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MicroRNAs as key modulators and therapeutic targets in glaucoma

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Abstract

Glaucoma is a leading cause of irreversible blindness characterized by optic nerve degeneration, Retinal Ganglion Cell (RGC) loss, and elevated Intraocular Pressure (IOP). MicroRNAs (miRNAs), small noncoding RNAs that regulate post-transcriptional gene expression, have emerged as key modulators of ocular homeostasis. This mini-review summarizes current evidence on miRNA involvement in glaucoma pathogenesis, their diagnostic biomarker potential, and therapeutic strategies targeting miRNAs. We focus on roles in Extracellular Matrix (ECM) remodelling, oxidative stress, inflammation, and apoptosis in trabecular meshwork and RGCs. Key miRNAs (e.g. miR-29b, miR-143/145, miR-182, miR-155) are discussed in terms of their targets, dysregulation, and functional studies. We also review studies assessing miRNAs in aqueous humor, plasma, or tears as non-invasive biomarkers, and highlight preclinical interventions using miRNA mimics or inhibitors. In conclusion, miRNAs show promising roles in glaucoma research, but large-scale standardized studies and translational efforts are needed to validate their clinical utility.

Keywords: Glaucoma; MicroRNAs (miRNAs); Retinal ganglion cells (RGCs); Trabecular Meshwork (TM); Iintraocular Pressure (IOP); Extra-Cellular Matrix (ECM) remodelling.

Introduction

The term “glaucoma” refers to a wide spectrum of different eye disorders which ultimately lead to irreversible damage to Retinal Ganglion Cells (RGCs) with progressive optic neuropathy. Most glaucoma cases are linked to elevated Intraocular Pressure (IOP), a primary risk factor contributing to oxidative stress, ischemia, and optic nerve damage [1]. Glaucoma currently affects millions of people worldwide and is expected to affect 111.8 million people by 2040 [2]. The multifactorial pathogenesis involves extracellular matrix remodelling, oxidative stress, inflammation, and apoptosis [3]. MicroRNAs (miRNAs) are emerging as critical molecular regulators in glaucoma because they modulate multiple pathogenic mechanisms simultaneously, including extracellular matrix remodeling, intraocular pressure regulation, oxidative stress responses, and neuroinflammation [4]. Unlike single-gene biomarkers, miRNAs control entire gene networks, making them powerful indicators of disease state and progression. Their remarkable stability in body fluids such as aqueous humor, tears, and serum makes them attractive noninvasive biomarkers for early detection and monitoring [5]. Moreover, because miRNAs are upstream regulators, they also represent promising therapeutic targets to modify disease pathways at a molecular level [6]. Although multiple individual studies have implicated miRNAs in glaucoma, the evidence remains fragmented. This review aims to concisely synthesize the current literature on the roles of miRNAs in glaucoma pathobiology, their diagnostic biomarker potential, and possible therapeutic applications.

Glaucoma

Glaucoma is often referred to as the "silent blinder" because many affected individuals remain unaware of their condition until significant vision loss has occurred [5]. Based on the anatomical relationship between the iris, lens, and trabecular meshwork, glaucoma is classified into two main types: open-angle and closed-angle [6]. In some cases, optic nerve damage can develop despite normal Intraocular Pressure (IOP), a condition known as normal-tension glaucoma [5]. Although early detection and timely intervention can help preserve vision, diagnosing glaucoma is complex and typically requires multiple clinical examinations, specialized equipment, and considerable expertise. Current therapeutic strategies primarily aim to lower IOP; however, they are not universally effective, may lack long-term stability, and are sometimes associated with adverse effects. Consequently, glaucoma management remains challenging, driving the search for novel diagnostic tools and treatment modalities that are more biocompatible, durable, and effective. In recent years, several advanced diagnostic technologies have emerged to facilitate earlier detection and more accurate monitoring of disease progression. (Table 1) summarizes commonly used glaucoma diagnostic techniques, while (Table 2) outlines typical treatment approaches.

Table 1: Glaucoma diagnostic techniques.

Diagnostic techniques	Reference
Visual acuity	Dietze J et al. 2023 [4]
Goldmann Applanation Tonometry	Bader J et al. 2023 [2]
Gonioscopy	Zeppieri M et al. 2023 [3]
Fundoscopy	Zeppieri M et al. 2023 [3]
Optical Coherence Tomography	Hong RK et al. 2024 [1]
Perimetry (Visual Field Test)	Dietze J et al. 2023 [4]
Pachymetry	Dietze J et al. 2023 [4]
Ultrasound Biomicroscopy or Anterior OCT	Halkiadakis I et al. 2024 [5]
Advanced algorithms trained on multi-modal data by Artificial Intelligence	AlShawabkeh M et al. 2024 [6]
Heidelberg Retinal Tomography	Song R et al. 2024 [7]
Artificial Intelligence based models like Convolutional Neural Network (CNN) and Support Vector Machine (SVM)	Song R et al. 2024 [7]
Central Corneal Thickness (CTT)	Katsimpris A et al. 2024 [8]
Scanning laser polarimetry	Schuman JS et al. 2025 [9]
Genetics	Kang JM et al. 2021 [10]
Magnetic Resonance Imaging	Gracitelli CPB et al. 2020 [11]

MicroRNA

MicroRNAs (miRNAs) are short, single-stranded, non-coding RNA molecules that regulate gene expression by inhibiting the translation of proteins or inducing the degradation of target mRNAs. They are widely expressed in human cells and are estimated to influence the expression of nearly 60% of all protein-coding genes. miRNAs play crucial roles in controlling key cellular processes such as proliferation, differentiation, and apoptosis. By binding primarily to the 3'-Untranslated Regions (3'-UTRs) of target mRNAs, they act as potent post-transcriptional regulators, modulating more than one-third of all human genes. Genomically, miRNA genes can be located in intergenic regions or within introns of protein-coding genes. They are generally transcribed as independent transcriptional units, either individually or as part of gene clusters, under the regulation of their own promoters.

Table 2: Treatment approaches for glaucoma.

Treatment category	Treatment type	Reference
Medical therapy	Prostaglandin F2α Analogue, Rho kinase inhibitor, β-Blocker, Alpha2 agonist, Carbonic anhydrase inhibitor, Cholinergic agonist	Kang JM et al. 2021 [10]
Laser therapy	Laser trabeculoplasty, Laser peripheral iridotomy and Cyclophotocoagulation.	Kang JM et al. 2021 [10]
	Selective laser trabeculoplasty	Zhou R et al. 2021 [12]
	Cyclophotocoagulation	Lim R et al. 2022 [13]
Surgical Interventions	Trabeculectomy	Binibrahim IH et al. 2017 [14]
	Tube shunt surgery	Chen J et al. 2019 [15]
	Goniotomy	Kaushik S et al. 2021 [16]
	Cataract	Xie J et al. 2023 [17]
	Minimally invasive glaucoma surgery	Ang BCH et al. 2023 [18]

Biogenesis of miRNA

The biogenesis of microRNAs (miRNAs) is a multistep process that spans from their initial transcription in the nucleus to the formation of mature functional molecules in the cytoplasm. Regulation of miRNA abundance involves six key stages: transcription of primary miRNA (pri-miRNA) transcripts, processing of pri-miRNAs into precursor miRNAs (pre-miRNAs), export of pre-miRNAs from the nucleus to the cytoplasm, further processing of pre-miRNAs into mature miRNA duplexes, recognition and subsequent repression or cleavage of target mRNAs, and control of mature miRNA stability and degradation. Each of these steps is tightly regulated, ensuring precise spatial and temporal control of gene expression.

Most miRNAs are transcribed by RNA polymerase II, initiating the canonical miRNA biogenesis pathway and producing primary transcripts (pri-miRNAs) that contain characteristic stem-loop structures. In the nucleus, the initiation or "cropping" step is carried out by the DROSHA-DGCR8 microprocessor complex, which cleaves pri-miRNAs into ~65 nucleotide precursor miRNAs (pre-miRNAs) with short stems and 2-nucleotide 3' overhangs. These structural features are recognized by Exportin-5 (XPO5), which mediates the transport of pre-miRNAs into the cytoplasm. Once in the cytoplasm, DICER1, an RNase III endo-

Type of microRNA	Role in Glaucoma	Reference
miR-29b	miR-29b downregulation leads to extracellular matrix (ECM) deposition in the trabecular meshwork by inhibiting collagen expression types through the PI3K/Akt/Sp1 and Wnt/β-catenin pathways, contributing to glaucoma pathogenesis.	Tabak S et al. 2021
miR-143/145	Promoting TM cell contraction and regulates IOP	Wang Y et al. 2021
miR-182	IOP regulation and optic nerve development	Tabak S et al. 2021
	Tetramethylpyrazine protects primary RGCs against H2O2-induced damage through suppressing apoptosis and oxidative stress via the miR-182	Tabak S et al. 2021
miR-200 family	Downregulation of miR-200a has been shown to promote retinal ganglion cell (RGC) apoptosis through activation of the FGF7-mediated MAPK signaling pathway, whereas overexpression of miR-200a exerts neuroprotective effects by inhibiting glial activation and reducing apoptosis.	Peng et al. 2019
miR-200c	Downregulating the expression of several genes involved in actin regulation and cell contraction, such as ZEB1, ZEB2, ETAR, LPAR1, FHOD1, RHOA.	Luna et al. 2012
	IOP reduction by intracameral injection	Luna et al. 2012
miR-155	Promotes neuroinflammation and the activation of immune cells in the optic nerve	Aggio-Bruce R et al. 2021 (26)
miR-146a	Inhibit neuroinflammation	Luna C et al. 2021
	Preventing alterations of the extracellular proteolytic activity of the TM by downregulating expression of PAI1.	Luna C et al. 2021
	IOP reduction by intracameral injection	Luna C et al. 2021
miR-93	Accumulation of ECM-related proteins as well as the down-regulation of MMP-related proteins	Xu M et al. 2023
	Inhibiting H2O2-stimulated ECM remodeling by blocking TGF-β2/Smad2 signaling pathway.	Xu M et al. 2023
miR-483–3p	Protecting TM cell from 300 μM H2O2 induced-fibrosis by inhibiting TGF-β2/Smad4 signaling pathway.	Shen W et al. 2015
miR-18a-5p	Reducing TGF-β2-mediated TM cell contractility and CTGF expression.	Knox et al. 2022
miR-137	Decreasing ECM production by blocking the YAP/TAZ signaling pathway.	Wang Y et al. 2021
miR-24	Targeting the subtilisin-like proprotein convertase and therefore disrupting the processing of TGF-β1 induced-fibrotic events.	Luna et al. 2012

nuclease, processes pre-miRNAs into 20-25 nucleotide duplexes composed of a guide strand (functional miRNA) and a passenger strand (miRNA*). DICER1, together with cofactors such as TARBP2 or PRKRA, facilitates the recruitment of Argonaute proteins (AGO1-AGO4) to form the miRNA-induced silencing complex (miRISC). During complex assembly, one strand of the duplex is selectively incorporated into an Argonaute protein to serve as the guide strand, while the complementary strand is degraded. This mature miRISC then mediates gene silencing through mRNA degradation or translational repression.

Changes in the expression of microRNA in glaucoma

MiRNAs primarily function as negative regulators of gene expression by suppressing translation or promoting mRNA degradation. Numerous extracellular miRNAs have been identified in various biofluids and are increasingly recognized as potential biomarkers for a wide range of diseases, including cancer, cardiovascular and metabolic disorders, and ocular diseases. In the eye, extracellular miRNAs have been detected in tears, Aqueous Humour (AH), and vitreous humour. Tenon's capsule fibroblasts, located within the connective tissue layer surrounding the eyeball, play a crucial role in maintaining the structural integrity of the capsule through synthesis and remodeling of the Extracellular Matrix (ECM). Among the miRNAs involved in ECM regulation, miR-29b is particularly significant. Downregulation of miR-29b is a major contributor to abnormal ECM accumulation in the Trabecular Meshwork (TM). This miRNA directly targets collagen types I, III, and IV, suppressing their expression through the PI3K/Akt/Sp1 signaling pathway, in which PI3K (p85α) and Sp1 act as direct targets. Additionally, miR-29b activates the Wnt/β-catenin pathway, which governs cell adhesion and ECM homeostasis. In glaucomatous TM cells, reduced miR-29b levels are linked to increased inhibitors of Wnt/β-catenin signaling, resulting in excessive ECM deposition [19].

The miR-143/145 cluster has been shown to increase Intraocular Pressure (IOP) by promoting the contractile activity of Trabecular Meshwork (TM) cells. This effect is mediated through enhanced myosin phosphorylation, which plays a central role in cellular contraction. Additionally, miR-143/145 strengthens contractility by elongating longitudinal F-actin stress fibers, a structural component essential for TM cell contraction. Through these mechanisms, miR-143/145 contributes to increased outflow resistance and elevated IOP [20].

miR-182 is found to be upregulated in the aqueous humour of patients with Primary Open-Angle Glaucoma (POAG) as well as in ageing Trabecular Meshwork (TM) cells. This microRNA plays a crucial role in regulating Intraocular Pressure (IOP) and

protecting against optic nerve damage. Functionally, miR-182 acts as an important antioxidant and anti-inflammatory molecule, contributing to the protection of Retinal Ganglion Cells (RGCs) from oxidative stress. One of its key targets is Toll-Like Receptor 4(TLR4), a component of the inflammatory signalling pathway in the retina. By inhibiting TLR4, miR-182 suppresses microglial activation and thereby mitigates retinal inflammation [19].

The miR-200 family consists of five members: miR-200a, miR-200b, miR-200c, miR-141, and miR-429. A key target of this family is PTEN (phosphatase and tensin homologue), and modulation of PTEN expression represents one of their principal regulatory functions. Downregulation of PTEN leads to the activation of the PI3K/Akt/mTOR signalling pathway, which promotes cell proliferation and inhibits cellular transformation [21]. Furthermore, Peng et al. demonstrated in a mouse model of ocular hypertension that reduced expression of miR-200a activated Mitogen-Activated Protein Kinase (MAPK) signalling, which in turn enhanced retinal ganglion cell (RGC) apoptosis [22]. These findings highlight the critical role of the miR-200 family in maintaining cellular homeostasis and neuronal survival through the regulation of key signaling pathways.

Neuroinflammation plays a critical role in the pathogenesis of optic nerve damage in patients with primary open-angle glaucoma (POAG). Among various regulatory molecules, miR-155 has been identified as a key promoter of microglial activation and inflammatory responses. Yan et al. demonstrated that knockout of the miR-155 gene in mice led to a marked reduction in retinal microglial numbers, their activation state, and the expression of inflammatory mediators, indicating that miR-155 is essential for the development of optic nerve inflammation [23]. In contrast, miR-146a primarily functions as a negative regulator of inflammation by suppressing microglial activation and dampening inflammatory cascades. Both miR-155 and miR-146a interact with the NF-κB signaling pathway, a central mediator of pro-inflammatory signaling, forming a dynamic feedback loop. NF-κB activation induces miR-155 expression, which in turn further enhances NF-κB activity, creating a positive feedback mechanism. Conversely, miR-146a targets interleukin-1 receptor-associated kinase 1 (IRAK1) and tumor necrosis factor receptor-associated factor 6 (TRAF6), thereby inhibiting NF-κB signaling and exerting an anti-inflammatory effect [24].

miR-93 can promote the development of glaucoma by activating Rho/ROCK signaling pathway to mediate the accumulation of ECM-related proteins as well as the down-regulation of MMP-related proteins [25].

Discussion

The complex pathogenesis of glaucoma involves extracellular matrix (ECM) remodeling, oxidative stress, apoptosis, and neuroinflammation, which collectively contribute to trabecular meshwork (TM) dysfunction and optic nerve damage. Recent evidence indicates that microRNAs (miRNAs) play central roles in orchestrating these pathogenic processes by acting as upstream regulators of multiple gene networks.

In the TM, miRNAs critically regulate ECM homeostasis, cytoskeletal dynamics, and cell contractility, directly impacting aqueous humor outflow and IOP. Dysregulation of specific miRNAs, results in excessive ECM deposition and enhanced TM cell contractility, thereby contributing to increased IOP. These observations highlight that miRNAs can exert both pathogenic and protective effects depending on their target pathways, emphasizing their dual role in glaucoma pathophysiology.

Therapeutically, miRNAs offer promising avenues for intervention. Preclinical studies using miRNA mimics or inhibitors have demonstrated the potential to restore normal TM function, reduce IOP, and protect RGCs. The ease of chemical synthesis and the ability to design highly specific oligonucleotides further enhance their appeal as therapeutic agents. However, clinical translation is limited by challenges including off-target effects, immune activation, rapid degradation, and difficulties in achieving tissue-specific delivery. Developing optimized delivery systems such as viral vectors, lipid nanoparticles, or hydrogel-based local delivery remains critical to harnessing the full therapeutic potential of miRNAs.

Beyond therapeutics, miRNAs are emerging as robust biomarkers for glaucoma. Their stability in ocular fluids (aqueous humor, tears) and systemic circulation (plasma, serum) allows minimally invasive detection, and their expression patterns reflect disease stage, TM dysfunction, and neuroinflammatory status.

Collectively, the evidence underscores that miRNAs act as key molecular regulators linking mechanistic pathways to clinical outcomes in glaucoma. Future research should focus on validating candidate miRNAs in larger, well-characterized cohorts, elucidating precise target networks, and developing safe, efficient, and tissue-specific delivery strategies. Such efforts could pave the way for mechanism-driven, personalized approaches that not only halt disease progression but also restore ocular homeostasis, ultimately bridging basic research with clinical application.

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