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Brief Communication

Allergic effects of Der p 38 and Der f 38: A Comparison

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Asthma is a chronic and allergic inflammation in the lung, mainly caused by house dust mites (HDM). Recent studies have reported Der p 38 and Der f 38 (*Dermatophagoides pteronyssinus* and *D. farinae*, respectively) as crucial allergens of HDMs. This study investigates the different allergic effects of Der p 38 and Der f 38 in an asthma-like mouse model. Lung infiltration of neutrophils was induced by intranasal administration of Der p 38 and Der f 38, with stronger infiltration being observed after exposure to Der p 38. Intranasal and intraperitoneal administration of Der p 38 induced the infiltration of neutrophils and eosinophils in the lung, which was similar to the effect subsequent to Der f 38 administration. Although the number of mast cells was increased, no significant difference was obtained between the effects of both allergens. In TLR4 knockout BALB/c mice, Der p 38 and Der f 38 had no effect on the infiltration of neutrophils, eosinophils, and mast cells. Additionally, allergenicity induced by Der p 38 and Der f 38 in the basophils of Der p38+/Der f 38+ asthmatic subjects was similar, although Der f 38 presented stronger allergenicity in basophils of Der p38+/Der f 38+ allergic patients than Der p 38. These findings contribute to understanding the role of similar allergen components derived from different species in the pathogenesis of allergic diseases.

Key Words: Asthma, Der p 38, Der f 38, Neutrophils

Asthma is a hyperreactive lung disease exhibiting leukocyte infiltration, mucus secretion, and bronchial constriction (Jo et al., 2018; Lee, 2022). House dust mites (HDMs) are classified into two main species: *Dermatophagoides pteronyssinus* (DP) and *D. farinae* (DF) (Jacquet, 2011; Miller, 2019). Recently, the terms Der p 38 and Der f 38 were approved by the World Health Organization/International Union of Immunological Societies Allergen Nomenclature Subcommittee (Sudharson et al., 2021). Der p 38 and Der f 38 are derived from DP and DF, respectively. Both allergens represent high allergenicity (more than 50%) in allergic subjects when using the skin prick test, indicating that both are important allergen components in allergy pathogenesis. This study investigates and compares the allergic effects induced by Der p 38 and Der f 38 to identify the different outcomes between the two main allergens.

The total RNA of live DP and DF were used to produce cDNA, which was then amplified by PCR and cloned into pETDuet-1 (Merck Millipore, Darmstadt, Germany). His-tagged Der p 38 and Der f 38 were purified using a nickel column (Merck Millipore).

Six-week-old female WT and TLR4 knockout (KO) BALB/c mice were divided into five experimental groups (n = 5 mice per group). Intranasal (IN) injections of Der p 38 or Der f 38 (25 μg/50 μL) were administered to the -/Derp p 38 and -/Der f 38 groups for one week without

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intraperitoneal (IP) injection. The Der p 38/Der p 38 and Der f 38/Der f 38 groups were IP administered with Der p 38 or Der f 38 (50 μg/50 μL), respectively, on days 1 and 14, followed by IN administration of Der p 38 or Der f 38

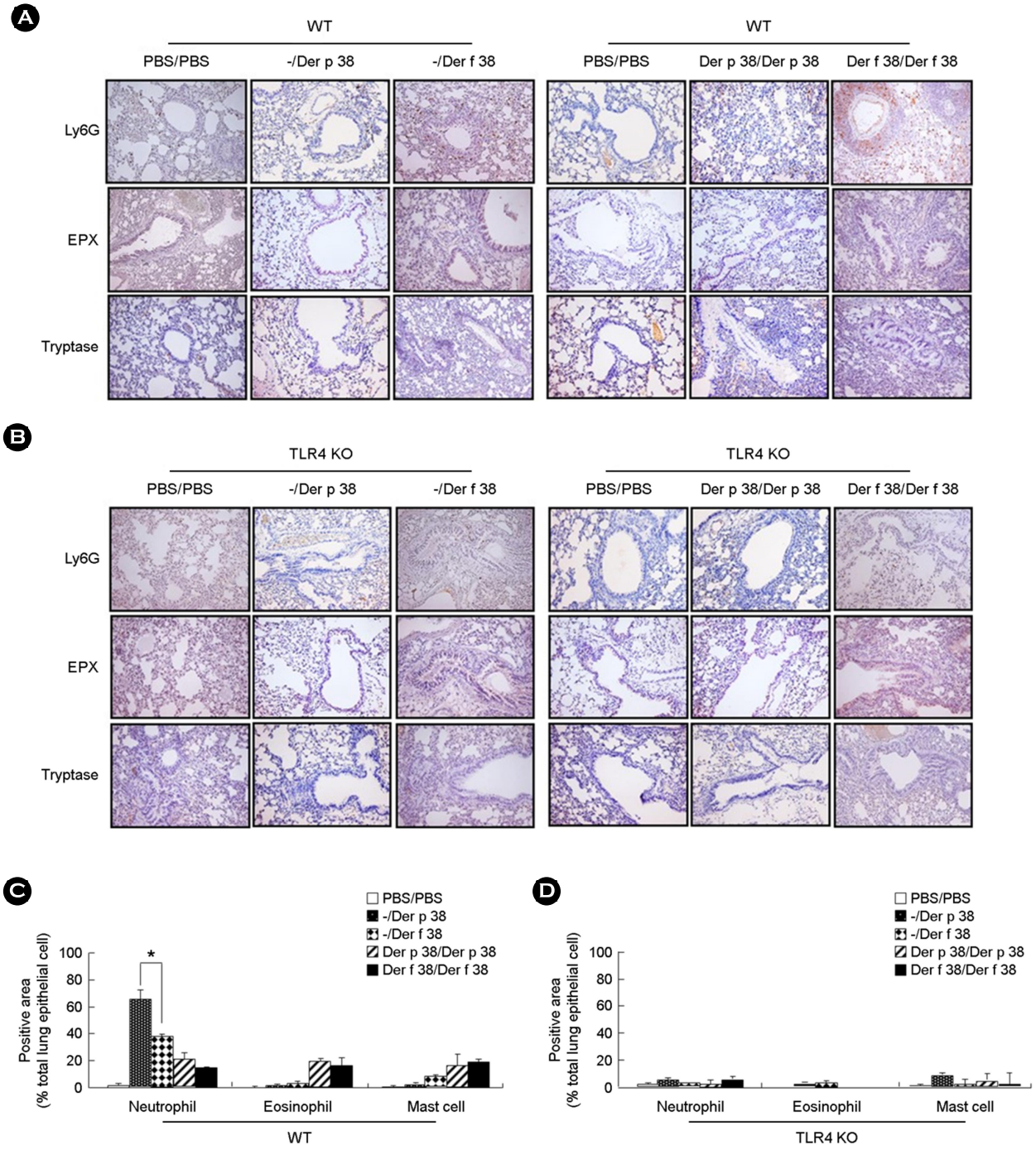

Fig. 1. Effects of Der p 38 and Der f 38 on inflammatory cells in wild type (WT) and TLR4 knockout (KO) BALB/c mice. Immunohistochemical staining was performed to detect neutrophils (Ly6G), eosinophils (eosinophil peroxidase; EPX), and mast cells (tryptase) in the lung, subsequent to Der p 38 or Der f 38 exposure in WT (A) and TLR4 KO (B) mice. The samples were examined under light microscopy (magnification, ×200). For histological evaluation of mouse lung tissues, increased numbers of neutrophils, eosinophils, and mast cells were calculated as the area of positive cells to the total cell area in the lung of WT (C) and TLR4 KO mice (D). *$P < 0.05$ indicates a significant difference between the Der p 38 and Der f 38 stimulated groups.

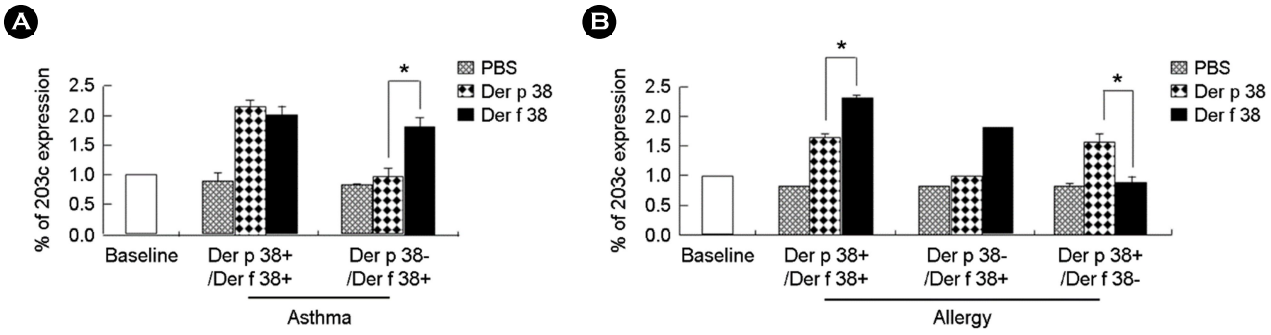

Fig. 2. Effect of Der p 38 and Der f 38 on basophil activation in allergic subjects. Granulocytes were isolated from asthma [Der p 38+/Der f 38+ (n = 3) and Der p 38-/Der f 38+ (n = 2)] (A) and allergic disease including allergic rhinitis and atopic dermatitis [Der p 38+/Der f 38+ (n = 5), Der p 38-/Der f 38+ (n = 1), and Der p 38+/Der f 38- (n = 4)] (B). The cells were stimulated with Der p 38 or Der f 38 (10 mg /mL). The CD203c expression of basophils was evaluated using flow cytometry. *$P < 0.05$ indicates a significant difference between the Der p 38 and Der f 38 stimulated groups.

(25 μg/50 μL), respectively, from days 21 to 27 daily. The PBS/PBS group was used as a negative control.

All animal experiments conducted in this study were approved by the Institutional Animal Care and Use Committee of Eulji University, Korea. At the end of the study, all experimental animals were euthanized, and the lung tissues were harvested, fixed, and embedded in paraffin. Immunohistochemical staining was performed as described in a previous paper (Hong et al., 2021). Hematoxylin and eosin staining was used to counterstain lung tissues.

Fifteen allergic subjects were recruited from Eulji University. The allergic status was evaluated by the presence of HDM-positive skin prick test results. This study was approved by the Institutional Review Board of Eulji University. All subjects in this study provided written informed consent. Basophil activation due to allergens was analyzed by evaluating the surface expression of CD203c. Granulocytes were isolated from the peripheral blood of healthy and allergic subjects using Ficoll-Hypaque. Erythrocytes and neutrophils were eliminated using the RBC lysis buffer and CD16 microbead magnetic cell-sorting kit (Miltenyi Biotec, Bergisch Glad-bach, Germany), respectively. Isolated cells were collected, washed with PBS buffer, and stimulated with Der p 38 or Der f 38 (10 μg/mL). The cells were incubated with PE-conjugated anti-human IgE and FITC-conjugated CD203c (Biolegend, San Diego, CA, USA) for 20 min on ice, followed by washing with PBS buffer. Using RF-500 (Sysmex Corporation, Kobe, Japan), the stained cells were analyzed for the intensity of CD203c in the IgE-positive cells (Fig. 2).

To compare the effects of Der p 38 and Der f 38 on the infiltration of inflammatory cells into the lung, the mice were administered IN or IP/IN injection of Der p 38 and Der f 38. As shown in Fig. 1, the IN administration of Der p 38 and Der f 38 induced marked neutrophil movement compared to other experimental groups. Compared to Der f 38, Der p 38 was more effective in increasing the neutrophil number. The IP/IN administration of Der p 38 and Der f 38 triggered the movement of neutrophils, eosinophils, and mast cells, with similar effects observed for both allergens. Previous papers have also demonstrated that Der p 38 and Der f 38 trigger the movement of neutrophils as well as eosinophils, which is consistent with the results of this study (Hong et al., 2021; Kim et al., 2021). Since Der p 38 and Der f 38 bind to TLR4 (Jeon et al., 2021), the effects of both allergens were compared. Compared to the control group, no alterations were observed in the lung inflammatory cells of TLR4 KO mice. The allergic effects of Der p 38 and Der f 38 using the basophil activation assay were examined in allergic patients. Both allergens induced the expression of CD 203c in Der p 38+/Der f 38+ asthmatic subjects, with no difference being obtained between the two. However, Der f 38 presented stronger effects on basophil activation in Der p 38+/Der f 38+ allergic subjects, including allergic rhinitis and atopic dermatitis. This indicates that Der p 38 is less effective on basophil activation in allergic patients than

in asthmatic subjects and may be an important allergen in allergic diseases, particularly asthma. This implies that Der p 38 does not alter the CD 203c expression in Der p 38-negative asthmatic and allergic subjects. Unfortunately, no Der p 38+/Der f 38- asthmatic subjects were detected in this study.

Based on the results of animal experiments, Der p 38 shows stronger effects on the increase of neutrophils, unlike eosinophils and mast cells. Nevertheless, the effect of Der p 38 on basophil activation is not different from that of Der f 38 in asthmatic subjects. The results from animal models were consistent or inconsistent with the data from human subjects with several limitations being stated in scientific experiments (Aun et al., 2017). First of all, animal models are limited for not being able to mirror all manifestations and phenotypes of human asthma. Although further studies may require to confirm the exact comparative effects of both allergens, the current study suggests that similar allergens from different species of HDM show varying effects on leukocyte movement and allergenicity.

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CONFLICT OF INTEREST

The authors have no conflicts of interest, financial or otherwise, to declare.

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