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The Role of IL-17 in a Lipopolysaccharide-Induced Rhinitis Model

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Purpose: Lipopolysaccharide (LPS) is a cell wall component of Gram-negative bacteria and important for pro-inflammatory mediators. This study aimed to establish a rhinitis model using ovalbumin (OVA) and LPS in order to evaluate the role of interleukin (IL)-17 in the pathogenesis of an LPS-induced non-eosionophilic rhinitis model. **Methods:** Mice were divided into 4 groups and each group consisted of 10 mice (negative control group, allergic rhinitis model group, 1-μg LPS treatment group, and 10-μg LPS treatment group). BALB/c mice were sensitized with OVA and 1 or 10 μg of LPS, and challenged intranasally with OVA. Multiple parameters of rhinitis were also evaluated to establish the LPS-induced rhinitis model. IL-17 knockout mice were used to check if the LPS-induced rhinitis model were dependent on IL-17. Eosinophil and neutrophil infiltration, and mRNA and protein expression profiles of cytokine in nasal mucosa or spleen cell culture were evaluated using molecular, biochemical, histopathological, and immunohistological methods. **Results:** In the LPS-induced rhinitis model, neutrophil infiltration increased in the nasal mucosa, and systemic and nasal IL-17 and interferon-gamma (IFN-γ) levels also increased as compared with the OVA-induced allergic rhinitis model. These findings were LPS-dose-dependent. In IL-17 knockout mice, those phenotypes (neutrophil infiltration, IL-17, and IFN-γ) were reversed, showing IL-17 dependency of LPS-induced rhinitis. The expression of vascular endothelial growth factor (VEGF), an important mediator for inflammation and angiogenesis, decreased in IL-17 knockout mice, showing the relationship between IL-17 and VEGF. **Conclusions:** This study established an LPS-induced rhinitis model dependent on IL-17, characterized by neutrophil infiltration and increased expression of IL-17.

Key Words: Rhinitis; lipopolysaccharide; interleukin-17; vascular endothelial growth factor

INTRODUCTION

Allergic diseases, such as allergic rhinitis, are characterized by increased eosinophil infiltration and degranulation in the target tissue with eosinophils playing an important role in T-helper type 2 (Th2)-mediated allergic disease. Recent studies have shown increasing evidence of inflammatory mechanisms other than eosinophilic inflammation to be involved in allergic airway diseases. It has been reported that neutrophils have an important role in severe forms of asthma.[1-3] Some studies have shown that patients with allergic rhinitis and allergic asthma share the same pattern of eosinophil and that neutrophil degranulation[4] and neutrophils are important for late-phase allergic inflammation.[5] In addition, since allergic rhinitis is on a spectrum of diseases, neutrophils may be an important effector cell in the pathogenesis of allergic rhinitis. However, the role of neutrophils in allergic rhinitis is still under debate and much needs to be clarified.

Lipopolysaccharide (LPS) is a Toll-like receptor 4 agonist and the major component of the bacterial cell wall of Gram-negative bacteria. It contributes greatly to the structural integrity of the bacteria. LPS is also an endotoxin inducing strong immune responses from normal animals and recruits neutrophils to the tissue.[6,7] In a recent paper, it has been reported that high levels of LPS induces T-helper type 1 (Th1) and T-helper type 17 (Th17) responses in the lower airways and up-regulates *in vivo* production of vascular endothelial growth factor (VEGF).[8] VEGF increases vascular permeability and plays an important role in angiogenesis and inflammation of allergic disease.[8] VEGF could be an important mediator in the pathogenesis of allergic rhinitis.

The present study aimed to establish a neutrophil dominant allergic rhinitis model using ovalbumin (OVA) and LPS and to elucidate the underlying mechanism of interleukin (IL)-17 in the pathogenesis of an LPS-induced neutrophil-dominant al-

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lergic rhinitis model. Since this model has a phenotype lying between allergic and nonallergic rhinitis, researchers of this study believe that application of this model can be extended from allergic rhinitis to nonallergic rhinitis through development of this model.

MATERIALS AND METHODS

Reagents

OVA and LPS (from *Escherichia coli* 0111:B4 by phenol extraction) were purchased from Sigma Aldrich Chemicals (St. Louis, MO, USA).

Animals

Four-week-old female BALB/c mice were obtained from Korea Biolink Co. (Eumsung, Korea), and IL-17A knockout mice were given generously from the laboratory of Prof. Chae-Seo Rhee. All animal experiments conducted in this study followed the guidelines and ethics of the Institutional Animal Care at the Clinical Research Institute of Dankook University Hospital.

Murine LPS-induced rhinitis model

The mice were divided into 4 groups and each group consisted of 10 mice (group A: negative control group, group B: allergic rhinitis model group, group C: 1-μg LPS treatment group, and group D: 10-μg LPS treatment group; Fig. 1A). The procedures for OVA sensitization and LPS treatment are summarized in Fig. 1A. Briefly, BALB/c mice were sensitized with a 25-μg OVA intraperitoneal injection (grade V; Sigma, St. Louis, MO, USA) and 1 μg of LPS (group C) and 10 μg of LPS (group D) on days 0, 1, 2, 7, and 14. In the allergic rhinitis model (group B), mice were sensitized with a 25-μg OVA intraperitoneal injection and 1 mg of aluminum hydroxide gel each on days 0, 7, and 14. After sensitization, mice were locally challenged with 100 μg of OVA into their nostrils from days 14 to 21.

Symptom score and tissue preparation

Five minutes after the final OVA challenge on day 22, a blinded observer recorded the frequencies of sneezing and nasal rubbing at 15-minute intervals. The mice were then euthanized 24 hours after the last OVA challenge. After perfusion with 4% paraformaldehyde, the heads of 5 mice from each group were removed *en bloc* and then fixed in 4% paraformaldehyde. Nasal mucosa was obtained from the 5 other mice for a reverse transcription-polymerase chain reaction (RT-PCR) and Western blot analysis, and then was immediately immersed in liquid nitrogen and stored at -70°C until use.

Eosinophil and neutrophil counts in the nasal septal mucosa

For the evaluation of nasal histology, nasal tissues were decalcified, embedded in paraffin, and sectioned coronally (4-μm thick) approximately 5 mm from the nasal vestibule. Each section was stained by Sirius red staining as previously described. The number of eosinophils was counted on both sides of the septal mucosa; each section of the neutrophil count was stained by immunohistochemistry using an anti-neutrophil antibody (NIMP-R14; Abcam, Cambridge, UK). The number of neutrophils in the submucosal area of the entire nasal septum was counted under a light microscope (×400 magnification).

Real-time RT-PCR in the nasal mucosa

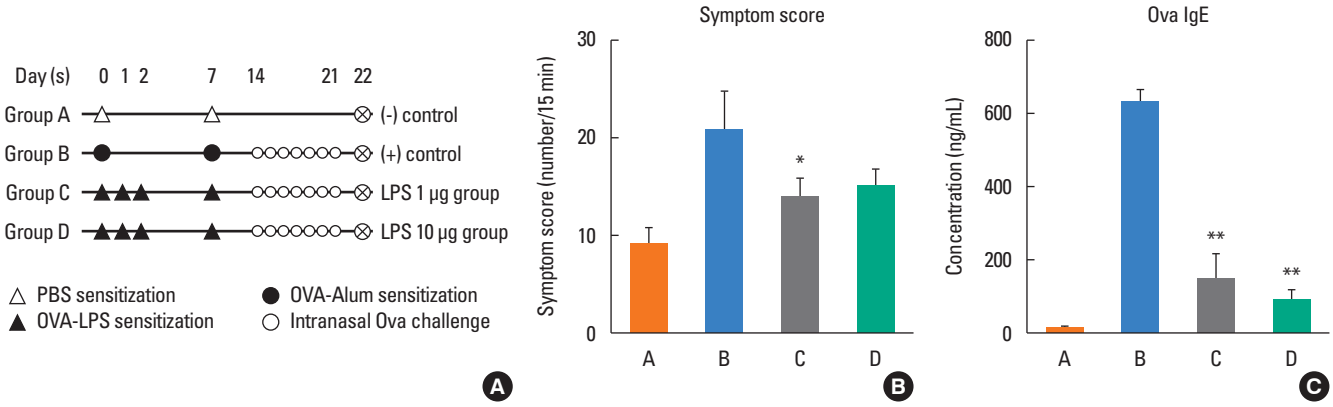
Total RNA was prepared from the nasal mucosa with a TriZol reagent (Invitrogen, Carlsbad, CA, USA). Complementary DNA (cDNA) was synthesized using Superscript reverse transcriptase (Invitrogen) and oligo(dT) primers (Fermentas, Burlington, Canada). For the analysis of IL-4 (Mm00445258_g1), IL-5 (Mm 00439646_m1), IL-6 (Mm00446190_m1), IFN-γ (Mm99999071_m1), IL-17 (Mm0439618_m1), and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (Mm03302249_g1), Pre-Developed Assay Reagent (PDAR) kits of primers and probes were purchased from Applied Biosystems (Foster City, CA, USA). Amplification of cDNA was carried out in MicroAmp optical 96-well reaction plates (Applied Biosystems, Foster City, CA, USA). The reaction was performed using a StepOnePlus™ Real-Time PCR System (Applied Biosystems). The average transcript levels of the genes were then normalized to GAPDH.

Measurement of cytokines (IL-4, IL-5, IL-6, IL-17, and IFN-γ) in the spleen cell culture

Cytokine enzyme-linked immunosorbent assay (ELISA) was performed as previously described.[9] In brief, spleen single-cell suspensions were plated on 24-well tissue culture plates at a final concentration of 3×10^6 cells/mL using complete media (RPMI-1640; Irvine Scientific, Irvine, CA, USA) supplemented with 10% heat-inactivated fetal bovine serum (FCS), 2 mM L-glutamine, 100 U/mL penicillin, and 100 μg/mL streptomycin. The cells were incubated in a CO_2 incubator at 37°C for 72 hours. They were then stimulated with OVA for 72 hours and stored at -70°C until cytokines were measured. Cytokines were assayed in a culture supernatant using a sandwich ELISA kit (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions. After measuring the optical density (OD) at 450 nm, the concentrations of IL-4, IL-5, IL-6, IL-17, and IFN-γ were determined by interpolation from a standard curve; all data are expressed as nanograms per milliliter.

Serum levels of OVA-specific immunoglobulin E (IgE)

A solid-phase ELISA measured serum levels of OVA-specific IgE. Serum samples collected from mice at the time of death were serially diluted and added to 96-well plates coated with purified anti-mouse IgE mAb (clone R35-72; BD Pharmingen, San Jose, CA, USA). To detect OVA-specific IgE, biotin-labeled OVA was added, followed by horseradish peroxidase (HRP)-labeled anti-biotin (Vector Laboratories, Burlingame, CA, USA).



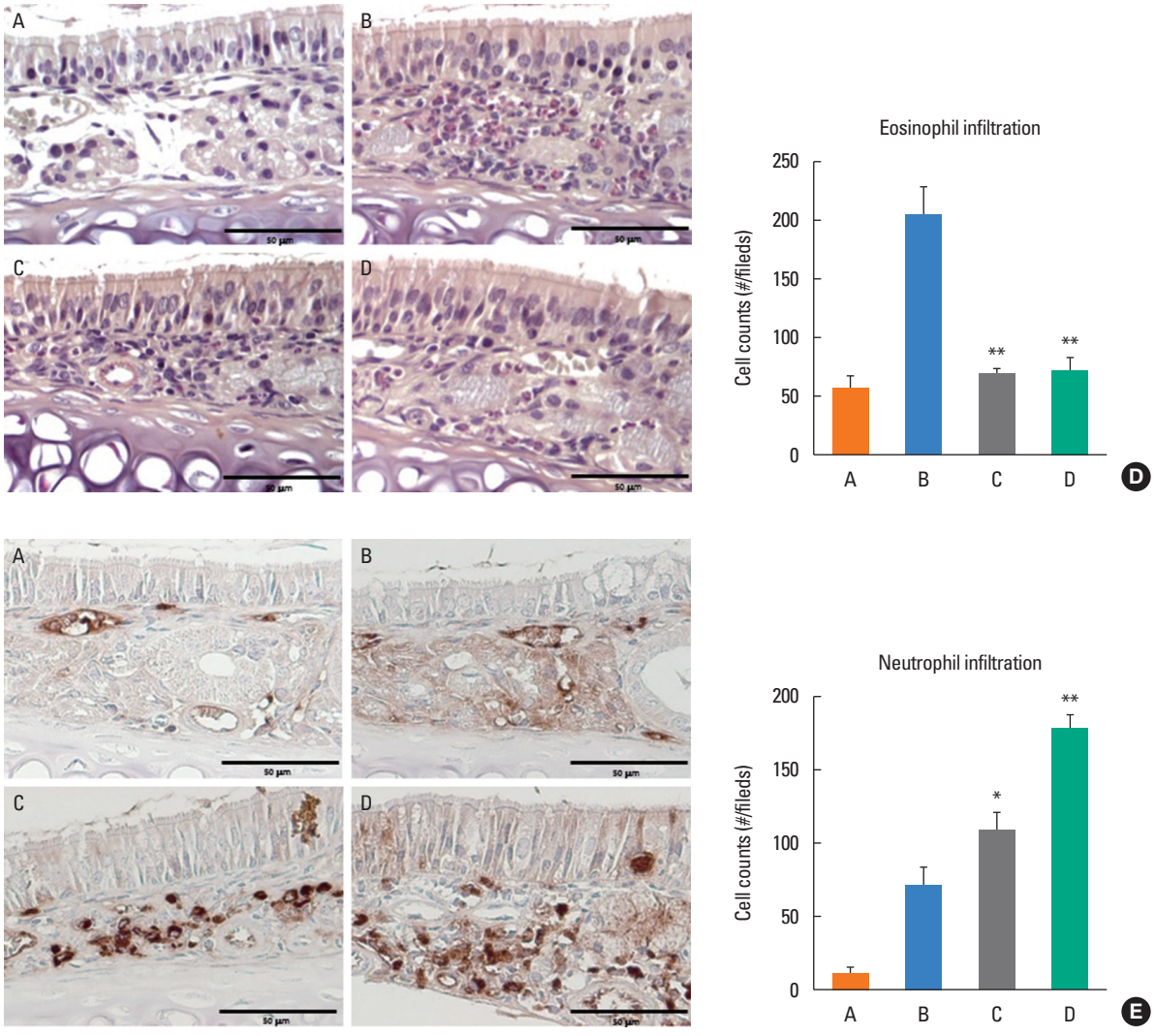


Fig. 1. (A) Experimental protocol for the LPS-induced rhinitis model. BALB/c mice were sensitized with OVA and 1 μg (group C) or 10 μg (group D) of LPS on days 0, 1, 2, and 7. Classical OVA with aluminum hydroxide gel sensitization was used in group B. All groups except group A received intranasal OVA from days 14 to 21. (B) Symptom score of sneezing and itching. (C) OVA-specific IgE. (D) Eosinophil infiltration in nasal septal mucosa (×200 magnification, Sirius red staining). Eosinophil count was not significantly different in LPS-treated groups C and D as compared to the control group (group A, $P>0.05$), while it was markedly increased in group B as compared to the control group ($P<0.01$). (E) Neutrophil infiltration in the nasal septal mucosa (×200 magnification, immunohistochemical staining for anti-NIMP-R14 antibody). Neutrophil infiltration was markedly increased in LPS-treated groups C and D ($P<0.05$ and $P<0.01$, respectively). The *P* values were compared with group B, and those less than 0.05 and 0.01 are represented by * and **. LPS, lipopolysaccharide; OVA, ovalbumin; IgE, Immunoglobulin E.

The reactions were developed using 3,3´,5,5´-tetramethylbenzidine (Moss Inc., Belfast, ME, USA) and terminated by adding 2 N H_2SO_4. The OD was recorded by a luminometer (iEMS Reader; Labsystems, Helsinki, Finland) set at 450 nm. The endpoint titers of OVA-specific IgE were expressed as the reciprocal $\log_2$ of the last dilution of a sample that resulted in an OD value that was 0.1 higher than background.

Immunohistochemistry for VEGF and neutrophil

Immunohistochemistry was undertaken using the following antibodies; anti-neutrophil antibody (NIMP-R14; Abcam, Cambridge, UK) and anti-VEGF (Abcam, Cambridge, UK) with activity-based costing (ABC) methods.

Statistical analysis

The Mann-Whitney test was used to analyze differences between the 2 groups. All parametric results are expressed as a mean±standard deviation (SD). A statistical significance was assumed as $P<0.05$ for all parameters. The P values of less than 0.05, 0.01, and 0.001 are represented by *, †, and ‡ to indicate statistical significance.

RESULTS

LPS- induced rhinitis model

To establish an LPS-induced rhinitis model, LPS, a cell wall component of bacteria, was administered to groups C (1 μg) and D (10 μg) with OVA. An LPS-induced rhinitis model was compared with a negative control (group A) and conventional eosinophilic allergic rhinitis model (group B). The allergic symptom score increased significantly in group B (20.8±3.50 counts, $P<0.01$), but only increased slightly in groups C and D (13.8±3.7 and 15.0±1.5 counts, respectively) as compared with group A (8.7±1.7 counts). OVA-specific IgE was slightly increased in the LPS- treated group (groups C and D, 144.9±75.1 ng/mL, 87.0±31.6 ng/mL, respectively) as compared with group A (7.0±3.9 ng/mL), but was much lower when compared with group B (629.3±41.3, Fig. 1C). Eosinophil infiltration was increased significantly in group B (202.3±25.6/HPF, $P<0.01$) as compared with group A (59.1±9.7/HPF). However, in the LPS-treated group (groups C and D), eosinophil infiltration did not increase significantly (68.7±6.4/HPF and 74.5±10.1/HPF, respectively, both $P<0.05$, Fig. 1D) as compared with group A. In contrast, neutrophil infiltration increased significantly in the LPS-treated group (109.8±11.9/HPF and 179.9±9.5/HPF in groups C and D, respectively) in a dose-dependent manner as compared with group A and B (11.8±5.1/HPF and 72.9±12.8/HPF, respectively), showing LPS dependenc (Fig. 1E).

Local and systemic cytokine profiles were also measured, showing similar trends. Nasal and systemic Th2 cytokines, IL-4, and IL-5 showed minimal increase without any statistical significance in the LPS-treated groups (groups C and D) as compared with group A (both $P<0.05$, Fig. 2A and B). Interferon (IFN)-γ increased significantly in the high-dose LPS-treated group, both in the nasal mucosa and systemically (Fig. 2A and B, $P<0.01$ and $P<0.05$, respectively). IL-17 increased significantly in both the low-dose and high-dose LPS-treated groups, not only locally but also systemically (Fig. 2A and B, all $P<0.01$). IL-6 showed a significant increase in the nasal mucosa ($P<0.05$), but decreased in the splenocyte culture ($P<0.05$). Since group D (LPS 10 μg) showed higher neutrophil infiltration and higher Th1 and Th17 cytokine increase than group C (LPS 1 μg), 10 μg of LPS was used in the following experiment.

IL-17 dependence of the LPS-induced rhinitis model

Since IL-17 showed a dose-dependent increase in the LPS-induced rhinitis model, IL-17A knockout mice were used to evaluate if IL-17A played a key role in the LPS-induced rhinitis model. Both wild type and IL-17A knockout mice were treated with 10 μg of LPS and OVA, using the same protocol of group D in the previous experiment (Fig. 3A). The nasal symptom score was significantly lower in IL-17A knockout mice when compared with that of wild type mice (wild type: 62.3±13.0 counts; knockout: 37.8±10.8 counts; $P<0.05$). However, OVA-specific IgE did not show any differences between the 2 groups ($P>0.05$). In terms of eosinophil and neutrophil infiltration, IL-17A knockout did not influence eosinophil infiltration (wild type: 15.5±5.3; knockout: 17.4±6.7; $P>0.05$) (Fig. 3D). However, neutrophil infiltration significantly decreased in the nasal mucosa of IL-17A knockout mice (wild type: 115.2±24.3; knockout: 73.9±4.9; $P<0.05$) (Fig. 3E), suggesting the role of IL-17A in neutrophilic infiltration.

Then, local and systemic cytokine expressions were evaluated. IL-5 and IL-6 mRNA expressions, but not IL-4 and IFN-γ expressions, decreased significantly in the nasal mucosa of IL-17A knockout mice (both $P<0.05$, Fig. 4A). Systemic cytokines obtained via splenocyte culture showed similar results. IL-4, IL-6, and IFN-γ in spleen culture decreased significantly in IL-17A knockout mice ($P<0.05$). IL-5 increased slightly without statistical significance ($P>0.05$, Fig. 4B). Since it has been reported that IL-17 increase production of VEGF in fibroblast[10,11] and VEGF is an important mediator of allergic inflammation,[8] the expression of VEGF in the nasal mucosa was evaluated. The expression level of VEGF was reduced in IL-17A knockout mice (Fig. 4C), suggesting a mediating role of VEGF in nasal inflammation.

DISCUSSION

The present study established a neutrophil-dominant rhinitis model induced by LPS and clarified that IL-17 and VEGF signaling is important for neutrophil infiltration in the nasal mucosa in an LPS- induced rhinitis.

Most murine rhinitis models have been Th2-driven eosino-

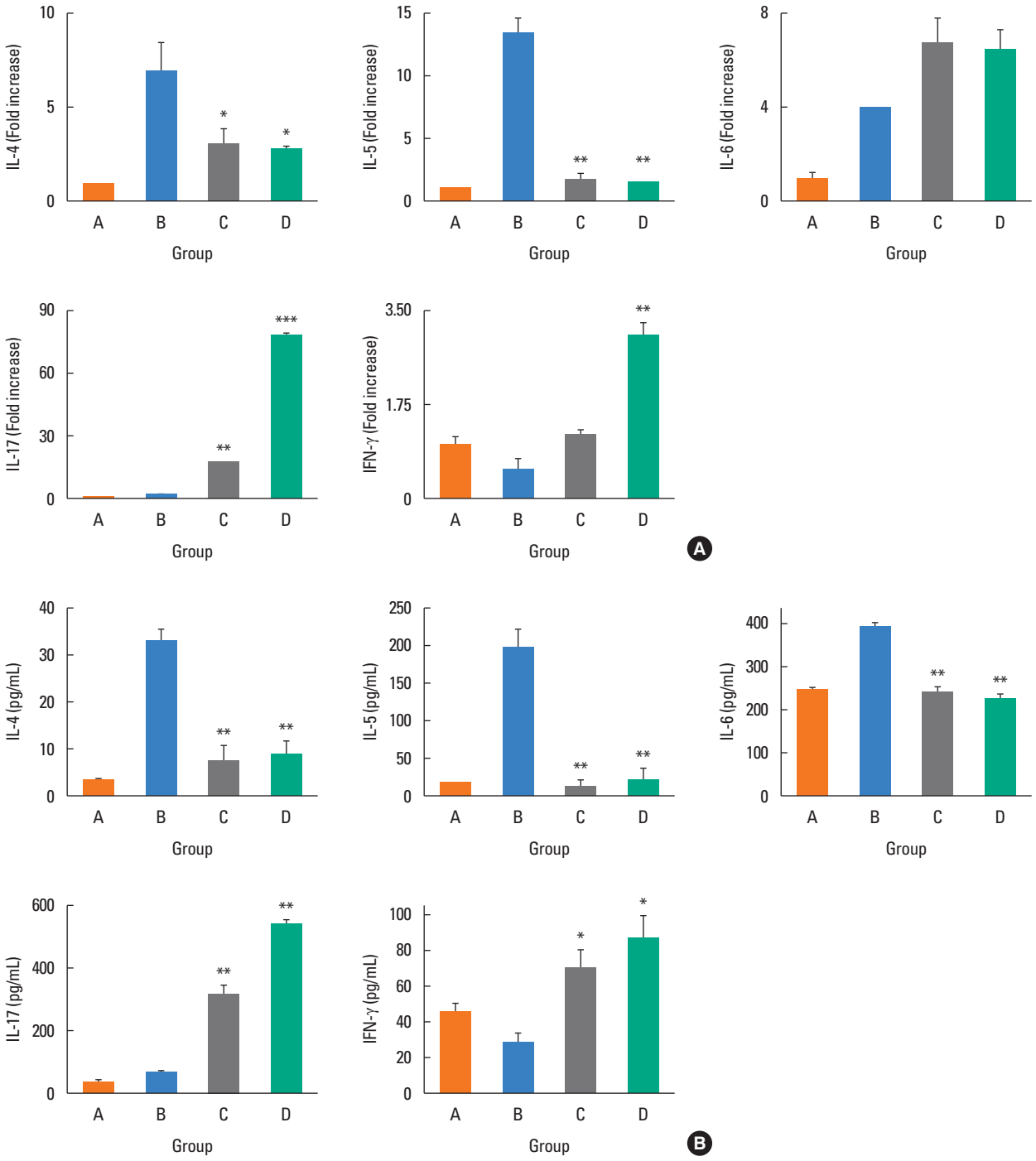


Fig. 2. Nasal and systemic cytokines from real-time PCR and splenocyte culture for 3 days. (A) mRNA expression levels in the nasal mucosa. Transcriptional activity of IL-17 and IFN-γ was markedly increased in groups C and D. (B) Cytokine levels of IL-17 and IFN-γ were significantly increased in groups C and D. The *P* values were compared with group B and those less than 0.05, 0.01, and 0.001 are represented by *, **, and ***. PCR, polymerase chain reaction; IL, interleukin; IFN, interferon.

phil-dominant models.[12-14] Few studies have previously shown Th1-or Th17-dominant rhinitis models. OVA and aluminum hydroxide gel the most common Th2 driving allergen and adjuvant. It has frequently been used in studies on allergic rhinitis; other allergens, such as house dust mites[15] or pollen,[16,17] have also been used for the allergic rhinitis model. However, rhinitis is a spectrum of diseases with multifactorial etiology and several studies have shown that Th1 or Th17 responses are also important in the pathogenesis of rhinitis.[18,19] In addition, the mechanism of non-allergic rhinitis has not been clearly re-

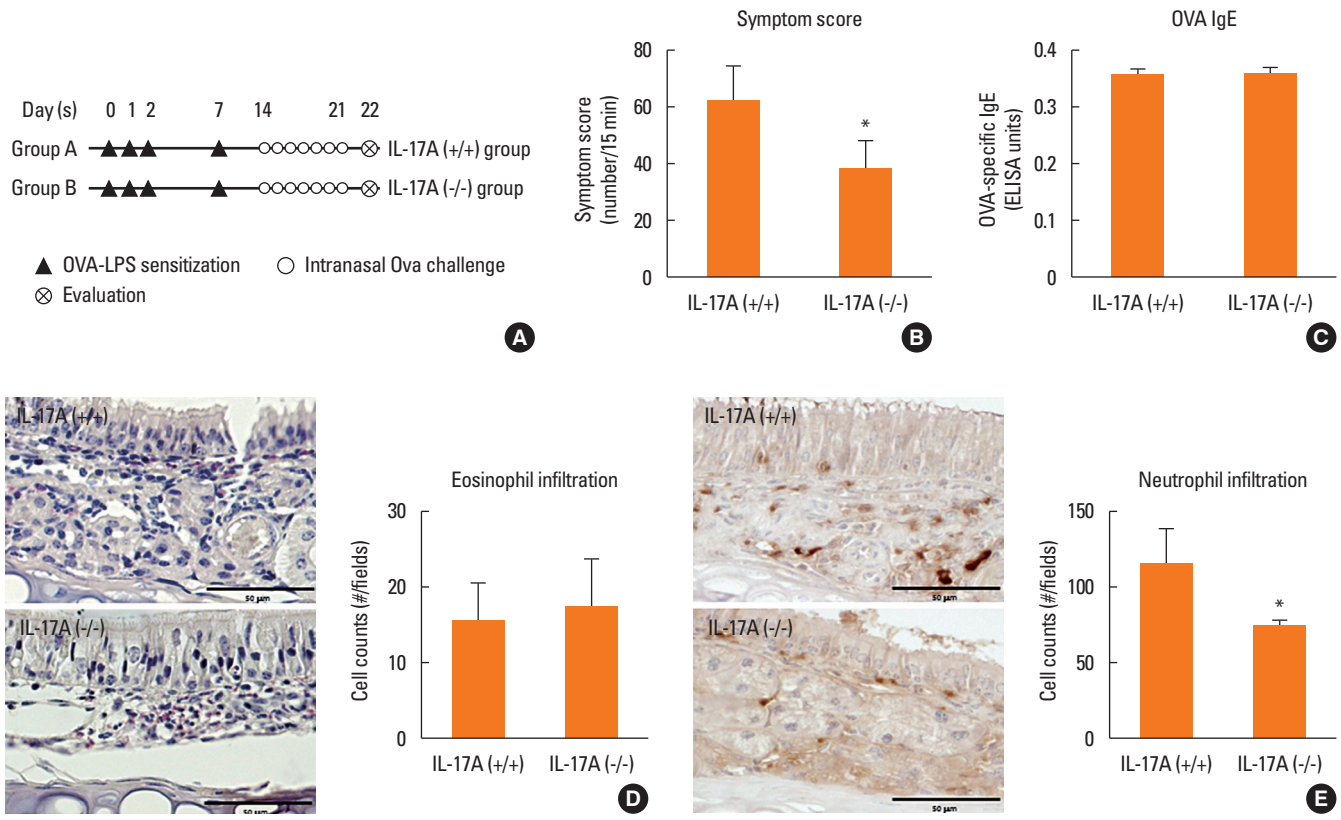


Fig. 3. (A) Experimental protocol for the LPS-induced rhinitis model in the IL-17A knockout and wildtype mice. The IL-17A knockout and wildtype BALB/c mice were sensitized with OVA and 10 μg (group B) of LPS on days 0, 1, 2, and 7. Both groups received intranasal OVA from days 14 to 21. (B) Symptom score of sneezing and itching. (C) OVA-specific IgE. (D) Eosinophil infiltration in nasal septal mucosa (×200 magnification, Sirius red staining). Eosinophil count was not significantly different between the IL-17A knockout and wildtype mice ($P>0.05$). (E) Neutrophil infiltration in the nasal septal mucosa (×200 magnification, immunohistochemical staining for anti-NIMP-R14 antibody). Neutrophil infiltration was markedly decreased in the IL-17A knockout mice as compared to the wildtype mice ($P<0.05$). The *P* values that were less than 0.05 are represented by * to indicate statistical significance (*$P<0.05$). LPS, lipopolysaccharide; IL, interleukin; OVA, ovalbumin; IgE, Immunoglobulin E.

vealed and much needs to be clarified. In that sense, our Th17-driven neutrophil-dominant rhinitis model can be used as a new methodology in revealing the mechanism of rhinitis, including allergic and non-allergic rhinitis.

In an LPS-induced rhinitis model, the symptom of sneezing and itching was relatively lower and the OVA specific IgE level was much lower when compared to those of conventional allergic rhinitis groups sensitized with OVA and aluminum hydroxide. LPS has been well known to induce Th1 response and to have anti-allergic effects in murine models of allergic asthma.[20] The decreased symptom score and OVA-specific IgE in an LPS-administered group can be explained by increased Th1 cytokine and decreased Th2 cytokine, which is consistent with our results. The interesting finding in the cytokine profile is that IL-17 increased in a dose-dependent manner of LPS. IL-17 is known to induce tissue neutrophilia.[6,7] Immunohistochemistry of nasal mucosa showed that neutrophil has also increased in a dose-dependent manner of LPS as nasal expression of IL-17 has increased accordingly. However, eosinophil infiltration in the nasal mucosa was not affected by administration of LPS. To evaluate IL-17 dependence of the LPS-induced rhinitis model, IL-17 knockout mice were used, which revealed that tissue neutrophilia was dependent on IL-17A. Cytokine analysis showed that IL-6 decreased significantly in IL-17A knockout mice. It has also been reported that IL-17 production is dependent on IL-6 produced by high-doses LPS, showing similar results with ours.[21] Kim *et al.*[21] showed that a Th17-immune response induced by high-dose LPS is abolished in IL-6 deficient mice, indicating that IL-6 is a key mediator in the development of the allergen-specific immune response.

VEGF is a key mediator of vascular angiogenesis and remodeling, and known to be induced by LPS.[21] The present study also revealed that IL-17 signaling is important for VEGF expression and that VEGF expression in nasal mucosa is decreased in IL-17 knockout mice. Some previous studies have shown that IL-17 enhances production of VEGF in a dose dependent manner,[10,11] suggesting the effect of IL-17 on angiogenesis and inflammation. It has also been reported that VEGF production in an ischemic state was reduced in IL-17 knockout mice, showing similar results with ours.[22]

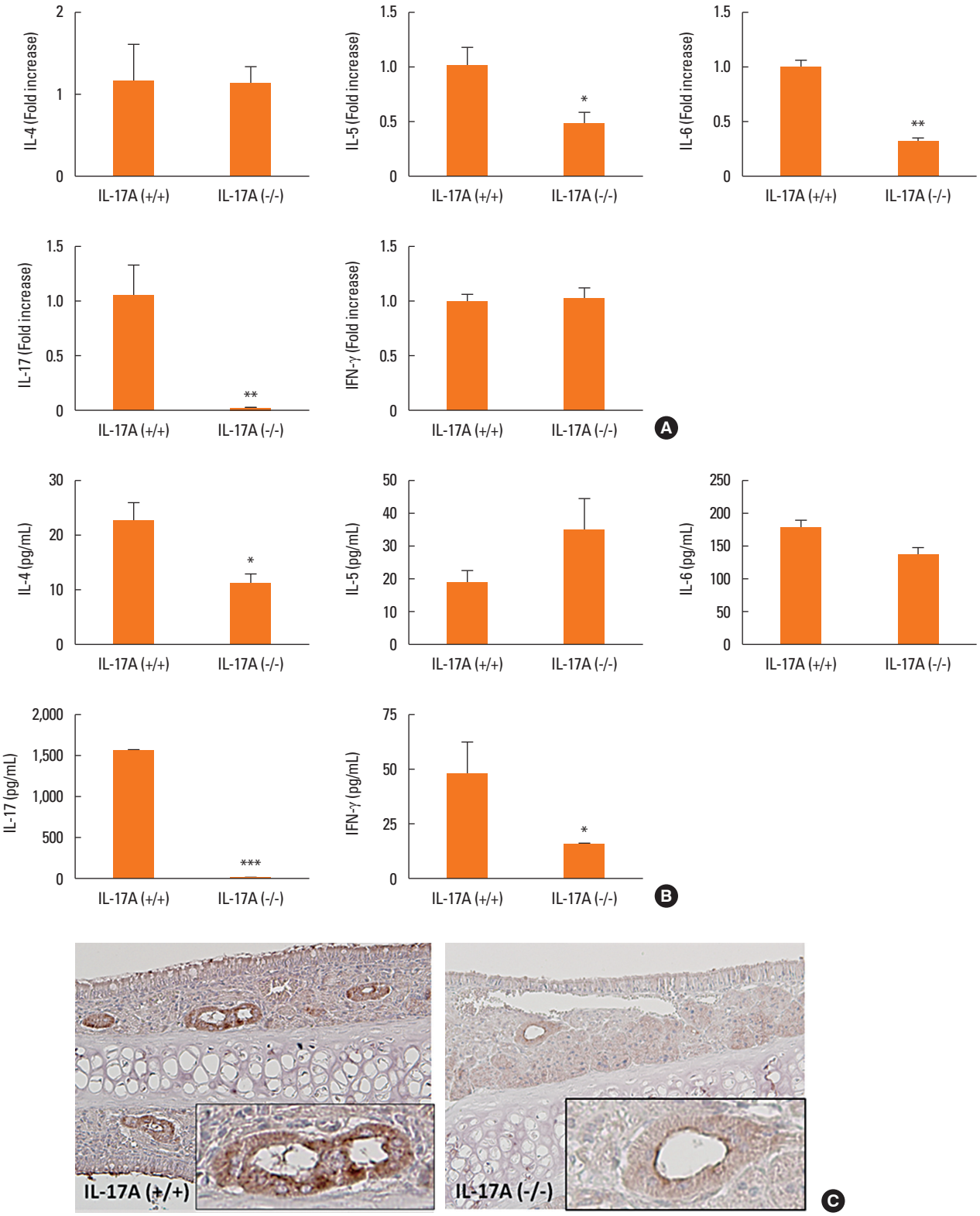


Fig. 4. (A) Nasal cytokine profiles in the IL-17A knockout mice. The mRNA expression levels in the nasal mucosa were measured by real-time PCR. The transcriptional activity of IL-17 was not detected, but those of IL-5 and IL-6 were decreased in the IL-17A knockout mice (both $P<0.05$). (B) Systemic cytokine from splenocyte culture. The levels of IL-17 and IFN-γ were significantly decreased in the IL-17A knockout mice ($P<0.001$ and $P<0.05$, respectively). (C) Immunohistochemical staining of VEGF. VEGF expression was markedly decreased in the IL-17A knockout mice. The *P* values that were less than 0.05, 0.01, and 0.001 are represented by *, **, and ***. IL, interleukin; PCR, polymerase chain reaction; IFN, interferon; VEGF, vascular endothelial growth factor.

In summary, a neutrophil dominant rhinitis model was established using LPS. This model will be capable of revealing the mechanism of various kinds of rhinitis. Neutrophil infiltration by this rhinitis model was dependent on IL-17 and VEGF interaction. Inhibition of VEGF signaling also reduced neutrophil infiltration and IL-17 production in the murine rhinitis model. This strategy will be used as a target therapy in rhinitis.

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