The Journal of Immunology

BRIEF REPORT | APRIL 15 2009

Cutting Edge: Lung Mucosal Th17-Mediated Responses Induce Polymeric Ig Receptor Expression by the Airway Epithelium and Elevate Secretory IgA Levels [1]

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J Immunol (2009) 182 (8): 4507–4511.
https://doi.org/10.4049/jimmunol.0900237

Cutting Edge

THE JOURNAL OF IMMUNOLOGY

Cutting Edge: Lung Mucosal Th17-Mediated Responses Induce Polymeric Ig Receptor Expression by the Airway Epithelium and Elevate Secretory IgA Levels[1]

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Polymeric Ig receptor (pIgR) is a central player in mucosal immunity that mediates the delivery of polymeric IgA and IgM to the apical surface of epithelial cells via transcytosis. Emerging evidence suggests that Th17 cells not only mediate autoimmunity but also play key roles in mucosal host defense against pathogens. We demonstrate that OVA-specific $CD4^+$ Th17 cells, in addition to causing neutrophilic inflammation in mice, mediated a pronounced influx of $CD19^+$ B cells into the lungs following Ag inhalation. Coincident with this recruitment was a striking induction in pIgR expression by the bronchial epithelium and a subsequent increase in airway IgM and secretory IgA levels. Intranasal administration of IL-17 revealed a crucial role for this cytokine in inducing pIgR expression by the epithelium. These findings support a key role for Th17 cells in pulmonary immune defense against respiratory pathogens by promoting pIgR-mediated transport of secretory IgA and IgM into the airway. ***The Journal of Immunology,*** **2009, 182: 4507–4511.**

The epithelium of the respiratory tract is persistently exposed to a myriad of airborne Ags and must therefore be poised to prevent epithelial colonization by pathogenic agents. Mucosal surfaces are protected by a first-line defense mediated by secretory IgA (SIgA)[4] which is composed of two IgA molecules associated with additional peptides, namely the J chain and the secretory component (SC). Epithelial cells play a critical role in maintaining IgA levels in the airway because they express the polymeric Ig receptor (pIgR) basolaterally, which serves to facilitate the transcytosis of dimeric IgA and IgM to the apical surface. During epithelial transcytosis, the pIgR is proteolytically cleaved and the cleaved pIgR peptide, derived from the extracellular domain of pIgR (SC), is released either in a free form or associated with IgA or IgM (1, 2). IgA associated with pIgR is thought to neutralize pathogens within intracellular vesicular compartments of epithelial cells (3), whereas free SC has innate antimicrobial properties and, when coupled to IgA, protects it from proteolytic degradation and anchors it to mucus lining the epithelial surface (4, 5). The pIgR is an integral component of airway and intestinal mucosal immunity, and typically its expression is restricted to mucosal and glandular epithelia and in hepatocytes in some rodent species (6, 7). Interestingly, pIgR expression in the airway is typically lower than that found in the intestine, likely due to the lower level of microbial stimulation.

Th17 cells, which are characterized by their production of IL-17, mediate autoimmunity but also play a crucial role in mucosal host defense against diverse pathogens (8). Effector cytokines produced by Th17 cells include IL-17A (IL-17), IL-17F, and IL-22 (9). The receptor for IL-17 is ubiquitously expressed in lung, spleen, kidney, and liver as well as various epithelial cells, isolated fibroblasts, and B cells (10). IL-17 has been implicated in the recruitment of neutrophils and the subsequent eradication of extracellular microorganisms (11). Moreover, IL-17 or IL-17F cooperate with IL-22 to enhance the expression of antimicrobial peptides that are associated with host defense, such as β-defensin 2 (9), suggesting that the Th17 lineage may have evolved to eliminate pathogens at mucosal surfaces. We demonstrate that Th17 cells play a crucial function in lung mucosal immune defense by promoting pIgR-mediated delivery of SIgA and IgM into the airway lumen where they contribute to airway immunity. Our observations show that pIgR expression in the airway epithelium is typically low but is rapidly up-regulated by IL-17.

Materials and Methods

Mice and preparation and differentiation of $CD4^+$ T cells

BALB/c and DO11.10 transgenic (The Jackson Laboratory) mice were used throughout (6–8 wk old) and housed under specific pathogen-free facilities. All mice were maintained in our animal facility and studies were performed in accordance with institutional guidelines. To prepare Th17 cells, $CD4^+$ T cells were purified from peripheral lymph node cells obtained from DO11.10 mice by negative selection and depletion of $CD8^+$ cells using MACS beads (Miltenyi Biotech). $CD4^+$ T cells (5×10^5/ml) were incubated for 4 days in the presence of mitomycin C-inactivated splenic APCs (1×10^6/ml), $OVA_{323–339}$ peptide (1 μg/ml; Mimotopes), IL-6 (10 ng/ml;

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Received for publication January 23, 2009. Accepted for publication February 24, 2009.

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[1] This work was supported by National Institutes of Health Grant R01-HL079189 and Center of Biomedical Research Excellence (COBRE) Grant P20RR017670.

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[4] Abbreviations used in this paper: SIgA, secretory IgA; BAL, bronchoalveolar lavage; LMC, lung mononuclear cell; pIgR, polymeric Ig receptor; SC, secretory component.

www.jimmunol.org/cgi/doi/10.4049/jimmunol.0900237

R&D Systems), TGF-β (2 ng/ml; Sigma-Aldrich), and blocking anti-IL-4 (5 μg/ml, clone 11B11; American Type Culture Collection (ATCC)), and anti-IFN-γ (5 μg/ml, clone R4-6A2; ATCC) Ab. Cells were then restimulated as before but in the presence of IL-23 (10 ng/ml; R&D Systems) for a further 4 days. Polarized DO11.10 Th2 cells were prepared as described previously (12).

Transfer of DO11.10 CD4$^+$ Th17 or Th2 cells

Eight-day polarized DO11.10 CD4$^+$ Th17 or Th2 cells (7×10^6 cells/mouse) were adoptively transferred into BALB/c animals by injection i.v. Mice (4–6 per group) were then intranasally challenged by exposure to aerosolized solutions of OVA (0.5%; Sigma-Aldrich) for 20 min/day over 7 consecutive days using a Wright's nebulizer. Control mice were exposed to OVA aerosols but did not receive DO11.10 T cells.

Level of pulmonary inflammation

Bronchoalveolar lavage (BAL) was collected and cell differential counts were determined by microscopic evaluation and expressed as absolute cell numbers as described previously (12). Lung tissue was obtained for histological analysis or dispersed by collagenase to prepare lung mononuclear cells (LMCs).

FACS analysis

BAL or LMCs were stained and analyzed on a FACSAria flow cytometer to enumerate CD4$^+$ T cells (using allophycocyanin-Cy7-conjugated anti-CD4 mAb, clone GK1.5; BD Biosciences) and OVA-specific T cells (PE-conjugated anti-TCR mAb, clone KJ1-26; Caltag Laboratories), or GR1$^+$ neutrophils (anti-Ly-6G mAb; BD Biosciences) and CD11b$^+$ cells (FITC-conjugated anti-CD11b mAb; Miltenyi Biotech). B cells were analyzed using anti-CD19 clone 6D5 and anti-CD5 clone 53-7.3 from BioLegend and anti-I-A/I-E clone M5/114 and anti-IgA clone C10-1 from BD Biosciences.

Lung histology

For immunofluorescent staining, lungs were frozen in Tissue-Tek OCT (Sakura). Cryosections were mounted on glass slides, blocked with 5% donkey serum, and stained using polyclonal goat anti-pIgR Ab (R&D Systems) and FITC-conjugated donkey anti-goat secondary Ab (Jackson ImmunoResearch).

IL-17 and Ig production

IL-17 levels in BAL fluid were measured by a commercially available ELISA kit (e-Bioscience). Measurement of IgA, IgM, IgG1, IgG2a, IgG2b, IgG3, and total Ig in BAL fluid and serum samples were performed using an Ig isotype panel ELISA kit and standards (SouthernBiotech) according to manufacturer's instructions.

SC and SIgA ELISA

For measurement of SC, plates were incubated with BAL fluid (1/50 dilution) overnight, followed by blocking and incubation with 1/200 goat anti-pIgR (R&D Systems). Plates were then incubated with 1/100 HRP-conjugated donkey anti-goat IgG (Jackson ImmunoResearch) followed by tetramethylbenzidine substrate (BD Biosciences). Known amounts of recombinant free SC (R&D Systems) were also analyzed to calibrate measurements. Because the detecting Ab available cannot discriminate between free and IgA-bound SC, both unassociated SC and SIgA are measured in this assay. For SIgA measurement, plates were coated with anti-pIgR (2 μg/ml) overnight, incubated with BAL fluid samples (1/50 dilution) and then HRP-IgA (SouthernBiotech) followed by tetramethylbenzidine. No SIgA standard is available; however, results are corrected per microgram of BAL protein and expressed as fold increase from control values.

Results and Discussion

Recruitment of B cells during Th17-mediated airway inflammation

The airway epithelium has evolved several disparate innate defense mechanisms that, in addition to maintaining homeostasis, can cooperate with a developing T cell immune response to protect the respiratory epithelium from invasion by specific pathogens. Th17 cells and associated cytokines promote the development of host resistance to pathogens at mucosal sites by facilitating neutrophil recruitment (13) and epithelial expression of antimicrobial peptides (9). With respect to the inflammatory response, IL-17 is able to induce epithelial cells to produce several chemokines that promote neutrophil migration, which include CXCL8 (IL-8) and CXCL5 (13). In the present study, we examined and contrasted Th17-mediated inflammation and associated effects on lung mucosal immunity with those evident during Th2-mediated responses. Th17 cells were generated from naive DO11.10 CD4$^+$ T cells by culture in the presence of IL-6, TGF-β, and IL-23 along with blocking IL-4 and IFN-γ Abs. CD4$^+$ Th17 cells produced high levels of IL-17 (but negligible IL-2 and IFN-γ) in response to TCR cross-linking, while Th1 and Th2 cells did not produce any IL-17 (supplemental Fig. 1).[5] In contrast, Th1 cells produced high levels of IFN-γ, whereas Th2 cells secreted IL-4, IL-5, and IL-13 as previously shown (12). Following the adoptive transfer of DO11.10 CD4$^+$ Th17 cells and subsequent exposure to OVA aerosols, a marked increase in neutrophils and macrophages was observed in the BAL fluid of Th17 recipient BALB/c mice (Fig. 1*A*). This was evidenced from a marked increase in the number of CD11b$^+$GR1$^{+\text{high}}$ neutrophils in the BAL from Th17 recipients compared with control mice or Th2 recipients (Fig. 1*B*). In sharp contrast, Th2 recipients developed a pronounced airway eosinophilic inflammation (Fig. 1*A*). Both Th17 and Th2 recipients that did not inhale OVA did not develop any pulmonary inflammation.

In addition, the number of lymphocytes present in the BAL fluid was also significantly augmented in animals that received Th17 or Th2 cells and inhaled OVA when compared with control mice (Fig. 1*A*). CD4$^+$ T cells expressing the OVA-specific transgenic TCR can be enumerated using the anti-clonotypic Ab KJ1-26. Using this approach, significantly increased numbers of CD4$^+$KJ1–26$^+$ T cells were found in the BAL from both Th2 and Th17 recipients (Fig. 1*B*), suggesting that both types of T cells can penetrate the airways. Consistent with elevated numbers of OVA-specific T cells, high amounts of IL-17, but not IL-4 or IFN-γ, were produced by lung cells obtained from Th17 recipients in response to $OVA_{323–339}$ peptide stimulation (supplemental Fig. 2), demonstrating that the transferred Th17 cells maintained their phenotype in vivo (without the emergence of IFN-γ-producing cells).

Surprisingly, the onset of lung mucosal Th17- but not Th2-mediated inflammation was associated with the recruitment of CD19$^+$CD5$^-$class II$^+$ surface Ig$^+$ B cells, which were present in large numbers in the BAL and the dissociated lung tissue and most evident after 7 days of challenge. The infiltrating CD19$^+$ cells were predominantly conventional B-2 cells, because they were class II$^+$CD5$^-$ and did not express surface IgA (Fig. 1*C*) but were surface IgG$^+$ (data not shown). The mechanism of airway B cell recruitment remains unclear; however, it has been shown that human Th17 cells produce the chemokine CXCL13 that promotes B cell chemotaxis (14), and IL-17 has been shown to promote germinal center formation in mice (15). Concomitant with onset of the airway inflammation, elevated levels of IL-17 were found in the BAL of Th17 recipients (Fig. 1*D*). In contrast, negligible levels of IL-17 were observed in the BAL from control and Th2 groups, although the latter had increased levels of IL-4 and IL-5 as previously shown (12).

[5] The online version of this article contains supplemental material.

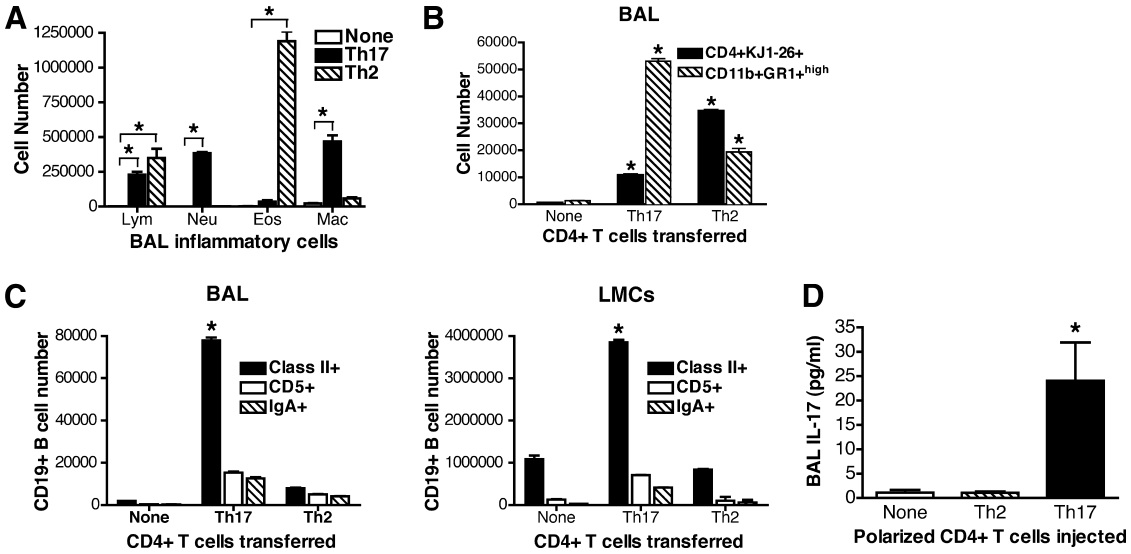

FIGURE 1. Th17 cells, but not Th2 cells, elicited a pronounced recruitment of neutrophils and B cells into the airways following OVA inhalation. DO11.10 $CD4^+$ Th17 or Th2 cells were transferred into BALB/c mice that were then exposed to OVA aerosols for 7 days. Control mice were OVA challenged but did not receive T cells (None). *A*, BAL cell differential counts were determined by microscopic evaluation and expressed as absolute cell numbers. Lym, Lymphocyte; Neu, neutrophil; Eos, eosinophil; Mac, macrophage. *B*, Number of $CD4^+KJ1\text{–}26^+$ T cells and $GR1^+$ neutrophils in the BAL fluid of control mice and Th17 or Th2 recipients as analyzed by FACS; results are expressed as total cell number per mouse. *C*, Number of $CD19^+$ B cells expressing class II, CD5, or IgA in the BAL (*left*) and LMCs (*right*) expressed per mouse. *D*, IL-17 levels in the BAL as determined by ELISA. Mann-Whitney *U* test was used; error bars represent means ± SEM (n = 6–8). *, $p < 0.05$, compared with control group.

Lung mucosal $CD4^+$ Th17 inflammatory responses result in the concomitant elevation of airway IgA and IgM levels

Given that pulmonary Th17 responses were associated with the migration of B cells into the airways, it was important to evaluate the Ig levels at this site. Typically, the most abundant classes of Ig present in respiratory tract are polymeric IgA and IgM. This arises as a consequence of the selective recruitment of IgA^+ and IgM^+ B cells to the mucosal site and the active transport of polymeric Ig across the epithelium into the airway lumen, a process mediated by pIgR (1). In the present study, a pronounced increase in the level of IgA and IgM was evident in the BAL fluid of mice that had received Th17 cells and inhaled OVA (Fig. 2*A*) when compared with OVA-challenged control (none) animals and recipients of Th2 cells. Importantly, the levels of IgA present in the serum was not affected by Th17 inflammation, suggesting that these changes were not caused by the simple diffusion of IgA from serum into the airways. No OVA-specific Ig was detected in BAL fluid of Th17, Th2, or control groups (mean OD values are 0.006, 0.001, and 0.002, respectively (n = 6)). This is likely due to the short duration of OVA aerosol exposure in this model (7 days in the absence of an adjuvant). Slight increases in IgG1 and IgG3 levels were noted

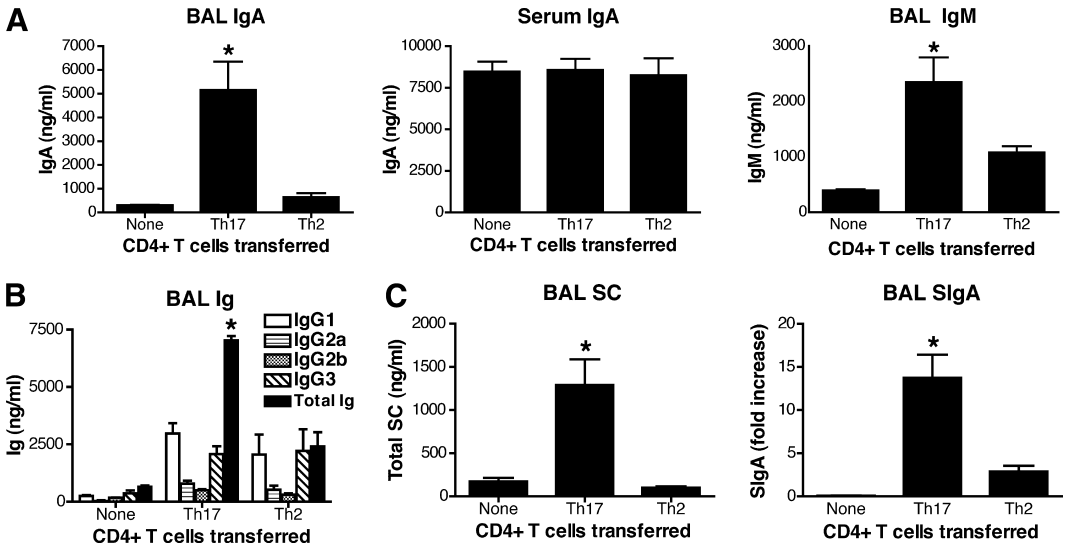

FIGURE 2. Lung Th17 responses and production of IL-17 resulted in marked elevation in the levels of IgA, IgM, SC, and SIgA in the airways. DO11.10 $CD4^+$ Th17 or Th2 cells were transferred into BALB/c mice that were then exposed to OVA aerosols for 7 days. Control mice did not receive T cells (none). *A*, IgA and IgM levels in the BAL and serum from control mice or Th17 or Th2 recipients were measured by ELISA. *B* and *C*, BAL levels of Igs (*B*), SC and SIgA (*C*) were determined by ELISA. Error bars represent means ± SEM (n = 6–8). *, $p < 0.05$, compared with control samples.

in the BAL of both Th17 and Th2 recipients (Fig. 2*B*). IgM and IgA present in the mucosa are typically associated with a SC that protects the latter from proteolytic digestion and governs its anchoring to mucins at mucosal surfaces (5). Measurement of SC revealed that in Th17 recipient mice the level of SC (both free and IgA-bound SC) in the BAL was increased 12-fold over levels in both control and Th2 mice (Fig. 2*C*). The detection of SIgA using anti-PIgR capture and anti-IgA detection Ab demonstrated >8-fold induction over levels in Th2 and control animals (Fig. 2*C*). Uncoupled SC present in mucosal secretions is typically produced by the airway epithelium via the action of proteases on pIgR. Free SC alone is known to display antibacterial properties against a range of pathogens, which include *Helicobacter pylori*, *Escherichia coli*, *Clostridium difficile*, and *Streptococcus pneumoniae* (16), and it can inactivate bacterial toxins (17). Consequently, the release of free SC and SIgA forms an additional epithelial-dependent defense mechanism operative against respiratory pathogens that couples both innate and adaptive immune responses.

Importantly, Th17-induced IgA and IgM Abs present in the BAL fluid were not OVA-specific, suggesting that the exposure to OVA aerosol over 7 days elicited a lung mucosal Th17 response by the transferred cells but was insufficient to prime the B cell response. Moreover, the B cell influx into the airways did not express surface IgA, implying that B cells recruited to the lung are not likely to be the source of the IgA present in the BAL. The majority of IgA that enters into mucosal secretions and the blood is produced at specifically adapted inductive sites in the intestine (Peyer's patch) and to a lesser extent in bronchus-associated lymphoid tissue of the respiratory tract (18). Our findings suggest that the $CD4^+$ Th17 response in isolation serves a pivotal role in promoting the development of effector mucosal immunity. Whether the Th17 response contributes to the formation of immune inductive sites in the lung is unclear, although the presence of a respiratory pathogen may be required for this to occur.

Lung mucosal Th17 cell production of IL-17 promotes pIgR expression by airway epithelial cells

Given that the elevation of Ab was restricted to IgA and IgM and lacked OVA specificity, it seemed likely that the rapid elevation in BAL polymeric Abs could be primarily caused by increased active transport of these Ig isotypes into the airways. Epithelial transcytosis of IgA and IgM is mediated by the pIgR, which is typically expressed by mucous and ciliated epithelial cells in the bronchi. It has been reported that pIgR expression is up-regulated by a range of factors that include microbial products through signaling by Toll-like receptors and the cytokines IL-1, IL-4, IFN-γ, and TNF-α, although vitamin A is required for such regulation to take place (19, 20). Given that a wealth of information is available regarding the expression of pIgR by intestinal epithelial cells, far less is know about the regulation of its expression in human or mouse airway epithelium. To evaluate the cellular distribution and level of lung pIgR expression, we examined pIgR expression in tissue sections of Th17 and Th2 recipients and control mice by immunofluorescent staining. To circumvent any effects attributable to endogenous respiratory infections, the mice used in this study were bred and maintained in aseptic conditions using individually ventilated isolator housing provided with autoclaved food and bedding. Interestingly, the level of pIgR expression by airway epithelial cells in Th2 recipients or control mice was negligible. However, the level of pIgR expressed by the airway epithelium was strikingly induced during Th17-mediated pulmonary inflammation (Fig. 3*A*). Expression was restricted to epithelial cells lining the small and large airways with no detectable staining of the alveolar epithelium or blood vessels.

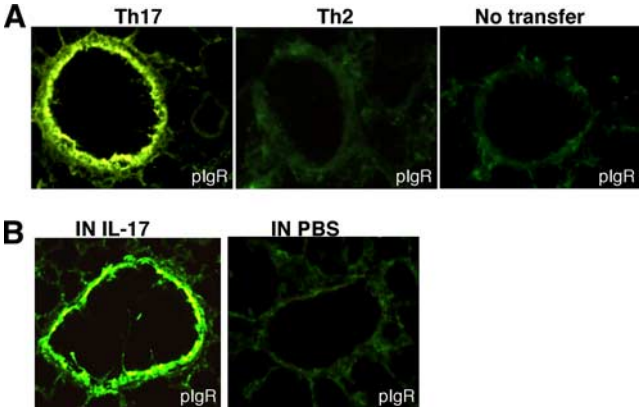

FIGURE 3. Lung Th17 responses and IL-17 induced the expression of pIgR by the airway epithelium. Expression of pIgR by lung tissue sections of OVA-challenged Th17 recipients, Th2 recipients, or control mice (no transfer) (*A*) and BALB/c mice given IL-17 (2 μg in 30 μl of PBS; R&D Systems) or PBS intranasally (IN) (*B*) was determined by immunofluorescent staining. Data are representative of four independent experiments.

These data suggest that the primary cause of Th17-augmented IgA and IgM BAL levels is the dramatic induction of pIgR expression and transcytosis of secretory Ig by the airway epithelial cells. In mice, 85% of the IgA present in serum is in a dimeric form. Consequently, the elevated pIgR expression by airway epithelium may promote the efficient transportation of serum IgA and IgM into the airways. The efficient delivery of polymeric Igs from blood vessels to airways has been reported in mice (21). To determine whether IL-17 produced during the Th17 inflammatory response was primarily responsible for the induction of pIgR expression, IL-17 or PBS was administered intranasally to mice and the level of pIgR expression was determined after 48 h. The administration of IL-17 (2 μg in 30 μl of PBS) alone proved effective at inducing pIgR expression by airway epithelial cells in lung tissue (Fig. 3*B*), strongly suggesting that this was the critical cytokine.

In total, the $CD4^+$ Th17 response is thought to be critical for the clearance of extracellular bacterial pathogens. Our studies show that effector Th17 cells, in addition to eliciting a marked pulmonary neutrophilic inflammation, played an important role in priming the respiratory mucosa by promoting bronchial epithelial expression of the pIgR, thereby facilitating transcytosis of polymeric Igs and release of SIg and SC into the airway. Given the latter role, it is particularly noteworthy that TGF-β is critical for both IgA isotope switching and Th17 differentiation, thus forming the basis of a coherent mucosal immune response. Our findings show that IL-17 can increase simultaneously the levels of innate and adaptive immunity mediated by the airway epithelium. These observations provide an important foundation on which to evaluate the relative roles of neutrophils, SC, and IgA on lung mucosal Th17 responses during opportunistic respiratory infections or exposure to environmental pollutants.

Acknowledgments

We thank P. Shaw (FACS Core) and D. Brooks (Histology Core) for technical assistance.

Disclosures

The authors have no financial conflict of interest.

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