



Th17/IL-17 Axis Regulated by Airway Microbes Get Involved in the Development of Asthma

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Abstract

Purpose of Review Bronchial asthma is a common respiratory disease induced by immune imbalance, characterized by chronic non-specific airway inflammation and airway hyperresponsiveness (AHR). Many factors induce asthma, among which respiratory infection is the important cause. In this review, we discuss how respiratory microbes participate in the occurrence and progression of asthma via Th17/IL-17 axis.

Recent Findings Pathogenesis of asthma has been considered as closely related to the imbalance in number and function of Th1/Th2 in the CD4⁺ T lymphocyte subsets. Recent studies have shown that Th17 cell and its secretory IL-17 also play an important role in AHR. Respiratory virus, bacteria, fungi, and other respiratory microbial infections can directly or indirectly induce the differentiation of Th17 cell and the production of related cytokines to induce AHR.

Summary Respiratory microbial infection can affect the Th17/IL-17A axis through a variety of mechanisms, thereby promoting the occurrence and development of asthma, and these specific mechanisms may provide new effective therapeutic ideas for asthma.

Keywords Respiratory microbes · Th17 · IL-17 · Asthma

Introduction

Bronchial asthma is a chronic airway inflammation, accompanied by recurrent wheezing, coughing, chest tightness, shortness of breath, and other symptoms, even reversible expiratory airflow limitation [1, 2]. Its morbidity and mortality have con-

tinued to increase over the past 20 years, with approximately 300 million people worldwide currently suffering from asthma [3, 4]. Traditionally, considered Th2 dominant, Th1/Th2 imbalance is the main mechanism of asthma, and cytokines such as IL-4, IL-5, IL-13 secreted by Th2 cells can promote the synthesis of IgE, the recruitment of eosinophil cells, and the secretion of mucus [5]. This induces airway hyperresponsiveness (AHR) and leads to the occurrence of allergic asthma. However, this cannot fully explain the cause of asthma. In recent years, numerous studies have shown that Th17 cells and their cytokines are to a greater extent associated with the development of asthma. Th17 cells are novel effector T cells unlike Th1 and Th2 cells, which secrete cytokines such as IL-17A/F, IL-21, IL-22, TNF- α [6], and participate in various autoimmune diseases, such as asthma, rheumatoid arthritis, systemic lupus erythematosus, and psoriasis [7–10]. In the pathogenesis of asthma, Th17/IL-17A can induce the accumulation of neutrophils in the airway and participate in the process of neutrophil-based asthma. In addition, the activation of Th17 cells and the massive secretion of IL-17 can increase the immune response of Th2 cells, thereby aggravating the severity of allergic asthma.

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Among the multiple factors that cause bronchial asthma, respiratory infections play an important role. It has been confirmed that respiratory viruses, bacteria, and fungi can induce or aggravate the onset of asthma, such as respiratory syncytial viruses (RSV), *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and fungi pathogens, which are associated with Th17 response. Therefore, this article will focus on how these respiratory microorganisms affect the development of asthma through Th17/IL-17A axis.

Differentiation and Function of Th17 Cells

Th17 cells are a specific subset of CD4⁺ T helper cells, which were distinguishable from Th0 cells under the induction of various cytokines such as TGF- β , IL-6, IL-21, and IL-23. IL-6, IL-21, and low concentrations of TGF- β initiate Th17 cell differentiation and inhibit Treg cell differentiation via transcription factor retinoic acid receptor-associated orphan nuclear receptor- γ t (ROR γ t) and signal transduction and activator of transcription 3 (STAT3) [11–13]. ROR γ t is the major transcription factor of Th17 cells, and ROR α can synergize with ROR γ t to promote the differentiation of Th17 cells [14]. IL-6 is combined with its receptor IL-6R, and the complex formed by binding to gp130 activate the downstream JAK/STAT3 signaling pathway, thereby promoting the differentiation of Th17 cells [15]. It was originally thought that IL-23 could induce Th0 cells to differentiate into Th17 cells. However, with more profound research, it was found that IL-23 could not initiate Th17 cell differentiation, but maintained the Th17 cell phenotype and further promoted the differentiation and maturation of Th17 cells [16, 17]. The subunit IL-12p19 of IL-23 binds to IL-23R receptor, activating downstream JAK2, which in turn directly causes the phosphorylation of STAT3, and the transcription of the target gene is induced after phosphorylated STAT3 enters the nucleus, thus promoting the differentiation of Th17 cells and the expression of IL-17. Furthermore, JAK2 can activate downstream PI3K/Akt and I κ B- α /NF- κ B signaling pathways. After PI3K/Akt mediates STAT3 phosphorylation, p-STAT3 and NF- κ B enter the nucleus to promote IL-17 expression [18]. McGeachy et al. [19] found out that the presence of IL-23 is required for Th17 cell differentiation to maintain its expansion and migration (Fig. 1).

Th17 cells can produce IL-17A, IL-22, IL-17F, and other cytokines, where the activation of IL-17A can stimulate epithelial cells, endothelial cells, fibroblasts, macrophages, cartilage cells, osteoblasts, etc. to produce a variety of inflammatory factors, such as IL-6, IL-8, TNF, matrix metalloproteinase, chemokine, and RANK ligands [20], inducing the activation and migration of neutrophils, and participating in a variety of immune and inflammatory responses. Th17 cells also

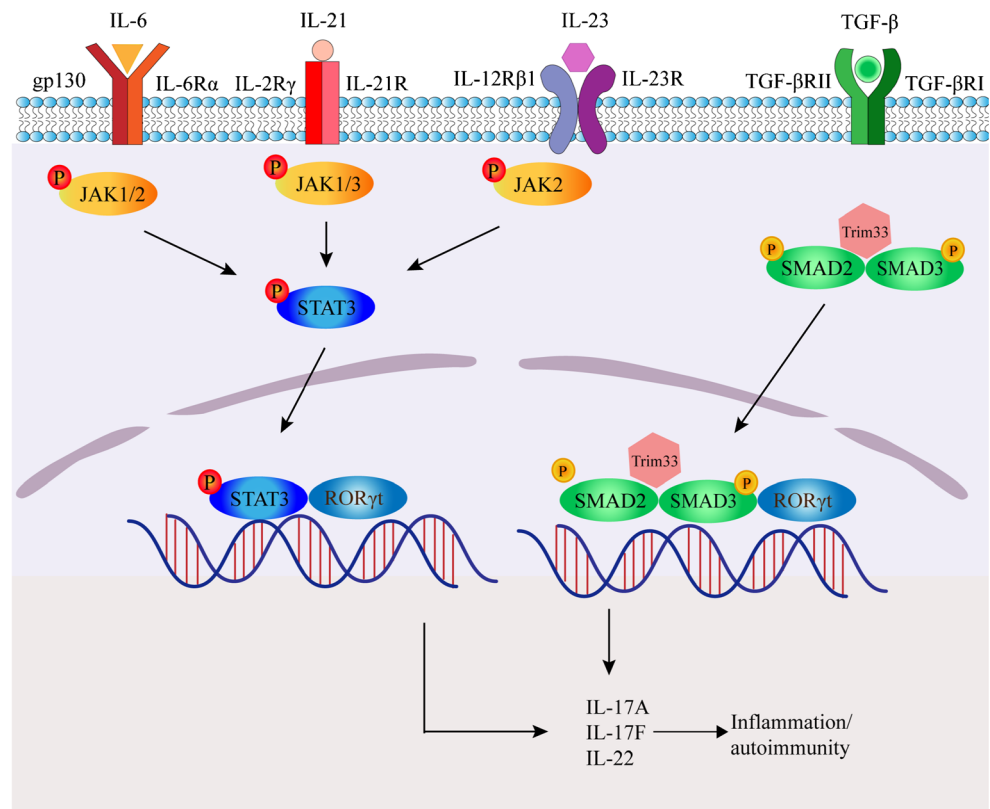
produce other pro-inflammatory cytokines, including IL-6, TNF- α , IL-22, and IL-21, besides IL-17 family. During the development of asthma, Th17 cells may exert their biological effects mainly through IL-17A, which is a required cytokine for allergic asthma attacks. Studies have shown that the expression level of IL-17A is proportional to the severity of asthma in patients' serum and airways [21, 22], indicating that Th17 cells and their secreted cytokines play a significant role in asthma, and that IL-17A is considered an important cytokine to induce the inflammatory response of neutrophil-mediated asthma [23].

Respiratory Syncytial Viruses Regulates Th17/IL-17 Differentiation

RSV is the main pathogen of lower respiratory tract infection in children, and studies have shown that RSV-induced bronchitis is related to the development of later asthma. Children who live with severe RSV infection-induced bronchiolitis in infancy increase the risk of recurrent wheezing or asthma significantly at the age of 13 [24]. Qin et al. [25] found out that human bronchial epithelial cells (BECs), which are continuously infected with RSV can promote the differentiation of Th2 and Th17, enhancing the release of lymphocyte factors such as IL-4, IFN- λ , and IL-17, and inhibiting the differentiation of Tregs.

Through a mice model, Khare et al. [26] demonstrated that early infection with RSV impairs the function of regulatory T cells, thereby increasing the susceptibility to allergic asthma. In addition, several studies have demonstrated that RSV primary infections on ovalbumin (OVA)-challenged mice may reduce airway inflammation via the reversal of the imbalance of Th17/Treg pathological response. When RSV is re-infected with OVA-sensitized mice, it enhances airway inflammation by exacerbating Th17-dominant Th17/Treg imbalance [27]. The above studies indicated that RSV infection can induce Th17 cell differentiation, leading to imbalance of Th17/Treg and affecting the occurrence and development of asthma.

RSV-infected BECs produced a range of factors that promote Th17 cell transcription factor ROR γ t and signal transduction STAT3 gene expression, and increase the secretion of IL-17 [28], while blocking IL-23 or using p38 MAPK inhibitors can significantly inhibit the differentiation of Th17 cells [29]. Wang et al. [30] found out that STAT3 may be involved in the p38 MAPK signaling pathway, and that p-STAT3 levels are reduced when p38 is inhibited. Therefore, these studies suggest that RSV-infected epithelial cells may induce differentiation of Th17 cells by activating the p38 MAPK signaling pathway through IL-23. Leptin, a protein expressed by adipocytes, is widely found in lung tissue and has been shown to be involved in a variety of immune and inflammatory responses.

Fig. 1 Regulation of Th17 cell differentiation

Qin et al. [31] found out that leptin secretion was significantly increased in RSV-infected BECs, and upregulated leptin may stimulate Th17 differentiation and inhibit Th1 cell differentiation by regulating ERK1/2 phosphorylation, indicating that RSV infection may upregulate leptin levels, promoting Th17 differentiation and mediating airway inflammation. The secretion of IL-17 is increased in septic mice after infection with RSV, which appears to be dependent on STAT3 rather than RORγt. After blocking IL-17, the survival rate of the mice increased and the airway mucus production decreased. This indicates that RSV infection in mice with sepsis increases the binding of STAT3 to the IL-17 promoter, thereby increasing IL-17 production [32]. Other studies have shown that RSV induces an increase in IL-6 production in human alveolar type II epithelial cells (A549), which activates the STAT-3 pathway [33]. In addition, activation of NF-κB, STAT3, COX-2, and MAPK signaling pathways were likewise detected in RSV-infected airway epithelial cells (AEC) [34]. The complement system and chemokines are also engaged in RSV-induced Th17 cell responses. RSV is able to promote IL-17A expression via the complement C3a-raplikin axis [35] and impair asthma tolerance by recruiting IL-17A-producing cells through CCR6-CCL20 signaling [36]. Our study demonstrates that non-structural proteins of RSV can bind with histone H2B and lead to demethylation of promoter and high level of expression of Nodal which is closely related to proliferation and EMT of BECs and subsequent Th2 and Th17

differentiation [37, 38]. RSV can also stimulate the differentiation of Th2 cells and Th17 cells in the airway microenvironment by activating the Notch-1/Jagged1 and Notch-1/Delta3 signaling pathway, respectively [39].

Mukherjee found out that the expression of IL-6, IL-23, and IL-17 was significantly increased in the lungs of RSV-infected mice, while the number of CD8⁺ T cells and viral protein expression were decreased in IL-17^{-/-} mice after infection with RSV [40]. Another study found out that the expression of IL-13 and the production of mucus in the lungs were reduced after blocking IL-17 in RSV-infected mice [41]. It speculated that IL-17-induced mucus production depends partly on IL-13 expression. The above studies indicate that RSV infection can participate in the development of asthma by promoting the differentiation of Th17 cells and the expression of IL-17.

Bacteria Regulate TH17/IL-17 Differentiation

In recent years, there has been increasing evidence that bacteria colonize the lower respiratory tract, which is linked to the onset of asthma. Studies have found an increased risk of developing asthma in newborns infected with bacteria such as *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis* in the respiratory tract [42]. In addition, *M. pneumoniae* and *C.*

pneumoniae are also closely related to the development of asthma [43].

H. influenzae is one of the principal pathogens involved in neutrophil asthma. In order to study the effects of bacterial colonization on asthma, Yang [44] successfully established a murine model of mild airway inflammation of bacterial colonization by exposing OVA-sensitive mice to low-dose *H. influenzae*, and found out that during OVA-induced allergic airway disease (AAD), long-term exposure to low-dose *H. influenzae* promoted Th17-associated neutrophil airway inflammation and led to increased airway mucin secretion and airway remodeling. Furthermore, a single *H. influenzae* infection may also be involved in the development of neutrophilic asthma. Mice infected with *H. influenzae* on the day of OVA sensitization showed that there are a greater number of neutrophils recruited into the airways in infected, allergic compared with uninfected, allergic groups, which is associated with infection-induced release of the Th17 cytokine IL-17 when challenged again with allergens [45]. Taken together, these results demonstrate that *H. influenzae* infection enhanced neutrophilic inflammation via the release of IL-17.

S. pneumoniae is an important pathogen causing community-acquired pneumonia in children and adults, and epidemiological studies have shown that *S. pneumoniae* infection is closely related to the development of asthma. Neonatal *S. pneumoniae* infection exacerbated adulthood hallmark features of AAD, with enhanced AHR and increased neutrophil recruitment into the airways, increased Th17 cells and the production of IL-17A. After intranasal inoculation of *S. pneumoniae* in neonatal (1-week old) female mice, then the mice were challenged with OVA in adulthood to establish an allergic airway disease model. Compared with uninfected allergic mice, OVA⁺ *S. pneumoniae* mice have increased Th17 cells and IL-17A in the lungs, with elevated neutrophil recruitment into the airways, while the expression of interferon- γ (IFN- γ) in BALF was decreased. IL-17A depletion alleviated AHR, and the level of IFN- γ was partially restored [46•]. In addition, *S. pneumoniae* infection in the neonatal period softened the expression of the airway smooth muscle (ASM) protein alpha-smooth-muscle-actin (α -SMA) and smooth-muscle-myosin-heavy-chain (SMMHC) in mice with allergic asthma [47], while IL-17A was associated with ASM cell proliferation and contraction. It is assumed that IL-17A can promote ASM remodeling and AHR by raising the levels of α -SMA and SMMHC.

M. catarrhalis is a mucosal pathogen that causes respiratory infections such as pneumonia, otitis media, and chronic obstructive pulmonary disease in children. Infection with *M. catarrhalis* increases the risk of asthma in neonates and chronic lung disease patients. The levels of IL-17A, IFN- λ , IL-5, and IL-13 in the lungs of HDM-sensitive mice infected with the bacteria were significantly increased, while the airways inflammation was alleviated with decreased level of

goblet cell and mucus in IL-17A^{-/-} infected allergic mice. Blocking TNF- α before infection in HDM-sensitized mice attenuated the activation of IFN- γ ⁺IL-17⁺ lymphocytes [48•], indicating that *M. catarrhalis* infection mainly through IL-17 and TNF- α -dependent inflammation exacerbates HDM-triggered allergic airway inflammation, and blocking IL-17 or TNF- α can prevent allergic asthma induced by infection.

M. pneumoniae is a pleomorphic pathogen that attaches primarily to the surface of the respiratory and reproductive tract. *M. pneumoniae* infection causes lower airway chronic inflammation by damaging the clearance of cilia and increasing mucus secretion. Wood et al. [49] identified 64% *M. pneumoniae* positive participants of 53 patients with acute asthma, 65% of those with refractory asthma. Furthermore, Kassinis et al. [50] recruited 180 children, of whom 130 had acute asthma, and the rate of *M. pneumoniae* infection in children with acute asthma was as high as 46%. Martin [51] found out that in the mice model infected with *M. pneumoniae*, the AHR was significantly higher than that in the control group, further verifying the interaction between *M. pneumoniae* infection and AHR. At present, the mechanism of asthma induced by *M. pneumoniae* infection is still unclear. Researchers have indicated that *M. pneumoniae* infection has a dual effect on allergic asthma. That is, infection with *M. pneumoniae* before allergen sensitization can inhibit airway inflammation and AHR, while infection with *M. pneumoniae* after exposure to allergens can aggravate airway inflammation [52]. Studies have found that IL-17A in the lungs is markedly elevated in mice after repeated infection with *M. pneumoniae*. In vitro, the levels of IL-17A and IL-10 in the culture medium were found to be upregulated with the increase of the concentration of the *M. pneumoniae* [53]. In the recovery period, the serum IL-17 level in atopic children with *M. pneumoniae* was significantly higher than that in the acute phase and also higher than serum IL-17 levels in children with atopic non-*M. pneumoniae* during recovery. This suggests that low levels of IL-17 in the acute period may cause more *M. pneumoniae* to reside in the respiratory mucosa, while unremoved *M. pneumoniae* persistent infections can lead to elevated levels of IL-17 during recovery, which in turn increases airway remodeling and airway mucus secretion [54]. The IL-23/Th17 axis is critical for *M. pneumoniae* infection, and *M. pneumoniae*-infected mouse primary lung cells results in increased concentrations of IL-23 and IL-17 in the culture medium [55]. In addition, mice infected with *M. pneumoniae* increased the IL-23 secreted by alveolar macrophages, and the levels of IL-17A, IL-17F, and IL-17C in mouse BALF were also significantly upregulated. However, after neutralizing IL-23p19, the expression of IL-17 and IL-17F was inhibited, accompanied by a decrease in aggregation of neutrophils in the lungs [56]. Moreover, STAT3 is critical for Th17 cell development and cytokine

production. Inhibiting STAT3 can reduce airway inflammation and airway remodeling in asthma model mice [57]. It is believed that *M. pneumoniae* infection activates IL-6/STAT3, which can promote the differentiation of Th17 cells and the secretion of cytokines to mediate the development of asthma.

C. pneumoniae is a major pathogen of acute respiratory infection in children, which can cause bronchitis, chronic obstructive pulmonary disease (COPD), otitis media, sinusitis, asthma, and other diseases. Infection with *C. pneumoniae* at different stages of life may have different effects on allergic asthma. Low-dose *C. pneumoniae* infection aggravates human serum albumin (HSA)-induced airway allergy, which is dependent on the TLR4-MyD88 signaling pathway, through which the level of Tregs in the lungs of mice is reduced [58]. In addition, *Chlamydia* can induce IL-17A expression via MyD88-dependent pathway after infection in mice. IL-17 increases IL-6 and human macrophage inflammatory protein 2 (MIP-2) cytokine production and induces neutrophil infiltration during *Chlamydia* infection to amplify the inflammatory response [59]. Studies have also shown that IL-23 and IL-17A in the lungs are significantly increased in mice infected with *C. pneumoniae*. IL-17A peaks on the 7th day after infection, and IL-17A-induced neutrophil aggregation and airway inflammation are associated with the release of keratinocyte chemoattractant (KC), MIP-2, and lipopolysaccharide (LPS)-induced C-X-C chemokine (LIX) [60].

Fungi

The Th17 response is essential for the early removal of fungi, but repeated fungal infections induce inflammation of Th17 cells in the airways and lungs, leading to the accumulation of neutrophils and tissue damages. *Alternaria alternata* is associated with the onset of acute asthma. It was noted that after infection with *A. alternata*, the expression of Th2 cytokines IL-4, IL-13, and IL-5 in the lungs of mice increased, and the AHR was aggravated. JAK/STAT6 is a downstream pathway of IL-4 and IL-13. Although blocking STAT6 can inhibit Th2-induced eosinophilic asthma, it promotes the secretion of IL-17A and aggravates neutrophilic inflammation. Therefore, blocking IL-4 or IL-13 therapy leads to the conversion of eosinophilic inflammation in the airways to neutrophilic inflammation. For patients with *A. alternata* allergy, combination therapy should be used to control eosinophil and neutrophil responses in the airways [61]. β -glucan is an integral part of all fungal cell walls, and studies have found that β -glucan plays a major role in the process of fungi-induced asthma exacerbation. Compared with mice sensitized with HDM alone, sensitized mice exposed to β -glucan induced Th17 cell immune response and promoted the expression of IL-6, IL-23, IL-17A, IL-17F, and IL-22 in the lungs, and further aggravate the HDM-induced Th2 response. This leads to a mixed

inflammatory response characterized by an increase in the number of neutrophils and eosinophils. Treatment of mice with β -glucan alone induces neutrophilic inflammation in the lungs. When mice are co-treated with β -glucan and HDM, β -glucan can induce the expression of Th17 cytokines and strengthen HDM-induced Th2 response by binding to its receptor Dectin-1 [62••]. Other studies have also found that β -glucan, which exposed to heat-killed *Cladosporium cladosporioides* spores, bind to Dectin-1 to promote the secretion of IL-6, IL-23, and other cytokines by DC, thus inducing a strong Th17 response and neutrophilic inflammation [63]. It can be seen that β -glucan is an effective component in fungal induced inflammation and AHR. Spleen tyrosine kinase (SYK) is an asthma-associated kinase that promotes the activation of NLRP3 inflammasome and IL-1 β secretion induced by β -glucan/Dectin-1 signaling pathway. The expression of IL-1 β leads to a Th17-predominant Th17/Treg imbalance, which exacerbates lung inflammation and tissue damage. MNS (SYK inhibitor) treatment can effectively inhibit β -glucan-induced Th17 cell inflammation and limit IgA secretion, reduce lung neutrophil aggregation, and improve airway inflammation [64].

Discussion

Microbial infection of the respiratory tract can affect the Th17/IL-17A axis in a variety of ways, including regulating of ROR γ t and STAT3 gene expression, the binding of STAT3 to the IL-17A promoter, regulating JAK2/STAT3 and p38MAPK/ERK1/2 signaling pathway, activating NOTCH1 signaling pathway, inhibiting IFN- γ expression levels and up-regulate IL-8 to promote Th17 cell differentiation, affecting the differentiation of Th17 cells, and secreting of IL-17A cytokines by complement system and chemokines. Moreover, upregulated IL-17A promotes aggregation of neutrophils in the airways and enhances Th2-mediated eosinophilic airway inflammation, inhibits differentiation of Treg cells, promotes mucus production in airways and ASM remodeling, decreases the number of CD8⁺ cells to reduce the removal of microorganisms, which may increase the susceptibility to asthma through repeated infections (Fig. 2).

However, respiratory microbial infections do not simply promote the development of asthma, and their effect on asthma is regulated by a variety of factors. First, infection of the same microbe at different stages of life may have different effects on asthma. For example, after infection with *C. pneumoniae* in neonates or early childhood, the risk of developing asthma in adulthood is greatly increased, while infection in the adult stage of *C. pneumoniae* can alleviate the symptoms of asthma. Second, allergic asthma mice infected with respiratory microorganisms before, during, and after allergies had different effects on asthma. *M. pneumoniae*

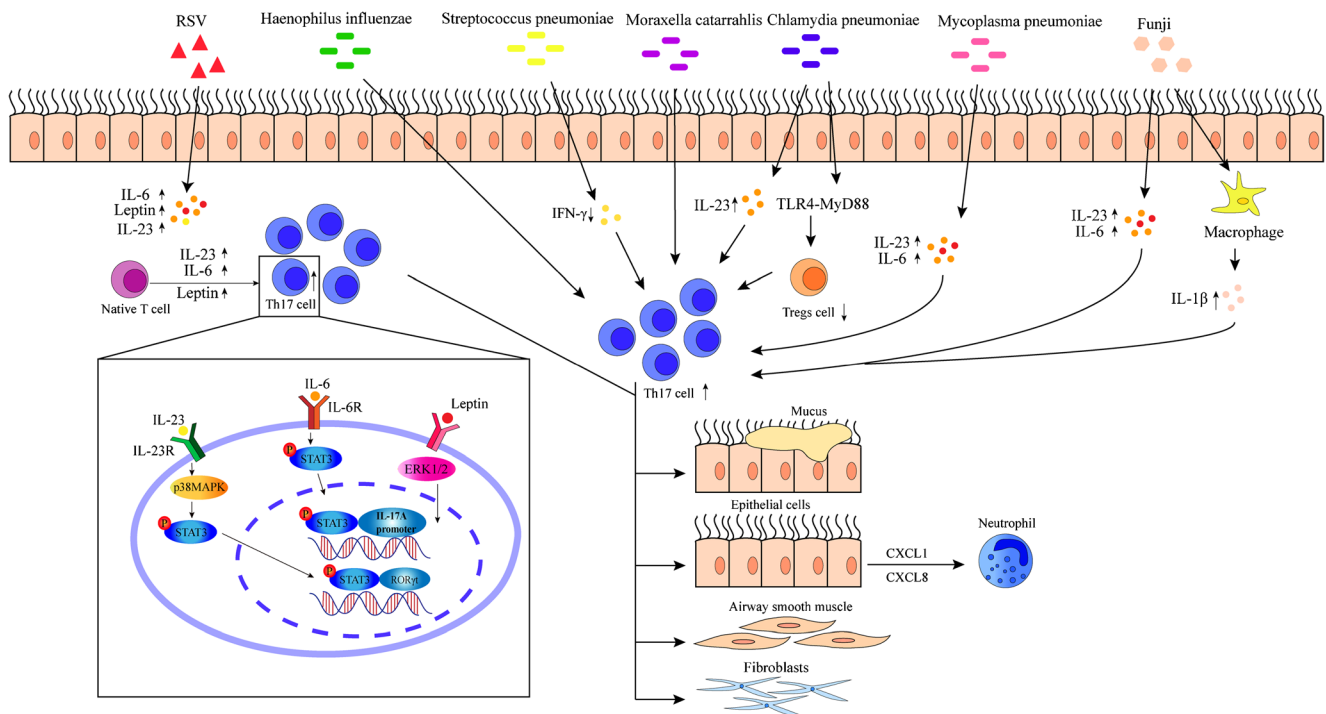


Fig. 2 TH17/IL-17 axis regulated by airway microbes affects the development of asthma

infection before allergy can inhibit airway inflammation and AHR, while infection after sensitization increases asthma symptoms. Third, the effects of microbial infections on asthma are related to the dose and severity of infection. Low doses of *C. pneumoniae* infection can enhance antigen sensitization. Conversely, severe infections caused by high doses of *C. pneumoniae* can inhibit allergic asthma. Finally, long-term recurrent infections of respiratory microbes and short-term acute infections may have different effects on asthma.

Some studies have shown that certain components of microorganisms can be used to treat asthma under certain conditions. Preston [65] found that infection or treatment with inactivated *S. pneumoniae* before challenge, or before or during sensitization suppressed hallmark features of AAD, and showed inactivated *S. pneumoniae* can upregulate the number of Treg cells to suppress the response of Th2 cell, resulting in a reduction in the number of eosinophils collected into the airways and airway inflammation. To investigate which antigens of *S. pneumoniae* play a major role in the inhibition of airway inflammation, Thorburn [66] examined the inhibitory capacity of type-3-polysaccharide (T3P), isolated cell walls, pneumolysoid (Ply), and CpG, and found that airway inflammation in mouse models of AAD was significantly alleviated after treatment with T3P+Ply. T3P+Ply can drive the differentiation of Tregs to inhibit the activation of natural killer T (NKT) cells and Th2 cell responses to alleviate allergic airway inflammation. Furthermore, the increased level of Tregs induced by T3P+Ply can limit IL-6 expression to inhibit Th17-

mediated asthma pathogenesis [67]. It can clearly be seen that *S. pneumoniae* T3P+Ply-induced Tregs response can be used as a novel immunotherapy for the prevention and treatment of asthma. *Mycobacterium tuberculosis* is also related to the treatment of asthma. After *M. tuberculosis* reference strain H37Rv infection, the Th2 cytokines IL-5, IL-4, and IL-13 in the lungs and BALF were significantly decreased from OVA-challenged mice, accompanied by an increase in IFN- γ [68•]. Kim [69] found that the heat-shock protein X (HspX), purified from *M. tuberculosis*, can regulate the balance of Th1 and Th2 immune responses by inhibiting GATA-3 expression and inducing T-bet expression to alleviate allergic airway inflammation and AHR. Secretory proteins from *M. tuberculosis* can effectively treat asthma by increased IFN- γ /IL-5 ratios [70], such as the Ag85 complex, is composed of Ag85A, Ag85B, and Ag85C. Moreover, administration of highly purified recombinant Ag85B (rAg85B) showed immune trends from Th2 response to Th1 and Th17-related immune responses [71]. Our previous studies have shown that in the OVA-induced asthma model, inactivated *Pseudomonas aeruginosa* prevented the development of AHR, airway eosinophilia, decreased IL-4 and IL-17, and increased IFN- γ productions in BALF. Act1 is a key component of IL-17A signaling and induces Th2 differentiation; inactivated *Pseudomonas aeruginosa* can significantly reduce Act1 mRNA expression on OVA-treated BEC, preventing the differentiation of Th17 and Th2 [72].

In general, infection of some respiratory microorganisms can promote the development of asthma by affecting the

Th17/IL-17A axis. There are many mechanisms by which microorganisms can influence the development of asthma by regulating Th17/IL-17A axis, but these specific mechanisms need further studies. Furthermore, certain components of airway microorganisms can be developed to treat asthma through regulation of the enhanced Th17/IL-17A axis.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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