

Th17 cells, Vitamin D, and Asthma

Tsvetelina Veselinova Velikova

Clinical Immunology, University Hospital Lozenetz, Sofia, Bulgaria

A number of childhood lung diseases have immunological mechanisms of development, such as bronchial asthma, allergic rhinitis, and cystic fibrosis.

Asthma is one of the most common lung diseases in children with a prevalence of 8–10% of all children. It is characterized by chronic inflammation of the airways, in the pathogenesis of which play inflammatory cells: T-lymphocytes, immunoglobulin E (IgE)-producing plasmocytes, eosinophils, mast cells, macrophages, epithelial cells, fibroblasts, as well as pro-inflammatory cytokines (i.e., interleukin [IL]-6, IL-8, IL-12, IL-4, IL-10, IL-13, interferon- γ , and IL-17).^[1] Thus, bronchial asthma is a complex and heterogeneous disease characterized by intermittent and reversible airway obstruction, chronic airway inflammation, bronchial hyperresponsiveness, and cell infiltration in the airway submucosa. Obstruction of the airways is variable and reversible, either spontaneously or under treatment. There is also an increase in the bronchial response to a variety of specific and nonspecific stimuli. About 80% of asthmatics are diagnosed before the 6th year of age, proving the early onset of the disease, whose natural course is manifested by a progressive decline in the respiratory function such as forced expiratory volume in one second.^[1] Management of the asthma is also influenced by the inflammatory and structural changes in the airways.

It is well-established that CD4 + Th2 participate in the pathogenesis of asthma. Th2 lymphocytes secrete IL-4, IL-5, and IL-13, which are believed to support the switch to IgE synthesis, differentiation of eosinophils, hyperresponsiveness of the mucous membranes by direct effects on smooth muscle cells. More recently described subpopulation of CD4 Th-lymphocytes that mainly produce IL-17 and called Th17 lymphocytes showed a critical role in the pathogenesis of non-specific bronchial reactivity, bronchial asthma, chronic bronchitis, obstructive pulmonary disease, cystic fibrosis, allergic rhinitis, allergic conjunctivitis and dermatitis, food

allergies, acute respiratory distress syndrome, Crohn's disease, ulcerative colitis, rheumatoid arthritis, multiple sclerosis, systemic lupus, psoriasis, kidney graft rejection, colorectal carcinoma, etc.^[2] However, Th17 cells are also involved in physiological functions of the body, especially in the defense on the epithelial and mucosal surfaces. In the airways, Th17 cells are the connection between innate and acquired immunity playing a key role in protecting the body against fungi and extracellular bacteria by rapid initiation of an acute inflammatory response to of neutrophils. Th17 promote effective immune responses and control against bacterial infections, such as *Propionibacterium acnes*, *Citrobacter rodentium*, *Klebsiella pneumoniae*, *Bordetella pertussis*, *Bacteroides* species, *Borrelia* species, Mycobacterium tuberculosis, as well as some fungi like *Candida albicans*. IL-17-mediated inflammation is characterized by triggering of initial pathogen or allergen and subsequent differentiation of IL-17 producing naive T lymphocyte cells. Th17 cells secrete also IL-17AF, IL-17F, IL-21, and IL-22, which induce innate immune cells to secrete a large amount of inflammatory cytokines and chemokines that locally attract mast cells, eosinophils, and basophils and lead to enhanced immune responses. Attracted cells, in turn, produce IL-25, which increases Th2 responses and IL-5 and IL-13 secretion, respectively.^[3] All these processes create preconditions for asthma or exacerbation of asthma. Free oxygen radicals and other mediators against microbial invasion contribute to tissue damage locally.

Still, mechanisms of Th17 involvement in bronchial asthma pathogenesis have been studied, but most studies suggest that asthma, particularly severe, is a Th2-induced inflammation of the airways along with the actions of Th17 lymphocytes. In bronchoalveolar lavage, serum and sputum, high levels of IL-17 have been obtained. The studies of Irvin *et al.* (2014) support the hypothesis that patients with predominantly simultaneous presence of Th2 and Th17 lymphocytes are less likely to undergo successful treatment, have more severe

Address for correspondence:

Tsvetelina Veselinova Velikova, Kozyak 1 Str., Sofia 1407, Bulgaria, Phone: 00359883306049.
E-mail: tsvelikova@medfac.mu-sofia.bg

© 2018 The Author(s). This open access article is distributed under a Creative Commons Attribution (CC-BY) 4.0 license.

obstructive airway obstruction and hyperactivity.^[4] Other researchers point out that the increased level of IL-17 is associated with enhanced bronchial reactivity, neutrophilic infiltration, exacerbation of asthma with poor response to therapy, especially to steroids, and remodeling of the airways. Increased serum IL-17 is also a marker and independent risk factor for severe asthma. Showed that asthma patients had a significantly higher percentage of Th17 cells compared to the healthy children and those with cystic fibrosis. Furthermore, stratifying the asthma group, the percentages of Th17 cells were higher in patients with severe asthma and that with poor control, suggesting that targeting of Th17/IL-17 could possibly be beneficial for those patients.^[5] Thus, having in mind the heterogeneity of the disease, the discovery of new mechanisms in the pathogenesis of asthma could aid the therapy of the patients with the most severe symptoms. On the other hand, the response to Th17 cells and their cytokines should be considered with great attention due to their essential physiological functions performed in the body.

Speaking of immunological mechanisms of asthma, Vitamin D has been intensively studied recently and described as an immunomodulator with the potential to influence the immune system. The biological functions of Vitamin D go beyond its known roles in calcium-phosphate homeostasis and bone metabolism. Receptors for Vitamin D have been found on many immune cells (activated T and B lymphocytes, monocytes, antigen-presenting cells, etc.) by which the Vitamin D exerts various cytokine-modulating effects. Vitamin D further reduces the differentiation and expansion of Th17 lymphocytes that potentiates a more severe and refractory to steroid treatment asthma in children.^[6] On the other hand, the data on the suppression of Th2-responses by Vitamin D are controversial. However, most studies showed that Vitamin D supplementation reduces IL-4 levels in bronchoalveolar fluid and Th2 inflammatory responses, blocking eosinophil migration and decreasing IL-5 levels in mouse models. In children, several large studies have shown an association between asthma and insufficiency or deficiency of Vitamin D.^[7] Moreover, the deficiency of Vitamin D is associated with a reduced pulmonary function in children

and adults, with more severe asthma symptoms, requiring anti-inflammatory medications. In South American children, aged 6–14, a proportional correlation between Vitamin D levels and total IgE and eosinophil was established. Based on this data, many studies have been conducted with Vitamin D supplementation in children and adults with atopy, allergic rhinitis and asthma, although the results are conflicting.^[8] Further studies are needed for the role of Vitamin D in asthma, both for therapeutic and prevention of asthma complications.

REFERENCES

1. Kerzel S, Dehne J, Rogosch T, Schaub B, Maier RF, Zemlin M, *et al.* Th17 cell frequency in peripheral blood from children with allergic asthma correlates with the level of asthma control. *J Pediatr* 2012;161:1172-4.
2. Aujla SJ, Alcorn JF. T(H)17 cells in asthma and inflammation. *Biochim Biophys Acta* 2011;1810:1066-79.
3. Newcomb DC, Peebles RS Jr. Th17-mediated inflammation in asthma. *Curr Opin Immunol* 2013;25:755-60.
4. Irvin C, Zafar I, Good J, Rollins D, Christianson C, Gorska MM, *et al.* Increased frequency of dual-positive TH2/TH17 cells in bronchoalveolar lavage fluid characterizes a population of patients with severe asthma. *J Allergy Clin Immunol* 2014;134:1175-86.
5. Velikova T, Lazova S, Perenovska P, Tumangelova-Yuzeir K, Miteva D, Velikov P, *et al.* Th17 cells in Bulgarian children with chronic obstructive lung diseases. *Allergol Immunopathol (Madr)* 2018;Pii: S0301-0546(18)30110-1.
6. Hamzaoui A, Berraies A, Hamdi B, Kaabachi W, Ammar J, Hamzaoui K, *et al.* Vitamin D reduces the differentiation and expansion of th17 cells in young asthmatic children. *Immunobiology* 2014;219:873-9.
7. Lange NE, Litonjua A, Hawrylowicz CM, Weiss S. Vitamin D, the immune system and asthma. *Expert Rev Clin Immunol* 2009;5:693-702.
8. Sutherland ER, Goleva E, Jackson LP, Stevens AD, Leung DY. Vitamin D levels, lung function, and steroid response in adult asthma. *Am J Respir Crit Care Med* 2010;181:699-704.

How to cite this article: TV Velikova. Th17 cells, Vitamin D, and Asthma. *Clin Res Immunol* 2018;1(1):1-2.