Abstract. Our previous study demonstrated that intranasal administration of histone deacetylase inhibitor sodium butyrate (NaB) exhibits therapeutic effects on a mouse model of allergic rhinitis (AR). However, whether NaB is effective on AR when administered orally and prophylactically, as well as its potential effects on gene expression, remained unknown. The present study aimed to investigate the preventive effect of NaB on AR when added to the diet of newly weaned mice and to evaluate the changes in long non-coding (lnc)RNA and mRNA expression profiles in the nasal mucosa. Mice were randomly divided into three groups as follows: i) Control (C) group, (no treatment); ii) AR group [treated with ovalbumin (OVA)]; and iii) NaB + AR group (treated with OVA and NaB). The NaB + AR group was administered NaB in their feed (30 g/kg chow), whereas the other two groups were fed normal feed between 3 and 6 weeks of age. At 7 weeks of age, OVA administration was initiated to induce AR in the AR and NaB + AR groups. Following model establishment, behavioral assessments, western blotting and gene expression analysis were performed. NaB exhibited a preventive effect in the murine AR model, diminished the increases in histone deacetylase 1 (HdAc1) and HdAc8 expression and increased OVA-induced acetylation of histone H3 at lysine 9. In addition, NaB increased the AR-associated low expression of interleukin 2 (IL-2), interferon γ and IL-17 and decreased the expression of IL-4, IL-5 and transforming growth factor β1. Gene Ontology and pathway analyses revealed the top 10 pathways among the groups. Octamer-binding transcription factor 1, ecotropic viral integration site 1 and paired box 4 were predicted to be target genes of lncRNA (NONMMUT057309). Thus, NaB may exhibit a preventive effect on AR. Additionally, the lncRNA and mRNA expression profiles in the nasal mucosa of mice with AR differed significantly following NaB treatment. These results may provide insights into the pathogenesis of AR and suggest new treatment targets.

Introduction

Allergic rhinitis (AR), a non-infectious disease of the nasal mucosa, is primarily mediated by immunoglobulin E (IgE) following contact with allergens (1). The self-reported prevalence of AR in 11 cities across Mainland China had wide variations in 2005, ranging between <10 and >20% (2); in 2011, the standardized prevalence of adult AR in the 18 major cities was 17.6%, with the highest prevalence of 23% in Shanghai and the lowest prevalence of 9.8% in Chengdu (3). The number of patients with AR in China has increased by 100 million between 2005 and 2011 (4). AR has traditionally been considered to originate from a T helper (Th1)/Th2 immune response imbalance, leading to allergic inflammation dominated by the Th2 immune response within the nasal mucosa (5). Following further study, the pathogenesis of AR has been extended from the Th1/Th2 model to a Th1/Th2/Th17 and T regulatory cell (Treg) model (6). However, as AR is a multi-factor disease induced by gene-environment interactions, its exact pathogenesis has not been elucidated.

Lysine acetylation is a reversible post-transcriptional modification that regulates changes in gene expression profiles (7). Two opposing enzymes function intracellularly to determine protein acetylation levels; specifically, histone acetyltransferase (HAT) catalyzes the addition of an acetyl group to lysine residues, whereas histone deacetylase (HDAC) catalyzes the removal of an acetyl group from lysine residues (7). The HAT/HDAC balance maintains histone acetylation levels and regulates gene transcription (8). Redox signaling, which is mediated by HAT-induced inactivation of histone...
acetylation, decisively contributes to the activation phase of the inflammatory cascade (9). Targeting HAT Tip60 inhibits intestinal allergies in a mouse model (10). The expression of HDAC1, HDAC5, HDAC6 and HDAC8 increases in asthmatic mice (11); HDAC11 (12) and HDAC1 (13) expression levels are increased in patients with AR, and HDAC1 also participates in the pathogenesis of childhood asthma (14).

Sodium butyrate (NaB) is an aliphatic acid and a nonspecific HDAC inhibitor (15). The results of our previous study indicated that NaB nasal drops decreased the expression of HDAC1 and HDAC3 and increased histone H3 acetylation at lysine 9 (H3-AcK9) (16). Butyrate is the final product of the anaerobic fermentation of dietary fiber by intestinal microorganisms (17), and butyrate levels in stool samples from patients with atopic dermatitis have been demonstrated to be decreased (18). Oral NaB may modulate brain metabolism (19) and attenuate experimental murine colitis in an IL-10 independent manner (20).

The objective of the present study was to investigate the preventive effect of NaB on AR by adding it to the diet of newly weaned mice at 3 weeks of age and to determine the changes in IncRNA and mRNA expression profiles in the nasal mucosa following NaB treatment.

**Materials and methods**

**Animals and trials.** BALB/C mice (3 weeks old; 6-8 g) were purchased from the Air Force Military Medical University (Xi’an, China). Mice were maintained in a pathogen-free environment under a 12/12-h light/dark cycle at 22˚C with free access to food and water. All animal experiments were conducted in accordance with the National Institutes of Health guidelines and approved by the Committee on Animal Research of the Air Force Military Medical University (approval no. KJ-2016-XJB543).

Mice were randomly divided into three groups (n=30 mice/group) as follows: i) Control (C) group (no treatment); ii) AR group [treated with ovalbumin (OVA)]; and iii) NaB + AR group (treated with OVA and NaB). Mice began to feed after weaning at 3 weeks of age. The mouse feed was premixed, 30 g/kg NaB (Sigma-Aldrich; Merck KGaA) was added, and granules were produced. Normal feed and NaB feed were provided by the Animal Center of the Air Force Medical University. Each mouse in the NaB + AR group consumed an average of 5 g feed/day, which contained 0.15 g NaB. The other 2 groups were provided with normal feed throughout the study period. At 7 weeks of age, mice in the AR and NaB + AR groups received intraperitoneal injections of mixed OVA solution (20 mg) and aluminum (2 mg) in 0.5 ml PBS on days 1, 3, 6 and 8, whereas the control mice were sacrificed by cervical dislocation, and the nasal mucosa was preserved in liquid nitrogen for further analysis.

**Histological observation.** The muscle tissue of the nose was removed, and the nasal cavity was fixed in 4% formaldehyde for 24 h at 37˚C. Following 10% EDTA decalcification for 24 h at 37˚C, the nose was embedded in paraffin, and 4-µm sections were cut. The sections (4-µm) were dewaxed, stained with hematoxylin (cat. no. 245880; Abcam) and anti-GAPdH (mouse; 1:1,000; cat. no. 187139; Abcam) and anti-H3-AcK9 (rabbit; 1:1,000; cat. no. 9649S; all from cell signaling technology, Inc.), anti-HdAc8 (rabbit; 1:1,000; cat. no. 5356), anti-H3 (rabbit; 1:1,000; cat. no. 4499), anti-H3-AcK9 (rabbit; 1:1,000; cat. no. 9649S; all from Cell Signaling Technology, Inc.), anti-HDAC8 (rabbit; 1:1,000; cat. no. 187139; Abcam) and anti-GAPDH (mouse; 1:1,000; cat. no. 686613; R&D Systems, Inc.) antibodies overnight at 4˚C.
Following exposure to horseradish peroxidase-conjugated anti-mouse and anti-rabbit IgG secondary antibodies (1:200; Sigma-Aldrich; Merck KGaA) for 1 h at 37˚C, immunoreactive bands were detected using an enhanced chemiluminescence western blotting system (Thermo Fisher Scientific, Inc.).

RNA microarray. The CapitalBio Technology Mouse LncRNA Array v1 was designed with four identical arrays per slide (4X180K format), with each array containing probes for 58,809 mouse lncRNAs and 39,027 mouse mRNAs. The lncRNA and mRNA target sequences were obtained by merging the results from multiple databases, including NCBI RefSeq (https://www.ncbi.nlm.nih.gov/), Ensembl (http://asia.ensembl.org/index.html), UCSC (http://www.genome.ucsc.edu/), FANTOM (https://fantom.org/), LncRNAdb (http://live.dbpedia.org/page/LncRNAdb/), NO NCODE V4.0 (http://www.noncode.org/), UCR (https://www.ucr.edu/), LncRNA Disease (http://www.cuilab.cn/Lncrnadisease) and LncRNA.org (https://Incipedia.org/). Each RNA was detected by probes based on ≥2 replicates. The array also contained 4,974 Agilent control probes.

RNA extraction, amplification, labeling and hybridization. The microarray assay was performed by Capital Biotech Corporation (Beijing, China) with the Agilent mouse LncRNA + mRNA Array V4.0 (4X180K) (Agilent Technologies, Inc.) according to the manufacturer’s instructions. Total RNA was extracted using TRIzol® reagent (Invitrogen; Thermo Fisher Scientific, Inc.) according to the manufacturer’s instructions. Briefly, 200 ng purified RNA from each sample was amplified and reverse-transcribed into cDNA. The cDNAs were transcribed into cRNAs at 70˚C for 5 min, 25˚C for 5 min and 4˚C for 2 min, and the cRNAs were transcribed into cDNAs using the WT Expression Kit (cat. no. 4411973; Thermo Fisher Scientific, Inc.) at 70˚C for 5 min, 25˚C for 5 min and 4˚C for 2 min, labeled with a fluorescent dye (Cy3-dCTP, Agilent Technologies, Inc.), denatured at 95˚C for 3 min and incubated in an ice bath for 5 min. Labeled cDNAs were hybridized onto
Microarray imaging and data analysis. The IncRNA and mRNA array data were analyzed for data summarization, normalization and quality control using Gene Spring software V12.0 (Agilent Technologies, Inc.). To identify the differentially expressed genes, the threshold values of fold-change ≥2 and ≤-2 and a Benjamini-Hochberg corrected P-value <0.05 were used. The data were log2-transformed and median-centered on genes using the ‘Adjust Data’ function of CLUSTER 3.0 software (Michiel de Hoon, University of Tokyo, Human Genome Center) prior to further analysis via hierarchical clustering with average linkage. Tree visualization was performed using Java Treeview 3.0 (Stanford University School of Medicine).

RNA isolation and reverse transcription-quantitative PCR (RT-qPCR). Total RNA was extracted using TRIzol® reagent (Invitrogen; Thermo Fisher Scientific, Inc.) according to the manufacturer's instructions. The concentration, quality and purity of RNA were assessed using the RNA 6000 Nano assay on the Agilent 2100 Bioanalyzer (Agilent Technologies, Inc.). No samples exhibited RNA degradation (ratio of 28S:18S ribosomal RNA ≥2) or contamination with DNA. For reverse transcription, samples were incubated in an Eppendorf PCR system at 42°C for 30 min, 90°C for 5 min and 5°C for 5 min. The samples were subjected to qPCR with specific primers (Table SI). qPCR was performed in a 10 µl total volume containing 1 µl cDNA, 5 µl SYBR® Green Real-time PCR Master Mix (Toyobo Life Science) and 1 µl of each primer under the following conditions: 95°C for 10 sec at; 40 cycles of 60°C for 5 sec and 72°C for 10 sec; and 65°C for 30 sec. Melting analysis of PCR products was conducted to validate the amplification of a specific product, and the relative fold-change was calculated using the $2^{-\Delta\Delta Cq}$ method normalized to GAPDH (22).

LncRNA-mRNA co-expression and construction of the coding-non-coding gene co-expression network. Differentially expressed mRNAs were used to construct a co-expression network to explore specific IncRNAs involved in the pathogenesis of AR. Pearson correlation coefficients (PCCs) were calculated between selected mRNAs and all differentially expressed lncRNAs. A PCC ≥0.99 indicated that the selected lncRNA and mRNA formed a significantly correlated pair. The coding-non-coding gene co-expression network was constructed based on the correlation analysis between differentially expressed IncRNAs and mRNAs. Significantly correlated pairs (based on PCC) were selected to construct the network. LncRNAs and mRNAs with PCCs ≥0.99 were

![Graphs showing serum ELISA results of IL-2, IFN-γ, TGF-β1, IL-4, IL-5 and IL-17. The expression levels of IL-2, IFN-γ and TGF-β1 were lower, whereas those of IL-4, IL-5 and IL-17 were higher in the AR group compared with the C group. NaB treatment increased the expression of IL-2, IFN-γ and TGF-β1 and decreased the expression of IL-4, IL-5 and IL-17 compared with the AR group, although significant differences in ELISA results were present between the C and NaB + AR groups. Data are presented as the mean ± SD. *P<0.05. IL, interleukin; INF-γ, interferon γ; TGF-β1, transforming growth factor β1; NaB, sodium butyrate; C, control group; AR, rats treated with ovalbumin; NaB + AR, rats treated with NaB and ovalbumin.]
selected to draw the network using the open-source bioinformatics software Cytoscape 3.7.2 (https://cytoscape.org/). For network analysis, a degree of centrality was defined as the number of links that one node had to others.

**Prediction of cis-acting and trans-acting lncRNA.** The prediction of cis-acting lncRNA was performed based on a strong correlation between the lncRNA and a group of expressed protein-coding genes (PCC ≥0.99). The lncRNAs were only selected if they resided at the genomic loci where a protein-coding gene and an lncRNA gene were within 10 kb of each other along the genome; ‘cis’ therefore refers to the same locus (not necessarily the same allele) regulatory mechanism, which included the antisense-mediated regulation of protein-coding genes by lncRNAs that in the same locus.

The trans-prediction was conducted using a Standalone BLAT v. 35 x 1 fast sequence search command line tool (http://hgdownload.cse.ucsc.edu/admin/exe/) to compare the full sequence of the lncRNA to the 3’-untranslated region of its co-expressed mRNAs using default parameter settings.

**Analysis of Gene Ontology (GO) and PANTHER pathways.** The functions of biological processes differentially expressed genes were identified by GO analysis (http://geneontology.org/). The differentially expressed mRNAs were analyzed using PANTHER analysis (http://pantherdb.org/).

**Statistical analysis.** Data are presented as the means ± SD. Analyses were performed using SPSS version 13.0 (SPSS, Inc.). Unpaired Student’s t-test was used to identify differences between two groups. One-way ANOVA followed by the least significant difference test was used to compare multiple groups. Analysis of mRNA, IncRNA and RT-qPCR fold-change data were performed by Student’s t-test using Microsoft Excel 15.17 (Microsoft Corporation). P<0.05 was considered to indicate a statistically significant difference.

**Results**

**Oral NaB decreases the AR-related behavioral score and improves nasal mucosal morphology.** NaB treatment decreased the behavioral scores of mice with AR (Fig. 2A). In

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*Figure 4. The protein levels of HDAC1, HDAC8 and H3-AcK9 in mouse nasal mucosa detected by western blot analysis. The expression of HDAC1 and HDAC8 increased, whereas that of H3-AcK9 decreased in the AR group compared with the C group. NaB treatment decreased the expression of HDAC1 and HDAC8 and increased the expression of H3-AcK9, although significant differences were still present in the western blot analysis results between the C and NaB + AR groups. Data are presented as the mean ± SD. *P<0.05. HDAC, histone deacetylase; H3-AcK9, histone H3 acetylated at lysine 9; NaB, sodium butyrate; C, control group; AR, rats treated with ovalbumin; NaB + AR, rats treated with NaB and ovalbumin.*
addition, mice fed NaB for 7 weeks did not experience diarrhea or other adverse effects and gained weight normally (Fig. 2B). Epithelial cells of the nasal mucosa in the AR group exhibited loss of cilia, edema of the sub‑mucosal tissue, small vessel proliferation, infiltration of eosinophils (Fig. 2C) and exuberant secretion of goblet cells (Fig. 2D). NaB treatment reduced nasal mucosal inflammation in AR mice (Fig. 2C and D). These results indicated that NaB could prevent AR, and that 7 weeks of NaB feeding did not affect mouse growth.

NaB rebalances Th1/Th2/Th17 and Treg ratios in AR mouse mucosa. Following treatment of AR mice with NaB, serum ELISA demonstrated that the expression of IL‑2 (a marker of Th1), IFN‑γ (a marker of Th1) and TGF‑β1 (a marker of Treg) was higher, whereas the levels of IL‑4 (a marker of Th2), IL‑5 (a marker of Th2) and IL‑17 (a marker of Th17) were lower in the NaB + AR group compared with that in the AR group. These results indicated that NaB could restore Th1/Th2/Th17 and Treg balance in AR mice (Fig. 3).

NaB normalizes the AR‑induced downregulation of H3‑AcK9 and upregulation of HDAC1 and HDAC8 expression in mouse mucosa. NaB partially reversed the downregulation of H3‑AcK9 and upregulation of HDAC1 and HDAC8 expression induced by AR in the nasal mucosa of mice (Fig. 4). These results suggested that NaB could restore the HDAC/HAT balance.

Differences in lncRNA and mRNA expression profiles in the nasal mucosa among the three groups. A scatter function was used to identify the differences in lncRNA and mRNA expression (log2 expression value) among the three groups. LncRNA analysis demonstrated that compared with the expression levels in the C group, 254 genes were upregulated and 109 were downregulated in the AR group, and 18 genes were upregulated and 47 were downregulated in the NaB + AR group. Compared with the AR group, 32 genes were upregulated and 230 were downregulated in the NaB + AR group (Fig. 5A). mRNA analysis revealed that compared with the expression levels in the C group, 319 genes were upregulated and 524 were downregulated in the AR group, and 159 genes were upregulated and 218 were downregulated in the NaB + AR group. Compared with the AR group, 114 genes were upregulated and 45 were downregulated in the NaB + AR group (Fig. 5B).

LncRNA (NONMUT057309), lncRNA (NONMUT016103) (Table I) and 33 mRNAs (Table II) were identified to be co‑expressed, and expression trends for these markers were consistent among the C, AR and NaB + AR groups. The 33 mRNAs encoded immunoglobulins, suggesting that lncRNA may regulate the expression of immunoglobulins during AR inflammation.

RT‑qPCR validation of microarray data. Statistically significant differences were identified at four mRNA (A‑65‑P07626, A‑52‑P50284, A‑66‑P10323 and A‑55‑P21872) and two
LncRNA (NONMMUT057309) loci between C vs. AR, NaB + AR vs. AR and NaB + AR vs. C groups in the microarray results. RT-qPCR validation results in the three groups were consistent with the microarray analysis results, with the exception of the LncRNA (NONMMUT016103) locus (Fig. 6).

LncRNA (NONMMUT057309)-mRNA co-expression analysis. LncRNA (NONMMUT057309) co-expression analysis of mRNA (data not shown) and target gene prediction (Fig. 7) revealed that only three target genes of LncRNA (NONMMUT057309) [octamer-binding transcription factor 1 (Oct-1), ecotropic viral integration site 1 (Evi-1) and paired box 4 (Pax-4)] were predicted between NaB + AR vs. AR, NaB + AR vs. C and AR vs. C groups.

GO and PANTHER pathway analyses. GO analysis was conducted to determine the enrichment of the differentially expressed mRNAs between the different groups in the categories of biological processes. The top 10 significantly enriched GO terms between each pair of groups are presented in Fig. 8.

Pathway analysis was conducted to determine the biological pathways represented by the significantly differentially expressed mRNAs between the groups. The top 10 significantly enriched PANTHER pathway terms among the three groups are presented in Fig. 9. Based on these results, inflammation mediated by chemokine and cytokine signaling pathways and T-cell activation were suggested to be involved in AR pathogenesis.

Discussion

HDAC inhibitors can be divided into four categories, including hydroxamates, cyclic peptides, aliphatic acids and benzamides. Suberoylanilide hydroxamic acid (SAHA) has been approved by the US Food and Drug Administration for the treatment of cutaneous T-cell lymphoma (7). HDAC inhibitors have also been demonstrated to exhibit therapeutic effects in cancer, arthritis, hearing loss and asthma (23-27). Since epigenetic modifications, which contribute to disease development, are neither permanent nor transient, identifying disease-specific epigenetic alterations may help identify novel therapeutic interventions (28,29). NaB can be dissolved without dimethyl sulfoxide, which is a solvent that also inhibits HDAC, thus enabling the sole evaluation of NaB and its effects (30,31). The results of our previous study demonstrated that NaB exhibited a therapeutic effect in an OVA-induced murine AR model when administered intranasally (16). The present study demonstrated that oral NaB prophylactically reduced AR-related behavioral scores, improved nasal mucosal morphology and restored Th1/Th2/Th17 and Treg cell balance. Thus, NaB may exhibit a preventive effect on AR. The present study demonstrated that NaB increased H3-AcK9 expression and

| Table I. LncRNA (NONMMUT057309) and lncRNA (NONMMUT016103) expression trends among the C, AR, and NaB + AR groups. |
|---------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| C vs. AR | NaB + AR vs. AR | NaB + AR vs. C | p-value | P-value | P-value | Regulation |
|---------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| LncRNA chr | Gene Id | P-value | Fc | Regulation | P-value | Fc | Regulation | P-value | Fc | Regulation |
|---------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| NONMMUT016103 | NONMMUG010108.2 | 0.04 | 3.8545 | Up | 0.04 | 11.5375 | down | 0.01 | 0.04 | 12.4342 | Up |
| NONMMUT057309 | NONMMUG035579.2 | 0.03 | 2.4944 | Up | 0.01 | 4.9847 | down | 0.01 | 4.9847 | down | 0.01 | 4.9847 | down |

LncRNA, long non-coding RNA; chr, chromosome; |Fc|, absolute fold-change; C, control group; AR, rats treated with ovalbumin; NaB + AR, rats treated with ovalbumin and sodium butyrate.
decreased of HDAC1 and HDAC8 expression in mice with AR. Accordingly, high HDAC1 and HDAC8 expression levels have been observed in OVA-sensitized asthmatic mice (11). In addition, an HDAC8-specific inhibitor was demonstrated to reduce the eosinophil-mediated inflammatory response and reduce the sensitivity of the airway in an asthma model (34). Therefore, blocking HDAC activity may be a novel therapeutic target in patients with AR (7).

LncRNA regulates gene expression at the transcriptional, RNA processing and translational levels (35). In addition, LncRNA dysregulation underlies certain human diseases caused by chromosome deletion and translocation (36). LncRNAs are also involved in the development, plasticity, disease and evolution of the mammalian nervous system (37). LncRNAs can promote the differentiation and activation of dendritic cells, B lymphocytes and T

Table II. co-expressed mRNAs encoding immunoglobulins (n=33) among the C, AR, and NaB + AR groups.

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MGI is the international database resource for the laboratory mouse, providing integrated genetic, genomic, and biological data to facilitate the study of human health and disease. C, control group; AR, rats treated with ovalbumin; NaB + AR, rats treated with both ovalbumin and sodium butyrate.
lymphocytes (38). Accordingly, a number of specific lncRNAs have been identified in Th1 and Th2 cells (39-42) and in the nasal mucosa of mice with AR (3). The results of the present study confirmed the differential expression of lncRNAs and mRNAs in the nasal mucosa of AR mice treated with NaB. A degree is the simplest and most important measure of gene centrality within a network that determines the relative importance of that gene (43). LncRNA (NONMMUT057309), which is 306 nt long and located on chromosome 6, is mainly expressed in the hippocampus, liver, and lung (44); however, to the best of our knowledge, no published studies on the mechanism associated with its function are currently available.

NaB, a pan-HDAC inhibitor, not only decreased the expression of HDAC1 and HDAC8, but also downregulated the expression of lncRNA (NONMMUT057309) and altered the expression of immunoglobulins in the present study. Previous studies have demonstrated that HDAC and Inc-H19 could be

Figure 6. Comparison of lncRNA and mRNA fold-change measured by microarray and RT-qPCR. RT-qPCR validation results among the three groups were consistent with the microarray analysis results, with the exception of the lncRNA (NONMMUT016103) locus. Microarray results are represented by blue bars; RT-qPCR results are represented by red bars. *P<0.05, **P<0.01. LncRNA, long non-coding RNA; RT-qPCR, reverse transcription-quantitative PCR; C, control group; AR, rats treated with ovalbumin; NaB + AR, rats treated with sodium butyrate and ovalbumin.

Figure 7. LncRNA (NONMMUT057309) target gene prediction. Oct-1, Evi-1, and Pax-4 were predicted between NaB+AR vs. AR, NaB + AR vs. C and AR vs. C groups of lncRNA (NONMMUT057309). LncRNA, long non-coding RNA; Oct-1, octamer-binding transcription factor 1; Evi-1, ecotropic viral integration site 1; Pax-4, paired box 4.
bidirectionally regulated (45), and the pan-HDAC inhibitors panobinostat and SAHA upregulated lnc-GAS5 expression in non-small cell lung cancer (46). Thus, it may be speculated that NaB could influence the nasal mucosa allergic response through lncRNA (NONMMUT057309) expression. LncRNA (NONMMUT057309) may act on its target genes to regulate the expression of immunoglobulin in the nasal mucosa to prevent AR.

Three target genes (Oct-1, Evi-1 and Pax-4) were predicted for lncRNA (NONMMUT057309). Oct-1 can co-regulate Th2 cytokine gene expression through Rhs-related transmembrane protein (47) and regulate the expression of IL-17 (48). Evi-1 participates in the pathogenesis of colorectal cancer through TGF-β signaling (49). The duodenum of functional dyspepsia rats displayed increased expressions of PAX4 (50).

Among the top 10 significantly enriched GO terms in C vs. AR groups, ‘extracellular matrix organization’ has been determined to exert effects on airway epithelial cells and fibroblast structure (51). The regulation of the immune system in early life by the microbiota may be associated with allergy development (52). The pathology of bronchial asthma demonstrates a multicellular process (53). AR rats exhibit microvascular remodeling of the nasal mucosa (54). In the top 10 significantly enriched GO terms in NaB + AR vs. AR groups, salmon cartilage proteoglycan attenuates allergic responses in mice (55). Inhibiting platelet activating factor can treat AR (56). Among top 10 significantly enriched GO terms in NaB+AR vs. C groups, immunoglobulin E (Igε) receptor on lymphocyte γ chain can mediate the receptor activator for NF-κB ligand, which is the primary cytokine required for osteoclastogenesis (57). ROS likely originates from inflammatory cells (eosinophils, neutrophils and macrophages), and their deleterious activity can result in oxidative DNA damage (58).

Maternal exposure to any type of stressor is associated with an increased risk of an atopic offspring (59). There are important connections between hemopoiesis and allergy/asthma (60). Immunotherapy decreases antigen-induced eosinophil cell migration into the nasal cavity (61). In patients with asthma, serum endotoxin concentrations significantly correlate with sputum chemokine motif ligand 2 concentrations (62).

The present study also determined the top 10 PANTHER pathways represented by the differentially expressed genes. ‘T-cell activation’, ‘B cell activation’, ‘Interleukin signaling
pathway’, ‘Inflammation mediated by chemokine and cytokine signaling pathway’ and ‘Histamine H2 receptor mediated signaling pathway’ participate in allergic inflammation (4,63‑64). ‘Apoptosis signaling pathway’ (65) and ‘Toll receptor signaling pathway’ (66) are also involved in the pathology of AR. The expression of endotherin 2 is increased in cigarette‑exposed asthmatic mice (67). Heme oxygenase‑1 protects airway epithelium against apoptosis by targeting the proinflammatory NLRP3‑RXR axis in asthma (68). Fibroblast‑specific integrin‑αV differentially regulates type 17 and type 2 driven inflammation and fibrosis (69). The p38 MAP‑kinase pathway is involved in the production of chloride voltage‑gated channel 3 in nasal epithelial AR cells induced by IL‑4 (70). The Wnt signaling pathway has also been demonstrated to be differentially regulated in patients with AR (71). TGF‑β/Smad signaling is involved in allergic diseases (72‑74). At present, to the best of our knowledge, no reports are available on the gonadotropin‑releasing hormone receptor, succinate to proportionate conversion or angiotensin H‑stimulated signaling through G proteins and β‑arrestin involvement in allergic inflammation pathogenesis, which is worth further study.

Together, previous findings along with the results of the present study may provide new options for the treatment of AR. However, in the present study, the gene sample was small, and further in vitro experiments are needed to further verify the role of lncRNA (NONMMUT057309), as well as the target genes (Oct‑1, Evi‑1, Pax‑4) and signaling pathways, in the prevention of AR in the nasal mucosa of NaB‑treated mice.

Acknowledgments
Not applicable.

Funding
This study was supported by the National Natural Science Foundation of China (grant nos. 81670925 and 81271069), Shaanxi Health Research Fund (grant no. 2018D006), Xi’an Health and Family Planning Commission Fund (grant no. J201902034) and Shaanxi Natural Science Foundation (grant no. 2019JQ‑434).

Availability of data and materials
The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.
Authors’ contributions

JW produced the animal model and was a major contributor in writing the manuscript. CM analyzed the gene data. SF performed the histological examination and western blotting. FC and JQ helped with the design, implementation, and revision of important contents of the experiments. The corresponding authors contributed equally to this work. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All animal experiments were conducted in accordance with the National Institutes of Health guidelines and approved by the Committee on Animal Research of the Air Force Military Medical University.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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