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

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 of Th1/Th2 cell has been recognized as a classical mechanism of allergic asthmopathogenesis. However, nonallergic asthma, usually demonstrate as severe asthma, displays a neutrophil infiltrating inflammation and airway remodeling, causing reversible airflow restriction, airway hyperresponsiveness, even steroid resistance, 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 to play a role in both the development and maintenance of Th1 and Th2 cells [14]. These cells are characterized by their ability to produce IL-17A, IL-17F, and IL-22, which are known to contribute to tissue damage and remodeling in chronic inflammation [15]. In asthma, Th17 cells have been implicated in the pathogenesis of airway remodeling, as they have been shown to promote epithelial damage and fibrosis [16].

*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
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).

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### 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 CD6+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, 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 (NGF), express 5-lipoxygenase (LOX), leukotriene 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 expression 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 process 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-κB 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 reparation causes complex tissue microenvironment of the asthmatic airway, so the fibroblasts differentiated into myofibroblasts. These cells excessively release fibrylary 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 been 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 prominent 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(MUC5AC) 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 STAT-6-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 erythematosus [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 tube 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.

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References


