int J Cancer 36: 69-73, 1985.
158. Subedi L, Lee SE, Madiha S, Gaire BP, Jin M, Yumnam S and Kim SY: Phytochemicals against TNFα-mediated neuroinflammatory diseases. Int J Mol Sci 21: 764, 2020.
159. Pegoretti V, Baron W, Laman JD and Eisel ULM: Selective modulation of TNF-TNFRs signaling: Insights for multiple sclerosis treatment. Front Immunol 9: 925, 2018.
160. Sivakumar V, Foulds WS, Luu CD, Ling EA and Kaur C: Retinal ganglion cell death is induced by microglia derived pro-inflammatory cytokines in the hypoxic neonatal retina. J Pathol 224: 245-260, 2011.
161. Cueva Vargas JL, Osswald IK, Unsain N, Aurousseau MR, Barker PA, Bowie D and Di Polo A: Soluble tumor necrosis factor alpha promotes retinal ganglion cell death in glaucoma via calcium-permeable AMPA receptor activation. J Neurosci 35: 12088-12102, 2015.
162. Lee JC, Park CW, Shin MC, Cho JH, Lee HA, Kim YM, Park JH, Ahn JH, Cho JH, Tae HJ, *et al*: Tumor necrosis factor receptor 2 is required for ischemic preconditioning-mediated neuroprotection in the hippocampus following a subsequent longer transient cerebral ischemia. Neurochem Int 118: 292-303, 2018.
163. Agarwal R and Agarwal P: Glaucomatous neurodegeneration: An eye on tumor necrosis factor-alpha. Indian J Ophthalmol 60: 255-261, 2012.
164. Levkovitch-Verbin H, Waserzoog Y, Vander S, Makarovsky D and Piven I: Minocycline upregulates pro-survival genes and downregulates pro-apoptotic genes in experimental glaucoma. Graefes Arch Clin Exp Ophthalmol 252: 761-772, 2014.
165. Taurone S, Ripandelli G, Pacella E, Bianchi E, Plateroti AM, De Vito S, Plateroti P, Grippaudo FR, Cavallotti C and Artico M: Potential regulatory molecules in the human trabecular meshwork of patients with glaucoma: Immunohistochemical profile of a number of inflammatory cytokines. Mol Med Rep 11: 1384-1390, 2015.
166. Choi JA, Maddala R, Karnam S, Skiba NP, Vann R, Challa P and Rao PV: Role of vasorin, an anti-apoptotic, anti-TGF-β and hypoxia-induced glycoprotein in the trabecular meshwork cells and glaucoma. J Cell Mol Med 26: 2063-2075, 2022.
167. Morgan MJ and Liu ZG: Reactive oxygen species in TNFalpha-induced signaling and cell death. Mol Cells 30: 1-12, 2010.
168. Madeira MH, Elvas F, Boia R, Gonçalves FQ, Cunha RA, Ambrósio AF and Santiago AR: Adenosine A2AR blockade prevents neuroinflammation-induced death of retinal ganglion cells caused by elevated pressure. J Neuroinflammation 12: 115, 2015.
169. Bozkurt B, Mesci L, Irkec M, Ozdag BB, Sanal O, Arslan U, Ersoy F and Tezcan I: Association of tumour necrosis factor-alpha-308 G/A polymorphism with primary open-angle glaucoma. Clin Exp Ophthalmol 40: e156-e162, 2012.
170. Lin HJ, Tsai FJ, Chen WC, Shi YR, Hsu Y and Tsai SW: Association of tumour necrosis factor alpha-308 gene polymorphism with primary open-angle glaucoma in Chinese. Eye (Lond) 17: 31-34, 2003.

171. Singh A, Ni J and Aggarwal BB: Death domain receptors and their role in cell demise. J Interferon Cytokine Res 18: 439-450, 1998.
172. Lavrik I, Golks A and Krammer PH: Death receptor signaling. J Cell Sci 118: 265-267, 2005.
173. Zalewska R, Zalewski B, Reszec J, Mariak Z, Zimnoch L and Proniewska-Skretek E: The expressions of Fas and caspase-3 in human glaucomatous optic nerve axons. Med Sci Monit 14: BR274-BR278, 2008.
174. Pawar M, Busov B, Chandrasekhar A, Yao J, Zacks DN and Besirli CG: FAS apoptotic inhibitory molecule 2 is a stress-induced intrinsic neuroprotective factor in the retina. Cell Death Differ 24: 1799-1810, 2017.
175. Tezel G: TNF-alpha signaling in glaucomatous neurodegeneration. Prog Brain Res 173: 409-421, 2008.
176. Yan X, Tezel G, Wax MB and Edward DP: Matrix metalloproteinases and tumor necrosis factor alpha in glaucomatous optic nerve head. Arch Ophthalmol 118: 666-673, 2000.
177. Yuan L and Neufeld AH: Tumor necrosis factor-alpha: A potentially neurodestructive cytokine produced by glia in the human glaucomatous optic nerve head. Glia 32: 42-50, 2000.
178. Tezel G, Li LY, Patil RV and Wax MB: TNF-alpha and TNF-alpha receptor-1 in the retina of normal and glaucomatous eyes. Invest Ophthalmol Vis Sci 42: 1787-1794, 2001.
179. Cheng S, Wang HN, Xu LJ, Li F, Miao Y, Lei B, Sun X and Wang Z: Soluble tumor necrosis factor-alpha-induced hyperexcitability contributes to retinal ganglion cell apoptosis by enhancing Nav1.6 in experimental glaucoma. J Neuroinflammation 18: 182, 2021.
180. Nakazawa T, Nakazawa C, Matsubara A, Noda K, Hisatomi T, She H, Michaud N, Hafezi-Moghadam A, Miller JW and Benowitz LI: Tumor necrosis factor-alpha mediates oligodendrocyte death and delayed retinal ganglion cell loss in a mouse model of glaucoma. J Neurosci 26: 12633-12641, 2006.
181. Hänninen VA, Pantcheva MB, Freeman EE, Poulin NR and Grosskreutz CL: Activation of caspase 9 in a rat model of experimental glaucoma. Curr Eye Res 25: 389-395, 2002.
182. Chi W, Li F, Chen H, Wang Y, Zhu Y, Yang X, Zhu J, Wu F, Ouyang H, Ge J, *et al*: Caspase-8 promotes NLRP1/NLRP3 inflammasome activation and IL-1β production in acute glaucoma. Proc Natl Acad Sci USA 111: 11181-11186, 2014.
183. Yang X, Zeng Q and Tezel G: Regulation of distinct caspase-8 functions in retinal ganglion cells and astroglia in experimental glaucoma. Neurobiol Dis 150: 105258, 2021.
184. Choudhury S, Liu Y, Clark AF and Pang IH: Caspase-7: A critical mediator of optic nerve injury-induced retinal ganglion cell death. Mol Neurodegener 10: 40, 2015.
185. Vigneswara V, Akpan N, Berry M, Logan A, Troy CM and Ahmed Z: Combined suppression of CASP2 and CASP6 protects retinal ganglion cells from apoptosis and promotes axon regeneration through CNTF-mediated JAK/STAT signalling. Brain 137: 1656-1675, 2014.
186. Seong H, Ryu J, Yoo WS, Kim SJ, Han YS, Park JM, Kang SS and Seo SW: Resveratrol ameliorates retinal ischemia/reperfusion injury in C57BL/6J mice via downregulation of caspase-3. Curr Eye Res 42: 1650-1658, 2017.
187. Thomas CN, Berry M, Logan A, Blanch RJ and Ahmed Z: Caspases in retinal ganglion cell death and axon regeneration. Cell Death Discov 3: 17032, 2017.
188. Ngan BY, Chen-Levy Z, Weiss LM, Warnke RA and Cleary ML: Expression in non-Hodgkin's lymphoma of the bcl-2 protein associated with the t(14;18) chromosomal translocation. N Engl J Med 318: 1638-1644, 1988.
189. Maes ME, Schlamp CL and Nickells RW: BAX to basics: How the BCL2 gene family controls the death of retinal ganglion cells. Prog Retin Eye Res 57: 1-25, 2017.
190. Singh R, Letai A and Sarosiek K: Regulation of apoptosis in health and disease: The balancing act of BCL-2 family proteins. Nat Rev Mol Cell Biol 20: 175-193, 2019.
191. Cottet S and Schorderet DF: Triggering of Bcl-2-related pathway is associated with apoptosis of photoreceptors in Rpe65-/- mouse model of Leber's congenital amaurosis. Apoptosis 13: 329-342, 2008.
192. Zalewska R, Reszeć J, Mariak Z and Sulkowski S: The expression of Bcl-2, Bcl-xl, Bak and Bax proteins in axons of the optic nerve in closed-angle glaucoma. Klin Oczna 106 (1-2 Suppl): S155-S157, 2004 (In Polish).
193. Takahashi A, Masuda A, Sun M, Centonze VE and Herman B: Oxidative stress-induced apoptosis is associated with alterations in mitochondrial caspase activity and Bcl-2-dependent alterations in mitochondrial pH (pHm). Brain Res Bull 62: 497-504, 2004.
194. Tatton WG, Chalmers-Redman RM and Tatton NA: Apoptosis and anti-apoptosis signalling in glaucomatous retinopathy. Eur J Ophthalmol 11 (Suppl 2): S12-S22, 2001.
195. Ye D, Shi Y, Xu Y and Huang J: PACAP attenuates optic nerve crush-induced retinal ganglion cell apoptosis via activation of the CREB-Bcl-2 pathway. J Mol Neurosci 68: 475-484, 2019.
196. González-García M, García I, Ding L, O'Shea S, Boise LH, Thompson CB and Núñez G: bcl-x is expressed in embryonic and postnatal neural tissues and functions to prevent neuronal cell death. Proc Natl Acad Sci USA 92: 4304-4308, 1995.
197. Liu XH, Collier RJ and Youle RJ: Inhibition of axotomy-induced neuronal apoptosis by extracellular delivery of a Bcl-XL fusion protein. J Biol Chem 276: 46326-46332, 2001.
198. Malik JMI, Shevtsova Z, Bähr M and Kügler S: Long-term in vivo inhibition of CNS neurodegeneration by Bcl-XL gene transfer. Mol Ther 11: 373-381, 2005.
199. Donahue RJ, Fehrman RL, Gustafson JR and Nickells RW: BCLX(L) gene therapy moderates neuropathology in the DBA/2J mouse model of inherited glaucoma. Cell Death Dis 12: 781, 2021.
200. Näpänkangas U, Lindqvist N, Lindholm D and Hallböök F: Rat retinal ganglion cells upregulate the pro-apoptotic BH3-only protein Bim after optic nerve transection. Brain research. Brain Res Mol Brain Res 120: 30-37, 2003.
201. Donahue RJ, Maes ME, Grosser JA and Nickells RW: BAX-depleted retinal ganglion cells survive and become quiescent following optic nerve damage. Mol Neurobiol 57: 1070-1084, 2020.
202. Wei Y, Fan T and Yu M: Inhibitor of apoptosis proteins and apoptosis. Acta Biochim Biophys Sin (Shanghai) 40: 278-288, 2008.
203. Levkovitch-Verbin H, Dardik R, Vander S, Nisgav Y, Kalev-Landoy M and Melamed S: Experimental glaucoma and optic nerve transection induce simultaneous upregulation of proapoptotic and prosurvival genes. Invest Ophthalmol Vis Sci 47: 2491-2497, 2006.
204. Kisiswa L, Albon J, Morgan JE and Wride MA: Cellular inhibitor of apoptosis (cIAP1) is down-regulated during retinal ganglion cell (RGC) maturation. Exp Eye Res 91: 739-747, 2010.
205. Levkovitch-Verbin H, Vander S, Makarovsky D and Lavinsky F: Increase in retinal ganglion cells' susceptibility to elevated intraocular pressure and impairment of their endogenous neuroprotective mechanism by age. Mol Vis 19: 2011-2022, 2013.
206. Ayub H, Micheal S, Akhtar F, Khan MI, Bashir S, Waheed NK, Ali M, Schoenmaker-Koller FE, Shafique S, Qamar R and Hollander AI: Association of a polymorphism in the BIRC6 gene with pseudoexfoliative glaucoma. PLoS One 9: e105023, 2014.
207. Carbone MA, Chen Y, Hughes GA, Weinreb RN, Zabriskie NA, Zhang K and Anholt RR: Genes of the unfolded protein response pathway harbor risk alleles for primary open angle glaucoma. PLoS One 6: e20649, 2011.
208. Kernt M, Neubauer AS, Eibl KH, Wolf A, Ulbig MW, Kampik A and Hirneiss C: Minocycline is cytoprotective in human trabecular meshwork cells and optic nerve head astrocytes by increasing expression of XIAP, survivin, and Bcl-2. Clin Ophthalmol 4: 591-604, 2010.
209. Liu L, Yang X, Zhang J, Jiang W, Hou T, Zong Y, Bai H, Yang K and Yang X: Long non-coding RNA SNHG11 regulates the Wnt/β-catenin signaling pathway through rho/ROCK in trabecular meshwork cells. FASEB J 37: e22873, 2023.
210. Levkovitch-Verbin H, Makarovsky D and Vander S: Comparison between axonal and retinal ganglion cell gene expression in various optic nerve injuries including glaucoma. Mol Vis 19: 2526-2541, 2013.
211. Murray-Zmijewski F, Lane DP and Bourdon JC: p53/p63/p73 isoforms: an orchestra of isoforms to harmonise cell differentiation and response to stress. Cell Death Differ 13: 962-972, 2006.
212. Lane DP, Lu X, Hupp T and Hall PA: The role of the p53 protein in the apoptotic response. Philos Trans R Soc Lond B Biol Sci 345: 277-280, 1994.
213. Peng Q, Lao X, Chen Z, Lai H, Deng Y, Wang J, Mo C, Sui J, Wu J, Zhai L, *et al*: TP53 and MDM2 gene polymorphisms, gene-gene interaction, and hepatocellular carcinoma risk: evidence from an updated meta-analysis. PLoS One 8: e82773, 2013.
214. Lin HJ, Chen WC, Tsai FJ and Tsai SW: Distributions of p53 codon 72 polymorphism in primary open angle glaucoma. Br J Ophthalmol 86: 767-770, 2002.

215. Chipuk JE, Kuwana T, Bouchier-Hayes L, Droin NM, Newmeyer DD, Schuler M and Green DR: Direct activation of Bax by p53 mediates mitochondrial membrane permeabilization and apoptosis. Science 303: 1010-1014, 2004.
216. Acharya M, Mitra S, Mukhopadhyay A, Khan M, Roychoudhury S and Ray K: Distribution of p53 codon 72 polymorphism in Indian primary open angle glaucoma patients. Mol Vis 8: 367-371, 2002.
217. Ara S, Lee PS, Hansen MF and Saya H: Codon 72 polymorphism of the TP53 gene. Nucleic Acids Res 18: 4961, 1990.
218. Fan BJ, Liu K, Wang DY, Tham CC, Tam PO, Lam DS and Pang CP: Association of polymorphisms of tumor necrosis factor and tumor protein p53 with primary open-angle glaucoma. Invest Ophthalmol Vis Sci 51: 4110-4116, 2010.
219. Gupta S, Chatterjee S, Chandra A, Maurya OPS, Mishra RN, Mukherjee A and Mutsuddi M: TP53 codon 72 polymorphism and the risk of glaucoma in a north Indian cohort: A genetic association study. Ophthalmic Genet 39: 228-235, 2018.
220. Guo Y, Zhang H, Chen X, Yang X, Cheng W and Zhao K: Association of TP53 polymorphisms with primary open-angle glaucoma: A meta-analysis. Invest Ophthalmol Vis Sci 53: 3756-3763, 2012.
221. Gohari M, Neámatzadeh H, Jafari MA, Mazaheri M, Zare-Shehneh M and Abbasi-Shavazi E: Association between the p53 codon 72 polymorphism and primary open-angle glaucoma risk: Meta-analysis based on 11 case-control studies. Indian J Ophthalmol 64: 756-761, 2016.
222. Blanco-Marchite C, Sánchez-Sánchez F, López-Garrido MP, Iñigez-de-Onzoño M, López-Martínez F, López-Sánchez E, Alvarez L, Rodríguez-Calvo PP, Méndez-Hernández C, Fernández-Vega L, *et al*: WDR36 and P53 gene variants and susceptibility to primary open-angle glaucoma: analysis of gene-gene interactions. Invest Ophthalmol Vis Sci 52: 8467-8478, 2011.
223. Neamatzadeh H, Soleimanizad R, Atefi A, Zare-Shehneh M, Gharibi S, Shekari A and Rahimzadeh AB: Association between p53 codon 72 (Arg72Pro) polymorphism and primary open-angle glaucoma in Iranian patients. Iran Biomed J 19: 51-56, 2015.
224. Wiggs JL, Hewitt AW, Fan BJ, Wang DY, Figueiredo Sena DR, O'Brien C, Realini A, Craig JE, Dimasi DP, Mackey DA, *et al*: The p53 codon 72 PRO/PRO genotype may be associated with initial central visual field defects in caucasians with primary open angle glaucoma. PLoS One 7: e45613, 2012.
225. Jeong BS, Hu W, Belyi V, Rabadan R and Levine AJ: Differential levels of transcription of p53-regulated genes by the arginine/proline polymorphism: p53 with arginine at codon 72 favors apoptosis. FASEB J 24: 1347-1353, 2010.
226. Dimasi DP, Hewitt AW, Green CM, Mackey DA and Craig JE: Lack of association of p53 polymorphisms and haplotypes in high and normal tension open angle glaucoma. J Med Genet 42: e55, 2005.
227. Silva RE, Arruda JT, Rodrigues FW and Moura KKVO: Primary open angle glaucoma was not found to be associated with p53 codon 72 polymorphism in a Brazilian cohort. Genet Mol Res 8: 268-272, 2009.
228. Mabuchi F, Sakurada Y, Kashiwagi K, Yamagata Z, Iijima H and Tsukahara S: Lack of association between p53 gene polymorphisms and primary open angle glaucoma in the Japanese population. Mol Vis 15: 1045-1049, 2009.
229. Saglar E, Yucel D, Bozkurt B, Ozgul RK, Irkec M and Ogus A: Association of polymorphisms in APOE, p53, and p21 with primary open-angle glaucoma in Turkish patients. Mol Vis 15: 1270-1276, 2009.
230. Chen SD, Wang L and Zhang XL: Neuroprotection in glaucoma: Present and future. Chin Med J (Engl) 126: 1567-1577, 2013.
231. Tahzib NG, Ransom NL, Reitsamer HA and McKinnon SJ: Alpha-fodrin is cleaved by caspase-3 in a chronic ocular hypertensive (COH) rat model of glaucoma. Brain Res Bull 62: 491-495, 2004.
232. Vigneswara V, Berry M, Logan A and Ahmed Z: Pharmacological inhibition of caspase-2 protects axotomised retinal ganglion cells from apoptosis in adult rats. PLoS One 7: e53473, 2012.
233. Monnier PP, D'Onofrio PM, Magharious M, Hollander AC, Tassew N, Szydlowska K, Tymianski M and Koeberle PD: Involvement of caspase-6 and caspase-8 in neuronal apoptosis and the regenerative failure of injured retinal ganglion cells. J Neurosci 31: 10494-10505, 2011.
234. Liu Y, Yan H, Chen S and Sabel BA: Caspase-3 inhibitor Z-DEVD-FMK enhances retinal ganglion cell survival and vision restoration after rabbit traumatic optic nerve injury. Restor Neurol Neurosci 33: 205-220, 2015.
235. Sánchez-Migallón MC, Valiente-Soriano FJ, Nadal-Nicolás FM, Vidal-Sanz M and Agudo-Barriuso M: Apoptotic retinal ganglion cell death after optic nerve transection or crush in mice: Delayed RGC loss with BDNF or a caspase 3 inhibitor. Invest Ophthalmol Vis Sci 57: 81-93, 2016.
236. Nakazawa T, Tamai M and Mori N: Brain-derived neurotrophic factor prevents axotomized retinal ganglion cell death through MAPK and PI3K signaling pathways. Invest Ophthalmol Vis Sci 43: 3319-3326, 2002.
237. Tawfik M, Zhang X, Grigartzik L, Heiduschka P, Hintz W, Henrich-Noack P, van Wachem B and Sabel BA: Gene therapy with caspase-3 small interfering RNA-nanoparticles is neuroprotective after optic nerve damage. Neural Regen Res 16: 2534-2541, 2021.
238. Ahmed Z, Kalinski H, Berry M, Almasieh M, Ashush H, Slager N, Brafman A, Spivak I, Prasad N, Mett I, *et al*: Ocular neuroprotection by siRNA targeting caspase-2. Cell Death Dis 2: e173, 2011.
239. Elewa HF, Hilali H, Hess DC, Machado LS and Fagan SC: Minocycline for short-term neuroprotection. Pharmacotherapy 26: 515-521, 2006.
240. Bosco A, Inman DM, Steele MR, Wu G, Soto I, Marsh-Armstrong N, Hubbard WC, Calkins DJ, Horner PJ and Vetter ML: Reduced retina microglial activation and improved optic nerve integrity with minocycline treatment in the DBA/2J mouse model of glaucoma. Invest Ophthalmol Vis Sci 49: 1437-1446, 2008.
241. Huang W, Gao F, Hu F, Huang J, Wang M, Xu P, Zhang R, Chen J, Sun X, Zhang S and Wu J: Asiatic acid prevents retinal ganglion cell apoptosis in a rat model of glaucoma. Front Neurosci 12: 489, 2018.
242. Hu X, Zhuang D, Zhang R, Sun X, Lu Q and Dai Y: The small molecule inhibitor PR-619 protects retinal ganglion cells against glutamate excitotoxicity. Neuroreport 31: 1134-1141, 2020.
243. Wu X, Pang Y, Zhang Z, Li X, Wang C, Lei Y, Li A, Yu L and Ye J: Mitochondria-targeted antioxidant peptide SS-31 mediates neuroprotection in a rat experimental glaucoma model. Acta Biochim Biophys Sin (Shanghai) 51: 411-421, 2019.
244. Shi Y, Ye D, Huang R, Xu Y, Lu P, Chen H and Huang J: Down syndrome critical region 1 reduces oxidative stress-induced retinal ganglion cells apoptosis via CREB-Bcl-2 pathway. Invest Ophthalmol Vis Sci 61: 23, 2020.
245. Dai Y, Lawrence TS and Xu L: Overcoming cancer therapy resistance by targeting inhibitors of apoptosis proteins and nuclear factor-kappa B. Am J Transl Res 1: 1-15, 2009.
246. McKinnon SJ, Lehman DM, Tahzib NG, Ransom NL, Reitsamer HA, Liston P, LaCasse E, Li Q, Korneluk RG and Hauswirth WW: Baculoviral IAP repeat-containing-4 protects optic nerve axons in a rat glaucoma model. Mol Ther 5: 780-787, 2002.
247. Visuvanathan S, Baker AN, Lagali PS, Coupland SG, Miller G, Hauswirth WW and Tsilfidis C: XIAP gene therapy effects on retinal ganglion cell structure and function in a mouse model of glaucoma. Gene Ther 29: 147-156, 2022.
248. Wang XC, Wang T, Zhang Y, Wang LL, Zhao RY and Tan W: Tacrolimus inhibits proliferation and induces apoptosis by decreasing survivin in scar fibroblasts after glaucoma surgery. Eur Rev Med Pharmacol Sci 22: 2934-2940, 2018.
249. Lee J, Choi JH and Joo CK: TGF-β1 regulates cell fate during epithelial-mesenchymal transition by upregulating survivin. Cell Death Dis 4: e714, 2013.
250. Honjo M and Tanihara H: Impact of the clinical use of ROCK inhibitor on the pathogenesis and treatment of glaucoma. Jpn J Ophthalmol 62: 109-126, 2018.
251. Wang J, Wang H and Dang Y: Rho-kinase inhibitors as emerging targets for glaucoma therapy. Ophthalmol Ther 12: 2943-2957, 2023.
252. Chen W, Yang X, Fang J, Zhang Y, Zhu W and Yang X: Rho-associated protein kinase inhibitor treatment promotes proliferation and phagocytosis in trabecular meshwork cells. Front Pharmacol 11: 302, 2020.
253. Garnock-Jones KP: Ripasudil: First global approval. Drugs 74: 2211-2215, 2014.
254. Sturdivant JM, Royalty SM, Lin CW, Moore LA, Yingling JD, Laethem CL, Sherman B, Heintzelman GR, Kopczynski CC and deLong MA: Discovery of the ROCK inhibitor netarsudil for the treatment of open-angle glaucoma. Bioorg Med Chem Lett 26: 2475-2480, 2016.
255. Tanna AP and Johnson M: Rho kinase inhibitors as a novel treatment for glaucoma and ocular hypertension. Ophthalmology 125: 1741-1756, 2018.

256. Testa V, Ferro Desideri L, Della Giustina P, Traverso CE and Iester M: An update on ripasudil for the treatment of glaucoma and ocular hypertension. Drugs Today (Barc) 56: 599-608, 2020.
257. Li DW, Liu JP, Schmid PC, Schlosser R, Feng H, Liu WB, Yan Q, Gong L, Sun SM, Deng M and Liu Y: Protein serine/threonine phosphatase-1 dephosphorylates p53 at Ser-15 and Ser-37 to modulate its transcriptional and apoptotic activities. Oncogene 25: 3006-3022, 2006.
258. Yang Z, Ge J, Yin W, Shen H, Liu H and Guo Y: The expression of p53, MDM2 and Ref1 gene in cultured retina neurons of SD rats treated with vitamin B1 and/or elevated pressure. Yan Ke Xue Bao 20: 259-263, 2004 (In Chinese).
259. Johnson KT, Rödicker F, Heise K, Heinz C, Steuhl KP, Pützer BM and Hudde T: Adenoviral p53 gene transfer inhibits human Tenon's capsule fibroblast proliferation. Br J Ophthalmol 89: 508-512, 2005.
260. Husain S, Ahmad A, Singh S, Peterseim C, Abdul Y and Nutaitis MJ: PI3K/Akt pathway: A role in δ-opioid receptor-mediated RGC neuroprotection. Invest Ophthalmol Vis Sci 58: 6489-6499, 2017.
261. Zhao N, Shi J, Xu H, Luo Q, Li Q and Liu M: Baicalin suppresses glaucoma pathogenesis by regulating the PI3K/AKT signaling in vitro and in vivo. Bioengineered 12: 10187-10198, 2021.
262. Xi X, Chen Q, Ma J, Wang X, Xia Y, Wen X, Cai B and Li Y: Acteoside protects retinal ganglion cells from experimental glaucoma by activating the PI3K/AKT signaling pathway via caveolin 1 upregulation. Ann Transl Med 10: 312, 2022.
263. Nie XG, Fan DS, Huang YX, He YY, Dong BL and Gao F: Downregulation of microRNA-149 in retinal ganglion cells suppresses apoptosis through activation of the PI3K/Akt signaling pathway in mice with glaucoma. Am J Physiol Cell Physiol 315: C839-C849, 2018.
264. Perkins TW, Faha B, Ni M, Kiland JA, Poulsen GL, Antelman D, Atencio I, Shinoda J, Sinha D, Brumback L, *et al*: Adenovirus-mediated gene therapy using human p21WAF-1/Cip-1 to prevent wound healing in a rabbit model of glaucoma filtration surgery. Arch Ophthalmol 120: 941-949, 2002.
265. Heatley G, Kiland J, Faha B, Seeman J, Schlamp CL, Dawson DG, Gleiser J, Maneval D, Kaufman PL and Nickells RW: Gene therapy using p21WAF-1/Cip-1 to modulate wound healing after glaucoma trabeculectomy surgery in a primate model of ocular hypertension. Gene Ther 11: 949-955, 2004.