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T helper 17 cells and corticosteroid insensitivity in severe asthma

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Abstract

Asthma is classically described as either a T2 eosinophilic phenotype or a non-T2 neutrophilic phenotype. T2 asthma usually responds to classical bronchodilation therapy and corticosteroid treatment. Non-T2 neutrophilic asthma is often more severe. Patients with non-T2 asthma or late-onset T2 asthma show poor response to the currently available anti-inflammatory therapies. These therapeutic failures result in increased morbidity and cost associated with asthma and pose a major healthcare problem. Recent evidence suggests that some non-T2 asthma is associated with elevated Th17 cell immune responses. Th17 cells producing interleukin 17A and 17F are involved in the neutrophilic inflammation and airway remodeling processes in severe asthma and have been suggested to contribute to the development of subsets of corticosteroid-insensitive asthma. This review explores the pathological role of Th17 cells in corticosteroid insensitivity of severe asthma and potential targets to treat this endotype of asthma.

Keywords

T helper 17 cells; corticosteroid insensitivity; severe asthma; T2 asthma; non-T2 asthma; airway neutrophilia; interleukin 17; interleukin 6; RhoA; Rho-associated kinase

Asthma is a common and chronic obstructive airway disease with a high healthcare burden. It is defined by clinical symptoms of recurrent wheezing, coughing, and shortness of breath varying with time and intensity, as well as variable expiratory airflow limitation[1]. Inflammation is viewed as the key factor in asthma, with anti-inflammatory corticosteroids as the mainstay of treatment. Severe asthma is defined as those patients who require high-dose inhaled corticosteroids plus a second drug and/or systemic corticosteroids to maintain

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control and whose symptoms worsen when treatment is decreased, or asthma where patients remain uncontrolled despite adherence to optimized maximal therapy[2]. Severe asthma is a costly public health burden, encompassing up to 10% of all asthma patients but contributing to most of the healthcare cost.

An asthma subset characterized by eosinophilic airway inflammation and abundant T helper 2 (Th2) cells is defined as type 2 (T2) asthma which is further defined by a sputum eosinophil count of ≥ 2%, a blood eosinophil count of ≥150 cells/μL, a fractional exhaled nitric oxide ≥ 20 ppb, and/or clinically allergy-driven asthma[3]. However, these biomarker numbers are arbitrary cutoffs within continuously distributed values and T2 inflammation exists on a continuum in asthma. Allergic asthma is characterized by asthma symptoms that occur with exposure to an aeroallergen with confirmatory allergen specific IgE and a total IgE of at least 30 IU/mL. There is considerable overlap between allergic and T2 asthma. Patients with allergic asthma are much more likely to have high eosinophil counts, and asthma patients with high eosinophil counts, especially those that develop asthma during childhood, often have concomitant allergies[4,5]. T2 asthma usually responds to classical bronchodilation therapy and corticosteroid treatment[6] and/or can be controlled with newly developed T2-targeted biologic therapies[7–11]. However, in some patients with severe asthma, especially late-onset T2 asthma, airway eosinophilic inflammation persists despite corticosteroid treatment (Figure 1)[12,13]. In addition, almost half of patients with severe asthma have non-eosinophilic airway inflammation or a lack of eosinophilic and neutrophilic airway inflammation. This group is defined as having non-T2 or T2-low asthma[14–17]. The non-T2 asthma is usually characterized by neutrophilic rather than eosinophilic airway inflammation and associated with a number of clinical features including obesity, later onset of disease, poor responsive to gcocorticoids and higher risks of exacerbation[18–24]. Paucigranulocytic asthma (PGA) is another subset of non-T2 asthma with persistent asthma symptoms but absence of both eosinophilic and neutrophilic airway inflammation[25]. This endotype may be due to changes in airway smooth muscle (ASM)[16,26] or airway inflammation not reflected in the lumen or detected by sputum cytometry[27]. Non-T2 asthma has a poor response to the currently available anti-inflammatory therapies. It is a problem urgently needing a solution, particularly for patients with late-onset and more severe asthma[12,28,29], which is characterized by a high rate of severe exacerbations that may require hospitalization and lead to further morbidities. Unfortunately, the disease mechanisms driving non-T2 asthma are poorly understood, and there is a lack of point of care biomarkers, both of which greatly hinders the development of new therapeutic strategies for this subset of asthma[26,30]. Bronchial Thermoplasty (BT) is an endoscopic procedure that uses temperature-controlled radiofrequency energy to impact airway remodeling[31]. BT is well tolerated and reduces asthma symptoms and improves the quality of life of patients[32]. Since BT ablates ASM mass and airway nerve fibers, both of which may reduce airway hyperresponsiveness (AHR)[33–35], it is a potential effective treatment in patients with severe asthma, including some non-T2 asthma patients with ASM remodeling and AHR[36]. It should be noted that although BT was approved by the US Food and Drug Administration in 2010, the National Asthma Education and Prevention Program currently suggests that BT treatment is limited for selected patients in a clinical trial or registry[37]. More clinical trials are needed to determine the potential application of BT for non-T2 asthma.

Recent evidence suggests that some, but not all non-T2 asthma is associated with elevated T helper 17 (Th17) cell immune responses and this tends to be more prominent in adult patients with severe and corticosteroid-insensitive asthma (Figure 1)[14,16]. Th17 cells producing the interleukin 17 (IL-17) family of cytokines are involved in the neutrophilic inflammation and airway remodeling processes in severe asthma[38,39], and these cells have been suggested to contribute to the development of at least some subsets of corticosteroid-insensitive asthma[40,41]. Here, we review corticosteroid-insensitive severe asthma by focusing especially on the pathological role of Th17 cells in non-T2 asthma and potential targets to treat this endotype of asthma.

NEUTROPHILIA IN SEVERE ASTHMA

Neutrophilia in severe asthma was first described in bronchial biopsy studies that aimed to distinguish eosinophilic asthma from non-eosinophilic asthma[42]. The Severe Asthma Research Program has identified neutrophilic inflammation as an important hallmark of a distinct cluster of patients with moderate to severe asthma[43]. A more recent study using biopsy samples also demonstrated that bronchial neutrophilia was present in 54% of mild-to-severe asthma patients, and this percentage rose to 68% when only severe asthma patients were considered[44]. In addition, bronchial neutrophilia is frequently present in sudden-onset fatal asthma in the absence of eosinophils and is associated with lung function alterations of increased airflow limitation, airway closure/air trapping, and altered reversibility patterns[44–46]. Importantly, these patients respond poorly to corticosteroid treatment, indicating the need for new therapies for this type of asthma[47].

Inflammatory phenotypes in asthma are best defined based on sputum cell counts. Thus, neutrophil percentages in sputum exceeding the numbers in healthy individuals were initially used to define ‘pathologic’ neutrophil percentages, leading to a cut-off of 61% to define ‘neutrophilic asthma’ [47,48]. This cut-off was later adjusted to 76% because of higher ‘normal’ values in healthy individuals[49,50]. However, sputum neutrophilia does not always predict neutrophilic bronchial inflammation[51]. In addition, although neutrophilic inflammation predominates in this cluster, neutrophilia can also coexist with eosinophilia[42,51,52], illustrating the complexity of severe asthma. Therefore, how to define neutrophilic asthma in relation to severe asthma remains an open question and there is a debate whether neutrophilic asthma represents a true endotype of disease[53] because so many factors can influence the presence and function of neutrophils in airways. Thus, it may be more useful to think of neutrophils as a manifestation of an inflammatory process that is contributing to airway pathology in multiple ways. For example, Th17 cells and innate lymphoid type 3 cells (ILC3) have been linked with neutrophilic airway inflammation (Figure 1). These cells secrete IL-17 cytokines (IL- 17A and IL- 17F) that stimulate the production and release of neutrophilic chemokines in airway epithelial cells and fibroblasts, leading to neutrophil recruitment to the airway[54,55]. Hence tissue neutrophilia may be a biomarker of elevated IL-17 activity. Several other factors may also contribute to neutrophilic inflammation[56]. Treatment with high dose inhaled or oral corticosteroids has been shown to contribute to the high number of airway neutrophils in asthmatics[57,58]. More neutrophilic airway inflammation was found in obese versus nonobese asthmatics[21]. Smoking worsens asthma symptoms and morbidity, and promotes neutrophilic

asthma[59,60]. In fact, smoking cessation decreased airway neutrophil number, alleviated clinical symptoms, and reduced total mortality in asthmatics[61–63]. The presence of airway bacteria has been suggested as contributing to airway neutrophilia[64]. There are significant differences in airway bacteria species in patients with neutrophilic versus eosinophilic asthma, which may alter the corticosteroid sensitivity in these patients[65]. Importantly, macrolide antibiotics that have antibacterial and anti-inflammatory effects are of some benefit for both T2 and non-T2 asthma[66–68]. A large randomized, double-blind, placebo-controlled clinical study demonstrated that add-on azithromycin significantly reduced asthma exacerbations with an improvement in quality of life in patients with persistent uncontrolled asthma[69,70]. Further studies showed that azithromycin treatment reduces key sputum cytokines associated with non-T2 asthma such as IL-6 and IL-1β[71].

How neutrophils may contribute to altered airway pathophysiology in asthma is largely based on circumstantial evidence[56]. For example, chemokines released by neutrophils attract monocytes/macrophages to the airway, thus altering airway inflammation[72]. Neutrophils can cause ASM hyperresponsiveness[73] and exosomes secreted from neutrophils also regulate ASM remodeling[74]. It was found that neutrophils in asthma patients secrete a higher level of transforming growth factor β (TGF-β) and matrix metalloprotease-9 (MMP-9) to promote airway remodeling, leading to poor lung function[75–77]. Increased neutrophil elastase in asthmatic patients can cause airway narrowing via induction of airway mucus gland hyperplasia, mucus secretion, and ASM cell proliferation[78,79]. In addition, increased neutrophils also reduced epithelial barrier function in the airways[80]. However, while targeting neutrophils inhibits airway inflammation and alleviates airway hyperresponsiveness in some animal models of asthma[81–83], this strategy failed to show benefit in asthma patients[84], leading to question the exact role of neutrophils in asthma[85]. Furthermore, neutrophils are heterogenous with proinflammatory and anti-inflammatory subsets[86]. For example, neutrophils in the airways of asthmatic patients consist of distinct subsets with different/increased activation states[87,88]. Thus, more precise characterization of neutrophil subsets and the delineating mechanisms for the phenotypic changes in the airways of asthmatics will be essential for the future development of neutrophil-targeting therapies. In addition, one also must take into account the importance of neutrophils in host defense mechanisms and the consequences that could develop as a result of their inhibition in the airways.

TH17 CELL DIFFERENTIATION

Th17 cells are a distinct $CD4^+$ T helper cell subset that is characterized by the expression of the transcription factor retinoic acid–related orphan receptor-γt (RORγt)[89]. They are derived from naïve $CD4^+$ T cells and play a key role in the pathogenesis of non-T2 neutrophilic asthma. Th17 cell differentiation relies on the coordination of several well-characterized cytokines and transcription factors, with TGF-β1, IL-6 and IL-23 as the most prominent drivers of Th17 cell differentiation. They induce specific transcription factors responsible for the expression of Th17 cell specific cytokines such as IL-17A and IL-17F. Multiple transcription factors have been shown to be important for the development of Th17 cells, including RORγt, signal transducer and activator of transcription 3 (STAT3), interferon regulatory factor 4 (IRF4), basic leucine zipper ATF-like transcription factor (BATF), and

runt-related transcription factor 1 (RUNX1). Of these, RORγt appears to be the master transcription factor that regulates the differentiation of Th17 cells[90].

TGF-β is a regulatory cytokine that has multiple effects on T cell development, homeostasis, and tolerance[91]. Interestingly, TGF-β is required for the development of both Th17 cells and regulatory T-cells (Tregs) by triggering the expression of their differentiating transcription factors, RORγt and forkhead box P3 (FOXP3), respectively[92]. In fact, both transcription factors are initially up-regulated after naïve $CD4^+$ T cells encounter TGF-β[93]. Whether subsequent differentiation of the cells is skewed towards a Treg phenotype or a proinflammatory Th17 cell phenotype depends mainly on the cytokine milieu. TGF-β alone induces differentiation of FOXP3-dependent Treg cells[94,95], whereas the presence of IL-6 inhibits Treg development and induces Th17 cell differentiation[94]. IL-6 also directly activates STAT3, whereas TGF-β both inhibits suppressor of cytokine signaling 3 (SOCS3), a negative regulator of STAT3 signaling, and activates SMAD2 to promote RORγt and IL-17A expression[96–98]. Additional cytokines can further drive Th17 cell differentiation. For example, IL-1β signaling was reported to enhance the phosphorylation of STAT3 by repressing SOCS3 to favor human Th17 cell differentiation[99]. Interestingly, FOXP3 is present in several isoforms due to alternative splicing. In the absence of a second signal from a proinflammatory cytokine, full length FOXP3 directly binds and inhibits RORγt function, thus driving Treg differentiation[100], whereas FOXP3 isoforms lacking exon 7 inhibit the function of full length FOXP3 in a dominant-negative manner[101,102]. A recent study showed that IL-1β can promote Th17 cell development through induction of FOXP3 isoforms lacking exon 7[102].

IL-23 is a proinflammatory cytokine that plays an important role in the regulation of numerous inflammatory diseases by integrating the innate and adaptive immune systems[103]. IL-23 is essential for the maintenance, expansion, and proper function of Th17 cells through a positive feedback loop[104]. During chronic inflammation, activated dendritic cells and macrophages produce IL-23 that promotes the development and differentiation of Th17 cells[105]. Importantly, IL-23 is required for full function of Th17 cells in vivo. In the absence of IL-23, Th17 cells activated with TGF-β1 plus IL-6 exhibit impaired pathogenic function in vivo despite increased IL-17 production[106]. In addition, IL-23 also enhances Th2 cytokine production and eosinophilic airway inflammation[107]. Serum IL-23 is elevated in asthmatic patients and is associated with airflow obstruction[108]. Deletion of *IL-23* gene or treatment with an anti-IL-23 antibody reduced airway inflammation and decreased airway resistance in mice[109,110]. However, in a recent phase 2a trial, the monoclonal anti-IL-23 antibody risankizumab reduced IL-23 target genes but had no clinical benefit in asthmatic patients[111]. Thus, further basic and clinical studies are needed to determine the pathological roles of IL-23 signaling pathways in asthma.

IL-17 CYTOKINES AND NEUTROPHILIA IN SEVERE ASTHMA

Th17 cells secrete Th17-associated cytokines IL-17A, IL-17F, IL-21, and IL-22. Among these cytokines, IL-21 acts in an autocrine manner to promote IL-17A production[112] whereas IL-22 enhances the proliferation and migration of human ASM cells[113,114], leading to airway remodeling and hyperresponsiveness[115]. IL-17A and IL-17F are particularly

important in immune responses against bacterial and fungal infections[116]. They belong to the IL-17 family (including IL-17A, IL-17B, IL-17C, IL-17D, IL-17E [known as IL-25], and IL-17F), and they share common receptor subunits, IL-17 receptor A (IL-17RA), and IL-17 receptor C (IL-17RC).116 IL-17A and IL-17F can form homodimers and heterodimers, and may have similar functions to induce neutrophil recruitment to the airway[117,118]. IL-17C, mainly released by epithelial cells[119], enhances IL-17A and IL-17F release from Th17 cells[120] whereas IL-25 promotes T2 inflammation through induction of IL-4, IL-5 and IL-13[121]. Little is known about IL-17D. A recent study found that IL-17D exerts anti-inflammatory effects via regulation of ILC3 function[122].

IL-17A and IL-17F are pro-inflammatory cytokines known to stimulate neutrophil maturation, migration, and function[55,123]. Overexpression of IL-17A in mice results in significant peripheral neutrophilia[124]. The number of cells positive for IL-17A was initially found to be increased significantly in sputum and bronchoalveolar lavage fluids of subjects with asthma in comparison with control subjects[125]. Subsequent studies demonstrated that IL-17A was elevated in bronchial tissues, peripheral blood mononuclear cells (PBMCs), and serum from asthmatic patients[126–132]. Importantly, IL-17A production in asthma patients positively correlates with AHR and clinical severity of asthma[38,127,131–135]. Similarly, IL-17F was also increased in asthma patients[126,136], correlated with both airway neutrophils and more severe disease[137,138]. A loss-of-function IL-17F mutant antagonizes wildtype IL-17F and is inversely related to asthma risk.[139,140]

Another study found a correlative increase in IL-17A and IL-17F in bronchial biopsies in patients with increasing asthma severity[39]. In addition, expression of specific IL-17 receptor subunits, IL-17RA and IL-17RC[118], were also increased in the bronchial tissues and PBMCs of asthmatic patients[128,129]. These findings indicate that IL-17A and IL-17F are likely important cytokines in the pathogenesis of neutrophilic asthma. It should be noted that in addition to Th17 cells, other cell types including ICL3, bone-marrow-derived neutrophils, B cells, IL-17-producing CD8+ T cells, natural killer T cells, mucosal-associated invariant T cells, etc. also release IL-17A and IL-17F in response to different cytokines (reviewed by Hynes and Hinks)[123]. It is not yet clear which are the main sources of IL-17A and IL-17F secretion and what are their contributions to the pathogenesis of neutrophilic asthma.

CONTRIBUTION OF TH17 CELLS AND IL-17 CYTOKINES TO CORTICOSTEROID INSENSITIVITY IN SEVERE ASTHMA

Glucocorticoids, a class of corticosteroids, are currently the most effective treatment for asthma. The anti-inflammatory effects of glucocorticoids are mediated by their intracellular receptors (GRα) while the GRβ variant acts as a dominant negative inhibitor of GRα[141]. Glucocorticoids bind to GRα in the cytoplasm and the glucocorticoid/GRα complex translocates into the nucleus to repress pro-inflammatory genes and transactivate anti-inflammatory genes, thus inhibiting activation, infiltration, and survival of inflammatory and epithelial cells, as well as the pro-inflammatory function of ASM cells[142–145]. Corticosteroid insensitivity can be inherited or acquired. GRα mutations were associated with insensitivity or hypersensitivity to glucocorticoids[146,147]. Reduced GRα expression[148],

defective GRα nuclear translocation[149], increased phosphorylation of GRα with impaired activity[150] and increased expression of the dominant negative GRβ[151] also play roles in the induction of corticosteroid insensitivity.

Corticosteroid-based drugs can effectively manage T2 inflammation via inducing apoptosis of Th2 cells and eosinophils and inhibiting T2 cytokine production. Thus, patients with allergic asthma generally respond well to corticosteroids, with improved lung function and reduced exacerbations. However, up to 10% of asthmatics respond poorly to corticosteroid-based therapies, called corticosteroid-insensitive, -refractory or -resistant asthma. Patients with corticosteroid-insensitive asthma account for a large percentage of the overall costs for asthma worldwide. Their asthma is less stable and more difficult to control, and they are subject to higher morbidity and mortality[152–155]. There are many reasons why asthma patients fail to benefit from corticosteroid-based therapies[155], including lack of adherence to prescribed therapy[156,157]. PGA manifests with no sputum eosinophilia or neutrophilia[25] and inhaled corticosteroids have limited effects in patients with PGA[27,158]. Airway neutrophils also play an important role in mediating severe and corticosteroid-insensitive asthma[159–161]. In fact, corticosteroids promote the apoptosis of eosinophils but inhibits neutrophil apoptosis, which may explain why increased neutrophils are associated with inhaled corticosteroid-treated severe asthma[162–164].

Mounting experimental and clinical evidence supports a role of Th17 and IL-17 cytokines in corticosteroid-insensitive asthma. McKinley *et al.*[165] first linked Th17 cells with corticosteroid-insensitive allergic airway disease in an animal model characterized by elevated neutrophil chemokines and growth factors as well as neutrophilic inflammation in the lung. Importantly, Th17-driven allergic airway disease was not abrogated by the corticosteroid treatments that were effective in inhibiting Th2-driven airway disease. Treatment with the corticosteroid drug dexamethasone significantly inhibited T2 cytokines but not IL-17 production *in vitro*[165]. The transfer of primed ovalbumin-specific Th2 cells into mice induces a corticosteroid-sensitive allergic asthma, whereas the transfer of ovalbumin-specific Th17 cells induces a severe corticosteroid-insensitive asthma[165]. Furthermore, after exposure to antigen, mice overexpressing the transcription factor RORγt exhibited predominantly neutrophilic airway inflammation with enhanced lung expression of IL-17 and IL-22. The neutrophilic airway inflammation in RORγ*t*-overexpressing mice was effectively suppressed by anti-IL-17 antibody, but not by dexamethasone[166]. In fact, dexamethasone was reported to enhance Th17 cell differentiation *in vitro*[167] and IL-17 can synergize with dexamethasone to induce neutrophil-promoting cytokine colony-stimulating factor 3 (CSF3) in both ASM cells and fibroblasts, leading to corticosteroid insensitivity[168]. Other mechanisms for Th17 cell-mediated corticosteroid insensitivity in severe asthma have been proposed, including up-regulation of the expression of GRβ in peripheral mononuclear cells[151] and increased expression of mitogen-activated protein kinase 1 (MEK1) in CD4+ T cells that inhibits GRα activity[169,170]. Human studies also suggest the involvement of Th17 cells and IL-17 cytokines in patients with severe corticosteroid-insensitive asthma[38,128,129]. These findings demonstrated that Th17 cells and IL-17 are sufficient to promote many of the hallmark characteristics of neutrophilic asthma *in vivo* and that these responses are corticosteroid-insensitive. It should be noted that IL-17 produced by ILC3 may play a role in corticosteroid insensitivity associated with the obesity phenotype of asthma[171].

Interestingly, dual positive Th2/Th17 cells were found in the blood, tissue, and bronchoalveolar lavage fluid of subjects with the most severe form of asthma and who manifest corticosteroid insensitivity[169,172,173]. In fact, there has been a shift from viewing asthma as T2 vs non-T2 as a binary situation. For example, some patients with severe asthma have a mixed neutrophilic and eosinophilic inflammation in their sputum[174]. These patients typically have the most severe asthma symptoms and poor response to inhaled corticosteroids[43,175–177]. Israel and Reddel have postulated that IL-6 and IL-17 may stimulate Th2 and Th17 cell responses in the airway, thus promoting both T2 and non-T2 inflammation[12]. Upon stimulation with IL-21, IL-1β, IL-6, and anti-IFN-γ, native T cells differentiate into dual-positive Th2-Th17 cells, leading to more severe asthma subtypes[178]. Deletion of *IL-17* and *RORγt* genes or treatment with an RORγt inhibitor blocked both Th2 and Th17 cell responses, leading to a reduction of neutrophilic and eosinophilic inflammation in mice with allergic asthma[179]. Interestingly, inhibition of Th2 cell cytokines augments Th17-dependent neutrophilia, whereas blockade of IL-17 augments Th2-stimulated eosinophilia in experimental allergic asthma[180], suggesting that Th2 and Th17 cell responses co-exist in airways and are reciprocally regulated. Hence combined blockade of both T2 and non-T2 inflammation might be able to achieve better therapeutic benefits in controlling severe corticosteroid-insensitive asthma.

THERAPEUTIC IMPLICATIONS OF TARGETING TH17 CELL RESPONSES IN CORTICOSTEROID-INSENSITIVE ASTHMA

Because corticosteroid-insensitive neutrophilic asthma is associated with excessive Th17 responses, inhibiting Th17 signaling might offer effective therapeutic options for corticosteroid-insensitive asthma. Potential therapeutic approaches include directly targeting Th17-related cytokines, cytokine receptors, and intracellular signaling pathways, as well as inhibiting Th17-specific transcription factors (Figure 2 and Table 1).

Blocking IL-17A and IL-17RA:

Blocking IL-17A by its monoclonal antibody was demonstrated to improve lung function in several experimental murine asthma models. Kudo *et al.*[181] found that IL-17A blocking antibodies can attenuate the contractile response of smooth muscle cells in the airways. Manni *et al.*[182] demonstrated that IL-17A contributes to AHR in an experimental model of corticosteroid-insensitive Th2/Th17 asthma. Camargo *et al.*[183] showed that treatment with IL-17A antibody alleviated pulmonary inflammation, remodeling, and oxidative stress in an experimental model of lipopolysaccharide (LPS)-exacerbated asthma. However, two clinical trials of humanized anti-IL-17A monoclonal antibodies, secukinumab (AIN457) and CJM112 failed to improve asthmatic symptoms in patients with severe asthma[184,185]. IL-17 binds to receptor complexes that have IL-17RA as the common subunit. Brodalumab, also known as AMG-827, is a humanized monoclonal antibody that binds to IL-17RA, thereby blocking the receptor and the downstream signal pathways of IL-17A, IL-17F and other IL-17 isoforms. The efficacy and safety of brodalumab was evaluated in patients on inhaled corticosteroids with inadequately controlled moderate to severe asthma[186]. Although a nominally positive response was seen in a subgroup with bronchodilator reversibility, no difference was observed in Asthma Control Questionnaire (ACQ) scores between subjects

treated with brodalumab compared to placebo in the overall study population. Since the patients in this clinical trial were not selected for non-T2 asthma and the trial design may have precluded detection of benefit for these agents in patients with heterogeneous phenotypes, it is possible that subgroups of patients, particularly those with high numbers of sputum neutrophils or with a high degree of lung function reversibility would respond more favorably[186–188]. It should be noted that the US Food and Drug Administration issued a black box warning after six patients treated with brodalumab across four clinical trials committed suicide, but no causal relationship was identified. Nonetheless, the relative lack of efficacy in the initial asthma clinical trial and a questionable safety issue has resulted in discontinuation of brodalumab studies for the treatment of asthma. Thus, further clinical studies are needed to determine the efficacy of targeting IL-17/IL-17RA signaling with other IL-17/IL-17RA drugs in more precisely defined patient subsets and/or endpoint selection. Furthermore, therapy with IL17A/IL17RA antibodies may have failed because other Th17-associated cytokines such as IL-22 also contribute to severe asthma independently from IL-17. Thus, a broader upstream approach that targets Th17 cells might be more effective than anti-IL-17/IL-17 receptor therapies[115]. In addition, it was reported that anti-IL-17A augmented Th2 cell responses and eosinophilia in experimental allergic asthma[180]. Thus, it may require combination therapies blocking both Th17 and Th2 cell responses to effectively control severe asthma[179,180].

Blocking IL-6 and IL6R:

IL-6 is an important cytokine for the induction of Th17 cell differentiation, as well as a downstream target of IL-17A. In the presence of TGF-β, IL-6 drives naive T cells to differentiate into Th17 cells[92,189,190]. Th17 cells release more IL-6 to further promote Th17 cell differentiation[191]. Studies also showed that IL-6 induced expression of IL-21 that amplified an autocrine loop to induce more IL-21 and IL-23 receptor in naïve $CD4^+$ T cells. Both IL-21 and IL-23 can induce IL-17 expression[192]. Chu *et al.*[193] observed that increased sputum IL-6 was associated with mixed eosinophilic-neutrophilic bronchitis and impaired lung function in patients. An anti-IL-6 antibody reduced neutrophilic and eosinophilic cytokines/chemokines and alleviated airway inflammation in mice[193]. In addition, IL-6 production was increased in IL-17A-induced corticosteroid-insensitive airway inflammation in an animal study of allergic airway inflammation, and both airway neutrophilia and AHR were effectively attenuated by treatment with an anti-IL6R antibody[166]. A more recent study showed that blockade of IL-6 signaling attenuates toluene diisocyanate-induced Th2/Th17 responses and ameliorates corticosteroid-insensitive asthma in mice[194]. IL-6 may also play a significant role in subtypes of obese non-T2 asthma. Peters *et al.*[195] found that patients with plasma IL-6-high asthma had worse lung function and asthma control. Blood neutrophils were increased in the plasma IL-6-high group, suggesting a role for systemic IL-6-mediated neutrophilic inflammation in mediating an “outside-in mechanism of lung dysfunction.” Conventional asthma research generally focuses on pathogenic factors that arise inside the lung (“inside out”) such as increases in airway inflammation. Peters’ work suggests that lung dysfunction can occur from pathogenesis outside the lung (“outside in”), such as the low-grade systemic inflammation that occurs during obesity. Indeed, a severe asthma research program 3 (SARP3) study of severe asthmatic patients demonstrated that obesity was associated with elevated plasma IL-6 levels and that plasma IL-6 levels

predicted asthma exacerbation risk independently of T2 biomarkers[196]. Furthermore, single nucleotide polymorphism (SNP) rs4129267 in the *IL6R* gene has been associated with an increased risk of asthma[197] whereas the SNP rs2228145 is linked with reduced lung function in severe asthma[198]. In addition to acting on Th17 cells and neutrophils, IL-6 can also bind to soluble IL6R and causes IL-6 trans-signaling (IL-6TS) on airway epithelial cells[199] and ASM cells[200], leading to impaired epithelial barrier function, airway inflammation and remodeling. These studies prompt consideration of treatment approaches for severe asthma via inhibiting cytokines associated with systemic inflammation (*e.g.,* IL-6). In a preliminary report, two patients with severe persistent, non-atopic asthma were treated with tocilizumab, a humanized anti-IL6R monoclonal antibody, and both patients exhibited decreased Th2 and Th17 cell responses and clinical improvement[201]. In the PrecISE clinical study sponsored by the U.S. National Heart, Lung, and Blood Institute to investigate several treatments for severe asthma, the efficacy of the anti-IL-6 monoclonal antibody clazakizumab will be examined[202].

Blocking IL-1β and its receptor (IL1R1):

IL-1β plays an important role in the pathogenesis of asthma[203]. Increased levels of IL-1β were detected in the airways or the sputum of patients with asthma[204,205] and was associated with increased neutrophil counts in elder patients with more severe asthma[206]. IL-1β signaling was reported to enhance the phosphorylation of STAT3 by repressing SOCS3 to favor human Th17 cell differentiation[99]. In the presence of IL-2 and TGF-β, IL-1β can also induce transdifferentiation of ILC2s into IL-17-secreting cells[207]. IL-1β is generated by the nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain-containing protein 3 (NLRP3) inflammasome, mainly in monocytes and macrophages. Neutrophilic airway inflammation, disease severity, and corticosteroid insensitivity in human asthma all correlate with NLRP3 and IL-1β expression[208]. Treatment with anti–IL-1β neutralizing antibody, caspase-1 inhibitor Ac-YVAD-cho, and NLRP3 inhibitor MCC950 each suppressed IL-1β responses and corticosteroid insensitivity in experimental murine models of neutrophilic asthma[208]. Furthermore, the expression level of IL1R1 strongly correlates with increased neutrophils in sputum and airflow limitation of asthmatic patients[209] and LPS-induced neutrophilic airway inflammation in healthy volunteers was attenuated by the IL1R1 antagonist anakinra[210]. In addition, IL-1β can modulate AHR in asthma via regulation of ASM contraction and relaxation[211,212]. IL-1β signaling is also involved in airway remodeling through hypersecretion of mucus in asthma[213]. These findings highlight the important role of IL-1β in the pathogenesis of asthma via both airway inflammation and remodeling. In a randomized double-blind placebo-controlled trial, IL-1β blocking antibody canakinumab significantly reduced the late asthmatic response in patients with mild asthma[214]. In addition, targeting IL-1β for airway inflammation in asthma by anakinra was to be tested in clinical trials, but was suspended due to the COVID-19 pandemic[215].

Blocking the transcription factor RORγt:

RORs are members of the nuclear receptors, a superfamily of structurally conserved, ligand-regulated transcription factors[216]. Two isoforms of RORγ, RORγ1 and RORγ2 (or RORγt), have been identified. RORγ1 is ubiquitously expressed, whereas RORγt is highly

expressed in specific sub-populations of immune cells[217]. RORγt is the key transcription factor required for Th17 cell differentiation and for production of Th17 cell cytokines by innate and adaptive immune cells. TMP778 and TMP920, two inverse agonists of RORγt, were shown to potently suppress Th17-cell generation and IL-17 secretion by differentiated Th17 cells *in vitro*[218]. TMP778 also inhibited human Th17 signature gene expression *in vitro* as well as murine Th17-cell differentiation *in vivo*[219,220]. In addition, mice with deletion of RORγt gene or treatment with the RORγt inhibitor ursolic acid had diminished Th17 and Th2 cell responses, leading to reduced neutrophil and eosinophil numbers in the airway[179]. Interestingly, RORγt-deficient T cells were defective in differentiating into Th2 cells but express a higher level of B-cell lymphoma 6 (BCL6) than wild-type T cells under Th2 cell differentiation conditions. BCL6 knockdown restored Th2 cell differentiation in RORγt-deficient T cells. BCL6 is known to suppress the differentiation of naive T cells into Th2 cells[221,222] via inhibition of GATA-3 expression[223] and BCL6-deficient mice exhibited a marked increase in Th2 cell responses[224]. Thus, RORγt blockade diminishes Th2 cell responses, at least in part, via upregulation of BCL6 in T cells[179]. Whitehead *et al.*[225] recently reported that the orally available selective RORγt inverse agonist VTP-938 not only attenuates Th17 cell development and neutrophilic inflammation of the airway, but also diminishes AHR in an environmentally relevant house dust mite extract–mediated model of asthma. Interestingly, a recent animal study suggests that RORγt inhibitors can block both Th17-associated IL-17 and IL-22, which might be more effective than anti-IL-17 alone to treat severe asthma[115]. Furthermore, JNJ-61803534, a potent and selective RORγt inhibitor, exhibited an acceptable biosafety profile in both preclinical and clinical trials[226]. However, genetic loss of RORγt contributes to chronic fungal infections in humans[227] and RORγt blockade with multiple agents has led to thymic lymphomas in mice[228]. Thus, although blockade of RORγt with small molecule agents might provide a novel strategy in the management of Th17-dependent neutrophilic asthma, further studies are needed to evaluate the potential on-target toxicities associated with chronic usage of these agents before considering therapeutic use for severe asthma in human subjects.

Blocking RhoA/ROCK signaling pathways:

Increased activation of Rho-associated kinase (ROCK) was observed in asthmatic patients, and this has been suggested as a potential therapeutic target for asthma[229,230]. This signaling pathway is the key regulator of T-cell maturation, activation and differentiation[231]. Ablation of RhoA or treatment with Y16, a specific RhoA inhibitor impaired Th17 cell differentiation via downregulation of STAT3 and RORγt, and alleviated house dust mite-triggered allergic airway inflammation in mice[232]. ROCK, a serine/threonine kinase, is one of the main downstream signaling molecules of RhoA. There are two highly homologous isoforms: ROCK1 and ROCK2[233]. Zanin-Zhorov *et al.*[234] reported that ROCK2 controls IL-17A secretion in human T-cells via the regulation of STAT3 and RORγt. KD025, a selective ROCK2 inhibitor, modulates inflammation by decreasing STAT3 activation and increasing the suppressive function of Tregs. Treatment of human T cells with KD025 induced a beneficial shift in the Th17/Treg balance[234]. It should be noted that the RhoA/ROCK signaling pathways also play important roles in ASM contraction, AHR, and airway remodeling[235–237]. Thus RhoA/ROCK antagonists with pleiotropic effects on numerous

inflammatory and airway cell signaling pathways could provide novel therapeutic benefit in corticosteroid-insensitive asthma.

CONCLUSION

Severe, corticosteroid-insensitive asthma is a significant clinical problem, adversely affecting quality of life, increasing healthcare costs, and lacking good therapeutic options. Both human and animal studies have demonstrated that excessive Th17 responses are likely a key factor in this type of corticosteroid-insensitive, neutrophilic asthma. Therefore, targeting Th17-associated cytokines may provide therapeutic approaches to reduce excessive Th17 signaling that could offer advantages over classic therapies, such as corticosteroids, for patients with severe asthma. However, Th17 cells are not homogenous, but rather consist of both non-pathogenic and pathogenic cell populations[106,238–241]. Therefore, the consequences of long-term inhibition of the Th17 pathway must be carefully evaluated to determine the risk versus benefit in blocking this pathway. Although a few trials have reported varying data targeting Th17 cell responses and Th17 related cytokines, there remain multiple challenges to identify, develop and implement the “ideal” Th17-targeted interventional strategy with respect to safety and the treatment of corticosteroid-insensitive neutrophilic asthma.

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Abbreviations used:

AHR	airway hyperresponsiveness
AQC	Asthma Quality Control
ASM	airway smooth muscle
BATF	basic leucine zipper ATF-like transcription factor
BCL6	B-cell lymphoma 6
BT	bronchial thermoplasty
CSF3	colony-stimulating factor 3
FOXP3	forkhead box P3
GATA3	GATA binding protein 3
GC	goblet cells
GM-CSF	granulocyte-macrophage colony-stimulating factor
GR	glucocorticoid receptor
IL1R1	Interleukin 1 receptor, type I

IL6R	interleukin 6 receptor
IL-6TS	IL-6 trans-signaling
IL-17	interleukin 17
IL-17RA	IL-17 receptor A
IL-17RC	IL-17 receptor C
ILC2	innate lymphoid type 2 cells
ILC3	innate lymphoid type 3 cells
IRF4	interferon regulatory factor 4
MMP-9	matrix metalloprotease-9
NLRP3	the nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain-containing protein 3
PBMCs	peripheral blood mononuclear cells
PGA	paucigranulocytic asthma
ROCK	Rho-associated kinase
RORγt	retinoic acid–related orphan receptor-γt
RUNX1	runt-related transcription factor 1
SARP3	severe asthma research program 3
SNP	single nucleotide polymorphism
SOCS3	suppressor of cytokine signaling 3
STAT3	**s**ignal transducer and activator of transcription 3
TGF-β	transforming growth factor β
Th2	T helper 2 cells
Th17	T helper 17 cells
Tregs	regulatory T-cells
T2	type 2
TSLP	thymic stromal lymphopoietin

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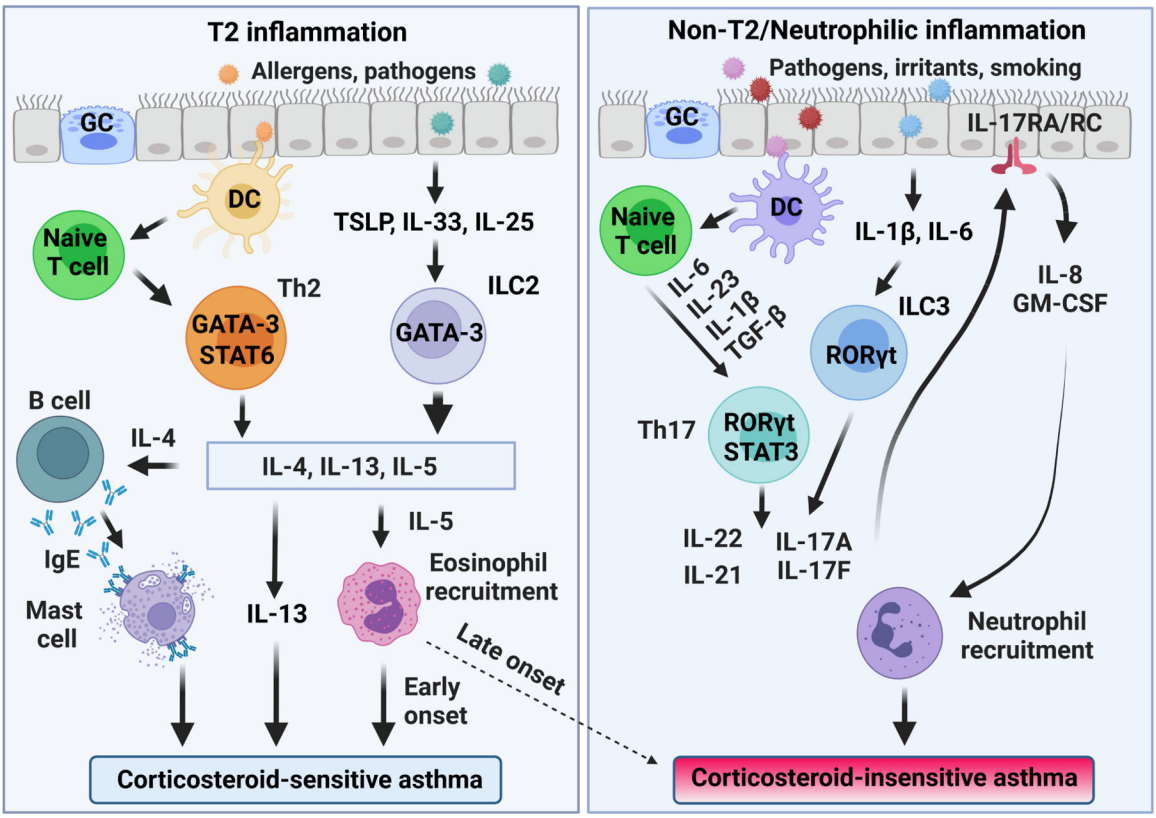

FIG 1.

T2 and non-T2 inflammation in corticosteroid-sensitive and -insensitive asthma. Airway epithelia stimuli result in the production of alarmins, thymic stromal lymphopoietin (TSLP), IL-33, and IL-25 that stimulate differentiation of innate lymphoid type 2 cells (ILC2). Dendritic cells (DC) induce the differentiation of Th2 cells. ILC2 and Th2 cells produce the T2 cytokines IL-4, IL-5, and IL-13 via GATA binding protein 3 (GATA3), contributing to the development of corticosteroid-sensitive asthma. Late-onset eosinophilic asthmatics can have persistent airway eosinophilia despite corticosteroid therapy (dashed line). Corticosteroid-insensitive asthma results from exposure to pathogens, irritants, and smoking triggering release of TGF-β, IL-6, IL-1β, and IL-23 that stimulate differentiation of Th17 cells via transcription factors RORγt and STAT3. Th17 cells produce cytokines IL-17A, IL-17F, IL-21, and IL-22 that stimulate the production of neutrophilic chemokines (e.g., IL-8 and GM-CSF). Innate lymphoid type 3 cells (ILC3) also produce IL-17 and play roles in obesity-associated, corticosteroid-insensitive asthma. GC, goblet cells; GM-CSF, granulocyte-macrophage colony-stimulating factor. Created with BioRender.com.

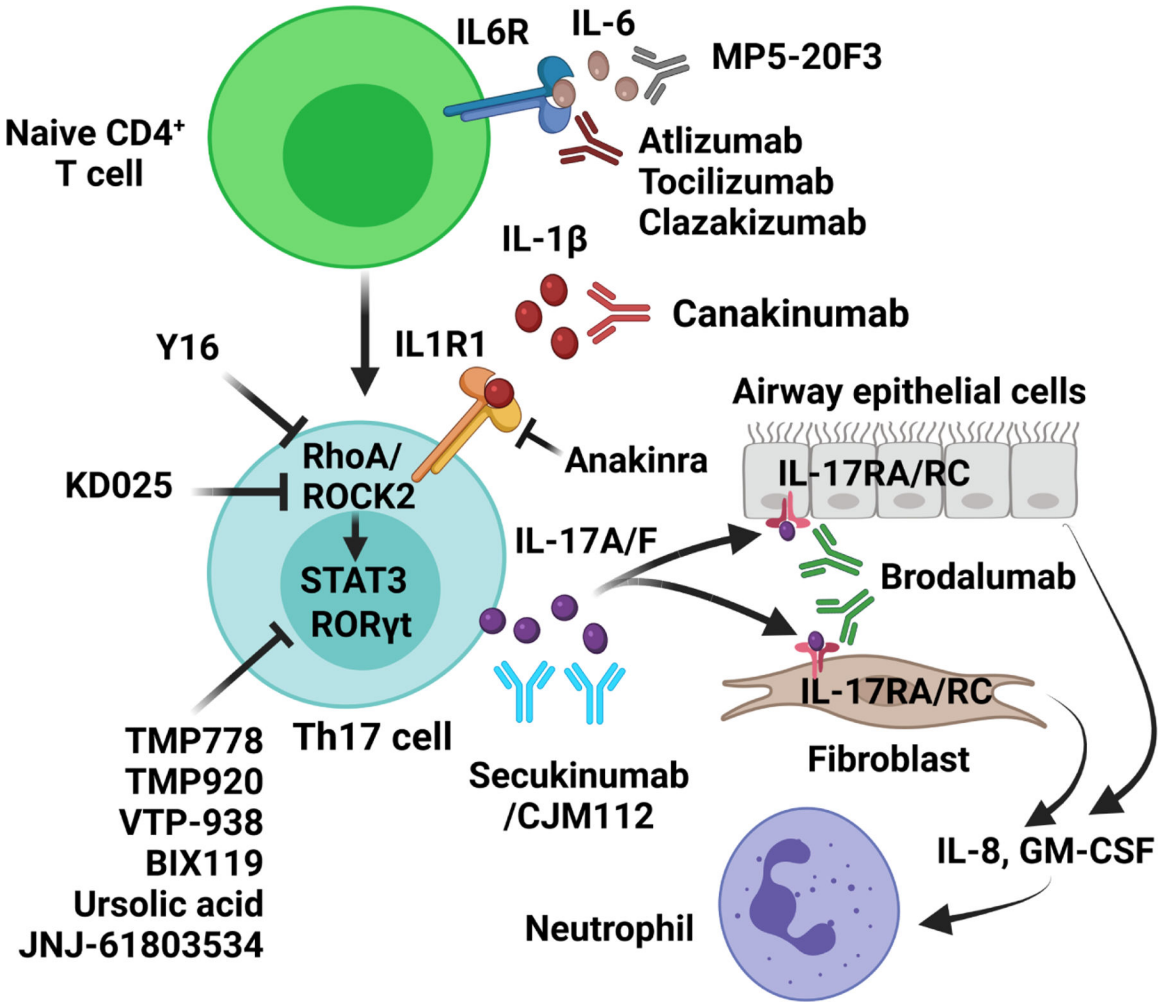

FIG 2.

Therapeutic agents targeting Th17 cell responses. TGF-β, IL-1β and IL-6 stimulate differentiation of naïve T cells into the Th17 lineage. Full differentiation of Th17 cells requires the cooperative action of RORγt and STAT3. Th17 cells produce the IL-17 family of cytokines including IL-17A and IL-17F, which stimulate the production and release of neutrophilic chemokines (e.g., IL-8 and GM-CSF) in airway epithelial cells and fibroblasts via its receptor IL-17RA and IL-1RC, leading to recruitment of neutrophils into the airways. GM-CSF, granulocyte-macrophage colony-stimulating factor; IL6R, IL-6 receptor; IL1R1, IL-1 receptor; IL-17RA, IL-17 receptor A; IL-17RC, IL-17 receptor C; RORγt, retinoic acid receptor-related orphan receptor-γt; ROCK2, Rho-associated kinase 2. Created with BioRender.com.

TABLE 1.

Emerging therapies targeting Th17 cell responses in corticosteroid-insensitive asthma

Target	Reagent	Type of drug	System	Reference
IL-17A	Anti-IL17A	mAb	Mice	183
	Secukinumab/CJM112	mAb	Human	184, 185
IL-17RA	Brodalumab	mAb	Human	186
IL-6	MP5-20F3	mAb	Mice	193
IL-6R	Atlizumab	mAb	Mice	166
	Tocilizumab	mAb	Human	201
	Clazakizumab	mAb	Human	202
IL-1β	Canakinumab	mAb	Human	214
IL-1R1	Anakinra	Antagonist	Human	210, 215
RORγt	TMP778/920	Inverse agonists	Cells	218–220
	Ursolic acid	Inhibitor	Mice	179
	VTP-938	Inverse agonist	Mice	225
	BIX119	Inhibitor	Mice	115
	JNJ-61803534	Inhibitor	Mice and human	226
RhoA	Y16	Inhibitor	Mice	232
ROCK2	KD025	Inhibitor	Mice	234