



T Helper 17 Cells in Airway Diseases

From Laboratory Bench to Bedside

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T helper 17 (Th17) cytokines are now widely believed to be critical for the regulation of various chronic immune diseases. Investigations have revealed a significant role for IL-17 cytokines in regulating inflammation and modulating lung and airway structural cells in asthma and COPD. In this review, our current understanding of the role of Th17-associated cytokines in airway diseases is summarized. Therapeutic approaches targeting IL-17 during asthma and COPD are also discussed.

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Abbreviations: AHR = aryl hydrocarbon receptor; D1-like-R = dopamine D1-like receptor; GC = glucocorticosteroid; GR = glucocorticosteroid receptor; IRF = interferon regulatory factor; mRNA = messenger RNA; ROR = related orphan receptor; TGF- β = transforming growth factor- β ; Th = T helper; TNF- α = tumor necrosis factor- α ; Treg = FoxP3+ human regulatory T cell

Cytokines are essential mediators for a number of airway diseases, including asthma, COPD, and pulmonary infections. Over the past 20 years, the implications of T helper (Th) 1 and Th2 cytokines in lung diseases have been extensively studied. Allergic diseases such as asthma are mostly associated with Th2-type cytokines, including IL-4, IL-5, and IL-13. Other cell-mediated immune diseases such as TB are more associated with Th1-like cytokines, including IL-2 and interferon- γ . Recently, new subsets of cytokines were described that are secreted by Th17 cells. These cytokines appear to be involved in a number of immune-mediated diseases, including asthma, COPD, psoriasis, rheumatoid arthritis, and Crohn's disease. Here, we summarize the current understanding of the role of IL-17 cytokines in asthma and COPD. Therapeutic approaches (novel or under clinical trial) targeting IL-17 cytokines are also discussed.

Th17/IL-17

IL-17 is a homodimeric protein that was cloned by Rouvier et al¹ in 1993 and first described as cytotoxic T-lymphocyte-associated antigen-8 (CTLA-8). In humans, the *IL-17* gene was first mapped to chromosome arm 2q31²; however, subsequent studies identified the gene on chromosome arm 6p12.³ Since the discovery of IL-17, many homologous proteins were identified and, hence, formed an IL-17 cytokine family consisting of IL-17A, B, C, D, E, and F.^{4,5} IL-17A and IL-17F share the greatest homology and may heterodimerize. They are perhaps the best characterized cytokines in the family, sharing the same receptor and regulatory elements.⁶ In contrast, IL-17E (also known as IL-25), is the most divergent member in the family.

IL-17 was first shown to be produced by activated CD4⁺ memory T cells. It was then determined that IL-17-producing CD4⁺ T cells comprise a distinct subtype, referred to as Th17 cells⁷ (Fig 1). Th17 cells are characterized by the predominant production of IL-17A, IL-17F, IL-6, tumor necrosis factor- α (TNF- α), and IL-22 expression.⁸ In addition to Th17 cells, other cell types express IL-17.⁹ Using immunohistochemistry, immunofluorescence, and real-time polymerase chain reaction, CD8⁺ T cells,¹⁰ $\gamma\delta$ T cells,¹¹ invariant natural killer T cells,¹² and lymphoid tissue inducer-like cells¹³ were all found to express and produce IL-17.⁹ FoxP3+ human regulatory T cells (Tregs)

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can produce IL-17 when they are strongly activated in the presence of proinflammatory cytokines, such as IL-1 β and IL-6.¹⁴⁻¹⁶ IL-17 messenger RNA (mRNA) has also been detected in neutrophils in response to stimulation with lipopolysaccharide.¹⁷ Of note, using flow cytometry and real-time polymerase chain reaction, we recently reported that human tonsillar B cells are a good source of IL-17A and IL-17F.¹⁸ IL-17 is involved in the pathogenesis of several autoimmune diseases,¹⁹ and B cells could be one of its main sources in such conditions. Although IL-17A and IL-17F are expressed most abundantly by Th17 T cells,²⁰ IL-17B, C, and D have been detected in a wide variety of tissues. mRNA of IL-17B was detected using RNA blot analysis in tissues of the GI tract, prostate, ovary, testicles, and spinal cord⁴; IL-17C was expressed in prostate and fetal kidney tissue⁴; and IL-17D was detected in muscle and adipose tissue as well as in the brain, lungs, and pancreas.⁵

Using flow cytometry, Kleinschek et al²¹ suggested that Th17 cells originate from CD161⁺ CD4 T-cell precursors detected in both human umbilical cord blood and thymus. IL-1 β , IL-23, IL-6, and transforming growth factor- β (TGF- β) emerged as critical factors for the differentiation of Th17 cells (Fig 1).²² IL-6, however, inhibited TGF- β -induced Tregs, which suppress adaptive T-cell responses and prevent autoimmunity.²³ Data from McGeachy et al²⁴ indicated that IL-23 is required for full functional activity of Th17 cells. Signaling through STAT3, which is activated by both IL-6 and IL-23, is required for induction of Th17 cells.²⁵ Allergen-induced complement anaphylatoxins C3a and C5a regulate the production of IL-17A and aryl hydrocarbon receptor (AHR) through the manipulation of dendritic cell-derived IL-23 production.²⁶ IL-21 was also shown to be required for human Th17 polarization.²⁷ Moreover, Ivanov et al²⁸ suggested that retinoic acid-related orphan receptor (ROR) γ t is one of the key transcription factors for the generation of Th17 cells. In addition to these pathways, interferon regulatory factors (IRFs) play a role in T-cell polarization. IRF4 promotes the development of Th17 cells, whereas IRF4-deficient mice exhibit decreased levels of IL-17 and IL-21.²⁹ Th1-specific T-bet, Treg-limited FoxP3, and Th17-specific ROR γ t transcription factors also play critical roles in regulating lineage commitment. These transcription factors and their signature cytokines are potential targets for controlling several chronic inflammatory and autoimmune diseases.

ROLE OF TH17 IN ASTHMA

IL-17A mRNA and protein levels of expression are upregulated in lung tissue of patients with asthma compared with healthy control subjects.^{30,31} Using

immunofluorescence assay, we were among the first to show that increased IL-17A and IL-17F levels correlate with asthma severity.^{32,33} In addition, the percentage of Th17 cells and the plasma concentrations of IL-17 and IL-22 increase with disease severity.³⁴ Elevated IL-17A levels correlate with increased AHR in patients with asthma.³⁵ The association of a specific IL-17F polymorphism with asthma suggests that IL-17F may also play an important role in the development of asthma.³⁶ Based on enzyme-linked immunosorbent assay findings, IL-17F was first reported in BAL cells from patients with asthma upon ragweed allergen stimulation.³⁷ IL-17A was suggested to contribute to asthma through its capacity to enhance recruitment of neutrophils to the site of airway inflammation.³⁸ IL-17 enhances the release of IL-6, IL-1 β , granulocyte-macrophage colony-stimulating factor, and chemokines CXCL1, CXCL2, and IL-8 from human epithelial and vascular endothelial cells.^{38,39} Moreover, human fibroblasts produce neutrophil-activating factors IL-6 and IL-8 in response to IL-17A and IL-17F cytokines.³ These factors promote the expansion of neutrophils from the bone marrow and their survival and recruitment to the airways⁴⁰ (Fig 1). Overexpression of IL-17F in mouse lung tissue results in enhanced recruitment of neutrophils.⁴¹ In addition to IL-17A and IL-17F, IL-17E induces a different set of cytokine genes and is involved in Th2-type immune response. Transgenic overexpression of IL-17E results in eosinophilia in the mouse airway and in an elevated level of gene expression of several Th2 cytokines, including IL-4, IL-5, IL-13.⁴² The balance between eosinophilia and neutrophilia seems to be determined by a balance between IL-4 and IL-17. IL-4 has been described as a potent inhibitor of IL-17 development in mice.⁴³ Exogenous administration of IL-17A, on the other hand, reduces pulmonary eosinophil recruitment in the asthma mouse model.⁴⁴ It appears that Th17-directed neutrophil infiltration is inversely linked to the Th2 (IL-4)-mediated eosinophil recruitment, similar to inverse relationships of Th1 and Th2 cells.

Besides its role in inflammatory cells, IL-17 was extensively reported to modulate airway structural cells, leading to tissue remodeling (Fig 1). IL-17A induces the expression of two mucine genes (*MUC5AC* and *MUC5B*) in bronchial human and murine epithelial cells.⁴⁵ Overexpression of IL-17F in mice results in goblet cell hyperplasia and mucin gene expression.⁴¹ Moreover, IL-17A and IL-17F induce several profibrotic cytokines. IL-17A enhances the production of IL-6 and IL-11 from human bronchial fibroblasts,³¹ whereas IL-17F induces the expression of TGF- β in human umbilical vein endothelial cells.⁴⁶ Of note, using an in vitro cell migration assay, we have shown that Th17-associated cytokines IL-17A, IL-17F, and

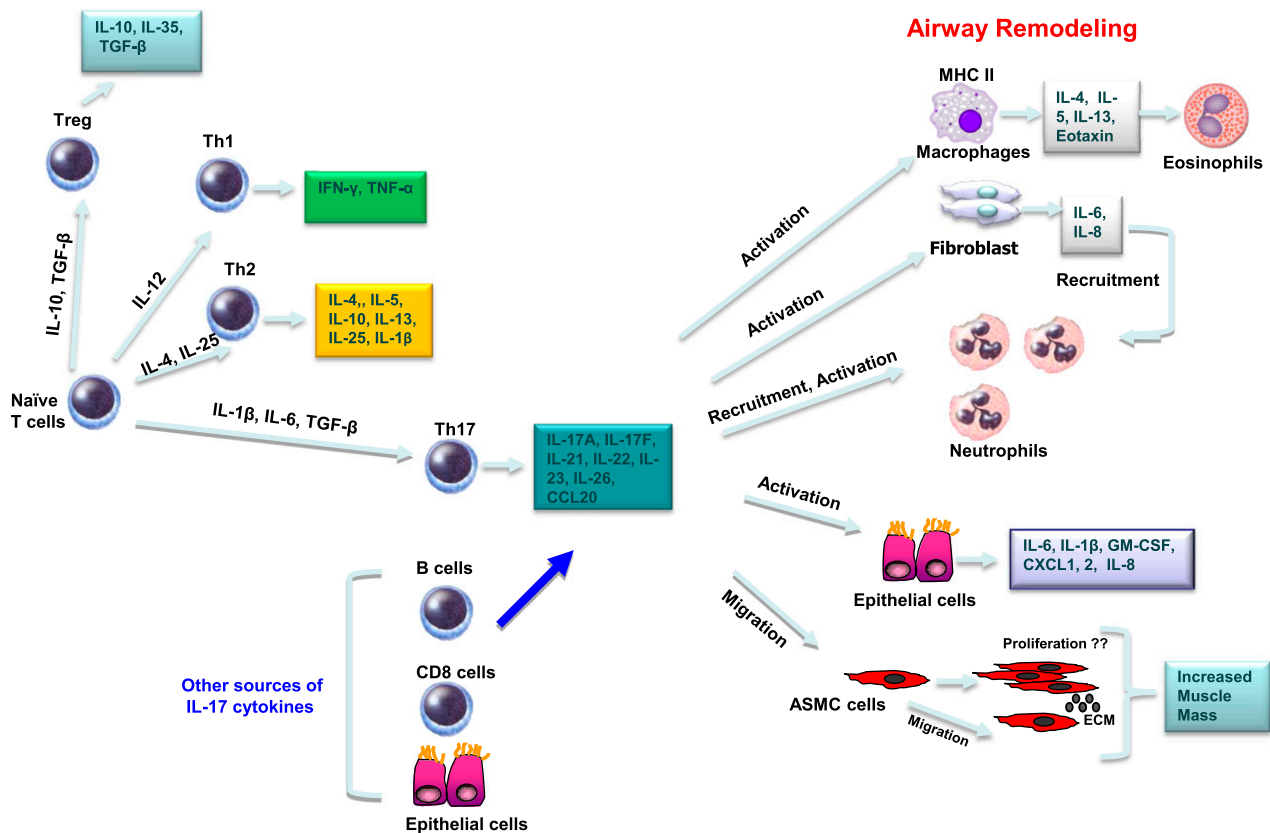


FIGURE 1. Th17 production, regulation, and role in asthma and COPD. ASMC = airway smooth muscle cell; ECM = extracellular matrix; GM-CSF = granulocyte-macrophage colony-stimulating factor; IFN- γ = interferon- γ ; MHC II = major histocompatibility complex class II; TGF- β = transforming growth factor- β ; Th = T helper; TNF- α = tumor necrosis factor- α ; Treg = FoxP3+ human regulatory T cell.

IL-22 promote migration of human airway smooth muscle cells (ASMCs). These effects are mediated by selective activation of receptors on ASMCs, with IL-17A and IL-17F acting through p38 mitogen-activated protein kinase activation. IL-22, on the other hand, acts through a distinct nuclear factor κ B-dependent signaling pathway.⁴⁷ These study findings indicate a role of IL-17 in asthma pathogenesis leading to airway remodeling.

TH17 IN COPD

Neutrophils and macrophages are known to play an important role in promoting COPD pathogenesis. Interest in the predicted role of IL-17 in COPD developed after the role of IL-17 in the recruitment of neutrophils and macrophages was revealed.^{40,48} IL-17 drives the production of matrix metalloproteinase 9 in mouse airway, which may directly link to the tissue destruction observed in COPD.⁴⁹ Using immunofluorescence, we and others confirmed that expression of IL-17A and IL-17F in human bronchial submucosa^{10,50} is significantly upregulated in patients with COPD compared with healthy control subjects. The frequency of IL-22+ and IL-23+ cells

in the bronchial epithelium and IL-17+ cells in the submucosa is significantly elevated in patients with COPD.⁵¹ Furthermore, ASMCs from patients with COPD express IL-17RA and respond to stimulation by IL-17.⁵² Similarly, a murine COPD model exhibited enhanced IL-17 production in lung tissue. Increased levels of IL-17-dependent gene products, such as IL-6, IL-8, granulocyte colony-stimulating factor, and monocyte chemoattractant protein-1, as well as neutrophilia were also reported in a mouse COPD model.⁵³ These data further confirm a potential role for IL-17 in COPD.

In addition to COPD, IL-17 may be involved in the development of other respiratory diseases. Enhanced recruitment and activation of neutrophils in the airways is believed to predispose to several inflammatory diseases in the airways, such as nonspecific bronchial hyperreactivity, chronic bronchitis, cystic fibrosis, and ARDS.⁵⁴ Although the precise role of IL-17 in these lung diseases is not clear, the critical role of IL-17 in neutrophil recruitment to the airways predicts its key role in the development of these diseases. In fact, data showed that tissue-infiltrating Th17 cells are present in diverse chronic inflammatory diseases, including psoriasis, rheumatoid arthritis,

and inflammatory bowel disease.^{9,55} IL-17A was shown to be associated with the development of obliterative bronchiolitis in mice.^{9,56-58} Neutralizing IL-17A prevented obliterative bronchiolitis during murine orthotopic lung transplantation and downregulated acute rejection.⁵⁷

ROLE OF TH17 CELLS IN LUNG AIRWAY INFECTIONS

In addition to their role in inflammatory lung diseases, IL-17-producing CD4⁺ T cells are believed to be necessary for protective immunity against airborne pathogens.⁵⁹ For instance, IL-17-producing cells play a critical role in protective immune responses to mucocutaneous candidiasis mainly through the recruitment of interferon- γ -producing CD4⁺ T cells.⁶⁰ Of note, $\gamma\delta$ T cells were reported to be the initial source of IL-17A during infections with *Mycobacterium tuberculosis* or *Mycobacterium bovis* bacillus Calmette-Guérin.⁶¹ IL-17 induction of neutrophil activation and migration is important in the defense against a variety of microorganisms that infect the lung.⁵⁴ IL-23 p19-deficient as well as IL-17R-deficient mice were unable to develop full neutrophil response to *Klebsiella pneumoniae* infection in the airways and, hence, were more susceptible to lung infection than normal controls.⁶² Th17 cells and IL-17A were also involved in protection against fungal infection (*Candida albicans*) in human subjects⁶³ as well as in transgenic mice.⁶⁴ Taken together, these findings suggest that Th17 cells are critical for normal immunity against microbial infections of the airways.

TARGETING TH17 AS A THERAPEUTIC APPROACH FOR ASTHMA AND COPD

Many approaches to therapeutically target IL-17 have already been investigated, and plenty of studies

described the mechanisms modulating production, regulation, and function of IL-17. These approaches are targeting regulation of IL-17 production and stability, IL-17 binding to its receptor IL-17R, and signaling pathways stimulated upon IL-17R triggering (Fig 2).

Therapeutic Approaches Targeting IL-17 Production and Stability

IL-23, IL-6, IL-1 β , and TNF- α regulate the development and stability of IL-17 cytokines. Inhibition of IL-23 is a promising therapeutic approach to reducing IL-17 production in inflammatory and autoimmune diseases. Antibodies against the p40 subunit of IL-23/IL-12 were effective in controlling gut and skin inflammation in mouse models. Several phase 2 clinical studies were conducted mostly in patients with Crohn's disease and psoriasis to evaluate the safety and efficacy of the anti-p40 treatment.^{65,66} This treatment downregulated the secretion of IL-23, IL-12, and IL-6 from mononuclear cells in the lamina propria of patients with Crohn's disease,⁶⁷ and clinical improvements were noticed following anti-p40 treatment in all phase 2 studies.⁶⁵⁻⁶⁷ Alternatively, the use of apilimod mesylate,⁶⁸ an IL-23 transcription inhibitor, as well as a fusion protein consisting of the IL-12/IL-23 p40 subunit were tested, and these approaches controlled the inflammatory responses in the lamina propria of patients with Crohn's disease.⁶⁹

IL-6 and IL-1 β are other key regulators and inducers of Th17 cells.⁷⁰ Inhibiting IL-6 activity using an anti-IL-6 receptor antibody was effective in treating juvenile idiopathic arthritis.⁷¹ However, targeting IL-6 should consider its effect on controlling Treg in addition to IL-17 production. On the other hand, recombinant human IL-1 receptor antagonist effectively suppressed symptoms in an asthma animal model.⁷² Further analyses of the efficacy of targeting IL-1 in regulating IL-17 are needed.

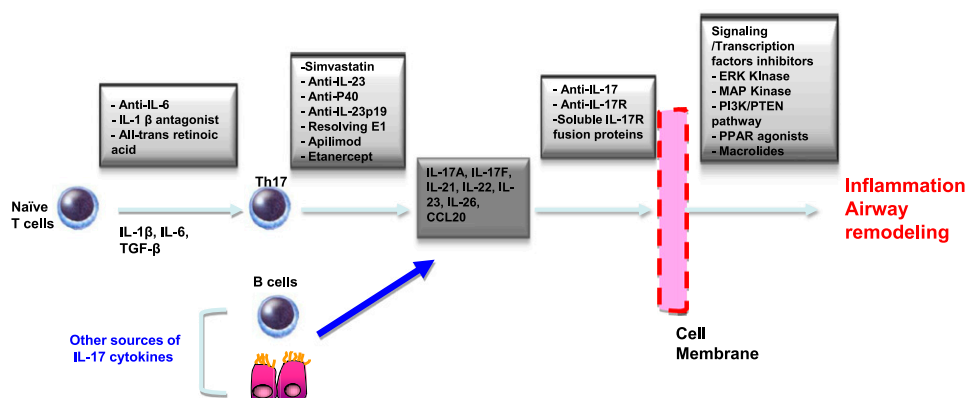


FIGURE 2. Targeting Th17/IL-17. ERK = extracellular-signal-regulated kinase; MAP = mitogen-activated protein; PI3K/PTEN = phosphoinositide 3-kinase/phosphatase and tensin homolog; PPAR = peroxisome proliferator-activated receptor. See Figure 1 legend for expansion of other abbreviations.

Many other approaches for targeting factors upstream of IL-17 that regulate IL-17 production or stability are being investigated but are still at preliminary stages. *All-trans* retinoic acid, a vitamin A metabolite, inhibits Th17 differentiation by inhibiting the expression of IL-6 and IL-23 receptors while enhancing TGF- β signaling.^{73,74} In addition, resolving E1, a product of ω -3 fatty acids, was shown to inhibit the development of airway inflammation in an asthma mouse model by blocking the release of IL-23 from dendritic cells.⁷⁵ This led to the reduction of IL-17 protein levels in the lung tissue.⁷⁵ Of note, simvastatin, a clinically used cholesterol-lowering agent, attenuates the expression of IL-6 and IL-23 and suppresses the expression of RORCvar2 transcription factor, resulting in inhibition of IL-17 secretion.⁷⁶ Dendritic cell-derived dopamine induces Th17 differentiation through dopamine D1-like receptor (D1-like-R). The D1-like-R antagonist suppresses Th17-mediated neutrophilic airway inflammation, raising the possibility that antagonizing D1-like-R is a promising new strategy for treating neutrophil-dominant severe asthma.⁷⁷

Therapeutic Approaches Blocking IL-17 Receptors and Signaling

Another approach under extensive investigation is to directly block IL-17 activity using monoclonal antibodies or IL-17 receptor fusion proteins. Studies conducted on asthma animal models showed that treatment with anti-IL-17 antibodies reduces the levels of neutrophils and macrophages in lung tissue.⁷⁸ Treatment of human bronchial epithelial cells with anti-IL-17R antibodies decreases activity of the IL-17 cytokine.⁷⁹ In addition, inhibition of IL-17 was effective in mouse models of Crohn's disease, multiple sclerosis, and rheumatoid arthritis.⁸⁰⁻⁸² Treatment with anti-IL-17 antibodies reduced the levels of IL-4, IL-5, and IL-13 cytokines in BAL fluid and AHR in an asthma mouse model.⁸³ Soluble IL-17A or IL-17C receptor-immunoglobulin fusion protein was used to inhibit IL-17 as an alternative to anti-IL-17 antibody.⁸⁴ Of note, clinical trials evaluating the efficacy, safety, and tolerability of anti-IL-17 antibodies used for the treatment of various inflammatory diseases, such as Crohn's disease, psoriasis, and rheumatoid arthritis, are currently ongoing.

Approaches involving blocking the signaling proteins of the IL-17 pathway have been investigated. Several reports indicated a critical role of mitogen-activated protein kinases in regulating signaling through IL-17 receptors. Inhibition of the p38 as well as extracellular-signal-regulated kinases were shown to decrease IL-17-induced release of IL-6 and IL-8 in addition to other potent neutrophil chemoattractants in human bronchial epithelial cells.³⁹ Phosphoinositide 3-kinase/phosphatase

and tensin homolog pathways regulated IL-17 expression, and phosphoinositide 3-kinase inhibitors attenuated the increase of IL-17 in mouse lung tissue following allergen-induced airway inflammation.⁸⁵ Moreover, using agonists for nuclear receptor superfamily (peroxisome proliferator-activated receptor), which regulate gene expression, decreased expression of IL-17 protein and mRNA in the lung tissue of an asthma mouse model.⁸⁶

Interaction Between Corticosteroids and IL-17

Elevated levels of Th17 cells was suggested to be insensitive to glucocorticosteroid (GC) treatment in allergic airway disease in mice. Production of IL-17A and IL-22 by Th17 cells was not affected by steroid treatment in vitro.⁸⁷ Th17-derived inflammation was not abrogated by GC treatment, whereas GCs were effective in inhibiting Th2-driven disease. GC treatment enhanced airway neutrophilia in Th17-transferred mice. In addition, dexamethasone, a GC receptor agonist, did not attenuate the IL-17-induced release of IL-8 from human ASMCs.⁸⁸ Contrary to these reports, corticosteroids inhibited IL-17 induction of IL-8, GRO- α , and granulocyte chemotactic protein-2 from epithelial cells and fibroblasts in vitro.⁸⁹ In addition, dexamethasone inhibited the release of IL-17 by blocking Th17 differentiation and inhibiting ROR γ t expression in an asthma mouse model.⁹⁰ On the other hand, we reported a role for IL-17 in enhancing corticosteroid resistance through the regulation of GC receptor levels.⁹¹ GC receptor (GR)- β is an alternative splicing isoform and a negative regulator of the active GR- α . GR- β is associated with corticosteroid insensitivity in a number of autoimmune inflammatory disorders.⁹²⁻⁹⁴ We showed that GR- β is associated with corticosteroid resistance in airway epithelial cells from patients with asthma, and notably, Th17 cytokines upregulated the expression of these receptors on epithelial cells.⁹¹ Furthermore, we observed that IL-17A and IL-17F contribute to steroid insensitivity in patients with severe asthma by enhancing the expression of GR- β on peripheral blood mononuclear cells.⁹⁵ These data indicate that IL-17 cytokines contribute to corticosteroid resistance through a mechanism involving the upregulation of GR- β expression levels.

Limitations for Targeting IL-17 in Asthma and COPD

Although many approaches targeting IL-17 activity have passed preclinical investigations and are now being assessed at the clinical stage, these approaches are not without limitations. Inhibiting broad cytokine networks, such as targeting IL-23, IL-12, IL-6, or

TNF- α , bears great potential risk for impairing a patient's host defense. Although such risk could be minimized by modulating IL-17 or IL-17R, this still needs to be done with high precautions. Besides its role in neutrophil recruitment and, hence, controlling bacterial and fungal infections, IL-17 is involved in regulation of tumor immunity.⁹⁶ IL-17 may suppress tumor cell growth through the promotion of an antitumor cytotoxic T-cell response.⁹⁶ Therefore, when modulating IL-17 activity, one should keep in mind that blockade of IL-17 could be associated with an increased risk of opportunistic infections as well as for tumor activity.

CONCLUSIONS

IL-17 is now widely accepted as a key player in regulating inflammation in asthma and COPD as well as in many other chronic inflammatory diseases. IL-17 is implemented in steroid responsiveness and in airway remodeling. Using asthma animal models or human studies, the data supporting the therapeutic potential of strategies inhibiting IL-17 expression in airway inflammation are accumulating. More work, however, is needed to confirm the long-term safety and efficacy of these approaches.

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