

Mini Review

Role of Interleukin-25 in allergic airway inflammation and vascular damage

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T helper 2 (Th2) cells induce allergic inflammation through the production of Th2 cytokines such as IL-4, IL-5, and IL-13. In addition, it has been demonstrated that IL-25 (IL-17E) is a product of activated Th2 cells and initiates and augments Th2-type immune responses. Moreover, recent studies have shown that IL-25 is produced by a number of cell type including, epithelial cells, mast cells, eosinophils, and macrophages. It has also been shown that IL-25 induces Th2-type immune responses through the activation not only of Th2 cells but also of NKT cells and innate cells including MHC IIhigh CD11clow cells, multipotent progenitor cells, natural helper cells, and nuocytes. *In vivo*, we and others have shown that IL-25 is expressed in the airways in murine asthma models and is involved in the induction of antigen-induced airway inflammation. In human, IL-25 is suggested to be involved in the pathogenesis of asthma and Churg-Strauss syndrome.

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Abbreviations:

CC10: Clara cells-10kd protein

TARC: thymus- and activation-regulated chemokine

CSS: Churg-Strauss syndrome

AHR: airway hyperresponsiveness

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IL-25 as a Th2-promoting IL-17 family cytokine

Over the past decade, five cytokines homologous to IL-17 (IL-17A), namely IL-17B, IL-17C, IL-17D, IL-25 (IL-17E), and IL-17F have been identified by database searching^{1,2}. Among them, IL-25 is less homologous to other IL-17 family members and *in vivo* and *in vitro* biological activities of IL-25 are markedly different from those described for IL-17A and other IL-17 family cytokines^{1,2}. For instance, it has been shown that the systemic

administration of IL-25 induces eosinophilia through the production of IL-5³⁻⁵, whereas other IL-17 family cytokines such as IL-17A and IL-17F induce neutrophilia⁶⁻⁸. In addition, IL-25 induces elevated gene expression of IL-4 and IL-13 in multiple tissues and induces Th2-type immune responses including increased serum IgE levels and pathological changes in the multiple tissues³⁻⁵. Because IL-25-mediated Th2 cytokine production is still observed even in mice lacking T cells^{3,5}, it is suggested that IL-25 is capable of enhancing Th2-type immune re-

sponses in the absence of Th2 cells.

Role of IL-25 in allergic airway inflammation

Many studies have shown that allergic airway inflammation is mainly induced by Th2 cells through the production of Th2 cytokines such as IL-4, IL-5, and IL-13^{9, 10}. Using murine asthma models, we and others have provided evidence that IL-5-producing CD4⁺ T cells mediate antigen-induced eosinophil recruitment into the airways of sensitized mice^{11, 12}. In addition, it has been shown that IL-13 is a key cytokine that induces goblet cell hyperplasia and airway hyperresponsiveness (AHR)^{13, 14}.

Regarding the role of IL-25 in allergic airway inflammation, we have shown that IL-25 mRNA is expressed in the airways of antigen-sensitized, antigen-inhaled mice¹⁵, although we have not identified cell type of IL-25-producing cells at the site of allergic airway inflammation. Furthermore, we have investigated the effect of IL-17RB-Fc fusion protein (sIL-17RB), which is able to neutralize the bioactivity of IL-25, on antigen-induced airway inflammation and have found that the administration of sIL-17RB significantly inhibits antigen-induced eosinophil and CD4⁺ T cell recruitment into the airways¹⁵. A recent study using anti-IL-25 antibody confirmed the role of IL-25 in allergic airway inflammation¹⁶. We have also shown that antigen-induced eosinophil and CD4⁺ T cell recruitment and Th2 cytokine production in the airways are significantly enhanced in lung-specific IL-25 transgenic mice (CC10 IL-25 mice) as compared with those in wild type mice¹⁵. On the other hand, without the inhaled antigen challenge, no inflammatory cell infiltration is observed in the lung of CC10 IL-25 mice¹⁵. These studies suggest that IL-25 is not sufficient for the induction of allergic airway inflammation but is involved in the enhancement of antigen-induced allergic airway inflammation.

IL-25-producing cells at the site of allergic airway inflammation

An original study has shown that the expression of IL-25 mRNA is restricted to Th2 cells³. In addition, recent studies have shown that other cell types including bone marrow-derived mast cells upon IgE cross-linking¹⁷, alveolar macrophages after particle inhalation¹⁸, stem cell factor-stimulated eosinophils and basophils^{19, 20}, lung epithelial cells upon allergen stimulation²¹, and intestinal epithelial cells²² can express IL-25 mRNA. However, at present, cell type of IL-25-producing cells and type of stimulation for IL-25 production at the site of antigen-induced airway inflammation are not fully understood.

IL-25-responding cells at the site of allergic airway inflammation

The biological effects of IL-25 are mediated through the receptor consisting of IL-17RB and IL-17RA^{1, 2}. Initial studies using RAG1-deficient mice have demonstrated that IL-25 could act on non-B/non-T cells expressing high levels of MHC class II and low levels of CD11c³. In addition, T cells, especially memory Th2 cells²⁰, CD14⁺ cells²³, and subpopulation of natural killer T (NKT) cells^{24, 25} have been shown to respond to IL-25. Moreover, recent studies have shown that a multipotent progenitor cell population in the gut-associated lymphoid tissue²⁶, natural helper cells²⁷, and nuocytes²⁸ are able to respond to IL-25 and produce Th2 cytokines.

Regarding IL-25-responding cells at the site of allergic airway inflammation, we have shown that depletion of CD4-expressing cells by *in vivo* administration of anti-CD4 antibody results in the inhibition of IL-25-mediated enhancement of antigen-induced airway inflammation¹⁵. We have also shown that STAT6, a signaling molecule under IL-4/IL-13 receptor, is required for IL-25-mediated enhancement of antigen-induced airway inflammation¹⁵. These findings suggest that Th2 cells are key mediators of IL-25-mediated enhancement of antigen-induced airway inflammation, although there is no direct evidence showing that Th2 cells are direct targets of IL-25. On the other hand, it has recently been shown that a subpopulation of NKT cells expressing CD4 and IL-17RB is preferentially located in the lung and produces IL-13 upon stimulation with IL-25^{24, 25}. It has also been shown that the transfer of IL-17RB-expressing NKT cells but not of IL-17RB-negative NKT cells into NKT cell-deficient mice reconstituted IL-25-mediated AHR²⁴. Moreover, a recent report has shown that Th9 cells, a new subset of helper T cells producing IL-9²⁹, express IL-17RB and are able to produce IL-9 in response to IL-25 in a murine asthma model³⁰. These findings suggest that not only Th2 cells but also NKT cells and Th9 cells could be involved in IL-25-mediated airway inflammation in mice.

On the other hand, previous studies have demonstrated that the intranasal administration of large amounts of recombinant IL-25 induces Th2 cytokine production and eosinophil infiltration even in RAG1-deficient mice which lack both T cells and NKT cells^{3, 5}. In this situation, CD11c⁺ alveolar macrophage-like cells express IL-17RB and produce IL-5 and IL-13 following IL-25 administration³¹. Taken together, these results suggest that IL-25 could induce allergic inflammation by two different mechanisms. In a situation where IL-25 is abundant, IL-25 itself is sufficient for causing allergic inflammation through

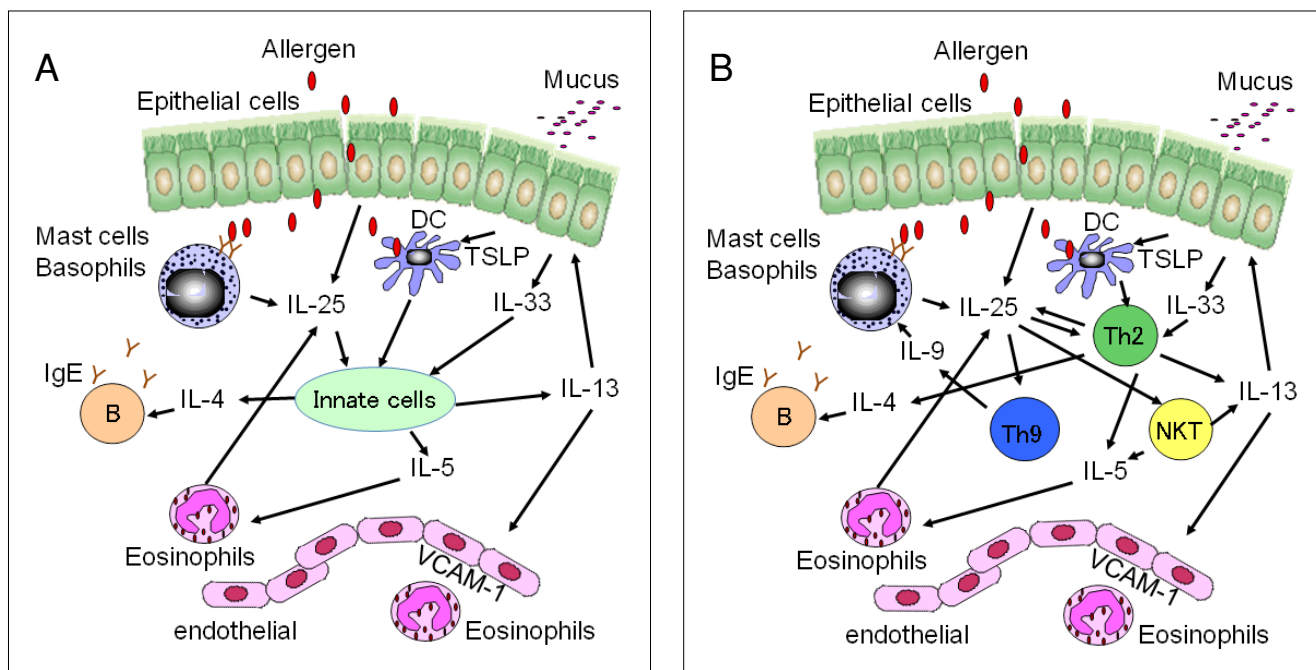


Fig.1 Possible mechanisms for IL-25-mediated enhancement of Th2-type immune responses

Th2 cells, mast cells, eosinophils, and epithelial cells produce IL-25 upon activation. In a situation where IL-25 is abundant (A), IL-25 directly functions on innate cells to induce Th2 cytokines and then causes allergic inflammation. In contrast, in other situation where the amounts of IL-25 are limited (B), collaboration with Th2 cells, Th9 cells, and/or NKT cells are required for causing IL-25-mediated allergic inflammation. Because the levels of the endogenously produced IL-25 in the lung are limited, it is suggested that in a pathophysiological setting such as bronchial asthma, IL-25 needs antigen-activated Th2 cells, Th9 cells, and/or NKT cells to exert its function.

the induction of IL-4, IL-5, and IL-13 from innate cells (Fig.1A). In contrast, in other situation where the amounts of IL-25 are limited, collaboration with Th2 cells, Th9 cells, and/or NKT cells is required for IL-25-mediated allergic inflammation (Fig.1B). Because the levels of the endogenously produced IL-25 in the lung are limited, it is suggested that in a physiological setting, IL-25 needs antigen-activated Th2 cells, Th9 cells, and/or NKT cells to exert its function.

The pathways by which IL-25 induces Th2-type immune responses remain poorly understood. The expression of TARC, a specific ligand for CC chemokine receptor 4 (CCR4), is enhanced in the lung upon IL-25 stimulation⁴ and TARC induces chemotaxis of T cells, especially of Th2 cells^{32,33}, and plays a significant role for the induction of Th2 cell-mediated eosinophil recruitment into the airways in a murine asthma model³⁴, suggesting that IL-25 may induce the recruitment of Th2 cells through the induction of TARC. Future studies identifying IL-25-responding cells at the site of allergic airway inflammation could help the understanding of the pathways by which IL-25 induces Th2-type immune responses.

Role of IL-25 in human allergic diseases

Very little is known about the role of IL-25 in human allergic diseases. It has been demonstrated that mRNA levels of IL-25 and IL-17RB are elevated in chronic asthmatic bronchus and atopic dermatitis skin lesions as compared to normal bronchus and normal skin, respectively²⁰. In addition, it has been shown that some of IL-25-expressing cells in the bronchial submucosa of asthmatic patients seem to be eosinophils³⁵. Moreover, recent study has shown that IL-25 levels are increased in the serum of patients with active Churg-Strauss syndrome (CSS), which is characterized by systemic vasculitis and blood and tissue eosinophilia, and that IL-25 levels are correlated with disease activity and eosinophil levels³⁶. The same group has shown that eosinophils are the main producer of IL-25, whereas memory CD4⁺ T cells are the main responder cells to IL-25 in patients with CSS³⁶. Furthermore, we found that the enforced expression of IL-25 in the lung caused pulmonary vascular damage in C57BL/6 background mice (Kawashima et al., in preparation). These findings suggest that IL-25 may be involved in the vascular damage in CSS.

Closing remarks

Accumulating evidence including ours raises the possibility that IL-25 is involved in the enhancement and/or prolongation of Th2 cell-mediated allergic diseases such as asthma and CSS, suggesting that IL-25 could be a possible target of allergic diseases.

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