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Abnormal Expression of lncRNA SNHG7 in Dry Eye Disease and Its Effect on Human Conjunctival Epithelial Cells

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Analyzing the pathogenic mechanism of dry eye disease provides a new research point for the treatment of patients. A total of 86 patients with dry eye disease and the same number of healthy individuals were recruited as the patient group and normal group. The levels of small nucleolar RNA host gene 7 (SNHG7) in tear samples and human conjunctival epithelial cells (HCECs) were determined by a quantitative real-time PCR (RT-qPCR). Meanwhile, TNF-α and IL-6 mRNA levels in HCECs were also detected by RT-qPCR. The molecular mechanism of SNHG7 was analyzed by biological prediction and luciferase activity assay. The correlation between the expression of SNHG7 and microRNA-146a-5p (miR-146a-5p) with clinical indicators in dry eye disease patients using Pearson analysis. SNHG7 expression in tears samples and HCECs from dry eye disease patients was significantly increased ($P < 0.001$). The levels of TNF-α mRNA and IL-6 mRNA were upregulated in the HCECs model group while silencing SNHG7 suppressed their expression ($P < 0.05$). SNHG7 level was negatively correlated with miR-146a-5p, break-up time (BUT) and Schirmer's test (SIT) value, while positively correlated with corneal fluorescein staining (CFS) score ($P < 0.001$). miR-146a-5p was positively proportional to BUT and SIT, and inversely proportional to CFS score ($P < 0.001$). SNHG7 expression was enhanced, while miR-146a-5p expression was decreased in dry eye disease. Down-regulation of SNHG7 reduced the level of inflammation in HCECs. SNHG7 and miR-146a-5p were closely related to the development of disease, probably as biological targets for treatment in dry eye disease.

Keywords: dry eye disease; human conjunctival epithelial cell; IL-6; miR-146a-5p; SNHG7
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Introduction

Dry eye disease, also known as kerato-conjunctival xerosis, is typically characterized by eye fatigue, foreign body sensation, and dryness (Weng et al. 2023). The global incidence of dry eye disease is about 50%, with a higher prevalence among women than men, and the increase in age increases the prevalence (Chang and Wu 2022). Currently, the pathogenesis of dry eye disease is not clear, and it is generally believed to be caused by a variety of factors, including inflammation, autoimmune diseases, and corneal nerve abnormalities (Xie et al. 2024). Dry eye disease not only brings discomfort to patients, but also may lead to perforation, infection, and even blindness in severe cases, which causes considerable burden to patients and society (Kong et al. 2024). In the treatment of dry eye disease, the measures of artificial tears, tear spot closure, and contact lenses are often used, but the effect is not ideal. Therefore, it is urgent to develop more targeted and cost-effective treatment options.

Long non-coding RNAs (lncRNAs) have been identified as hot-spot factors involved in a variety of diseases. In recent years, it has been found that it is abnormally expressed in different eye diseases and is related to the development of the disease (Hu et al. 2023; Lu and Lu 2023). For example, lncRNA-XR_002792574.1 as a biomarker provides a new reference for the treatment of myopic retinal ganglion cell damage in the latest study (Wang et al. 2023). LncRNA small nucleolar RNA host gene 7 (SNHG7) is a 2,157 bp long RNA without coding ability located on chromosome 9q34.3 (Wang et al. 2021). SNHG7 was revealed to have an oncogenic role in previous studies, such as its notably expressed in breast cancer, liver cancer, and glioma (Chen et al. 2020; Li et al. 2020; Deng et al.

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2021). Meanwhile, there is also evidence for the regulation of SNHG7 in diabetic retinopathy (Cao et al. 2022). However, the effect of SNHG7 has not been proven in the discussion of dry eye disease.

Although the causes of dry eye disease are various, the core mechanism of its pathogenesis is the instability of tear film and the increase of osmotic pressure (Yuan et al. 2023). Therefore, the imbalance of inflammatory regulation is closely related to the development of the disease. Tumor necrosis factor-alpha (TNF-α) is a kind of inflammatory cytokines, related to cell apoptosis and immune response (Pinci et al. 2020). Studies have pointed out that the level of TNF-α in dry eye disease appears to increase (Lee et al. 2021). In addition, interleukin-6 (IL-6), as a multifunctional cytokine, has been found to have a wide range of immunomodulatory effects (Du et al. 2022). Dammak et al. (2023) determined that IL-6 and TNF-α are upregulated in the conjunctiva and tear of dry eye disease patients. Therefore, TNF-α and IL-6 have potential as indicators of dry eye disease.

In this study, the effect of dysregulated SNHG7 on the expression of inflammatory factors was analyzed by measuring SNHG7 levels in tears samples and human conjunctival epithelial cells (HCECs) from dry eye disease patients. Furthermore, the downstream targets and molecular mechanisms of SNHG7 were verified, and the clinical significance of SNHG7 in dry eye disease was analyzed to provide a new direction for the treatment of patients with dry eye disease.

Materials and Methods

Recruited research subjects

A total of 86 dry eye disease patients admitted to Beijing Jishuitan Hospital, Capital Medical University from March 2023 to April 2024 were selected as the study objects. Inclusion criteria: patients met the diagnostic criteria for dry eye disease (Liu 2020); patients had no eyelid or other eye diseases; patients without a history of ocular surgery. Exclusion criteria: patients with a history of ocular inflammation and treatment prior to enrollment; patients exist congenital tearless disease and other diseases; patients who did not cooperate with sampling and examination. The same number of healthy volunteers were selected as the control group, and all of them underwent ophthalmic examination without abnormalities.

The study was carried out after the approval of the Ethics Committee of our hospital, and all recruited personnel participated voluntarily.

Collection of tear samples

In a quiet room without light stimulation, 60 μL sterilized saline was added to the subject's conjunctiva sac, and 2~3 drops of tears were collected in centrifuge tubes and immediately stored in a –80℃ refrigerator.

Detection of clinical indicators

Serological parameters including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and immunoglobulin G (IgG) were routinely measured by the clinical pathology laboratory of our hospital.

A drop of 2% sodium fluorescein was applied to the conjunctival sac of the subjects. After multiple blinking, the time from the last blink to the appearance of the first randomly distributed dark spot was observed under a slit lamp with a cobalt blue filter and recorded as tear film break-up time (BUT). If BUT less than 10s may be as abnormal. Washes were performed with 0.25% chloramphenicol at the end of the examination.

Ocular surface anesthetic was dropped into the conjunctival sac of the subjects, and the length of tear wetting was recorded from the outer 2/3 of the lower eyelid margin using Schirmer's test (SIT) filter paper strip. The test should be performed with the eyes lightly closed and held for 5 min, and a recorded length of less than 10 mm was considered positive.

A drop of 1% fluorescein solution was added to the conjunctiva sac of the subjects, and the cornea was irradiated with cobalt blue light. The fluorescence staining was observed and the score of corneal fluorescein staining (CFS) was recorded.

Collection and culture of human conjunctival epithelial cell samples (HCECs)

HCECs were purchased from ATCC as control group, which were induced by H_2O_2 (100 μmol/L) and treated for 60 min as the model group.

The obtained HCEC samples were spread on a flat plate containing DMEM medium and 10% FBS, which were cultured in a 5% CO_2 incubator at 37℃. Follow-up experiments were performed when the cell density reached 85% to 90%.

RT-qPCR assays

TRIzol lysate and chloroform were added to tear and cell samples, and isopropyl alcohol solution was added after centrifugation. The quality and quantity of total RNA was determined using a NanoDrop 2000 spectrophotometer (Thermo Scientific). RNA reverse transcription cDNA was performed by M-MLV reverse transcription (Promega, USA). The reaction system was configured with the SYBR Premix Ex Taq TM Kit (Takara, Beijing) and amplified by PCR in the Applied Biosystems 7500 System. The sequences used in RT-PCR were as follows: SNHG7, forward 5′-TTGCTGGCGTCTCGGTTAAT-3′ and reverse 5′-GGAAGTCCATCACAGGCGAA-3′; miR-146a-5p, forward, 5′-GCCGAGUGAGAACUGAAUUC-3′ and reverse 5′-CAGTGCGTGTCGTGGAGT-3′; TNF-α, forward, ACCTTATCTACTCCCAGGTTCT-3′ and reverse 5′-GGCTGACTTTCTCCTGGTATG-3′; and IL-6 forward, 5′-GCCAGAGTCATTCAGAGCAATA-3′ and reverse 5′-TTAGGAGAGCATTGGAAGTTGG-3′. The levels of

SNHG7, miR-146a-5p, TNF-α mRNA and IL-6 mRNA were evaluated by $2^{-\Delta\Delta CT}$ method.

Cell transfection assays

si-NC and si-SNHG7 are synthesized by GenePharma Shanghai of China. They were transferred to HCECs by lipofectamine 3000 (Invitrogen, USA).

Luciferase activity assays

The downstream targets of SNHG7 were predicted by ENCORI, LncACTdb 3.0, LncBook 2.0 and DIANA Tools online databases, and Venn diagram was obtained. Meanwhile, ENCORI was used to predict the binding sites of SNHG7 and miR-146a-5p. Then wild-type (WT-SNHG7) and mutant-type (MUT-SNHG7) vectors were constructed and co-transfected into HCECs with control, mimic NC, miR-146a-5p mimic, inhibitor NC or miR-146a-5p inhibitor. At last, the luciferase activity of the cells was evaluated.

Statistical analysis

The experimental data with SPSS and GraphPad software for processing. Measurement data were tested by Student-*t* (two groups) or ANOVA (three and more groups) analysis with Bonferroni adjustment. The correlation between SNHG7 or miR-146a-5p and clinical indicators in patients with dry eye disease was conducted by Pearson analysis. $P < 0.05$ was considered statistically significant.

Results

General data analysis of patients with dry eye disease

Through the analysis of general information, serological indicators and clinical indicators of healthy participants and dry eye disease patients, it was found that there was no obvious difference in age, sex and body mass index (BMI) between the two groups ($P > 0.05$; Table 1). However, patients with dry eye disease had higher levels of CRP, ESR, IgG, and CFS than healthy participants, while BUT and SIT levels decreased ($P < 0.001$; Table 1). This indicates that there are obvious differences between the recruited healthy controls and dry eye disease patients, which are comparable.

SNHG7 expression in tears and HCECs

The expression changes of SNHG7 in the samples was detected by RT-qPCR. The results showed that SNHG7 was prominently expressed in tears of dry eye disease patients compared with the normal group (Fig. 1A). Additionally, increased SNHG7 expression in HCECs of model group was also confirmed by RT-qPCR assay (Fig. 1B).

Levels of inflammatory factors in HCECs

si-SNHG7 transfection assay was performed in HCECs to construct SNHG7 low expression cells (Fig. 2A). Furthermore, the levels of TNF-α mRNA and IL-6 mRNA in model group were significantly higher than those in control group, while the levels of TNF-α mRNA and IL-6 mRNA in si-SNHG7 group was downregulated (Fig. 2B).

Prediction of downstream targets of SNHG7

ENCORI, LncACTdb 3.0, LncBook 2.0 and DIANA Tools online databases were used to analyze the potential downstream targets of SNHG7. Venn diagram shows there are four possible results in Fig. 3A. The levels of miR-449b-5p (Fig. 3B), miR-181d-5p (Fig. 3C), and miR-34a-5p (Fig. 3D) in tear samples were evaluated by RT-qPCR. miR-146a-5p was negatively expressed in dry eye disease (Fig. 3E). ENCORI online network confirmed the existence of binding sites between SNHG7 and miR-146a-5p. Moreover, co-transfection of miR-146a-5p mimic with WT-SNHG7 reduced the luciferase activity of HCECs, but

Table 1. Inclusion of clinical information on individuals.

Items	Control (n = 86)	Dry eye disease (n = 86)	*P* value
General information			
Age (years)	45.27 ± 8.22	45.70 ± 7.21	0.715
Sex (Male/Female)	38/48	35/51	0.646
BMI (kg/m^2)	22.79 ± 3.45	23.04 ± 1.64	0.540
Serological indicators			
CRP (mg/L)	1.53 ± 0.71	1.81 ± 0.44	0.002
ESR (mm/h)	10.04 ± 3.60	19.76 ± 4.83	< 0.001
IgG (g/L)	11.92 ± 1.57	16.55 ± 3.42	< 0.001
Clinical indicators			
BUT (s)	11.19 ± 3.27	3.06 ± 0.26	< 0.001
SIT (mm)	10.19 ± 1.15	4.56 ± 0.44	< 0.001
CFS (score)	1.44 ± 0.28	5.30 ± 1.07	< 0.001

BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IgG, immunoglobulin G; BUT, break-up time; SIT, Schirmer's test; CFS, corneal fluorescein staining.

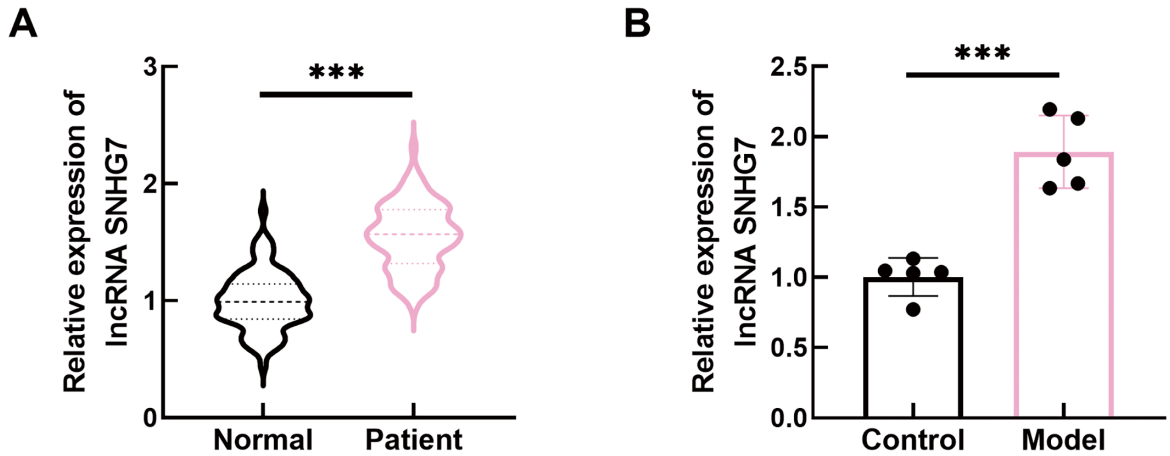

Fig. 1. SNHG7 expression in dry eye disease.
(A) SNHG7 was upregulated in tear samples from patients with dry eye disease. (B) Increased levels of SNHG7 in the human conjunctival epithelial cells model group compared to the control group. ***P < 0.001

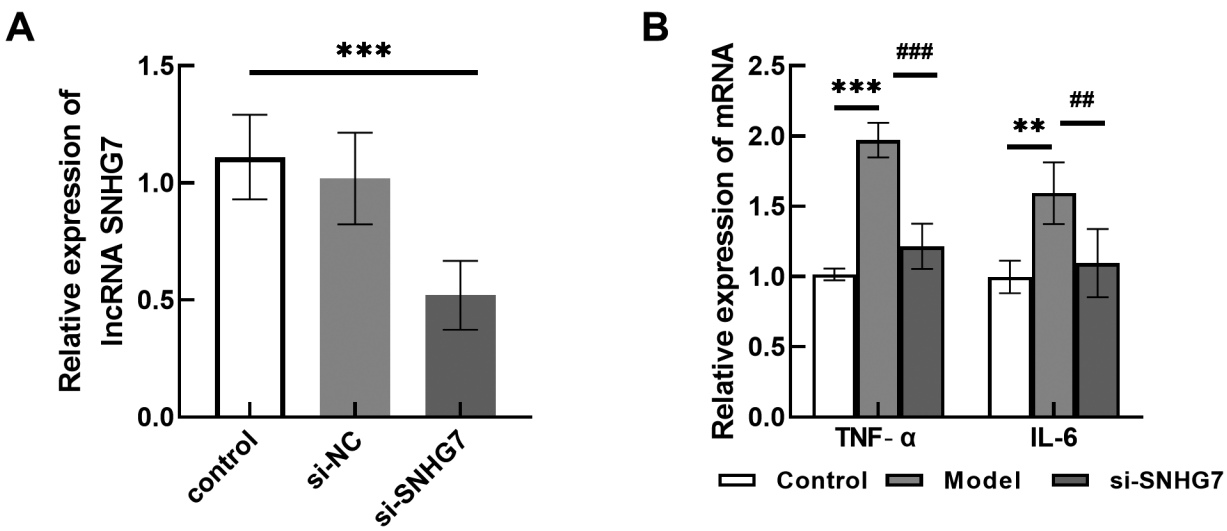

Fig. 2. Levels of inflammatory factors in human conjunctival epithelial cells.
(A) SNHG7 level was markedly downregulated in human conjunctival epithelial cells after SNHG7 knockdown. (B) Compared with the control group, TNF-α and IL-6 levels in the model group were enhanced, while SNHG7 silencing reduced their expression. ***P < 0.001 vs. control group; $^{\#\#}P$ < 0.01, $^{\#\#\#}P$ < 0.001 vs. model group

co-transfection with MUT-SNHG7 had no significant effect on HCECs (Fig. 3F).

Correlation between SNHG7 and miR-146a-5p expression with clinical indicators in dry eye disease patients

Pearson correlation analysis shows a negative correlation between the SNHG7 and miR-146a-5p expression in dry eye disease (r = –0.602, P < 0.001). In addition, the results in Table 2 state that SNHG7 expression was also inversely proportional to BUT and SIT values (r = –0.530, r = –0.593, P < 0.001), which was significantly positively correlated with CFS scores (r = 0.617, P < 0.001). On the contrary, miR-146a-5p expression was positively correlated with BUT and SIT values (r = 0.525, r = 0.499, P < 0.001), which negatively correlated with CFS scores (r = –0.561, P < 0.001).

Discussion

Based on the development of electronic products, the deterioration of environmental problems and the change of the nature of work, increased incidence of dry eye disease around the world. Unfortunately, there is still a lack of specific measures for the treatment of dry eye disease in clinical practice, so it is particularly important to explore the therapeutic means through lncRNA.

SNHG7 was confirmed to have increased expression in tears samples from patients with dry eye disease in this study. Similarly, SNHG7 was found to be upregulated in gastric cancer and silencing SNHG7 mediated cisplatin resistance in cells (Pei et al. 2021). SNHG7 was also prom-

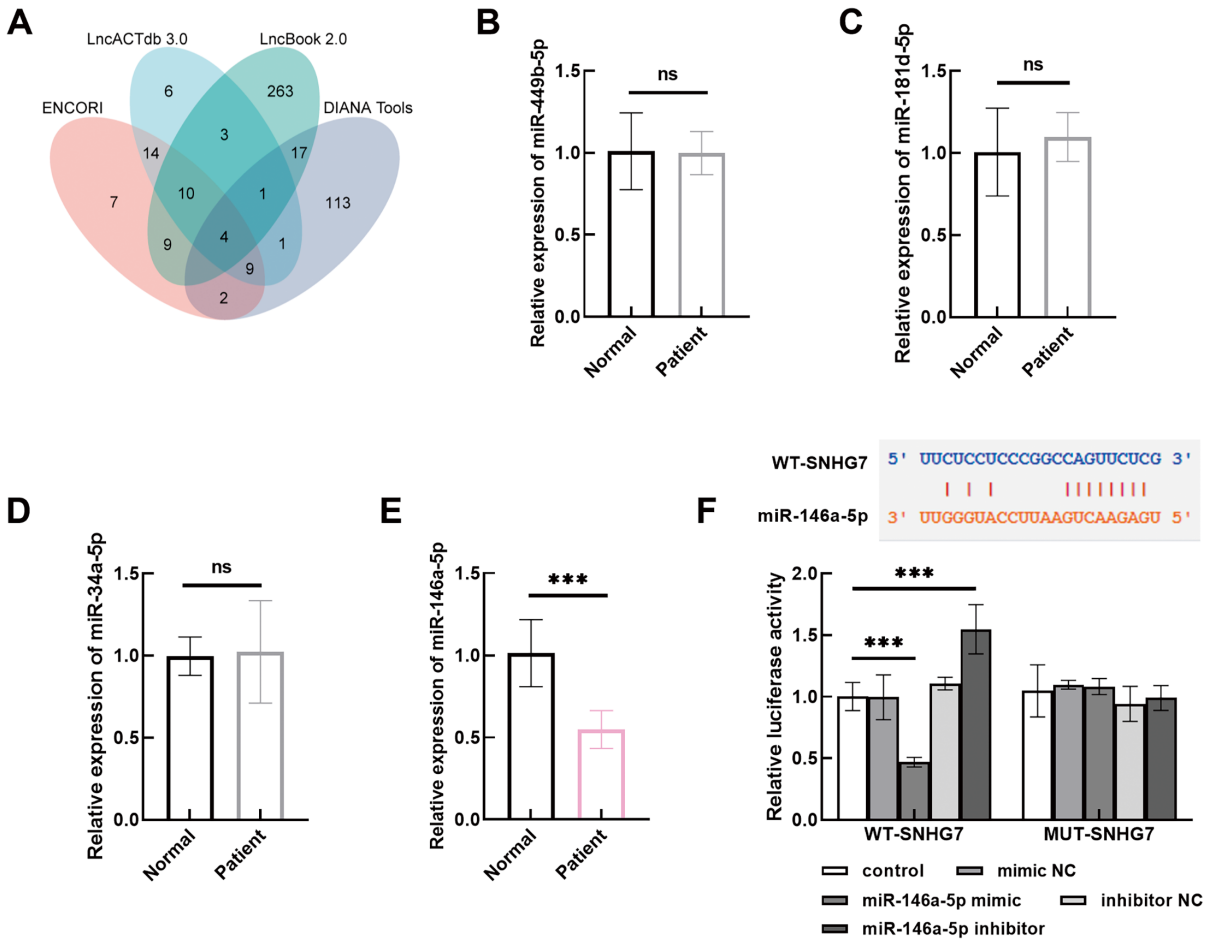

Fig. 3. Evaluation of the relationship between SNHG7 and miR-146a-5p.
(A) Venn diagram analysis of potential downstream targets of SNHG7. (B-E) Detection of four miRNAs expression in normal and patient tear samples. (F) Bioinformatics analysis and luciferase activity assay for SNHG7 and miR-146a-5p. $^{ns}P > 0.05$, $^{***}P < 0.001$.

Table 2. Relationship of clinical indicators dry eye disease.

Items	SNHG7		miR-146a-5p	
	r	*P*	*r*	*P*
BUT (s)	−0.530	< 0.001	0.525	< 0.001
SIT (mm)	−0.593	< 0.001	0.499	< 0.001
CFS (score)	0.617	< 0.001	−0.561	< 0.001
miR-146a-5p	−0.602	< 0.001	–	–

BUT, break-up time; SIT, Schirmer's test; CFS, corneal fluorescein staining.

inently expressed in neonatal sepsis, which may be regarded as an indicator for the diagnosis and prognosis of patients (Li et al. 2022). Additionally, to further understand the function of SNHG7 in dry eye disease, we cultured and induced HCECs. The results illustrated the increased levels of SNHG7, TNF-α, and IL-6 in model group. Some scholars believe that inflammatory factors are involved in the occurrence of dry eye disease, and their increased levels reduce the secretion of tears, representing an increased risk of dry eye disease (Wei et al. 2022). When SNHG7 was knocked down, the TNF-α and IL-6 levels in HCECs reduced, which speculated that upregulation of SNHG7 may aggravate the inflammatory response by promoting the secretion of inflammatory factors, and then cause the deterioration of dry eye disease.

MicroRNAs (miRNAs) are dysregulated in eye tissues, cells and tears, which mediate the development of disease (Benavides-Aguilar et al. 2023). For instance, Chen et al. (2023) revealed that miR-124 improved neural retinal function in rats with diabetic retinopathy by curbing glial cell

activity and inflammatory responses. Wei et al. (2024) described miR-144-3p targeting FOXO1 to alleviate diabetic keratopathy. In addition, the role of miRNAs in dry eye disease was described in the existing literature (Pucker et al. 2022). miR-146a-5p was revealed to be underexpressed in dry eye disease and is involved in pathological mechanisms by mediating IRAK1 level (Yin et al. 2021). This study also confirmed the low expression of miR-146a-5p in the tears of patients with dry eye disease. miR-146a-5p was the downstream target of SNHG7 and was negatively regulated by SNHG7. Moreover, correlation analysis also explained that miR-146a-5p expression was positively correlated with BUT and SIT values, but negatively correlated with CFS scores. SNHG7 had the opposite correlation trend. BUT reflects the stability of tear film (Wang et al. 2022). The BUT of dry eye patients is significantly lower than that of healthy people, indicating that the stability of tear film is poor. SIT represents the basal tear secretion, and low levels of SIT indicate that dry eye patients have reduced tear secretion (Narnoli et al. 2021). CFS assesses damage to the corneal epithelium, and a higher score indicates more severe disease (Lee et al. 2022). Combined with the above results, SNHG7 and miR-146a-5p expression were closely correlated with BUT, SIT, and CFS, which clarify that the abnormal expression of SNHG7 and miR-146a-5p affected the stability of tear film and participated in the process of dry eye disease. This suggests that SNHG7 and miR-146a-5p may be considered as indicators of dry eye disease.

This study still has limitations: First, the specific regulatory mechanisms of SNHG7 and miR-146a-5p in dry eye disease need to be further verified; Second, the impact of SNHG7 and miR-146a-5p in the prediction and prognosis of dry eye disease has not been deeply explored; Third, the small number of cases included in the study may have biased the results.

In conclusion, SNHG7 was highly expressed in dry eye disease, and silencing SNHG7 inhibited the levels of TNF-α and IL-6, thereby improving the inflammatory response of dry eye disease patients. In addition, SNHG7 targeted and negatively regulated miR-146a-5p, and they are related to the severity of dry eye disease, which provided a new idea for the clinical protection and treatment of dry eye disease patients.

Conflict of Interest

The authors declare no conflict of interest.

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