

Invited Review Article

Bidirectional roles of IL-22 in the pathogenesis of allergic airway inflammation

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ABSTRACT

Asthma is the most prevalent allergic disease of the airway, which is characterized by eosinophilic inflammation, mucus hyperproduction, and airway hyper-responsiveness. Although these pathognomonic features are mainly mediated by antigen-specific Th2 cells and their cytokines, such as IL-4, IL-5, and IL-13, recent studies have revealed that other inflammatory cells, including Th17 cells and innate lymphoid cells (ILCs), also play a critical role in the pathogenesis of asthma. IL-22, one of the cytokines produced by Th17 cells and type 3 ILCs, has distinct functional properties, as IL-22 exclusively acts on non-hematopoietic cells including epithelial cells of mucosal surface and exhibits a broad range of action in regeneration and host protection. In accordance with the fact that lung epithelial cells play a critical role in the pathogenesis of asthma, we and other groups have shown that IL-22 is involved in the regulation of allergic airway inflammation. In this review, we discuss recent advances in the biology of IL-22 and its involvement in the pathogenesis of allergic airway inflammation.

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Introduction

Asthma is one of the most prevalent chronic lung diseases, which is characterized by eosinophilic airway inflammation, goblet cell hyperplasia, and airway hyper-responsiveness.^{1–3} Increasing evidence supports the concept that these pathophysiological features of asthma are mainly mediated by antigen-specific Th2 cells and their cytokines, including IL-4, IL-5, IL-9 and IL-13.^{1–3} Histologically, asthma is characterized by a large number of infiltrating Th2 cells, which is correlated with eosinophilic airway inflammation. Moreover, experiments with mice lacking each Th2 cytokine have provided strong evidence that Th2 cells and their cytokines are essential for the development of the pathognomonic features of asthma.^{1–3} The importance of Th2 cytokines in the pathogenesis of asthma is further confirmed by recent clinical trials in which the efficacy of monoclonal antibodies against Th2 cytokines was evaluated.^{4–6} Dupilumab, a humanized anti-IL-4 receptor α antibody which suppresses signaling of both IL-4 and IL-13, has been shown

to improve lung function and reduce the frequency of exacerbation in asthmatic patients with peripheral eosinophilia. In addition, antibodies targeting the IL-5-IL-5 receptor pathway such as Mepolizumab, Reslizumab, and Benralizumab have been shown to decrease the frequency of exacerbation in severe asthmatics with eosinophilia. These findings indicate that Th2-cell derived cytokines promote the development of cardinal features of asthma in both mice and humans.

However, the fact that the effects of these monoclonal antibodies against Th2 cytokines are limited to a subset of asthmatic patients revised the concept that asthma is uniformly mediated by Th2 cytokines.^{4,5} Consistent with the thought, recent comprehensive analyses of lung epithelial cells or sputum from asthmatic patients confirmed that asthma is a heterogeneous disease driven by diverse immunological and inflammatory mechanisms.⁷ Moreover, cluster analyses which incorporate information of various clinical parameters and biomarkers have revealed that asthma is composed of several different phenotypes, and that the most severe phenotype is associated with sputum neutrophilia.⁸ The fact that neutrophilic inflammation is a hallmark of Th17 cell-mediated diseases suggests that Th17 cells and their cytokines play a key role in the pathogenesis of severe asthma.⁸ Indeed, IL-17A, a key cytokine of Th17 cells, has been shown to be associated with airway remodeling, hyperresponsiveness, and mucous cell metaplasia.^{9–11}

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Furthermore, a recent study has revealed that the expression of Th17 cell-derived cytokines is elevated in airway mucosa of asthmatics who are prone to exacerbation.¹² These results suggest that not only Th2 cells and their cytokines but also Th17 cell-related cytokines are involved in the pathogenesis of asthma.

IL-22, a member of IL-10 family of cytokines, has received considerable attention because IL-22 is one of Th17 cell-derived cytokines which mediates skin acanthosis upon IL-23 stimulation.¹³ Although IL-22 was originally regarded as a Th17 cell-derived cytokine, subsequent studies identified a broad range of IL-22-producing cells, including Th22 cells, Th1 cells, $\gamma\delta$ T cells, NKT cells, and ILCs.¹⁴ Moreover, IL-22 has been shown to possess a unique trait that, unlike other members of IL-10 family cytokines, IL-22 exclusively functions on non-hematopoietic cells such as epithelial cells and stromal cells of mucosal surfaces, and regulates their regeneration and barrier function.¹⁴ In accordance with increasing evidence that lung epithelial cells play a critical role in the development of allergic airway inflammation, recent studies including ours revealed the role of IL-22 in the regulation of allergic airway inflammation.^{15–18} In this review, we discuss current understandings of the biology of IL-22 and its involvement in the pathogenesis of asthma.

The biology of IL-22 and IL-22 receptor

IL-22, originally named as IL-10-related T cell-derived inducible factor (IL-TIF),¹⁹ was identified in 2000 as a new member of IL-10 family of cytokines, together with IL-19, IL-20, IL-24, IL-26, IL-28, and IL-29. In humans, IL22 gene is located at chromosome 12q15 and encodes a 179–amino acid protein, whereas the murine *Il22* gene is located at chromosome 10 and encodes a 179–amino acid protein with 79% homology to human IL-22.²⁰

The IL-22 receptor (IL-22R) is a type 2-cytokine receptor, which is composed of a heterodimer of IL-22R1 and IL-10R2 (Fig. 1); the former is a component of the receptor for IL-20 and IL-24, and the latter is a component of the receptor for IL-10, IL-26, IL-28, and IL-29.¹⁴ Notably, while IL-10R2 is ubiquitously expressed on hematopoietic and non-hematopoietic cells, IL-22R1 expression, which defines target cells of IL-22, is restricted to non-hematopoietic cells such as epithelial cells and stromal cells.^{21,22} Consistently, subsequent studies have revealed that IL-22 is essential for the regeneration of epithelial cells to maintain barrier function after injury and for the prevention of further tissue damage by regulating

inflammation.²³ Given that IL-22R1 expression in the lung is restricted to pan-epithelial cells,^{15,16} it is suggested that IL-22 is involved in the pathogenesis of allergic airway inflammation by modulating the function of lung epithelial cells.

IL-22-producing cells

Although initial studies reported that IL-22 is expressed in thymus and brain, subsequent studies revealed that IL-22 is expressed in a broad range of tissues, including liver, lung, skin, pancreas, GI tract, and synovial tissues.^{14–16,24–27} At cellular levels, IL-22 is produced by both innate and adaptive immune cells, such as $\alpha\beta$ T cells, $\gamma\delta$ T cells, NKT cells, and ILCs¹⁴ (Fig. 1). IL-22 production by $\alpha\beta$ CD4⁺ T cells is mainly attributed to Th17 cells in mice,²⁸ whereas IL-22 production is detected in Th1 cells as well as Th17 cells in humans.²⁹ In addition, several groups identified a novel subset of human CD4⁺ T cells that are characterized by the production of IL-22 without IFN- γ , IL-4, or IL-17 production and named Th22 cells.³⁰ At this time, it remains unclear how Th22 cells differentiate and what is the role of Th22 cells in allergic inflammation in humans.

In addition to CD4⁺ T cells, ILCs, a newly identified lymphoid cell population lacking the expression of antigen-specific T or B cell receptors, have been shown to express IL-22.^{31,32} ILCs can be classified into three distinct populations based on cytokine profiles and the expression of master transcription factors, and among them, type 3 ILCs (ILC3s) have been identified as a potent cellular source of IL-22.³³

In murine asthma models, cellular sources of IL-22 remain controversial. While our group has shown that CD4⁺ T cells are main producers of IL-22,^{15,16} another group has shown that ILC3s largely contribute to IL-22 production.³⁴ These findings may not be mutually exclusive because IL-22 production could be attributed to different cell populations depending on the phase of allergic airway inflammation; e.g. ILC3s contribute to early IL-22 production, whereas CD4⁺ T cells contribute to late IL-22 production. Further studies are needed to define the precise cellular sources of IL-22 in each phase of allergic airway inflammation.

In humans, Pennino *et al.* have investigated IL-22-producing cells in the lung in patients with asthma, and have reported that the majority of IL-22-producing cells are CD4⁺ T cells which co-produce IFN- γ , followed by CD4⁺ T cells showing Th0-type, which produce IL-17 as well as IFN- γ , or Th22-type of cytokine profiles.³⁵

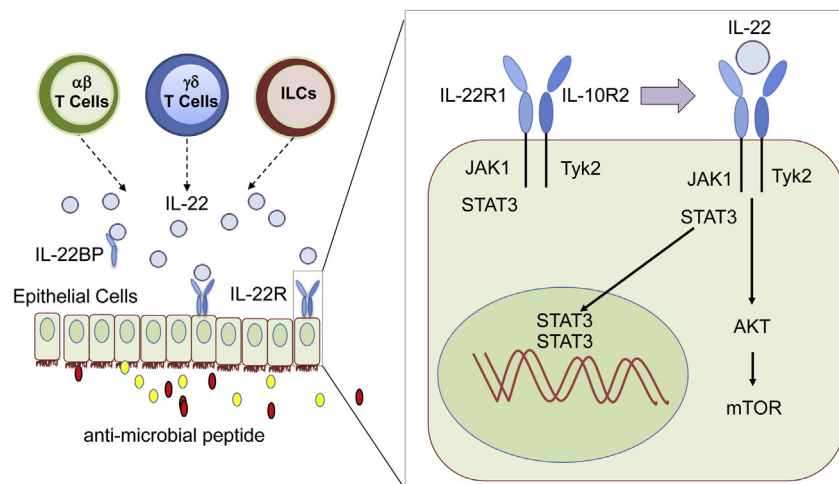


Fig. 1. Physiological and immunological views of IL-22-IL-22R-mediated responses. Schematic representation of IL-22-producing cells and its receptor and signaling pathways. IL-22R, IL-22 receptor; JAK1, Janus kinase 1; Tyk2, Tyrosine kinase 2; STAT3, Signal transducer and activator of transcription 3; mTOR, mammalian target of rapamycin.

It remains unknown whether other lineages of cells including ILCs are involved in IL-22 production in the lung in patients with asthma.

The regulators of IL-22 production and its bioactivity

It has been shown that IL-22 production from CD4⁺ T cells and ILCs depends on STAT3 and aryl hydrocarbon receptor (AhR).^{12,36,37} Importantly, AhR-deficient mice have been reported to show enhanced eosinophilic inflammation and Th2 cytokine production in a cockroach allergen-induced asthma model,³⁸ suggesting that AhR has a protective role in the development of allergic airway inflammation. Given that AhR inhibits the development of colitis via the production of IL-22,³⁹ the protective roles of AhR for the development of allergic airway inflammation could be mediated by its capacity to promote IL-22 production. Although data which show the direct link between AhR and human asthma are still lacking, involvement of AhR-IL-22 pathways in human asthma is also speculated, as mRNA levels of AhR and IL-22 are increased in PBMCs from patients with uncontrolled allergic asthma as compared to those from controlled asthma or healthy subjects.⁴⁰ On the other hand, Kärner *et al.* recently reported that miR-323-3p is highly expressed in CD4⁺ T cells from patients with asthma and inhibits IL-22 production by suppressing mRNA expression of STAT3.⁴¹ The involvement of other miRNAs in the regulation of IL-22 expression is also reported.⁴² These findings indicate that the production of IL-22 is intricately controlled by multiple mechanisms.

In addition to the above intracellular mechanisms, the bioactivity of IL-22 is regulated by a soluble IL-22 receptor, which is known as IL-22-binding protein (IL-22BP).^{43,44} IL-22BP binds to IL-22 with higher affinity than IL-22R, and acts as an intrinsic inhibitor of IL-22 signaling (Fig. 1). Although there is no direct evidence showing the involvement of IL-22BP in allergic diseases, it is possible that IL-22BP is involved in the pathogenesis of asthma by regulating bioactivity of IL-22.

Signaling pathways of IL-22

The signal of IL-22R is mainly transduced by the JAK-STAT pathway, an evolutionarily conserved signaling pathway from drosophila to mammals.⁴⁵ The binding of IL-22 to IL-22R complex causes the activation of JAK1 and Tyk2,^{14,46} and subsequently phosphorylates STAT3, STAT5, and STAT1 (Fig. 1). Among these STAT proteins, it is believed that STAT3 mainly contributes to the biological activities of IL-22, as intestinal epithelial cells lacking STAT3 show impaired regeneration and reduced production of anti-microbial peptides upon IL-22 stimulation.⁴⁷ Contrary to prediction, however, it has been shown that mice lacking STAT3 in lung epithelial cells are impaired in the development of allergic airway inflammation,⁴⁸ suggesting that epithelial STAT3 plays multiple roles in the pathogenesis of asthma. In addition to the JAK-STAT pathway, IL-22 activates phosphoinositide 3-kinase (PI3K)-AKT-mTOR pathway,⁴⁹ although the precise roles of the pathway in IL-22 signaling remain to be determined.

Roles of IL-22 in the pathogenesis of allergic airway inflammation in mice

Consistent with the fact that IL-22 exhibits both pro-inflammatory and anti-inflammatory properties, murine studies investigating the roles of IL-22 in allergic airway inflammation have yielded conflicting results. Several studies, including ours, revealed protective roles of IL-22 in the development of allergic airway inflammation.^{15–18} Fang *et al.* found that IL-22 transgenic mice

showed decreased numbers of eosinophils in lung tissue, reduced mucus hyperplasia in the airways, and reduced airway hyper-responsiveness.¹⁷ In addition, Nakagome *et al.* showed that IL-22 inhibits antigen-induced allergic airway inflammation by inducing IL-10-producing T cells.¹⁸ Moreover, in accordance with the fact that IL-22 acts mainly on lung epithelial cells, we found that IL-22 inhibits the production of epithelial cytokines which promote the development of allergic airway inflammation (Fig. 2).^{15,16} Mechanistically, we found that IL-22 induces the production of Reg3γ, which is known as an anti-microbial peptide, from lung epithelial cells, and subsequently suppresses IL-33 and TSLP production upon antigen re-stimulation (Fig. 2).¹⁵ These findings suggest that IL-22 down-regulates the development of allergic airway inflammation through multiple pathways. Furthermore, it has been revealed that IL-22 plays an important role in epithelial proliferation and repair following injury,²³ suggesting that IL-22 could also be involved in the regeneration of lung epithelial cells and the homeostasis of epithelial barrier function during allergic airway inflammation (Fig. 2). Because IL-22 enhances the expression of the antioxidants,^{50,51} which are implicated in the pathogenesis of asthma,⁵² it is also possible that IL-22 regulates the development of asthma through the induction of antioxidants in the airways (Fig. 2).

On the other hand, IL-22 has been suggested to have a pro-inflammatory role in allergic airway inflammation induced by fungi. Lilly *et al.* found that allergic airway inflammation induced by the inhalation of *Aspergillus* is partially dependent on IL-22.⁵³ Subsequently, the same group reported that IL-22 is produced by γδ T cells, NKT cells, and CD4⁺ T cells and that the production is promoted by IL-7 signaling.⁵⁴ In addition, Besnard *et al.* found that IL-22 promotes allergen sensitization through the skin, although IL-22 inhibits the development of allergic inflammation during the challenge phase.⁵⁵ Consistently, Leyva-Castillo *et al.* have recently shown that epicutaneous sensitization promotes the development of IL-22-expressing CD4⁺ T cells which co-produce IL-17A and exacerbate airway inflammation and airway hyper-responsiveness.⁵⁶ These findings are consistent with the fact that IL-22 promotes the inflammation at the skin and suggest that the

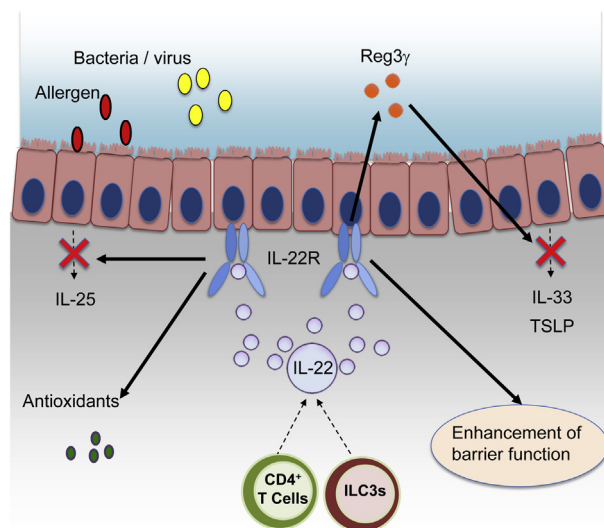


Fig. 2. Roles of IL-22 in the pathogenesis of allergic airway inflammation. Schematic representation of the roles of IL-22 in the regulation of allergic airway inflammation in mice. (1) IL-22 inhibits the expression of lung epithelial cell-derived cytokines such as IL-33, TSLP, and IL-25. (2) IL-22 enhances barrier function of airway epithelium. (3) IL-22 stimulates lung epithelial cells to produce antioxidants and prevents from oxidative stress in the airways. Reg3γ, Regenerating islet-derived protein 3γ.

roles of IL-22 in the pathogenesis of asthma may depend on the routes of sensitization.

IL-22 in the pathogenesis of human asthma

There are several reports which suggest the involvement of IL-22 in the pathogenesis of human asthma. Besnard *et al.* found that the levels of IL-22 are increased in sera from patients with allergic asthma as compared to those from control subjects.⁵⁵ In addition, Zhao *et al.* showed that the levels of serum IL-22 are correlated with the severity of asthma.⁵⁷ Moreover, Johnson *et al.* reported that the expression levels of IL-22 and IL-22 receptor in the airways are increased in asthmatic patients.⁵⁸ Taking into consideration the fact that the administration of recombinant IL-22 into the airways inhibits eosinophilic airway inflammation,¹⁶ we assume that IL-22 is elevated in severe asthma to serve as a negative feedback machinery for attenuating airway inflammation. Mechanistically, Pennino *et al.* found that IL-22 inhibits IFN- γ -induced secretion of pro-inflammatory chemokines, CCL5 and CXCL10, in the primary human bronchial epithelial cells.³⁵ Because IFN- γ is implicated in the pathogenesis of severe asthma through smooth muscle contraction and activation of innate immune systems,⁵⁹ it is possible that IL-22 inhibits the development of severe asthma through the suppression of IFN- γ function. Further studies are needed to clarify the precise roles of IL-22 in the pathogenesis of human asthma.

Regarding the airway remodeling in human asthma, Johnson *et al.* reported that IL-22 partly promotes TGF- β 1-mediated epithelial–mesenchymal transition in primary bronchial epithelial cells from patients with severe asthma.⁵⁸ Moreover, Chang *et al.* found that IL-22 is capable of enhancing proliferation of human airway smooth muscle cells through ERK1/2, MAPK, and NF- κ B pathways.⁶⁰ Thus, contrary to the anti-inflammatory properties, IL-22 may promote airway remodeling by multiple mechanisms in the pathogenesis of asthma.

Concluding remarks

Not only murine studies but also human studies suggest that IL-22 is involved in the pathogenesis of asthma. IL-22 itself or some molecules which suppress the function of IL-22BP may have potential to be applied as a novel therapeutic strategy for asthma due to its inhibitory effect on allergic airway inflammation. However, we should recognize that IL-22 has the dual nature in the mechanisms of asthma. Further studies to reveal the precise mechanisms of IL-22 action will be needed to make it a more attractive candidate for the treatment of asthma.

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Conflict of interest

The authors have no conflict of interest to declare.

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