Background: Chronic rhinosinusitis with nasal polyposis (CRSwNP) in Western countries is characterized by eosinophilia, IgE production, and TH2 cytokine expression. Type 2 innate lymphoid cells from polyps produce IL-5 and IL-13 in response to IL-25 and IL-33, although the relevance of this axis to local mucosal T-cell responses is unknown. Objective: We sought to investigate the role of the IL-25/IL-33 axis in local mucosal T-cell responses in patients with CRSwNP. Methods: Polyp tissue and blood were obtained from patients undergoing nasal polypectomy. Control nasal biopsy specimens or blood were obtained from healthy volunteers. Tissue was cultured in a short-term explant model. T-cell surface phenotype/intracellular cytokines were assessed by means of flow cytometry. T-cell receptor variable β-chain analysis was performed with the immunoSEQ assay. Microarrays were performed for gene expression analysis. Results: IL-25 receptor (IL-17RB)–expressing TH2 effector cells were identified in nasal polyp tissue but not the healthy nasal mucosa or periphery. IL-17RB⁺CD4⁺ poly-derived TH2 cells coexpressed ST2 (IL-33 receptor) and responded to IL-25 and IL-33 with enhanced IL-5 and IL-13 production. Within IL-17RB⁺CD4⁺ T cells, several identical T-cell receptor variable β-chain complementarity-determining region 3 sequences were identified in different subjects, suggesting clonal expansion driven by a common antigen. Abundant IL-17–producing T cells were observed in both healthy nasal mucosal and polyp populations, with TH17-related genes the most overexpressed compared with peripheral blood T cells. Conclusion: IL-25 and IL-33 can interact locally with IL-17RB⁺ST2⁺ polyt T cells to augment TH12 responses in patients with CRSwNP. A local TH17 response might be important in healthy nasal mucosal immune homeostasis. (J Allergy Clin Immunol 2015;:..::--) Key words: Chronic rhinosinusitis with nasal polyps, nasal mucosa, IL-25, IL-33, IL-17RB, ST2, T-cell phenotype, TH2 cells, TH17 cells, T-cell receptor Vβ repertoire, microarray

Chronic rhinosinusitis with nasal polyposis (CRSwNP) is an umbrella term for a heterogeneous group of inflammatory disorders characterized by persistent polypoid inflammation of the sinonasal mucosa (≥12 weeks) and nasal obstruction. Symptoms are often severe and only partially responsive to treatment, and disease is commonly associated with difficult-to-treat asthma. There is an urgent unmet clinical need to understand the immunopathology of CRSwNP. Several studies have indicated regional variation in CRSwNP endotypes. Western countries show a predominance of eosinophilic TH2-associated polyps, and *Staphylococcus aureus* superantigens have been implicated in driving the TH12 response. Conversely, CRSwNP in patients from southern Asia is associated with neutrophilic infiltration and a local TH1/TH17 signature. Although potential sources of proeosinophilic cytokines in patients with CRSwNP include T cells, type 2 innate lymphoid cells (ILC2s), mast cells, and eosinophils, the local immune mechanisms regulating cytokine production remain poorly understood. Relatively little is also known of T-cell responses in the healthy nasal mucosa, although the local microenvironment appears to suppress TH12 responses.
Recently, the epithelial cell–derived cytokines IL-25 and IL-33, acting through their respective receptors IL-17RB and ST2, have been implicated in promoting T_{H}2 responses in animal models of allergic inflammation.8,9 Expression of IL-17RB has been demonstrated on human peripheral blood T_{H}2 cells differentiated in vitro by thymic stromal lymphopoietin–treated dendritic cells and on freshly isolated CD4\(^+\) T cells from patients with Churg-Strauss syndrome.10,11 IL-25 is also expressed within the bronchial mucosa of asthmatic patients and in the skin during allergen-induced late responses.11,12 Furthermore, IL-25 coexpresses IL-17RB and ST2 and produces IL-5 and IL-13 in response to IL-25 and IL-33.14,15 ST2 is associated with T_{H}2 immune responses in mice.16,17 and expression is increased in ILC2s and eosinophils from patients with CRSwNP.18-20 In human subjects baseline levels of IL-33 mRNA in epithelial cells derived from treatment-recalcitrant nasal polyps are increased compared with levels in cells derived from treatment-responsive nasal polyps.21 However, the local mucosal T-cell response in patients with CRSwNP and the potential interaction of T cells in the nasal mucosa with IL-25 or IL-33 have not been explored.

Therefore we hypothesized that the IL-25/IL-33 axis is involved in directing local mucosal T_{H}2 responses in patients with eosinophilic CRSwNP. To test this hypothesis, we extensively phenotyped nasal T-cell responses from tissue explants of patients with CRSwNP and healthy control subjects.

METHODS

Detailed methods used in this study and reagent sources can be found in the Methods section in this article’s Online Repository at www.jacionline.org. Clinical and demographic data for patients with CRSwNP and healthy volunteers are shown in Table E1 in this article’s Online Repository at www.jacionline.org.

RESULTS

Nasal polyp explant T cells are of an effector memory phenotype

The majority of donor-matched polyp- and peripheral blood–derived CD4\(^+\) and CD8\(^+\) T cells were determined to be αβ T cells. γδ T cells formed a minor proportion of the T-cell population (see Fig E1 and Table E2 in this article’s Online Repository at www.jacionline.org). After short-term culture, both polyp and blood populations expressed high levels of CD45RO, which is consistent with a memory phenotype after restimulation. The majority of T cells in polyp cultures expressed significantly less CD62 ligand and CCR7 compared with blood T cells and displayed higher expression of CD49a, an integrin expressed by tissue-resident memory cells, suggesting that nasal polyp–derived T cells were predominately of an effector memory phenotype.22,23

T_{H}17 and T_{H}2 cytokine profiles are detected in nasal polyps

Intracellular cytokine staining was performed on CD4\(^+\) T cells expanded from polyp explants and peripheral blood in parallel to establish the T_{H}1 cell cytokine profile. CD4\(^+\) T cells derived from polyps expressed significantly higher percentages of IL-17\(^+\) and IL-22\(^+\) cells together with T_{H}2 cytokine (IL-5, IL-9, and IL-13)–producing cells (Fig 1, A and B), all of which showed negligible expression in expanded peripheral blood CD4\(^+\) T cells from the same donors. In addition, coexpression of IL-17 with IL-22 and IFN-γ was detected (see Fig E2 in this article’s Online Repository at www.jacionline.org). A significantly higher percentage of polyp T cells produced the proinflammatory cytokine TNF-α, although IFN-γ expression was equivalent in CD4\(^+\) T cells from both sources.

T_{H}2 cytokine production is specific to CRSwNP, but T_{H}17 cytokines are produced by nasal T cells from normal and inflamed tissue

We next examined whether this cytokine expression profile in polyp explants was disease or tissue specific. Therefore T-cell phenotypes were compared with those from nasal mucosal biopsy specimens from healthy volunteers. IL-17 was produced by a comparable percentage of T cells derived from healthy nasal and nasal polyp explants (Fig 1, C) and confirmed at the protein level in cell-culture supernatants. Minimal IL-13\(^+\) cells were observed in the healthy nasal mucosa (Fig 1, C). Although IL-4 expression was not examined by using flow cytometry, significantly increased IL-4 levels, in addition to IL-5 and IL-13 levels, were detected in the supernatants of polyp explant cultures compared with those seen in healthy nasal mucosa explants (see Fig E3 in this article’s Online Repository at www.jacionline.org).

IL-17RB is expressed by in vitro T_{H}2-polarized but not T_{H}1-polarized cells

We next examined whether T-cell expression of IL-17RB is associated with T_{H}2 cells and the promotion of T_{H}2 responses.9,11 We sought to examine IL-17RB expression in homogenous human T_{H}1/T_{H}2 CD4\(^+\) populations differentiated from naive peripheral blood T cells, as previously described.23 Differentiated cells were highly polarized toward a T_{H}1 (IFN-γ\(^+\), T-box transcription factor [T-bet]\(^+\), and IL-12 receptor β2 [IL-12Rβ2]\(^+\)) or T_{H}2 (IL-4\(^+\), IL-5\(^+\), GATA-3\(^+\), and chemoattractant receptor-homologous molecule expressed on T_{H}2 cells [CRTH2]\(^+\)) phenotype, and a significant increase in IL17RB gene expression was observed in T_{H}2 versus T_{H}1 cell lines (Fig 2, A). IL-17RB expression increased with time in in vitro T_{H}2-polarized T-cell cultures only (Fig 2, B and C), which followed similar kinetics to type 2 cytokine production (data not shown). Furthermore, IL-17RB expression was correlated with IL-13 expression in T_{H}2 cell cultures (Fig 2, D). Together, these data suggest IL-17RB to be a robust marker of human T_{H}2 cells.

IL-17RB\(^+\) cells are a distinct T_{H}2 cell population present in nasal polyps

We next examined whether T-cell expression of IL-17RB is also a feature of target organ tissue CD4\(^+\) cells in eosinophilic polyps. A substantial proportion of polyp CD4\(^+\) T cells expressed
IL-17RB, whereas negligible IL-17RB expression was observed in matched peripheral blood or healthy nasal mucosal specimens (Fig 3). Coexpression of IL-17RB with the Th2-associated prostaglandin D2 receptor CRTH2 (Fig 3, B) was also detected, but IL-17RB expression was negligible on Th17-associated CCR6+ or Th1-associated CXCR3+ cells. Consistent with the high frequency of IL-17+ cells, an abundance of CCR6-expressing cells was also found in both healthy nasal mucosa and polyp explants (Fig 3, A and C). CD8+ cells showed similar surface molecule expression patterns to CD4+ cells, although lower percentages of cells positive for the surface molecules examined were generally observed (see Fig E4 in this article’s Online Repository at www.jacionline.org).

Although short-term cultures were used to generate sufficient cell numbers for experimentation, flow cytometric analysis of polyp tissue T cells immediately after collagenase digestion confirmed IL-17RB expression was not a culture artifact (see Fig E5 in this article’s Online Repository at www.jacionline.org). Furthermore, percentages of Th2 and IL-17–producing cells were increased in digested polyp- versus blood-derived cells, which is consistent with findings from explant cultures.

**IL-17RB+CD4+ cells derived from nasal polyp explants represent in vivo differentiated memory Th2 cells**

To further address the phenotype of IL-17RB+CD4+ cells from nasal polyp explants, explant-derived cells were sorted by means of fluorescence-activated cell sorting for IL-17RB+CD4+ expression after short-term expansion. IL-17RB+CD4+ cells were also sorted for comparison. Th2-associated genes, including **IL4**, IL5, IL9, IL13, and GATA3, showed considerable upregulation in activated IL-17RB+CD4+ versus activated IL-17RB-CD4+ cells (Fig 4, A), with differential expression for a majority of these genes reaching statistical significance (see Table E3 in this article’s Online Repository at www.jacionline.org). Furthermore, correspondingly lower expression of Th1-associated genes, including **IFNG**, LTA, and CCL3, was

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**FIG 1.** Differential expression of Th2/Th17 cytokines by polyp- and normal nasal mucosa-derived CD4+ cells. A, Representative staining on paired CD4+ blood and polyp cells. B, Percentages of polyp versus blood CD4+ cells producing cytokines (Wilcoxon matched-pairs signed-rank test, n = 6-18). C, IL-17 and IL-13 histograms for CD4+ biopsy and polyp cells (n = 3). Each row indicates an individual subject. Gray, Resting; red, activated. NM bx, Healthy nasal mucosa biopsy specimen. *P < .05, **P < .01, and ***P < .001.
identified. Moreover, the genes for promelanin-concentrating hormone and prostaglandin-endoperoxide synthase 2 were preferentially expressed in IL-17RB\(^1\) cells in line with data from \textit{in vitro} polarized TH2 cultures (Fig 2, A) and previously published findings.\textsuperscript{26,27} Microarray-based gene expression results were confirmed by using quantitative RT-PCR analysis (see Fig E6 in this article’s Online Repository at www.jacionline.org).

**IL-17RB\(^+\) cells predominantly and selectively produce TH2 cytokines**

We next examined whether IL-17RB expression colocalized with TH2 cytokines in nasal polyp explant T-cell cultures. Fig 4, B, shows the percentage of cells expressing IL-17RB when segregated by cytokine production. IL-5-producing, IL-13-producing, and IL-5/IL-13–coproducing cells were approximately 5 times more likely to coexpress IL-17RB compared with TH1/TH17 cytokine–producing cells (ie, 52% of IL-5–producing cells were IL-17RB\(^1\), whereas 8% of IFN-\(\gamma\)–producing cells were IL-17RB\(^-\)). In addition, IL-17RB\(^-\) cells were accountable for the majority of IL-5/IL-13–coproducing T cells (59%; Fig 4, B). Notably, percentages of IFN-\(\gamma\)– and IL-17–producing cells were significantly lower in the IL-17RB\(^-\) population compared with those in the IL-17RB\(^+\) population. A similar trend was observed for TNF-\(\alpha\) and IL-22.
The IL-33 receptor ST2 is also expressed by IL-17RB⁺ cells

T cells from nasal polyp explants were next examined for mRNA expression of the IL-33 receptor ST2. Expression of transmembrane and soluble isoforms (sST2) of ST2, as measured by using quantitative RT-PCR, were increased in activated IL-17RB⁺ cells compared with IL-17RB⁻ cells (Fig 4, C), suggesting that IL-17RB⁺ T cells might also be IL-33 responsive.

IL-17RB and ST2 are functional and potentiate Th2 cytokine production by nasal polyp T cells

Th2 cytokine expression was determined by means of flow cytometry in polyp explants cultured in the presence of recombinant human IL-25 or IL-33 to evaluate whether IL-17RB and ST2 expressed on polyp T cells were functional (Fig 4, D). Recombinant cytokines were added either on the day of explantation or day 7 after stimulation. Analysis was performed 7 days later. Addition of IL-25 induced a mean
FIG 4. Polyp-derived CD4+ IL-17RB+ cells have a T H2 profile and respond to IL-25 and IL-33. A, Heat map of 42 differentially expressed genes in polyp IL-17RB+ versus IL-17RB- cells (n = 3). B, Cytokine-producing cells coexpressing IL-17RB (n = 5-13). C, Transmembrane and soluble ST2 mRNA expression (n = 4; Mann-Whitney test). D, Representative staining for polyp CD4+ cells with or without IL-25/IL-33. E, IL-5/IL-13+ cells coexpressing IL-17RB with or without IL-25/IL-33. Open symbols, Day 0 addition (n = 5); solid symbols, day 7 addition (n = 8). The Wilcoxon test was used. *P < .05, **P < .01, and ***P < .001.
A 1.5-fold increase in the percentage of IL-17RB<sup>+</sup>IL-5<sup>+</sup>CD4<sup>+</sup> T cells and a 1.4-fold increase in the percentage of IL-17RB<sup>+</sup>IL-13<sup>+</sup>CD4<sup>+</sup> T cells in explant cultures (Fig 4, E). Addition of IL-33 had a comparable effect to IL-25, with a mean 1.4-fold increase in the percentage of IL-17RB<sup>+</sup>IL-5<sup>+</sup>CD4<sup>+</sup> T cells and a 1.2-fold increase in the percentage of IL-17RB<sup>+</sup>IL-13<sup>+</sup>CD4<sup>+</sup> T cells. Time of recombinant cytokine addition had no effect on the response of IL-17RB<sup>+</sup>ST2<sup>+</sup> cells. Addition of IL-25 to polyp-derived T cells at day 7 after stimulation was still associated with a significant increase in IL-17RB<sup>+</sup>IL-5<sup>+</sup> and IL-17RB<sup>+</sup>IL-13<sup>+</sup> CD4<sup>+</sup> T-cell counts (data not shown).

**Nasal polyp epithelium and eosinophils express IL-25**

Cellular sources of IL-25 within nasal polyp tissue were investigated by using immunohistochemistry. Immunostaining...
CD4<sup>+</sup> T-cell populations were also sorted from paired nasal explant and peripheral blood cultures for transcriptome profiling (see Fig E9 in this article’s Online Repository at www.jacionline.org). Preferential expression of Th<sub>17</sub>-associated genes was observed in activated nasal CD4<sup>+</sup> cells. Of note, the 5 genes that were most highly overexpressed in nasal versus peripheral blood CD4<sup>+</sup> T cells were all Th<sub>17</sub> associated: IL17F, IL22, CCL20, KLRB1 (CD161), and IL1R1 (see Table E4 in this article’s Online Repository at www.jacionline.org). Significant overexpression of the gene for the DNA-sensing inflammasome component absent in melanoma 2 (AIM2) was also observed in nasal mucosal T cells. Analysis of additional selected Th<sub>17</sub>-associated genes further revealed preferential expression of IL17A, IL21, IL23, IL23R, aryl hydrocarbon receptor (AHR), and RORC (Fig 5, C) by activated nasal CD4<sup>+</sup> cells. These data suggest that the healthy, homeostatic T-cell response in the nasal mucosa is associated with a strong Th<sub>17</sub> signature compared with the periphery.

**T<sub>17</sub> cells in nasal polyps have a potentially protective immune homeostatic role associated with reduced IFN-γ coexpression**

Th<sub>17</sub> cells can coproduce IFN-γ and IL-22. IL-17/IFN-γ double-positive cells have been associated with a pathogenic proinflammatory phenotype, whereas IL-17/IL-22 double-positive cells have been reported to have protective properties by inducing expression of antimicrobial peptides. Lower coexpression of IFN-γ by IL-17<sup>+</sup> T cells from polyp explants was found compared with that seen in blood-derived cells (Fig 5, D). No difference was observed in the percentages of IL-17<sup>+</sup> cells coexpressing IL-22.

**DISCUSSION**

Recently, ILC2s have been identified in nasal polyps, and the presence of Th<sub>17</sub>2 cells in white patients with CRSwNP has been demonstrated. However, the local T-cell response itself remains relatively uncharacterized. Here, using a short-term explant model to expand and study T cells from surgical specimens, we report a significant population of IL-17RB–expressing Th<sub>17</sub>2 cells in nasal polyps with a gene expression profile akin to that of highly polarized Th<sub>17</sub>2 cells. Approximately 50% of IL-5<sup>+</sup>IL-13<sup>+</sup> polyp-derived CD4<sup>+</sup> T cells expressed IL-17RB, suggesting IL-17RB<sup>+</sup> cells represent a subset of Th<sub>17</sub>2 cells.

We demonstrate that IL-17RB<sup>+</sup>CD4<sup>+</sup> cells from polyps express mRNA for both transmembrane and soluble isoforms of ST2 on activation and respond to both IL-25 and IL-33 with augmented IL-5 and IL-13 production. ST2 expression by

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**TABLE I. TCR Vβ repertoire analysis of IL-17RB<sup>+</sup> cells**

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>HKP020</th>
<th>HKP023</th>
<th>HKP026</th>
<th>HKP036</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell population</td>
<td>IL-17RB&lt;sup&gt;+&lt;/sup&gt;</td>
<td>IL-17RB&lt;sup&gt;+&lt;/sup&gt;</td>
<td>IL-17RB&lt;sup&gt;+&lt;/sup&gt;</td>
<td>IL-17RB&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total clones (productive)</td>
<td>4,871</td>
<td>1,146</td>
<td>969</td>
<td>1,381</td>
</tr>
<tr>
<td>Unique clones (no.)</td>
<td>33</td>
<td>91</td>
<td>28</td>
<td>97</td>
</tr>
<tr>
<td>Shared clones</td>
<td>0</td>
<td>1</td>
<td>25</td>
<td>11</td>
</tr>
<tr>
<td>Common clones</td>
<td>4,871</td>
<td>1,146</td>
<td>969</td>
<td>3,801</td>
</tr>
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</table>

Numbers of unique TCR clones present in sorted polyp-derived CD4<sup>+</sup>IL-17RB<sup>+</sup> and CD4<sup>+</sup>IL-17RB<sup>−</sup> populations analyzed by using the immunoSEQ assay are shown (n = 4 separate donors). Amino acid sequences represent CDR3 regions of 2 common clones identified within the IL-17RB<sup>+</sup> population of at least 3 of the 4 donors.
in vitro differentiated human peripheral blood T\(_{H2}\) cells has been described,\(^{11}\) and both IL-25 and IL-33 receptors are expressed and functional on human and murine ILC2s.\(^{14,18,19,34}\) However, the role of these pathways in human mucosal T-cell responses has not been examined. These data now establish a direct link of IL-25, IL-33, and T\(_{H2}\) cells in human disease and suggest that IL-17RB\(^{\ast}\)T\(_{H2}\) cells likely contribute to CRSwNP pathogenesis through the IL-25/IL-33 axis. We found increased IL-25 immunostaining in polyops, localizing to eosinophils and epithelial cells, which is consistent with previously published reports.\(^{11-13}\) and in agreement with the increased IL-25 mRNA expression seen in patients with eosinophilic CRSwNP reported by Iinuma et al.\(^{35}\) In addition, constitutive expression of IL-33 was detected in epithelium and endothelium of both healthy and polyp nasal tissue, which is in line with mRNA expression studies.\(^{31,36-37}\) These findings suggest that these cells might be endogenous sources of IL-25 and IL-33 in nasal polyops. However, the mechanism of IL-33 release is yet to be elucidated.

Colonization with \(S\) \(aureus\) in nasal polyposis is associated with high levels of IgE,\(^{38}\) and \(S\) \(aureus\) superantigens, such as staphylococcal enterotoxin B, can drive the T\(_{H2}\)-type response in eosinophilic polyops.\(^{39,40}\) Here we demonstrate that nonrandom segregation of unique CDR3 clones occurs with 2 CDR3 clones present in the IL-17RB\(^{\ast}\) population in 3 of 4 samples analyzed. Although these results require confirmation in a larger study, they are suggestive of oligoclonality in the TCR \(\beta\) repertoire within the IL-17RB\(^{\ast}\) population. The \(V\) \(\beta\) 3 family is preferentially expressed by cutaneous lymphocyte–associated antigen–positive cells responding to the superantigen staphylococcal enterotoxin A in patients with atopic dermatitis and induced by the toxic shock syndrome toxin 1 superantigen, respectively.\(^{30,41}\) Although speculative, this raises the possibility that local IL-17RB\(^{\ast}\) T\(_{H2}\) cells in patients with CRSwNP undergo antigen-specific expansion in response to common but as yet undefined epitopes with an additional non–antigen-specific component mediated by superantigens.

We demonstrate that the T\(_{H}\) response in the healthy nasal mucosa is heavily biased toward T\(_{H17}\) responses compared with the periphery. Although we did not examine the relative dominance of the T\(_{H17}\) phenotype compared with other T\(_{H}\) cell phenotypes, we observed that the 5 most overexpressed genes in normal nasal mucosal T cells compared with peripheral blood T cells were all strongly T\(_{H17}\) associated. We propose that a significant population of nasal T cells differentiate into T\(_{H17}\) cells in vivo, with the propensity to produce IL-17 and related cytokines should they become activated in vivo.\(^{42}\) We hypothesize that this T\(_{H17}\) phenotype represents a key part of the nasal mucosal host defense response. Priming of autologous monocytes with pathogens, such as \(S\) \(aureus\) and \(Candida\) \(albicans\), induces T\(_{H17}\) responses in naive human T cells,\(^{43}\) suggesting that chronic exposure of the nasal mucosa to nonpathogenic and pathogenic microorganisms, such as \(Staphylococcus\) \(epidermidis\), \(S\) \(aureus\), and corynebacteria, could be the mechanism behind this response.

Within the T cells derived from healthy nasal tissue, we found that transcripts encoding IL-17F and IL-22 were the most highly upregulated. IL-17A and IL-17F are homologous molecules sharing 55% amino acid identity.\(^{24}\) Both induce expression of numerous chemokines, cytokines, and adhesion molecules, although IL-17A is more effective at inducing inflammatory gene expression.\(^{28,45-47}\) IL-17F is expressed by a wide variety of tissue, including in the lung,\(^{47,48}\) and can also potentiate IL-22–induced expression of antimicrobial peptides.\(^{28}\) Thus the presence of T cells able to produce IL-17F and IL-22 is suggestive of a function for these cells in nasal mucosal immune homeostasis. Microarray analysis also identified overexpression of AIM2 mRNA in nasal explant CD4\(^{\ast}\) T cells. The AIM2 inflammasome is activated by intracellular pathogens, leading to caspase-1–dependent IL-1\(\beta\) secretion.\(^{39,40}\) Further studies will be needed to examine whether this innate pathway is functional in nasal T\(_{H17}\) cells.

Our study has some limitations. For example, memory T cells were phenotyped after short-term expansion. Therefore it is possible that a proportion of CD45RA\(^{\ast}\) peripheral blood T cells acquired CD45RO expression during culture and might have retained some of their baseline CD62 ligand and CCR7 expression characteristics. In addition, IL-17RB–expressing T cells were mainly characterized after in vitro expansion. Analysis of freshly isolated IL-17RB\(^{\ast}\) T cells from digested polyops was hampered by low cell numbers and lower IL-17RB expression, possibly reflecting the effects of enzymatic digestion, and therefore data were obtained from fewer cases. The IL-17RB mAb used in these studies did not prove suitable for immunohistochemical analysis, and further studies will be needed for in vivo expression analysis of IL-17RB. Finally, the effect of IL-25 and IL-33 stimulation on T\(_{H2}\) responses in vitro was modest, although the concentrations of recombinant IL-25 and IL-33 used in this study were similar to previously published reports.\(^{12,35}\)

Nonetheless, our data establish a biological link between IL-17RB expression and responsiveness to IL-25 in T\(_{H2}\) cells derived from polyops. Further optimized culture studies will be needed to characterize this response fully. Although 2 recent studies have reported the existence of IL-17RB\(^{\ast}\) cells in patients with CRSwNP,\(^{15,51}\) our findings represent the first direct colocalization of IL-17RB with T\(_{H2}\) cells.\(^{35}\)

In conclusion, we identify functional IL-17RB as a marker of local T\(_{H2}\) cells present in chronically inflamed nasal polyop tissue from patients with CRSwNP. Coexpression of ST2 by these cells, in addition to ILC2s, indicates that the IL-25/IL-17RB and IL-33/ST2 pathways could be attractive therapeutic targets. In addition, these data also provide novel insights into mechanisms of nasal immune homeostasis and suggest a role for T\(_{H17}\) cells in this process.

We thank Drs Mikila Jacobson and Cailong Fang for assistance with immunohistochemistry and the staff of the BRC Flow Core Facility and Genomics Facility at Guy’s and St Thomas’ NHS Trust for assistance with cell sorting and microarrays. We also thank Dr Paul Lavender for assistance with microarray studies and Professor Andrew Wardlaw for critical reading of the manuscript.
Key messages

- For the first time, we show that local IL-17RB^+ T^h2 cells in nasal polyps coexpress ST2 and that both receptors function, in response to their respective ligands IL-25 and IL-33, to potentiate T^h2 cytokine production.
- IL-17RB^+ T^h2 cells express common TCR clones, which is suggestive of recognition, clonal expansion, or both of T cells driven by a common antigen or antigens in patients with CRSwNP.
- T^h17 cells are present in the nasal mucosa as part of the normal homeostatic immune response.

REFERENCES


