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REVIEW: T-cell responses in asthma exacerbations

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Abstract

Objective: Asthma is a chronic lung disease comprising multiple endotypes, and characterized by periodic exacerbations. A diverse array of T cells have been shown to contribute to all endotypes of asthma in pathogenic and regulatory roles. Here, we review the contributions of CD4+, CD8+, and unconventional T cells in allergic and non-allergic asthma.

Data Sources: Review of published literature pertaining to conventional and unconventional T-cell types in asthma.

Study Selections: Recent peer-reviewed articles pertaining to T cells in asthma, with additional peer-reviewed studies for context.

Results: Much research in asthma has focused on the roles of CD4+ Th cells. Roles for Th2 cells in promoting allergic asthma pathogenesis have been well-described, and the recent description of pathogenic Th2a cells provides additional insight into these responses. Other Th types, notably Th1 and Th17, have been linked to neutrophilic and steroid-resistant asthma phenotypes. Beyond CD4+ T cells, CD8+ Tc2 cells are also strongly associated with allergic asthma. An emerging area for study is unconventional T-cell types, including gd T, iNKT, and MAIT cells. While data in asthma remains limited for these cells, their ability to bridge innate and adaptive responses likely makes them key players in asthma. A number of asthma therapies target T-cell responses, and, although data are limited, appear to modulate T-cell populations.

Conclusion: Given the diversity and heterogeneity of asthma and T-cell responses, there remain many rich avenues for research to better understand the pathogenesis of asthma. Despite the breadth of T cells in asthma, approved therapeutics remain limited to Th2 networks.

Keywords

Asthma; CD4+ T helper cells; CD8+ Cytotoxic T cells; γδT cells; iNKT cells; MAIT cells; Biologic therapies

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Introduction

Asthma is a chronic respiratory disease characterized by periods of reversible airway hyperreactivity that affects approximately 260 million people worldwide and caused an estimated 460,000 deaths in 2019[1]. Asthma is a heterogeneous disease, including both allergic and non-allergic endotypes[2]. Allergic asthma is characterized by the induction of IgE antibodies to otherwise innocuous aeroallergens, is the most prevalent form of asthma in children, and accounts for approximately 50% of asthma in adults[3], whereas non-allergic asthma is typically adult-onset. While standard therapies result in disease control for the majority of asthma patients, a subset of 5–10% of patients remain refractory to treatment and frequently utilize healthcare resources[4]. A greater understanding of asthma pathogenesis is essential in order to effectively treat patients in whom standard care fails.

A diverse array of T-cells contribute to asthma development and exacerbation. These T-cells are influenced by a myriad of factors, including allergen and virus exposures, sex hormones, and obesity. While early life exposures and infections are important in immune development and asthma inception[5–7], asthma and immune responses evolve over a lifetime[8,9], adding to the complexity of T-cell mechanisms underlying asthma. In this review, we will discuss the roles of T-cells in asthma, with a major focus on the roles of CD4+ T-cells in allergic asthma and the impact of therapeutic intervention on T-cell populations.

Current perspectives on CD4+ T-cells in asthma

CD4+ T helper (Th) cells, can differentiate into a number of subsets with distinct functions, and are a major focus of asthma research. These functions encompass promotion of allergic inflammation (Th2, Th9), anti-viral and extracellular bacteria immune defense (Th1, Th17), immune regulation (Treg), and promotion of antibody responses (Tfh). Furthermore, Th-subset differentiation is plastic, and can be impacted by local inflammatory cues[10]. Here, we review the roles of diverse Th-subsets in allergic and non-allergic asthma, depicted in Figure 1.

Th2 cells and pathogenic subsets:

Of the Th-subsets, Th2 cells are the most commonly ascribed to asthma pathogenesis, due to their key role in allergen responses. Th2-polarization is induced by dendritic cells (DC) that are primed by the innate cytokines IL-25, IL-33, and thymic stromal lymphopoietin (TSLP)[11], leading to the upregulation of the transcription factor GATA3 in T-cells[12]. Upon allergen exposure, Th2 cells promote IgE production (IL-4, IL-13), mucus hypersecretion (IL-13), and eosinophil recruitment to the airways (IL-5), culminating in airway hyperreactivity (AHR)[11]. Th2 cells also express the chemoattractant receptors CCR4 and CRTH2, which aid in the trafficking of cells to inflamed tissue[13,14]. Recent work has shown that cells in different locations perform distinct functions, with circulating Th2 cells trafficking to the lung and promoting eosinophil recruitment, while tissue-resident cells promote mucus production and eosinophil activation[15], and can induce AHR in the absence of peripheral Th2 cells[16]. Th2 responses have also been associated with BMI and AHR in mouse models of high-fat diet-induced obesity and asthma[17], and sputum IL-5 is elevated in

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individuals with obese versus non-obese severe asthma[18]. This may be mediated via leptin, which can promote the proliferation, survival, and cytokine production of Th2 cells[19].

Within the Th2 subset, there is a recently-described subpopulation of pathogenic cells known as Th2a. These cells are characterized by their co-expression of CRTH2, the tissue-homing integrin CD49d, and the natural killer (NK)-cell receptor CD161, and their capacity to secrete IL-4, IL-5, IL-9, and IL-13[20,21]. Th2a share features with pathogenic effector Th2 cells (peTh2), a subpopulation defined by the surface markers CRTH2 and CD161, and high expression of IL-5 and IL-13[22]. Th2a are the predominant phenotype of allergen-specific CD4+ T-cells and are present at increased frequencies in allergic individuals and reduced frequencies in desensitized individuals after immunotherapy, suggesting a key role for this population in allergic responses[21,23,24]. In addition to canonical and pathogenic Th2 cells, there exist “atypical” Th2 cells with mixed phenotypes. One such population is Th2/Th17 cells which co-express the transcription factors GATA3 and RORγt, and secrete IL-4 and IL-17A[25], a key driver of neutrophilic inflammation. These cells are enriched in the airways of individuals with severe asthma and induce asthma exacerbations in mice[25,26]. Overall, Th2 cells are a key player in the pathogenesis of allergic asthma, but are not the only Th subset to play a role.

Th1 cells:

Th1 cells are key mediators of anti-viral responses. Th1-skewing is induced by IL-12, resulting in expression of the transcription factor T-bet and signature cytokines (IFN-γ, TNF-α). Much discussion of Th1 cells in allergic asthma has focused on Th1/Th2 counter-regulation[27–31], and the notion that Th1 responses are deficient in allergic asthmatics, particularly in the context of respiratory viral infections[32,33]. By contrast, other studies have either failed to identify deficient anti-viral responses in allergic asthmatics, or observed enhanced responses[34–38]. It is possible that temporal differences account for these differences, with deficient early anti-viral responses giving rise to elevated viral titers and inflammation later in infection[39,40], although data are conflicting[34,37,41,42].

Mouse models are contradictory as to the roles of Th1 cells in asthma. Mice lacking Th1 cells spontaneously develop AHR, and Th1-cell adoptive transfer suppresses Th2 inflammation and AHR, supporting a Th2 counter-regulatory role[43,44]. Conversely, other mouse studies have demonstrated increased airway inflammation and cooperative recruitment of Th2 cells into the airways following Th1-cell adoptive transfer[45–48], an IFN-γ requirement for the induction of AHR[49], and a role for IFN-γ in RSV-induced exacerbations[50]. In humans, elevated IFN-γ and Th1 cells have been observed in the lungs of asthmatics[51–55], including during exacerbation[56,57]. Th1 cells have also been implicated in severe, steroid-resistant[58–62] and obesity-associated asthma[63–65]. There are several potential pathogenic effects of Th1-associated cytokines. IFN-γ can activate mast cells and induce AHR[66,67], and TNF-α is a potent pro-inflammatory mediator with potential roles in the recruitment of immune cells and airway remodeling[68–71]. The complex interplay between Th1 and Th2 cells in viral and non-viral asthma exacerbations remains a key research topic.

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Th17 cells:

Th17 cells are potent promoters of neutrophilic inflammation, and play a key role in host defense against extracellular bacteria. Th17 cells express the transcription factor RORγt and differentiate in response to IL-6 and IL-23, as well as neutrophil cytoplasts released by NETosis[72]. Th17 cells produce the signature cytokines IL-17A and IL-17F, as well as IL-21 and IL-22. IL-17 exerts pleiotropic effects in the airways, including promotion of neutrophilia, mucus production, AHR, and remodeling[73,74]. Numerous studies report increased Th17 cells and IL-17 in the blood and airways of asthmatic patients, which links with neutrophilia, AHR, and reduced asthma control[75–77]. IL-17 also exerts differential effects on allergic sensitization in mice depending on timing, with IL-17 promoting eosinophilic inflammation during asthma development, but suppressing eosinophilic inflammation in established disease[78]. Interestingly, rhinovirus, a major trigger of allergic asthma, has been shown to downregulate IL-17A in a mouse model of allergic asthma[79]. Th17 inflammation is also a feature of non-allergic asthma when compared to children with allergic asthma[80]. In mice, adoptive transfer of Th17 confers steroid-resistant AHR, which is reduced in mice that lack Th17 cells[81,82]. Interestingly, increased production of IL-17 by Th17 cells has been observed in female versus male severe asthma patients, as well as in mouse models in response to estradiol, implicating Th17 cells in sex differences in asthma[83].

Th9 cells:

First described in 2008[84,85], Th9 cells are characterized by their production of IL-9 and expression of the lineage-defining transcription factor PU.1, which is induced by IL-4 and TGF-β[84–87]. In contrast with Th2a cells, Th9 cells lack expression of IL-4 and IL-13[85]. In mice, adoptive transfer of Th9 cells are sufficient to induce AHR to a similar extent as Th2 cells[88,89]. Importantly, AHR following the adoptive transfer of Th9, but not Th2 cells, is steroid-resistant in mice[90]. In humans, circulating Th9 cells are more frequent in allergic asthmatic versus healthy controls, and are linked to increased IgE[89,91]. IL-9+ T-cells are also increased in the lungs of asthmatics, with IL-9 levels linked to reduced FEV1[92]. IL-9 promotes the survival and proliferation of cells that express IL-9R, including its major cellular target, mast cells[93]. Importantly, IL-9 activates Th2 and Th17 cells and promotes Th17 differentiation in mice[94–96], while it inhibits IFN-γ production by CD4+ T-cells[97]. IL-9 has also been shown to directly promote mucin expression by airway epithelial cells[98,99], IgE production by B cells in humans[97,100,101], and may be a survival factor for eosinophils[91], indicating a potential key role in asthma pathogenesis.

Tregs:

As their name suggests, regulatory T-cells (Tregs) play a key role in tolerance and the control of inflammation in asthma. Tregs express the transcription factor FOXP3, high levels of CD25, and the anti-inflammatory cytokines IL-10 and TGF-β. In keeping with their suppressive role, reduced frequencies and functional impairment of Tregs, and Treg/effector cell imbalance have been described in asthma[56,102–106], as has loss of Treg function following rhinovirus infection[107]. Reduced circulating Tregs have also been reported for non-allergic late-onset asthma[61], and Treg-associated genes in the lung are inversely

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correlated with asthma severity[108]. In contrast, increased numbers of Tregs have also been reported in the asthmatic lung and following allergen exposure, possibly in response to increased inflammation and/or due to reduced regulatory capacity[109–111].

In mice, the presence of dysfunctional Tregs in early life promote progression to an asthmatic phenotype later in life[112]. Furthermore, Tregs can convert to pathogenic types in response to inflammatory signals including IL-4 and viral infection[113,114]. Accordingly, circulating CRTH2+ Tregs that produce IL-4, IL-5, and IL-13 are increased in allergic asthmatics, link to poor asthma control, and induce bronchial epithelial barrier dysfunction *in vitro*[115,116]. Similarly, dysregulated ST2+ Tregs, which produce IL-5 and IL-13, have been reported in the airways of mice[117,118]. IFN-γ+ and IL-17+ Tregs are also associated with reduced lung function in allergic asthmatics[119]. Androgen receptor signaling stabilizes Treg function and inhibits ST2+ Treg generation, potentially linking Treg dysfunction to increased asthma prevalence in female adults[120]. Treg dysfunction is also thought to play a role in obesity-associated asthma[121,122], possibly attributable to inhibition by leptin[123].

Tfh cells:

T follicular helper cells (Tfh) play a key role in the establishment of allergic sensitization through the promotion of IgE production[124]. Named for their capacity to enter B-cell follicles in secondary lymphoid organs, Tfh are essential in the regulation of germinal center reactions, and express the follicle-homing chemokine receptor CXCR5, the transcription factor Bcl-6, and IL-21. In keeping with a role in promoting IgE production, increased numbers of circulating Tfh have been observed in asthmatics, have been found to correlate with elevated IgE, and have been shown to increase IgE production in *in vitro* co-culture assays[125,126]. Tfh are further subcategorized according to expression of cytokines and chemokine receptors broadly analogous to corresponding Th types, and link to the production of Ig subclasses[127]. Accordingly, circulating Tfh2-polarized cells have been linked to elevated IgE and FeNO in allergic asthmatic subjects[128], whereas regulatory B cells and Tfr are decreased in asthma[129,130]. Recently, IL-13+ IL-4+ IL-5+ IL-21− Tfh, termed Tfh13, were linked to high-affinity IgE production in house dust mite (HDM)-sensitized mice[131]. Furthermore, IL-4+ Tfh are required for the development of Th2 effectors and can differentiate into lung-homing Th2 effectors upon secondary HDM challenge in mice, implicating Tfh in the development of Th2 responses[132].

CD8+ T-cells in asthma

The role of CD8+ T-cells in asthma has been less well-studied than CD4+ T-cells. CD8+ T cytotoxic (Tc) cells play key roles in host defense against intracellular pathogens and cancers, and are named for their capacity to directly kill infected cells. Similar to CD4+ cells, CD8+ cells differentiate into diverse subsets, including Tc1, characterized by the production of TNF-α and IFN-γ. In certain mouse and rat models of asthma, CD8+ T-cells fulfill a protective role through the production of IFN-γ and counter-regulation of Th2 responses[133–138]. CD8+ T-cells in adult male mice produce greater quantities of IFN-γ that suppress IL-4 production by CD4+ cells[139], consistent with reduced asthma prevalence in adult males. In contrast, mice lacking CD8+ T-cells do not develop airway inflammation

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and hyperreactivity in response to HDM sensitization and challenge[140]. Type 2 cytokine-producing Tc2 cells have also been described in allergic asthma (reviewed in [141]), are linked to increased AHR, and provide a steroid-resistant source of type 2 cytokines in both human and mouse models of allergic asthma[142,143]. Tc2 differentiation and activation occurs in response to type 2 cytokines, mast cell-derived lipid mediators (LTE4 and PGD2), allergen exposure, and hypoxia[144–147]. In some cases, CD8+ cells are more strongly linked to asthma severity than their CD4+ counterparts[148], making them an important topic for research.

Defining roles for unconventional T-cells in asthma

Unconventional T cells, including γδT-cells, invariant NKT (iNKT) cells, and mucosal-associated invariant T (MAIT) cells, are an emerging field of study. In contrast with MHC I- and II-restricted conventional T-cells, unconventional T-cells do not recognize peptides presented by MHC molecules. Instead, these cells recognize a more limited set of antigens presented by MHC-I-like molecules, with a more limited receptor repertoire. These cells share features of innate immunity, responding rapidly after antigen encounter[149]. Their features are extensively described in [150–154], and summarized in Table 1. Further research is needed to define the role of unconventional T-cell types in asthma.

γδ T-cells:

While conventional T-cells express TCRs composed of α and β chains, a minority of T-cells instead express γ and δ chains. These γδT-cells respond to phosphorylated antigens and lipoproteins in an MHC-independent manner, and have a number of potential functions, including cytotoxic killing, cytokine production, and antigen presentation[150,154]. Mice that lack γδT-cells demonstrate increased AHR upon allergen challenge, suggesting a regulatory role[155–157]. Accordingly, reduced numbers of γδT cells have been reported in the blood of asthmatic patients[158,159], although others have found no differences in asthmatic versus healthy individuals[160]. In mice and humans, airway γδT-cells are increased in response to respiratory viral infection in asthma, and inhibition of γδT-cell responses in mice results in increased AHR and eosinophilic inflammation[161]. In contrast, other mouse studies report an essential role for γδT cells in the induction of IgE, production of Th2 cytokines, and eosinophil recruitment[162,163]. In humans, γδT-cells that produce IL-5, IL-13, and reduced IFN-γ have been observed in the asthmatic lung after allergen challenge[164]. In mice, γ-chain usage appears to be linked to suppressive versus pro-inflammatory roles, with Vγ4+ cells suppressing inflammation, and Vγ1+ cells promoting inflammation[165,166].

Invariant Natural Killer T-cells and Mucosal-Associated Invariant T-cells:

Invariant natural killer T (iNKT) and MAIT-cells share many similarities and a few key differences. Both express invariant chain TCRs that recognize unconventional antigens presented by MHC I-like molecules, can be further classified according to single-positive and double-negative (DN) expression of CD4 and CD8, and express the NK-cell receptor CD161[167,168].

Invariant natural killer T-cells recognize glycolipid antigens presented by CD1d molecules[169]. The potential role of iNKTs in asthma is controversial[170]. In some mouse

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models of asthma, IL4+ and IL-13+ iNKTs are both necessary and sufficient for the induction of AHR[171–173]. In contrast, similar induction of allergic inflammation in the lung was observed in mice that lack CD1d, and therefore iNKTs, as compared to mice with normal iNKT populations[174]. In humans, there are conflicting reports about the presence of iNKTs in the asthmatic lung, with some reporting increased numbers in the lungs of severe asthmatics as compared with controls[175], and others reporting no differences[176,177]. More recently, increased frequencies of circulating iNKTs were observed in children within 24 hours of an asthma attack[178], as well as in severe treatment-refractory asthma, although this was independent of atopy[179]. Furthermore, IL-4 production by iNKTs was elevated in children undergoing asthma exacerbation[178], and circulating IL-4+ iNKTs in adult asthmatics links to reduced FEV1[180]. Activation of iNKTs has also been linked to obesity and asthma in mice[181].

MAIT-cells are activated via TCR recognition of microbial vitamin B metabolites presented by MR1 molecules[182,183], or else in a receptor-independent manner by cytokines[184]. Little is known about MAIT-cells in asthma. In keeping with a potential regulatory function, MAIT-cell numbers are reduced in the blood and lungs of patients with asthma[185], and MAIT-cells regulate ILC2 responses and AHR in mouse models of *Alternaria* challenge[186]. Furthermore, increased MAIT-cell numbers at 1 year of age has been linked to reduced risk of developing asthma by 7 years[187], suggesting that MAIT play a protective role in asthma development. In contrast, IL-17+ MAIT-cells have been observed in asthmatic children and adults with neutrophilic asthma, and are associated with symptoms and an exacerbator phenotype[188–190].

Impact of therapeutic interventions on T-cell populations

Inhaled and oral steroids, which broadly and non-specifically modulate immune responses and are generally considered immunosuppressive, are commonly prescribed for the treatment of asthma. Importantly, glucocorticoid receptors are expressed by T-cells, among other cell types. Th subsets are thought to exhibit differential sensitivity to both direct and indirect steroid effects, with steroids inhibiting Th1 and Th2, but not Th17 cytokine production[191,192]. However, for many individuals the use of steroids does not result in asthma control. The development of targeted biologic therapies represent a major advance in the treatment of asthma. Here, we will review the potential effects of targeted biologic therapies on T-cell responses; however, it is important to note that these cytokines and receptors are also expressed by and impact other cell types beyond the scope of this review.

Th2-targeted therapies:

Th2 inflammatory pathways constitute a major target for therapeutic intervention in asthma, and data are limited about impacts on T-cell responses. Therapies that directly target Th2-skewing and activation are expected to enact a pronounced effect on Th2 cell populations. The recently approved monoclonal therapy tezepelumab targets TSLP, which plays a key role in Th2 cell differentiation[193–196]. Although tezepelumab decreased serum IL-5 and IL-13 in adult asthmatics, no effect was observed on airway submucosal CD3+ or CD4+ T-cells[197]. Research in mice suggests that TSLP blockade provides the greatest benefit during

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the initiation of allergic disease, versus established disease[198]. Anti-IL-4Ra (dupilumab), which targets both IL-4 and IL-13 signaling, is approved for use in eosinophilic asthma. Dupilumab disrupts Th2-skewing by IL-4, and blocks effects of Th2 cell-derived IL-4 and IL-13. While studies of effects on T-cells in asthma in humans are lacking, studies in atopic dermatitis found decreases in Th2 and increases in Th17 cells in the circulation[199–201]; however, no long-term changes in Th-skewing were detectable after 1 year[199].

In addition to dupilumab, numerous therapies target T-cells downstream of Th-skewing. The CRTH2 antagonist fevipiprant, which blocks activation and chemotaxis of CRTH2+ cells, has also been explored as a type 2-targeted therapy. *In vitro* inhibition studies showed effects on human CD4+ and CD8+ T-cell populations, including inhibition of Th2 and Tc2 cytokine production, cell survival, migration, and tissue-remodeling networks in Tc2 cells[202,203]. Fevipiprant was pulled from development due to insufficient efficacy during phase 3 clinical trials[204,205]. Multiple therapies that target IL-5 are approved for use in allergic asthma. While mepolizumab and reslizumab block soluble IL-5, benralizumab also promotes antibody-directed cell-mediated cytotoxic killing of IL-5Ra+ cells, including eosinophils and basophils[206]. Increases in Tregs have been reported following mepolizumab treatment in patients with severe eosinophilic asthma[207]. Interestingly, reduced frequencies of CD8+ and NKT-like cells were observed following treatment with mepolizumab, but not benralizumab[208]. Anti-IL-13 (lebrikizumab) is also under investigation for use in asthma, but T-cell data are lacking. While anti-IgE (omalizumab) is not expected to directly affect T-cells, reductions in IgE-facilitated antigen presentation and/or alterations in the inflammatory milieu might alter T-cell responses. Some studies have found no difference in T-cell numbers or function in the blood of asthmatics treated with omalizumab[37,209], whereas decreased numbers of lung CD4+, CD8+, and IL-4+ cells, and circulating IL-13+ T-cells have been observed following treatment[210,211]. Further, studies found decreased circulating Tfh, Tfh2, and type 2 cytokine production, and/or increased Treg and Tfr cells following omalizumab, indicating a shift from a Th2 to a regulatory immune state[130,212–214]. While studies of the immune impacts of long-term treatment with omalizumab are limited, CD4+ T-cell activation in the circulation has been observed in asthmatics receiving treatment for at least 3 years[215].

Th17-targeted therapies:

Th17 cells pose attractive therapeutic targets in allergic asthma, particularly in individuals with neutrophilic inflammation. IL-17A disruption by blocking antibodies and IL-17R knockout reduces AHR and neutrophil recruitment into the airways in mice, and abolishes airway smooth muscle contraction in tracheal rings stimulated *in vitro*[73,216,217], although impacts did not extend to Th2 cells[216]. Similarly, administration of anti-IL-23 in an OVA mouse model of asthma results in reduction of AHR and lung-infiltrating Th17 and Tc17 cells[218], supporting the strategy of targeting Th17 inflammation in asthma.

While biologics targeting Th17 pathways are approved for a number of diseases including severe plaque psoriasis and psoriatic arthritis, none are currently approved for use in asthma. Phase 2 trials for anti-IL-17A and anti-IL-17R in asthmatics (secukinumab and brodalumab, respectively) were terminated due to a lack of improvement in asthma control

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(ClinicalTrials.gov Identifiers: NCT01478360 and NCT01902290), and results are not yet available from a phase 2 trial of anti-IL-17A/IL-17AF (NCT03299686). Anti-IL-23 therapies that target Th17 development are also available (anti-IL-12/23, ustekinumab; anti-IL23, guselkumab & risankizumab). A recent phase 2a study of risankizumab for severe asthma resulted in worse patient outcomes, with a reduced time to first asthma worsening, and increased exacerbation rates in those treated with the drug[219]. Interestingly, risankizumab was found to downregulate a number of T-cell-associated genes in the sputum (*CD3E*, *CD8A*), including genes encoding RORγt (*RORC*), T-bet (*TBX21*), genes involved in T-cell anti-viral responses and cytotoxic killing (*IFNG*, *GZMB*), indicating impacts on Th1, Th17, and CD8+ T cells[219]. This additional impact on airway immunity might contribute to poor outcomes. It is also likely that Th17-focused drugs would have greater efficacy if targeted to patients with Th17-high, neutrophilic asthma.

Other Th-targeted therapies:

The use of therapies targeting Th1, Th9, and Tfh pathways have also been proposed. Antagonism of the Th1 and pro-inflammatory cytokine TNF-α by etanercept in severe asthmatics resulted in improvement of lung function and restoration of steroid sensitivity, further supporting a role for Th1 responses in steroid-resistant asthma[220,221]. However, etanercept and another anti-TNF-α therapy, golimumab, did not significantly improve lung function or exacerbation rates and, importantly, the golimumab study was terminated early due to increased risk for infection and malignancies in the treatment group[222,223]. The Th17-targeting therapy ustekinumab is known to also inhibit Th1-skewing[224]; however, data are lacking in asthma. Although IL-9 blockade has shown promise in mouse models of asthma[88], the anti-IL-9 monoclonal antibody MEDI-528 failed to significantly improve asthma control or lung function in a DBPC trial[225]. Dupilumab could also affect Th9-skewing, but data are currently lacking. In mice, administration of anti-ICOS-L, which disrupts ICOS/ICOS-L interactions necessary for Tfh phenotype maintenance[226], depleted lung Tfh, and resulted in reduced IgE production, AHR, and IL-13[227]. While no anti-ICOS-L therapies are currently under investigation for asthma, ICOS-L antagonists are in development for cancer immunotherapy[228]. Thus, there remains a need for therapies that target non-Th2 pathways.

Conclusion

T cells perform diverse roles in the immunopathogenesis of asthma, from conventional CD4+ and CD8+ T-cells, to innate-like unconventional T-cell types. Great strides have been made in understanding mechanisms of Th2 responses in allergic asthma, including the identification of pathogenic Th2 subsets. Beyond Th2 cells, there is an increasing appreciation of the roles of diverse Th-cells in asthma, including Th17-associated neutrophilic asthma and Th1-associated severe steroid-resistant asthma. CD8+ T-cells and unconventional T-cell types, including γδT, iNKT, and MAIT cells, have also been linked to asthma outcomes in both pathogenic and protective capacities. While much remains unclear about unconventional T-cell responses, these cells are capable of acting in a manner reminiscent of Th2 and Th17 cells, in addition to providing regulatory functions.

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While there are indications that asthma treatment with biologics such as anti-IgE can shift T-cell populations away from Th2 types, more research is needed into the effects of Th2-targeted biologics on T-cells in asthmatics, including the long-term effects of treatment, and persistence beyond the withdrawal of treatment. Although a number of Th2-targeted therapeutics are currently approved for use in asthma, there remains a need for additional treatments targeting other, non-allergic aspects of the asthmatic immune response. It is important to note that, while Th2-targeted drugs are employed in patients with Th2 biomarkers including elevated IgE and eosinophil counts, similar screening strategies are lacking for non-Th2 therapies. Given the heterogeneity of asthma and the difficulty in identifying effective asthma therapeutics across multiple inflammatory pathways, the importance of understanding patients' underlying immune profiles for the appropriate selection of therapeutics is clear.

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Abbreviations:

AHR	airway hyperreactivity
DC	dendritic cell
DN	double negative
HDM	house dust mite
iNKT	invariant natural killer T
MAIT	mucosal-associated invariant T
NK	natural killer
peTH2	pathogenic effector Th2
Tc	T cytotoxic
TCR	T cell receptor
Tfh	T follicular helper
Th	T helper
Treg	T regulatory
TSLP	thymic stromal lymphopoietin

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Key Messages

- Th2 cells, including the recently described pathogenic subsets of Th2a and peTh2 cells, play a key role in the establishment and exacerbation of allergic asthma.
- Non-Th2 cell subsets provide complex pathogenic (Th1, Th9, Th17, Tfh, Treg) and protective (Th1, Treg) roles in allergic asthma, as well as neutrophilic, obesity-associated, and steroid-resistant asthma.
- Unconventional T cells (γδ T, iNKT, MAIT) may play key roles in both asthma protection and pathogenesis, and have been shown to produce classic Th2 and Th17 cytokines.
- Approved biologic therapies that target Th2 pathways both upstream (tezepelumab, dupilumab) and downstream (omalizumab, meoplizumab, benralizumab, dupilumab) of Th2-skewing have been shown to decrease Th2 responses in asthmatic patients.
- There is a need for asthma therapies that target non-Th2 pathways, although these treatments may only be efficacious in specific disease endotypes.

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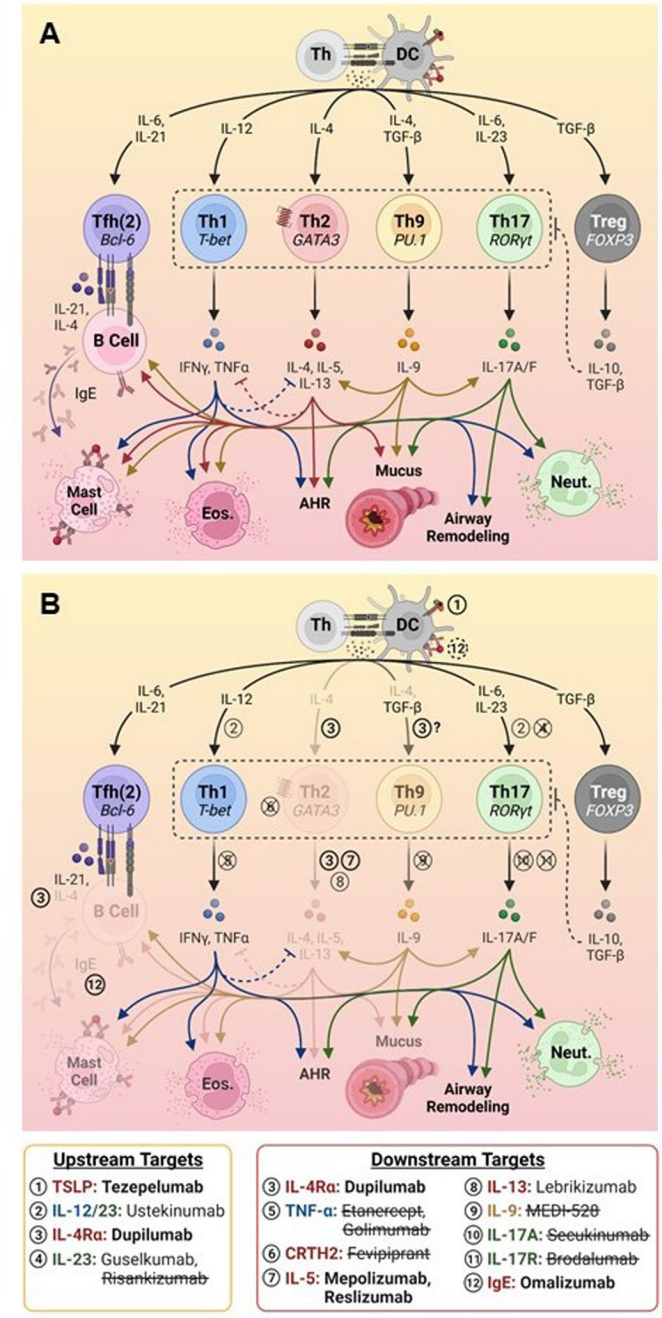

Figure 1. Differentiation and therapeutic targeting of Th cells involved in asthma pathogenesis.

(A) Overview of the differentiation of Th subsets, production of key effector cytokines, and their downstream effects. **(B)** Therapeutic targeting of T-cell responses, denoted numerically. Treatments approved for use in asthma are denoted in bold font, with faded downstream immune pathways; treatments that are no longer in development and/or that lacked efficacy in clinical trials for asthma are struck through; treatments requiring further investigation are depicted in normal font. Figure created using BioRender.com.

AHR, airway hyperreactivity; DC, dendritic cell; Eos., eosinophil; Neut., neutrophil, Th, T helper

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Table 1.

Comparison of human conventional and unconventional T cells.

	Conventional		Unconventional		
	CD4+ (Th) cell	**CD8+ (Tc) cell**	**γδT cell**	**iNKT cell**	**MAIT cell**
TCR chain repertoire	αβ (Diverse)		γδ (Limited)	Invariant αβ (Limited)	
Antigen	Peptides	Peptides	Phosphoantigens	Glycolipids	Microbial metabolites
Restriction	MHC II	MHC I	Butyrophylin-dependent	CD1	MR1
CD4+	+	−	+ (rare)	+*	+ (rare)
CD8+	−	+	+ (minor)	+*	+ (major)
DN	−	−	+ (major)	+*	+ (minor)
CD161+	+/++ (Th17)	+	+++	+++	++++
Initial response	7–10 days		Hours-days		

* Reports are contradictory about the relative proportion of these subsets[229–231]

DN, double negative; Tc, cytotoxic T; Th, T helper; TCR, T cell receptor.