

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

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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.

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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).

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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- α (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

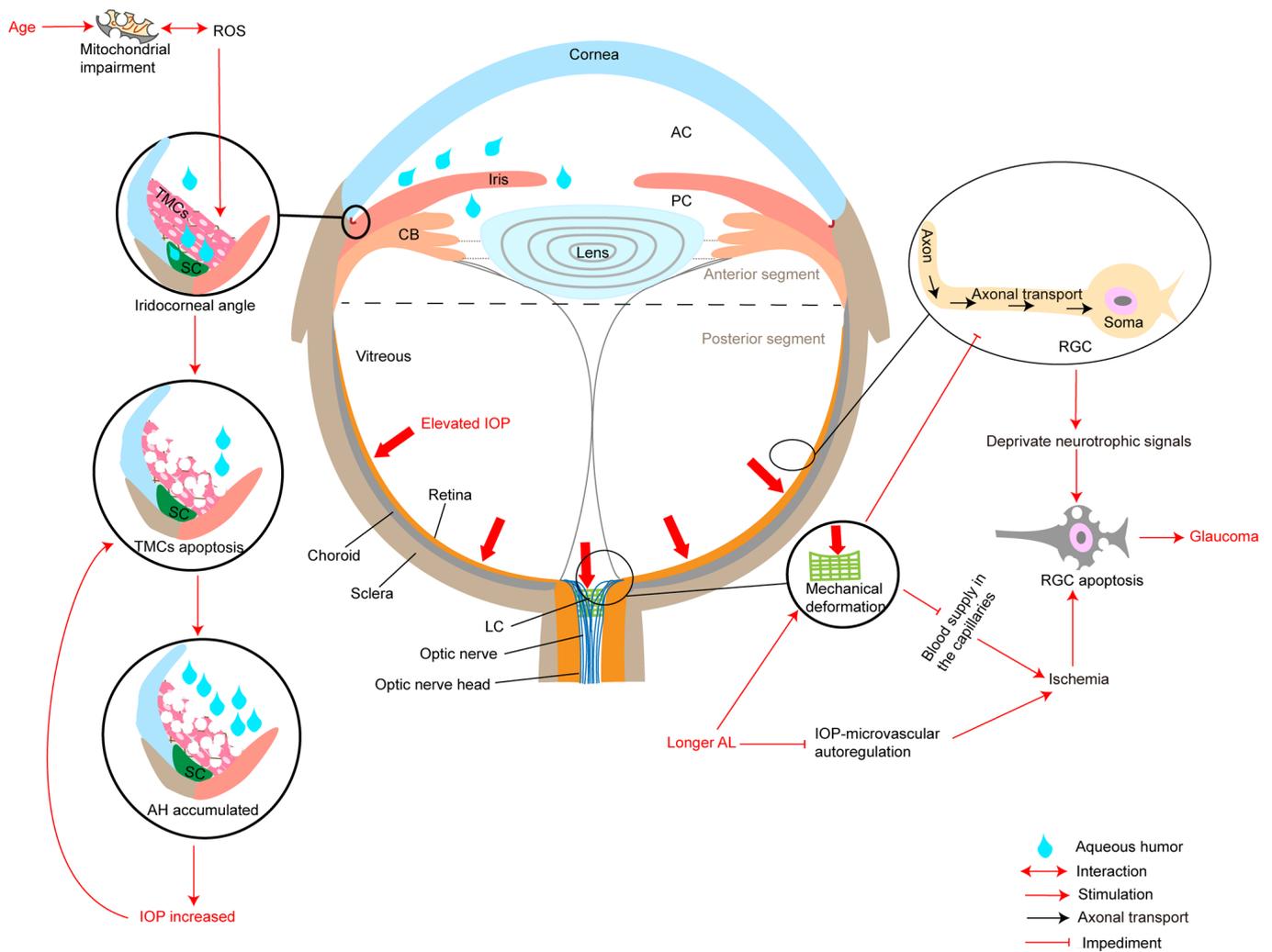


Figure 1. Elevated IOP, age and myopia play important roles in glaucoma. As age increases, the production of mitochondrial ROS increases, which may exacerbate mitochondrial damage and induce oxidative stress-induced apoptosis of TMCs, leading to the accumulation of AH and ultimately an increase in IOP. 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 (eIF2 α)/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 α 4 (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

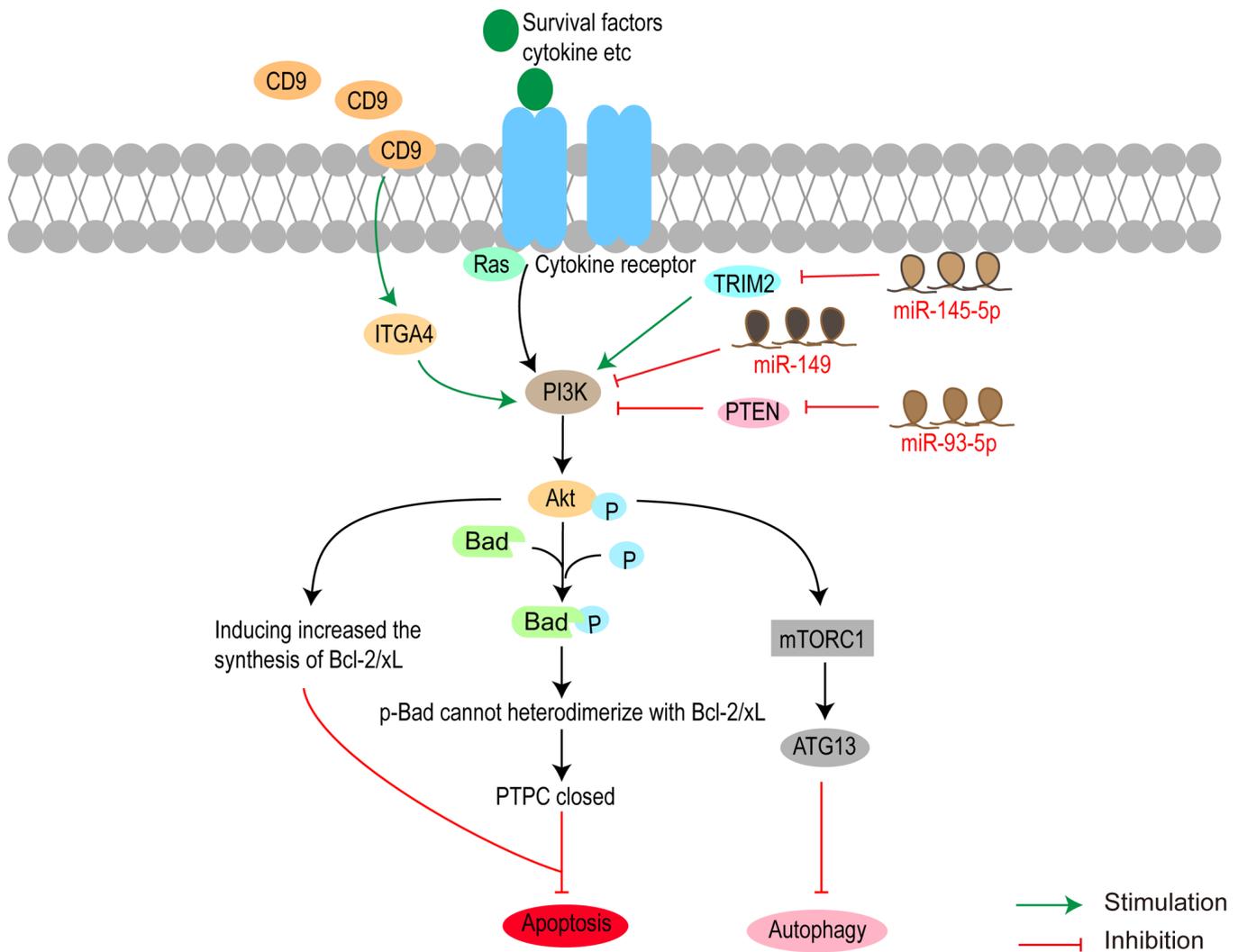


Figure 2. PI3K/Akt pathway in glaucoma. Upregulation of CD9 or Ras integrating survival and other factors, can activate PI3K and induce Akt phosphorylation. Phosphorylated Akt induces an increase in new synthesis of Bcl-2/xL and phosphorylates Bad, preventing heterodimerization of Bad/Bcl-2, thereby 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- β 2, 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 cribiform, 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- β 2 and collagen 1, are also involved in glaucomatous RGC loss. The experimental results revealed that TGF- β 2 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- β 2 deposition in the retina significantly decreases, whereas MMP-9 increases. TGF- β 1 regulates the mRNA and protein levels of MMP-9, similar to its inhibitor TIMP-2 (91). Furthermore, the effect of TGF- β 2 depends on its concentration and specificity in targeting cells (92). The biphasic behaviour of TGF- β explains why both the low levels of TGF- β 2 found in the RGC layer and the high levels of TGF- β 2 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 TNF α and FasL are TNF receptor1 (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 (Cyt_c) 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 Cyt_c and forms a disc-shaped heptamer (Cyt_c-Apaf-1)₇, called apoptosome (104).

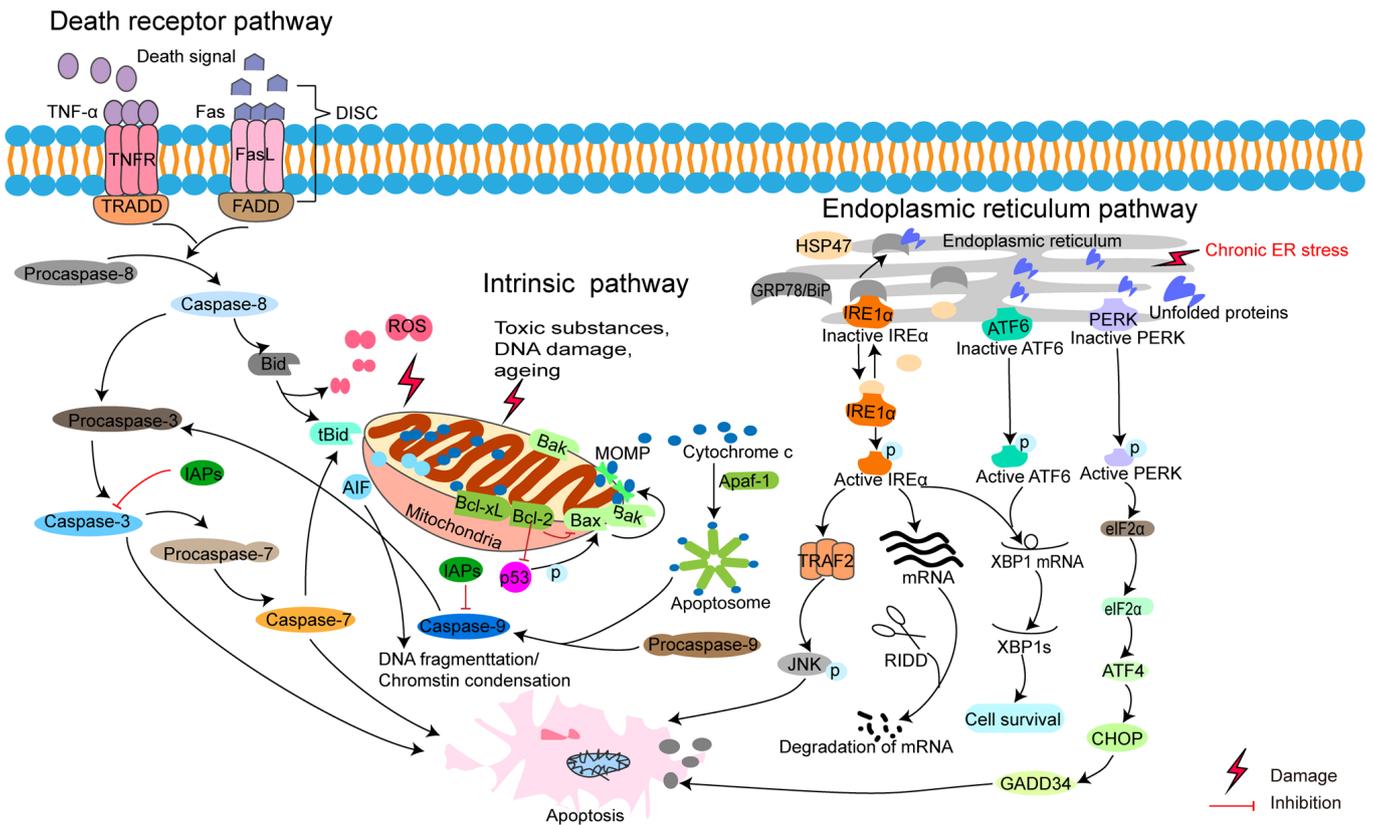


Figure 3. The mechanism of apoptosis in glaucoma. In the death receptor pathway, death signals, death receptors and death domain adaptors such as FADD and TRADD form the DISC to activate caspase-8. The latter activates the latter effector to execute apoptosis. The intrinsic pathway is initiated by internal damage including toxic substances, DNA damage, ageing 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 1 α (IRE1 α) 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; IRE1 α , inositol-requiring enzyme 1 α ; 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 1 α (IRE1 α) 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 sensor and activates their downstream molecular signal (116). The phosphorylated form of IRE1 α (p-IRE1 α) 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 IRE1 α -JNK signalling pathway is involved in ERS of glaucoma. Besides, p-IRE1 α 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-IRE1 α 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, IRE1 α is a crucial protein that regulates cell survival or induces apoptosis in response to surrounding ERS.

PERK is activated in a similar way to IRE1 α . Activation of PERK induces translational attenuation of p-eIF2 α . Under excessive or prolonged ERS, p-eIF2 α 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 eIF2 α /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 IRE1 α 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-1 β -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)
sTNF α	Proapoptotic	Binding to TNFR1 to promote inflammation and induce RGC death	(159,160)
tTNF α	Survival signalling	Glia-derived sTNF α modulates neuronal death	(161)
DR	Transmit signal	Binding to TNFR2 to activate the PI3K/Akt signalling pathway	(159,162,163)
Caspases	Proapoptotic	Increased expression level of TNF- α and TNFR1 cause RGC apoptosis, involving in caspases	(97,163)
Bcl-2/Bcl-xL	Antiapoptotic	Mediating the apoptotic pathway	(181,183)
Bax, Bak	Proapoptotic	Inhibiting Bax/Bak homo-oligomerization in the MOMP	(108)
IAPs	Antiapoptotic	Inducing the formation of MOMP to release Cyt c into the cytoplasm	(107,109)
p53	Increase individual susceptibility to glaucoma	Inhibiting the activity of the caspase	(202)
		<i>p53</i> 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^{ACS} 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 TNF α and soluble TNF α . 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). TNF α 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). TNF α binds to two types of TNF- α receptors (TNFR1 and TNFR2) to perform its multiple biological functions (158,159). Soluble TNF- α (sTNF α) preferentially binds to TNFR1, which results in neuroinflammation and cell death (160). In addition, Cueva Vargas *et al* (161) reported that glia-derived sTNF α modulates neuronal death in glaucoma via calcium-permeable AMPA receptor activation. Conversely, transmembrane TNF- α (tTNF α) 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 TNF α or IL-1 β significantly inhibits monocyte infiltration and RGC apoptosis caused by surgical injury and global trauma (36). Additionally, the expression levels of IL-1 β and TNF α in the TM of patients with POAG were significantly greater than those in the control group and TNF α induced TM cell death (165,166). TNF α stimulates mitochondria to form a stress response, which sequentially releases ROS, Cyt c and Bax to activate caspase-9 and a downstream caspase cascade to initiate apoptosis (167). Moreover, neutralizing the action of TNF α and IL-1 β prevents the loss of RGCs induced by elevated hydrostatic pressure or lipopolysaccharide (168). Previous studies demonstrated that patients with the TNF α -308 G/A polymorphism may have increased susceptibility to glaucoma (169,170). However, the relationship between the TNF α -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 TNF α is increased in the glaucomatous retina and ONH which caused RGCs death through its direct or indirect neurotoxicity (175). Increased immunostaining for TNF α 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 TNF α and TNFR1 in astrocytes and microglia is increased (177). In severe glaucomatous damage, RGC axons express TNFR1, which may be a direct target for TNF α mediated optic nerve degeneration (177). The mRNA and protein expression levels of TNF α and TNFR1 are greater in the inner retinal layers in glaucomatous eyes and TNFR1 is expressed at high levels in RGCs, whereas TNF α , is expressed mainly in glial cells (178). In rat model of experimental glaucoma, TNF α 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 TNF α 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-1 β (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-3 β -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 para-central 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 signaling 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- β 1 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 Inhibitors	Activating the PI3K/Akt pathway	Optic nerve crush or transection in mice	(235,236)
		BIRC4 inhibits of retinal caspase-3 activity	A chronic intraocular hypertension rat model of glaucoma induced by hypertonic saline	(231)
Bcl-2 family	siRNA	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)
		Selectively silence caspase-3 expression to block apoptosis in post-mitotic neurons	A preclinical glaucoma model of optic nerve crush in adult rats	(237)
Bcl-2 family	siRNA	Elicit RNAi-mediated cleavage of caspase-2 mRNA	Optic nerve crush injury in rat	(238)
	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)
p53	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 SS-31	Neuroprotection by promoting parkin-mediated mitophagy Neuroprotection by upregulating expression of Bcl-2,	Excitotoxicity model A rat experimental glaucoma model induced by injection of polystyrene microspheres	(242) (243)
IAPs	PP-1	downregulating expression of Bax and reducing Cyt c release Dephosphorylate p53 at Ser-15 and Ser-37, negatively modulates its transcriptional and apoptotic activity	Cultured human lens epithelial cells	(257)
	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 Direct or indirect inhibition of caspase-8 and caspase-3	Cultured Human Tenon's capsule fibroblasts Rabbit model of glaucoma surgery Primate model of glaucoma surgery	(259,264,265)
Survival signals	SNC-121	Caspase-dependent and caspase-independent mechanism (such as NF- κ B) Activating the PI3K/Akt pathway	A chronic intraocular hypertension rat model of glaucoma induced by hypertonic saline A magnetic microbead mouse model of induced ocular hypertension	(246) (247)
	Baicalin	Activating the PI3K/Akt pathway and inhibit autophagy	A chronic intraocular hypertension rat model of glaucoma induced by hypertonic saline A mouse model of glaucoma induced by episcleral venous occlusion with cauterization	(260) (261)
Survival signals	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 *CYP11B1*, 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.

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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.

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Competing interests

The authors declare that they have no competing interests.

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