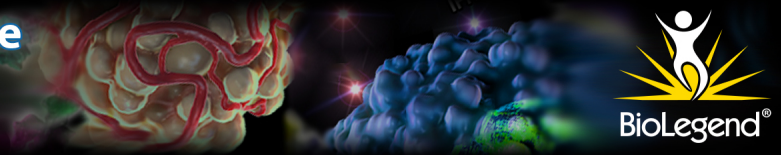


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A Functional IL-13 Receptor Is Expressed on Polarized Murine CD4⁺ Th17 Cells and IL-13 Signaling Attenuates Th17 Cytokine Production¹

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IL-17A is produced from Th17 cells, and is involved in many autoimmune and inflammatory diseases. IL-13R has not previously been reported to be functionally expressed on T cells; however, we found that purified BALB/c CD4⁺ cells polarized to Th17 with TGF- β , IL-6, and IL-23 have increased mRNA and protein expression of IL-13R α 1 and mRNA expression of IL-4R α compared with Th0, Th1, or Th2 polarized cells. The addition of IL-13 at Th17 polarization negatively regulated IL-17A and IL-21 expression, and reduced the number of CD4⁺ T cells producing IL-17A. Further, adding IL-13 at the time of Th17 cell restimulation attenuated IL-17A expression. CD4⁺ Th17 polarized cells from IL-4 knockout (KO) mice also had IL-13-induced inhibition of IL-17A production, but this was not observed in IL-4R KO and STAT6 KO mice. Addition of IL-13 at polarization increased IL-13R expression in wild-type Th17 cells. Further, IL-13 administration during Th17 polarization down-regulated retinoic acid-related- γ T, the transcription required for Th17 development; increased STAT6 phosphorylation, and up-regulated GATA3, the transcription factor activated during the development of Th2 cells. This IL-13-mediated effect was specific to Th17 cells as IL-13 neither decreased IFN- γ expression by Th1 cells nor affected Th2 cell production of IL-4. Collectively, we have shown that Th17 cells express a functional IL-13R and that IL-13 negatively regulates IL-17A and IL-21 production by decreasing retinoic acid-related- γ T expression and while increasing phosphorylation of STAT6 and GATA3 expression. Therefore, therapeutic intervention inhibiting IL-13 production could have adverse consequences by up-regulating Th17 inflammation in certain disease states. *The Journal of Immunology*, 2009, 182: 5317–5321.

Th17 cells are a recently described class of CD4⁺ T cells that have a distinct lineage from Th1 and Th2 cells (1, 2). These cells are known to be involved in autoimmune and inflammatory disorders, such as the experimental autoimmune encephalitis (EAE)³ model of multiple sclerosis and rheumatoid arthritis (reviewed in Ref. 3). Th17 cells are also critical for the clearance of extracellular pathogens, such as the Gram-negative bacteria *Klebsiella pneumoniae* (4) or *Mycoplasma pulmonis* (5). Differentiation of Th17 cells requires the cytokines TGF- β and IL-6 or IL-21 in the mouse, (6, 7) and IL-6 and IL-1 β in the humans (8). Until recently, it was also believed that IL-23, a member of the IL-12 cytokine family, was also required for Th17 differentiation. However, studies using IL-23 knockout (KO) mice

have shown CD4⁺ cells are capable of differentiating into Th17 cells in the absence of IL-23, but that IL-23 is required for Th17 proliferation and sustainability (8, 9). Th17 cell differentiation and proliferation is negatively regulated by the Th2 cytokine IL-4 and the Th1 cytokine IFN- γ (1). Polarizing Th17 cells from CD4⁺ splenocytes cultured in the presence of anti-IFN- γ and anti-IL-4 increases IL-17A production from Th17 cells (1).

Recently, in an in vivo model of EAE, Kleinscheck and colleagues (9) reported that exogenous IL-25 administration induced the production of the Th2 cytokine IL-13, which then negatively regulated Th17 responses. IL-13 effects intracellular signaling via the IL-13R, which is composed of the heterodimer IL-13R α 1 and IL-4R α . Although T cells have been shown to express IL-4R α , IL-13R α 1 has never been described to be present on murine CD4⁺ T lymphocytes (9, 10). Therefore, Kleinscheck and colleagues (9) speculated that in the EAE model, IL-13 might act by inhibiting dendritic cell function, and this was supported by their observation that IL-13 blocked dendritic cell production of the Th17-promoting factors IL-1 β , IL-6, and IL-23. However, an alternative hypothesis is that CD4⁺ Th17 cells, in contrast to Th1 and Th2 cells, express IL-13R and that IL-13 can negatively regulate CD4⁺ Th17 cytokine expression directly through this receptor. We tested this hypothesis by polarizing purified naive CD4⁺ cells in the presence of cytokines that promote differentiation to Th17 cells, and show for the first time that Th17 cells express a functional IL-13R, and IL-13 inhibits the total number of CD4⁺ Th17 cells producing IL-17A in WT BALB/c mice. Further, we show that IL-13 decreases polarized Th17 cell production of the Th17 cytokine IL-21 and a transcription factor that is critical for Th17 development, retinoic acid-related (ROR)- γ T. IL-13 also increases STAT6 phosphorylation and GATA3 expression in Th17-polarized T cells.

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³ Abbreviations used in this paper: EAE, experimental autoimmune encephalitis; KO, knockout; ROR, retinoic acid-related.

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Collectively, these data demonstrate that IL-13R α 1 is expressed on Th17 cells and that the IL-13R is functional. These results suggest that inhibiting IL-13 expression or function may up-regulate Th17 inflammation in certain disease states.

Materials and Methods

Mice

Pathogen-free 8- to 10-wk-old female BALB/c mice were purchased from Charles River Laboratories. IL-4 KO, IL-4R α KO, and STAT6 KO BALB/c mice were purchased from The Jackson Laboratory, and breeding colonies were established. In caring for the animals, the investigators adhered to the revised 1996 Guide for the Care and Use of Laboratory Animals prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council.

T cell isolation and Th17 cell polarization, activation, and restimulation

CD4⁺ T cells were purified from the spleens of mice as previously described (11). T cells were activated with anti-CD3 (5 μ g/ml) and anti-CD28 (1 μ g/ml) (BD Biosciences) in 96-well plates for 4 days. T cells were differentiated into Th17 cells by adding rmIL-23 (10 ng/ml), rhTGF- β (5 ng/ml), rmIL-6 (20 ng/ml), anti-IFN- γ (10 μ g/ml), and anti-IL-4 (10 μ g/ml). Th1 and Th2 cells were differentiated as previously described (1). In select cultures, rmIL-4 (1–10 ng/ml) or rmIL-13 (1–10 ng/ml) was also added. In other experiments involving Th17 cells, anti-IL-13 (0–10 μ g/ml) or goat IgG isotype control was used instead of anti-IL-4. To stimulate effector cytokine production, the cells were restimulated with anti-CD3 for 24 h in the presence of rmIL-4 or rmIL-13 (0 ng/ml to 10 ng/ml). All Abs and rmIL-23, rmIL-4, rmIL-13, and rmIL-12 were purchased from R&D Systems. rmIL-6 and rmTGF- β were purchased from PeproTech.

Quantitative PCR

A two-step real-time PCR assay using SYBR green mix (Bio-Rad) was used to detect IL-13R α 1, IL-4R α , common γ -chain, ROR γ T, and GATA3 as previously described (11). Primer sequences were as follows: IL-13R α 1: F 5' TTCCAGTCTTTGTCGCAGTG, R 5' CAGGATCAGGAATTG GAGGA 3'; IL-4R α : F 5' GGTGGAGTCCAGTCCACACT 3'; R 5' CT GTGATCAAGCATCGCTGT 3'; common γ -chain: F 5' TGCTAGTGT GGATGAGCTG 3'; R 5' CAGGCTGGCTCCATTTACTC 3'; ROR γ T: F 5' GCG GCT TTC AGG CTT CAT GGA G 3'; R 5' R GGG CGC TGA GGA AGT GGG AAA A 3'; GATA3: F 5' GGCGAGATGGTAC CGGGCACTA 3'; R 5' CCCCATAGCGTTCCTCCTCCAGA 3'.

ELISA

Protein levels of cytokines from cell culture supernatant were measured by commercially available Duoset or Quantikine ELISA kits (R&D Systems) following the manufacturer's instructions.

Flow cytometry and intracellular staining

Four days after polarization, Th0 and Th17 CD4⁺ T cells were harvested and restimulated with PMA and ionomycin for 5 h in the presence of Golgi-stop (BD Biosciences) at 37°C, 5% CO₂. Cells were blocked with anti-FCR Ab 2.4G2 (BD Biosciences) and surface stained with PE-Cy7 conjugated anti-CD4 (BD Biosciences). For intracellular staining, cells were permeabilized with cytofix/cytoperm (BD Biosciences), washed thoroughly, and stained with PE-conjugated anti-IL-17A (BD Biosciences). Cells were analyzed using a LSR II flow cytometer (BD Biosciences), and data were analyzed using Flow Jo 7.2 software (Tree Star).

Immunoblotting

Cells were lysed using radioimmunoprecipitation assay buffer and total protein was extracted and resolved by 4–20% SDS-PAGE gel, transferred to a nitrocellulose membrane (Bio-Rad), and probed with phospho-STAT6 (Cell Signaling Technology), total STAT6 (Cell Signaling Technology), IL-13R α 1 (Santa Cruz Biotechnology), normal goat IgG isotype control (Santa Cruz Biotechnology), or actin (Santa Cruz Biotechnology). Signals were amplified and visualized with HRP-conjugated secondary Ab (Bio-Rad) and chemiluminescence solution (Pierce).

Statistical analyses

Data are presented as mean \pm SEM. Data were analyzed with ANOVA followed by the Tukey post hoc test using GraphPad Prism 4 (GraphPad Software) with values being considered significant when $p < 0.05$.

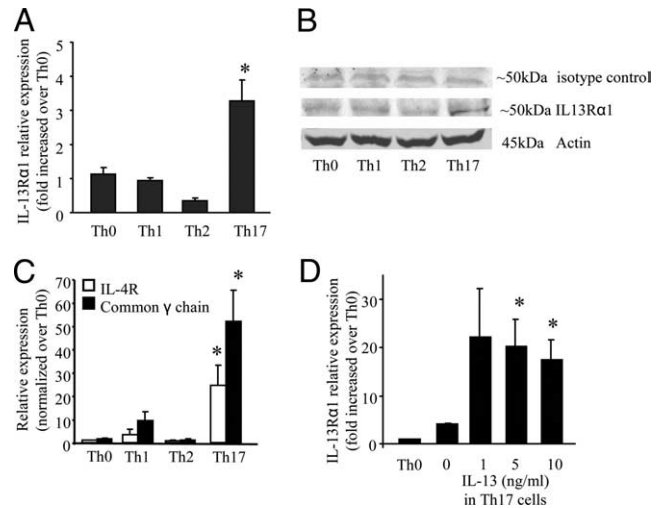


FIGURE 1. IL-13R α 1 expression is increased in Th17 polarized T cells. Total RNA or protein was isolated from naive (Th0), Th1, Th2, or Th17 cells 4 days after polarization. **A**, Real-time PCR was performed for IL-13R α 1. **B**, Western blot for IL-13R α 1 (blot is representative of three individual blots). **C**, Real-time PCR was performed for IL-4R α and the common γ -chain mRNA expression. **D**, IL-13R α 1 mRNA expression in Th17 cells polarized in the presence of IL-13. For all real-time PCR experiments, data are normalized to GAPDH and relative expression is compared with Th0 cells. Data are compiled from three experiments for **A**, **C**, and **D**; $n = 5$; *, $p < 0.05$ compared with Th0 cells in **A** and **C** and compared with Th17 cells (no IL-13) in **D**, ANOVA.

Results

IL-13R expression is increased on Th17 polarized cells, but not Th1 or Th2 cells

IL-13R α 1 has been reported to not be expressed on the surface of T cells (9, 10). As IL-13 negatively regulated Th17 responses in the EAE model (9), we hypothesized that Th17 cells expressed IL-13R α 1. Cells were polarized to Th1, Th2, or Th17 cells and total RNA was collected 4 days after polarization and examined for IL-13R α 1 expression by real-time PCR. Th17 cells had a significant increase in IL-13R α 1 relative expression when compared with naive T cells (Th0), Th1, and Th2 cells (Fig. 1A). Th17 cells also showed an increase in IL-13R α 1 protein expression (Fig. 1B) that was not seen in Th0, Th1, or Th2 cells. Th17 cells also had a significant increase in the mRNA expression of IL-4R α and the common- γ -chain, the heterodimeric components of the IL-4 receptor (Fig. 1C). The full-length decoy soluble receptor, IL13R α 2, was undetectable in Th17 cells by real-time PCR (data not shown). Finally, increasing concentrations of IL-13 in Th17 polarized cells caused a significant increase in IL-13R α 1 mRNA expression (Fig. 1D).

IL-13 attenuates IL-17A production from Th17 differentiated cells

Based on the increased relative expression of IL-13R α 1 on CD4⁺ purified Th17 polarized cells, we hypothesized that IL-13 would directly decrease IL-17A production by these cells. T cells were polarized to Th17 cells in the presence of IL-13 or IL-4 and IL-17A protein production was measured in cultured supernatants 4 days after polarization. As previously reported, IL-4 (10 ng/ml) attenuated IL-17A protein production (1); however, IL-13 also significantly attenuated IL-17A protein production (Fig. 2A). Similar to IL-17A, protein expression of IL-21, an autocrine cytokine produced by Th17 cells, was also attenuated in the presence of IL-4 or IL-13 (Fig. 2B).

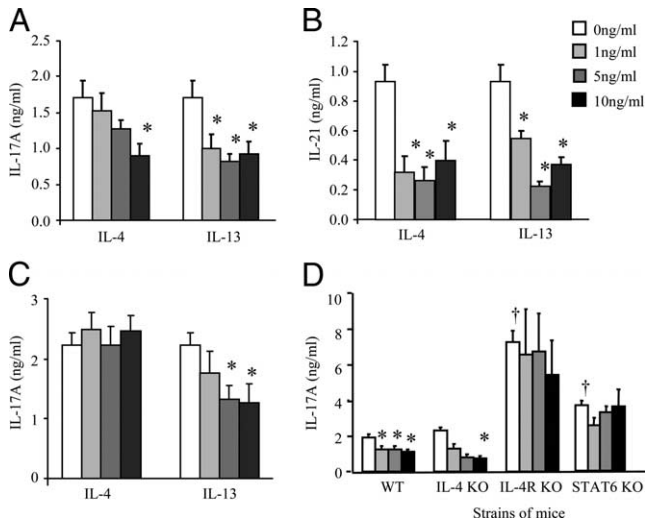
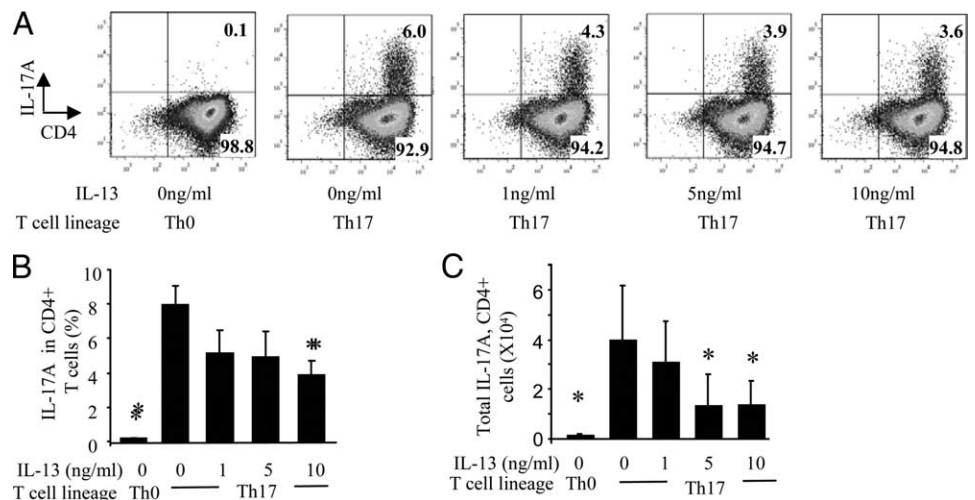


FIGURE 2. IL-13 attenuates IL-17A production from Th17 differentiated T cells in WT and IL-4 KO mice but not IL-4R KO and STAT6 KO mice. IL-4 or IL-13 (0–10 ng/ml) was added at the time of Th17 polarization and cultured supernatants were collected 4 days after polarization, and examined for IL-17A (A) and IL-21 (B) protein production. C, T cells were polarized to Th17 cells and restimulated with plate-bound anti-CD3 in the presence of IL-4 or IL-13 (0–10 ng/ml) and IL-17A protein production was measured 24 h after restimulation. D, WT, IL-4 KO, IL-4R KO, and STAT6 KO CD4⁺ T cells were polarized to Th17 cells in the presence of IL-13 and IL-17A protein production was measured 4 days after polarization. Data are compiled from three separate experiments; *n* = 6–14; *, *p* < 0.05 compared with Th17 cells (no IL-13) from respective strain of mice; †, *p* < 0.05 compared with Th17 cells (no IL-13) from WT mice, ANOVA.

CD4⁺ cells were also polarized to Th17 cells (in the absence of IL-4 or IL-13) for 4 days and then restimulated with anti-CD3 in the presence of IL-4 or IL-13. Restimulation of Th17 in the presence of IL-4 has been previously shown to have no effect on IL-17A protein production (1), and we found the same result (Fig. 2C). However, the higher concentrations of IL-13 (5–10 ng/ml) were able to significantly inhibit IL-17A protein production (Fig. 2C). Taken together, these data suggest that IL-13, as well as the previously reported IL-4, negatively regulated IL-17A protein production from Th17 cells at the time of polarization. In contrast to IL-4, IL-13 attenuated IL-17A protein production at restimulation.

FIGURE 3. IL-13 decreases the number of IL-17A-producing CD4⁺ Th17 polarized T cells. T cells were restimulated with PMA and ionomycin in the presence of Golgi-stop and stained with PE-Cy7 conjugated anti-CD4 and PE conjugated anti-IL-17A Abs. A, Dots plots of IL-17A producing T cells in naive and Th17 polarized T cells in the presence of IL-13 (0–10 ng/ml). B, Quantification of the percentage of IL-17A producing CD4 T cells. C, Total number of IL-17A-producing CD4⁺ cells. Dot plots are representative of three independent experiments; *n* = 4–6; *, *p* < 0.05 compared with Th17 cells (no IL-13), ANOVA.



Th17 polarized cells were also cultured from IL-4 KO, IL-4R KO, and STAT6 KO mice. IL-4 KO mice showed an IL-13-dependent attenuation of IL-17A protein production (Fig. 2D). IL-4R KO and STAT6 KO mice had a significant increase in IL-17A protein production compared with WT mice in Th17 polarized cells without IL-13. However, IL-4R KO and STAT6 KO mice did not have an IL-13-mediated decrease in IL-17A protein production (Fig. 2D). These data demonstrate that IL-13 attenuates IL-17A protein expression from Th17 cells in an IL-4R-signaling specific manner.

IL-13 decreases the percentage of CD4⁺ polarized Th17 cells producing IL-17A

Th17 cells were restimulated with PMA and ionomycin in the presence of Golgi-stop and IL-17A intracellular staining was analyzed on CD4⁺ cells within the lymphocyte gate. In the presence of IL-13, there was a decrease in the percentage of Th17 polarized CD4⁺ T cells producing IL-17A (Fig. 3, A and B), and also a decrease in the total number of CD4⁺ T cells producing IL-17A (Fig. 3C). However, neither the mean fluorescent intensity of IL-17A nor the total number of CD4⁺ T cells were altered with the addition of IL-13 (data not shown), suggesting that IL-13 decreases the number of Th17 cells present, but not the amount of IL-17A produced from each Th17 cell.

Anti-IL-13 augments IL-17A production from Th17 differentiated T cells

As previously reported, anti-IL-4 (10 μg/ml) increases Th17 differentiation (1). Because IL-13 added at the time of Th17 polarization inhibited IL-17A protein production, we hypothesized that the administration of an anti-IL-13 Ab at the time of Th17 polarization augments IL-17A protein secretion. Compared with isotype control Ab, anti-IL-13 (10 μg/ml) added during Th17 polarization, in conjunction with the Th17 polarizing cytokines listed above and anti-IFN-γ, increased IL-17A protein production (Fig. 4A).

To determine whether the attenuation of IL-17A was specific to the rIL-13 protein, CD4⁺ T cells were polarized to Th17 cells in the presence of IL-13 and either anti-IL-4 or increasing concentrations of anti-IL-13 (0.1–10 μg/ml). Using anti-IL-13 in combination with IL-13, decreased IL-17A protein production at the lower Ab concentration but not the higher Ab concentration (Fig. 4B). These data suggest that IL-13 specifically attenuates cytokines from Th17 polarized cells.

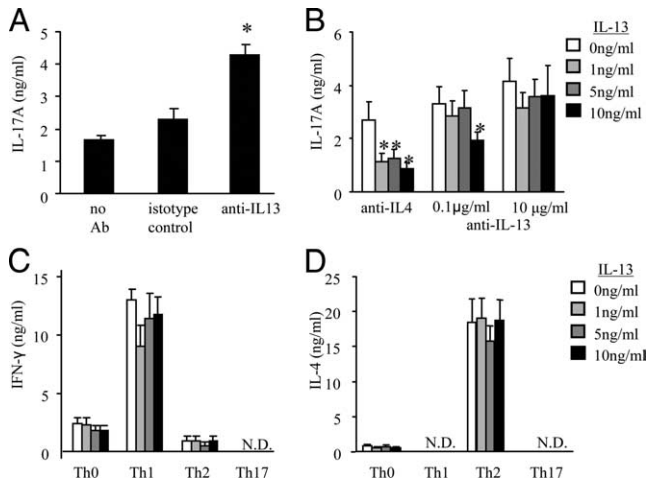


FIGURE 4. IL-13 specifically inhibits IL-17A production from Th17 polarized cells and does not regulate cytokine production in Th1 or Th2 polarized cells. *A* and *B*, Th17 cells were polarized cells using anti-IL-13 (0–10 μ g/ml), anti-IL-4 (10 μ g/ml), isotype control, or no Ab (no anti-IL-13 or isotype control) and examined for IL-17A protein production. *C* and *D*, Th1 or Th2 polarized T cells were measured for IFN- γ and IL-4 protein production, respectively. N.D., cytokine values were below the limit of detection for the ELISA. Data are compiled from three independent experiments. *A*, $n = 6$ –10; *, $p < 0.05$ compared with Th17 cells without anti-IL-13 (no Ab); *B*–*D*, $n = 6$; *, $p < 0.05$ compared with T cells without IL-13 from respective group.

IL-13 regulates cytokine production by Th17 cells, but not Th1 or Th2 cells

To determine whether IL-13 regulated cytokine production from Th1 and Th2 cells, T cells were polarized to Th1, Th2, or Th17 cells in the presence of IL-13. Four days after these polarizations, cultured supernatants were collected and examined for IFN- γ , IL-4, and IL-17A protein. As previously noted in Fig. 2, IL-13 added at the time of polarization attenuated IL-17A protein production in the Th17 cells, and IL-17A was undetectable in Th1 or Th2 polarized cells (data not shown). IFN- γ protein production was only observed in Th1 polarized cells and was not affected by the presence of IL-13 (Fig. 4*C*). IL-4 protein production was only detected in Th2 cells and IL-13 had no effect on IL-4 protein expression (Fig. 4*D*). Th17 polarized cells did not have detectable protein levels of IFN- γ and IL-4. These data show that IL-13 inhibits IL-17A protein production but has no effect on the production of IFN- γ in Th1 cells or IL-4 secretion in Th2 cells. This data correlate with IL-13R α 1 expression occurring on Th17 cells (Fig. 1*A*).

IL-13 decreases ROR- γ T expression while increasing STAT6 phosphorylation and GATA3 expression on Th17-polarized T cells

IL-13 reduced Th17 cytokine production and because ROR- γ T is an essential transcription factor for the development of the Th17 lineage, we hypothesized that IL-13 administered during Th17 polarizing conditions decreases ROR- γ T expression. We found that polarized Th17 CD4⁺ cells exposed to IL-13 have decreased ROR- γ T mRNA expression (Fig. 5*A*), and IL-13-mediated attenuation of Th17 cell cytokine production paralleled this decrease in ROR- γ T mRNA expression.

We further hypothesized that because IL-13R α 1 signaling is mediated through STAT6, IL-13 administration during Th17 polarizing conditions up-regulates phosphorylated STAT6 in this setting. In human carcinoma cell lines, IL-13 binds to the IL-13R α 1

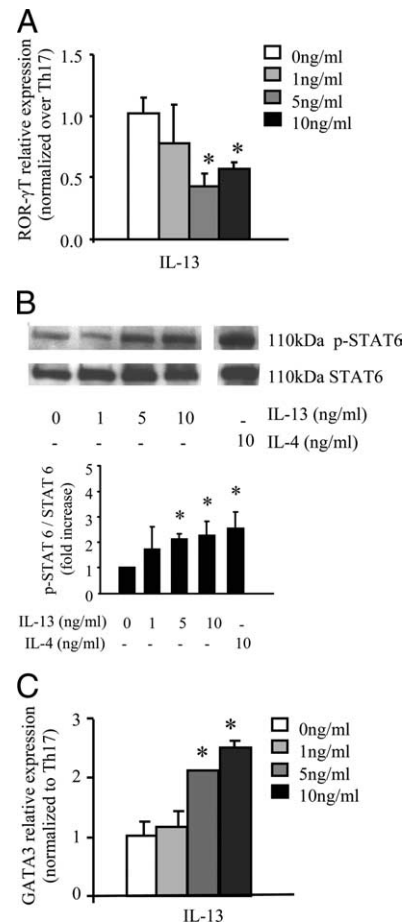


FIGURE 5. IL-13 signaling through IL-13R decreases in ROR- γ T relative expression and increases in STAT6 phosphorylation and GATA3 relative expression. *A*, ROR- γ T mRNA expression with each sample normalized to GAPDH and relative expression compared with Th17 cells polarized without IL-13 present. *B*, Total protein was harvested 3 days after polarization and phospho-STAT6 and total STAT6 levels were determined. Blot is representative of three separate experiments with densitometry is shown graphically below blot. *C*, GATA3 mRNA expression with each sample normalized to GAPDH and relative expression compared with Th17 cells polarized without IL-13 present. Data are compiled from three different experiments; $n = 3$ –5; *, $p < 0.05$ compared with Th17 cells (no IL-13), ANOVA.

portion of the IL-13 heterodimer receptor with intermediate affinity (10) and causes activation of Tyk2, JAK1, and JAK3 leading to the phosphorylation of the transcription factor STAT6 at the Tyr-641 residue (12–14). Polarized T cells were collected 3 days after polarization in the presence of IL-13 and total protein was assayed for STAT6 Tyr-641 phosphorylation and total STAT6 by immunoblotting in the setting of increasing concentrations of IL-13. STAT6 phosphorylation was increased in a concentration-dependent manner in IL-13-treated Th17 cells (Fig. 5*B*), but STAT6 phosphorylation was not altered in similarly treated Th1 or Th2 cells (data not shown). These data support previous reports by Andrews and colleagues (15) that STAT6 activation and translocation is maintained 72 h after stimulation. We further hypothesized that because IL-13 is able to successfully signal through STAT6 in CD4⁺ Th17 cells that express the functional IL-13R, there would be an increase in the expression of the Th2 transcription factor GATA3. Indeed, as shown in Fig. 5*C*, GATA3 expression was increased in Th17 polarized T cells exposed to IL-13.

Discussion

Our data demonstrate that IL-13R is functionally expressed by Th17 polarized CD4⁺ T cells. Th17 cells had a 3-fold increase in IL-13R α 1 mRNA expression as quantified by real time PCR and IL-13R α 1 expression was seen in Th17 cells and not in naive (Th0), Th1, or Th2 cells. There was also a >5-fold increase in the mRNA expression of the other component of the IL-13R, IL-4R α , by real time PCR in Th17 cells compared with Th0, Th1, and Th2 cells. We clearly show that the IL-13R is functional in our system as IL-13 negatively regulates Th17 cell production of IL-17A at the polarization and restimulation stages, and IL-21 production at the Th17 polarization stage. This is in contrast to IL-4, which only down-regulated Th17 cytokine production at the polarization phase and not at restimulation, as has also been shown by Harrington and colleagues (1). We further show that IL-13 decreases the number of IL-17A-producing CD4⁺ cells, but not the amount of IL-17A produced by each cell. IL-13R α 1 expression was only increased on Th17 polarized cells, and not Th1 or Th2 polarized cells. This provides an explanation as to why IL-13 had no effect on cytokine production in Th1 and Th2 polarized T cells, but attenuated Th17 cytokine secretion in Th17 cells. In addition, the presence of IL-13 during Th17 polarization increased the phosphorylation of STAT6 and the mRNA expression of the Th2 transcription factor GATA3 in these cells, which has not been reported in either Th1 or Th2 CD4⁺ cells.

The IL-13-mediated attenuation of IL-17A production also paralleled a decrease in IL-21 production and ROR- γ T relative mRNA expression. ROR- γ T is the transcription factor responsible for Th17 proliferation and sustainability (16) and expression of ROR- γ T is increased in the presence of IL-21 (7). IL-21 and ROR- γ T cause an increase in IL-23R expression on the T cells (7, 17, 18), and IL-23 has shown to be essential in sustaining Th17 cells (7). Therefore, the observed decreases in IL-17A production could potentially be caused by decreased IL-21 production and ROR- γ T expression leading to decreased IL-23R expression on Th17 cells. However, more studies will need to be conducted to confirm this hypothesis.

Although it remains to be formally demonstrated in this article, it seems likely that human Th17 cells will behave similar to mouse Th17 cells. Therefore, because IL-13 inhibits IL-17A production, therapeutic interventions that block IL-13 activity might have unanticipated effects in disease states that are driven by Th17-mediated inflammation. IL-13 has been identified as a potential therapeutic target in allergic diseases, such as asthma, as this cytokine is recognized as a central mediator of mucus production, airway responsiveness, and lymphocyte infiltration in animal models (12, 19). Molecules that block IL-13 activity, either through Ab neutralization or by soluble receptor, result in reduced airway responsiveness, mucus hyperplasia, inflammation, and chemokine production, such as CCL11, CCL5, and CXCL1, in mice or monkeys (19–22). Therefore, based on the results of our study, the use of IL-13 inhibitors in these disease states may have the unintended consequence of up-regulating Th17 cytokine production. Increased production of IL-17A could potentially cause induction or exacerbation of autoimmune diseases, such as the EAE model or Crohn's disease, as mouse models of these diseases are critically dependent on IL-17A (reviewed in Ref. 3). In contrast, diseases that cause increases in IL-13 levels might lead to the attenuation of Th17 cytokine production. In this setting, IL-13-mediated down-regulation of IL-17A could increase disease severity from extracellular pathogens, such as *Klebsiella pneumoniae* (4) or *Mycoplasma pulmonis* (5), that require IL-17 to resolve the infection.

In summary, we show that Th17 polarized T cells express a functional IL-13R and provide a mechanism by which IL-13, an abundantly produced Th2 cytokine, negatively regulates IL-17A production.

Disclosures

The authors have no financial conflict of interest.

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