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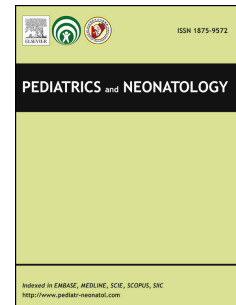
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Role of Th22 and IL-22 in Pathogenesis of Allergic Airway Diseases:

Pro-inflammatory or Anti-inflammatory Effect?

Running title: Th22 and IL-22 in Pathogenesis of Allergic Airway Diseases

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Role of Th22 and IL-22 in Pathogenesis of Allergic Airway Diseases: Pro-inflammatory or Anti-inflammatory Effect?

Running title: Th22 and IL-22 in allergic airway diseases

Abstract. A new population of T cells known as Th22 was described for the first time in 2009. These cells are usually identified by the production of IL-22. However, this cytokine is also secreted by other cells such as Th1, Th2, Th17, natural killers, and innate lymphoid cells. Th22 is known as a pro-inflammatory agent in allergic skin diseases. Recently, more evidence has emerged showing associations between these cells and other diseases. The role of Th22 in asthma and allergic rhinitis is controversial: some authors suggest that Th22 has a pro-inflammatory effect, while others state that Th22 has anti-inflammatory properties. The aim of this article was to review the role of Th22 and IL-22 in allergic airway diseases based on the most recent literature. This review suggests that Th22 plays a significant role in the pathogenesis of allergic airway diseases and has predominantly anti-inflammatory properties. More studies are needed to clarify the role of Th22 in more detail.

Key words: Th22; IL-22; asthma; rhinitis; allergy; airway.

Introduction

The immune system plays an important role in the pathogenesis of many diseases. New cells and cytokines are continually being found. This allows a more comprehensive understanding of the development of different diseases. A new T cell subpopulation so-called T helper (Th) 22 was first described in the scientific literature in 2009.¹⁻⁵ The first studies showed that Th22 cells were involved in the pathogenesis of inflammatory skin diseases through production of interleukin (IL) 22.^{1-4, 6} Later research described the role of Th22 in various autoimmune, allergic, and oncological diseases such as rheumatoid arthritis, psoriasis, thyroiditis, multiple sclerosis, asthma, allergic rhinitis, and hepatocellular carcinoma.⁷⁻¹³ This review article focuses on the data concerning the role of Th22 and IL-22 in allergic airway diseases.

Characteristics of Th22 and IL-22

Th22 cells differentiate from naive precursor cells, like other Th cells.^{2, 4, 14} Tumor necrosis factor-alpha (TNF-alpha) and IL-6 create a specific microenvironment for this process. Th22 cells have many receptors on their surface (Table 1),¹⁴ but they are usually identified by the production of IL-22.¹⁵ These cells also secrete other cytokines, such as IL-13 and TNF-alpha, but in very

small quantities.¹⁴ IL-22 was first described in 2000.¹⁶ IL-22 is a member of the IL-10 family of cytokines and plays its role via a heterodimeric transmembrane receptor complex consisting of IL-22R1 and IL-10R2 and subsequent Janus kinase-signal transducers and activators of transcription (JAK-STAT) signaling pathways.¹⁷ IL-22 is produced by Th22, but this cytokine can also be secreted by other cells including Th1, Th2, Th17, natural killers, and innate lymphoid cells.¹⁴ In some cases, IL-22 acts synergistically with other cytokines such as TNF-alpha, IL-1beta, and IL-17, but most functions of IL-22 are unique.^{15, 17} IL-22 induces innate, non-specific immune responses (for example, it may induce expression of antimicrobial peptides known as defensins), protects tissues from damage, and enhances their regeneration.¹⁷ Chronic, T cell-mediated diseases manifest by an elevated level of this cytokine. Target cells of IL-22 are keratinocytes as well as cells of the digestive tract, pancreas, liver, lungs, and kidney.¹⁷

The impact of Th22 cells and IL-22 on inflammatory diseases is described mainly with reference to their effect on keratinocytes in skin diseases. Moreover, there are studies on the role of IL-22 in the pathogenesis of asthma and allergic rhinitis.¹⁸⁻²⁰ However, the data published in these articles are controversial: some authors suggest that IL-22 has a pro-inflammatory effect, while others state that this cytokine and also Th22 have anti-inflammatory effects.^{18, 21-23}

Pro-inflammatory effect of Th22 in allergic airway diseases

Asthma is usually characterized by chronic airway inflammation.²⁴ It is a common chronic respiratory disease affecting from 1%–18% of the population in different countries.²⁴ Asthma is usually analyzed by dividing it into different phenotypes.²⁵ Allergic asthma is one of the most common asthma phenotypes. The majority of patients with asthma have concurrent rhinitis, which is also a common allergic disease.^{24, 26} The pathogenesis of these two diseases has yet to be fully investigated.

As mentioned above, the role of Th22 in respiratory inflammation has not been completely identified. The impact of Th22 on these diseases is analyzed through investigation of IL-22, a cytokine released by these cells. Some studies showed that the IL-22 level in serum and sputum from patients with asthma was higher than in healthy individuals.^{18, 19, 27} It was reported that the concentration of IL-22 was associated with severity of disease: the study carried out by Sherkat et al showed a significantly higher level of IL-22 in serum and sputum samples from severe adult asthmatic patients in comparison to patients with moderate asthma.¹⁹ Another study performed by Farfariello et al in a pediatric population revealed that increased IL-22 mRNA levels were documented in patients with chronic severe asthma as compared to those with moderate asthma.²⁷ Moreover, this pediatric study also found a positive correlation between IL-22 mRNA and serum total IgE

levels in asthmatic subjects.²⁷ These findings suggest that IL-22 is associated with asthma severity and atopy. Johnson et al hypothesized that IL-22 could be involved in epithelial-mesenchymal transition in asthmatic bronchial epithelial cells through transforming growth factor beta 1 (TGF-beta1).²⁸ However, the mechanism of this interaction should be investigated more extensively. Experimental studies carried out by Besnard et al showed that ovalbumin-challenged and IL-22-deficient mice had a low level of eosinophils in bronchoalveolar lavage and lung tissue. Moreover, in airway tissue from IL-22-deficient mice, reduced leukocyte infiltration, low level of IL-5 (which activates angiogenesis and differentiation of eosinophils, increases chemotaxis of these cells), and low levels of IL-13 and IL-33 (which induce the differentiation of IL-5+ IL-4- CD4+ Th cells from naive T cells, attracts Th2 cells and can influence dendritic cells maturation and activity) were documented as well.^{9, 18}

Search in the PubMed database revealed few articles that investigated the role of Th22 and IL-22 in the pathogenesis of allergic rhinitis. Some studies reported the number of Th22 cells and level of serum IL-22 to be significantly higher in patients with allergic rhinitis when compared to healthy individuals.^{20, 27} The concentration of Th22 in peripheral blood from patients with allergic rhinitis correlated with nasal congestion and rhinorrhea, while the level of IL-22 was significantly associated with the level of IgE specific to the allergens of house dust

mites (HDM; *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*) in patients with allergic rhinitis.²⁰ These findings are in agreement with a previously described study performed by Farfariello et al and provide evidence to support a relationship between the IL-22 level and atopy. IL-22 may be involved in the pathogenesis of allergic rhinitis through the impact on IFN-gamma-induced expression of chemokine CXCL10, which is involved in the recruitment of lymphocytes.²⁹⁻³¹

Asthma and allergic rhinitis are usually related to atopy. A skin disease such as atopic dermatitis is a chronic inflammatory disease which is also associated with increased sensitivity to different allergens. The pathogenesis of atopic dermatitis has many similarities to the pathogenesis of allergic airway diseases. There are data to support a pro-inflammatory effect of Th22 in skin allergic diseases. A higher level of Th22 cells was found in the skin of patients with atopic dermatitis than those with healthy skin.^{32, 33} Th22 cells may induce keratinocyte proliferation and migration; in inflamed skin, these cells can contribute to the amplification of immune responses by enhancing the TNF-alpha-induced cytokines and chemokines released by keratinocytes.³⁴ There is evidence that dendritic cells and Langerhans cells located in derma can activate Th22 cells to produce IL-22.³² Accumulation of Th22 cells in the skin may also be induced by an infectious process: a higher level of Th22 was found in patients with atopic dermatitis who

additionally had skin infection.³⁵ As in cases of asthma and allergic rhinitis, the concentration of Th22 was also associated with the disease severity: a higher level of these cells was observed in adults with moderate-to-severe atopic dermatitis.³⁶ However, children with newly diagnosed atopic dermatitis did not show an increased Th22 level.³⁶ This finding could be explained by Th22 involvement in the development of disease chronicity and severity. The study authors suggested that immune development, disease chronicity, or recurrent skin infections might contribute to the absence of Th22 in young children.³⁶ In an experimental HDM-sensitized dog model, acute atopic dermatitis skin lesions developed immediately after epicutaneous allergen challenge, and high levels of Th2 and Th22 cytokines were found.³⁷ These findings were associated with the activation of itch-promoting pathway, which includes pruritogenic cytokines such as IL-31, cathepsins and mast cell proteases, nerve growth factor, neuromedin-B, and enzymes involved in the synthesis of leukotriene-B4 and histamine.³⁷

Pro-inflammatory effects of IL-22 are summarized in Table 2.

Anti-inflammatory effect of Th22 in allergic airway diseases

Recent studies involving experimental animal models have shown results contradicting those reported previously; Th22 and IL-22 have an anti-inflammatory effect in airway inflammation.^{21, 22} Some studies using animals reported that IL-22-

positive mice had a reduced number of eosinophils and a lower level of IL-13 (which usually increases bronchial hypersensitivity) in the bronchoalveolar lavage and mucus-producing cells in the airways after ovalbumin stimulation when compared with IL-22-negative mice.^{21, 22, 38} Moreover, an *in vitro* study with bronchial epithelial cells from healthy and asthmatic subjects revealed that IL-22 might inhibit the IFN-gamma-induced expression of CD54 (intercellular adhesion molecule 1, which plays an important role in T cell migration and recruitment), and chemokines CCL5 (chemoattractant for eosinophils, T lymphocytes, and monocytes) and CXCL10 (important for the recruitment of lymphocytes).^{29, 30, 39-41} These findings suggest that IL-22 may have an anti-inflammatory effect on airway inflammation.

Besnard et al noted that IL-22 was necessary for the induction of inflammation in animal and human. However, during continuous allergen challenge, the lack of IL-22 may exacerbate allergic airway inflammation.¹⁸ During antigen challenge, IL-22-negative mice showed significantly increased levels of Th2 cytokines, eosinophils, neutrophils and increased expression of IL-17A and IL-17F, which may induce airway epithelial cells to produce pro-inflammatory mediators.^{9, 18} After the addition of exogenous recombinant IL-22, during antigen challenge, concentrations of IL-5, IL-13, and IL-17A were decreased.^{18, 42} Another study by Taube et al showed a reduced level of IL-13 and considerable

amelioration of airway constriction and inflammation in an experimental airway allergic inflammation model in mice treated with IL-22.²² Taken together, these recent studies show that IL-22 may have an anti-inflammatory effect, especially in the late phase of allergen-induced airway inflammation.

Contrary to the study by Besnard et al, an animal study performed by Nakagome et al revealed that IL-22 could have an immunosuppressive effect during the early stage of an immune response.²³ An IL-22-producing plasmid vector that was delivered before the sensitization with ovalbumin suppressed eosinophilic airway inflammation. However, this effect was not observed when the IL-22-producing plasmid vector was delivered immediately before challenge with ovalbumin. Delivery of the IL-22 gene increased the level of IL-10 known as an anti-inflammatory cytokine inhibiting production of pro-inflammatory cytokines.^{23, 43} This study strengthens the evidence for the anti-inflammatory effect of IL-22 in airway inflammation induced by an allergen. The mechanism of IL-22 in allergic response in lungs has not been completely elucidated, but experimental studies have shown that continuous expression of IL-22 in the airways is able to activate downstream signaling molecule STAT3 without inducing any considerable pathological changes in the lungs.^{21, 22}

Anti-inflammatory effects of Th22 are summarized in Table 2.

Conclusions

To sum up, Th22 plays a significant role in the pathogenesis of allergic airway diseases by increased secretion of IL-22 and regulation of different pathways of the immune system. Th22 possesses pro-inflammatory properties in allergic skin diseases. There are also some data concerning a pro-inflammatory impact of these cells on allergic airway diseases through the activation of IL-5, IL-13, IL-33, and TGF-beta1. Besides similarities in the pathogenesis between allergic skin and airway diseases, currently there is an accumulating body of evidence that Th22 has anti-inflammatory properties in allergic airway diseases through the effect on IL-10 and decrease of pro-inflammatory cytokines and eosinophils. However, more research, especially on humans, needs to be conducted in order to clarify the role of Th22 in more detail.

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Table 1 Characteristics of Th22.^{2, 4, 14}

Th22		
Receptors on surface	Intracellular receptors	Production and release of mediators
CD3	AHR	IL-22
CD4		IL-13
CD28		IL-10
CCR10		TNF-alpha
CCR6		
CCR4		
PGDFR		

TCR – T cell receptors

PGDFR – platelet-derived growth factor receptor

IL – interleukin

TNF-alpha – tumor necrosis factor alpha

AHR – aryl hydrocarbon receptor

Table 2 Effects of IL-22 in allergic airway diseases.^{9, 18-23, 27-31, 38-42}

Pro-inflammatory effect of IL-22		References	Experimental details
↑IL-13	↑bronchial hypersensitivity	Besnard et al, 2011 [18]	In vivo, with mice challenged with ovalbumin
↑IL-33	↑Induction of the differentiation of IL-5+ IL-4- CD4+ Th cells ↓ ↑eosinophilic inflammation	Besnard et al, 2011 [18]	In vivo, with mice challenged with ovalbumin
↑TGF-beta1	↑epithelial-mesenchymal transition in asthmatic bronchial epithelial cells ↓ ↑remodeling of airway tissue	Johnson et al, 2013 [28]	In vitro, blood sample taken from children with allergic rhinitis or allergic asthma
↑eosinophil count	↑eosinophilic inflammation	Besnard et al, 2011 [18]	In vivo, with mice challenged with ovalbumin
↑IL-5	↑activation of angiogenesis, differentiation and chemotaxis of eosinophils ↓ ↑eosinophilic inflammation	Besnard et al, 2011 [18]	In vivo, with mice challenged with ovalbumin
Anti-inflammatory effect of IL-22			
↑IL-10	↓pro-inflammatory cytokines	Nakagome et al, 2011 [23]	In vivo, with mice challenged with ovalbumin
↓IL-13	↓bronchial hypersensitivity	Taube et al, 2011 [22]	In vivo, with mice challenged with ovalbumin
		Fang et al, 2014 [21]	In vivo, with mice challenged with ovalbumin
		Besnard et al, 2011 [18]	In vivo, with mice challenged with ovalbumin (after addition of exogenous

			<i>recombinant IL-22 during the antigen challenge)</i>
↓IL-33	↓Induction of the differentiation of IL-5+ IL-4- CD4+ Th cells ↓ ↓eosinophilic inflammation	Besnard et al, 2011 [18]	In vivo, with mice challenged with ovalbumin (<i>after addition of exogenous recombinant IL-22 during the antigen challenge)</i>
↓IL-17	Inhibition of airway epithelial cells to produce CXCL1 and CXCL8 ↓ ↓attraction of neutrophils and cytokines ↓ ↓promotion of the activation of Th17 cells ↓ ↓stimulation of other cells to release IL-21 and IL-23	Besnard et al, 2011 [18]	In vivo, with mice challenged with ovalbumin (<i>after addition of exogenous recombinant IL-22 during the antigen challenge)</i>
↓IL-5	↓activation of angiogenesis, differentiation and chemotaxis of eosinophils ↓ ↓eosinophilic inflammation	Taube et al, 2011 [22] Besnard et al, 2011 [18]	In vivo, with mice challenged with ovalbumin In vivo, with mice challenged with ovalbumin (<i>after addition of exogenous recombinant IL-22 during the antigen challenge)</i>
↓IFN-gamma	↓expression of CD54, CCL5 and CXCL10 ↓ • ↓recruitment of lymphocytes • ↓chemoattraction of	Pennino et al, 2013 [39]	In vitro, T-cell lines derived from lung biopsy specimens of asthmatic patients

	eosinophils, T lymphocytes, and monocytes • dysregulation of T-cell transmigration and recruitment		
↓eosinophil count	↓eosinophilic inflammation	Fang et al, 2014 [21] Taube et al, 2011 [22] Nakagome et al, 2011 [23]	In vivo, with mice challenged with ovalbumin In vivo, with mice challenged with ovalbumin In vivo, with mice challenged with ovalbumin
↓mucus producing cells	↓mucus production	Fang et al, 2014 [21]	In vivo, with mice challenged with ovalbumin