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# Expression of miR-802 in glaucoma and its diagnostic significance

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## Abstract

**Introduction and Objective**. Glaucoma ranks as the second leading cause of blindness globally. The key factors leading to glaucoma are increased intraocular pressure and retinal ganglion cell apoptosis. Glaucoma is an irreversible disease that causes blindness in the eye, characterized by progressive optic nerve damage and visual field defects. The expression of miR-802 is abnormal in the plasma of glaucoma patients, but its function and mechanism remain unclear. The aim of the study is to investigate the expression of miR-802 in glaucoma and retinal ganglion cells, and the effect of miR-802 on 661W cells under oxidative stress.

**Materials and Method.** The study used RT-qPCR to detect the expression level of miR-802 in 661W cells and glaucoma patients. Receiver operating characteristic curve (ROC) was used to assess the diagnostic value of miR-802 in glaucoma. Cell viability was assessed using the Cell Counting Kit-8 (CCK-8) assay, while cell apoptosis was detected via flow cytometry.

**Results.** In glaucoma patients, miR-802 expression was significantly downregulated and correlated with elevated IOP, reduced RNFL, and increased eGFR. MiR-802 demonstrated exceptional diagnostic value for the onset of glaucoma. In addition, decreased miR-802 expression was a risk factor associated with glaucoma. MiR-802 accelerated the proliferation of 661W cells and slowed down the apoptosis rate. Moreover, miR-802 mimic inhibited H2O2-induced 661W cell apoptosis.

**Conclusions.** Upregulation of miR-802 alleviated oxidative stress-induced damage in 661W cells. miR-802 might be used as a marker for detecting glaucoma.

## Key words

oxidative stress, glaucoma, MiR-802, 661W cells, apoptosis rate

## INTRODUCTION

Glaucoma is an irreversible disease that causes blindness in the eye, characterized by progressive optic nerve damage and visual field defects. It is the second leading cause of blindness [1], with increased eye pressure and retinal ganglion cell apoptosis being the key causes of glaucoma [2]. It must be noted that heavy metals released from agricultural and industrial activities are discharged into the air, water bodies, and soil, and through the food chain, humans ultimately come into contact with heavy metals such as cadmium and lead. These heavy metals can eventually enter the human body via the olfactory system or direct eye contact, leading to increased intraocular pressure and retinal cell abnormalities, ultimately triggering glaucoma [3]. Intense light stimulation is also one of the significant risk factors for the onset of glaucoma [4]. Although glaucoma can be controlled through medication and surgery, the postoperative recovery effect of patients is not ideal, or they continue to lose vision due to the apoptosis of retinal ganglion cells. Therefore, early diagnosis and intervention are crucial for delaying the progression of glaucoma.

MicroRNAs (miRNAs) are a group of short endogenous non-coding RNAs (~22nt). They can bind to the 3'-UTR of target mRNAs and thereby inhibit the expression of target genes [5]. As key gene expression regulators, miRNAs modulate over one-third of human genes and act as core mediators of cellular signal transduction. For therapeutic and diagnostic purposes, they can be modified via post-transcriptional chemical alterations or biomolecular conjugation to improve cellular targeting, and translocate to the nucleus to fine-tune transcriptional efficiency and amplify signal transduction [6–8]. Among them, miR-802, as an important miRNA, is associated with the pathogenesis of various diseases. Earlier studies have shown that miR-802 inhibits the occurrence of pancreatic cancer by suppressing the carcinogenic KRAS-induced ADM [9]. miR-802 is highly expressed in obesity, and it can damage insulin transcription and secretion, and can be used as an auxiliary marker for diagnosing type 2 diabetes (T2DM), and may be a therapeutic target for T2DM [10, 11]. Crozp et al. used the expression microarray method to detect the expression levels of 20 new miRNA molecules in the aqueous humour of patients with pseudo-exfoliation glaucoma (PEXG), and found that miR-802 was down-regulated in the aqueous humour of PEXG patients [12]. From this, it can be inferred that miR-802 may be involved in regulating the onset and development of glaucoma. However, its regulatory mechanism and clinical value in glaucoma remain unclear.

The 661W cell line is the immortalized cell line derived from a mouse retinal tumour [13]. Previous studies have demonstrated that 661W cell line not only represents a cone photoreceptor cell line, but also functions as RGC precursor-like cells [14]. This cell line simultaneously expresses cone-specific markers, such as RBPMS, Brn3b and OPN1MW, and possesses the capacity for neuronal differentiation [14, 15]. Currently, 661W cells are extensively utilized in research

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on retinal diseases, including glaucoma [16] and retinitis pigmentosa [17], establishing themselves as an indispensable *in vitro* model in retinal research.

This study aims to detect miR-802 levels in glaucoma patients and establish an oxidative stress model using $H_2O_2$-induced 661W cells to further investigate the molecular mechanisms by which miR-802 regulates glaucoma.

## MATERIALS AND METHOD

*Study subjects.* The study was approved by the Ethics Committee of The First People's Hospital of Xiaoshan District. Sample size calculations for the independent samples t-test were performed using G*Power 3.1 software with the following parameters: two-tailed test, effect size (Cohen's d) = 0.8, significance level (α) = 0.05, statistical power (1-β) = 0.90. Calculations indicated that each group (glaucoma patients and healthy controls) required at least 34 participants, resulting in a total sample size of 68 subjects. Ultimately, a total of 105 glaucoma patients were included, together with 105 healthy people as controls. The age composition of the two groups was matched, and all participants signed informed consent. Inclusion and exclusion criteria were as follows:

*Inclusion criteria.* Age ≥18 years old. Glaucoma group: Subjects with an intraocular pressure (IOP) higher than 21 mmHg; anterior chamber angle examination confirming an open angle; and a prior clinical diagnosis consistent with the established clinical diagnostic criteria for glaucoma. Healthy control group: Subjects confirmed as healthy through epidemiological investigation, without significant visual impairment, with normal intraocular pressure, and free from any ocular diseases.

*Exclusion criteria.* Secondary glaucoma; Glaucoma patients with serious eye diseases other than glaucoma; Active period of acute or chronic infection, haematopoietic system diseases, severe liver and gallbladder diseases, other neurodegenerative diseases, systemic autoimmune diseases, and malignant tumours; taking drugs that affect blood cell composition or serum biochemical profile.

*Sample collection.* The fundamental pathological characteristics of the subjects were obtained by reviewing the case records. Peripheral venous blood samples were collected on an empty stomach on the second day of hospitalization or physical examination. Blood samples were collected by centrifugation at 2,500 rpm for five minutes and serum samples subsequently harvested using a serum separation tube (BD Biosciences). Serum samples were stored at -80 °C for further experiments. The number of freeze-thaw cycles must not exceed two.

**Cell treatment and transfection.** 661W cells were obtained from ATCC and cultured in DMEM medium containing 10% FBS, 0.1% streptomycin and penicillin after resuscitation. Cell culture was performed at 37 , 5 % $CO_2$ and 95 % humidity. Cells were cultured until the logarithmic growth phase before transfection.

Cloning was performed using pCDH-CMV-MCS-EF1-coGFP (System Biosciences, USA) to construct miR-802 mimic and miR NC. miR-802 mimic or miR NC was transfected into 661W cells using lipo2000, and the expression of miR-802 detected using qRT-PCR. The transfected cells were divided into two groups. In one group, miR-802 expression, cell proliferation and apoptosis rate were measured, and the expression and cell apoptosis rate were measured in the other group after $H_2O_2$ treatment. The cells were treated with $H_2O_2$ as follows: 661W cells were inoculated into 96-well plates at the concentration of $1\times10^5/cm^2$. Different concentrations of $H_2O_2$ (100 μM, 200 μM, 400 μM) were added and cultured for 24 h to prepare the oxidative stress injury model. The results showed that 100 μM, 200 μM and 400 μM $H_2O_2$ could induce apoptosis of 661W cells. Then 661W cells were treated with the highest concentration of 400 μM $H_2O_2$ for 24 h, and the above experiment was repeated [18].

**Extraction of total serum RNA.** The collected serum samples were mixed with Trizol reagent (Thermo, USA) and left on ice for five minutes. Chloroform was added into the mixture and centrifuged at 12,000g for 15 minutes. The supernatant was mixed with isopropyl alcohol and allowed to stand for 20 minutes and centrifuged again at 12,000 g at 4 °C for 10 minutes. The precipitation was washed with 75% ethanol, and the total RNA was dissolved by adding RNA-free water. The ratio of OD260 / OD280 was 1.8–2.0, indicating high purity of isolated RNA and no DNA contamination, which could be used for subsequent experiments.

**Quantitative real time reverse transcription PCR (qRT-PCR).** The total RNAs was acquired by RNAiso Plus (Takara, Dalian, China). cDNA was obtained by ToYoBo (Shanghai, China). qPCR was performed by SYBR Green qPCR Mix (ToYoBo, Shanghai, China). Reaction conditions were preheated at 95 °C for two minutes, followed by 42 cycles of 95 °C for 15 seconds, 60 °C for 15 seconds and 72 °C for 30 seconds. U6 was used as an internal reference gene. Gene expression levels were quantified using the $2^{-\Delta\Delta CT}$ method. Primer sequence of miR-802 (Forward: CGTTGTGTAGCTTATCAGACTG, Reverse: AATGGTTGTTCTCCACACTCTC).

**Cell Counting Kit-8 (CCK-8).** CCK-8 method was used to detect the cell proliferation rate of each group. Cells in the logarithmic growth phase were seeded at a concentration of $5 \times 10^3$ cells / well into 96-well plates and incubated at 37 °C for 24 h. Then 10 μL CCK-8 reagent (Transgen, China) was added to each well, and the cells incubated at 37 °C in the dark for two hours to determine OD450.

**Cellular apoptosis analysis.** Annexin V-FITC/PI apoptosis detection kit (Solarbio, Beijing, China) was used to analyze the apoptosis rate. Incubated for 24 hours and then Annexin V-FITC and propyl iodide (PI) added. Incubated for 15 minutes away from light. Apoptosis rate analyzed by flow cytometry (BD Biosciences, SAN Jose, CA, USA).

**Statistical analysis.** SPSS 27.0 and GraphPad Prism 9.0 software were used for data analysis. All experiments were repeated three times, and three independent measurements were performed, respectively. All data were expressed as mean ± SD, which met the experimental standards. Categorical variables were analyzed using chi-square tests, while normally distributed variables were assessed using t-tests and one-way analysis of variance (ANOVA). Tukey's *post hoc* test was

performed. ROC curve was used to analyze the diagnostic ability of miR-802 level in glaucoma. The risk factors of glaucoma were analyzed by logistic regression analysis. The correlation between miR-802 level and clinicopathological characteristics of patients was analyzed by chi-square test. $P < 0.05$ was considered statistically significant.

## RESULTS

**Basic information about healthy people and patients with glaucoma.** Table 1 presents baseline data for the 105 healthy controls and 105 glaucoma patients. No significant differences were found in age ($P$=0.593) or gender ($P$=0.331). The glaucoma group exhibited higher IOP ($P$<0.001), lower RNFL ($P$<0.001), higher eGFR ($P$=0.012), NLR ($P$=0.099), LDL-C ($P$=0.016), and lower HDL-C ($P$=0.094), compared to controls. CCT showed no difference ($P$=0.067).

**Table 1.** General information about study subjects

| | Healthy (n=105) | Glaucoma (n=105) | *P* value |
|---|---|---|---|
| Age (years) | 62.30±7.52 | 62.83±6.81 | 0.593 |
| Gender (male/female) | 57/48 | 64/41 | 0.331 |
| IOP (mmHg) | 17.13±2.22 | 24.41±2.82 | <0.001 |
| CCT (μm) | 525.09±13.81 | 529.24±18.47 | 0.067 |
| RNFL (μm) | 109.86±7.40 | 84.57±6.74 | <0.001 |
| eGFR (mL/min) | 92.70±11.35 | 97.11±13.66 | 0.012 |
| NLR | 1.97±0.73 | 2.13±0.69 | 0.099 |
| LDL-C (mmol/L) | 2.86±0.71 | 3.11±0.79 | 0.016 |
| HDL-C (mmol/L) | 1.41±0.26 | 1.35±0.28 | 0.094 |

IOP – intraocular pressure; CCT – central corneal thickness; RNFL – retinal nerve fibre layer; eGFR – estimated glomerular filtration rate; NLR – neutrophil-to-lymphocyte ratio; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol

**Diagnostic value of miR-802 in glaucoma.** The results showed that miR-802 was significantly reduced in patients with glaucoma compared to healthy people (Fig. 1A). ROC curve analysis showed that miR-802 had significant diagnostic value between glaucoma patients and healthy controls (AUC = 0.888; sensitivity=88.6%; specificity=75.2; cutoff value= 0.905) (Fig. 1B).

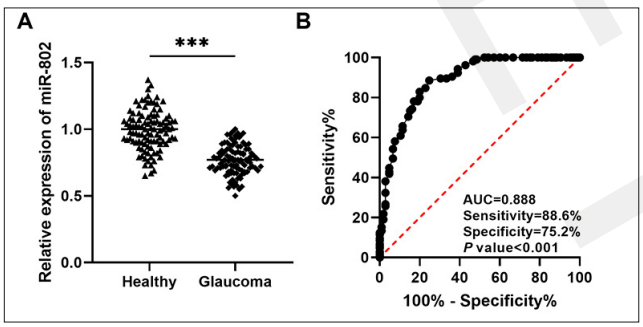


**Figure 1.** Expression of miR-802 and ROC analysis in healthy people and glaucoma patients. (A) Expression of miR-802 significantly reduced in glaucoma compared with healthy subjects. (B) Assessment of the diagnostic and prognostic value of miR-802 in glaucoma (AUC = 0.888, Sensitivity=88.6%, Specificity=75.2%).
***$P < 0.001$

**Level analysis of related risk factors.** Patients were divided into low-expression (n=57) and high-expression (n=48) groups, based on the mean value of miR-802 in the serum of glaucoma patients as the cutoff value. According to the results, IOP is a significant risk factor for glaucoma, and miR-802 and RNFL may be protective factors ($P < 0.05$). Other factors, such as age, gender, CCT, eGFR, NLR, LDL-C and HDL-C were not significantly associated with the development of glaucoma ($P > 0.05$) (Table 2).

**Table 2.** Analysis of risk factors associated with glaucoma

| | OR | 95% CI | P value |
|---|---|---|---|
| miR-802 | 0.009 | 0.003–0.031 | <0.001 |
| Age(years) | 1.545 | 0.505–4.728 | 0.446 |
| Gender | 1.718 | 0.580–5.084 | 0.329 |
| IOP (mmHg) | 3.381 | 1.067–10.717 | 0.039 |
| CCT (μm) | 2.788 | 0.962–8.077 | 0.059 |
| RNFL (μm) | 0.344 | 0.120–0.987 | 0.047 |
| eGFR (mL/min) | 0.377 | 0.127–1.125 | 0.080 |
| NLR | 2.278 | 0.813–6.387 | 0.117 |
| LDL-C (mmol/L) | 2.910 | 0.965–8.777 | 0.058 |
| HDL-C (mmol/L) | 0.404 | 0.138–1.183 | 0.098 |

OR – odds ratio; IOP – intraocular pressure; CCT – central corneal thickness; RNFL – retinal nerve fibre layer; eGFR – estimated glomerular filtration rate; NLR – neutrophil-to-lymphocyte ratio; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol

**Relationship between miR-802 and clinicopathological features in patients with glaucoma**. The average expression of miR-802 in the eyes of glaucoma patients was used as a threshold, and they were divided into high and low expression groups. The correlation between the expression levels and the clinicopathological characteristics of the patients was assessed. Down-regulation of miR-802 significantly accelerated the increase of IOP and eGFR ($P < 0.05$), but significantly inhibited RNFL ($P < 0.05$) (Tab. 3).

**Effects of overexpression of miR-802 on apoptosis and proliferation of 661W cells.**The results showed that miR-802 expression in the miR-802 mimic group was significantly higher than that of blank and negative controls after transfection (Fig. 2A). Overexpression of miR-802 slowed down the apoptosis of 661W cells (Fig. 2B) and accelerated the proliferation of 661W cells (Fig. 2C).

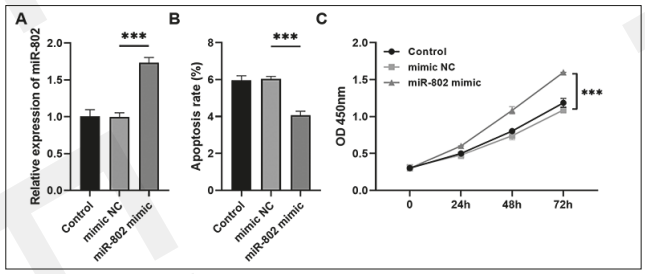


**Figure 2.** miR-802 expression after miR-802 mimic transfection and its effect on cells. (A) Comparison of miR-802 expression after transfection of miR-802 mimic, blank control and negative control. (B) Comparison of the apoptosis rate of miR-802. (C) Comparison of the effect of miR-802 on cell proliferation.
***$P < 0.001$

**Effects of overexpression of miR-802 before and after on 661W cells induced by oxidative stress.** The data indicated that the expression of miR-802 in 661W cells significantly decreased with the increase of $H_2O_2$ treatment concentration (Fig. 3A), and the apoptosis rate of 661W cells significantly

**Table 3.** Association between clinicopathological features and miR-802 expression levels in glaucoma patients

| Variable | Total | miR-802 | | *P* value |
|---|---|---|---|---|
| | (n=105) | Low(n=57) | High(n=48) | |
| Age (years) | | | | |
| <63 | 49 | 24 | 25 | 0.307 |
| ≥63 | 56 | 33 | 23 | |
| Gender | | | | |
| Male | 64 | 37 | 27 | 0.365 |
| Female | 41 | 20 | 21 | |
| IOP (mmHg) | | | | |
| <24.41 | 45 | 18 | 27 | 0.011 |
| ≥24.41 | 60 | 39 | 21 | |
| CCT (μm) | | | | |
| <529.24 | 52 | 24 | 28 | 0.098 |
| ≥529.24 | 53 | 33 | 20 | |
| RNFL (μm) | | | | |
| <84.57 | 55 | 35 | 20 | 0.044 |
| ≥84.57 | 50 | 22 | 28 | |
| eGFR (mL/min) | | | | |
| <97.11 | 52 | 23 | 29 | 0.040 |
| ≥97.11 | 53 | 34 | 19 | |
| NLR | | | | |
| <2.13 | 47 | 23 | 25 | 0.166 |
| ≥2.13 | 58 | 35 | 23 | |
| LDL-C (mmol/L) | | | | |
| <3.11 | 51 | 24 | 27 | 0.149 |
| ≥3.11 | 54 | 33 | 21 | |
| HDL-C (mmol/L) | | | | |
| <1.35 | 60 | 37 | 23 | 0.080 |
| ≥1.35 | 45 | 20 | 25 | |

IOP – intraocular pressure; CCT – central corneal thickness; RNFL – retinal nerve fibre layer; eGFR – estimated glomerular filtration rate; NLR – neutrophil-to-lymphocyte ratio; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol.

increased with the increase of $H_2O_2$ treatment concentration (Fig. 3B). Transfection with miR-802 mimic significantly upregulated miR-802 expression in $H_2O_2$-treated cells compared with the mimic NC groups, confirming successful overexpression (Fig. 3C). Overexpression of miR-802 markedly reduced the apoptosis rate induced by $H_2O_2$ (Fig. 3D).

## DISCUSSION

Glaucoma severely affects patients' ability to work and quality of life [19], and its treatment options have been the focus and challenge of global ophthalmic research [20]. In addition, since the early symptoms of glaucoma are not easy to detect, once detected, the damage caused is irreversible [21]. There is an urgent need for a marker as a means of early diagnosis.

Previous studies have demonstrated that miRNAs can achieve diagnostic and therapeutic purposes by modulating glaucomato-related risk factors. The relative expression level of miR-146a-5p in plasma was significantly elevated in the pseudophakic exophthalmic glaucoma (PEG) group, suggesting its potential as a minimally invasive diagnostic biomarker for PEX/PEG [22]. In a rat model of age-related macular degeneration (AMD), miR-21–5p promoted retinal pigment epithelial (RPE) cell necroptosis through targeted regulation of the Peli1 gene [23]. The miR-29 family exerts an anti-fibrotic role in TGF-β-driven fibrosis during glaucomatous optic neuropathy by negatively regulating extracellular matrix (ECM) synthesis and interacting with TGF-β signalling pathways, while its downregulation exacerbates pathogenic ECM deposition [24].

In this study, it was found that the miR-802 level was significantly reduced in patients with glaucoma, indicating that miR-802 may play a protective role in maintaining retinal health. Meanwhile, the high miR-802 expression in serum and ROC curve showed excellent diagnostic value, proving that miR-802 may have diagnostic value in glaucoma. It is noteworthy that existing studies have proved the importance of IOP detection in the treatment of glaucoma [25].

The experimental findings in the current study reveal significantly elevated IOP in glaucoma patients, who exhibited low levels of miR-802 and demonstrated higher IOP. Therefore, it was speculated that miR-802 may influence the progression of glaucoma by affecting IOP. The combined protective effect of RNFL and miR-802 attracted the attention

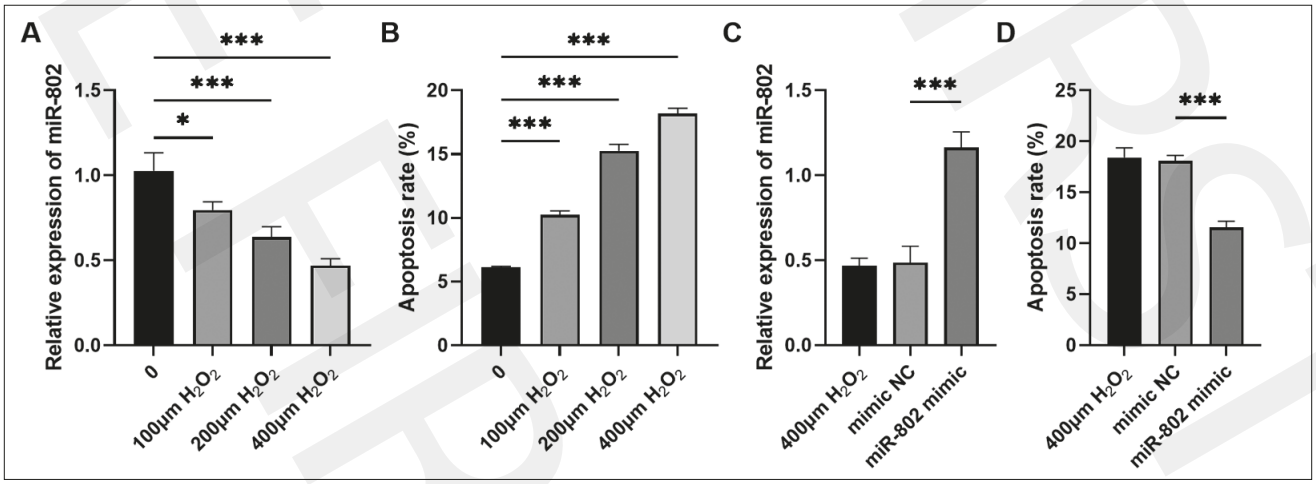


**Figure 3.** Effects of different concentrations of $H_2O_2$ treatment on miR-802 expression in 661W cells. (A) Effect of different concentrations of $H_2O_2$ on miR-802 expression. (B) Effect of different concentrations of $H_2O_2$ on apoptosis rate of 661W cells. (C) Changes in miR-802 levels following transfection. (D) miR-802 mimic inhibits apoptosis. *$P$ < 0.05; ***$P$ < 0.001

of the authors. Down-regulation of miR-802 is closely related to RNFL thinning, suggesting that miR-802 may delay disease progression by protecting 661W cells, which is consistent with previous studies. Loss of RGCs can be manifested by thinning of the RNFL [26, 27]. Experiments by Kim et al. demonstrated that the combined metric of pattern-evoked retinal potential ratio (PERG ratio) and RNFL significantly improves diagnostic accuracy, compared to using PERG ratio alone [28]. These data fully demonstrate the potential protective effect and diagnostic value of miR-802 in glaucoma patients.

Subsequent cell experiments by the authors showed that overexpression of miR-802 could slow down the apoptosis of 661W cells and promote the proliferation of 661W cells, hoping to provide an important target information for future therapy. Previous studies have shown that chronic oxidative stress (COS) is associated with the pathophysiology of trabecular reticulum (TM) in glaucoma [29, 30]. $H_2O_2$ treatment significantly downregulates miR-17-5p expression in human trabecular meshwork cells (TMCs). Overexpression of miR-17-5p alleviates oxidative stress damage by promoting cell proliferation and inhibiting apoptosis through targeting PTEN [31]. The authors' experiment also proved that miR-802 expression decreased greatly with the increase of $H_2O_2$ treatment concentration. Therefore, it is speculated that miR-802 may inhibit the occurrence of glaucoma by participating in the protection of TM activity during $H_2O_2$ stress process. Current research indicates that miR-802 may influence mitochondrial function during apoptosis by regulating the expression of MCL1, PPP2CB, and SOD2 genes, thereby altering intraocular pressure changes and optic nerve degeneration progression in glaucoma patients [12]. This aligns with the authors' experimental findings, suggesting that miR-802 may reduce intraocular pressure and inhibit retinal cell apoptosis by regulating the aforementioned related genes.

**Limitations of the study.** The study has certain limitations. The limited clinical sample size may not cover all scenarios. *In vitro* experimental models struggle to replicate the complex in vivo microenvironment, potentially weakening the persuasiveness of the findings. As 661W cells are retinal ganglion precursor-like rather than mature RGCs, they may not fully replicate the phenotype and pathophysiology of primary mature retinal ganglion cells *in vivo*. Future research will expand the clinical sample size for multicentre validation, integrate in vivo animal models to explore molecular regulatory mechanisms in depth, and employ multiomics technologies to uncover potential synergistic regulatory pathways. These efforts aim to further investigate the regulatory role of miR-802 in glaucoma.

## CONCLUSION

This study is the first to describe the effects of miR-802 on 661W cells under oxidative stress injury conditions through cellular experiments. According to the results, the authors believe that regulating the level of miR-802 may slow down the effect of oxidation on 661W cells. miR-802 may become a diagnostic marker for glaucoma in the future. The current investigation is only in its preliminary stages and more in-depth research will be undertaken in the future.

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