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Pathogenesis and prospects for therapeutic clinical application of noncoding RNAs in glaucoma: Systematic perspectives

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Abstract

Noncoding ribonucleic acids (ncRNAs) are an increasingly studied class of RNA molecules with extensive biological activities, including important roles in human development, health, and disease. Glaucoma is a neurodegenerative disease of the retina, and one of the leading causes of blindness worldwide. However, the specific roles of ncRNAs in the development and progression of glaucoma are unclear, and related reports are fragmented. An in-depth understanding of ncRNAs participating in the pathogenesis and progression of glaucoma would be helpful for opening up new avenues to facilitate the early diagnosis and clinical treatment. Therefore, in this review, we aimed to discuss the current research progress, the potentialfuture clinical applications and the research limitations of three critical classes of ncRNAs in glaucoma, namely microRNAs, long noncoding RNAs, and circular RNAs.

KEYWORDS

circular RNAs, glaucoma, long noncoding RNAs, microRNAs

1 | INTRODUCTION

Glaucoma is a progressive neurodegenerative disease affecting the retina that is characterized by the progressive loss of optic ganglion cells and neuronal axons, as well as excavation of the optic nerve head (ONH). These changes result in the development of visual field defects and irreversible vision loss, making them some of the leading causes of blindness. In 2013, worldwide, the number of people between 40 and 80 years of age with glaucoma was estimated to be 64.3 million; this number increased to 76.0 million in 2020 and is projected to reach 111.8 million by 2040 (Tham et al., 2014). At present, the specific pathogenic mechanisms leading to glaucoma are not completely understood, but the disease is known to be multifactorial, and there are no effective measures available to completely prevent glaucoma or reverse its progression. Glaucoma patients not only suffer from vision loss, but many also experience other physical and mental health problems, including a high prevalence of anxiety and depression (Wu et al., 2019). In addition, the changes associated with such comorbid psychological illnesses can significantly impact patients' ability to adhere to prescribed treatment regimens, making their conditions worse.

With the recent technological advances that have led to the development of high-throughput and next-generation sequencing, we have gained a deeper understanding of the pathogenesis of glaucoma and the various changes in biological functions that occur at the genetic level inside the cell. Less than 2% of the genetic

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material in the human genome encodes proteins, whereas at least 75% is devoted to noncoding RNAs (ncRNAs) (Sullenger & Nair, 2016), which belong to a large class of nongenetic material that has recently been found to be widely distributed in humans. These molecules could affect the posttranscriptional modification of genes and regulate epigenetic changes, thereby playing an important functional role in organisms and in the development of certain disease states. These ncRNAs are mainly categorized based on their housekeeping and regulatory functions, which are defined and summarized in Table 1. Based on the length of the molecules in nucleotides (nt), small ncRNAs comprising fewer than 200 nt include microRNAs (miRNAs), transfer RNAs (tRNAs), piwi-interacting RNAs (piRNAs), small interfering RNAs (siRNAs), tRNA-derived small RNAs (tsRNAs), and small nucleolar RNAs; longer ncRNA sequences with greater than 200 nt include ribosomal RNA (rRNA) and long ncRNA (lncRNA), as well as an important class of circular RNAs (circRNAs) (Dragomir et al., 2020; Watson et al., 2019). These molecules are derived from many genetic subclasses and are produced either as a result of an exon-skipping mechanism or by the splicing of precursor mRNA (pre-mRNA) sequences by RNA polymerase II, which links the 5′ and 3′ splice positions via back-splicing (Jeck & Sharpless, 2014). With the progress of sequencing technology, the databases of ncRNAs are constantly being updated and improved (Fan et al., 2018). The mechanistic networks of ncRNAs in biological development and disease are also being explored, which can enrich our understanding of the functional picture of the human genome (Anastasiadou et al., 2018; Jusic & Devaux, 2020; Regier & Shepherd, 2020).

A growing number of studies have found abnormal expression of ncRNAs in patients with glaucoma. For example, a study of the aqueous humor (AH) in patients diagnosed with primary open angle glaucoma (POAG) and cataracts assessed differences in expression levels of ncRNAs using microarray analyses and real-time quantitative polymerase chain reaction and found that 3627 lncRNAs and 2228 mRNAs were significantly upregulated in the AH of POAG patients, whereas 1,520 lncRNAs and 820 mRNAs were downregulated, and seven lncRNAs were positively correlated with the expression of glaucoma-associated genes (Xie et al., 2019). Although ncRNAs are involved in the pathogenesis of many diseases and are abundantly expressed in the eye, studies assessing the relationships between ncRNA expression and glaucoma remain sparse. Therefore, the main aim of this review was to summarize the current knowledge about changes in ncRNAs and their association with glaucoma, as a better understanding of its pathogenesis will greatly promote progress toward more efficacious clinical treatment options and improve the life quality of patients.

2 | PATHOGENESIS OF GLAUCOMA

POAG is one of the main types of glaucoma, with the main pathological changes being the selective death of retinal ganglion cells (RGCs) due to high intraocular pressure (IOP), ischemia, immune system-mediated injury, and cross-neuronal degradation caused by degeneration of the trabecular meshwork (TM) cells (Sun et al., 2017), which is the main path of aqueous humor outflow. It has been presumed that increased IOP caused by impaired AH outflow through the TMis the primary cause of POAG; however, the biological basis mediating the occurrence and progression of glaucoma has not been fully elucidated. Clinical studies have found that the risk of glaucoma was highest when optic examinations revealed an increased cup-disk ratio (CDR), CDR asymmetry, elevated IOP, or a disc hemorrhage (Hollands et al., 2013). In addition, several other risk factors, including genetic background(Sakurada & Mabuchi, 2018), age (Mukesh et al., 2002), the expression levels of certain

TABLE 1 The classification and biologic function of ncRNAs

Length of ncRNAs	Role	ncRNAs	Molecular function
Small RNAs (<200 nt)	Functional	tRNAs (transfers RNA)	Participating in the transport of amino acids
	Regulatory	siRNAs (small interfering RNAs)	Silencing target mRNAs
		miRNAs (microRNAs)	Translation inhibition, mRNA cleavage and deadenylation
		piRNAs (piwi-interacting RNAs)	Binding with piwi protein family to regulate gene transposon silencing
Longer ncRNAs (>200 nt)	Functional	rRNAs (ribosomal RNAs)	Forming the ribosome backbone; participating in protein translation
		snRNAs (small nuclear RNAs)	Being involved in mRNAs splicing
		snoRNAs (small nucleolar RNAs)	Engaging in posttranscriptional modification and maturation of various RNAs
	Regulatory	lncRNAs (long non-coding RNAs)	Affecting transcriptional silencing, transcriptional activation, chromosome modification, nuclear transport, etc.
		circRNAs (circular RNAs)	miRNA sponge, regulating splicing, and transcription

inflammatory factors (Wei et al., 2019), a thinner corneal thickness (Jiang et al., 2012), and vascular dysregulation (Grzybowski et al., 2020) have been reported to contribute to glaucoma progression, although the ultimate cause of ganglion death remains unknown.

Over the past several decades, researchers have mainly focused on identification of specific molecular pathways that lead from glaucomatous insult to RGC death; however, as glaucoma is complex and multifactorial, a variety of molecular signals may be acting alone or in cooperation with other pathways to promote RGCs death. These mechanisms include changes leading to axonal transport failure, neurotrophic factor deprivation, increased production of toxic pro-neurotrophic factors, mitochondrial dysfunction, activation of intrinsic and extrinsic apoptotic signaling cascades, oxidative stress, excitotoxic damage, reactive gliosis, and the loss of synaptic connectivity (Almasieh et al., 2012; Quigley et al., 2000; Williams et al., 2017). While the exact etiology is unknown, many studies have reported that ncRNAs may drive the changes that lead to the progression of glaucoma and contribute to RGC death through one or more of these pathophysiological processes (Figure 1).

3 | MICRORNAS

Widely expressed in eukaryotic cells, miRNAs belong to a class of endogenous ncRNAs. They are single-stranded RNA molecules with a length of about 21–23 nt. Study suggests that the entire human genome encode approximately 1100 miRNAs capable of modulating the expression of more than 60% of all protein-coding genes (Friedman et al., 2009). The exact discovery of miRNAs can be traced back to 1993, when Lee et al. first isolated a 22-nt single-stranded RNA from a nematode (Lee et al., 1993). In 2003, Lagos-Quintana et al. (2001) identified seven species of miRNA expressed in the eyes of adult rats. To date, more than 2000 miRNAs have been identified, and their roles in the fields of medicine and biology have gained increasingly widespread attention. These miRNAs participate in almost all the biologic activities in cells that have been reported to date, and it is now known that these molecules play important roles in the initiation and progression of various diseases, such as those involving tumor growth, neurodegenerative diseases, and immunological diseases (Fransquet & Ryan, 2018; Rupaimoole & Slack, 2017; Serafin et al., 2014). Naturally, an increasing number of studies have begun to assess the potential clinical applications of miRNAs in clinical diagnosis and treatment, as miRNAs can regulate cellular functions by inhibiting the expression of certain target genes. Their main mechanisms of action include the suppression of target gene translation, cleavage, and degradation of mRNAs in the following manner: (1) miRNAs can inhibit the synthesis of ribosomes or prevent the initiation and extension of the translation process, and some miRNAs can promote the shedding of ribosomes during translation, thereby prematurely terminating translation (Lee et al., 2003); (2) the base sequences of some miRNAs can be completely complementary to those of their downstream target mRNAs, and miRNAs can disrupt the complementary region of the target mRNA sequences causing a loss of their biological activities (Blaszczyk et al., 2001); and (3) miRNAs promote the degradation and inactivation of mRNAs from the 5′ or 3′ end (Gregory et al., 2004). We also exhibited mechanism diagram in Figure 2.

3.1 | miRNAs in glaucoma

Many studies have confirmed that miRNAs exert a wide range of effects in ocular cells, including participating in processes related to the formation and transmission of visual information in mammals (Pinter & Hindges, 2010), regulating ocular cell proliferation, and playing roles in apoptosis and cellular differentiation (X. Wang et al., 2019; Yin & Chen, 2019); they are also known to regulate the metabolic activity and immune responses of ocular cells (Lin et al., 2011). Changes in miRNA activities are closely related to the development and/or progression of a variety of ophthalmic diseases; these regulatory mechanisms are known to be large and complex, although the specific regulatory pathways have yet to be clearly elucidated. The study of the mechanisms through which miRNAs contribute to ocular pathophysiology will provide a new theoretical basis for molecular models of ophthalmic diseases. It has been proven that miRNAs not only exist in ocular structures, but are

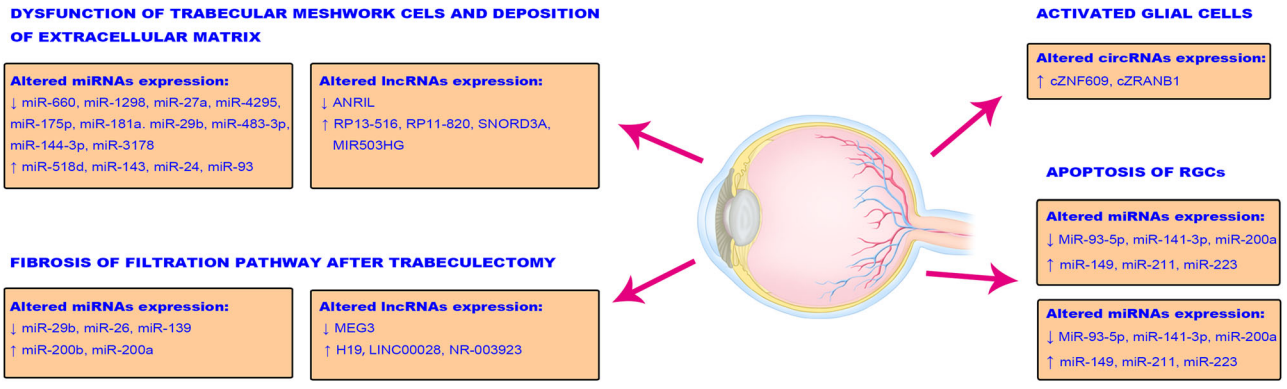

FIGURE 1 The expression of related microRNAs, long noncoding RNAs and circular RNAs in the different pathological process of glaucoma

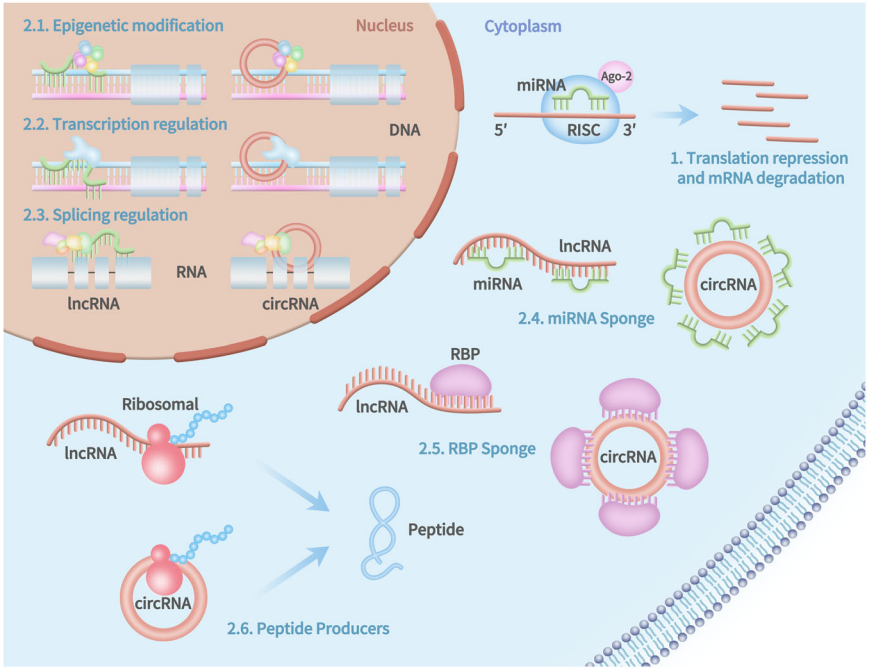

FIGURE 2 Recognized function mechanisms of microRNAs, long noncoding RNAs, and circular RNAs in eukaryotic cells

widely distributed in human fluids, including the blood, tears, and AH. In glaucoma, the expression of miRNAs has been shown to be greatly altered in the cornea (Xu et al., 2007), ciliary body (Wang et al., 2010), TM cells (Ryan et al., 2006), and the retina (Tanaka et al., 2014). It is unknown, however, whether these abnormal changes in expression are a key cause of the development and progression of glaucoma or whether they are merely the indirect result of other abnormal physiological changes. A better understanding of the causal relationships between these factors still requires a greater knowledge of the complete network affected by these mechanisms.

3.1.1 | The role of miRNAs in TM cells and the extracellular matrix (ECM)

The anatomical characteristics of the anterior chamber explain why the TM is mainly responsible for draining AH from the eye and producing a framework for the deposition of the extracellular matrix (ECM), as the major aqueous outflow resistance depends on the juxtacanalicular region of the TM and the inner wall basement membrane of the Schlemm canal. The dysfunction of TM cells under oxidative stress and a disruption in the balance between ECM synthesis and degradation may result in alterations in aqueous outflow and an increase in the IOP. Earlier studies compared AH samples collected from POAG patients and a normal control group, and found that the expression of two miRNAs, miR-518d and miR-143, were significantly upregulated, whereas another miRNA, miR-660, was downregulated; these miRNAs were predicted to be closely related to the regulation of cellular proliferation and may reduce ECM remodeling and the activity of ubiquitin-mediated proteolytic pathways such as autophagy, as these pathways work to degrade and clear proteins from the outflow channels. Changes in the normal activity of all of these processes would result in increased outflow resistance and an elevated IOP (Jayaram et al., 2017). However, the inhibitory effects induced by the upregulated miRNAs could be counterbalanced by the downregulation of miR-660 (Keller & Wirtz, 2017), though further studies are needed to verify the specific molecular mechanisms related to abnormal alterations in the TM and ECM, and to guide the direction of future research of miRNAs in glaucoma.

Hydrogen peroxide (H_2O_2) is usually used to induce an acute oxidative stress injury in human trabecular meshwork cells (HTMCs) to generate a model to study functional changes of the TM in vitro (Izzotti et al., 2009). One group found that cyclic mechanical stress could induce the upregulation of miR-24, leading to the downregulation of Furin, a subtilisin-like proprotein convertase that participates in a variety of cellular activities by catalyzing the maturation of various cellular proteins, such as growth factors and receptors (Bassi et al., 2001; Varshavsky et al., 2008; Zhou et al., 2009). It has been shown that miR-24 can participate in the regulation of the transforming growth factor beta (TGF-β) signaling pathway by directly targeting Furin, ultimately promoting the contraction and proliferation of HTMCs (Luna et al., 2011). However, after exposure to chronic oxidative stress, the expression of miR-1298 and the number of HTMCs decreased significantly in this animal model of glaucoma, further confirming that miR-1298 can protect against oxidative damage and ECM deposition by inhibiting and activating the TGF-β/smooth muscle actin (Smad) and canonical Wnt/β-catenin signaling pathways, respectively (Ruibin et al., 2018). The well-known TGF-β/Smad pathway is capable of inducing the transcription of mRNA molecules involved in cellular growth and apoptosis, and extracellular matrix regeneration (Hu et al., 2018), whereas the Wnt/β-catenin pathway is known to affect cellular proliferation, differentiation, fibrosis, and migration by mediating the phosphorylation and dephosphorylation

of downstream proteins (Clevers & Nusse, 2012). Similarly, the expression of miR-27a was shown to be downregulated in the same model, and further experiments indicated that exogenous supplementation could alleviate H_2O_2-induced apoptosis of HTMCs by activating the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) and Wnt/β-catenin pathways (Zhao, Du, et al., 2019). In addition, oxidative damage caused by decreased expression of miR-4295 was mediated through the inhibition of the PI3K/Akt and the extracellular signal-regulated kinase (ERK) signaling pathways (Liu & Zhang, 2019). In another study, it was shown that the downregulation of miR-175p could increase the expression of the phosphatase and tensin homolog (PTEN), leading to increased apoptosis and decreased proliferation of HTMCs under oxidative stress conditions (Liu & Zhang, 2019; X. Wang et al., 2019). As a major negative regulator of the Akt signaling pathway, PTEN indirectly affects cellular proliferation and apoptosis (Feng et al., 2017; Ronen et al., 2017).

Nuclear transcription factors can bind to specific DNA sequences. When the cell is stimulated by external factors, the nuclear transcription factor will translocate from the cytoplasm to the nucleus where it is able to combine with its target DNA enhancer and promoter region, regulating gene transcription and expression (Lambert et al., 2018). Overexpression of miR-181a has been shown to inhibit H_2O_2-induced apoptosis by blocking the nuclear factor kappa B (NF-kB) and c-Jun N-terminal kinase pathways in HTMCs (Y. Wang et al., 2018). Another study found that the expression of miR-93 in glaucoma trabecular meshwork (GTM) cells was significantly higher, and miR-93 may regulate apoptosis in GTMs by targeting nuclear factor erythroid 2-like 2 (Wang et al., 2016).

In the oxidative stress model of HTMCs described above, researchers found increased ECM synthesis and a downregulated expression of miR-29b. Further, transfection of molecules mimicking miR-29b into HTMCs revealed that miR-29b could directly target and reduce ECM synthesis, as well as decrease the expression of structural proteins such as collagen, thereby alleviating the obstructed aqueous outflow (Luna et al., 2009). Similarly, the decreased expression levels of miR-483-3p and miR-3178 under oxidative stress were able to inhibit the expression of ECM-related proteins and reduce ECM deposition (Shen et al., 2015; Shen et al., 2020). Another study showed that the overexpression of miR-144-3p promoted the proliferation and invasion of HTMCs by inhibiting the expression of fibronectin-1 (FN-1) under oxidative stress (Yin & Chen, 2019). FN-1 participates in cell-to-cell and cell-to-matrix adhesion in vivo, and it can promote ECM deposition to inhibit the formation of the TM (Medina-Ortiz et al., 2013). These results suggest that miRNAs can directly affect the deposition of the ECM by altering ECM-related proteins.

Later studies identified three miRNAs (miR-125b-5p, miR-302d-3p, and miR-451a) in AH samples whose expression levels differed significantly between the POAG and control groups, five miRNAs (miR-122-5p, miR-3134-3p, miR-320a, miR-320e, and miR-630) that differed between the exfoliative glaucoma (XFG) group and the control group, and one miRNA (miR-302d-3p) whose expression differed between the POAG and XFG groups. Pathway analyses revealed that these differentially expressed miRNAs were involved in the structural changes in and the accumulation of the ECM that have been previously implicated in the pathogenesis of glaucoma. These miRNAs are also known to be associated with some pathophysiological pathways in glaucoma that regulate focal adhesion, the formation of tight junctions, and regulate TGF-β signaling (Drewry et al., 2018). Exfoliation syndrome is currently one of the most common causes of secondary open-angle glaucoma and is a degenerative disease that mainly occurs in elderly and male patients. Therefore, these results have important implications for the clinical diagnosis and treatment of XFG.

3.1.2 | Regulation of RGC function by miRNAs

The PI3K/Akt signaling pathway extensively modulates biological activity in vivo, including playing important roles in the regulation of cellular metabolism, proliferation, survival, transcription, and protein synthesis. In a mouse model of chronic glaucoma, the expression of miR-149 was found to be upregulated in RGCs, and the silencing of miR-149 promoted the viability of RGCs by increasing the activation of the PI3K/Akt signaling pathway (Nie et al., 2018). Another group showed that after *N*-methyl-D-aspartic acid injection into the vitreous of Sprague-Dawley (SD) rats, which is a commonly used model of the pathogenesis driving the glutamate excitotoxicity seen in glaucoma, the viability and number of RGCs decreased significantly. This change was primarily the result of the downregulation of miR-93-5p, which can negatively regulate PTEN through the Akt/mammalian target of rapamycin (mTOR) signaling pathway, affecting the survival of RGCs (Li et al., 2018).

Other studies have shown that miRNAs participate in processes related to the glaucomatous damage of RGCs through the modulation of the well-known mitogen-activated protein kinase (MAPK) cascade signaling pathway, which plays an important regulatory role in many basic biological processes, including cellular proliferation, apoptosis, and stress responses. A recent study demonstrated that the upregulation of miR-141-3p inhibited the activation of MAPK signaling pathway-induced RGC death. Moreover, the upregulation of miR-141-3p can reduce the expression of vascular endothelial growth factor (VEGF) and inhibit the proliferation and tube formation of vascular epithelial cells in the retina, which may play an important role in the pathogenesis of neovascular glaucoma (L. Q. Zhang et al., 2019). Similar studies have reported that regulation of the MAPK pathway resulting from increased miR-211 expression may be an important mechanism for high IOP-induced cellular apoptosis (Yang et al., 2018). In addition, the downregulation of miR-200a in the RGCs of mice with glaucoma can increase the apoptosis of RGCs and the inactivation of Müller cells by increasing the activation of MAPK signaling pathways (Peng et al., 2019). A total of 31 miRNAs have been shown to be upregulated or downregulated in a rat model of acute ocular hypertension (AOH), and these differentially expressed miRNAs were shown to regulate microglia-mediated neuroinflammation or neuronal apoptosis by activating the p38-MAPK signaling pathway (J. Wang et al., 2017). These experiments suggest that miRNAs may play important roles in the

protection of RGC function following glaucomatous injury by regulating the MAPK signaling pathway.

Another study proved that the miR182/B-cell lymphoma 2 (Bcl2) interacting protein 3 (BNIP3)/mitochondrial apoptotic pathway was necessary for mediating oxidative stress and apoptosis associated with the development of glaucoma in RGCs. This is explained by the fact that BNIP3 is a member of the Bcl2 family of proteins, which are key factors in the apoptotic pathway induced by mitochondrial dysfunction (Li et al., 2019).

Heat shock protein 70 (HSP-70) is an important member of the heat shock protein family; in high pressure stress conditions, the cellular expression of HSP-70 is rapidly upregulated, which can contribute to antistress responses in organisms. Exogenous upregulation of miR-223 can inhibit the proliferation of RGCs, and can induce apoptosis and inflammatory responses by reducing the expression of HSP-70 (Ou-Yang et al., 2020).

Researchers have also found that supplementation of mesenchymal stem cells (MSCs) in the vitreous cavity can inhibit caspase-8-mediated apoptosis of RGCs, as well as the activation of microglia in an AOH mouse model. In vitro experiments confirmed that miR-21 and its target molecule, programmed cell death protein 4, could regulate MSCs to enhance the secretion of stanniocalcin-1 and other neuroprotective factors (Su et al., 2017).

Ultimately, miRNAs can participate in the important biological processes of HTMCs and RGCs by targeting diverse molecular pathways, and understanding these mechanisms could help identify novel treatment targets for glaucoma.

3.1.3 | Circulating miRNAs in glaucoma

Mature miRNAs are formed in the cytoplasm, some of which will be released into the circulatory system and become a constituent of various bodily fluids, such as blood, urine, saliva, and lymph, by binding to RNA binding proteins (RBP) or through the secretion of microvesicles. These types of miRNA molecules are called circulating miRNAs (Cortez et al., 2011). Circulating miRNAs are usually stably expressed within the circulatory system (Chen et al., 2008), and studies have shown that they may be important targets for the diagnosis and treatment of certain diseases, and could act as markers for evaluating prognosis (Bialek et al., 2015; Wang et al., 2013). Some miRNAs are differentially expressed in the blood of glaucoma patients at levels at least 1.5 times higher than those in healthy controls; these include miR-637, miR-1306-5p, and miR-3159 (Hindle et al., 2019). In addition, miR-210-3p was found to be significantly upregulated in the venous blood of POAG patients, which was in accordance with the results of clinical visual field testing and measurements of the average retinal nerve fiber layer thicknesses (Liu, Wang, et al., 2019). Tanaka et al. collected AH samples from glaucoma patients and found that 11 miRNAs were significantly upregulated and 18 miRNAs were significantly downregulated compared with the samples from the control group (Tanaka et al., 2014). Another study showed that several miRNAs were differentially expressed in the AH samples collected from POAG and XFG patients compared with the control group without glaucoma (Drewry et al., 2018). Moreover, they reported differences in expression of 16 miRNAs in the AH between POAG eyes from those with severe and moderate visual field injuries (Liu et al., 2018). These studies have fully proven that the differential expression of miRNAs in the AH of glaucoma patients has important diagnostic significance. Interestingly, a previous study compared the supernatant collected from the tears of POAG patients and healthy controls, and reported that there was a significant increase in the expression of miR-126 in the POAG group (Tamkovich et al., 2019). Patients with glaucoma may remain asymptomatic until a relatively late stage of progression, often leading to delayed diagnosis. Therefore, the wide distribution of circulating miRNAs and the convenience of sampling, they may prove to be effective diagnostic biomarkers in conditions when ophthalmic examinations cannot be performed, and this could vastly improve glaucoma screening.

3.1.4 | Reducing fibrosis after glaucoma filtering

Glaucoma trabeculectomy is a classic surgical method for the treatment of glaucoma. Maintaining patency of the postoperative filter passage is essential for ensuring a successful operation; however, scarring of postoperative filter blebs often leads to obstruction of the filter tract and poor drainage, resulting in failed surgery. Many studies have confirmed that TGF-β can induce the proliferation of human Tenon's capsule fibroblasts (HTFs), enhance the deposition of ECM, and increase the proliferation of collagen fibers, leading to glaucoma filtration Tenon capsule fibrotic scarring, as well as differential expression of miRNAs (Li et al., 2012; Ran et al., 2015; Yu et al., 2015). For example, miR-29b, which targets a set of essential mRNAs that encode fibrosis-related proteins such as PI3K and type I collagen-α1 (Col1A1), was shown to be downregulated following trabeculectomy. Overexpression of miR-29b after trabeculectomy in rabbits significantly reduced collagen fibroblast proliferation and the expression of Col1A1 in the sclera and conjunctival area (Yu et al., 2015). These results indicate that miR-29b plays an important role in maintaining follicular function after glaucoma filtration surgery (GFS). Other experiments confirmed that downregulation of miR-26 can reversibly regulate the expression of connective tissue growth factor (CTGF) (Bao et al., 2018). In addition, the expression of miR-26a was also significantly decreased in filtered tract scars, and its overexpression led to the reduced expression of CTGF, thereby impairing the viability and migration capacity of HTFs (Wang, Deng, et al., 2018). In vitro experiments in cells have shown that the concentrations of type I collagen and smooth muscle actin (SMA) in HTFs induced by TGF-β were significantly increased, whereas the expression of miR-139 decreased. A previous study found that the Smad2/3/4 complex could bind to the miR-139 promoter region to inhibit miR-139-related transcriptional activity; this suggests a participatory role for miR-139 in the regulation of the Wnt/β-catenin signaling pathway that affects the proliferation of

HTFs (Deng et al., 2019). Another study showed that increased expression of miR-200b induced by the same stimulation could directly inhibit cellular proliferation- and cell cycle progression-related genes to promote the proliferation of HTFs (Tong et al., 2014). In addition, miR-200b can target PTEN; the decreased expression of PTEN is related to the increased expression of α-smooth muscle actin (α-SMA), FN-1, and COL1A1 (Tong et al., 2019). Similarly, studies have found that the upregulation of miR-200a altered the signaling mediated by β-catenin, which is another protein that can regulate HTF fibrosis (Zhu et al., 2020). In addition, miRNAs can alter an organism's response to drugs used to prevent the proliferation and fibrosis of HTFs, such as hydroxycamptothecin (HCPT). HCPT is one of the most widely studied, naturally-occurring antitumor drugs that can be used to inhibit the proliferation of HTFs and induce apoptosis by downregulating the expression of miR-216b (Xu et al., 2014).

Certain sequence variants of miRNAs will affect their function and cause changes in the expression of corresponding mRNAs that are known to be closely associated with the development of glaucoma (Shi et al., 2016). By analyzing the polymorphisms of miRNA-related genes, it is possible to identify individuals who are at a higher risk of developing glaucoma (Zhang & Wang, 2019). Certain single nucleotide polymorphisms (SNPs) of miRNAs may have theoretical significance as biomarkers that could lead to new innovations to improve glaucoma diagnosis.

4 | LONG NONCODING RNAs

Expressed in both the nucleus and cytoplasm, lncRNAs are a group of ncRNA molecules with a transcript length greater than 200 nt. These molecules can be sub-classified according to the position of the lncRNAs relative to the coding genes on a chromosome. These molecules include antisense lncRNAs, intronic lncRNAs, divergent lncRNAs, intergenic lncRNAs, upstream promoter lncRNAs, promotor-associated lncRNAs, and transcription start site-associated lncRNAs (Ransohoff et al., 2018; Rinn & Chang, 2012; Scheuermann & Boyer, 2013). Earlier, it was believed that lncRNAs were merely "noise" or byproducts of RNA polymerase II genomic transcription that had no biological function. In 1991, however, a study revealed that lncRNA Xist (X-inactive specific transcript) participated in the regulation of the X chromosome inactivation process (Borsani et al., 1991). Since that time, multiple biological functions of lncRNAs in gene regulation have been identified, and this class has gradually attracted widespread attention. The secondary structure of lncRNAs allows them to combine with certain proteins to facilitate chromatin remodeling and modification, and the linear control of transcription factors. Meanwhile, lncRNAs interacting with miRNA could indirectly regulate the subsequent expression of associated mRNAs, and the ability of lncRNAs to directly bind to mRNAs allows them to regulate translation, shearing, and degradative processes (Guttman & Rinn, 2012; Mercer et al., 2009; Ponting et al., 2009; Rinn & Chang, 2012). In addition, lncRNAs play a role in the transcription of target genes and the cis or trans regulation of biological processes; in other words, they can regulate their own transcribed neighboring regions (cis), or they can control gene expression in remote regions of the genome or other cell-localized regions (trans) (Fatica & Bozzoni, 2014; Kornienko et al., 2013). A previous study showed that lncRNAs can be attracted to ribosomes, some of which can then become translated into small peptides (Ingolia et al., 2011). More recently, some lncRNAs have also been found to have small open reading frames, which can encode short peptides with important biological functions (Matsumoto et al., 2017), and studies of these short peptides are currently focused on tumorigenic diseases (J. Wang et al., 2019). The regulation of gene expression by lncRNAs relies on a precise and complex network that contains many biological mysteries waiting to be explored (Figure 2).

Many clinical studies have found that changes in lncRNA expression or activity are closely associated with a variety of human diseases, such as cancer, neurodegenerative diseases, cardiovascular diseases, and diabetes (Hrdlickova et al., 2014; Li et al., 2013; Liu et al., 2014; Ng et al., 2013; Prensner & Chinnaiyan, 2011). In addition, lncRNAs have been found to be associated with the pathogenesis of ocular diseases such as glaucoma, cataracts, corneal diseases, diabetic retinopathy, and ocular tumors (L. Zhang, Dong, et al., 2019).

4.1 | lncRNAs related to the pathogenesis of glaucoma

4.1.1 | Effects of lncRNAs on the functions of HTMCs and ECM

Among the studies that have assessed H_2O_2-induced oxidative stress in HTMCs, one group showed that 70 lncRNAs were differentially expressed, of which 24 were identified as belonging to the lncRNA–miRNA–mRNA interaction network (Yao et al., 2020). Some have suggested that lncRNAs effectively act as "sponges" that bind to and competitively inhibit the function of miRNAs. In other words, there are a large number of specific miRNAs binding sites on lncRNAs, and miRNAs can be absorbed by lncRNAs in large quantities, similar to the absorption of water by a sponge. LncRNAs can strongly inhibit the activity of miRNAs, thereby indirectly regulating the expression of the downstream target genes of miRNAs (Thomson & Dinger, 2016), interactions between these families of molecules are collectively known as the competing endogenous RNA (ceRNA) network. Investigations of this lncRNA-associated ceRNA network could contribute to the identification of novel pathophysiological mechanisms of glaucoma or potential therapeutic targets to treat it. Four lncRNAs, RP13-516, RP11-820, SNORD3A, and MIR503HG, were shown to be significantly upregulated by the same oxidative stress conditions. Furthermore, one study found that downregulating lncRNA-RP11-820 could significantly increase the expression of miR-3178, resulting in the increased expression of FN-1, laminin, and type I collagen, and a reduction in ECM proliferation (Shen et al., 2020). In addition, overexpression of ANRIL can reduce oxidative damage in HTMCs by downregulating miRNA-7 and activating the mTOR and

mitogen-activated protein kinase (MEK)/ERK pathways (Zhao, Sun, et al., 2019). Exogenous upregulation of lncRNA expression can regulate the oxidative damage that occurs in HTMCs, which could have important clinical significance.

4.1.2 | Effects of lncRNAs on the function of RGCs

In our previous work, we reported that the expression levels of lncRNA- metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) were reduced in RGCs in a rat model of chronically high IOP, and that the overexpression of MALAT1 could reduce the mRNA and protein expression of PI3K/Akt signaling molecules, causing a decrease in the number of apoptotic RGCs (Li et al., 2017). In another experiment, we detected that the expression of the growth arrest-specific 5 (GAS5) molecule was reversibly upregulated, and that silencing of GAS5 inhibited RGC apoptosis through the modulation of enhancer of zeste homolog 2 (EZH2), the trimethylation of lysine 27 on histone H3 (H3K27me3), and the modulation of ATP-binding cassette transporter A1 (ABCA1) (Zhou et al., 2019). In vitro experiments involving H_2O_2-induced oxidative stress revealed that upregulating the expression of lncRNA taurine upregulated 1 (TUG1) could significantly reduce reactive oxygen species (ROS) production and cellular apoptosis by positively regulating the nuclear factor erythroid-2 related factor (Nrf2) protein level, which is a central regulator of resistance to oxidative stress (Gong et al., 2019). The lncRNA Mbd2-AL1 was found to participate in methyl-CpG binding domain protein 2 (Mbd2)-mediated retinal ischemia and reperfusion (I/R)-induced apoptosis in RGCs. I/R injury is one of the pathophysiological etiologies of glaucoma. Mechanistically, Mbd2 promoted the expression of lncRNA Mbd2-AL1 through promoter hypomethylation, resulting in the downregulation of miR-188-3p expression, ultimately leading to the inhibited expression of the apoptosis inducer tumor necrosis factor (TNF) receptor-associated factor 3 (Traf3) (Ge et al., 2020).

4.1.3 | Effects of lncRNAs on filtration channel scarring after GFS

A previous study showed that increased expression of lncRNA H19 can result in the downregulated expression of β-catenin by competitively binding to miR-200a, thereby promoting the proliferation and fibrosis of HTFs (Zhu et al., 2020). LINC00028 was also shown to be upregulated by competitively targeting miR-204-5p to regulate the biological function of HTFs (Sui et al., 2020); thus, lncRNAs can indirectly regulate related proteins by targeting downstream miRNAs, affecting the cellular functions of HTFs. Relevant human studies have confirmed the regulatory role of lncRNAs in mediating follicular scarring after GFS. One study found that 1638 lncRNAs were upregulated and 1455 were downregulated in the fascia of glaucoma patients. Among these, the expression of NR_003923 was significantly increased, which, in turn, reduced the expression of miR-760 and miR-215-3p. Subsequently, there was increased expression of related proteins in the HTFs such as α-SMA and FN-1, as well as inhibition of E-cadherin and β-catenin, ultimately resulting in the promotion of TGF-β-induced cell proliferation and fibrosis of HTFs (Y. Zhao, Zhang, et al., 2019). Another study showed that the decreased expression level of lncRNA MEG3 resulted in the TGF-β2-induced proliferation of HTFs after GFS by positively affecting the expression of Nrf2 proteins (Y. Wang et al., 2017). These experiments showed that lncRNAs can be used as important biomarkers to allow for postoperative evaluation of recovery in glaucoma patients, and that lncRNAs play an important regulatory role in the maintenance of regular follicular functions.

Currently, there are relatively few identified pathogenic genes related to glaucoma, but the ones that have been described include myocilin, WD repeat domain 36, and optineurin (OPTN) (Fingert, 2011). While the specific mechanisms through which these gene mutations lead to the pathogenesis of glaucoma remain obscure, one study showed that a total of 69 lncRNAs were significantly down- or upregulated in the retinas of OPTN (E50K) transgenic mice (Y. Li, Jin, et al., 2017). Another study revealed that variations in the lysyl oxidase-like 1 (LOXL1) gene greatly increased the risk of developing XFG. These mutations mainly occur within the promoter region of lncRNA LOXL1-AS1, resulting in the expression of altered transcripts, and LOXL1-AS1 dysregulation has been shown to contribute to XFS pathogenesis (Hauser et al., 2015). Pseudoexfoliation syndrome (PEX)-related SNPs, which are also located on the promoter of lncRNA LOXL1-AS1 and selectively bind to the proteins, are critical for the regulation of overall gene expression in ocular cells. Dysregulation of LOXL1-AS1 induced by SNPs associated with PEX would inhibit the proper functioning of the conventional outflow pathway, suggesting the occurrence of glaucoma (Schmitt et al., 2020).

Variations in genes known to increase the risk of glaucoma will also affect the expression levels of their corresponding lncRNAs, thereby affecting disease progression, although there are still many unknowns in this area that require greater in-depth exploration. A better understanding of these variations will be a crucial step for future glaucoma-related gene research. In the future, studies of the diversity of lncRNAs and their wide distribution in various cell types will gradually become as common as studies assessing the functional role of a certain proteins in these disease states.

5 | CIRCULAR RNA

CircRNA is a class of endogenous ncRNAs characterized by covalently closed, continuous loop structures that regulate gene expression in eukaryotic cells. CircRNAs play an important role in many cellular activities, including proliferation, migration, and metastasis. CircRNAs can be divided into the following three categories based on their structural differences: exoniccircRNAs, exonic intronic circRNAs, and intronic circRNAs (Kristensen et al., 2019). Most exoniccircRNAs exist in the cytoplasm, whereas the other two types are mainly localized within the cell nucleus. They are highly abundant,

conserved, and dynamically expressed in the eye (George et al., 2019).

CircRNA cZNF609 has been found to be expressed in neurons and endothelial cells (Boeckel et al., 2015; Rybak-Wolf et al., 2015). In the SD rat model of chronic glaucoma, the expression of cZNF609 in the retina and AH has been shown to be significantly higher than in the same regions in the control group. Silencing of cZNF609 has been shown to reduce retinal reactive glial hyperplasia and glial cell activation, protecting RGCs from the damage caused by increased IOP resulting from the activation of glial cells and the exacerbation of neuronal injury through the release of proinflammatory cytokines, nitric oxide, or reactive oxygen species (Martin et al., 2002; Tezel & Wax, 2000). Müller glial cells play important roles in several RGC functions, including synapse formation and plasticity, maintaining homeostasis of neurotransmitters and ions, as well as redox metabolism (Fruhbeis et al., 2012). Furthermore in vitro experiments have found that cZNF609 can directly regulate Müller cell functions and indirectly regulate RGCs because increased expression of cZNF609 may act as a "sponge" for miR-615. This competitive combination directly results in increased miR-615 expression, as well as miR-615-mediated inhibition of meteorin (METRN) expression, the upregulation of which has been shown to contribute to Müller cell activation (Wang, Liu, et al., 2018). More specifically, METRN is a secreted protein that plays significant roles in both glial cell differentiation and axonal network formation during neurogenesis (Nishino et al., 2004; Park et al., 2008).

In addition, cZRANB1 is constitutively expressed in the retina, especially in the cytoplasm of glial cells. Its mechanism of action in the chronic glaucoma model is similar to that of cZNF609. Overexpression of cZRANB1 competitively combines with miR-217 under conditions of oxidative stress or glutamate excitotoxicity, mediating the suppressive effects of miR-217 on runt-related transcription factor 2 (RUNX2) expression (Wang, Shan, et al., 2018). RNA sequencing of the retina is based on the chronic high intraocular pressure model indicating that thousands of circRNAs are expressed differently. Furthermore, the presence of hsa_circ_0023826 and mRNA of Tenm4 was confirmed in the AH of glaucoma. Compared with cataract patients, the results were largely consistent with the RNA sequencing (X. Chen et al., 2020). The construction of abnormal expression profiles of circRNAs and mRNAs after HTMs damage induced by oxidative stress has certain suggestive significance for the pathogenesis of POAG. At the same time, it was observed that circHBEGF directly targeted miR-646 as a miRNA sponge to regulate the expression of EGFR in HTMCs under oxidative stress, and that EGF signaling pathways can transcriptionally activate ECM genes, accordingly promoting ECM production. This fibrotic process is believed one of the predominant causes of POAG (Shen, Wang et al., 2020). At present, studies of the role of circRNAs in the pathophysiology of glaucoma is lacking; however, based on several circRNAs mentioned above, it appears that they may exert their effects by suppressing the expression of miRNAs, thereby increasing the translation and stability of the related mRNA targets at the post-transcriptional level. In other words, circRNAs may exert their effects by "sponging" up miRNAs competitively to help mediate biological effects in other diseases states, which is also termed as the ceRNA mechanism (Lu et al., 2019). CircRNAs can also influence translation by directly binding to mRNAs or RBPs, or simply through modulating their own translation; ultimately, they may serve as chief regulators of RNA and protein expression. However, these mechanisms are rarely reported in glaucoma, and it is believed that circRNAs mainly exert their effects in eukaryotes with the following ways: (1) they interact with miRNAs competitively by acting as sponges, which in turn induce the expression of target mRNA; and (2) they compete with different RBPs to modulate gene expression (Du et al., 2017). (3) they could become small peptides producer to exert biologic function (Figure 2).

Normal aging is characterized by progressive and time-dependent functional decline (Kenyon, 2010). A previous study found that several circRNAs accumulated in aging photoreceptors and eyes, including circRNAs affecting genes that are required for optimal visual function and/or photoreceptor health (Stegeman et al., 2018). In addition, Han et al. (2017) detected circRNAs in the postnatal rat retina; analysis of these circRNA species revealed that some were related to processes mediating neuronal apoptosis in the developing nervous system. Because of the closed circular structure of circRNAs, they are relatively stable and degradation is difficult; therefore, they may continuously accumulate over time, which may explain their association with many age-related neurodegenerative diseases (Mehta et al., 2020).

With an increase in age, circRNAs accumulate in the eye, and age is one of the main risk factors associated with glaucoma; this suggests that accumulated circRNAs may be a cause of the pathophysiological changes and RGC death that occur in glaucoma. Moreover, there are still more circRNAs that are known, and further studies may reveal specific roles for these molecules in functions related to the development of glaucoma. A greater understanding of the mechanisms through which circRNAs contribute to the progression of glaucoma could help identify potential diagnostic markers or novel treatment targets.

6 | CLINICAL APPLICATIONS

There are currently three types of effective treatments for glaucoma; these include the use of drugs to lower the IOP pharmacologically, through laser treatment, or surgical intervention. Despite the availability of these effective therapies to reduce IOP, in some cases, the treatments may only delay the progression of glaucoma. In the early stages, those with glaucoma can appear to be asymptomatic, leading to an underestimation of the number of affected individuals. Population-level surveys suggest that only 10% to 50% of people with glaucoma are aware of it. Therefore, many patients are not diagnosed until the middle and late stages of the disease. As a result, early diagnosis and timely intervention are of great clinical significance. Noncoding RNAs are widely distributed in the eye with abundant expression. Several miRNAs, lncRNAs, and circRNAs have

obvious changes in expression in aqueous humor, tears and peripheral venous blood, as well as in HTFs after filtration surgery (Figure 3), which could have the potential to become highly effective and sensitive early diagnostic or prognostic biomarkers and improve the prognosis of glaucoma. One or a combination of several noncoding RNAs can be used in combination with existing clinical diagnostic methods, such as measurements of IOP, the anterior chamber angle, and visual field, to increase the early detection rate.

Reducing IOP is an effective means to delay glaucoma progression and vision loss in the early stages of the disease, and inhibiting the contraction of TM cells is an effective way to increase AH backflow. Earlier studies using a rat model confirmed that after transfecting miR-200c into HTMCs or the anterior chamber, cell contraction was significantly inhibited and the IOP of the injected eye had decreased (Luna et al., 2012). Another study reported that silencing miR-143/145 could regulate the dynamics and contractility of the actin cytoskeleton by inhibiting the expression of the actin-related protein complex (ARPC) and myosin light chain kinase (MLCK), thereby reducing the contractility of HTMCs and increasing the outflow of the AH (Li, Zhao, et al., 2017).

The mammalian retina lacks the ability to produce supplemental neurons after injury, although Müller cells have the potential to transdifferentiate into neurons. Therefore, finding a way to successfully induce Müller cells to transdifferentiate into RGCs is, fundamentally, the dominant obstacle to treating glaucoma (Mahato et al., 2020). Müller cells cultured in vitro display insufficient axonal growth as well as signal transduction defects. On the other hand, Müller glial cells that have been isolated and subsequently induced to dedifferentiate into retinal stem cells, followed by injection of the miR-124-transfected retinal stem cells into the eyes of glaucoma model rats, have been shown to be able to promote the growth of RGC axons (He et al., 2018). A previous study also identified miR-132, VEGF, and PTEN as key regulators of the process through which human periodontal ligament-derived stem cells are able to successfully transdifferentiate into functional RGCs (Cen et al., 2018). Recent studies have revealed the mechanism through which miRNAs in foods can be absorbed through the mammalian digestive system (Q. Chen et al., 2020); a better understanding of this process will aid in the development of oral delivery-based small RNA therapeutics. Studies have shown that the increased expression of lncRNA MALAT1 and lncRNA ANRIL detected in the serum of glaucoma patients correlated with the pathological classifications of the patients. Statistical analysis of the data showed that the diagnostic specificity and sensitivity of the combined detection of both RNA molecules were higher than those of either of the two molecules alone (Zheng et al., 2020).

Some studies have described the construction of the POAG-related ceRNA network, including lncRNA–miRNA–mRNA interactions. Analysis of this network has led to the identification of some pivotal lncRNAs involved in the pathophysiology of glaucoma, such as OIP5-AS1, DNAJC27-AS1, AF121898, and SNX29P2. Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis revealed that the ceRNA network was closely related to the MAPK and Wnt signaling pathways, as well as those mediating endocytotic processes (Zhou et al., 2020). As mentioned earlier, this network of miRNAs, lncRNAs, and circRNAs helps maintain the delicate but dynamic balance needed for the regulation of cellular homeostasis, which becomes disrupted during glaucoma progression. Some ncRNAs were found to be differentially expressed in glaucoma, and the levels of these ncRNAs could be useful as potential noninvasive biomarkers to aid in the

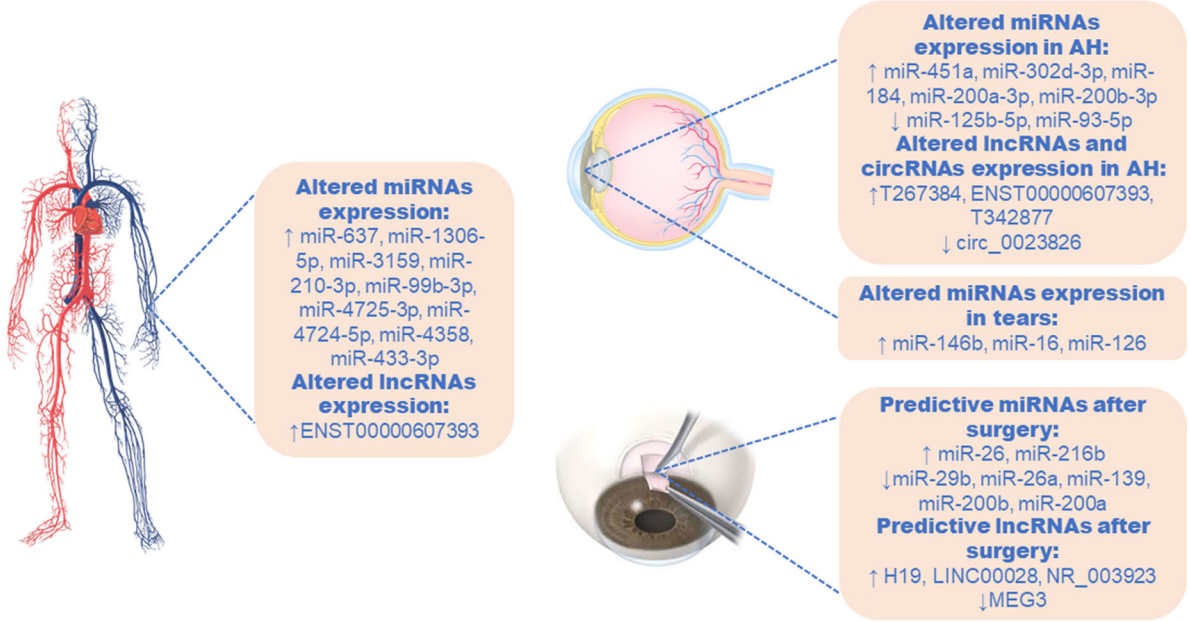

FIGURE 3 The expression of associated microRNAs, long noncoding RNAs, and circular RNAs in the different part of glaucoma patients, which could be a diagnostic marker of glaucoma and a prognostic indicator after surgery

diagnosis and monitoring of the progression of glaucoma. At present, some ncRNAs, mainly miRNAs, have been used experimentally in humans as clinical endpoints to quantify treatment effects (Slack & Chinnaiyan, 2019). However, the delivery of miRNA mimics remains challenging in humans, as there is a risk of RNA degradation and inactivation when transported through the systemic circulation. Methods to reduce or inhibit the carcinogenic activity of lncRNAs are also in the early stages of clinical investigation. In addition, ncRNAs appear to be particularly well-suited for local or transient therapeutic applications. The local delivery of ncRNAs directly into the eye could be a fine therapeutic option, and ncRNAs may become the most competitive class of therapeutics for intraocular delivery. Studies combining materials chemistry and ncRNA delivery have not been reported in the field of ophthalmology, especially in the treatment of glaucoma, but this is a research direction worth exploring in the future, as the use of supramolecular nanofibers combined with small extracellular vesicles to encapsulate miRNA molecules has been shown to improve the therapeutic efficacy of drugs used for kidney repair (Zhang et al., 2020).

Some ncRNAs could also be used as protein antagonists (also called aptamers), especially in the treatment of ocular diseases, and are a desirable target for clinical development. For instance, ncRNA aptamers have been synthesized against several proteins that are thought to be important therapeutic targets for treating ocular conditions; these targets include VEGF, platelet-derived growth factor (PDGF), and complement component 5 (C5), and some molecules targeting these proteins have completed Phase 3 clinical trials (Drolet et al., 2016). Identifying and validating an important protein target and developing a matching aptamer will be a new milestone in the treatment of glaucoma. We believe that further studies into such applications could help in developing these molecules as "first in class" diagnostic, therapeutic, and prognostic tools for the treatment of glaucoma and other eye conditions. To this end, we have compiled the reported functions of important miRNAs, lncRNAs, and circRNAs in different positions of the eye and the signal pathways involved (Table 2).

7 | PROSPECTS AND DILEMMAS

The continuous innovations leading to improvements in genomic research technology and the integrated use of both biochemical and bioinformatics tools have allowed for the identification and characterization of the diverse functions of a greater number of ncRNAs in biological development, human health, and disease states, and ncRNAs are constantly being found to play key roles in a wide range of cellular activities.

As mentioned above, several reports have discussed the proven influence of microRNAs, lncRNAs, and circRNAs on important pathological processes of glaucoma. At present, it is believed that ncRNAs can function in a variety of ways. They can directly regulate the process of gene transcription and translation (Panni et al., 2020), combine with RBP (Singh et al., 2018), affect the process of epigenetic modification (Coker et al., 2019), or combine with exosomes (Fan et al., 2018) to exert biologic functions. LncRNAs or circRNAs can also translate functional short peptides (Matsumoto et al., 2017). Consequently, when conducting subsequent research on the content of ncRNAs and glaucoma, more possible mechanisms should be considered, and rigorous experimental design and diverse experimental methods should be used. Discovering the specific mechanisms through which ncRNAs are involved in the pathophysiology of glaucoma could lead to more comprehensive perspectives towards the causes of this disease and identification of novel biomarkers for early disease monitoring and targets for timely intervention.

7.1 | Limitations

In this review, we mainly summarized the effects that ncRNAs are known to have on the functions of the TM, glial cells, the activity of RGCs, and the fibrosis of the filtration pathway that occurs after trabeculectomy, although ncRNAs may play other important regulatory roles in gene expression, such as in the regulation of certain genes known to be associated with glaucoma (Shen et al., 2020). However, ncRNA research is mainly limited to the analysis of expression patterns and changes in regulatory functions, and we also need to analyze the functional impact of structural changes that occur within the cell, such as those related to sequence variations. Research is also mainly restricted to the study of miRNAs at present (Conte et al., 2015; Hughes et al., 2011; Iliff et al., 2012; Liu et al., 2016). Moreover, while it is important to recognize the roles of lncRNAs and circRNAs in dysregulated networks, it also important to identify the ways that sequence variations may contribute to the pathological phenotypes of glaucoma (Deng et al., 2020; Qi et al., 2019). There is also a need to standardize experimental methods used to confirm and identify new ncRNA in both cellular and animal models. Although analysis of the ceRNA network is the most recently reported, classical model for identifying functional roles of lncRNAs and circRNAs, whether these ceRNA mechanisms are universal is still questionable. It has been reported that, based on the results of bioinformatic analysis and experimental verification, the circRNA–miRNA functional model may be problematic (Militello et al., 2017), as most of the circRNAs that are currently being studied have fewer binding sites for miRNAs, which greatly reduces the possibility of circRNAs interacting with and binding to them. Therefore, the "sponge" functional model of lncRNAs or circRNAs interacting with miRNAs or RBPs requires further validation. One ncRNA can, theoretically, target and bind to multiple molecules, and multiple ncRNAs can bind to the same target; therefore, when studying diseases, the role of one specific ncRNA should not be assessed in isolation, and targeting a single ncRNA alone may not achieve the desired therapeutic effect.

Another restriction is that recent studies have reported that some ncRNAs can also encode small, functional proteins (Anderson et al., 2015; Bazzini et al., 2014; Matsumoto et al., 2017), often referred to as small peptides, emphasizing the likelihood that

TABLE 2 Related ncRNAs in glaucoma

Type of ncRNAs	ncRNAs (name)	Location	Expression in glaucoma	Related molecules/pathways	Affected phenotypes	References
miRNAs	miR-518d/miR-143	Aqueous humor	Upregulation	Activity of ubiquitin-mediated proteolytic pathways such as the autophagy pathway	Reducing ECM remodeling, increasing outflow resistance	Jayaram et al. (2017)
	miR-24	HTM cells	Upregulation	TGF-β signaling pathway, FURIN	Promoting contraction and proliferation of HTM cells	C. Luna et al. (2011)
	miR-1298	HTM cells	Downregulation	TGF-β/Smad and Wnt/β-catenin pathways	Against oxidative damage and ECM deposition	W. Ruibin et al. (2018).
	miR-27a	HTM cells	Downregulation	PI3K/AKT and Wnt/β-catenin pathway	miR-27a exogenous supplement can alleviate H2O2-induced apoptosis of HTM cells	J. Zhao et al. (2019)
	miR-17-5p	HTM cells	Downregulated	PTEN, Akt signaling pathway	Increasing apoptosis of HTMC cells under oxidative stress	X. Wang et al. (2019)
	miR-4295	HTM cells	Downregulation	PI3K/AKT and ERK signaling pathways	Inhibiting miR-4295 can cause oxidative damage to HTMCs	Y. Liu et al. (2019)
	miR-181a	HTM cells	Downregulation	NF-kB, JNK pathways	Overexpression of miR-181a can inhibit HTMCs apoptosis	Y. Wang et al. (2018)
	miR-93	GTM cells	Upregulation	Nuclear factor erythrocyte-like 2	Regulating the apoptosis of GTMCs	Y. Wang et al. (2016)
	miR-29b	HTM cells	Downregulation	ECM synthesis and deposition-related downstream proteins	Inhibiting the generation and deposition of ECM	C. Luna et al. (2009)
	miR-483-3p/miR-3178	HTM cells	Downregulation	ECM deposition-related proteins	Reducing the ECM deposition	W. Shen et al. (2020)
	miR-144-3p	serum and TM cells	Downregulation	Fibronectin-1	Overexpression of miR-144-3p can promote proliferation and invasion of HTMC cells	Yin and Chen (2019)
	miR-149	RGCs of mouse	Upregulation	PI3K/Akt signaling pathway	Inducing apoptosis of RGCs	X. G. Nie et al. (2018)
	miR-93-5p	RGCs of SD rat	Downregulation	PTEN, AKT/mTOR pathway	Suppressing the autophagy of RGCs	R. Li et al. (2018)
	miR-141-3p	RGCs of mouse	downregulation	MAPK cascade signaling pathway, VEGF, DOK5	Overexpressing miR-141-3p can induce RGCs apoptosis; inhibit the proliferation and tube formation of retinal vascular epithelial cells	L. Q. Zhang et al. (2019)
	miR-211	aqueous humor; RGC-5	upregulation	MAPK pathway, P38, ERK	Affecting viability of RGC-5	J. Yang et al. (2018)
	miR-200a	RGCs of mouse	downregulation	MAPK signaling pathway	Increasing apoptosis of RGCs and inactivation of Muller cells	H. Peng et al. (2019)
	miR-182	RGCs of mouse	downregulation	BNIP3; mitochondrial apoptosis pathway	Affecting the oxidative stress and apoptosis of RGCs	X. Li et al. (2019)
	miR-223	RGCs of rabbit	upregulation	HSP-70	Inducing RGCs apoptosis and inflammatory response	Y. Ou-Yang et al. (2020)
	miR-21	RGCs of mouse	downregulation	caspase-8, PDCD4	Overexpressing miR-21 can inhibit RGCs apoptosis and microglia activation	W. Su et al. (2017)
	miR-29b	HTF cells	downregulation	fibrosis-related proteins such as PI3K, p85-α, Sp1, and Col1A1; Nrf2	Overexpression of miR-29b can inhibit collagen proliferation and fibrosis of HTFs	N. Li et al. (2012); J. Yu et al. (2015); W. Ran et al. (2015)

TABLE 2 (Continued)

Type of ncRNAs	ncRNAs (name)	Location	Expression in glaucoma	Related molecules/pathways	Affected phenotypes	References
	miR-200b	HTF cells	upregulation	p27/kip1 and RND3; cyclin, cyclinD1 and PCNA; PTEN, α-sma, COL1A1,	Affecting cell proliferation	J. Tong et al. (2014); J. Tong et al. (2019)
	miR-200a	HTF cells	upregulation	β-catenin	Affecting viability, proliferation and extracellular matrix (ECM) deposition of HTFs	H. Zhu et al. (2020)
	miR-26	HTF cells	downregulation	connective tissue growth factor	Affecting HTFs proliferation	H. Bao et al. (2018)
	miR-26a	HTF cells	downregulation	connective tissue growth factor	Overexpression of miR-26a can reduce HTFs viability and migration capacity	W. H. Wang et al. (2018)
	miR-139	HTF cells	downregulation	Smad2/3/4 complex; Wnt/β-catenin signaling pathway	Overexpression of miR-139 can alleviate cells apoptosis and fibrosis	M. Deng et al. (2019)
	miR-216b	HTF cells	downregulation	HCPT, Beclin 1	Overexpression of miR-216b can suppress the autophagy and apoptosis of HTFs	X. Xu et al. (2014)
	miR-143/miR-145	HTF cells	upregulation	ARPC, MLCK	Affecting the contraction of HTMCs and the outflow of aqueous humor	X. Li et al. (2017)
	miR-27a	HTF cells	downregulation	PI3K/AKT and Wnt/-catenin pathways	Affecting HTM cells apoptosis	J. Zhao et al. (2019)
	miR-4295	HTF cells	downregulation	PI3K/AKT and ERK signaling pathways	Overexpressing miR-4295 can reduce HTMs oxidative damage and apoptosis	Y. Liu et al. (2019)
lncRNA	RP11-820	HTF cells	upregulation	miR-3178, fibronectin, laminin and type I collagen	Downregulation of lncRNA-RP11-820 can reduce ECM proliferation under oxidative stress	W. Shen et al. (2020)
	ANRIL	HTF cells	downregulation	miRNA-7, mTOR and MEK/ERK pathways	Overexpressing ANRIL can reduce oxidative damage of HTMCs	J. Zhao et al. (2019)
	ENST00000607393	aqueous humor and plasma	upregulation	bone morphogenetic protein 2	Knockdown of ENST00000607393 reduces the calcification of HTMCs under oxidative stress and protect the outflow tract of aqueous humor	L. Xie et al. (2019)
	MALAT1	RGCs of rat	downregulation	PI3K/Akt signaling pathway	Overexpressing MALAT1 can reduce RGCs apoptosis	H. B. Li et al. (2017)
	TUG1	HTM cells	downregulation	Nrf2; ROS	Overexpression of TUG1 could reduce ROS production	W. Gong et al. (2019)
	H19	HTF cells	upregulation	β-catenin; miR-200a	Affecting the proliferation and fibrosis of HTFs	H. Zhu et al. (2020)
	LINC00028	HTF cells	upregulation	miR-204-5p	Affecting HTFs proliferation, migration, invasion and EMT, fibrosis, and autophagy	H. Sui et al. (2020)
	NR_003923	HTF cells	upregulation	miR-760; miR-215-3p; IL22RA1; α-SMA and fibronectin (FN); E-cadherin and β-catenin	Affecting the expression of miR-760 and miR-215-3p, HTFs proliferation, migration, autophagy, and fibrosis	Y. Zhao et al. (2019)

(Continues)

TABLE 2 (Continued)

Type of ncRNAs	ncRNAs (name)	Location	Expression in glaucoma	Related molecules/pathways	Affected phenotypes	References
circRNA	cZNF609	retina and aqueous humor of SD rat; Müller cell and RGCs of SD rat	upregulation	cytokines, nitric oxide or reactive oxygen species; miR-615, METRN	Silencing cZNF609 can reduce retinal reactive glial hyperplasia and glial cell activation, and protect RGCs	K. R. G. Martin et al. (2002); Tezel & Wax (2000); J. Y. Wang et al. (2018)
	cZRANB1	retina and the cytoplasm of glial cells	upregulation	miR-217, RUNX2	cZRANB1 knockdown reduces retinal reactive gliosis and contributes to RGC survival	J. J. Wang et al. (2018)
	circ_0023826	aqueous humor	downregulation	TENM4	circ_0023826 was identified as a diagnostic marker for glaucoma	X. Chen et al. (2020)
	circHBEGF	HTM cells	upregulation	miR-646; EGFR; EGF signaling pathways; ECM	Regulating ECM production in HTMCs induced by oxidative stress	W. Shen, Wang, et al. (2020)

Abbreviations: AH, aqueous humor; circRNAs, circular RNAs; lncRNA, long noncoding RNA; miRNAs, microRNAs; SD, Sprague-Dawley.

additional transcripts currently thought of as ncRNAs may, in fact, encode proteins with significant biological activities that are not being taken into account. This area is currently unexplored in glaucoma research and is worthy of greater attention and discussion. We believe that understanding the current limitations of ncRNA studies will advance the field and lead to novel insights into the pathophysiology of glaucoma.

Clinically, ncRNAs could be used as biomarkers, either alone or in combination with other currently available diagnostic markers and imaging technologies to improve their clinical applications. In addition, the basic factors that affect the expression of ncRNAs, such as sex, age, environment, and comorbid conditions, need to be understood in greater detail. It is hoped that the study of the regulation of ncRNAs will provide novel insights into the basic principles of gene expression that affect the development and progression of glaucoma. Currently, the major clinical applications of ncRNAs are in the degradation of nucleases and the release of drug molecules from the endosome during endocytosis. Considerable improvements have been made in terms of drug delivery methods, including chemical modifications and the use of novel material carriers to improve efficiency and optimize the pharmacokinetics of drug action. The greatest challenge for developing an optimal drug delivery system is overcoming the potential for immune stimulation and the lack of specificity in the ability to deliver a drug to the target area. To date, the application of ncRNAs in the treatment of disease states is still limited to in vitro cellular experiments and in vivo animal models; the challenges described here will still need to be overcome before a ncRNA therapy could be successfully applied to the patient.

8 | CONCLUSION

Compared with the field of oncology, ophthalmology-related research of miRNAs, lncRNAs, and circRNAsis still immature and should arouse wider attention. With the continuous development of materials technology and the in-depth study of the role of ncRNAs in the development and progression of glaucoma, ncRNAs will eventually become valuable diagnostic tools and therapeutic targets that could bring new hope for the treatment of glaucoma patients in the near future.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

This review based on our team's previous works. Rong Rong and Mengxiao Wang completed the first draft, and Mengling You, Haibo Li assisted in preparing the figures and tables. Xiaobo Xia and Dan Ji

developed the idea, and supervised the writing process. All authors participated in revision of the manuscript, and approved its final version.

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