Research progress on molecular therapy for glaucoma (Review)

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Abstract. Glaucoma is a notable public health concern as it can lead to irreversible vision loss; however, it remains challenging to treat effectively. Current options focus solely on managing intraocular pressure (IOP) to delay the progression of vision loss. The present review describes the multifaceted mechanisms of glaucoma and concludes by describing future promising treatment options that target specific mechanisms. Gene editing therapy is a promising option for patients with mutations known to cause glaucoma. Modulating the expression of genes involved in IOP regulation or neurodegeneration is another potential approach. Additionally, therapies targeting relevant molecular and metabolic pathways are also currently under investigation. The present review aims to highlight the most promising avenues for molecular intervention in glaucoma and guide future research efforts toward effective, long-term solutions for preserving vision.

Contents

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1. Introduction

Glaucoma is a group of progressive optic neuropathies characterized by retinal ganglion cell (RGC) loss and optic nerve damage that can lead to irreversible blindness (1,2). Estimates indicate that glaucoma is responsible for ~3.6 million cases of blindness among individuals aged ≥50 years (3). As the global population ages, the prevalence of glaucoma is expected to keep increasing. Therefore, research into this disease is of great significance for public health management and may have a profound socioeconomic impact.

Despite notable advances in medical and surgical treatments, ~12.5% of glaucomatous eyes will show fast vision loss and ~14.3% of patients with glaucoma will be blind in one eye within 20 years (4). The estimates highlight the need for novel and more effective treatments. Molecular biomarkers have been widely studied in glaucoma research (5), and molecular therapy could be a promising new approach (6). Recent advances in gene therapy, RNA interference (RNAi), cell-based strategies and small-molecule inhibitors have demonstrated marked preclinical success in animal models of glaucoma (5,6).

The present review provides a comprehensive overview of the current research progress on molecular therapies for glaucoma, encompassing the multifactorial mechanisms of glaucoma, emerging molecular treatment strategies and future directions.

2. Mechanisms of glaucoma

Classical pathological mechanisms. The central pathological mechanism of glaucoma is trabecular meshwork (TM) dysfunction and increased intraocular pressure (IOP), which exert stress on the retina and neurons, progressively leading to vision loss (5). The TM regulates IOP by facilitating aqueous humor outflow and its dysfunction increases outflow resistance, leading to IOP elevation (5). Beyond IOP and translaminar pressure gradients, anatomical features of the optic nerve head, including the optic disc size and lamina cribrosa morphology, serve an important role in glaucoma (7). Larger discs are more susceptible to lamina cribrosa displacement under pressure gradients, which has been associated with impaired hemodynamics and reduced oxygen availability (7,8). Furthermore,

vascular dysregulation may lead to chronic vasoconstriction, restricting nutrient and oxygen delivery to the retina and thereby contributing to glaucomatous damage (9).

Nevertheless, optic nerve degeneration at the optic nerve head has been reported to precede RGC injury, suggesting a window of therapeutic opportunity before actual RGC damage (10). Thus, by identifying and targeting these early molecular mechanisms, it may be possible to intervene before irreversible damage to the RGCs occurs, which could markedly improve the prognosis for patients with glaucoma.

Metabolic pathways and cell death. Oxidative stress can directly damage the TM and impair aqueous humor outflow, leading to increased IOP; it also activates the RGCs, triggering inflammatory mediators that worsen damage and oxidative stress (11). Furthermore, both external and mitochondrial reactive oxygen species (ROS) can harm mitochondria, creating a cycle of increasing ROS, lower energy production and increased cell damage (11,12). Oxidative stress also triggers endoplasmic reticulum stress and DNA damage, both of which can harm RGCs (12,13).

A recent Mendelian randomization study highlighted the bidirectional causal effects of oxidative stress and glaucoma (14), supporting the view of a self-sustained vicious circle. Systemic biomarkers of oxidative stress such as total antioxidant capacity are elevated in patients with elevated IOP (15). Notably, oxidative stress is a complex condition that also involves exogenous factors; results from the large-scale National Health and Nutrition Examination Survey (NHANES) study indicated that elevated oxidative balance scores (calculated based on nutritional and lifestyle factors) were associated with glaucoma (16). Physical activity may have favorable impacts on glaucoma progression through decreased oxidative stress (17). Therefore, these results highlight the importance of oxidative stress in glaucoma pathogenesis and pathophysiology.

Mitochondrial abnormalities serve a critical role in the pathogenesis of primary open angle glaucoma (POAG), particularly through their involvement in ROS production, energy metabolism and cell survival (18). Elevated IOP, aging, neuroinflammation, vascular impairment, neurotrophic factor deprivation and oxidative stress collectively disrupt the delicate balance of mitochondrial fission and fusion (18). This imbalance leads to reduced mitochondrial efficiency, increased ROS production and compromised cellular energy supply, all of which exacerbate RGC damage (18).

Inflammation, closely associated with oxidative stress and mitochondrial dysfunction, is a central process in increased IOP and glaucoma (19,20). Intermediate inflammation (or para-inflammation) is an adaptive process that involves stresses and malfunctions in the retina and is involved in preserving tissue homeostasis and function. However, it may be deleterious if sustained over long periods (20). Such inflammation could contribute to impaired aqueous outflow and increased IOP (21). C-reactive protein is a biomarker of systemic low-grade inflammation and has been associated with glaucoma in a recent meta-analysis (22). Another NHANES analysis linked the systemic inflammatory response index with the incidence of glaucoma (23).

Furthermore, RGC injury leads to RGC death (24). As RGCs cannot regenerate and reconnect to the visual pathway, their death will lead to progressive vision loss (24,25). Notably, recent research identified that different subtypes of RGCs have different vulnerability levels in the pathogenesis of glaucoma, which could have implications for glaucoma management (25). Historically, apoptosis was considered the most important RGC death mechanism, but focusing on apoptosis led to disappointing results as saving RGCs through caspase inhibition still ultimately leads to cell death through mitochondrial dysfunction (26).

Ferroptosis is a recently identified iron-dependent programmed cell death triggered by lipid peroxidation and relying on iron-generated ROS, and it is involved in RGC death (27,28). Ferroptosis induction is associated with higher blood iron (which is associated with a higher risk of glaucoma), excitotoxicity, neuroinflammation, ischemia/reperfusion injury and a pathologically high IOP, which also all participate in glaucoma (24,29). Pyroptosis is another programmed cell death path involved in glaucoma RGC death; however, the exact mechanism remains elusive (24). Under high IOP, the glial cells are activated and their recruitment, except for the RGCs, precedes RGC death. Glial cells participate in inflammation, and pyroptosis is associated with inflammation (24).

Molecular pathways. Mitochondrial fission, fusion and function depend on proteins such as optic atrophy protein 1 (OPA1), dynamin-related protein 1 (DRP1), A-kinase anchoring protein 1 (AKAP1) and nicotinamide nucleotide adenylyltransferase 1 (NMNAT1). *OPA1* mutations can cause optic neuropathies, and single nucleotide polymorphisms in *OPA1* have been associated with POAG and normal tension glaucoma (30). Acute high IOP raises DRP1 levels, leading to early neurodegenerative events, increased gliosis and RGC apoptosis (31). AKAP1 expression appears decreased or lost in glaucoma, suggesting its role in RGC injury and death (31). NMNAT1 is involved in NAD^+ synthesis, mitigating mitochondrial dysfunction and related diseases (32). Decreased NAD^+ levels have been associated with glaucoma and retina survival depends upon adequate NAD^+ (33).

Mutations in several genes increase the susceptibility to glaucoma. Myocilin (MYOC) is a protein involved in the formation and maintenance of the TM, a structure involved in aqueous humor drainage. Mutations in the *MYOC* gene are associated with protein misfolding and dysfunctional TM and account for ~5% of POAG cases (34). Mutations in the cytochrome P450 family 1 subfamily B member 1 (*CYP1B1*) gene are responsible for ~20% of the cases of childhood glaucoma in Japan (35) and are associated with congenital glaucoma (36). The forkhead box C1 (*FOXC1*) gene encodes a transcription factor, and mutations in *FOXC1* lead to ocular drainage dysfunction (35). Optineurin (OPTN) is an adapter protein involved in several metabolic processes. Mutations in the *OPTN* gene are connected to neurodegenerative disorders and glaucoma (37,38). Recent studies have also implicated the mutations in ataxin 2 (associated with reduced RGC survival and elevated IOP) (39), EGF containing fibulin extracellular matrix protein 1 (linked to juvenile or adult-onset hereditary isolated glaucoma) (40) and paired box 6 (critical for prenatal ocular development, leading to secondary glaucoma) (41).

Therefore, the large number of genes associated with glaucoma illustrate the complexity of the disease.

Besides mutations in specific genes, Moazzeni *et al* (42) identified 18 transcription factors, 195 microRNAs (miRNAs/miRs), 106 long non-coding RNAs and two circular RNAs as being involved in glaucoma pathogenesis, highlighting the multifaceted pathophysiology of glaucoma. A proteomic study identified 176 dysregulated proteins in cells and 7 in extracellular vesicles, suggesting numerous potential glaucoma biomarkers (43). A metabolomic study reported that patients with POAG displayed decreased levels of phenylalanine, phenylacetate, leucine, *N*-acetylated compounds, formic acid and uridine in their tears, and increased taurine, glycine, urea, glucose and unsaturated fatty acids, allowing the non-invasive detection of POAG with 100% sensitivity and 83% specificity (44). Exosome density and aqueous humor programmed death-ligand 1 levels can also provide information about retinal damage in patients with glaucoma (45).

In conclusion, mitochondria-associated proteins regulate mitochondrial function through complex interactions, and their dysregulation is closely associated with optic neuropathies, including glaucoma. Several gene mutations increase the susceptibility to glaucoma by affecting the function of the TM, metabolic processes and ocular drainage structures, highlighting the complexity of this disease and its therapeutic challenges. Multiple molecules, including transcription factors, non-coding RNAs, dysfunctional proteins and metabolites, are involved in the pathogenesis of glaucoma. These may collectively provide potential biomarkers and non-invasive testing methods for the diagnosis, prognosis and treatment of glaucoma.

3. New applications of molecular therapy in glaucoma

An improved understanding of the classical, metabolic and molecular factors involved in glaucoma may help to elucidate several potential treatment targets, several of which are already in the preclinical stages and appear promising.

Gene therapy in glaucoma. Mutations in several genes are involved in the pathogenesis of glaucoma, including *MYOC*, *CYP1B1*, *FOXC1* and *OPTN*, among others. Although certain treatments can be effective in certain patients with gene mutation-related glaucoma, the only possible curative option is the correction of the mutated allele(s) using gene therapy (46). Several studies have assessed different methods for editing several genes involved in glaucoma (Table I). For instance, gene editing targeting *MYOC* mutations can reduce endoplasmic reticulum stress caused by the accumulation of misfolded MYOC and restore the MYOC protein function in the TM, leading to reduced IOP in animal models (47-49). Introducing viral vectors that express a functional protein can also be used instead of gene editing, and such an option is being explored for the *OPTN* gene as *OPTN* is involved in ~19% of POAG cases (50). Nevertheless, nerve regeneration using gene therapy is an intense area of research, and it could ultimately be used to regenerate RGCs (51). Aquaporin 1 (*AQP1*) is involved in aqueous humor production and targeting *AQP1* decreases aqueous humor production and IOP (52). Elevated transforming growth factor β 2 (*TGFβ2*) expression is associated with pathological changes in the TM, and POAG shows elevated *TGFβ2* expression (53). Interfering with *TGFβ2* expression using CRISPR technology could be used to manage POAG (54). Additionally, suppressing the phosphatase and tensin homolog (*PTEN*) gene also appears neuroprotective in RGCs (55). Therefore, gene editing could also be used to improve surgical outcomes. Lee *et al* (56) reported that targeting the connective tissue growth factor gene using CRISPR technology could reduce fibrosis after glaucoma filtration surgery. Moreover, a recent study reported that the disruption of the *AQP1*/β2 adrenergic receptor/rho-associated protein kinase 1/rho-associated protein kinase 2 genes using CRISPR-CasRx technology reduced IOP and RGC damage in mice (57). Therefore, these genes may be targeted to improve glaucoma outcomes.

Gene therapy can also modulate beneficial or harmful protein production in glaucoma; however, its success is limited, potentially due to the complex genetic basis of the disease (46). Nevertheless, the expression of several therapeutic genes have been explored (Table I), including brain-derived neurotrophic factor (*BDNF*) (58-61), tropomyosin-related kinase receptor-B (*TrkB*) (58,61), brain-specific homeobox/POU domain protein 3b (*Brn3b*) (62,63), B-cell lymphoma-xl (*Bcl-xl*) (64), Myc-associated protein X (*MAX*) (65), neuroprotective intracellular transcription factor 2 (*Nrf2*) (60), superoxide dismutase 2 (*SOD2*) (66), ATP-binding cassette A1 (67), C3 (68), mouse γ-synuclein (*mSncg*) (69), *K-Ras* (70) and matrix metalloproteinase-3 (*MMP-3*) (71). The proposed therapies target mechanisms such as neuroprotection (*BDNF*, *TrkB*, *MAX*, *Nrf2*, *C3*, *K-Ras* and *mSncg*), apoptosis (*Brn3b*, *Bcl-xl* and ATP-binding cassette A1), oxidative stress (*SOD2*) and aqueous humor outflow (*MMP-3*). Although several genes can be theoretically modulated to influence IOP and glaucoma progression, compensatory mechanisms from other genes are often observed, and adverse effects of modulating genes must be avoided (46). However, several companies are exploring the use of genes involved in IOP and RGC neuroprotection as drugs (72). NADH-quinone oxidoreductase-based gene therapy can improve mitochondrial function and reduce oxidative stress (73). Additionally, CRISPR/Cas technology can be used to disrupt genes related to high IOP. For example, *AQP1* is involved in aqueous humor production, and its disruption decreases IOP (47,51). Such a disruptive approach could also be used for *TGFβ2*, which is elevated in ~50% of patients with POAG, and participates in extracellular matrix (ECM) remodeling and elevated IOP (46,54). Caveolin-1 also serves a role in the response of RGCs to increased IOP, and ablating caveolin-1 in animal models has been reported to improve the glaucoma phenotype (74).

RNAi techniques. An alternative to gene editing or introducing a novel copy of a gene is RNAi, which works by interfering with the mRNA of the target gene, offering a non-permanent regulatory approach. Small interfering RNAs (siRNAs) can be delivered using vesicles, and their effect is transient. Although it can necessitate repeated injections, this method avoids the ethical and safety issues associated with manipulating the genome of an individual. Furthermore, siRNAs can be delivered locally (such as in the aqueous humor) to perform their

Table I. Summary of the molecular targeting therapies for glaucoma.

Category	Gene, protein or biomarker	Experimental model	Molecular mechanism	(Refs.)
Gene editing	*MYOC*	Mice and an *ex vivo* human organ culture system	Knockdown the expression of mutant *MYOC* and relieves ER stress	(48)
Gene editing	*MYOC*	Mice	Knockdown the expression of mutant *MYOC* and relieves ER stress	(49)
Gene editing	*PTEN*	Human RGCs	Neuroprotection	(55)
Therapeutic gene expression	*BDNF* and *TrkB*	Mice and rats	Neuroprotection	(58)
Therapeutic gene expression	*BDNF* and *TrkB*	Mice	Neuroprotection	(48)
Therapeutic gene expression	*BDNF*	Rats	Neuroprotection	(59)
Therapeutic gene expression	*Brnb3*	Rats	Anti-apoptosis and neuroprotection	(62,63)
Therapeutic gene expression	*Bcl-xl*	Mice	Anti-apoptosis and neuroprotection	(64)
Therapeutic gene expression	*MAX*	Rats	Neuroprotection	(65)
Therapeutic gene expression	*Nrf2* and *BDNF*	Mice	Neuroprotection	(60)
Therapeutic gene expression	*SOD2*	Rats	Antioxidative	(66)
Therapeutic gene expression	*ABCA1*	Mice	Anti-apoptosis	(67)
Therapeutic gene expression	*C3*	Rats	Neuroprotection	(68)
Gene editing	Aquaporin 1	Mice	Aqueous humor production	(52)
Therapeutic gene expression	*MMP-3*	Mice	Aqueous humor outflow	(71)
Therapeutic gene expression	*mSncg*	Mammalian RGCs	Neuroprotection	(69)
Gene editing	*TGFβ2*	Mice and human cells	Trabecular mesh	(54)
Therapeutic gene expression	*K-Ras*	Human RGCs	Neuroprotection	(70)
RNA interference	*Aqp1*/*Adrb2*/*Rock1*/*Rock2*	Mice	Aqueous humor production and outflow	(57)
Potential novel biomarker	ACTA2	Humans (proteomics)	-	(43)
Potential novel biomarker	MAGI1	Humans (proteomics)	-	(43)
Potential novel biomarker	GCOM1	Humans (proteomics)	-	(43)
Potential novel biomarker	RAD23B	Humans (proteomics)	-	(43)
Potential novel biomarker	Tear taurine	Humans (metabolomics)	-	(44)
Potential novel biomarker	Tear glycine	Humans (metabolomics)	-	(44)
Potential novel biomarker	Tear urea	Humans (metabolomics)	-	(44)
Potential novel biomarker	Tear glucose	Humans (metabolomics)	-	(44)
Potential novel biomarker	Tear unsaturated fatty acids	Humans (metabolomics)	-	(44)
Potential novel biomarker	High exosome density	Humans	-	(45)

MYOC, myocilin; ER, endoplasmic reticulum; PTEN, phosphatase and tensin homolog; RGCs, retinal ganglion cells; BDNF, brain-derived neurotrophic factor; TrkB, tropomyosin-related kinase receptor-B; Brn3b, brain-specific homeobox/POU domain protein 3b; Bcl-xl, B-cell lymphoma-xl; MAX, Myc-associated protein X; Nrf2, neuroprotective intracellular transcription factor 2; SOD2, superoxide dismutase 2; ABCA1, ATP-binding cassette A1; MMP-3, matrix metalloproteinase-3; mSncg, mouse γ-synuclein; TGFβ2, transforming growth factor β2; Aqp1/Adrb2/Rock1/Rock2, aquaporin 1/β2 adrenergic receptor/rho-associated protein kinase 1/rho-associated protein kinase 2; ACTA2, actin α2; GCOM1, GRINL1 complex 1.

effect in a limited area, such as the retina (75,76). RNAi technology is excellent for short-term or local treatments due to its reversibility and suitability for local applications (75). This allows the selection of the most appropriate strategy based on the specific pathological mechanisms and treatment needs of glaucoma, thereby maximizing treatment effectiveness while minimizing potential risks (76).

Stem cell therapy. Stem cells, particularly mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs),

embryonic stem cells (ESCs) and retinal progenitor cells, offer the potential to restore damaged tissue and replace lost or dysfunctional cells (77). Restoring TM function and regenerating damaged RGCs are key goals in glaucoma treatment (77).

Restoring TM function. Restoration of TM cellularity and function could repopulate the outflow pathway, re-establish physiological aqueous humor drainage and durable IOP control. Native TM stem cells (TMSCs), iPSC-derived TM cells (iPSC-TMs) and MSCs have been investigated for TM regeneration, each with distinct advantages and translational profiles (78-80). Human TMSCs can be isolated from donor TM tissue and display label-retaining, slow-cycling properties, multipotency and the capacity to home specifically to TM tissue after intracameral delivery (78,80). In preclinical mouse models, intracameral injection of expanded human TMSCs resulted in TM engraftment without notable inflammation and the appearance of TM marker expression within days, suggesting *in situ* differentiation and niche restoration (78,81). Complementary work has reported that transplanted iPSC-TMs not only survive in perfused human anterior segments and animal models, but also stimulate proliferation of endogenous TM cells, increase TM cellularity and improve outflow facility (79,82). These findings support a model in which exogenous cells can both directly replace lost TM cells and act via paracrine or contact-dependent cues to recruit endogenous progenitors.

Several groups have extended these approaches to disease models and shown functional benefit. For instance, in mouse glaucoma models, intracameral transplantation of TMSCs or iPSC-TMs decreased IOP and restored outflow facility, whereas adipose-derived stem cells and MSCs improved TM cellularity and ECM turnover, leading to partial normalization of IOP (80,81). Mechanistically, cell therapies act via the following: i) Direct replacement of TM endothelial-like cells; ii) secretion of matrix-remodeling enzymes and trophic factors that normalize ECM deposition; and iii) activation of endogenous TM progenitor proliferation (78-82). Notably, in certain studies only a small fraction of transplanted cells persisted long-term; nevertheless, the therapeutic effect has often been associated with increased proliferation of resident TM cells, pointing to an important inductive or paracrine role for the graft (79,82).

Despite robust preclinical progress, key translational challenges remain. These include the following: Ensuring the tolerability and safety of intracameral cell delivery (avoiding inflammation, angle obstruction or aberrant neovascularization); defining optimal cell sources and differentiation protocols to yield stable TM phenotypes; scaling good manufacturing practice (GMP)-compliant manufacturing; and establishing long-term functional endpoints in large-animal models and human *ex-vivo* perfusion systems prior to first-in-human studies (81). In addition, TM regional heterogeneity and disease-associated niche alteration (such as in POAG eyes with pronounced ECM remodeling) may require combinatorial strategies (pairing cell replacement with ECM-modulating enzymes or gene-editing of resident cells) to achieve durable restoration (78-82). In summary, stem-cell based TM regeneration has advanced to compelling preclinical proof-of-concept and the next translational steps (standardized manufacturing, safety testing in large animals and controlled early clinical trials) are now tractable priorities for the field.

Regenerating damaged RGCs. Stem cell-based approaches for regenerated damaged RGCs target two complementary therapeutic goals: i) Neuroprotection of surviving RGCs and their axons; and ii) replacement or repopulation of lost RGCs to restore visual function (83). Several cell types have been investigated preclinically, including MSCs, ESCs, neural progenitor cells and iPSC-derived retinal ganglion-like cells (iPSC-RGCs) (83-87). The therapeutic actions of transplanted cells are multifactorial and include paracrine secretion of neurotrophic factors (such as BDNF and ciliary neurotrophic factor), immunomodulation (reduction of microglial activation and inflammatory cytokines), antioxidative effects, delivery of mitochondria or mitochondrial rescue factors and, in certain contexts, direct differentiation or fusion with host retinal neurons (83,84). Over the past decade, attention has also shifted to cell-free therapies based on stem cell-derived extracellular vesicles (EVs; including exosomes), which recapitulate several paracrine benefits whilst reducing risks associated with live-cell transplantation (immune rejection and ectopic growth) (85).

Multiple preclinical studies have reported efficacy in models relevant to glaucoma (84-86). In optic nerve crush models, intravitreal or periocular delivery of human Wharton's jelly MSCs enhanced long-term RGC survival, promoted axonal regeneration and, in a report, enabled partial reconnection to central visual targets up to 120 days post-injury (86). These experiments used quantitative histology, anterograde axon tracing to assess regeneration and functional readouts such as visually evoked potentials. In ocular hypertension models, intravitreal injection of MSC-derived EVs reduced RGC apoptosis, decreased glial reactivity and preserved inner retinal structure and function on electroretinogram/visually evoked potential testing (84,85). Notably, studies have identified miRNA cargoes (such as miR-21 and miR-146a) and protein factors within EVs that mediate antiapoptotic and anti-inflammatory signaling, which can be validated by gain-/loss-of-function experiments (84,85).

Efforts toward RGC replacement have advanced using human PSC technologies (87,88). Protocols now differentiate ESCs or iPSCs into RGC-like neurons expressing canonical markers (such as brain-specific homeobox 3A, RNA-binding protein with multiple splicing and synuclein γ) and functional properties (such as spiking and synaptic proteins) (87,88). Transplantation of iPSC-RGCs into rodent retina results in survival and partial integration within the ganglion cell layer (87). Certain studies have reported axon extension toward the optic nerve head, but long-distance and target-specific reconnection to thalamic or collicular targets remains rare without additional pro-regenerative manipulations (87,88). Recent work emphasizes combinatorial strategies, such as pairing cell replacement with gene or pharmacological enhancement of intrinsic regenerative programs and modulation of the inhibitory extracellular environment, to improve integration and functional outcome (88).

Clinical translation is progressing cautiously. Several early-phase clinical initiatives (such as the Stem Cell Ophthalmology Treatment Study, SCOTS/SCOTS2; clinicaltrials.gov NCT03011541) have investigated autologous bone

marrow-derived stem cells for optic nerve and retinal diseases, reporting safety signals (no surgical complications, no need for immunosuppression and no teratoma formation) but mixed efficacy outcomes and methodological heterogeneity. A systematic review and meta-analysis indicated that stem cell therapies show promise in improving surrogate visual outcomes in optic neuropathies (89); however, high-quality randomized data for glaucoma specifically remain lacking and long-term safety requires continued vigilance (89).

Nevertheless, key technical and translational challenges persist, including the following: i) Cell survival and targeted delivery: The vitreous and inner retinal milieu can be hostile and cell engraftment rates are typically low; ii) immune and tumorigenic risks: Allogeneic cells may provoke immune responses and pluripotent cells carry teratoma risk unless rigorously purified; iii) functional integration: Even when transplanted RGC-like cells survive, forming correct synaptic connections with bipolar/amacrine cells and extending axons through the optic nerve to central targets is notably difficult in the adult mammalian central nervous system; and iv) standardization and potency assays: Reproducible manufacturing, potency assays and release criteria for cell therapy products are still being refined (90). To address these, current preclinical trends focus on the following: i) EV-based therapies as a safer, cell-free approach; ii) biomaterial scaffolds and hydrogel matrices that improve cell retention and oriented axon growth; iii) combination approaches that include gene editing (such as CRISPR to modulate PTEN pathways), neurotrophic factor delivery and local immunomodulation; and iv) careful stepwise clinical translation with standardized endpoints, long-term follow-up and registries (84,88,90).

In summary, stem cell therapies provide compelling preclinical evidence for restoration of the TM and neuroprotection in glaucoma models and offer a plausible route toward regenerative strategies. Nevertheless, major biological and translational hurdles must be overcome before routine clinical application. Priorities for the field include rigorous mechanism-of-action studies, standardized manufacturing and potency assays, well-designed early-phase clinical trials with objective functional endpoints and the development of combination strategies to enable true structural and functional restoration of the TM and RGC pathway (91).

Use of specific molecular mechanisms. Once damaged, RGCs are unable to regenerate or reconnect to the visual pathway (6,24). Therefore, preventing their death is a critical strategy for preserving vision in patients with glaucoma (5,6,24). To achieve this, the disease process can be intervened through certain molecular mechanisms (5,6,24,92-97).

Inhibiting ferroptosis (including using iron chelators such as deferiprone and deferoxamine, lipid ROS scavengers such as ferrostatin-1 and endogenous iron-regulating proteins such as transferrin) (24), blocking pyroptosis (including applying caspase-1 inhibitors such as fluoromethyl ketone and NLR family pyrin domain containing 3 inhibitors such as baicalin extract) (24) and modulating inflammatory responses can help to slow down RGC damage (6).

In addition, a variety of molecules have shown potential in glaucoma treatment. Insulin has been reported to stimulate the regeneration of RGC dendrites and synapses during ocular hypertension (92). However, glucocorticoid treatment, which is commonly associated with increased IOP, involves the activation of glucocorticoid receptors (93). Therefore, blocking these ocular receptors may represent a potential strategy to prevent IOP elevation. Additionally, given that glaucoma involves both histaminergic and nitrergic systems, combining a histamine H3 receptor antagonist with a nitric oxide donor could offer an effective approach to managing IOP (94). Furthermore, NAD^+ depletion serves a marked role in several neurodegenerative diseases, including glaucoma. Oral niacinamide treatment has demonstrated the ability to improve visual outcomes in patients with glaucoma, suggesting its potential as a therapeutic option (95). In a preclinical study, stable gastric pentadecapeptide body protection compound 157 therapy has been reported to alleviate signs and symptoms of glaucoma in rat models (96). Another promising avenue involves the activation of σ-1 receptors, as their low expression is associated with RGC degeneration (97).

Moreover, neuroprotection serves an important role in glaucoma treatment. Several growth factors (such as ciliary neurotrophic factor, nerve growth factor and brain-derived growth factor) have notable neuroprotective effects and can protect and repair RGCs (6). In addition, metabolic abnormalities have been reported to be involved in the pathogenesis of glaucoma, particularly in the occurrence and development of RGC damage (6). Therefore, intervening in the progression of glaucoma through metabolic regulation is of great significance. For example, metformin, insulin and glucagon-like peptide-1 receptor agonists are not only effective for type 2 diabetes but also show potential therapeutic value for glaucoma (6). Taken together, these findings suggest that targeting several molecular pathways could pave the way for more effective therapies.

Nanomedicine. Nanomedicine, the application of nanoscale drug carriers and delivery platforms, improves the ocular penetration of traditional eye drops, provides sustained and controlled release, enables targeted delivery to anterior- or posterior-segment structures and supports co-delivery of multi-modal payloads (such as IOP-lowering agents plus neuroprotectants) (98). Nanomedicine represents promising avenues for glaucoma management, spanning IOP control, neuroprotection and combination approaches that may reduce dosing burden and enhance disease modification in the future (99,100).

Common nanocarrier classes for glaucoma include liposomes, solid lipid nanoparticles (SLNs) and nanostructured lipid carriers, polymeric nanoparticles [such as poly(lactic-co-glycolic acid) (PLGA)], nanoemulsions, niosomes, dendrimers and hybrid/hydrogel embedded nanoparticle systems (98,100). Lipid-based systems are particularly attractive for lipophilic prostaglandin analogs; preclinical work has reported that latanoprost or bimatoprost loaded into liposomes or SLNs can markedly extend ocular residence and prolong IOP lowering after a single administration compared with eye drops (101). For example, Satyanarayana *et al* (101) developed bimatoprost-loaded SLNs that provide extended *in vivo* release and tolerability in rabbits, supporting the potential to reduce dosing frequency.

For hydrophilic drugs (such as timolol), mucoadhesive gelatin or polymeric nanoparticles embedded in viscous vehicles have been reported to improve corneal retention and sustain delivery, translating into longer pharmacodynamic effects in preclinical studies (98,102). Polymeric PLGA nanoparticles have been used to encapsulate neuroprotective small molecules (such as memantine) to enhance posterior-segment delivery and RGC protection in experimental glaucoma models (103). Niosomes and proniosomal gels have been explored to sustain the release of brimonidine, increasing ocular residence and potentially enhancing its documented neuroprotective actions independent of IOP lowering (104). Furthermore, nanoemulsions and contact-lens/insert reservoirs represent alternative platforms to achieve prolonged release whilst maintaining patient comfort and compliance (98,100).

Beyond single-agent delivery, nanocarriers enable combination strategies: Co-encapsulation of an IOP-lowering drug with an anti-inflammatory or antioxidant payload can concurrently reduce pressure and modulate pathogenic microenvironments that contribute to RGC loss. Nanocarriers can also be surface-modified (PEGylation, targeting ligands and mucoadhesive coatings) to tune corneal uptake, reduce clearance and direct payloads toward TM, ciliary body or posterior tissues when needed (98,100).

However, despite promising preclinical data, several translational barriers remain. Safety concerns include local ocular irritation, inflammation, corneal toxicity and the long-term fate of non-biodegradable nanomaterials. Manufacturing at GMP scale with batch-to-batch consistency, stability during storage, sterilization without compromising carrier integrity and regulatory pathways for combination products (device + drug) are non-trivial hurdles (98,100). Immunogenicity of certain surface chemistries and the potential for ocular accumulation with repeated dosing require long-term biocompatibility studies. Moreover, economic and commercial considerations (such as cost of goods, patient acceptance and delivery form factors) also influence which nanoplatforms progress to clinical trials (98,99).

4. Conclusions and future directions

In conclusion, conventional glaucoma treatment methods have limitations in efficacy and struggle to meet clinical needs. Therefore, future treatment directions should focus on emerging technologies such as gene therapy, gene editing, stem cell therapy and molecular targeted therapy. These methods offer new possibilities for glaucoma treatment by precisely intervening in disease mechanisms.

Although current gene therapies are unable to reverse vision loss caused by RGC death, they can effectively delay or even halt disease progression, thereby preventing further visual impairment. If applied in the early stages of the disease, such treatments may also completely avoid notable vision loss and achieve improved prognostic outcomes. However, these cutting-edge therapies are still in the developmental stage, and their clinical translation faces certain challenges. Although certain gene-editing-based clinical trials (such as NCT04560790, NCT01949324, NCT02862938, NCT04577300 and NCT03872479) (105) are ongoing or have been completed, most therapeutic strategies remain in the preclinical research phase and have not yet been widely applied in clinical practice. Therefore, further efforts are needed to strengthen basic research and clinical trials to validate the safety and efficacy of these therapies, facilitating their earlier entry into clinical application.

Several genes have been associated with POAG, highlighting the complex and diverse genetic basis of glaucoma (106). However, the specific functions of several of these genes and their roles in the disease mechanism remain incompletely understood, indicating that numerous potential molecular targets still await further investigation. Future research may not only uncover additional gene targets associated with glaucoma but also offer new approaches and strategies for molecular therapy.

Notably, glaucoma may share certain pathophysiological mechanisms with other neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease (107,108). These shared mechanisms include apoptosis, ferroptosis, pyroptosis, mitochondrial dysfunction, oxidative stress and inflammation (107,108). These common mechanisms suggest that glaucoma may have similar neuroprotective and neuroregenerative requirements as these diseases. Therefore, effective therapeutic approaches for neurodegenerative diseases may also be applicable to the treatment of glaucoma. Exploring these shared mechanisms may uncover new treatment strategies for glaucoma and foster interdisciplinary research.

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Authors' contributions

WW drafted the original article. GC, QZ, SW and LZ edited, validated and revised the original article. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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