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T Cells in Severe Childhood Asthma.

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Abstract

Severe asthma in children is a debilitating condition that accounts for a disproportionately large health and economic burden of asthma. Reasons for the lack of a response to standard anti-inflammatory therapies remain enigmatic. Work in the last decade has shed new light on the heterogeneous nature of asthma, and the varied immunopathologies of severe disease, which are leading to new treatment approaches for the individual patient. However, most studies to date that explored the immune landscape of the inflamed lower airways have focused on adults. T cells are pivotal to the inception and persistence of inflammatory processes in the diseased lungs, despite a contemporary shift in focus to immune events at the epithelial barrier. This article outlines current knowledge on the types of T cells and related cell types that are implicated in severe asthma. The potential for environmental exposures and other inflammatory cues to condition the immune environment of the lung in early life to favor pathogenic T cells and steroid resistance is discussed. The contributions of T cells and their cytokines to inflammatory processes and treatment resistance are also considered, with an emphasis on new observations in children that argue against conventional type 1 and type 2 T-cell paradigms. Finally, the ability for new technologies to revolutionize our understanding of T cells in severe childhood asthma, and to guide future treatment strategies that could mitigate this disease, is highlighted.

Introduction

Asthma now affects 1 in 13 of the world's population, and is the most common chronic disease of childhood, according to recent numbers provided by the U.S. Centers for Disease Control and World Health Organization. By any estimate, the prevalence of this disease is staggering, and the numbers continue to rise. Severe asthma is poorly controlled using standard therapies. Although severe asthma constitutes only a small fraction (~5%) of asthma, it accounts for a disproportionate amount of hospitalizations for asthma exacerbations and economic burden of the disease.[1, 2] Severe asthma in children is highly heterogeneous based on age of onset, duration, allergic status, lung function and the degree of airflow limitation.[3] However, recent advances that link clinical phenotypes to discrete immunopathologies are now leading to new treatment approaches.

Work in both humans and animal models, has revealed diverse T-cell types that contribute to asthma severity. However, insight into the nature of T cells in severe asthma of childhood is

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rudimentary owing, in part, to limited accessibility of the lower airways. Here, we summarize clinical and experimental data that support a role for T cells in severe asthma, discuss the relevance to childhood disease, and consider how this might inform treatment.

T Cells and Severe Asthma: Current Concepts

T Cells and Asthma Endotypes.—For many years, asthma was viewed as an allergic disease. Allergic asthma encompasses a constellation of immune features that includes the presence of serum IgE to inhalant allergens, blood and lung eosinophilia, and CD4+ T cells that secrete the canonical type 2 cytokines, IL-4, IL-5 and IL-13 (Table 1). These cytokines orchestrate the production of IgE (IL-4), eosinophil survival and recruitment to the airways (IL-5), as well as mucus production and airway hyperreactivity (AHR)(IL-13). Mouse models have established that type 2 responses are necessary and sufficient to reproduce the features of asthma that manifest in humans.[4] Nonetheless, evidence of a strict type 2 response is lacking in both mice and man. Moreover, not all types of asthma are allergic. Thus, in order to better understand the T-cell landscape in asthma, it is necessary to examine multiple T helper (Th) types in well-defined patient populations. These include Th1 cells that secrete IFN-γ, Th17 cells that produce IL-17, and IL-9-producing Th9 cells (Table 1).[5,6,7] Additionally, multiple permutations of each Th type exist, that arise *de novo*, or else derive from parent Th types in response to inflammatory cues in the lungs. The relative abundance of specific T-cell subsets, in conjunction with other immune cells, lung pathology, and clinical phenotype, constitute the various asthma endotypes that are now re-defining treatment. Thus, understanding the origins and relative contributions of T cell types to disease is fundamental to clinical care.

Overview of T-cell Types and Related Cells.—CD4+ and CD8+ T cells constitute the two major populations of T lymphocytes. These T cells recognize peptide antigens presented in the context of MHC II and MHCI molecules respectively. The characteristic cytokine profiles of major Th subsets are determined by lineage-specifying transcription factors that regulate the transcription of cytokine genes during T-cell differentiation (Table 1).[8] These include signal transducer and activator of transcription (STAT) family proteins, and the master regulators of Th1, Th2 and Th17 development (T-bet, GATA-3, and RORγt, respectively). Specific Th types also express their own array of surface molecules, including receptors that bind cognate ligands expressed in the inflamed lower respiratory tract, and guide T-cell entry into the lungs. The chemokine receptors, CXCR3 and CCR4, expressed on Th1 and Th2 cells respectively, are notable examples. Although less well studied in asthma, CD8+ T-cell signatures corresponding to their CD4+ counterparts are well described in the immunology literature; however, knowledge of their role in severe disease remains nascent (Table 1).[9] Natural killer (NK)-like CD8+ T cells that express prototypical markers of NK cells (eg. CD56) have also been linked to disease.[10]

A role for less abundant T-cell types in asthma is evolving (Table 1). Both mouse and human studies have implicated invariant NKT cells (iNKT) in the pathogenesis of allergic asthma.[11–14] These cells express T-cell receptors (TCR) of limited diversity that recognize lipid antigens presented by the “non-classical” MHC molecule, CD1d.[15] However, they comprise less than 2% of T cells in bronchoalveolar lavage (BAL) fluid from children with severe

asthma.[16] A similar cell type, mucosal-associated invariant T (MAIT) cells, is abundant in the human lungs, and also displays limited TCR diversity.[11, 12] These cells respond to microbial-derived vitamin B2 metabolites presented by the MHC class I-related molecule MR1, and exert anti-microbial effects by their cytotoxic activity and secretion of IFN-γ and IL-17.[17] They are also directly activated by pro-inflammatory cytokines in response to bacteria and viruses, including influenza virus,.[18–21] In school-age children with asthma, numbers of IL-17-producing MAIT cells (MAIT-17) were found to be positively correlated with the frequency of exacerbations, and inversely related to symptoms as judged by the asthma control test.[22] By contrast, other work from a subset of infants in the Urban Environment and Childhood Asthma (URECA) birth cohort implied that higher numbers of MAIT cells that were associated with IFN-γ-producing CD4+ T cells, exerted a protective role in asthma development.[23] Another minor population of T cells that may be relevant to childhood asthma is γδ T cells.[24] These innate cells, which respond to unprocessed peptides, microbial alkylamines and organic phosphate molecules, sense antigens directly without requiring MHC. Their variety, enrichment at mucosal sites, and presence in the lungs of mouse models of virus-induced exacerbations, points to protective or pathogenic roles, depending on context.[25–27]

Innate lymphoid cells (ILCs) have garnered the spotlight in recent years. ILCs share many features of CD4+ T cells and originate from a common lymphoid precursor; however, they lack CD3, CD4 and TCR, and do not require STATs for their development. Different ILC subtypes are well described (Table 1).[28] In animal models of type 2 asthma, group 2 ILCs (ILC2) are often viewed as initiators of the inflammatory cascade based on their “upstream” anatomical localization and rapid response to the alarmins, IL-25, IL-33 and TSLP secreted by airway epithelial cells in response to environmental triggers. IL-33 is induced by protease allergens, which also cleave IL-33 to a shorter more active form.[29, 30] ILC2s contribute to the recruitment of eosinophils by secreting IL-5, and to mucus production and AHR via IL-13 (Figure 1).[31] They may also present antigen, albeit inefficiently, in the context of MHC class II.[32] The relative contributions of ILC2s and T cells to early events that govern certain facets of asthma continues to be debated, as evidenced by a recent report of a requirement for IL-13+CD4+ T cells, but not ILC2s, in the initiation of AHR.[33] Beyond ILC2s, ILC3-like cells that secrete IL-17 have also been described in murine models (Table 1), most notably in relation to obesity-induced asthma and steroid-resistant disease.[34, 35] ILCs may be particularly important in conditioning the lung immune response for the development of asthma, and this is elaborated on later.

T-Cell Circuits in Human Asthma.—The immune pathways that govern the differentiation of CD4+ and CD8+ T-cell types are reviewed elsewhere.[83637] Here, we highlight concepts on effector T-cell induction and trafficking that aid in understanding how T cells contribute to asthma pathogenesis. The T-cell circuitry in asthma is best understood for CD4+ T cells, and is discussed in this context. Exposure to environmental triggers at the epithelial barrier is pivotal to T-cell priming, differentiation and activation.[38] The classical view is that allergens favor the induction of Th2 cells, whereas microbes, including respiratory bacteria and viruses, induce a Th1 response. In *in vitro* systems, naïve T cells differentiate into Th1 cells in the presence of IL-12 and IFN-γ, Th2 cells are induced by

IL-4, and Th17 cells require TGF-β, IL-6 and IL-23. However, myriad factors contribute to Th differentiation *in vivo*, beginning at the epithelial barrier. Notable examples are TSLP and IL-33, which are elevated in the airways of severe asthmatics with worse lung function[39]. These cytokines have each been implicated in Th2 differentiation, but may also augment Th2 effector function.[40, 41]

At the epithelial barrier, allergens and respiratory viruses, as well as immune adjuvants such as bacterial lipopolysaccharide (LPS) and particulate matter, bind to an array of surface receptors (Figure 1). These include toll-like receptors (TLR) that bind molecular motifs known as pathogen-associated molecular patterns, and C-type lectin receptors that interact with carbohydrate moieties commonly found on fungal pathogens and allergens. Receptor signaling and cell stress triggers the rapid secretion of alarmins by airway epithelial cells. Dendritic cells integrate signals from these mediators, and from surface pattern recognition receptors, resulting in their maturation and migration to regional lymph nodes. Upon their arrival, dendritic cells direct the differentiation of naive T cells to specific Th types, depending on T-cell cues generated from TCR engagement with peptide/MHCII, and T-cell differentiating mediators and surface molecules (Table 1). The resulting Th cells preferentially home to the inflamed airways, where they release their cytokine payload and rapidly exert effector functions upon TCR triggering or cytokine activation (Figure 1). Chemokine receptors expressed on Th1 (CXCR3 and CCR5), Th2 (CCR4) and Th17 (CCR6) cells aid in their recruitment to target organs via interactions with cognate ligands expressed in inflamed tissue. These include CXCL10 (ligand for CXCR3), CCL3 and CCL4 (ligands for CCR5), CCL17 and CCL22 (ligands for CCR4), and CCL20 (ligand for CCR6) (Table 1). Although the CCL17/CCR4 interaction has long been implicated in asthma [42, 43], high levels of both Th1- and Th2-associated cytokines in the lower airways of children with severe asthma, suggests the milieu is conducive to recruitment of a variety of Th types.[44]

Knowledge of T-cell circuits in asthma mostly comes from mouse models. For obvious reasons, it is difficult to define T-cell trafficking pathways in human asthma, both from inception and during acute episodes. Nonetheless, studying T cells in the blood can yield important clues. T cells that have been primed by antigen acquire a memory signature (CD45RO+CD45RA-). These can be further classified into subsets that preferentially home to lymphoid organs (central memory (T_{CM})) or tissue (effector memory (T_{EM})) based on differential expression of CCR7 (CCR7+ and CCR7- respectively). By analyzing these and other tissue-directing markers, we can identify candidate pathogenic T cells in the blood whose function can be probed in *in vitro* assays. Although this may circumvent sampling the airways to a degree, circulating T cells may differ from those in the lungs owing to the T-cell modifying environment in the inflamed organ. Moreover, certain T-cell types relevant to disease constitute only a small fraction of total T cells in human blood. Thus, *in vitro* expansion is needed to detect them. The use of peptide/MHCII tetramers allows precise and sensitive detection of antigen-specific T cells in the blood, with minimal *in vitro* manipulation. However, reports of their use to analyze T cells in the asthmatic airways are few. One study that sampled the airways of adults with allergic asthma identified low numbers of allergen-specific CD4+ T cells by tetramer staining that were enriched for cells that co-expressed receptors for the alarmins IL-33 (ST2), and IL-25, and prostaglandin D2 (CRTH2). Receptor expression was enhanced after segmental allergen challenge.[45] The

same study reported a correlation between ST2 expression on allergen-specific T cells and Th2 cytokine levels in BAL fluid, which would be consistent with IL-33-mediated triggering. Thus, this work confirmed the presence of allergen-specific T cells in the asthmatic airways, molecular signatures related to a lung-specific environment, and their responsiveness to allergen.

Mechanisms That Shape the Lung's Immune System: Setting the Stage for T-Cell Responses in Asthma.

Complex mechanisms govern lung homeostasis and development of the immune system in the lungs in early life. Environmental exposures can modify these processes, and are likely pivotal to the evolution of severe asthma during this critical developmental window. Here, we discuss insights from mouse models that could inform human disease. These are summarized schematically in Figure 2. We emphasize the role of ILCs, owing to their prominent role as both as sentinels at the airway epithelial barrier, and engagers of multiple cell types that modulate T-cell differentiation and function.

ILCs in the Evolution of Asthma in Early Life—Work in mice indicates that Th2-biased responses in early life might set the stage for asthma, and that ILC2s are integral to this process.[46] ILC2s are the most abundant innate lymphoid cell population in mouse lungs, despite their rarity in the total leukocyte population.[47] They seed the epithelial and mucosal barriers and organs early in life, and are important in organogenesis and barrier homeostasis.[28] Numbers of lung ILC2s are higher in fetal and neonatal mice compared with adults, and these cells are armed to respond to IL-25 and IL-33, which are key mediators of ILC2 activation.[48–50] De Kleer et al reported increased airway levels of IL-33 in neonatal mice during the most active period of alveolar septation, a time frame corresponding to 2–3 years of age in humans.[51] In the same study, IL-13-producing ILC2s induced migration to draining lymph nodes and Th2 licensing in CD11b+CD103+ lung dendritic cells.

Although IL-33-responsive ILCs can mediate airway eosinophilia and AHR without the need for an adaptive response in mice [5253, 54], the contribution of such ILCs to the development of severe asthma in children is unknown. IL-33 is expressed in the lower airways of children with severe asthma.[55] Moreover, increased ILC2s are present in the blood, BAL and induced sputum of children with steroid-resistant asthma compared with children who have recurrent lower respiratory tract infections.[56, 52–54]In those patients with an allergic predisposition, allergens may be pivotal to the activation of ILC2s. In neonatal and adult mouse models, inhaled allergens arm ILC2s to respond to IL-33 and to mediate allergic inflammation.[52] Other factors not classically thought of as immune stimulants may also activate ILCs. An example relevant to childhood asthma is hyperoxia, which results from respiratory support provided to preterm infants, and has been linked to a risk of asthma later in life. [5758] In mice, neonatal hyperoxia was found to favor the induction of eosinophilic asthma via IL-33-dependent ILC2 responses.[59] The same study also revealed correlations between IL-33 and both IL-5 and IL-13 (but not IL-4) in the serum of preterm infants, implying involvement of ILC2s.

ILCs can also be triggered by respiratory pathogens that may increase the risk of asthma. Notable examples include rhinovirus (RV) and respiratory syncytial virus (RSV), which induce expansion and activation of ILC2s in the lungs of neonatal mice, in conjunction with the development of features of asthma. [60–62] In neonatal mice, the lung microenvironment favors higher production of ILC2-activating cytokines such as IL-33 and IL-25 in response to viruses compared with adults.[61, 62] Consistent with this, elevated levels of IL-33 are measurable in nasal aspirates of infants with acute RSV infection.[62] Beyond ILC2s, viruses may induce other ILC signatures in the lungs depending on the cytokine milieu and ILC plasticity, most notably ILC1s in the presence of IL-12 and IL-18. [63–66] Given that ILC1s may be a feature of Th1-driven respiratory diseases such as COPD[66], it is plausible that they might also contribute to Th1 responses in severe asthma.[44] Alternatively, in scenarios where IL-33 is more abundant than IL-25, IL-17-producing ILC2s may result.[67] Dynamic regulation of the receptors for IL-33 and IL-25 on ILC2 during development might also contribute to age dependent effects and differential effects of certain viruses on the risk for asthma development later in life.[62, 68]

Innate Mechanisms: New Concepts—Viral exposures can alter subsequent immune response to allergens through innate immune mechanisms, and this effect may be long-lived. [61, 62, 69] This process might involve imprinting mediated by ILCs that possess “memory”, despite their lack of antigen specificity. Such cells respond in an accelerated fashion as a result of previous priming. [70, 71] Memory ILCs, which include ILC1 and ILC2 subsets, appear to be sustained autonomously and are maintained for weeks in the lung and lung-draining lymph nodes of mice. These findings echo the notion of “trained immunity” in other innate cells (eg. macrophages, NK cells and granulocytes), which arises from transcriptional and epigenetic reprogramming in response to various triggers. [72] Together, these facets might further shape the T-cell response in the human lung.

In addition to ILCs instructing T-cell responses by virtue of their “memory” attributes, there is evidence that ILCs may directly engage and activate CD4+ T cells. Although expression of classical co-stimulatory molecules (eg. CD80 and CD86) on ILCs is low or absent, molecules that are less efficient at stimulating naïve T cells such as OX40L and ICOSL are expressed. In some allergic mouse models, ILC2s were found to be required for the induction of Th2 responses to allergen, and for potentiating memory Th2 responses, possibly via OX40L.[73–75] However, these processes may involve licensing dendritic cells for migration to lymph nodes and for secretion of Th2 chemoattractants, as opposed to direct effects on T cells per se. Cross-talk between T cells and ILCs may be bi-directional, based on the ability for antigen-stimulated T cells to promote ILC activation and function via direct interactions.[76] ILCs are also integral to innate cell networks that include NK cells, iNKT cells, and alveolar macrophages, all of which respond differently in the developing child versus the adult immune system. [76–79] Crosstalk between these cells shapes their phenotype and function. This is exemplified by the ability for ILC1s and ILC2s obtained from the sputum of asthmatic adults to polarize alveolar macrophages to corresponding phenotypes (ie. M1 and M2 respectively) in cell co-cultures.[80] Similarly, seeding of alveolar macrophages in the lungs of neonatal mice, and their acquisition of an M2 phenotype has been linked to IL-13 secreted by ILC2s.[50] Cellular interactions are likely also important for

conferring “memory” attributes to innate cells. This was elegantly demonstrated in a mouse model, wherein interaction with IFN-γ-producing CD8+ T cells induced by respiratory viral infection conferred long lasting memory functions in alveolar macrophages against a subsequent bacterial infection.[81]

Regulatory T Cells: New Concepts—T regulatory cells (Tregs) counter-regulate inflammatory pathways that promote asthma. Their potential role in modifying the development of asthma in childhood is reviewed in detail elsewhere. [82] Here, we highlight a few points that are pertinent to shaping the lung environment in early life. Tregs can be broadly categorized as thymus-derived natural and peripherally induced Tregs that arise outside the thymus. Recent work in mice found that induced Tregs developed *in vivo* during a strict neonatal time-window, and protected against allergen-induced airway inflammation. Moreover, their generation depended on interactions with PD-L1[83] and the presence of an age-specific lung microbiome in the neonatal period.[84] Thus, we might predict that perturbation of the microbiome in early life compromises lung homeostasis through effects on Tregs.[85]

Although the conventional view is that Tregs suppress Th cells, they can also inhibit ILC2s in mouse asthma models via production of IL-10 and TGF-β. [86, 87] Suppression of human ILC2s involves the same cytokines [8688] Several molecules known to activate ILC2s, most notably IL-33, are also pivotal to the generation and function of iTregs and Th2 cells, thereby providing strict regulation of Th2 responses at the ILC2 interface. [53, 75, 76, 83, 89] On the other hand, factors that may set the stage for asthma in early life can subvert Treg function. For example, repeated RSV infection in mice lead iTregs to acquire a Th2-like phenotype [90], whereas signaling via a human variant of IL-4Rα results in a Th17 phenotype. [91] Each of these scenarios might be expected to allow airway inflammation to proceed unchecked. More work is needed to address the mechanistic relevance to human asthma, and children in particular.

Steroid Resistance—Mechanisms that modify the immune environment in the lungs during early life may also set the stage for steroid resistance. There are several indirect lines of evidence to support a relationship between IL-33, ILC2s, and the development of corticosteroid (CS) resistance asthma in children. IL-33 is readily detected in BAL fluid of children with severe treatment-refractory asthma.[44] Notably, sensitization to inhaled fungi in such patients correlates with higher IL-33 levels and resistance to steroid therapy, thereby implicating fungal exposure in the induction of IL-33. [449255] In neonatal mice, exposure to *Alternaria alternata* induced CS-resistant AHR associated with higher airway IL-33 levels and increased numbers of IL-13+ ILCs and Th2 cells compared with exposure to dust mite. These features were reduced in mice that lacked IL-33 receptor, suggesting that IL-33 might orchestrate these effects.[55] IL-33 pathway can induce IL-17 production in ILC2s, and thus, might also contribute to Th17 responses, which are a feature of severe asthma in children. [44, 67]

Another notable alarmin implicated in steroid resistance is TSLP. *In vitro* studies have shown that treatment of ILC2s with dexamethasone induces the upregulation of IL-7Rα, a subunit of TSLP receptor complex, which in turn augments TSLP-induced STAT5/MEK

signaling and TSLP-mediated steroid resistance.[93] In the same study, CS resistance of ILC2s in BAL fluid of adults with severe asthma correlated with TSLP levels in BAL, but was not a feature of ILC2s in the blood. Notably, RV-16 and IL-13 synergistically induced TSLP expression, and dexamethasone sustained activation of TSLP pathway in ILC2s, thereby augmenting steroid resistance.

There is intriguing evidence to suggest that cytokines linked to the adaptive response can influence the steroid responsiveness of developing airway smooth muscle in humans. Specifically, IFN-γ, the hallmark cytokine of Th1 cells, in conjunction with TNF-α, was found to blunt the anti-inflammatory effects of fluticasone propionate in a cell model that used human tracheobronchial tissue obtained at 18–22 weeks of gestation.[94] In this system, IFN-γ augmented the effects of TNF-α via pro-inflammatory pathways involving NF-κB and STAT1, but had no effect on glucocorticoid receptor (GR) expression. These data, in conjunction with other findings, led to the theory that Th1 inflammation promotes CS resistance by modifying the expression of inflammatory proteins at the post-transcriptional or post-translational level, and thus, overrides negative signals generated via GR.

Sequestration of innate and adaptive cells within anatomical niches in the lungs may also contribute to steroid resistance. This may arise from changes in the architecture of the immune system that begin in early life as a result of chronic inflammatory processes. In mice, allergic inflammation gives rise to the formation of ectopic lymphoid-like structures called inducible bronchus-associated lymphoid tissue (iBALT). These harbor ILC2s and Th2 cells, participate in the immune response to pulmonary antigens, and are more abundant in children and infants versus adults.[47, 95, 96] Such structures, which are also IL-33-rich [95], may not only provide a niche for perpetuating steroid resistance, but also for re-shaping the lung environment in response to environmental antigens in the longer term, through their resident cells.

T Cells in the Evolution of Severe Asthma

Much work on the development of childhood asthma has focused on the evolution of IgE responses. Although allergic sensitization and eosinophilia is a feature of a subset of school age children with severe disease, the role of IgE in promoting severe asthma remains unclear. Serum IgE antibodies can be detected within the first 2–3 months of life, and discrete patterns of emergence of IgE against foods and inhalants are well described.[9798, 99] The susceptibility to develop IgE is governed by complex mechanisms that remain ill-understood. Even less is known about the evolution of Th types in childhood, their relation to environmental exposures, and their contributions to asthma pathogenesis and disease severity. By definition, severe asthma fails to respond to standard treatment, and inflammation persists in the face of high dose inhaled corticosteroids. The presence of activated T cells in the lower airways of infants from 6 months of age who fail to respond to treatment, implies a pathogenic role for T cells in early life.[44] On the other hand, treatment failure highlights how little we understand about the role of T cells and response to existing therapies. Adding to the complex picture, wheeze in preschool children is often linked to respiratory infections and does not necessarily reflect the presence of asthma. Thus, caution must be exercised when interpreting data obtained in younger versus older children. We refer

the reader to Table 2 for details pertaining to clinical and mechanistic studies related to human T cells that are cited in this article.

Microbes and Allergens in the Etiology of Severe Asthma.—Infections with respiratory viruses have been implicated in the development of asthma.[46, 100] Additionally, both viral and bacterial infections present a major risk factor for asthma exacerbations. RSV has garnered much attention owing to its predilection to infect the lower airways and to inflict considerable morbidity in infancy. Nonetheless, its link to the development of asthma in later childhood remains controversial. Recent work from clinical trials that were designed to prevent RSV infections, suggests that the development of asthma is confined to an at-risk subgroup of children.[101] In the largest study to date of healthy pre-term infants, a link was found between severe RSV infection in infancy and current wheeze at 6 years of age, but only in those children without an atopic predisposition.[102] In addition to infecting epithelial cells, RSV can infect both human CD4+ and CD8+ T cells, and the numbers of infected CD4+ T cells in the blood correlate with infection severity in children.[103] Whether or not virus-specific T cells persist in the tissues after infection is cleared is a question that is central to asthma pathogenesis. In mice, respiratory exposure to RSV favors the accumulation of virus-specific T cells in the lung parenchyma.[104] Additionally, lung-resident virus-specific memory T cells are found in anatomical niches of the lung, where they respond rapidly to infection.[105] These T cells do not re-circulate, are maintained by various mediators/inflammatory cues, and are replenished by circulating virus-specific T cells. In mice, iBALT primarily harbor virus-specific CD4+ T cells, whereas their CD8+ counterparts reside in repair-associated memory depots (RAMDs) found at sites of tissue regeneration. Such structures may persist for several months.[105] Thus, in scenarios where re-infection to respiratory viruses is common (eg, rhinovirus), persistence of virus-specific T cells, and their chronic reactivation in the human lung, seems plausible.

Bacteria that have been linked to severe asthma in children include *Moraxella catarrhalis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*.[44, 106] These intracellular bacteria colonize the neonatal airways and, along with viral pathogens, are potent inducers of Th1 responses. Folsgaard and colleagues examined the association between bacterial colonization of the hypopharynx and cytokines in the mucosal lining fluid of 662 neonates from the Copenhagen Prospective Study of Asthma in Childhood 2010 birth cohort. [107] Colonization with *M. catarrhalis* and *H. influenzae* was found to induce a milieu that might promote airway inflammation, which included a mixed Th1/Th2/Th17 response with high levels of pro-inflammatory cytokines including CCL4, a ligand for CCR5. Other work assessed the relationship between asthma and cytokine responses to *H. influenzae, M. catarrahlis* and *S. pneumoniae* using PBMCs collected from 292 infants at 6 months of age. [108] Cells from those children who had asthma by 7 years of age produced more IL-5, IL-13 and IL-17 than non-asthmatics, but were less skewed towards IFN-γ, which the authors suggested might indicate an aberrant T-cell response to colonizing bacteria that sets the stage for asthma.

Although a definitive role for respiratory pathogens in the etiology of severe asthma in humans has not been established[100], work by Raundhal and colleagues used a mouse model of severe asthma to establish proof-of concept in this regard.[109] In that study, co-

administering allergen in the challenge phase with cyclic -di-GMP, a second messenger produced by intracellular bacteria, resulted in a more pronounced Th1 signature, increased neutrophils, and increased AHR compared with mice sensitized and challenged with allergen alone. Moreover, IFN-γ was found to be critical for AHR, and inflammation was only partially reduced by dexamethasone, indicating steroid-resistance.

Our group reported a dominant Th1 signature in the lower airways of children across a broad age range (ages 0.5–17 years) who had severe treatment-refractory asthma, most of whom had evidence of current or past exposure to respiratory bacteria and viruses.[44] Airway T cells were markedly enriched for IFN-γ+ and IFN-γ+IL-17+ cells compared with T cells in the blood. By contrast, Th2 cells were rare, even in older patients with high IgE levels. Notably, levels of the type III interferon, IL-28A, and IL-33, were higher in the airways of children who were sensitized to fungal allergens, dust mite and ryegrass. The results echoed earlier studies that implicated fungal allergens and IL-33 in severe asthma. These included reports of a relationship between exposure to outdoor fungal spores and asthma hospitalizations, higher levels of IL-33 in the airways of children with severe asthma who were sensitized to fungi, and the involvement of IL-33 in airway remodeling and steroid resistance.[13, 55, 92, 110] Given that Th1 responses are integral to anti-fungal host defenses, these findings raise questions about how certain allergens shape Th types in the airways that may favor severe asthma. They also highlight the complexity of the cytokine milieu *in vivo*, which is likely to be highly individualized according to the interplay between allergen and microbial exposures in early life.

Lessons from Virus-Induced Exacerbations.—Rhinovirus, a major cause of common cold, is an important risk factor for acute wheezing episodes in children with allergic asthma. Studying these events might provide insight into T-cell mechanisms of the development and persistence of disease in childhood. Although knowledge is scant in this area, there are clues that hint at a key role for T cells. Virus-induced asthma typically coincides with exposure to outdoor pollens, and a peak in viral infections in the Fall.[111–113] Work in an experimental infection model in humans indicated that virus and allergy interact to promote airway inflammation. Specifically, adult asthmatics experimentally infected with HRV who had higher IgE experienced worse respiratory symptoms.[114] Similarly, in the hospital setting, asthmatic children with high IgE to dust mite and who tested positive for HRV, had the highest risk of acute wheezing episodes.[115] Conversely, blocking IgE by downregulating IgE receptor using omalizumab (anti-IgE), reduced the prevalence of seasonal asthma exacerbations in asthmatic children.[112, 116–119] These data suggest that the inflamed airways of allergic asthmatics contribute to dysregulated anti-viral responses and that this effect is reversed by anti-IgE treatment. In agreement with this notion, HRV was found to induce Th2-promoting cytokines in cultured bronchial epithelial cells from patients with severe or allergic asthma, and experimental infection induced the expression of many more genes in nasal epithelial cells of asthmatics compared with controls.[120–122] Similarly, levels of TSLP or IL-33 were elevated in the airways of young asthmatic children and adult patients infected with HRV.[123124] Such effects might be predicted to modulate downstream T-cell responses as discussed earlier. Other work implied that anti-viral responses, and arguably Th1 responses by default, are altered in allergic asthmatics. Although there is

evidence that IgE can inhibit secretion of the anti-viral cytokine IFN-α, by human plasmacytoid dendritic cells[125], other studies using cultured bronchial epithelial cells and experimental infection in humans, suggest that interferon responses to HRV, as well as other respiratory viruses, remain largely intact, even in patients with severe disease.[126–129]

If we consider the interplay between virus and allergy, there is evidence to suggest that type 1 and type 2 responses can cooperate in airway inflammation. This notion was exemplified in a mouse model of severe asthma, wherein the ability for mast cells to respond to IFN-γ contributed to IgE-dependent features of disease [130] Similarly, in a human-based system, IFN-α2 and IFN-γ could induce mediator release from mast cells, and infection of mast cells with RSV reproduced this phenomenon (Figure 1).[131] This cross-talk between type 1 and type 2 responses in the lungs may be augmented by enhanced recruitment of circulating Th2 cells mediated by Th1 cells activated by virus.[132] The type of viral exposure may also be pertinent to the nature of the T-cell response in the airways. For example, in a mouse asthma model, enterovirus D68, the causative agent of a 2014 outbreak of severe asthma-like symptoms in children, induced IL-17-dependent neutrophilic airway disease when co-administered with house dust mite (HDM) allergen.[25] Interestingly, both RORγt+ ILC3 cells and γδT cells were a source of IL-17, and their numbers were increased in the airways as compared with mice that received a minor HRV strain. Notably, higher levels of *IL17* mRNA were found in the nasopharynx of children from the 2014 epidemic compared with children infected with HRV-A. These findings underscore the need to better understand how T-cell responses to respiratory viruses drive severe asthma.

Th Cells and Mechanisms of Severe Asthma

Th2 Cells and the Role of IL-4, IL-5 and IL-13.—Airway expression of canonical type 2 cytokines is a hallmark of “Th2-high” asthma. This type of asthma is often linked to atopy, elevated numbers of eosinophils in the blood, sputum and lungs, as well as elevated levels of serum periostin, a marker expressed by epithelial cells in response to IL-13 [133–135] However, the criteria for Th2-high asthma are somewhat arbitrary, immune profiles are mixed, and clear evidence of a relationship to severe clinical phenotypes is lacking. Certain data indicate that Th2-high asthma can be more mild and responsive to CS; however, there are notable exceptions, as evidenced by Th2-high eosinophilic severe disease that is treatment-refractory.[136]

In the era of “big data”, advances are being made in linking Th2 signatures to severe disease. A recent study of adult asthmatics used “unsupervised” topological data analysis to connect lung pathologies indicative of more severe disease, to clinical and immune parameters, including gene expression profiles.[137] This strategy identified a patient subcluster that had reticular basement membrane thickening defined by early-onset moderate-to-severe asthma, a Th2 high gene expression signal in bronchial biopsy samples, and high sputum and tissue eosinophil counts. In the same study, a different subcluster was identified that had increased airway smooth muscle defined by adult-onset severe disease, high neutrophil counts and Th17 gene expression. However, there was considerable heterogeneity within each subcluster. A different study that used targeted profiling of 105 genes in nasal airway brushings in a small sample of children with asthma, reported Th2-high signatures based on

IL13, IL5 and POSTN (encoding periostin) that were linked to atopic asthma and blood eosinophila.[138] Notably, *IL13* expression levels were highest in children who experienced an asthma exacerbation in the past year. Although both of these studies suggested that Th2 and Th17 gene signatures tend to be mutually exclusive, other work at the protein level supports co-existence of type 2 responses with other Th signatures. For example, we found that Th2 cells were readily identified in the lower airways of children with severe asthma, even though IFN-γ+ and IL-17+ T cells were far more abundant.[44] Despite their low numbers, the percentage of Th2 cells related to serum total IgE, supporting a link to allergic status. Mingling of different Th types also manifests at the single-cell level, as evidenced by the presence of dexamethasone-resistant IL-4+IL-17+ T cells that co-express GATA-3 and RORγt, in the airways of adults with severe asthma.[139] Similarly, sorted circulating Th2 cells from patients with acute asthma were found to secrete IL-17F and IFN-γ upon activation, and display more complex patterns of transcription factor expression as compared with Th2 cells from patients with stable asthma.[140] In that study, cluster analyses revealed a Th2-high signature linked to asthma exacerbation rates, whereas Th17 cells related to poor asthma control and worse lung function.

Prostaglandin D2 receptor, CRTH2, is a marker of central memory human Th2 cells that are maintained by TSLP.[141] Increased numbers of either CD4+ or CD8+ T cells bearing this receptor are present in the blood or airways of adults with severe disease.[142, 143] Interestingly, the lipid mediators PGD_2 and cysteinyl leukotriene E4, both of which are increased in the airways of adults with severe eosinophilic asthma, can synergistically activate CRTH2+CD8+ T cells independent of TCR, pointing to innate mechanisms. Recent work on CD4+ T cells identified a CRTH2+ Th2 signature (CRTH2+CD49d+CD161+) in the blood of allergic patients that captured most allergen-specific Th2 cells.[144] These cells had the capacity to secrete higher levels of IL-5 and IL-9, and expressed higher levels of genes encoding receptors for IL-33 (ST2) and TSLP, compared with conventional CRTH2+ Th2 cells. Whether these cells preferentially migrate to the asthmatic airways in allergic patients with severe disease, or else reflect tissue-resident memory T cells (T_{RM}) in the lungs, is unknown. Animal models found allergen-specific T_{RM} cells to be pivotal to asthma.[145] Notably, IL-33 produced within bronchus-associated lymphoid tissue may serve to maintain a subset of pathogenic ST2+ T_{RM} cells that secrete IL-5 in allergic asthma.[95] These findings, along with the ability for ST2+CD4+ T cells that are steroid-resistant to promote eosinophilic airway inflammation in mice, suggest that more work is needed to understand the role of pathogenic Th2 subsets in severe childhood asthma.[146]

Th1 Cells and IFN-γ.—As already mentioned, there is mounting evidence in animals and humans to support the involvement of IFN-γ+CD4+ T cells in the etiology and maintenance of severe asthma; however, the concept of IFN-γ in asthma pathogenesis is not new. In 1998, ten Hacken and colleagues reported a link between higher serum levels of IFN-γ, and increased AHR and the variation in circadian peak expiratory flow, in allergic asthmatics.[147] Soon thereafter, adoptive transfer experiments in mice supported the ability for Th1 cells to augment AHR independent of Th2 cytokines[148], and for Th1 cells to cooperate with Th2 cells in eosinophilic airway disease.[149, 150] The high numbers of Th1 cells in the lower airways of children with severe asthma[44] may also contribute to CS resistance. Steroid-

resistance can arise from mutations in GR that alter its binding affinity or density for CS, binding interference caused by a dominant negative isoform, and inhibition of translocation of GR from the cytosol to the nucleus as a result of phosphorylation by p38-MAP kinase. This kinase is activated by IL-33, and may be relevant to CS resistance of Th1 cells in an inflamed milieu, given the high expression of ST2 on activated Th1 effectors.[151–153]

We have mentioned the potential role of IFN-γ in mediating CS resistance in the developing airways.[94] Two additional reports identify molecules that may be pivotal to CS resistance in established Th1-driven disease. The first study implicated the transcription factor IRF5, which is expressed in BAL cells of adults with severe asthma.[154] This molecule was previously found to promote transcription of *IL6, IL12* and *IL23p19* in human macrophages and induction of Th1/Th17 responses in co-cultured CD4+ T cells.[155] In a severe asthma model, knockout of *IRF5* in dendritic cells attenuated Th1 and Th17 responses while enhancing Th2 responses and rendering the T-cell response sensitive to CS.[154] The other study explored the potential link between Th1 cells and CS resistance, based on the presence of Th1 cells in the airways of half of severe asthmatic adults on high dose therapy. Using a mouse model, that study found that, in the presence of CS and IFN-γ, GR, and STAT1 were recruited to regulatory elements within the promoter of the gene encoding *CXCL10*, whose protein product binds CXCR3.[156] The findings inferred that CS resistance was not explained by impaired nuclear translocation of GR, but rather by CS enabling the IFN-γ/CXCL10 axis to promote persistent type 1 inflammation in severe disease, presumably by recruiting additional Th1 cells to the response. Commandeering of GR to “pro-inflammatory”, rather than “anti-inflammatory”, DNA elements constitutes a novel mechanism of CS resistance that might explain the high numbers of Th1 cells in the airways of children with severe asthma.

Th17 Cells and IL-17.—IL-17 induces steroid-resistant airway inflammation and neutrophilic inflammation in animal models.[157, 158] Elevated numbers of IL-17+CD4+ T cells have been reported in the lower airways of adult patients with severe asthma, compared to adults without asthma.[139] However, few studies have focused on Th17 signatures in children with severe disease. In one such study, higher levels of serum IL-17 and numbers of IL-17+ T cells in the blood were present in those who had moderate to severe persistent asthma compared with healthy controls.[159] In a different study, Th17 cells were markedly enriched in the lower airways of children with severe disease compared with the blood, indicating trafficking of Th17 cells to the lungs.[44] The connection between IL-17 pathways and severe asthma is also a recurring theme of recent transcriptomic studies.[137, 160] IL-17 has been implicated in many facets of asthma pathogenesis and its relationship to neutrophilia is well described.[161] However, the mode of action of IL-17 remains ill-defined in severe asthma, and its relevance is widely debated. Work in mice suggests that IL-17 cooperates with type 2 asthma to augment IL-13-driven disease.[162] Thus, it may synergize with other mediators to heighten inflammation in severe asthma.

Several studies have explored the origins of Th17 cells in severe asthma. IL-1β and IL-6, each of which are critical to Th17 differentiation, are expressed at high levels in the inflamed airways of children with severe asthma.[44] Fungal exposure has been linked to increased serum IL-17A and asthma severity in children, although this effect may arise from potent T-

cell adjuvant effects of fungi, rather than their antigenic properties per se.[163] The differentiation and function of Th17 cells is closely related to regulatory T cells, and there is evidence that a genetic variant of IL-4 receptor alpha chain that is linked to severe asthma might favor their induction. This was exemplified in mice, wherein Th17 cells were induced from Tregs by signaling through a novel branch of IL-4 receptor pathway in cells expressing this human genetic variant.[91] Moreover, in the presence of IL-4, T cells from patients with the mutation showed Th17 skewing with defective induction of Tregs, which might explain the Th2/Th17 signature observed in severe disease. Th17 differentiation in a mouse model of severe asthma has also been reported to involve neutrophil cytoplasts via their interaction with dendritic cells.[164] These enucleated cell bodies derive from neutrophil extracellular traps, and retain the ability to secrete cytokines and interact with other immune cells. Nuclear cytoplasts are present in the lower airways of patients with severe asthma and high neutrophil counts, and correlate with IL-17 levels.[164] While these findings imply a pathogenic role for neutrophils in severe asthma, a conflicting report found increased intraepithelial neutrophils in children with severe disease who had better lung function.[165]

Other IL-17-producing T cells have been linked to severe asthma. For example, numbers of circulating MAIT cells that express IL-17 were found to correlate with the number of severe exacerbations in children with asthma.[22] However, other work in adults that sampled lung tissue, failed to identify relationships between MAIT cells or Th17 cells and severe disease.[166] As already mentioned, ILCs can also express IL-17. Circulating ILCs that co-express IL-13 and IL-17A have been identified in the blood of patients with severe asthma, and these cells can express IL-22 upon activation, which is a trait of ILC3 cells (Table 1).[167] Although ILC3 cells have been found in the BAL fluid of obese patients with severe asthma[34], nothing is known about their relationship to disease in children. These collective findings underscore the conflicting data on IL-17 in severe asthma, and highlight the need for more research.

Future Research Directions and Clinical Implications

In order to optimize clinical care, it is imperative to know which cell(s) or immune component(s) is the most appropriate target in a given patient. To make this determination, it is not only necessary to identify the relevant cell or molecule, but also to establish its role in asthma pathogenesis. The mere presence of a specific T-cell type in the inflamed airways, even in copious amounts, need not infer a pathogenic role. Indeed, the presence of Th1 and Th17 cells in asthmatic airways and lung tissue might simply arise from CS treatment. Arguing against this, animal models have established proof-of-concept for the pathogenicity of these T-cell types in severe disease. Furthermore, novel cell types and pathways are emerging that connect type 1 and type 17 components to type 2-mediated disease, suggesting a high degree of coordination by diverse immune components that do not adhere to existing T-cell paradigms. Moving forward, it will be imperative to thoroughly evaluate the T-cell landscape in asthmatic children with well-defined clinical phenotypes, and to establish T-cell effector functions.

Defining pathogenic T-cell responses in the lower airways of children with severe asthma presents unique challenges, including identification of the appropriate control groups for comparison. Given that Th1/Th17 cells are a component of mucosal immunity in the healthy

host, obtaining cells from the lungs of healthy children could further inform their relevance to disease; however, such specimens are often not available for research purposes. Similarly, comparisons with children who have milder disease phenotypes and are not receiving corticosteroids may be useful; however, since these patients constitute a distinct endotype, it is difficult to discern whether T-cell differences observed in severe versus milder disease are iatrogenic or else disease-specific and of pathologic consequence. It is also important to analyze T cells in lung tissue, as opposed to in the airways, given the role of the lung microenvironment in directing T-cell trafficking, function, retention and renewal. Looking forward, these limitations may be largely offset by applying powerful new technologies that generate a wealth of cellular data, which is unprecedented in its scope and detail. Such methods promise to identify novel relationships between specific T-cell populations, inflammatory mediators, and immune pathways, thereby leading to mechanistic insights, and the discovery of novel biomarkers and drug targets that could revolutionize our understanding of severe disease. With these considerations in mind, new cytometry platforms can analyze more than 40 cell markers at the single-cell level, enabling rigorous assessment of multiple immune cell types in parallel, or else identification of complex phenotypes within a given cell type.[168, 169] Such systems biology approaches can construct a bird's eye view of the immune response in asthma and can be adapted to small amounts of sample, which is a key consideration in children. It is now also feasible to integrate reagents into these methods that detect antigen-specific T cells. In the future, more work is needed to solidify the relationship between gene expression/protein signatures and T-cell responses in children with severe disease[169]. Given the critical importance of gene accessibility to determining T-cell fate, epigenetics is now shedding light on the evolution of T-cell responses in early life. A recent small-scale study found increased histone acetylation of *IL13* and *FOXP3* in PBMCs from children with allergic asthma, while a much larger epigenome-wide meta-analysis of DNA methylation identified CpG marks acquired after birth that related to increased activity of CD8+ T_{EM} cells, and were strongly associated with asthma.[170171]

Similar to adults, children with severe asthma likely encompass a broad immune spectrum. Nonetheless, expression of the same cytokine across multiple T-cell types and subtypes can be exploited by specific therapies (Figure 3).[172, 173] Several monoclonal antibodies are in clinical use that target type 2 responses, and reduce asthma exacerbations in adults with moderate-to-severe Th2-high/eosinophilic disease. In addition to anti-IgE (omalizumab), these include biologics that block IL-5 and its receptor (mepolizumab, reslizumab and benralizumab), and a new addition that inhibits IL-4 and IL-13 signaling (dupilumab) by blocking IL-4Rα, a shared subunit of IL-4 and IL-13 receptors. Although each of these biologics is now approved by the Food and Drug Administration for use in children above a specified age (6 or 12 years), efficacy studies of these and other emerging biologics constitute a major unmet need in children with severe disease.[174] Regarding other T-cell-targeting biologics, promising results of a recent trial of a CRTH2 antagonist (fevipiprant) in adult patients with severe eosinophilic asthma, bodes well for its future clinical use.[175] Additional clinical trials in adults are ongoing that focus on antibodies that block receptors for innate cytokines, including TSLP receptor (tezepelumab) and ST2.[174]

By contrast, strategies for treating type 1- and type 17-associated severe disease are not well developed. In children, the rationale for this approach will rely on clarification of the link between type 1 and type 17 responses and severe asthma. A study of anti-IL17A (brodalumab) in adults with moderate-to-severe asthma showed no improvement in asthma control.[176] However, given the extensive cross-talk between different Th pathways, this is arguably not surprising. Another important aspect to consider in children is whether preventing multiple "hits" to the immune system from microbial exposures in early life, could halt or slow the disease trajectory. Antibiotics have shown benefits in clinical trials in non-eosinophilic severe asthma, as exemplified by fewer exacerbations and lower respiratory infections in patients treated with azithromycin.[177] Despite these advances, more large-scale clinical trials in highly characterized patients with severe asthma are needed to optimize personalized medicine for the disease.[178]

In summary, the rapid pace of scientific breakthroughs in the field of severe asthma in adults bodes well for improving knowledge of the immunopathology of disease in children. From a bench-to-bedside viewpoint, analyzing specimens from lung tissue and the lower airways of asthmatic children will be pivotal to informing the rational use of targeted therapies in the individual patient. The complex T-cell signatures present in severe asthma underscore the need to consider a multi-pronged approach, and to re-frame our thinking outside current paradigms, in order to improve the health of children suffering from this debilitating disease.

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Abbreviations

AHR	airway hyperresponsiveness
BAL	bronchoalveolar lavage
CS	corticosteroid(s)
GR	glucocorticoid receptor
iBALT	inducible bronchus-associated lymphoid tissue
ILC	innate lymphoid cell
HDM	house dust mite
iNKT	invariant natural killer T
MAIT	mucosal-associated invariant T
NK	natural killer
pDC	Plasmacytoid dendritic cells
STAT	signal transducer and activator of transcription

TCR	T-cell receptor
Th	T helper
TLR	toll-like receptor
T_{RM}	tissue-resident memory T cell
Tregs	T regulatory cells

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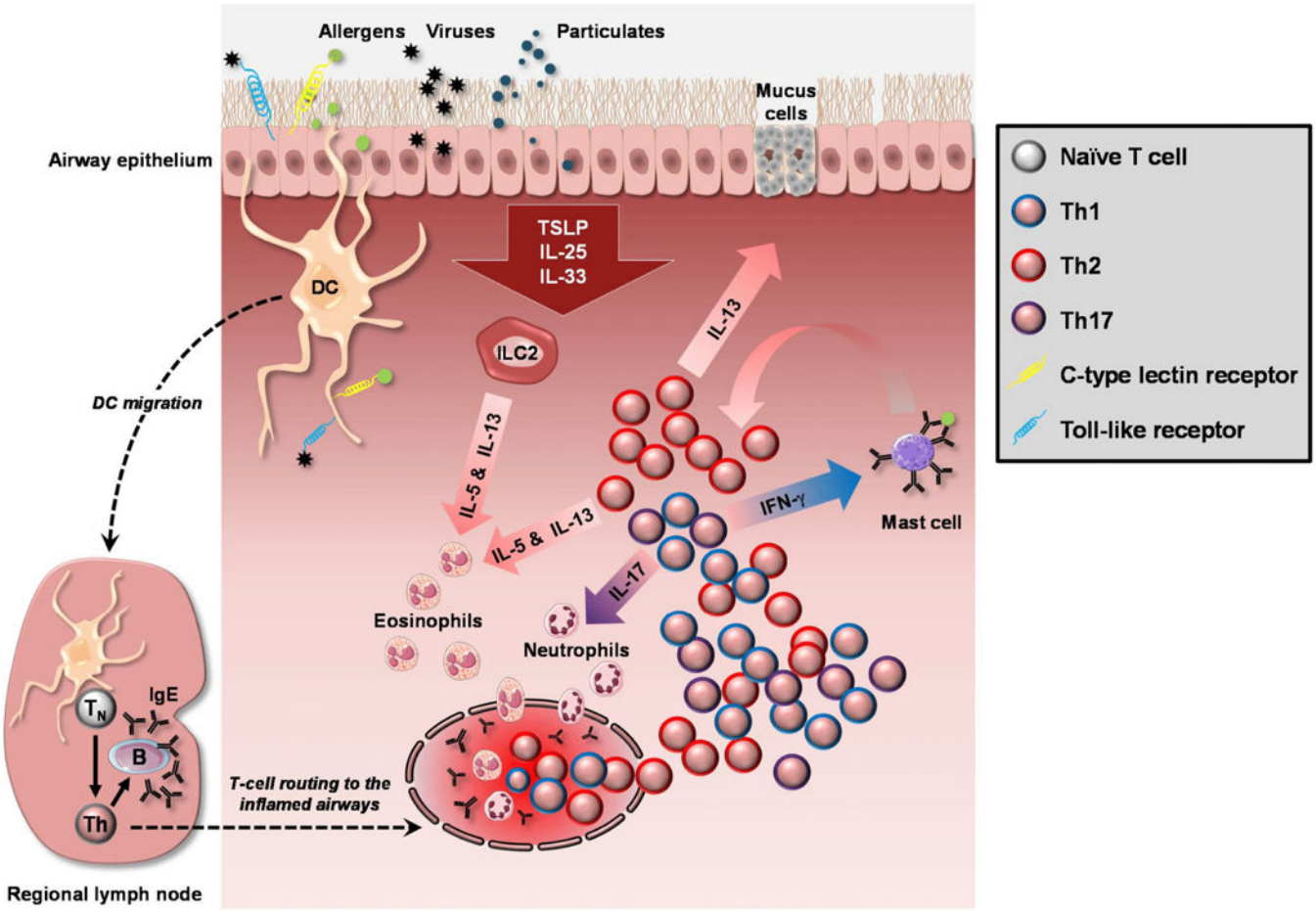


Figure 1. Theoretical Model of T-Cell Circuits in Asthma.

In asthma, dendritic cells proximal to the epithelial barrier are coordinately primed by exposure to a variety of antigens and cytokines produced by epithelial cells. This results in their maturation and migration to regional lymph nodes where they engage naive T cells, resulting in Th differentiation. These effector cells are armed to traffic to the respiratory tract where they exit the circulation and exert their effector function by releasing characteristic cytokines. The T-cell landscape in children with severe asthma is “mixed”, and there is likely a complex interplay between different Th types.

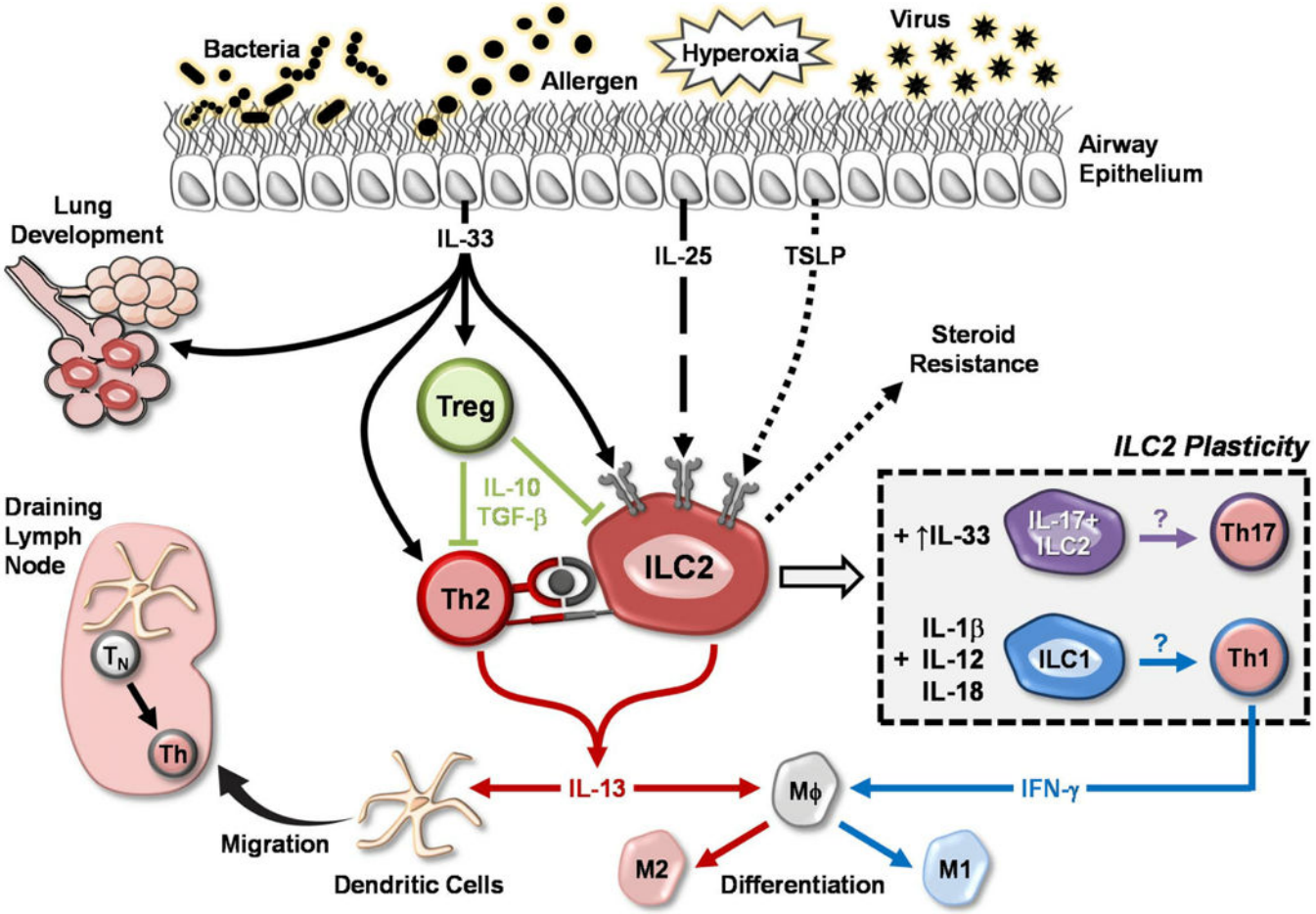


Figure 2. Mechanisms that Condition the Lung's Immune System for Asthma.

Innate lymphoid cells bridge innate and adaptive responses, and are likely to be integral to T-cell outcomes in asthma. The figure summarizes concepts derived from mouse models of asthma, including early life models, and from *in vitro* systems. Theoretical links to specific Th subsets that have been implicated in severe asthma of childhood are depicted.

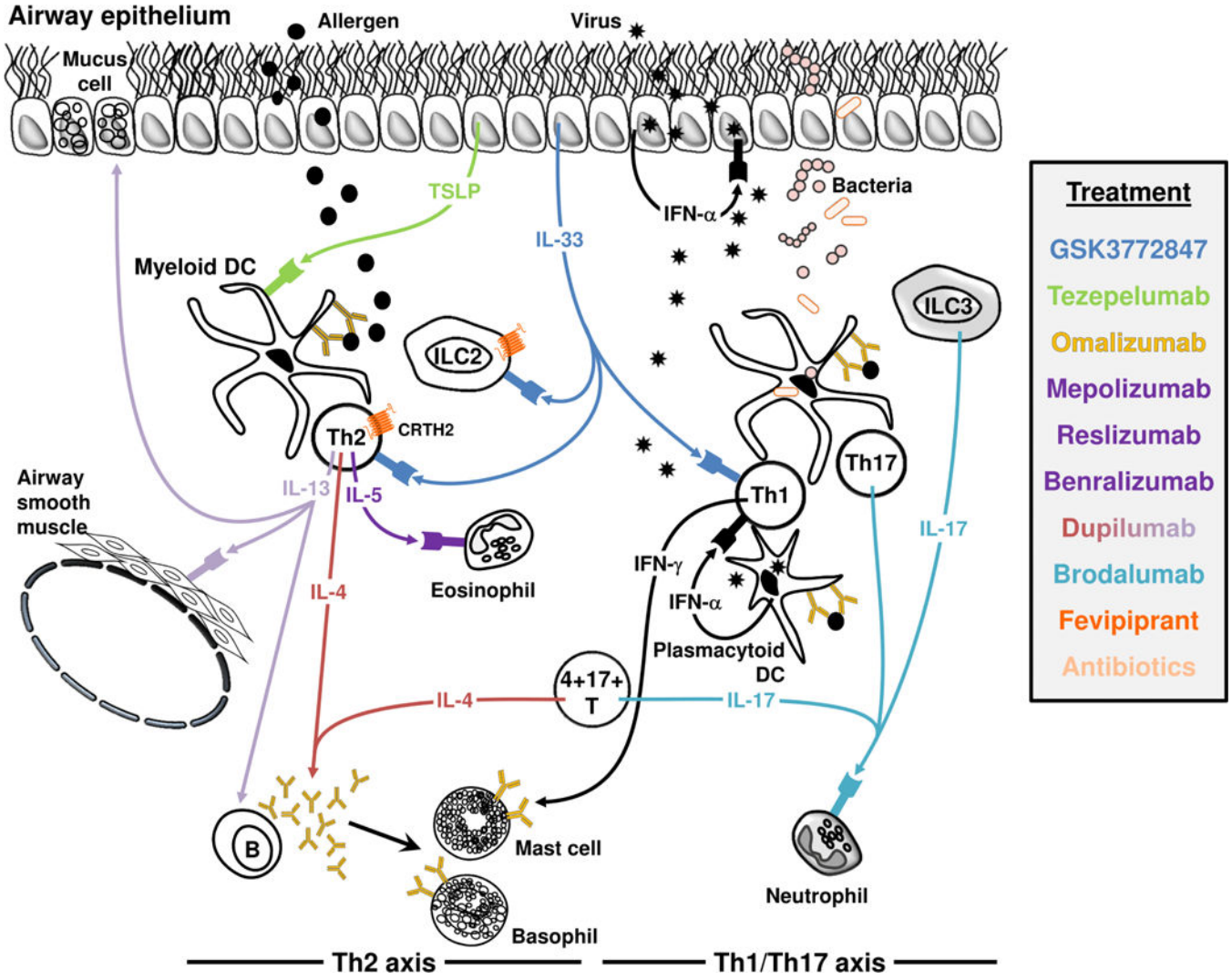


Figure 3. New and Emerging Treatments for Severe Asthma.

Drugs that exert a potential T-cell-modulatory effect are depicted. Each drug and its corresponding target molecule(s)/ pathway(s) is colored accordingly. Some drugs have the potential to impact both type 2 responses and type 1/type 17 responses, for example, by acting on T cells that co-express IL-4 and IL-17 (brodalumab), or by blocking the inhibitory role of IgE on IFN-α production in pDC (omalizumab). Although some treatments have been shown to reduce blood/sputum eosinophils, the effects on T cells remain unknown.

Table 1:

Lymphoid Cell Types Implicated in Asthma Pathogenesis and Their Defining Characteristics.

Cell type	Transcription factors	Cytokines	Chemokine receptors	Chemokine ligands	Other receptors	Other effector molecules	Inducing factors	Cells attracted	Refs.
CD4$^+$ T cells									
Th1	T-bet (STAT4)	IFN-γ	CXCR3 CCR5	CXCL10 CCL3, CCL4, CCL5	IL-12Rβ2	granzyme B, perforin	IL-12, IFN-γ		5, 6, 8, 44
Th2	GATA-3 (STAT6)	IL-4, IL-5, IL-13	CCR4 CCR6 CCR8 CCR3 CX3CR1	CCL17 CCL22 CCL20 I-309 eotaxin MCP-4 CX3CL1	IL-4Rα, IL-33R, TSLPR, IL-25R, CRTH2		IL-4, TSLP, IL-33, PGD2	eosinophils, ILC2's	4, 5, 6, 8, 44, 45
Th9	PU.1, ETV5, FOXO1, SMAD2/3/4, mTORC2[1], STAT6, STAT5[1], IRF1, IRF8[1]	IL-9	CCR3 CXCR3 CCR6	eotaxin MCP-4 CXCL10 CCL20	CLA, IL-4Rα	CCL17, CCL22	IL-2 / TGF-β1 / IL-4[1], IL-1β, IL-7, nitric oxide, IL-33[1], TSLP	Th17, neutrophils, mast cells, eosinophils, IFN-γ$^+$ / TNF-α$^+$ Th	5, 6, 7, 8
Th17	RORγt, STAT3, RORα, IRF-4, SMAD2/3	IL-17	CCR4 CCR6	CCL17 CCL22 CCL20	CD161		TGF-β1 / IL-6, / IL-23	neutrophils	6, 8, 44
CD8$^+$ T cells									
Tc1	T-bet	IFN-γ	CCR5 CXCR3	CCL3, CCL4 CXCL10		granzyme B, perforin			9
Tc2	GATA-3	IL-13, IL-5, IL-4, IL-22, IL-9, GM-CSF	CCR4	CCL17 CCL22	CRTH2, IL-6Rα, BLT1, CysLT1		IL-4, PGD2, LTB4	eosinophils	9
Tc17	STAT3, RORγt	IL-17	CCR6	CCL20				Th17	6
Tc9	STAT6, IRF-4	IL-9							9
NK-like CD8$^+$ T cells									
CD8[2]		IL-5, IL-13, IL9			BLT1, CD57, CD56, CD161, CD16, CD94	granzyme B, perforin	IL-4, IL-6, IL-9		10
NK T cells									
iNKT1	T-bet	IFN-γ, IL-4			IL-12Rβ2, IL-18R				11, 12
iNKT2	PLFZ	IL-4, IL-13	CCR6; CXCR6	CCL20; CXCL16	IL-33R, IL-25R, TSLPR				11, 12
iNKT17	RORγt	IL-17, IL-22			IL-23R			neutrophils	11, 12, 15

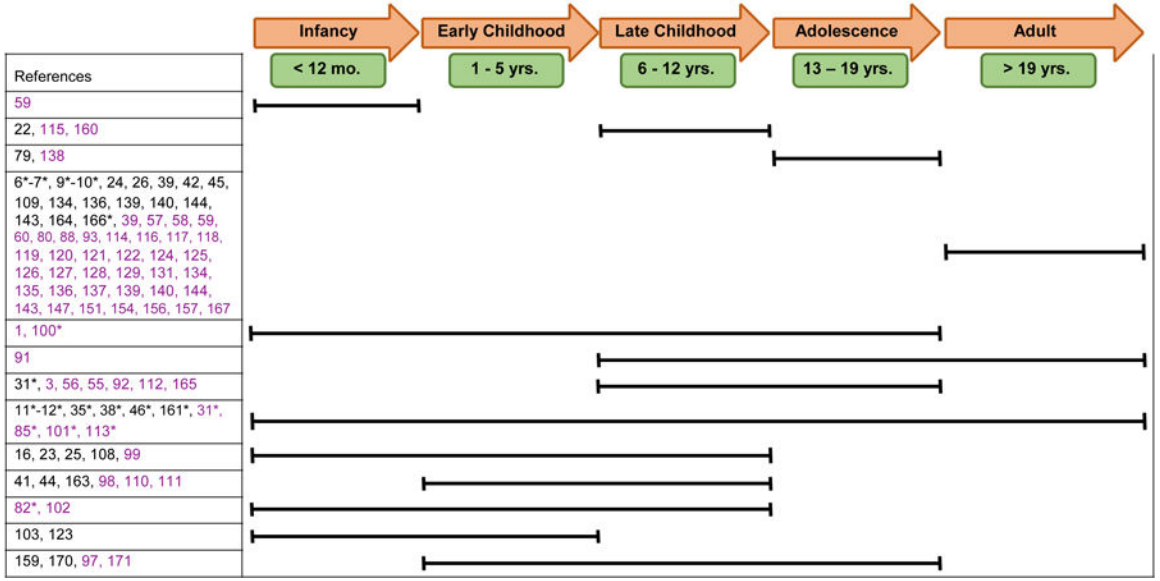
Cell type	Transcription factors	Cytokines	Chemokine receptors	Chemokine ligands	Other receptors	Other effector molecules	Inducing factors	Cells attracted	Refs.
iNKT9		IL-9						mast cells	14
MAIT cells									
MAIT	PLFZ	IFN-γ, IL-17, IL-4, IL-13, TNF-α	CCR5; CCR6; CXCR6	CCL3, CCL4; CCL20; CXCL16	CD161, IL-18R, IL-12Rβ2, IL-23R, CD127	granzyme B, perforin			11, 12, 22
Gamma Delta T cells									
Vγ9δ2		IFN-γ, IL-17						neutrophils	27
Vγ1δ1		IL-4							24
Innate Lymphoid Cells									
ILC2	GATA-3	IL-13, IL-4, IL-5, IL-9	CCR4	CCL17 CCL22	DR3, IL-33R, IL-25R, IL-2Rα, CRTH2, TSLPR, CysLT1R[$], CD161, CD127, ICOS, ICOSL, IL-17RB, ICAM-1[$]	IL-4[1]		eosinophils, M2[1], Th2[1]	31
ILC3	RORγt	IL-17, IL-22	CXCR6	CXCL16	LTα1β2, CD161, CD12, c-Kit, CD49a, TSLPR, Delta-like1	BAFF,APRIL, IFN-γ, Lymphotoxin	AhR ligands, retinoids, IL- 23, IL-1β	neutrophils	34, 35

[1]Data obtained solely in mice

[2]"Pro-inflammatory" CD8+ T cells. Defining characteristics are compiled from data in the general immunology literature.

Table 2.

Human Studies of The Immune Response in Asthma According to Age.



T cell studies (black); mechanistic studies (magenta); *review.