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Protective Effect of Circular RNA (CircRNA) Ddx17 in Ovalbumin (OVA)-Induced Allergic Rhinitis (AR) Mice

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: CircRNAs are involved in multiple biological processes, especially when they act as sponges of miRNA. Thus, the present study investigated the effect of circDdx17 on allergic rhinitis (AR) in an animal model, and determined the miRNA that was involved in this effect.

Material/Methods: The AR model was created by repetitive stimulation of ovalbumin (OVA). The levels of mRNAs in plasma were determined by qPCR. CircDdx17 stability was assessed using RNase R. The interaction between circDdx17 and miR-17-5p was predicted by bioinformatics and confirmed by dual luciferase assay. Moreover, the frequencies of rubbing and sneezing and pathological changes were recorded, and OVA-specific IgE, tumor necrosis factor (TNF)-α, interleukin (IL)-4, and IL-5 levels were detected by ELISA.

Results: Levels of circDdx17 were decreased in OVA-induced AR mice, and miR-17-5p interacted with circDdx17 in spleen cells derived from mice. Moreover, circDdx17 overexpression reduced the expression of miR-17-5p, OVA-specific IgE, TNF-α, IL-4, and IL-5, as well as the frequencies of rubbing and sneezing, and alleviated pathological changes in OVA-induced AR mice.

Conclusions: CircDdx17 appears to have a protective effect on mice in the progression of AR. Specifically, overexpression of circDdx17 inhibited the expression of miR-17-5p and alleviated the condition of AR. Therefore, circDdx17 appears to be a good candidate for use in prevention of AR. However, the detailed mechanism underlying the circDdx17/miR-17-5p regulatory pathway requires further study.

MeSH Keywords: **Inflammation • Microbial Interactions • MicroRNAs • Rhinitis, Allergic, Seasonal**

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Background

Allergic rhinitis (AR) is a common nasal allergic disease mediated by IgE [1,2]. Clinical manifestations of AR are nasal itching, sneezing, rhinorrhea, and rhinobyon [1,2]. In patients with long-term induction of high levels of allergens, antigen-presenting cells (APCs) transmit allergens to CD4+ T lymphocytes, and then induce B cells to differentiate into plasma cells and further generate IgE antibodies to trigger inflammatory allergic reactions [3,4]. AR is a chronic recurrent disease that is difficult to cure in otolaryngological practice [1,2]. AR does not directly threaten the life of patients, but it affects the nose and eyes, and complications seriously affect patients' quality of life, and it is becoming a global health problem [1,2]. The clinical treatment of AR mainly includes avoiding contact with allergens, drug treatment, and immunotherapy. However, studies on effective drugs in prevention and treatment of AR progress slowly, and immunotherapy still remains the most effective treatment in clinical practice [5]. Thus, it is urgent to develop novel approaches to the treatment of AR.

Evidence shows that circRNAs can regulate gene expressions, and many circular RNAs (circRNAs) can act as competing endogenous RNAs [6,7] and are expressed by exons or introns [8]. Recent studies showed that endogenous circRNAs can act as miRNA sponges, binding to miRNAs to inhibit the functions of miRNAs, and miRNAs are involved in many types of human diseases such as osteoarthritis, diabetes, and oral cancer [9,10]. Therefore, the activity of circRNA sponging also affects the biological processes of these diseases [11]. A class of circRNAs was found to play an important role in trimming immune responses and in protecting against infection by microorganisms [12]. However, few studies have explored the relationship between circRNA and allergic disease, or the role of circRNA in AR progression.

Researchers recently demonstrated that circDdx17 can act as a tumor suppressor in colorectal cancer [13]. RNA helicase DDX17 controls the expressions of proneural microRNAs in neuronal differentiation [14]. Hypoxia-induced polyubiquitination of DDX17 reduces anti-stemness miRNA biogenesis to promote transcription of stemness-related genes [15]. DDX17 ensures the targeting to specific chromatin *loci* through modulating the activities of various ribonucleoprotein complexes [16]. Thus, the present study investigated the effect of circDdx17 in an AR animal model, showing that miRNA is involved in the effect of circDdx17.

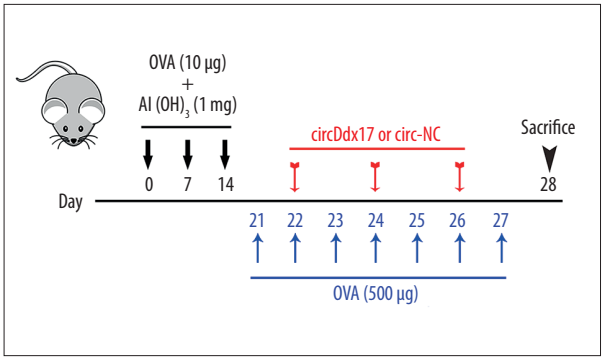

Figure 1. The protocol of the present study is shown. Mice were first sensitized by ovalbumin (OVA, 10 μg) and $Al(OH)_3$ (1 mg) on days 0, 7, and 14, and then treated again with 500 μg OVA to stimulate allergic rhinitis (AR) condition in the presence or absence of circDdx17 from days 21 to 27. The mice were sacrificed on day 28.

Material and Methods

Animal housing

We purchased 8-week-old female BALB/c mice (n=40) from the Model Animal Resource Information Platform of Nanjing University. The study was approved by the Ethics Committee of Tongliao Hospital and was conducted in accordance with the Animal Ethics guidelines of the hospital. The mice were fed standard chow and water, and were housed at 20±2°C with approximately 40% humidity and a 12-h: 12-h light–dark (LD) cycle.

Modeling and protocol

Mice weighing 20±2 g were divided into control (n=10), ovalbumin (OVA) (n=10), circ-NC (n=10), and circDdx17 (n=10) groups. On days 0, 7, and 14, the mice were sensitized by intraperitoneal injection of 500 μL PBS containing 10 μg OVA and 1 mg aluminum hydroxide ($Al(OH)_3$) via the peritoneal cavity from days 21 to 27, and AR was induced by intranasal challenging the mice using 500 μg OVA dissolved in 20 μL PBS for 7 days. The mice injected with 50 μg circDdx17 (loaded in pLCDH-cir [Ribobio, Guangzhou, China]) or an empty vector (pLCDH-cir) via tail vein before intranasal OVA challenge on days 22, 24, and 26 were assigned to the circDdx17 group and circ-NC group, respectively. Mice in the control group were treated by intraperitoneal injection of PBS. On day 27, 20 min after the final challenge of OVA, frequencies of nasal rubbing and sneezing of the mice were recorded by blinded observers (Figure 1).

Extraction of spleen cells

Briefly, on day 28, the mice in control group were placed on a wax plate and sacrificed by cervical dislocation. After disinfecting the abdomen of the mice with iodine, the spleens were

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immediately removed after opening the abdominal cavity, and then placed in a petri dish containing 5 mL Hank's Balanced Salt Solution (HBSS) (12350039, Medium 199, Hanks' Balanced Salts, Thermo Fisher, Waltham, USA). After cutting one end of the spleen using ophthalmic scissors, 5 mL Hank's solution was slowly injected into the spleen via the other end of the spleen to allow the spleen cell suspension to flow into the plate until the spleen became pale. After the plate was tilted for 10 min, the cell suspension was aspirated by a clean pipette and centrifuged in a 10-mL EP tube at 1500 rpm for 10 min. Next, the supernatant was discarded, and 1 mL red blood cell lysate (R7757, Sigma-Aldrich, MO, USA) was added to the cells and thoroughly mixed in 9 mL Hank's solution. Cell suspension was then centrifuged again at 1500 rpm for 10 min to 1 mL in RPMI 1640 (21875091, Thermo Fisher, Waltham, USA), and further incubated at 37°C with 5% CO_2.

qPCR

Total RNAs were extracted from nasal mucosa of the mice using TRIzol reagent (15596018, Thermo Fisher, Waltham, USA). Briefly, using the PrimeScript RT reagent kit (Takara Biotechnology Co., Dalian, China), cDNAs of circDdx17, Ddx17, GAPDH, miR-17-5p, U6, tumor necrosis factor (TNF)-α, interleukin (IL)-4, and IL-5 were obtained from the RNAs. As described from FastStart Universal SYBR Green Master (Rox) (4913850001, Roche, Shanghai, China) kit, 4 μL cDNA template, 12 μL 2×SYBER Green master mix, 1 μL forward primer (10 μM), reverse primer 1 μL (10 μM), and 7 μL ddH2O were mixed together. A Bio-Rad IQ5 thermocycler (Bio-Rad, CA, USA) was used for the qPCR procedure, which was conducted as follows: preparation at 95°C for 2 min; 40 cycles at 95˚C for 30 s; extended at 65°C for 30 s. Relative mRNA expressions were calculated by $2^{-\Delta\Delta Ct}$ method. For the measurement of RNase R resistance, total RNA was extracted from spleen cells derived from normal mice. The RNAs were treated with or without 3 U/mg RNase R reagent (RNR07250, Lucigen Corporation, WI, USA) for 30 min at 37°C. GAPDH served as an internal reference. The transcriptional levels of circDdx17 and GAPDH were measured by qPCR. Primers used in the study are shown in Table 1.

Dual luciferase assay

The target gene of circDdx17 was predicted by Starbase (*http://starbase.sysu.edu.cn*). The miRNA-target interaction was predicted by intersecting the predicted target site of the miRNA with the binding site of the Ago protein, which was derived from CLIP-seq data. The miRNA-circRNA interaction was predicted using the miRanda program. We collected 3×10^4 spleen cells and transfected them with or without miR-17-5p mimic (GenePharma, Shanghai, China), followed by the mutation of circDdx17 created by Quick-Change Site-Directed Mutagenesis kit (Stratagene, CA, USA). pRL-TK (Promega, WI, USA) coding for Renilla luciferase was co-transfected with miR-17-5p using Lipofectamine™ 3000 (L3000015, Thermo Fisher, Waltham, MA, USA). The activity of luciferase was determined by Dual-Glo luciferase assay kit (Promega, WI, USA) 48 h after culturing. The normalization of firefly luciferase values was set to that of Renilla.

Table 1. primers used in the study.

Primer name		Sequence (5'–3')
circDdx17	Forward	TGCCAACCACAACATCCTCCA
	Backward	CGCTCCCCAGGATTACCAAAT
Ddx17	Forward	GACAAAGAGGCGCTGTGATGAC
	Backward	AGGAGCCTTTCCAGATCGGAAC
miR-17-5p	Forward	CAAAGTGCTTACAGTGC
	Backward	GTGCAGGGTCCGAGGT
TNF-α	Forward	GTGCCTATGTCTCAGCCTCT
	Backward	TGGTTTGTGAGTGTGAGGGT
IL-4	Forward	CCCCAGCTAGTTGTCATCCT
	Backward	TGGTGTTCTTCGTTGCTGTG
IL-5	Forward	GAATCAAACTGTCCGTGGGG
	Backward	TCCATTGCCCACTCTGTACT
GAPDH	Forward	AGTGTTTCCTCGTCCCGTAG
	Backward	GCCGTGAGTGGAGTCATACT
U6	Forward	AGAGAAGATTAGCATGGCCCCTG
	Backward	ATCCAGTGCAGGGTCCGAGG

HE staining

Briefly, nasal mucosa were extracted and quickly fixed by 4% formaldehyde after the mice were sacrificed and perfused in PBS. After 24 h, the samples were cut into pieces, embedded in paraffin, and then cut into sections. After HE staining, the sections were stained by hematoxylin (#14166, CST, MA, USA) and eosin (E4009, Sigma-Aldrich, MO, USA) after dewaxing the sections with xylene substitute (A5597, Sigma-Aldrich, MO, USA). The sections were visualized by under a light microscope and photographed.

ELISA

After mice were sacrificed, plasma in each group was collected. The levels of OVA-specific IgE (MBS702947, MyBioSource, Inc., CA, USA), TNF-α (ab208348, Abcam, San Francisco, CA, USA), IL-4 (ab221833, Abcam, San Francisco, CA, USA) and IL-5 (ab204523, Abcam, San Francisco, CA, USA) in the plasma were determined by ELISA kit.

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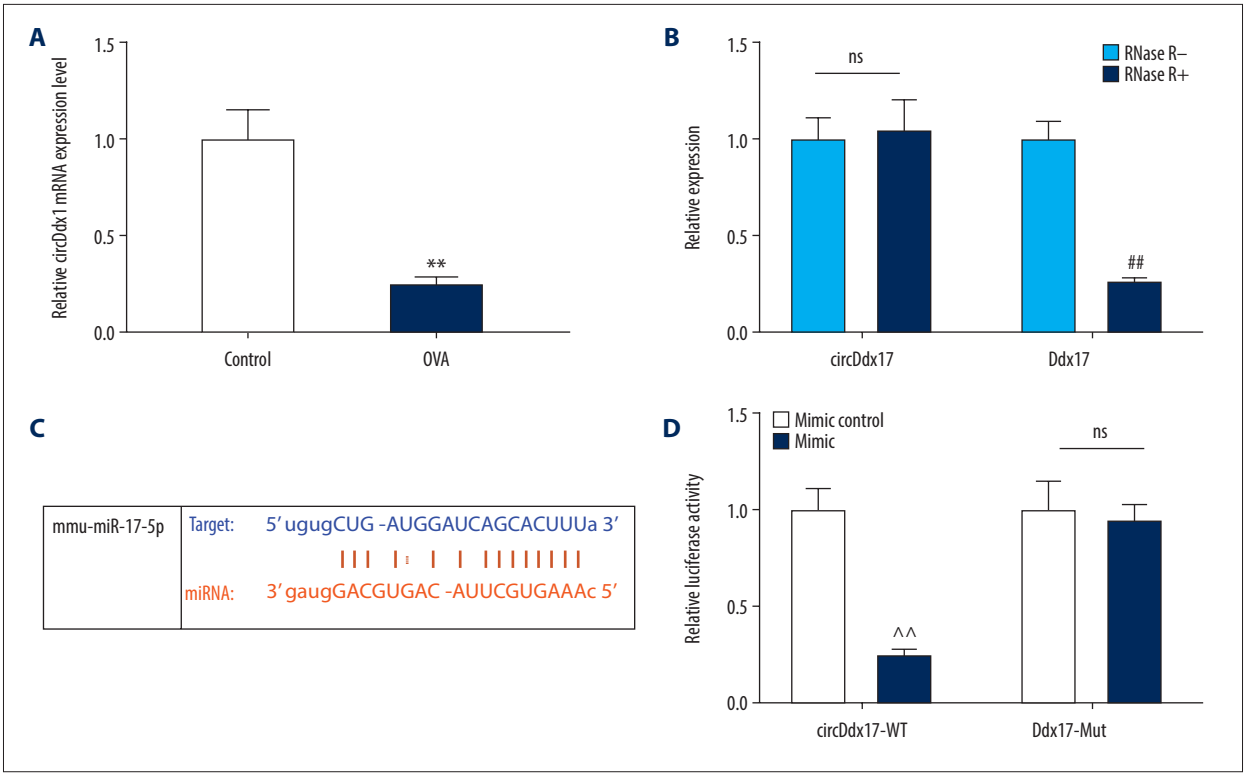

Figure 2. The expression level and target of circDdx17 are shown. (**A**) Relative circDdx17 expression levels in control and OVA groups were detected. (**B**) Relative circDdx17 or linear Ddx17 mRNA expression with or without RNase R were detected. (**C**) Possible complementary sequences between circDdx17 and miR-17-5p were detected. (**D**) Relative luciferase activity in spleen cells of mice treated by miR-17-5p mimic control or mimic when circDdx17 was wild or mutant were measured. Bars stand for means±standard deviation (SD). ** P<0.001 versus control group; ## P<0.001 versus RNase R– group; @@ P<0.001 versus mimic control group.

Statistics

The data in the present study were processed by GraphPad prism 8.0. The *t* test was performed for comparing the data between 2 groups, while one-way analysis of variance (ANOVA) was used for comparisons among multiple groups. In addition, Tukey's test was used for comparisons between 2 groups among multiple groups.

Results

CircDdx17 was decreased in OVA-induced AR mice and targeted miR-17-5p in spleen cells extracted from mice

The expression of circDdx17 in nasal mucosa from OVA-induced AR mice was determined to investigate its alteration under AR condition. RNase R resistance of circDdx17 and the target gene in spleen cells extracted from normal mice were investigated. We discovered that the relative expression of circDdx17 was lower in the OVA group than in the control group (Figure 2A, ** P<0.001), while the relative expression of circDdx17 in the RNase R+ group was not significantly different from that in the RNase R– group, and there was a statistically significant difference between the RNase R+ and RNase R– groups in Ddx17 mRNA expressions (Figure 2B, ## P<0.001). Furthermore, bioinformatic prediction showed that circDdx17 had a possible sequence, which paired to part of the sequence of miR-17-5p (Figure 2C). Meanwhile, the relative luciferase activity was lower in the circDdx17-WT group transfected with miR-17-5p mimic as compared with that in the mimic control group (Figure 2D, ^^ P<0.001). No differences were found between the circDdx17-Mut groups with and without miR-17-5p mimic (Figure 2D). These results suggested that circDdx17 expression was reduced in OVA-induced AR mice, and that miR-17-5p interacts with circDdx17 to exert its function.

CircDdx17 overexpression lowered miR-17-5p expression and alleviated AR condition in OVA-induced AR mice

The effect of circDdx17 on OVA-induced AR mice was investigated, and the results showed that relative circDdx17 expression in nasal mucosa from the OVA group was lower than in the control group, but it was lower in the OVA+circDdx17

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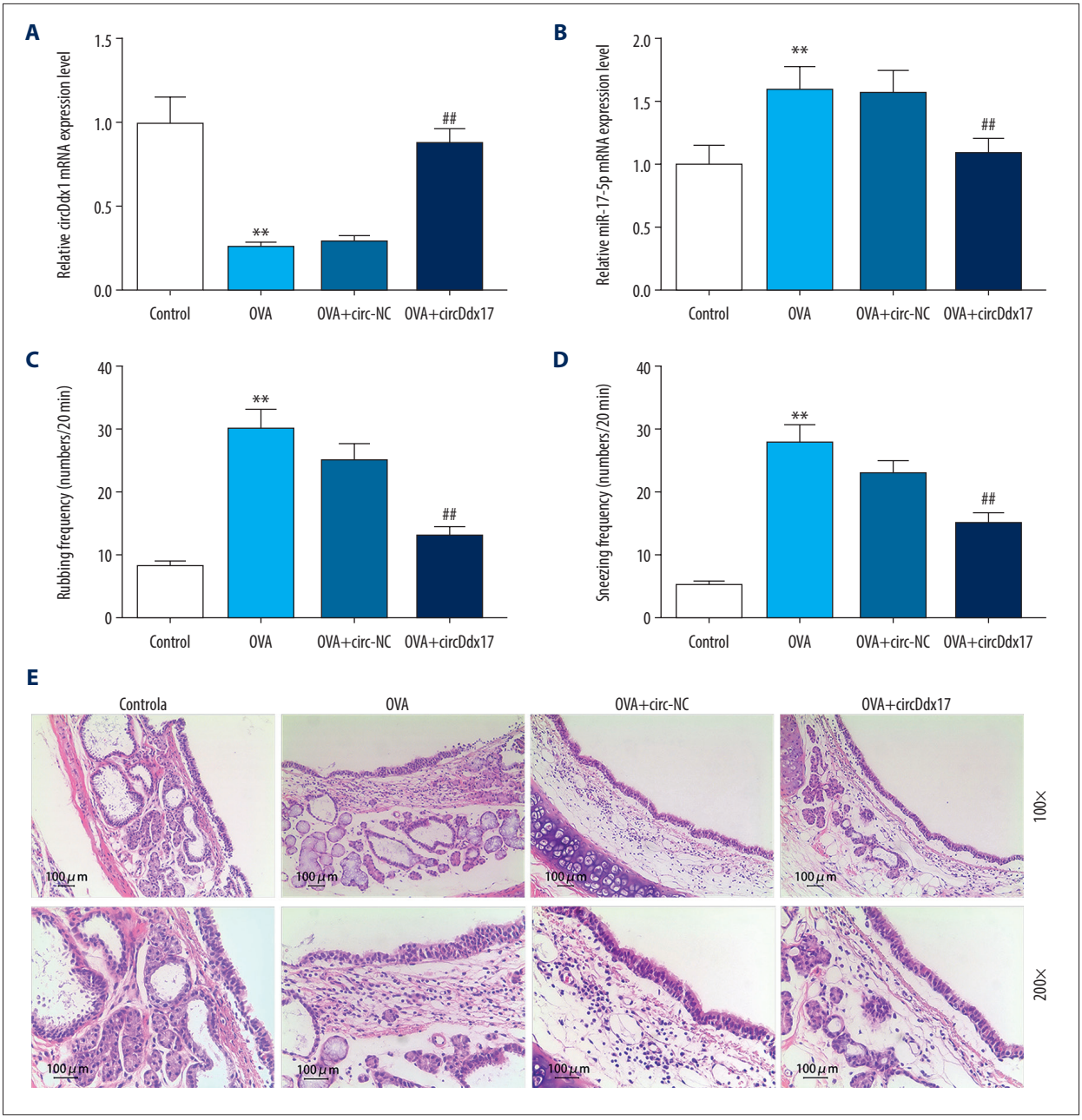

Figure 3. The effects of circDdx17 on AR are shown. (**A**) Relative circDdx17 and (**B**) miR-17-5p expression levels in control, OVA, OVA+circ-NC, and OVA+circDdx17 groups were measured. (**C**) Rubbing (numbers/20 min) and (**D**) Sneezing frequencies (numbers/20 min) in groups were detected. (**E**) Pathological alterations in different groups were identified. Bars stand for means±SD. ** P<0.001 versus control group; ## P<0.001 versus OVA+circ-NC group.

group than in the OVA+circ-NC group (Figure 3A, ** P<0.001, ## P<0.001). Moreover, relative miR-17-5p expression was higher in the OVA group than in the control group, but it was lower in the OVA+circDdx17 group than in the OVA+circ-NC group (Figure 3B, ** P<0.001, ## P<0.001). Nose rubbing and sneezing frequencies in the OVA group were higher than in the control group, but were lower in the OVA+circDdx17 than in the OVA+circ-NC group (Figure 3C, 3D, ** P<0.001, ## P<0.001).

In comparison with the control group, the pathological condition in nasal mucosa was worse in the OVA group, in which there were nasal mucosa epithelial congestion, edema, necrosis, structural abnormalities, and a large influx of eosinophils (Figure 3E). However, these pathological changes were alleviated in the OVA+circDdx17 group, and the number of eosinophils was significantly lower than in the OVA+circ-NC group (Figure 3E). Taken together, the data suggested that circDdx17

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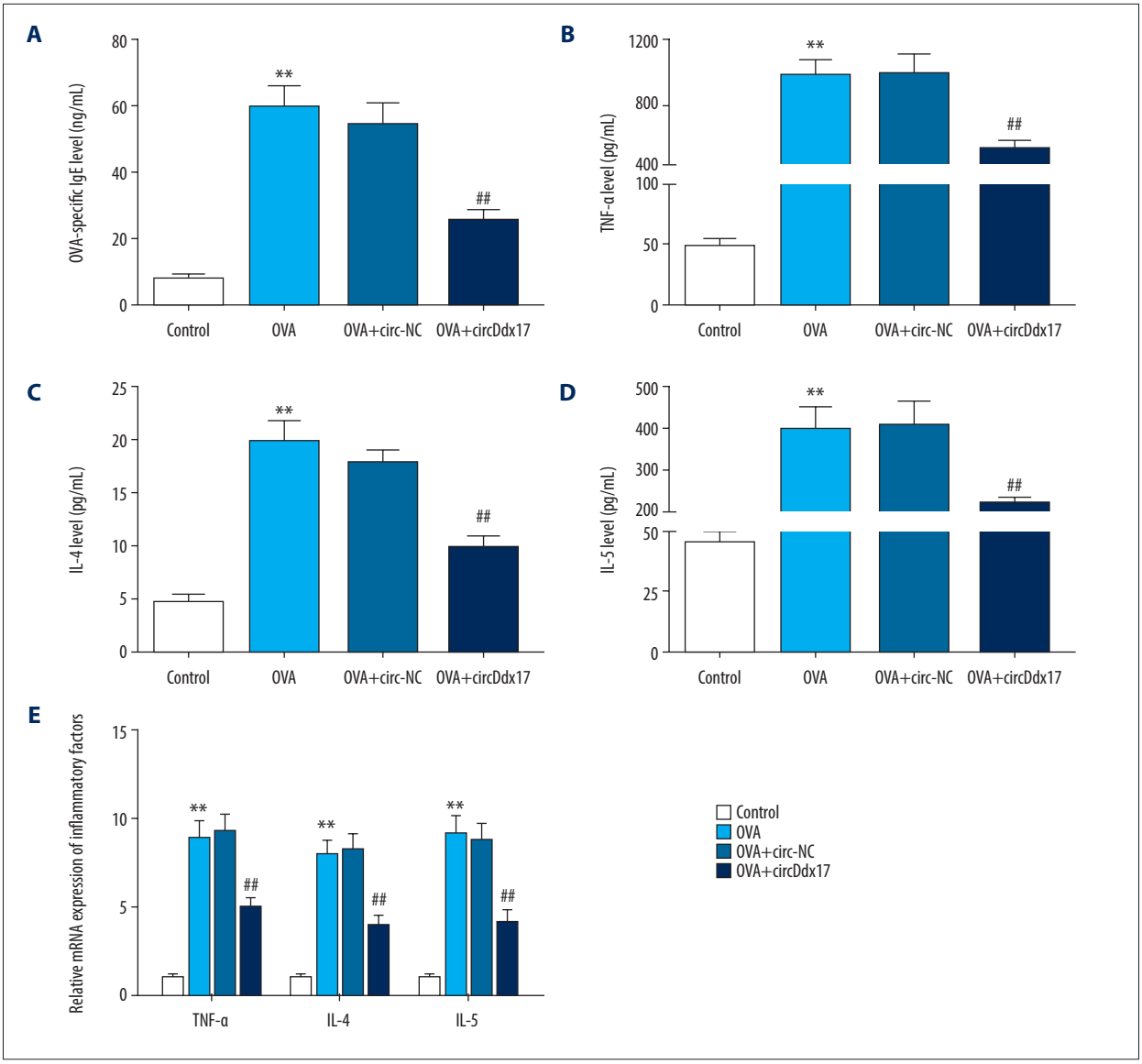

Figure 4. The changes of inflammatory factors in control, OVA, OVA+circ-NC, and OVA+circDdx17 groups are shown. The levels of (**A**) OVA-specific IgE (ng/mL), (**B**) tumor necrosis factor (TNF)-α (pg/mL), (**C**) interleukin (IL)-4 (pg/mL), and (**D**) IL-5 (pg/mL) in plasma of different groups were detected. (**E**) Relative mRNA expressions of TNF-α, IL-4, and IL-5 in different groups were detected. Bars stand for means±SD. ** P<0.001 versus control group; ## P<0.001 versus OVA+circ-NC group.

might be able to down-regulate miR-17-5p expression and alleviate AR symptoms and pathological condition.

CircDdx17 overexpression decreased the levels of OVA-specific IgE and inflammatory factors in OVA-induced AR mice

To observe whether circDdx17 affected inflammation, we assessed the levels of OVA-specific IgE, TNF-α, IL-4, and IL-5 in OVA-induced AR mice after modeling and circDdx17 injection. We found that the levels of OVA-specific IgE, TNF-α, IL-4, and IL-5 in the serum from OVA-induced AR mice were higher in the OVA group than in the control group (Figure 4A–4D, ** P<0.001, ## P<0.001). However, their expression levels in the OVA+circDdx17 group were lower than those in the OVA+circ-NC group (Figure 4A–4D, ** P<0.001, ## P<0.001). Similarly, the mRNA expression levels of TNF-α, IL-4, and IL-5 in nasal mucosa were higher in the OVA group than in the control group, but were lower in the OVA+circDdx17 group than in the OVA+circ-NC group (Figure 4E, ** P<0.001, ## P<0.001). Thus, circDdx17 appears to play an anti-inflammatory role in AR progression.

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Discussion

In our study, AR condition was successfully generated by OVA, and it was found that circDdx17 expression decreased in OVA-induced AR mice and that miR-17-5p could be targeted by circDdx17. We also discovered that overexpressed circDdx17 alleviates the symptoms and pathological condition in AR model mice, and this was accompanied by decreased levels of OVA-specific IgE, TNF-α, IL-4, and IL-5. Our findings suggest that the effect of circDdx17 in controlling AR condition is a promising treatment for AR.

After establishing AR condition in mice via OVA injection, nose rubbing and sneezing frequencies increased, and the mice showed pathological hypersensitivity and increased levels of OVA-specific IgE, TNF-α, IL-4, and IL-5. Moreover, in OVA-induced AR mice, circDdx17 was reduced and was affected by RNase R, showing a stabilized structure as a circle RNA. IgE, which is an immunoglobulin discovered in 1967 [17], mainly mediates immediate allergic reaction and is synthesized and secreted by plasma cells [18–20]. On one hand, IgE is a cytophilic antibody, and its Fc segment specifically binds to the high-affinity receptor FcεR I on the surface of basophils or mast cells [21,22]. When bivalent or higher antigen binds to IgE on the surface of cells, the IgE molecule will be bridged in the presence of Ca^{2+} [21,22]; as a result, IgE leads to the release of intracellular biologically active substances to trigger allergic reactions [21,22]. On the other hand, it has been shown that Th2 lymphocytosis and Th1/Th2 immune imbalance are the main mechanisms underlying the pathogenesis of AR [23]. Through the production of IL-4 and IL-5, Th2 cells act on B lymphocytes, mast cells, and granulocytes, leading to a cascade of inflammation during the development of AR nasal mucosal inflammation [23–25]. TNF-α is also considered to be involved in the inflammatory process [24,26]. Kim et al. demonstrated that AR status was successfully stimulated in mice by OVA [27]. Onishi and Nobukazu et al. showed that sneezing frequency, total IgE, total IgG1, and inflammatory factors were increased in OVA-induced mice [28]. In the present study, eosinophils were not quantified under the pathological condition in nasal mucosa, and the viability of spleen cells were not measured, which were 2 limitations in the present study. However, our results show that the AR model was successfully established and circDdx17 was downregulated in AR mice.

Interestingly, the results of the present study revealed that circDdx17 overexpression greatly lowered the frequencies of nose rubbing and sneezing, OVA-specific IgE, expressions of TNF-α, IL-4, and IL-5, and alleviated the condition of pathological changes. Huang et al. showed that circRNAs were closely associated with the progression of allergic bronchopulmonary aspergillosis through transcriptome analysis of human peripheral blood [29]. Gerthoffer et al. demonstrated that in allergic sensitized lung tissue, there was an alteration of the expression patterns of circRNAs [30]. In addition, Gao et al. revealed that the development of chronic glomerulonephritis might be related to circRNAs in rats [31]. Thus, the previous findings suggested that circRNAs participate in the process of allergic disease, and circDdx17 is involved in and exerts a protective role directly or indirectly in AR.

Bioinformatic prediction showed that miR-17-5p was a target gene of circDdx17, which was further confirmed by dual luciferase assay. miR-17-5p expression was elevated in OVA-induced AR model mice, and its expression was reduced by circDdx17 overexpression. Liu et al., using bioinformatics-based approaches, showed that miR-17-5p exerts its function via ABCA1 and CD69 in the pathogenesis of seasonal AR [32]. Mohammadi Nejad et al. demonstrated that CD69 expression in natural killer cells from human peripheral blood derived from AR patients was elevated [33]. Moreover, Huang et al. revealed that the injury of nasal epithelial cells induced by lipopolysaccharide was aggravated by miR-17-5p [34]. Thus, we hypothesized that the overexpressed miR-17-5p contributed to the development of AR, while circDdx17 exerted a regulatory role that could balance the expression of miR-17-5p and modulate the process of triggering AR.

Conclusions

In conclusion, the present study found that circDdx17 has a protective effect in the development of AR. Specifically, overexpressed circDdx17 inhibited the expression of miR-17-5p and further alleviated the condition of AR. Therefore, circDdx17 could be considered as a candidate in the prevention of AR. However, the detailed mechanism underlying the circDdx17/miR-17-5p regulatory pathway should be further studied.

Conflicts of interest

None.

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