

Development and function of T_H17 cells in health and disease

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T_H17 cells are the newest member of the T_H cell family and are characterized by their ability to produce specific cytokines such as IL-17, IL-22, IL-17F, and CCL20. In this review, conditions for the differentiation of T_H17 cells are defined in both murine and human systems, with discussion of T_H17-specific cytokines and transcription factors. Functionally, T_H17 cells contribute to host defense as a new effector T_H cell subset with a role in protection against extracellular bacteria through activities on immune and nonimmune cells. Their activities, however, are also pivotal in the development of autoimmune diseases under pathologic conditions. T_H17 cells are also beginning to be associated with the development and pathophysiology of allergic diseases, such as allergic contact dermatitis, atopic dermatitis, and asthma. Lymphoid tissue inducer-like cells and natural killer-like cells, termed ROR γ t⁺NKp46⁺ or NK-22 cells, might also play a role in allergic diseases because of their propensity to produce IL-17 and IL-22. (*J Allergy Clin Immunol* 2009;123:1004-11.)

Key words: T_H17 cell, T_H cell, allergy, cytokines, IL-23, IL-17, IL-22

The activities of T and B lymphocytes are central to the existence and efficacy of the adaptive immune response. Whereas the role of B cells in the immune response is determined in part by the effector functions of the immunoglobulin subclass produced, T_H cell function is dictated by the ability to produce specific combinations of cytokines that cooperate in mounting an appropriate response to invading pathogens or injury. The subdivision of T-cell subsets according to their cytokine-production profiles and functions has now revealed a new effector T_H cell classification that plays an important role in autoimmunity and protection from bacteria. This review describes the discovery of these cells, designated T_H17 cells, and the conditions for their development in mice and human subjects. It also reviews their functions *in vivo*, with a focus on their role in autoimmune disorders, pathogen defense, and allergic diseases. Finally, other innate cell types capable of producing the T_H17-associated cytokines IL-17 and IL-22 are discussed.

IL-17-PRODUCING CD4⁺ T CELLS: A DISTINCT T_H CELL SUBSET

The adaptive immune system is crucial for the elimination of infectious agents, but dysregulation of adaptive immune

Abbreviations used

AD:	Atopic dermatitis
AHR:	Aryl hydrocarbon receptor
BAL:	Bronchoalveolar lavage
CD:	Crohn disease
CIA:	Collagen-induced arthritis
DC:	Dendritic cell
EAE:	Experimental autoimmune encephalomyelitis
FOXP3:	Forkhead box protein 3
G-CSF:	Granulocyte colony-stimulating factor
HIES:	Hyper-IgE syndrome
IBD:	Inflammatory bowel disease
IL-17R:	IL-17 receptor
IL-23R:	IL-23 receptor
iNKT:	Invariant natural killer T
LTi:	Lymphoid tissue inducer
NK:	Natural killer
OVA:	Ovalbumin
PGE ₂ :	Prostaglandin E ₂
ROR:	Retinoic acid receptor-related orphan receptor
STAT3:	Signal transducer and activator of transcription 3
TCR:	T cell receptor
Treg:	Regulatory T
TSLP:	Thymic stromal lymphopoietin

responses can also lead to the development of inflammatory and autoimmune diseases. In 1986, Mosmann et al¹ proposed the T_H1-T_H2 paradigm of CD4⁺ T cell lineage commitment in which they described the presence of 2 different T_H cell subsets, each expressing a distinct cytokine profile. T_H1 cells develop in the presence of IL-12, a heterodimeric cytokine composed of p35 and p40 subunits; produce primarily IFN- γ , IL-2, and lymphotoxin; and are involved in cell-mediated immunity. T_H2 cells differentiate in the presence of IL-4; produce IL-4, IL-5, and IL-13; and are critical for humoral immunity.

T_H1 cells, IL-12, and IFN- γ were thought to be critical for the development of inflammatory diseases, such as psoriasis, multiple sclerosis, arthritis, and inflammatory bowel disease (IBD), but inconsistencies arose when corresponding murine disease models were studied in more detail. Injection of IL-12 or IFN- γ blocked experimental autoimmune encephalomyelitis (EAE), and conversely, mice deficient in IFN- γ or the IFN- γ receptor were not resistant to EAE but instead were more susceptible to disease. The discovery that IL-12p40 could pair with another subunit reconciled these unexpected findings. IL-23 is a heterodimeric cytokine composed of the IL-12-shared p40 subunit and a unique p19 subunit. It signals through an IL-23 receptor complex consisting of the IL-12 receptor β 1 chain, which is shared with the IL-12 receptor β 1/ β 2 complex, and a specific IL-23 receptor (IL-23R) subunit. Despite their similarities in ligand structure and receptor complexes, it quickly became evident that IL-12 and IL-23 had common but also divergent activities.² In 2 landmark studies

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Cua and colleagues showed that mice deficient in IL-12p40 (thus lacking both IL-12 and IL-23) or IL-23p19 (lacking IL-23 but not IL-12) were resistant to EAE and collagen-induced arthritis (CIA), whereas IL-12p35^{-/-} mice (lacking IL-12 but not IL-23) were more susceptible to disease,^{3,4} demonstrating that IL-23, but not IL-12, is critical during the development of organ-specific autoimmune inflammation. On studying the mechanism of this observation, it was revealed that IL-23p19^{-/-} mice had normal T_H1 responses but did not produce IL-17 (ie, IL-17A), whereas IL-12p35^{-/-} mice exhibited an increased number of IL-17-producing CD4⁺ T cells in inflamed tissues.

Since its identification, IL-17 has been described as a T cell-derived cytokine that is highly expressed during autoimmune disorders and is able to activate epithelial cells during inflammatory responses. In accordance with these findings, mice deficient in IL-17 were resistant to EAE or CIA, whereas overexpression of IL-17 exacerbated disease.^{5,6} The link between IL-23 and IL-17 was established at the cellular level after the observation that activation of memory T cells in the presence of IL-23 resulted in IL-17 production⁷ and such induction was blocked by IL-12 or IFN- γ . It was suggested that IL-23 promoted a T cell subset distinct from T_H1 cells that expressed IL-17. Passive transfer of these IL-23-generated IL-17-producing CD4⁺ T cells was sufficient to induce EAE.⁸ It thereby became clear that the IL-23/IL-17 pathway, rather than the IL-12/IFN- γ pathway, was critical for EAE disease development; the concept of a new T_H cell subset was established and subsequently designated T_H17. Gene expression analysis of IL-23-driven T_H17 cells revealed a cytokine profile distinct from that of T_H1 cells, consisting of not only *IL17* but also *IL17F*, *TNF α* , *IL22*, and *IL6*. Retinoic acid receptor-related orphan receptor (ROR) γ t was identified as a specific T_H17 cell transcription factor that acts as a master regulator for this subset,⁹ and increasing evidence also points to a requirement for signal transducer and activator of transcription 3 (STAT3) in T_H17 development.¹⁰⁻¹² Forced expression of ROR γ t, however, is not sufficient to induce IL-22 production,¹³ and Veldhoen et al¹⁴ have identified the aryl hydrocarbon receptor (AHR) as a crucial transcription factor for induction of IL-22 in murine T_H17 cells.

T_H17 CELL DEVELOPMENT

Mouse T_H17 cell development

IL-23 was clearly essential for inducing IL-17-producing CD4⁺ T cells and autoimmunity *in vivo*. *In vitro* studies, however, revealed that it did not drive the differentiation of murine naive CD4⁺ T cells toward a T_H17 phenotype. This observation was not completely unexpected because naive T cells do not express IL-23R. Instead, studies by Bettelli et al,¹⁵ Mangan et al,¹⁶ and Veldhoen et al¹⁷ showed that TGF- β and IL-6 together were required to induce the development of T_H17 cells (Fig 1). The involvement of TGF- β was surprising because research at the time had primarily been focusing on its anti-inflammatory properties through induction of forkhead box protein 3 (FOXP3) and generation of regulatory T (Treg) cells, which play a suppressive role in autoimmunity and a protective role in tissue injury. These new studies, however, showed that in the presence of IL-6, TGF- β was now able to drive ROR γ t upregulation and the subsequent induction of IL-17-producing cells, exemplifying how an immune response can be finely regulated depending on the inflammatory microenvironment. IL-6 had previously been shown to downregulate FOXP3 expression and the development of Treg cells,

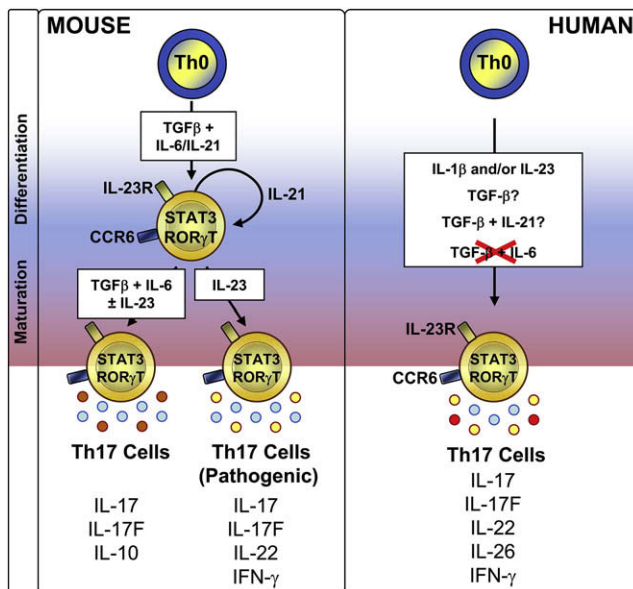


FIG 1. Differentiation and maturation of murine and human T_H17 cells. In the mouse system TGF- β , together with IL-6 or IL-21, is a crucial mediator driving the activation of STAT3, the upregulation of ROR γ t, and the subsequent differentiation of naive CD4⁺ T cells into T_H17 cells. Importantly, IL-6 and IL-21 induce expression of IL-23R on these cells. IL-23 is central to the effector function of pathogenic T_H17 cells. If TGF- β and IL-6 are present, T_H17 cells produce IL-10 and do not induce disease. In human subjects the combination of TGF- β and IL-6 is not able to induce T_H17 lineage commitment from circulating or cord blood naive CD4⁺ T cells. IL-1 β and IL-23 consistently emerge as critical factors in the induction of human T_H17 cell development.

and therefore this work extended these findings by showing that IL-6 could upregulate IL-23R expression on naive T cells, thereby rendering them sensitive to IL-23. The critical role of TGF- β and IL-6 in promoting T_H17 differentiation was also confirmed *in vivo*: TGF- β transgenic mice presented with exacerbated EAE and increased T_H17 responses, and mice deficient in IL-6 had increased numbers of Treg cells and did not develop EAE. It was soon demonstrated, however, that T_H17 cells could also develop independently of IL-6. IL-21, a member of the IL-2 cytokine family, was identified as another cytokine able to act together with TGF- β in driving murine T_H17 development.¹⁸⁻²⁰ Similarly to IL-6, IL-21 upregulated ROR γ t and *IL23R* expression on naive T cells and inhibited development of TGF- β -induced FOXP3⁺ Treg cells, and the combination of TGF- β and IL-21 was able to support differentiation of T_H17 cells in IL-6-deficient mice. IL-6 or IL-21 itself can induce expression of IL-21 in T_H17 cells, suggesting that IL-21 might act as an autocrine factor in T_H17 expansion. In support of this, T_H17 cells, but not T_H1 or T_H2 cells, produce high levels of IL-21, and T_H17 development is impaired in the absence of IL-21 signaling. Although these early studies proposed a crucial role for IL-21 in autoimmunity, recent reports have suggested that IL-21 or IL-21 receptor is dispensable for T_H17 lineage commitment *in vivo* and for the development of autoimmune disease in the EAE model,^{21,22} bringing into question the usefulness of pursuing IL-21 signaling pathways as therapeutic targets in chronic inflammatory diseases.

Because IL-23 did not appear to be required for the early polarization of T_H17 cells, it was subsequently proposed that the

cytokine could be important in the expansion, maintenance, and/or survival of the T_H17 cell subset. Recently, McGeachy et al²³ demonstrated that IL-23 is critical to T_H17 cell-mediated pathogenicity. In fact, passive transfer of T_H17 cells derived through TGF- β and IL-6 did not induce EAE, which is in contrast to T cells differentiated in the presence of IL-23. It was demonstrated that in addition to IL-17, TGF- β - and IL-6-cultured cells, but not IL-23-cultured cells, also produced the anti-inflammatory cytokine IL-10 (Fig 1). This IL-10 exerted a suppressive bystander effect on EAE development when TGF- β - and IL-6-derived cells were passively transferred together with disease-inducing IL-23-cultured T_H17 cells.²³ By using IL-23R-deficient mice, new data show the requirement of IL-23 signaling *in vivo* for the terminal differentiation of activated T cells into functional effector T_H17 cells, as well as for brain autoimmunity.²⁴

Human T_H17 cell development

Human T_H17 cells were first identified from the peripheral blood and intestines of healthy individuals and patients with Crohn disease (CD).^{25,26} Interestingly, both IL-17⁺/IFN- γ ⁻ and IL-17⁺/IFN- γ ⁺ T_H17 cells were found in the intestines of patients with CD. Human T_H17 cells are characterized by the expression of the chemokine receptor CCR6 and IL-23R.²⁵⁻²⁷ Interestingly, the C-type lectin CD161 was also recently identified as a hallmark of human T_H17 cells, and virtually all CD161⁺CD4⁺ T cells are within the CCR6⁺ T-cell population.^{28,29} After the identification of T_H17 cells in mice, several groups sought to determine whether human T_H17 cell development follows similar cytokine requirements as its murine counterpart. Although the studies published thus far agree that the combination of TGF- β and IL-6 does not induce human T_H17 cell lineage commitment,^{13,27,28,30-33} the precise conditions for human T_H17 cell development remain controversial (Fig 1). From all the studies assessing the cytokines implicated in human T_H17 cell development, IL-23 and IL-1 β consistently emerge as critical factors, whereas the precise role of TGF- β in this process is still not completely understood and remains a matter of debate. Chen et al,³⁴ Acosta-Rodriguez et al,³⁰ and our group²⁷ initially proposed that the presence of IL-1 β or IL-23 was sufficient to drive T_H17 differentiation from circulating human naive T cells without the addition of exogenous TGF- β . Such *in vitro*-derived T_H17 cells express *ROR γ t*, IL-17, IL-22, IL-17F, IL-26, CCL20, CCR6, and IL-23R, and interestingly, both IL-17 and IL-17/IFN- γ producers are observed. IL-6 enhances IL-1 β -driven IL-17 production, and TGF- β downregulates IL-17 production induced by IL-23 or by the combination of IL-1 β and IL-6. In contrast, subsequent studies reported a requirement for TGF- β in induction of human T_H17 lineage commitment.^{13,32,33} Volpe et al³³ described the combination of TGF- β , IL-23, IL-1 β , and IL-6 as the cytokine cocktail required to induce T_H17 differentiation from umbilical cord blood cells or circulating naive CD4⁺ T cells. On the other hand, Manel et al¹³ suggested that the combination of TGF- β , IL-23, and IL-1 β was optimal for T_H17 polarization of naive cord blood CD4⁺ T cells and that IL-6 and IL-21 were not necessary for T_H17 cell development. In contrast, Yang et al³² proposed that the combination of TGF- β and IL-21 triggered the development of T_H17 cells that expressed IL-17 but not IFN- γ or IL-22. Manel et al,¹³ however, did not detect production of IL-17 under the same conditions. Finally, the recent work of Cosmi et al²⁸ suggests that human T_H17 cells could originate from umbilical

cord blood CD161⁺CD4⁺ T cell precursors in the absence of exogenous TGF- β in the presence of both IL-1 β and IL-23. In a separate publication the same group proposed that TGF- β is not critical for development of human T_H17 cells but instead indirectly contributes to T_H17 cell expansion through inhibition of T_H1 cells.³⁵ Interestingly, Burgler et al³⁶ have recently shown that TGF- β was not required for but enhanced production of IL-17 induced by IL-1 β , IL-23, and IL-6, but TGF- β was necessary for expression of *RORC2*, the closest human relative of murine *ROR γ t*.³⁵

Understanding the factors involved in T_H17 cell development, regulation, or both is critical in therapeutically targeting this pathway in patients with inflammatory diseases. Importantly, T_H17 cell regulation also occurs in response to agents other than cytokines. For example, retinoic acid is a potent inhibitor of T_H17 differentiation and promotes the development of FOXP3⁺CD4⁺ Treg cells in mice. In this regard it was recently reported that prostaglandin E₂ (PGE₂), together with IL-23, favors the expansion of circulating human T_H17 cells.³⁷ We further showed that PGE₂ acts in concert with IL-23 and IL-1 β in promoting human T_H17 differentiation and maturation of circulating naive T cells.³⁸ PGE₂ was already known to exacerbate inflammation in murine models of IBD and CIA through the IL-23/IL-17 pathway, effects attributed to the activities of PGE₂ on innate immune cells.³⁹⁻⁴¹ The inflammatory microenvironment thus plays a critical role in the development and regulation of T_H17 responses.

T_H17 CELLS IN ANTI-PATHOGEN RESPONSES AND AUTOIMMUNITY

Despite being involved in various autoimmune inflammatory disorders, not all T_H17 effector functions are detrimental. T_H17 cells play a significant role in defense of the host against certain extracellular bacteria and fungi, and emerging information suggests that this cell subset might be indirectly involved in immune protection against virus-associated pathologies as well.

T_H17 cell-produced IL-17 promotes neutrophil maturation and chemotaxis, which are important in conferring protection against bacteria and fungi. For instance, mice deficient in IL-17 or IL-17 receptor (IL-17R) A are susceptible to pulmonary infection with the extracellular pathogen *Klebsiella pneumoniae*,⁴² and similarly, IL-17RA-deficient mice are greatly susceptible to *Candida albicans*.⁴³ T_H17 cells are not the sole producers of IL-17, but the susceptibility of individuals with hyper-IgE syndrome (HIES), who do not develop T_H17 cells, to bacterial and fungal infections demonstrates that these cells are important for protective immunity. In addition, patients with chronic mucocutaneous candidiasis exhibit reduced production of IL-17 and IL-22, suggesting a defect in T_H17 cell responses in these patients.⁴⁴

The neutrophil-promoting role of IL-17 is clearly important in supporting innate antibacterial responses, but other T_H17 -associated cytokines, such as IL-17F and IL-22, also appear to be indispensable for control of bacterial infections. Aujla et al⁴⁵ and Zheng et al,⁴⁶ using *K. pneumoniae* and *Citrobacter rodentium* infection, respectively, determined that IL-23-dependent production of IL-22 is crucial for epithelial induction of antimicrobial defense genes and full protection of the host. In addition, IL-17F also plays a nonredundant role in protection against *C. rodentium*.⁴⁷ Thus, IL-17, IL-17F, and IL-22 act synergistically on the epithelium to combat bacterial infections and emerge as important factors in defense against pathogens. However, during

C. rodentium infection, dendritic cells (DCs) appear to be mainly responsible for the induction of IL-22, and IL-17F is produced by T cells, innate cells, and epithelial cells^{46,47}; therefore the relative contribution of T_H17 cells versus other cells in the production of these cytokines still needs to be delineated.

Defense against viruses, on the other hand, has been well characterized to involve CD8⁺ T and T_H1 cells. In a recent study Brechley et al⁴⁸ investigated whether T_H17 cells might also be involved in antiviral protection. On finding IL-17⁺CD4⁺ memory T cells in human peripheral blood, they examined whether T_H17 cells specific for a variety of pathogens could be observed. Although IFN- γ -producing CD4⁺ memory T cells could be seen after restimulation of cells with antigens from HIV, adenovirus, cytomegalovirus, influenza virus, or EBV, IL-17 was not readily detectable. In contrast, IL-17 production by CD4⁺ memory T cells was observed after stimulation with antigens from *Staphylococcus aureus* or *C. albicans*, tetanus toxoid, or streptococcal kinase.⁴⁸ This evidence suggests that T_H17 cells might not be directly involved in immunity against several common viruses. However, the study authors found a significant loss of T_H17 cells in the gastrointestinal tracts of HIV-infected patients, and because increased intestinal permeability and enteropathy are associated with chronic HIV infection, T_H17 cells might be involved in protecting against secondary conditions involving gastrointestinal microbes.

In contrast to their protective role during host defense, T_H17 cells are thought to promote tissue destruction during inflammation, and the IL-23/IL-17 pathway appears to be more and more involved in the development and maintenance of chronic inflammatory diseases.⁴⁹ Indeed, mice deficient in IL-17, IL-23p19, or IL-12/IL-23p40 are resistant to EAE, IBD, or CIA, whereas the absence of IL-12 or IFN- γ signaling worsens disease. T_H17 cells were first isolated from patients with CD, and increased expression of IL-23, IL-17, and other T_H17-associated cytokines has been described in the circulation or inflamed tissues of patients with diverse autoimmune diseases, such as multiple sclerosis, CD, psoriasis, or arthritis.⁵⁰ In support of a role for T_H17 cells in autoimmune diseases, ongoing clinical trials with neutralizing IL-12/IL-23p40 mAbs are showing promising results in the treatment of CD or psoriasis. Furthermore, genetic studies have suggested an association between *IL23R* gene polymorphisms and susceptibility to psoriasis or CD.^{51,52}

Although T_H17 cells have been consistently associated with certain pathologic conditions, one has to keep in mind that evidence exists for the involvement of T_H1 cells in inflammation as well. In fact, T_H1, T_H17, and T_H2 cells have been isolated from the inflamed tissues of patients with psoriasis, CD, rheumatoid arthritis, or severe asthma, again exemplifying the complexity of inflammatory disorders.⁵³

T_H17 CELLS IN ALLERGIC DISEASES

T_H17 cells and their related cytokines are now beginning to show an association with allergic diseases as well. T_H17 cells are highly involved in the development and maintenance of psoriasis,⁵² and a possible role for IL-17, IL-22, and T_H17 cells in allergic contact dermatitis or atopic dermatitis (AD) is also now emerging. Nickel-specific T_H0, T_H1, or T_H2 clones from patients with allergic contact dermatitis have been found to produce IL-17,^{54,55} and allergen-specific T_H17 cells have been found in the peripheral blood of patients with nickel allergy.⁵⁶ Investigating the production of IL-17 during AD, Koga et al⁵⁷ recently detected

the cytokine in skin biopsy specimens of patients with AD. Interestingly, acute AD lesions showed more IL-17⁺ cells than chronic lesions, suggesting that IL-17 functions primarily in the acute T_H2 phase rather than the subsequent T_H1-dominated chronic phase of AD.⁵⁷⁻⁵⁹ Examination of peripheral blood from patients with AD identified CD4⁺ T cells producing IL-17, the percentage of which correlated with the severity of the disease.⁵⁷ Thus, T_H17 cells appear to be involved not only in psoriasis but also in the acute phase of AD. Here T_H17 cells might work in partnership with eosinophils present during the acute phase of the disease because Cheung et al⁵⁸ have demonstrated that IL-17, IL-17F, and IL-23 promote human eosinophil production of CXCL1 and IL-8, whereas IL-17F and IL-23 induce the release of IL-1 β and IL-6, which, as described earlier in this review, could reciprocally support the continued activation of T_H17 cells.

Whether a specific role exists for T_H17 cells in asthma, however, is still largely controversial. Several studies report the presence and function of IL-17 in asthmatic responses, supporting the possible involvement of T_H17 cells in the pathophysiology of the disease. The expression of IL-17 in the sputum of patients with persistent asthma correlates with influx of airway neutrophils, and Laan and colleagues⁶⁰ have demonstrated that instillation of human IL-17 into the airways of rats induces selective neutrophil recruitment. In addition, IL-17 can enhance human bronchial fibroblast production of IL-6, IL-8, and CXCL1; human bronchial epithelial cell expression of IL-8, CXCL1, CCL20, intercellular adhesion molecule 1, and granulocyte colony-stimulating factor (G-CSF); and human airway smooth muscle cell production of IL-6 and IL-8.⁶¹⁻⁶⁵ IL-8 and CXCL1 are neutrophil chemoattractants, whereas IL-6 and G-CSF function in neutrophil development and granulopoiesis. Thus, IL-17 likely plays a critical role in the neutrophil activation and proliferation common in so-called nonatopic or noneosinophilic asthma.

The function of IL-17 in eosinophilic asthma, however, has been more complex to decipher. Studies from Schnyder-Canadrian et al⁶⁶ and Nakae et al⁶⁷ used IL-17RA-deficient or IL-17-deficient mice, respectively, to show that antigen-specific T cell responses are reduced in the absence of IL-17 signaling in an ovalbumin (OVA)-induced asthma model, suggesting that IL-17 is required to initiate T_H2 responses. Studies by He et al,⁶⁸ Hellings et al,⁶⁹ and Fujiwara et al⁷⁰ showed that neutralizing IL-17 in the priming and challenge phases of the model decreased bronchoalveolar lavage (BAL) neutrophils specifically, whereas the study by Schnyder-Canadrian et al⁶⁶ found an increase in the number of BAL fluid eosinophils upon anti-IL-17 administration. In addition, this study showed that intranasal coadministration of OVA with IL-17 was able to reduce lung eosinophilic infiltration and mucus production. Thus, it appears that although IL-17 is required for the development of T_H2 responses, the cytokine might instead play a suppressive role during the effector phases of allergic asthma. A recent publication by Hsu et al,⁷¹ however, indicates that IL-17 might be important in setting up germinal center formation, which could factor into the reduced antigen-specific T cell responses in mice lacking IL-17 or IL-17RA. In addition, it has recently been described in mice that IL-25, a cytokine produced by activated T_H2 cells that works in an autocrine fashion to amplify T_H2 responses, might signal through both IL-17RB and IL-17RA (ie, IL-17R).⁷² Thus, studies with IL-17R-deficient mice might block this important T_H2-associated cytokine and its effects as well.

A confounding factor in linking asthma-associated IL-17 with T_H17 cells is that several cell types are capable of producing IL-17. Other than $CD4^+ T_H17$ cells, $CD8^+$ T cells, natural killer (NK) cells, $\gamma\delta$ T cells, and NK T cells can also be a source of IL-17, and *IL17* mRNA has also been found in eosinophils and neutrophils. In fact, a recent publication by Song et al⁷³ indicates that alveolar macrophages and specifically not T, B, or NK cells are the major producers of IL-17 during a murine model of asthma. Thus, IL-17 in the lung could, but does not necessarily, correlate with T_H17 cell activation.

The most compelling data supporting a specific role for T_H17 cells in asthma comes from recent studies performed by Wakashin et al⁷⁴ using an adoptive transfer model. Naive DO11.10 $CD4^+$ T cells, which express an OVA-specific T cell receptor (TCR), were polarized into T_H2 or T_H17 cells *in vitro* and adoptively transferred into mice before challenge with inhaled OVA. Transfer of polarized T_H2 or T_H17 cells resulted in eosinophil or neutrophil recruitment into the airways, respectively. However, transfer of both T_H2 and T_H17 cells together more than doubled the number of airway eosinophils, suggesting that T_H17 cells can amplify T_H2 responses. However, a recent publication by Lee et al⁷⁵ suggests that polarized T_H17 cells demonstrate continued plasticity after differentiation, and polarization of OVA-specific T_H17 cells in the Wakashin et al⁷⁴ study resulted in only about half of the cells producing IL-17, leaving open the narrow possibility that the remaining cells might not have been completely polarized toward the T_H17 pathway and might have been able to support T_H2 responses *in vivo* when coadministered with polarized T_H2 cells.

In support of T_H17 cells playing a role in neutrophilic but not eosinophilic asthma, He et al⁶⁸ performed a series of elegant studies comparing epicutaneous versus intraperitoneal sensitization of mice with OVA. Epicutaneous sensitization and subsequent challenge with inhaled OVA resulted in a 5-fold increase in lung *IL17* mRNA expression, whereas intraperitoneally sensitized mice did not upregulate lung expression of IL-17 but showed greater induction of the T_H2 cytokines IL-4 and IL-13. Although both routes of sensitization resulted in greater than 50% eosinophils in the BAL fluid, neutrophil percentages correlated with the presence of IL-17 in epicutaneously sensitized mice, being 15% of the BAL fluid constituents compared with 2.5% in intraperitoneally immunized mice. Similarly, IL-17 was detectable in the BAL fluid of only epicutaneously sensitized mice after inhaled OVA challenge, and IL-17-producing $CD4^+$ T cells were present only in the lungs of epicutaneously but not intraperitoneally sensitized animals. The ability of skin-derived DCs to direct the differentiation of naive $CD4^+$ T cells into T_H17 cells instead of T_H2 cells traced back to their selective ability to produce IL-23, although neutralization of IL-6 and TGF- β also reduced $CD4^+$ T cell production of IL-17. These studies suggest that the route of sensitization might be important in directing T_H17 versus T_H2 responses in allergic lung conditions. In addition, they show that T_H17 cells do not appear to be present in the lungs of mice with eosinophilic nonneutrophilic asthma.

Because the differentiation of T_H17 cells is inhibited by the T_H2 cytokine IL-4,⁷⁶ the question arises as to whether T_H17 cells would develop in T_H2 conditions. The above study by He et al⁶⁸ suggests that T_H17 cells can develop despite robust T_H2 responses. In support of this, a recent publication by Tanaka et al⁷⁷ addressed this question by looking at the polarization of human T_H2 and T_H17 cells. Thymic stromal lymphopoietin (TSLP)-activated DCs induce naive T cells to differentiate into

inflammatory T_H2 cells expressing IL-4, IL-5, IL-13, and TNF. Activating DCs with both TSLP and Poly(I:C), a double-stranded RNA analog and Toll-like receptor 3 ligand, induced naive T cells to polarize not only into IL-13-producing T_H2 cells but also into IL-17-producing T_H17 cells. Thus, TSLP-activated DCs, which are known to strongly induce proallergic T_H2 responses, can simultaneously induce T_H17 cells under certain conditions. Because Poly(I:C) is an analog for viral nucleic acid and viral infections often aggravate asthma, this might explain one manner in which viral infections can exacerbate allergic asthma and induce more severe disease.

In any case, it is clear that IL-17 production seems to correlate more closely with neutrophil- rather than eosinophil-associated responses. Continuing to elucidate the mechanisms behind neutrophilic asthma is important, however, because studies have shown that only half of all asthma cases are primarily attributable to eosinophilic infiltrate in the airways. Corticosteroids have historically been the gold standard for treatment of eosinophilic asthma because of their ability to downregulate T_H2 genes, such as *IL5* and *IL13*, but a recent publication by McKinley et al,⁷⁸ suggesting that T_H17 cells mediate steroid-resistant airway inflammation and hyperresponsiveness, begs the question of whether treating subjects with eosinophilic asthma with corticosteroids could possibly create the neutrophil-driven responses associated with severe asthma.

T_H17 cells, or rather their absence, also appear to be involved in the pathology associated with HIES, a complex immunologic disease clinically characterized by high circulating IgE levels (>2000 IU/mL), eczema, eosinophilia, and susceptibility to bacterial infections.⁷⁹ Several groups have recently demonstrated that individuals with HIES have mutations in *STAT3* and are unable to generate IL-17-producing T_H17 cells,⁸⁰⁻⁸² likely contributing to the extracellular bacterial and fungal infections common to patients with HIES. Because *STAT3* is directly involved in the signal transduction pathways of several cytokines, including IL-6, IL-10, IL-21, IL-22, IL-23, and oncostatin M and the conditions for the differentiation and maintenance of human T_H17 cells are just beginning to be understood, more work will need to be done to determine which *STAT3*-dependent pathways are responsible for the T_H17 cell defect in patients with HIES.

TCR $\gamma\delta^+$ T CELLS, INVARIANT NK T CELLS, NK-22 CELLS, AND LYMPHOID TISSUE INDUCER-LIKE CELLS: ADDITIONAL SUBSETS OF IL-17- AND/OR IL-22-PRODUCING CELLS

As mentioned above, in addition to the $CD4^+ TCR\alpha\beta^+$ T_H17 cells that are predominantly involved in the adaptive immune response, other cell subsets, such as TCR $\gamma\delta^+$ T cells, NK T cells, and certain NK cells, are also able to produce IL-17 in the early innate response. The rapid production of IL-17 by these cells is important for the activation and recruitment of neutrophils to sites of inflammation. It is important to note that many $\gamma\delta$ T cells in the periphery seem to be effector memory cells that are primed to rapidly produce IL-17, which is important under physiologic circumstances in the regulation of granulopoiesis. Neutrophil homeostasis is controlled by a regulatory feedback loop that is initiated by phagocytosis of apoptotic neutrophils by tissue macrophages and DCs, which induces their production of IL-23 and subsequently stimulates IL-17 production by $\gamma\delta$ T cells and

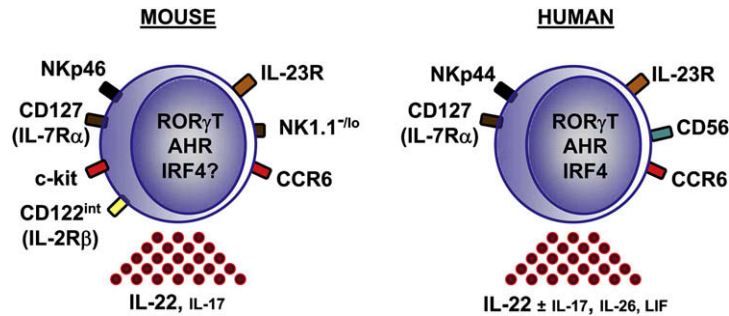


FIG 2. Characteristics of $ROR\gamma t^+ NKp46^+ CD3^-$ NK-22 cells in mice and human subjects. *IL-7R*, IL-7 receptor.

results in the generation of new neutrophils and their recruitment through the induction of G-CSF.⁸³

Invariant NK T (iNKT) cells comprise a distinct population of NK T cells that express a restricted TCR repertoire composed of the invariant $V\alpha 24-J\alpha 18/V\beta 8.2$ in mice and respond to lipid antigens in the context of the nonpolymorphic MHC class I-like molecule CD1d. A characteristic of this subset is its ability to rapidly produce high levels of cytokines after activation. A subset of $NK1.1^-$ iNKT cells is able to produce IL-17 after activation with synthetic α -galactosylceramide or natural lipid ligands or through culture in the presence of IL-23.⁸⁴ These $NK1.1^-$ iNKT cells express *RORγt* and *IL23R* and can be either $CD4^+$ or $CD4^-$. More importantly, IL-17 production by these $NK1.1^-$ iNKT cells has been shown to play a role in airway neutrophilia induced by intranasal α -galactosylceramide or LPS instillation and in the pathogenesis of CIA.⁸⁵ In addition to IL-17, iNKT cells can produce other T_H17 cytokines, such as IL-22.⁸⁶

Very recently, attention has been drawn to 2 other cell populations in human subjects and mice that might eventually play a role in allergic diseases because of their propensity to produce IL-17, IL-22, or both: $ROR\gamma t^+ NKp46^+$ cells or NK-22 cells and lymphoid tissue inducer (LTi)-like cells. Whereas most $NKp46^+ CD3^-$ NK cells produce IFN- γ , are able to kill target cells through granzyme- or perforin-dependent cytotoxicity, and are dependent on IL-15 for their development, a subset of $NKp46^+ CD3^-$ NK cells displaying different characteristics and ontogeny has now been described. This NK cell population displays greatly reduced cytotoxic activity and IFN- γ production but instead produces large amounts of IL-22 in response to IL-23. The phenotype of these cells is characterized by expression of NKp46, CD127 (IL-7 receptor α), CD122 (IL-2 receptor β), c-kit, and IL-23R (Fig 2). In contrast to traditional murine NK cells, they are either $NK1.1^{lo}$ or $NK1.1^-$ cells, and interestingly, these cells express *RORγt*.⁸⁷⁻⁸⁹ Found predominantly in the skin and in the gut lamina propria, it is thought that the production of IL-22 by these cells induces the production of antimicrobial molecules, such as RegIII β and RegIII γ , thereby playing a role in the maintenance of epithelial homeostasis.^{88,90} Importantly, mice lacking IL-22-producing $NKp46^+ CD3^-$ NK cells were more susceptible to *C. rodentium* infection^{89,90} and development of IBD.⁹¹ These $ROR\gamma t^+ NKp46^+$ cells were present in the lamina propria of IL-15^{-/-} mice, indicating that the differentiation pathway of these cells is distinct from that of traditional $ROR\gamma t^- NKp46^+ CD3^-$ NK cells. In fact, based on their phenotype and location, it is possible that $ROR\gamma t^+ NKp46^+$ cells are actually derived from LTi-like cells. LTi cells have been shown to initiate lymph node organogenesis during embryogenesis, and LTi-like cells participate in gut-associated lymphoid tissue development in the adult intestine.⁹² In

support of their association with $ROR\gamma t^+ NKp46^+$ cells, LTi-like cells are absent from the guts of *RORγt*-deficient animals, and strong evidence for the interrelationship between these 2 cell types comes from the human system. Cupedo et al⁹³ showed that in human subjects LTi cells from fetal mesenteria and lymph nodes, as well as postnatal tonsils, are $CD4^+ CD3^- ROR\gamma t^+ CD127^+$ cells that can give rise to NK cells expressing CD56, CD127, and *RORC* (the gene encoding the transcription factor *RORγt*) and produce both IL-17 and IL-22 after activation with phorbol 12-myristate 13-acetate/ionomycin.⁹³ The *RORC*⁺*CD56*⁺*CD127*⁺ NK subset was also characterized at the same time by Cella et al⁸⁹ as NK-22 cells, $CD56^+ NKp44^+$ NK cells that produce IL-22, IL-26, and leukemia inhibitory factor, but not IL-17, in response to IL-23. In addition to CD56, CD127, and NKp44 markers, these cells express CCR6, *AHR*, and interferon regulatory factor 4. Human LTi-like cells and the *RORC*⁺*CD56*⁺*CD127*⁺ NK-22 cells are generally found in the skin, intestine (Peyer patches), mucosal-associated lymphoid tissue, and tonsils, but not in the circulation.^{89,93} In mice LTi-like cells have been identified in the spleen, where they produce IL-17 and IL-22; express *IL23R*, *AHR*, and CCR6; and respond to IL-23 and zymosan.⁹⁴ Based on the cytokines they produce, their location in the body, and their similarity to T_H17 cells and other cell types, LTi-like cells and $ROR\gamma t^+ NKp46^+$ cells might eventually be shown to participate in allergic diseases involving IL-17 and IL-22.

CONCLUDING REMARKS

Even though the field of murine and human T_H17 cell biology has blossomed over the past few years, the role of T_H17 cells in allergic diseases is just beginning to be understood. Although progress has been made, further work will need to delineate the specific functions of T_H17 cells from those of other cell types that are capable of producing T_H17 -associated cytokines, such as IL-17 and IL-22.

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