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Th17-mediated inflammation in asthma

Dawn C. Newcomb and R. Stokes Peebles Jr.

Vanderbilt University Medical Center, Department of Medicine, Nashville, TN 37232

Abstract

Asthma is a heterogeneous disease with many different phenotypes. Moderate and severe asthma phenotypes have been associated with increased neutrophils and increased Th17 cytokines, IL-17A, IL-17F, and IL-22, in the bronchoalveolar lavage fluid of patients. Th17 cytokines recruit neutrophils to the airway by increasing secretion of epithelial-derived neutrophilic chemokines. In addition, Th17 cytokines also induce mucous cell metaplasia and have pleotropic effects on airway smooth muscle resulting in airway narrowing. The role of Th17 cytokines in regulating Th2 cytokine expression and allergic airway inflammation remains unclear with conflicting reports. However, the role of Th17 cells in asthma will be answered in ongoing clinical trials with therapeutics targeting IL-17A and IL-17 receptor signaling.

Introduction

Asthma is a heterogeneous disease with different phenotypes, pathologies, responses to therapeutics, and triggers for exacerbations [1]. The hallmarks of asthma are increased airway inflammation, airway remodeling, mucous cell metaplasia, and increased airway reactivity (AR). CD4⁺ T helper (Th) cells are vital for the adaptive immune responses in asthma. Based on the cytokine milieu present at the time of T cell activation, CD4⁺ T cells are differentiated into effector T cell subsets which secrete various cytokines (Figure 1). In this review we will focus on Th17 cells and cytokines. Th17 cells are a subset of CD4⁺ T cells associated with the more severe phenotypes of asthma which are less responsive to corticosteroids [2–4]. Th17 cells are differentiated when a naïve T cell is activated in the presence of TGF- β , IL-6, IL-1 β , and IL-23, resulting in activation of the transcription factors signal transducer and activator of transcription (STAT)-3 and RORC2 (Figure 1) [5]. In mice, the cytokines TGF- β , IL-6, and IL-23 are essential for Th17 cell differentiation [5]. Th17 differentiated cells from both humans and mice secrete IL-17A, IL-17F, IL-22, and IL-21, in addition to other cytokines and chemokines [6]. IL-17A forms a homodimer or heterodimer with IL-17F and signals through the IL-17RA/IL-17RC receptor complex [7]. IL-17A, IL-17F, and IL-22 are increased in the bronchoalveolar lavage (BAL) fluid and bronchial biopsies of patients with moderate and severe asthma, and have been positively correlated with disease severity and AR [8–11]. Other cells, including $\gamma\delta$ T cells, innate lymphoid cells, and granulocytes secrete IL-17A, IL-17F, and IL-22 [12]. However, in this review we will focus on the role of Th17 cells and IL-17A, IL-17F, and IL-22 in increased airway inflammation, mucous cell metaplasia, and smooth muscle proliferation and migration as shown in Figure 2.

Corresponding author: Dawn Newcomb, PhD, 1161 21st Avenue, T-1218 Medical Center North, Vanderbilt University Medical Center, Nashville, TN 37232. dawn.newcomb@vanderbilt.edu, Telephone: (615)-343-1776, Fax Number: (615)-343-7448.

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Role of IL-17A in airway inflammation

IL-17A protein expression in sputum positively correlated with increased neutrophil and increased AR with methacholine challenge in patients with asthma [6;13]. IL-17A binding to the IL-17R complex on human primary differentiated airway epithelial cells increased NF- κ B activation and secretion of neutrophil chemokines, including CXCL-8 [5]. In mice, adoptive transfer of ovalbumin (OVA)-specific D011.10 Th17 cells secreting IL-17A and IL-17F into WT naïve mice followed by OVA challenge increased neutrophil and lymphocyte infiltration into the lungs of mice [14;15]. IL-17A also increased secretion of IL-1 β , IL-6, GM-CSF from airway epithelial cells, endothelial cells, and fibroblasts leading to increased neutrophil infiltration [6].

ROR- γ T transgenic mice sensitized and challenged with OVA had increased IL-17A protein expression and increased AR to methacholine challenge and neutrophilic inflammation compared to WT controls [***16]. Further, OVA sensitized and challenged ROR- γ T transgenic mice had steroid-insensitive increases in AR and inflammation compared to either similarly sensitized and challenged GATA3 transgenic mice, with increased Th2 inflammation, or WT control mice. OVA sensitized and challenged ROR- γ T transgenic mice treated with anti-IL-17A antibody or a CXCR2 antagonist, a chemokine receptor expressed on neutrophils, had a significant decrease in AR and inflammation compared to isotype control antibody or vehicle. Combined, these results show IL-17A mediated neutrophil infiltration into the airway.

Several different inflammatory signatures have been identified with asthma phenotypes. Some patients with asthma appear to have IL-17A-mediated airway inflammation, with increased airway neutrophils. Others have a predominant Th2-mediated allergic inflammation with increased eosinophils in BAL fluid, increased IgE hypersecretion, and increased CD4⁺ Th2 cytokine secretion of IL-4, IL-5, and IL-13 [3;4;17]. However, these phenotypes are not entirely discrete and some patients have what appears to be both Th17- and Th2-mediated inflammation. Therefore, understanding the role, regulation, and interplay between Th17 and Th2 cytokines is important for development of therapeutics for asthma patients with a combination of both of these inflammatory phenotypes. The Th2 cytokines, IL-4 and IL-13, and the regulatory cytokine, IL-10, negatively regulate IL-17A and IL-17F protein expression from Th17 cells [18–21]. While Th2 cytokines negatively regulate Th17 cytokine expression; the role of IL-17A and Th17 cells on allergic airway inflammation is conflicting in the literature. The timing of IL-17A neutralization or initiation may explain the reported variations. IL-17RA knockout (KO) mice, which are unable to respond to IL-17A or IL-17F, have decreased OVA-induced allergic airway inflammation compared to WT mice [22]. However, IL-17E, alternatively known as IL-25, also signals through IL-17RA and is required for initiation of Th2-mediated responses, providing a potential explanation for decreased OVA-induced inflammation [23]. It was also reported that increased IL-17A protein expression synergized with IL-13 that was present during allergic airway inflammation, resulting in increased AR in a complement C5a dependent manner [24]. Adoptive transfer of OVA-specific D011.10 Th17 cells into recipient mice that had received OVA-specific Th2 cells enhanced eosinophil recruitment in the lung and AR following airway OVA challenge compared to recipient mice that had been adoptively transferred only Th2 cells [14;25]. These results suggest that IL-17A increases Th2-mediated AR and airway inflammation. However, other groups have reported that IL-17A has an anti-inflammatory role in allergic airway inflammation. Instillation of recombinant mouse IL-17A during OVA-challenge decreased AR, eosinophil infiltration into the airways, and expression of CCL5, CCL11, and CCL17 [22]. Further, neutralization of IL-17A during allergic airway inflammation increased AR and eosinophil infiltration into the airways [***26].

IL-17A has also been associated with increased airway inflammation and AR following viral infections during ongoing allergic airway inflammation [27;*28]. Viral infections trigger the majority of asthma exacerbations, but the exact mechanisms of increased airway inflammation and asthma symptoms resulting from these infections remain unclear. IL-17A protein expression in whole lung homogenates was increased in mice following respiratory syncytial virus (RSV) infection during ongoing allergic airway inflammation compared to very low levels of IL-17A protein expression in the lung following OVA-induced allergic airway inflammation and undetectable IL-17A protein expression after RSV infection [27;*28]. We recently published that IL-17A KO mice infected with RSV during ongoing OVA-induced allergic airway inflammation had increased AR, IL-13 protein expression, and infiltration of eosinophils into the BAL fluid [*28]. These results suggest that IL-17A inhibits lung IL-13 expression and AR in the combined viral infection/allergic airway inflammation model. IL-17A and IL-17F have a varied role if present during the allergy sensitization, allergy challenge phases, and/or during viral infections [14;22;23;25–27,*28]. Therefore, further studies are needed to fully determine the effects of IL-17A and IL-17F on the immune response during allergic airway inflammation and viral infections.

Role of IL-22 in airway inflammation

IL-22, a member of the IL-10 family of proteins, has both pro-inflammatory and anti-inflammatory properties associated with airway inflammation. IL-22 is secreted from the CD4⁺ Th17, Th22, and Th1 subsets, as well as other cells types [29]. IL-22 binds to the IL-22R, which is expressed on airway epithelial cells and smooth muscle cells, but not lymphocytes and macrophages [30]. IL-22 serum concentrations are increased in patients with severe asthma compared to healthy controls or patients with milder phenotypes of asthma [29;31]. Further, IL-22-secreting cells in patients with severe asthma are CD4⁺ CCR6⁺ cells which are markers for Th17 cells [31]. Lack of IL-22 in mice undergoing OVA-induced allergic airway inflammation had varied responses depending on when IL-22 was depleted. IL-22 KO mice undergoing OVA-induced allergic airway inflammation had decreased airway eosinophils, IL-13 protein expression, AR, and mucus production compared to WT mice [29]. However, other laboratories have shown if IL-22 was neutralized with an antibody at the time of antigen challenge there was an increase in IL-25 and IL-13 protein expression and allergic airway inflammation [29;*32]. Intranasal administration of recombinant IL-22 during OVA challenge decreased Th2-mediated airway inflammation [29], likely by decreasing IL-25 and IL-13 protein expression in the lung [29;*32]. Combined these results suggest that IL-22 plays a dual role with pro and anti-inflammatory effects on allergic airway inflammation.

IL-17A, IL-17F, and IL-22 increase airway remodeling

Severe asthma is associated with increased airway remodeling, characterized by increased mucous cell metaplasia and increased airway smooth muscle mass (as shown in Figure 2). IL-17A increased airway mucous expression in human airway epithelial cells and mouse models of airway inflammation. In primary, differentiated human airway epithelial cells, IL-17A and IL-1 β increased mucin (MUC)5AC gene expression and protein production through an NF- κ B dependent pathway [33;34]. IL-17A also increased mucous cell metaplasia in mouse airway epithelial cells and in a mouse model of airway inflammation. *In vivo*, RSV infection of STAT1 KO mice increased mucous cell metaplasia and IL-17A and IL-13 protein expression in whole lung homogenates [35]. IL-13 signals through the transcription factor STAT6, and IL-13 was thought to be largely responsible for RSV-induced mucous cell metaplasia in STAT1 KO mice [35]. However, RSV-infected STAT1/STAT6 double KO mice had airway mucous cell metaplasia, revealing that mucous cell metaplasia is not entirely STAT6-dependent and likely a result of increased IL-17A

expression in these mice as a consequence of the viral infection.[15] Further, administration of IL-17A to primary, differentiated airway epithelial cells from STAT6 KO mice increased mucous cell metaplasia [35]. Thus, IL-17A increased mucous cell metaplasia in airway epithelial cells, suggesting an important role for this cytokine in asthma pathogenesis.

IL-17A, IL-17F, and IL-22 are associated with increased airway smooth muscle proliferation and migration [36;37]. Airway smooth muscle cells (ASMCs) isolated from non-asthmatic and asthmatic patients expressed IL-17RA, IL-17RC, and IL-22R1 and were stimulated with IL-17A, IL-17F, or IL-22. In both non-asthmatic and asthmatic ASMCs, IL-17A and IL-17F increased ASMC proliferation in an ERK1/2 dependent-manner and migration in a p38 dependent manner. IL-22 also increased ASMC proliferation and migration, but required ERK1/2 and NF- κ B for proliferation and NF- κ B for migration [36]. Further, IL-17A increased α -smooth muscle actin gene expression in fibrocytes, but unlike the IL-4 and IL13, IL-17A had no effect on increased collagen expression [38]. Smooth muscle constriction is associated with increased airway resistance and AR. Recombinant IL-17A, but not IL-17F and IL-22, increased contractility of smooth muscle in a NF- κ B, RhoA, ROCK2-dependent manner [*39]. Further, mice lacking α v β 8 integrin on dendritic cells had decreased IL-17A protein expression and decreased AR in response to OVA challenge [40]. Combined these results suggest that airway remodeling is increased by Th17 cytokines via the MAPK, RhoA, and NF- κ B signaling pathways.

Therapeutics targeting Th17-mediated inflammation in asthma

Patients with severe asthma respond poorly to current therapies for asthma, including corticosteroids. In a mouse model, Th17-mediated inflammation and AR were resistant to the corticosteroid dexamethasone [14], suggesting that IL-17A or IL-17R α signaling may be reasonable drug targets for patients with severe asthma. Therapeutics neutralizing IL-17A or IL-17RA signaling are currently in clinical trials for asthma. AIN 457 (Secukinumab) and LY-2439821 are monoclonal antibodies which neutralize IL-17A and that reduce clinical symptoms associated with psoriasis and rheumatoid arthritis, other Th17-mediated diseases [41]. AIN 457 is currently recruiting for a safety and efficacy Phase II clinical trial in patients with uncontrolled asthma, but results are not yet available [41].

A phase II clinical trial was recently completed for the anti-IL-17RA monoclonal antibody brodalumab, also known as AMG-827 [42]. This randomized, double-blinded, placebo control multi-dose trial in moderate-to-severe asthmatics was designed with change in Asthma Quality Control (AQC score) as the primary outcome. There was no difference in AQC score between subjects treated with anti-IL17RA compared to placebo. A clinically meaningful response was seen in bronchodilator reversibility in subjects taking anti-IL-17RA compared to placebo. However, more studies need to be conducted to determine the efficacy of targeting IL-17RA signaling in subjects with moderate-to-severe asthma.

Th17 cells are not a stable, fully differentiated lineage of CD4⁺ T cells. Based on epigenetic regulation of transcription factors and the cytokine microenvironment Th17 can express cytokines typically found in either Th1 or Th2 cells [43]. For example, Th2/Th17 CD4⁺ T cells which secrete IL-4, IL-13, and IL-17A have been reported to be detected in patients with severe asthma, but are not readily detected in healthy people or milder phenotypes of asthma [10]. Th2/Th17 intermediate cell subsets and Th2 and Th17 cytokine interactions are important to consider when enrolling patients with severe phenotypes of asthma in clinical trials targeting IL-13 and IL-13 signaling components [44, *45, 46–49]. Neutralizing IL-4 or IL-13 *ex vivo* in human Th17 differentiated cells increased IL-17A protein expression [20]. Further, in mouse models deficiencies in IL-13, IL-4, or IL-4R α , a component of the IL-13 receptor and the IL-4 receptor, increased Th17-mediated inflammation in mice [21].

Therefore, therapeutics which target IL-4, IL-13, or IL-4R α may decrease Th2-mediated inflammation and eosinophil infiltration, yet increase Th17-mediated inflammation and neutrophil infiltration into the airway. Such a strategy may unintentionally result in predominant neutrophilic inflammation that is associated with a severe, less corticosteroid responsive asthma phenotype. Therefore, determination of the airway inflammation underling the asthma phenotype of an individual asthma patient will be critical to avoid unintended consequences of biologic agents targeting the Th17 pathway.

Conclusions

Th17-mediated inflammation is increased in patients with severe asthma. As shown in Figure 2, IL-17A, IL-17F, and IL-22 increased airway neutrophil infiltration, airway mucous cell metaplasia, and airway remodeling. Patients with severe asthma comprise a small population of asthma patients, but have the highest health care costs among asthma phenotypes. Therefore, defining the role of Th17 cells and IL-17A, IL-17F, and IL-22 is imperative for designing, implementing, and tailoring therapeutics to successfully treat patients with asthma.

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Abbreviations

AQS	asthma quality score
AR	airway responsiveness
ASMCs	airway smooth muscle cells
BAL	bronchoalveolar lavage
MUC	mucin
OVA	ovalbumin
RSV	respiratory syncytial virus
STAT	signal transducer and activator of transcription
Th	T helper

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Highlights

- Th17 cells and cytokines are associated with the more severe phenotypes of asthma
- IL-17A and IL-17F are associated with increased neutrophils in the airway
- IL-17A, IL-17F, and IL-22 increase airway mucus production and smooth muscle mass

Figure 1. Differentiation of CD4+ effector T cells. Naïve T cells differentiate into CD4+ effector T cell subsets based on cytokines present at the time of antigen presentation and T cell activation. T helper cell subsets secrete various cytokines.

Figure 2.
Diagram of Th17-mediated inflammation in asthma.