Journal of Immunology, Infection & Inflammatory Diseases

Review Article

Th17 Cells and their Cytokines in the Asthmatic Airway Remodeling: What Do We Know?

This article was published in the following Scient Open Access Journal:
Journal of Immunology, Infection & Inflammatory Diseases
Received March 11, 2017; **Accepted** March 20, 2017; **Published** March 28, 2017

Yangyang Gu, Mengdie Qi and Hequan Li*

Department of Respiratory Diseases, The First Affiliated Hospital of Zhejiang University School of Medicine, Zhejiang University, Hangzhou, Zhejiang, China

Abstract

Asthma is commonly considered as a heterogeneous and chronic disease, characterized by reversible bronchoconstriction, airway hyper reactivity, mucus over-secretion, airway chronic inflammation and remodeling. The imbalance ofTh1/Th2 cell has been recognized as a classical mechanism of allergic asthmapathogenesis. However, nonallergic asthma, usually demonstrate as severe asthma, displays a neutrophil infiltrating inflammation and airway remodeling, causing reversible airflow restriction, airway hyperresponsiveness, even steroidresistance, which can hardly be explained by this mechanism. As a consequence, many recent investigations have shown that Th17 cells throw fresh light on the pathophysiological changes of asthma, here in this review we will focus on the recent findings on Th17 cells in the asthmatic airway remodeling.

Keywords: Th17 cells, Asthma, Chronic inflammation, Airway remodeling

Introduction

Asthma, widely recognized as a chronic airway inflammatory disease, is characterized by reversible bronchoconstriction, airway hyper reactivity, mucus hyper secretion, airway chronic inflammation. The chronic inflammation induced by the chemical mediators released from inflammatory cells can result in airway remodeling, and may have a profound impact on the airway narrowing and chronic progression of asthma [1]. Airway remodeling in asthma consists a variety of progressing pathophysiology changes, including epithelial changes, smooth muscle mass, myofibroblasts hyperactivity, goblet cell hyperplasia, and vascular changes [2]. All these modifications may result in reversible airflow restriction, airway hyper responsiveness, and even steroid resistance.

Classically, asthma is recognized as a typical Th2-relate disease. Many basic and clinical studies have suggested that during the progression of asthma, the T helper type 2 (Th2) cells get proliferated, inducing the imbalance between Th1 and Th2 cells. The Th2 cells move to the epithelium and secrete cytokines IL-4, IL-5 IL-9 and IL-13 [3]. These cytokines cause eosinophil infiltration into the airways, mucus production, forming a complex tissue microenvironment and stimulate the airway inflammation [4]. IL-4 is a key cytokine to modulate Th0 cells differentiate into Th2 cells [5,6]. IL-5 can control the bone eosinophil maturation and activation, as well as migration into the airway, and study showed that by using anti-IL-5 mAb, the numbers of peripheral blood and sputum eosinophils decreased [7]. IL-9 has been revealed to promote the proliferation of T cells, increase IgE production and promote the proliferation of mast cells [8]. Also, IL-9 is associated with airway hyperreaction (AHR) [9]. IL-13 is a key cytokine and play a multifunctional role in the Th2-relate asthma, including contractions of smooth muscle cells [10], mucus hypersecretion, subepithelial fibrosis [11]. However, recent researches indicate that only 50% of asthma patients showed relation with a Th2 immune response.These cases showed low IgE level, high infiltration of neutrophil, which was thought to contribute to the severity of the disease itself [12,13]. All these indicate that except for Th2 response, there may be other mechanisms involved in the pathophysiology of asthma.

Fortunately, the discovery of Th17 cells and IL-17 may throw fresh light on the understanding of asthma. Th17 cells, marked as the third subset of Th cells, are thought

***Corresponding Author:** Li Hequan, Department of Respiratory Diseases, the First Affiliated Hospital of Zhejiang University School of Medicine, Zhejiang University, Hangzhou, 310000, Zhejiang, China, Email: lihequan@zju.edu.cn

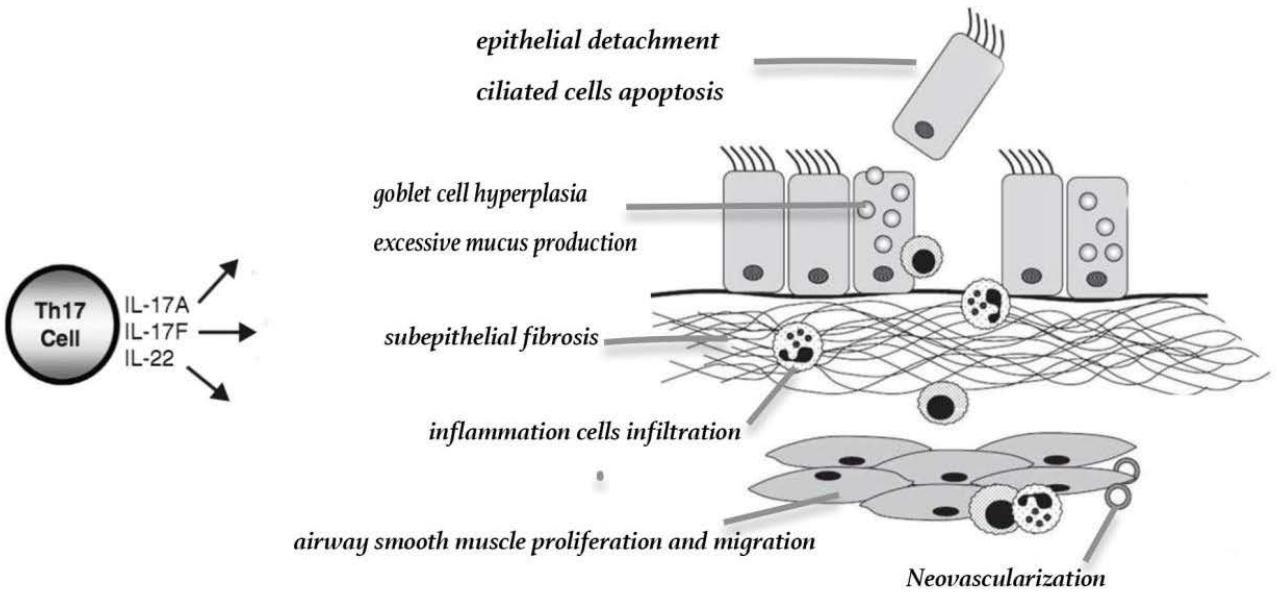

Figure 1: Diagram of Th17 mediate airway remodeling.

to play a key role in asthma [14]. In human, Th17 cells are differentiated from a naïve T cell by the activation of transcription factors signal transducer and activator of transcription (STAT)-3 and RAR-related orphan receptor C(RORC)-2 [15]. Loubaki has shown that bronchial fibroblasts from asthmatic subjects create a microenvironment characterized by an increased expression of IL-6, IL-1β, TGF-β and IL-23, and these are the key cytokines that promote the differentiation and proliferation of Th17 cells [16]. The Th17 cells secrete IL-17A, IL-17F, IL-22, TNF-α, IL-21 and other cytokines and chemokines. IL-17A, IL-17F, and IL-22 are found in the bronchoalveolar lavage (BAL) fluid and bronchial biopsies of asthmatic patients [17]. IL-17A is thought to contribute to the enhancement of the production of profibrotic cytokines (TGF-β, IL-11), proangiogenic factors (VEGF), and collagen [18], and IL-17F, IL-22 are also recognized to have the capacity to induce recruitment of neutrophils, monocytes, and macrophages in lung tissue, resulting in airway inflammation [17,19]. What's more, IL-17A can increase the secretion of IL-1β, IL-6, GM-CSF, VEGF from airway epithelial cells, endothelial cells, and fibroblasts leading to increased neutrophil infiltration and neovascularization, contributing to the pathophysiological changes in asthma [20] (Figure 1).

Th17 cells and their Cytokines in Asthmatic Airway Remodeling

Th17 immune response and epithelial alternations

The airway epithelium, serving as a barrier to prevent the antigens' access to the submucosa, is a source of pro-inflammatory cytokines and chemokines as well [21]. The airway epithelium alternation is a key feature of airway remodeling in asthmatic patients. Epithelial changes in asthmatic airways including the epithelial detachment, ciliated cells apoptosis, the upregulation of cytokines and chemokines [22]. A study has shown that airway inflammation induced STAT3 hyperactivity, which could lead to an expansion of Th17 cells secreting IL-17, then increased neutrophil infiltration and airway epithelium changes, and by inhibiting the STAT3 activation can greatly reduce the secretion of IL-17 [23]. The changed airway epithelial cells upregulated the production of CCL20 [24]. It is suggested to play a role in the recruitment of myeloid DCs (mDCs) and memory CCR6+CD4+ T cells and neutrophils to the airway by binding to the CCR6 expressed on these cells. A recent study revealed that using clusterin to modulate the CCL20 expression in the epithelial cells, the recruitment of inflammatory immune cells into the bronchial epithelium and allergic airway inflammation was attenuated [25]. In addition,the AEC revealed an IL-17– dependent upregulation in matrix metalloproteinase-9(MMP-9), causing collagen degrading, which may contribute to the airway remodeling [26]. Except for that, another study dug out IL-17A can utilize EGFR signaling to stimulate AEC to produce and secrete GM-CSF, that has potent regulatory effects on tissue-resident macrophages, neutrophils as well as eosinophils [27]. The recruited neutrophils degranulated, deploying harmful proteins and proteases such as elastase, myeloperoxidase (MPO), lactoferrin and matrix metalloproteinase-9 (MMP-9) to the extracellular milieu and increasing the capacity for epithelium injury [28]. The epithelium barrier is also defective, the eosinophils in airway tissue secreted the nerve growth factor (TGF), express 5-lipoxygenase, FLAP, and lekotriene C4 synthase, all of which are involved in the loss of epithelial integrity [29]. Recently, a research focused on the respiratory epithelium barrier function has revealed that IL-17 family cytokines (IL-17A, IL-22, and IL-26) can significantly disrupt epithelial barrier function, resulting in the increased paracellular permeability and reduced tight junction integrity [30]. IL-17 has also been found can upregulate collagen V espression and TGF-β expression in the epithelial cells to induce epithelial-mesenchymal transition, resulting in the organ fibrosis [31,32]. These changes make the epithelial cells exert low level expression of proliferating markers, revealing a potential failure in the epithelial injury-repair cycle in response to local inflammation and inhaled agents.

Role of Th17 in airway smooth muscle remodeling and myofibroblasts hyperactivated

Increased airway smooth muscle (ASM) mass is hallmark of airway remodeling in severe asthma, this change of ASM cells are regarded to be the crucial cause of airflow limitation. The ASM cells in the airway get greatly hyperplasia and hypertrophy, migrate towards the epithelium. In addition, the ASM participant in the remodeling progress by expressing a wide range of inflammatory factors (TGF-β1, TNF-α, IL-1β, IFN-γ, etc.), cellular adhesion molecules, cytokine receptors, chemokines and so on [33]. Th17 related cytokines (IL-17A, IL-17F and IL-22) are associated with the proliferation and migration of ASM cells through different signaling pathway [19]. IL-17RA, IL-17RC, and IL-22R1 were present on the ASMCs, IL-17A and IL-17F were bind to the 17RA and IL-17RC,increasing ASM cells proliferation and migration through p38 MAPK and ERK1/2 MAPK pathways, while IL-22 increased the proliferation, migration and reduces the apoptotic rate of ASM cells through ERK1/2 and NF-kB pathway, as is reported [19,34-36].

Fibroblasts are the most common cell types of the connective tissue in airway. In asthmatic patients, injury and repairmen causes complex tissue microenvironment of the asthmatic airway, so the fibroblasts differentiated into myofibroblasts. These cells excessively release fibrillary components such as collagen types I (COL1), III (COL3), and V (COL5) [37], and extracellular matrix components such as elastin, hyaluronan (HA),perlecan (heparan sulfate proteoglycan 2, HSPG2), tenascin-C (TNC) and laminin [18,38]. So the subepithelial fibrils are replaced by a kind of compact fibrous tissue, as we call subepithelium fibrosis. As has mentioned before, bronchial fibroblast can induce the expression of IL-17A, and IL-17A can significantly enhance the α-SMA and proliferate the fibrocytes, release large amounts of CXCL1, CXCL8, and TNF-α and may lead the mature fibrocytes accumulate in the airway [18]. These proliferated cells can secrete a large amount of IL-6 and leukemia inhibitory factor (LIF). CXCL1, CXCL8, IL-6 can influence neutrophil recruitment and has a key role in the transition from acute to chronic inflammation [39], and leukemia inhibitory factor can increase airway smooth muscles [40]. Another study showed that IL-17A and IL-17F can regulate fibrocyte functions so as to produce collagen in response to CD40 signaling and allows these cells to differentiate into a myofibroblastic phenotype [41]. IL-21, IL-22 and IL-23, binding to their receptors, can activate receptor-associated tyrosine kinases(JAK/SRC),and subsequently make the STAT3 phosphorylated, which enhances the persistence of lung airway fibroblasts and endothelial cells [42]. Also, IL-17A leads to the secretion of TGF-β1 of fibroblasts, which is a profibrotic cytokine and may implicate in the extracellular matrix changes observed in fibrosis. And a study has revealed that enhanced by Wnt5a, IL-17A can activate lung fibroblasts even at a very low level, which suggests there may be an IL-17A/TGF-β1/Wnt5a signaling pathway in asthmatically activated pulmonary fibroblasts [43].

Th17 cells and goblet cells hyperplasia

Goblet cells hypertrophy and hyperplasia are also involved in airway remodeling leading to excessive mucus production. MUC5AC and MUC5B are considered to be important mucins in the airway, while MUC5AC due to its high expression in mucus-secreting goblet cells, regarded as the most particular marker of mucus cell hyperplasia [44]. In primary study, IL-17A and IL-1β, as the proinflammatory cytokines, are powerful generators to enhance the mucin(MUC)5AC gene expression and protein synthesis through the NF-κB pathway [45]. In mice, RSV infection increased mucous cell metaplasia and mucin expression when IL-17A and IL-13 was increased in the lung sample. IL-13 was thought to bind to the transcription factor signal transducers and activators of transcription (STAT)−6, both of which deficient down regulating the airway mucous cell metaplasia with allergic airway inflammation. However, in the study of RSV-infected SATA-6 KO mice still came up with airway mucus production [46], showing that mucous cell metaplasia was not absolutely STAT6-dependent and more likely by IL-17A expression in these mice. What's more, overexpression of IL-17F in the airway of mice can also result in the goblet cell hyperplasia and elevation of MUC5AC gene expression [47]. And in our previous study, we demonstrated that Th17/IL-17 increased the expression of HB-EGF and could therefore act through EGFR to promote mucus secretion [48]. All of these revealing the Th17 relevant cytokines a crucial role in the asthma mucus secretion.

Th17 cells and neovascularization

Airway vascular remodeling is also a primary feature of airway remodeling. It has already been reported that an abnormal increasing number and size of microvessels within the bronchial tissue of asthmatic airways [49]. The neovascularization includes both angiogenesis and vasculogenesis, which means mature pulmonary microvascular endothelial cells (PMVECs) migrate and proliferate to form sprouts from parental vessel and vasculogenesis refers to the process that endothelial progenitor cells (EPCs) migrate, differentiate into mature endothelial cells, and then form new vessels [50]. Vascular endothelial growth factor (VEGF) plays a fundamental role in physiological and pathophysiological forms of this abnormality [51]. Studies have reported that the IL-17 cytokines worked as angiogenic mediators, inducing endothelial migration and tube formation, in the disease of rheumatoid arthritis, systemic lupus erythematous [52]. Consequently, Th17 cells and its cytokines may also involve in the asthma airway vascular remodeling. A study has revealed that in the asthmatic airway, the number of VEGF mRNA-expression cells were increasing, which we have already mentioned played a crucial role in the neovascularization. The major sources of VEGF are CD34+ cells, and IL-17F associated with CD40L expressed by the activated Th17 cells can enhance these cells to express VEGF and angiogenin, further participate in neovascularization in asthmatic airway [41]. In our previous study, we have found that neutralization of IL-17A led to reduced vascularity in the lung of OVA-challenged mice, whereas IL-17F antagonism did not markedly influence the microvascular regeneration. What's more, we found that IL-17A had no straight effect on the pulmonary microvascular endothelial cells proliferating, but did promote the tubule formation through the activation of PI3K/AKT pathway. In general, there was a progressing new microvascular formation around the bronchi with the participation of Th17 cells [50].

Conclusion

Asthma is a heterogeneous disease consists of different phenotypes, numerous studies have shown that Th17 cells and its cytokines participate in the pathophysiology progression in this disease, especially in airway remodeling. As is revealed

above, IL-17A/F, IL-22 and other cytokines induced epithelial changes, smooth muscle mass, fibroblasts hyperactivity, mucin hyperplasia, and vascularization through a variety of signal pathways. Targeting at the Th17 cells has already become a popular research topic these days. However, the steroid can only well relieve the Th2-type asthma, but rarely works with the Th17-type asthma. It's urgent to make further investigations of Th17 cells, in order to find more novel approaches to the diagnosis and therapies of asthma.

Acknowledgements

All authors contributed substantially to the work to take responsibility for the content and have read and approved the final version of the manuscript.

References

1. George L, Brightling CE. Eosinophilic airway inflammation: role in asthma and chronic obstructive pulmonary disease. *Ther Adv Chronic Dis*. 2016;7(1):34-51.
2. Al-Muhsen S, Johnson JR, Hamid Q. Remodeling in asthma. *J Allergy Clin Immunol.* 2011;128(3):451-462.
3. Barnes PJ. Th2 cytokines and asthma: an introduction. *Respir Res*. 2001;2(2):64-65.
4. Nakajima H, Hirose K. Role of IL-23 and Th17 Cells in Airway Inflammation in Asthma. *Immune Netw.* 2010;10(1):1-4.
5. Noben-Trauth N, Hu-Li J, Paul WE. IL-4 secreted from individual naive CD4+ T cells acts in an autocrine manner to induce Th2 differentiation. *Eur J Immunol*. 2002;32(5):1428-1433.
6. Aron JL, Akbari O. Regulatory T cells and type 2 innate lymphoid cell-dependent asthma. *Allergy.* 2017.
7. Takatsu K: Interleukin-5 and IL-5 receptor in health and diseases. *Proc Jpn Acad Ser B Phys Biol Sci.* 2011;87(8):463-485.
8. Koch S, Sopel N, Finotto S. Th9 and other IL-9-producing cells in allergic asthma. *Semin Immunopathol.* 2017;39(1):55-68.
9. Oh CK, Raible D, Geba GP, Molfino NA. Biology of the interleukin-9 pathway and its therapeutic potential for the treatment of asthma. *Inflamm Allergy Drug Targets.* 2011;10(3):180-186.
10. Risse PA, Jo T, Suarez , et al. Interleukin-13 inhibits proliferation and enhances contractility of human airway smooth muscle cells without change in contractile phenotype. *Am J Physiol Lung Cell Mol Physiol.* 2011;300(6):L958-966.
11. Zhu Z, Homer RJ, Wang Z, et al. Pulmonary expression of interleukin-13 causes inflammation, mucus hypersecretion, subepithelial fibrosis, physiologic abnormalities, and eotaxin production. *J Clin Invest.* 1999;103(6):779-788.
12. Douwes J, Gibson P, Pekkanen J, Pearce N. Non-eosinophilic asthma: importanceand possible mechanisms. *Thorax.* 2002;57(7):643-648.
13. Pavord ID. Non-eosinophilic asthma and the innate immune response. *Thorax*. 2007;62(3):193-194.
14. Cosmi L, Liotta F, Maggi E, Romagnani S, Annunziato F.Th17 cells: new players inasthma pathogenesis. *Allergy.* 2011;66(8):989-998.
15. Korn T, Bettelli E, Oukka M, Kuchroo VK.IL-17 and Th17 Cells. *Annual Reviews of Immunology.* 2009;27:485-517.
16. Loubaki L, Hadj-Salem I, Fakhfakh R, et al. Co-culture of human bronchial fibroblasts and CD4+ T cells increases Th17 cytokine signature. *PloS One.* 2013;8(12):e81983.
17. Newcomb DC, Peebles RS Jr.Th17-mediated inflammation in asthma. *Curr Opin Immunol.*2013; 25(6):755-760.
18. Bellini A, Marini MA, Bianchetti L, Barczyk M, Schmidt M, Mattoli S. Interleukin(IL)-4, IL-13, and IL-17A differentially affect the profibrotic and proinflammatory functions of fibrocytes from asthmatic patients. *Mucosal Immunol*. 2012;5(2):140-149.
19. Chang Y, Al-Alwan L, Risse PA, et al. TH17 cytokines induce human airway smooth muscle cell migration. *J Allergy Clin Immunol*. 2011;127(4):1046-1053.
20. Alcorn JF, Crowe CR, Kolls JK. TH17 cells in asthma and COPD. *Annual Review of Physiology.* 2010;72:495-516.
21. Hackett TL, Singhera GK, Shaheen F, et al. Intrinsic phenotypic differences of asthmatic epithelium and its inflammatory responses to respiratory syncytial virus and air pollution. *Am J Respir Cell Mol Biol.* 2011;45(5):1090-1100.
22. Halwani R, Al-Muhsen S, Hamid Q. Airway remodeling in asthma. *Curr Opin Pharmacol*. 2010;10(3):236-245.
23. Gavino AC, Nahmod K, Bharadwaj U, Makedonas G, Tweardy DJ. STAT3 inhibitionprevents lung inflammation, remodeling, and accumulation of Th2 and Th17 cells in a murine asthma model. *Allergy* 2016;71(12):1684-1692.
24. Ito T, Carson WF, Cavassani KA, Connett JM, Kunkel SL. CCR6 as a mediator of immunity in the lung and gut. *Exp Cell Res*. 2011;317(5):613-619.
25. 25. Hong GH, Kwon HS, Moon KA, et al. Clusterin Modulates Allergic Airway Inflammation by Attenuating CCL20-Mediated Dendritic Cell Recruitment. *J Immunol*. 2016;196(5):2021-2030.
26. Fogli LK, Sundrud MS, Goel S, et al. T cell-derived IL-17 mediates epithelial changes inthe airway and drives pulmonary neutrophilia. *J Immunol.* 2013;191(6):3100-3111.
27. Acciani TH, SUZUKI T, Trapnell BC, Le Cras TD. Epidermal growth factor receptor signalling regulates granulocyte-macrophage colony-stimulating factor productionby airway epithelial cells and established allergic airway disease. *Clin Exp Allergy*. 2016;46(2):317-328.
28. Hoenderdos K, Lodge KM, Hirst RA, et al. Hypoxia upregulates neutrophil degranulation and potential for tissue injury. *Thorax.* 2016;71(11):1030-1038.
29. Pawankar R, Hayashi M, Yamanishi S, Igarashi T. The paradigm of cytokine networks in allergic airway inflammation. *Curr Opin Allergy Clin Immunol*. 2015;15(1):41-48.
30. Ramezanpour M, Moraitis S, Smith JL, Wormald PJ, Vreugde S. Th17 Cytokines Disrupt the Airway Mucosal Barrier in Chronic Rhinosinusitis. *Mediators Inflamm.* 2016;9798206.
31. Sohal SS, Ward C, Walters EH. Importance of epithelial mesenchymal transition (EMT) in COPD and asthma. *Thorax.* 2014;69(8):768.
32. Vittal R, Fan L, Greenspan DS, et al. IL-17 induces type V collagen overexpression and EMT via TGF-β-dependent pathways in obliterative bronchiolitis. *Am J Physiol Lung Cell Mol Physiol.* 2013;304(6):L401-414.
33. Kudo M, Ishigatsubo Y, Aoki I. Pathology of asthma. *Front Microbiol*. 2013;4:263.
34. Farahani R, Sherkat R, Hakemi MG, Eskandari N, Yazdani R. Cytokines (interleukin-9,IL-17, IL-22, IL-25 and IL-33) and asthma. *Adv Biomed Res.* 2014;3:127.
35. Chang Y, Al-Alwan L, Risse PA, et al. Th17-associated cytokines promote human airway smooth muscle cell proliferation. *FASEB J.* 2012;26(12):5152-5160.
36. Yeganeh B, Xia C, Movassagh H, et al. Emerging mediators of airway smooth muscle dysfunction in asthma. *Pulm Pharmacol Ther*. 2013;26(1):105-111.
37. Roche WR, Beasley R, Williams JH, Holgate ST. Subepithelial fibrosis in the bronchi of asthmatics. *Lancet.* 1989;1(8637):520-524.
38. Roberts CR. Is asthma a fibrotic disease? *Chest*. 1995;107(3 Suppl):111S-117S.
39. Silver JS, Hunter CA. gp130 at the nexus of inflammation, autoimmunity, and cancer. *J Leukoc Biol.* 2010;88(6):1145-1156.
40. Knight D. Leukaemia inhibitory factor (LIF): a cytokine of emerging importance inchronic airway inflammation. *Pulm Pharmacol Ther*. 2001;14(3):169-176.
41. Hayashi H, Kawakita A, Okazaki S, Yasutomi M, Murai H, Ohshima Y. IL-17A/FModulates Fibrocyte Functions in Cooperation with CD40-Mediated Signaling. *Inflammation.* 2013;36(4):830-838.
42. Halwani R, Sultana A, Al-Kufaidy R, Jamhawi A, Vazquez-Tello A, Al-Muhsen S. Th-17regulatory cytokines inhibit corticosteroid induced airway structural cells apoptosis. *Respir Res.* 2016;17:6.

43. Peters M, Kohler-Bachmann S, Lenz-Habijan T, Bufe A. Influence of anAllergen-Specific Th17 Response on Remodeling of the Airways. *Am J Respir Cell Mol Biol*. 2016;54(3):350-358.

44. Reid CJ, Gould S, Harris A. Developmental expression of mucin genes in the humanrespiratory tract. *Am J Respir Cell Mol Biol.* 1997;17(5):592-598.

45. Fujisawa T, Velichko S, Thai P, Hung LY, Huang F, Wu R. Regulation of airwayMUC5AC expression by IL-1beta and IL-17A; the NF-kappaB paradigm. *J Immunol.* 2009;183(10):6236-6243.

46. Newcomb DC, Boswell MG, Sherrill TP, et al. IL-17A induces signal transducers andactivators of transcription-6-independent airway mucous cell metaplasia. *Am JRespir Cell Mol Biol*. 2013;48(6):711-716.

47. Liu ZJ, Yadav PK, Su JL, Wang JS, Fei K. Potential role of Th17 cells in thepathogenesis of inflammatory bowel disease. *World J Gastroenterol.* 2009;15(46):5784-5788.

48. Wang Q, Li H, Yao Y, Xia D, Zhou J. The overexpression of heparin-binding epidermal growth factor is responsible for Th17-induced airway remodeling in an experimental asthma model. *J Immunol.* 2010;185(2):834-841.

49. McDonald DM. Angiogenesis and remodeling of airway vasculature in chronic inflammation. *Am J Respir Crit Care Med.* 2001;164(10 Pt 2):S39-45.

50. Lu S, Li H, Gao R, et al. IL-17A, But Not IL-17F, Is Indispensable for Airway Vascular Remodeling Induced by Exaggerated Th17 Cell Responses in Prolonged Ovalbumin-Challenged Mice. *J Immunol* 2015;194(8):3557-3566.

51. Orihara K, Dil N, Anaparti V, Moqbel R. What's new in asthma pathophysiology and immunopathology? *Expert Rev Respir Med*. 2010;4(5):605-629.

52. Pickens SR, Volin MV, Mandelin AM 2nd, Kolls JK, Pope RM, Shahrara S. IL-17 contributes to angiogenesis in rheumatoid arthritis. *Journal of Immunology*. 2010;184(6):3233-3241.