Th22 and Th17 mediated inflammation in allergic airway diseases

TH22 IR TH17 VAIDMUO ALERGINIŲ KVĖPAVIMO TAKŲ LIGŲ METU

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Summary. The most common allergic airway diseases are allergic rhinitis and allergic asthma, characterized by chronic inflammation of the upper and lower airways. Interaction between asthma and rhinitis is well known: over 80% of patients have both allergic asthma and allergic rhinitis, and 10%–40% of patients with allergic rhinitis develops allergic asthma. Allergic asthma and allergic rhinitis are complex and heterogeneous diseases; however, they share almost identical immune mechanisms. The main role is given to T lymphocyte helper (Th2) and their produced IL-4, IL-5 and IL-13, which cause type 2 inflammation. However, recent studies have been focusing on the new Th cell population: Th22 and Th17. There is evidence that Th17, Th22 cells and their cytokines play crucial roles in the pathogenesis of autoimmune diseases such as inflammatory bowel disease, multiple sclerosis and rheumatoid arthritis. The aim of this article is to review the newest evidence of the role of Th22 and Th17 in allergic airway diseases.
Keywords: Th22, Th17, IL-22, IL-17, allergic rhinitis, allergic asthma.
Santrauka. Dažniausios alerginės kvėpavimo takų ligos yra alerginis rinitas (AR) ir alerginė astma, kurioms būdingas lėtinis uždegimas viršutiniuose ir apatiniuose kvėpavimo takuose. Šios dvi ligos yra glaudžiai susijusios: net 80 proc. sergančiųjų astma serga ir AR, 10–40 proc. AR sergančių pacientų diagnozuojama astma. Alerginė astma ir AR yra heterogeniškos ligos, kurioms būdingi panašūs imunologiniai mechanizmai. Mokslinėje literatūroje plačiausiai nagrinėjamas 2-o tipo uždegimas, kurį lemia 2–o tipo T limfocitai pagalbininkai (Th2) bei šių ląstelių išskiriami IL-4, IL-5, IL-13. Vis tik gilėjant alerginių kvėpavimo ligų patogenezės sampratai, dėmesys krypsta į naujas ląstelių populiacijas: Th22 ir Th17. Jau žinoma, kad šių ląstelių išskiriami citokinai atlieka svarbią funkciją autoimuninių ir lėtinių uždegiminių ligų, tokių kaip reumatoidinis artritas, išsėtinė sklerozė ir uždegiminių žarnyno ligų, patogenezėje. Šios apžvalgos tikslas yra pristatyti naujausią informaciją apie Th22 ir Th17 ląstelių bei jų išskiriamų citokinų reikšmę alerginių kvėpavimo ligų metu.
Reikšminiai žodžiai: 22 tipo ląstelės pagalbininkės, 17 tipo ląstelės pagalbininkės, IL-22, IL-17, alerginis rinitas, alerginė astma.

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INTRODUCTION

The prevalence of allergic diseases is increasing worldwide. The most common allergic diseases are allergic rhinitis (1) and allergic asthma (2). These diseases are associated with poorer life quality, disturbed social life, daily activity and increased leave day at school and work (3, 4).

Immunologic mechanisms play a significant role in the development of allergic asthma and allergic rhinitis; however, the pathogenesis of these diseases is not fully investigated yet. Allergic airway diseases manifest in different phenotypes, which may depend on endotypes (5, 6). The main role is given to type 2 inflammation which is mediated by T lymphocyte helper (Th) 2 producing interleukin (IL) 4, IL-5 and IL-13 (5–7). However, there is evidence about the importance of Th17 and Th22 on allergic airway diseases. These cells and their produced mediators are already known as important factors in autoimmune and chronic non–allergic airway disorders (7, 8).

Despite the evidence that Th17 and Th22 and their main cytokines can be important in the pathogenesis of allergic asthma and allergic rhinitis, it is not known if they act as a proinflammatory agent or anti-inflammatory agent (9, 10). The aim of this article is to review the newest evidence of the role of Th22 and Th17 in allergic airway diseases.

MATERIALS AND METHODS

Experimental and clinical studies in the English language performed during the past five years were searched in the PubMed database. The Medical Subject Heading (MeSH) terms of "rhinitis" or "asthma" and "IL-22" or "IL-17" or "Th22" or "Th17" were used. In addition, combined text words of (allergic rhinitis AND IL-22) OR (allergic asthma AND IL-22) OR (allergic rhinitis AND IL-17) or (allergic asthma AND IL-17) were used to find relevant studies.

Th22 and IL-22 in allergic rhinitis and allergic asthma

IL-22 was firstly described in 2000 (11). This cytokine 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) signalling pathways (12). Initially, it was thought that it was secreted only by Th17. However, a new T cell subpopulation, Th22, which was identified by the production of IL-22, was described in 2009 (13). Now it is known that Th22 also produce and secrete other cytokines such as IL-13, IL-10 and TNF-α (10). IL-22 can be secreted by numerous immune cells such as Th1, Th2, Th17, Th22, natural killers, and innate lymphoid cells (14).

Th22 cells differentiate from naive precursor cells. Tumour necrosis factor–alpha (TNF-α) and IL-6 create a specific microenvironment for this process (9, 10). In some cases, IL-22 acts synergistically with other cytokines such as TNF-α, IL-1β, and IL-17, but most functions of IL-22 are unique. IL-22 induces innate, non-specific immune responses, protects tissues from damage, and enhances regeneration (9, 10). The impact of Th22 cells and IL-22 on inflammatory diseases is described mainly with reference to their effect on keratinocytes in skin diseases.

During the last five years, several new experimental and clinical studies and some review articles focusing on Th22 and IL-22 on allergic airway inflammation were published. One experimental research aimed to investigate the role of IL-22 in the development of allergic airway inflammation induced by intratracheal administration of house dust mites (15). Results revealed that allergic airway inflammation and Th2 and Th17 cytokine production were exacerbated in IL-22-deficient mice. Scientists also found that IL-22 induced Reg3γ production from lung epithelial cells through STAT3 activation and that neutralization of Reg3γ significantly exacerbates house dust mites induced eosinophilic airway inflammation and Th2 cytokine induction (15). These results suggest that IL-22 reduces house dust mites induced allergic airway inflammation, possibly by inhibiting cytokine production from lung epithelial cells. Another experimental study performed by Castillo et al. showed that epicutaneously sensitization caused a systemic IL-22 response (16). Intranasal ovalbumin (OVA) challenge significantly more increased IL-22 mRNA levels in the lungs in mice epicutaneously sensitized with OVA, compared to control mice epicutaneously sensitized with saline (16). Scientists provided opposite data than Ito el. concluding that IL-22 was important for airway inflammation and airway hyperresponsiveness in epicutaneously sensitized mice intranasally challenged with antigen and IL-22 and TNF-α synergized neutrophil airway inflammation.

Clinical studies also provide controversial data on the role of IL-22 in allergic airway diseases. According to Bayrak Degirmenci, et al.and Shahsavan et al., plasma or serum IL-22 level was higher in patients with allergic rhinitis than control patients (17, 18). However, Shahsavan et al. showed that serum IL-22 level and IL-22 gene expression was significantly higher in patients with moderate/severe allergic rhinitis than patients with mild allergic rhinitis (18). Moreover, Shahsavan S. et al. also found significant positive correlations between serum level of IL-22 and total IgE, specific IgE, the degree of eosinophil infiltration into the nasal mucosa and total nasal symptom score (TNSS) in patients with allergic rhinitis (18). Bayrak Degirmenci did not find a link between IL-22 and disease severity (17). The study which investigated IL-22 level in allergic airway diseases (allergic rhinitis with or without asthma) revealed a tendency that IL-22 level in serum and nasal lavage was increased in patients with allergic airway diseases caused by house dust mite and positively correlated with IL-10 level in serum and nasal lavage (19). Moreover, IL-22 level in nasal lavage negatively correlated with eosinophil count in a nasal smear in patients with allergic rhinitis and allergic asthma. A negative link was found between serum IL-22 and (Rhinoconjunctivitis Quality of Life Questionnaire) RQLQ in patients with allergic airway diseases (19). A systematic review analysing six clinical studies which investigated IL-22 level in patients with allergic airway diseases showed that IL-22 level and IL-22 gene expression in serum, plasma and nasal mucosa was higher in children and adults with allergic airway diseases than in healthy individuals (20). The majority of studies revealed a significant positive correlation between IL-22 level and disease severity and symptom score (19).

Th17 and IL-17 in allergic rhinitis and allergic asthma

In 2005 a third T-cell subset, known as Th17, was identified (21). These cells are characterized by the production of IL-17 and expression of retinoic acid-related orphan receptor gamma t (RORγt) (22), but also secrete other cytokines such as TNF-α, IL-22, IL-26 and IFN-γ (23). IL-17 was firstly described in 1995–1996 (24). This cytokine is known to be expressed not only by Th17 but also by other adaptive and immune cell types, including CD8+ T cells, γδ T cells, natural killer T (NKT) cells, and innate lymphoid cells (25). It is known six IL-17 family cytokines: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F, but IL-17A and IL-17F are best studied and most closely related (26). IL-17 family cytokines bind to the receptor IL-17R, which is expressed on non-immune cells, including epithelial cells, airway smooth muscle cells and fibroblastic cells (26). Upon IL-17R activation, proinflammatory cytokines such as IL-1, IL-6, tumor

necrosis factor (TNF) and IL-8 are released, making the tissue more amenable to cellular infiltration and tissue inflammation (27). IL-8 is one of neutrophil chemoattractant witch induces neutrophilic recruitment into the inflamed lung tissues (28).

IL-6 and transforming growth factor – β (TGF-β) are commonly recognized cytokines to induce differentiation of the Th17 subset (29, 30). The main function of Th17 cells is to clear extracellular and intracellular pathogens, such as *Candida*, *Klebsiella*, *Mycobacterium tuberculosis*, *Chlamydia trachomatis* and viruses (22, 31). Another critical role is to protect mucosal homeostasis and to enhance neutrophil response (31). However, under certain conditions, these cells can also be associated with the pathogenesis of allergic airway diseases (32). Recent researches focused on Th17 and IL-17 contribution to type 2 low asthma, which is usually present in severe and corticosteroid–resistant asthma phenotype (33). Increased levels of IL-17 have been found in lung specimens, BALF, sputum as well as in peripheral blood of patients with severe asthma (34–36). High levels of IL-17 in asthma regulates the expression of proinflammatory cytokines and neutrophilic chemokines (34). The regulatory mechanisms of neutrophilic inflammation are not well understood. Peripheral neutrophils from allergic asthmatics are known to express higher IL-17 cytokine levels than those from healthy subjects: stimulating asthmatic neutrophils with IL-21, IL-23, and IL-6 cytokines enhanced the production of IL-17A and IL-17F at significantly higher levels compared to healthy controls (28). These findings suggest that modulated neutrophils provide a feedback mechanism that sustains inflammation.

Induction of asthma starts with professional antigen–presenting cells and specifically dendritic cells (DCs). DCs are the key for priming and inducing T helper cell response in asthma and allergy (37). A study of the murine asthma model proposes that the presence of IL-17 in asthma and allergy leads to enhanced activation, migration, and antigen presentation by dendritic cells, which contributes to the development and the course of the disease (34). A targeted approach aimed at DC migration and activation could be aimed in IL-17 dependent asthma.

IL-17 immunity has been linked to asthma exacerbations (33). A study of genome transcriptomic analysis of epithelial brushings and bronchial biopsy specimens from asthmatic patients showed that patients with IL-17 phenotype had reduced expression of several genes regulating tight epithelial junctions and mucosal barrier mechanisms (38). These finding, together with decreased microbiota diversity and IL-17 activation, could implicate susceptibility to infections and exacerbations seen in these patients (38). Another hypothesis of increased exacerbation is the dual Th2/Th17 mechanism. The Th2 and Th17 immune pathways are generally viewed as separate, but significant interactions have been found between bronchial neutrophilia and eosinophilia: high neutrophilic asthmatics had increased serum IgE levels (35, 36). This data suggests that in a subset of neutrophilic asthmatics, allergic mechanisms may deviate to dual Th2/Th17 mediated immune response and are associated with increased frequency of exacerbation (36).

A number of studies have found high levels of serum IL-17 in patients with allergic rhinitis (17, 39, 40). The idea that Th17 cells and IL-17 are important in the pathogenesis of this disease was shown by active Th17 cells in a symptomatic period of both seasonal and perennial allergic rhinitis (17). Allergic rhinitis is typically associated with Th2 mediated immune response and eosinophil infiltration; however, recent studies suggest neutrophilic inflammation to be involved in allergic airway diseases (28). A significant correlation has been found between serum IL-17 and eosinophil cationic protein (ECP) (39). In a Th2 dominant environment, IL-17 can promote eosinophils survival and degranulation, leading to chronic nasal inflammation

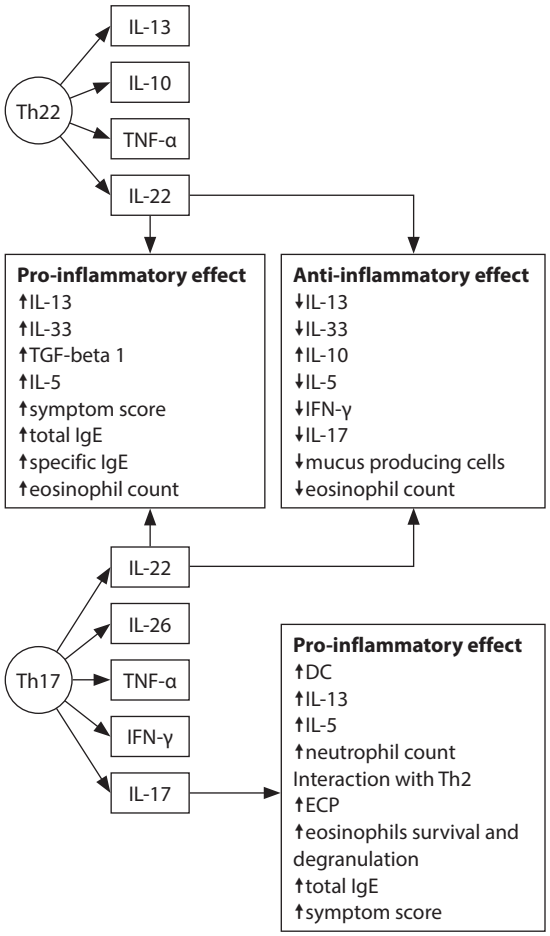

Figure. Main effect of IL-17 and IL-22 in allergic airway diseases

in allergic rhinitis (41). Besides, IL-17 enhances IL-13 induced STAT6 phosphorylation leading to eotaxin – 3 production (42). These factors contribute to eosinophilic inflammation. In addition to supporting the role of IL-17 in allergic rhinitis, IL-17 up–regulates thymic stromal lymphopoietin (TSLP) production by nasal fibroblasts in patients with allergic rhinitis (43). TSLP can activate DCs that prime the differentiation of CD4+ Th lymphocytes into Th2 cells, promoting Th2 inflammation (43).

Lipopolysaccharide (LPS) is a component of the Gram-negative bacteria cell wall witch as an endotoxin, induces strong immune responses and recruits neutrophils to the tissue (28). A study aimed to elucidate the underlying mechanism of IL-17 in the pathogenesis of an LPS induced neutrophilic allergic rhinitis murine model. Immunohistochemistry of nasal mucosa showed that IL-17 and neutrophils increased in a dose-dependent manner of LPS (44). These findings prove that tissue neutrophilia is dependent on IL-17 and indicate the potential role of Th17/IL-17 in allergic airway pathogenesis.

The main effect of IL-22 and IL-17 in allergic airway diseases is summarized in the figure.

CONCLUSION

Th22 and Th17 and their main cytokines play an important role in the pathogenesis of allergic rhinitis and allergic asthma. Th17 and IL-17 are associated with neutrophilic inflammation and severe asthma but also may activate Th2 response and promote eosinophilic inflammation in allergic rhinitis. The role of Th22 and IL-22 is still controversial, and more studies need to be performed to evaluate the properties of these immune components.

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