TRANSATLANTIC AIRWAY CONFERENCE

Helper T-Cell Type 17 Cytokines and Immunity in the Lung

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Abstract

The HIV epidemic has clearly demonstrated the critical role $CD4^+$ T cells play in preventing opportunistic infections in the lung. The types of $CD4^+$ effector T-cell populations in the lung have significantly expanded over the last 8–10 years with the discovery of helper T type 17 cells, and this review summarizes the field and discusses how these effector cells may be exploited to augment mucosal immunity in the lung.

Keywords: interleukins; epithelium; pneumonia

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Acquired immune deficiency syndrome (AIDS) came to light in the United States in 1981 with the report of five patients with *Pneumocystis* pneumonia. Within a few years of this report it was shown that the risk of this infection was inversely related to the $CD4^+$ T-cell count in peripheral blood (1) and that the virus that leads to AIDS, human immunodeficiency virus (HIV), infects $CD4^+$ cells, leading to depletion of $CD4^+$ T cells (1). Moreover, depletion of $CD4^+$ T cells in mice also conferred susceptibility to *Pneumocystis* infection (2). The first $CD4^+$ T-cell subsets were described in 1986 and were termed helper T type 1 (Th1) cells for cells that secreted IFN-γ, and Th2 cells for those that secreted IL-4 (3). The Th1 and Th2 paradigm was the foundation of $CD4^+$ T-cell immunology for the next 20 years. What emerged from this pioneering work was that there existed a division of labor among $CD4^+$ T cells. For example, Th1 cells and their signature cytokine IFN-γ were critical for granuloma infection and host immunity against intracellular pathogens such as *Mycobacteria tuberculosis* and *Listeria monocytogenes* (4). Th2 cells, on the other hand, were required for expulsion of helminthic infection (4). So what about *Pneumocystis*? *Pneumocystis* elicits both Th1 and Th2 responses in the lung, with a dominant Th2 response in Th2-biased BALB/c mice (5). However, work by Garvy and colleagues showed that IFN-γ and IL-4 were dispensable for clearance of *Pneumocystis* (6, 7). IL-17 was cloned in 1993 and was also expressed by $CD4^+$ T cells (8, 9), and in murine $CD4^+$ T cells the expression of IL-17 was associated with the expression of tumor necrosis factor-α and granulocyte-macrophage colony-stimulating factor but independent of IFN-γ (10), suggesting unique effector mechanisms of this T-cell effector. To investigate whether this was the missing link of host susceptibility to *Pneumocystis* infection we experimentally infected IL-17 receptor–deficient mice, but these mice cleared the infection similar to wild-type mice. In contrast to *Pneumocystis*, these mice were subsequently shown to be susceptible to *Klebsiella pneumoniae* pulmonary infection (11), systemic candidiasis (12), and oropharyngeal candidiasis (13), the latter infection being associated with HIV infection. Pioneering work from several laboratories in 2005 showed that IL-17 can be made by a distinct lineage of $CD4^+$ T cells, Th17 cells, that develop independent of Th1 and Th2 cells under the transcription factors STAT3 (signal transducer and activator of transcription-3), retinoid-related orphan receptor α (RORα), and RORγT (14–17). In addition to these cells, reports have identified other $CD4^+$ T-cell lineages that make IL-9 (Th9 cells) and IL-22 (Th22 cells), and a critical subset for B-cell helper function, follicular helper T cells (18) that make IL-21. Here we review the Th17 lineage and how these cells play key roles in lung immunity.

Th17 Cells and Other IL-17–Producing Cells

IL-17 can be rapidly induced within hours to days in the lung in response to LPS (19), gram-negative bacteria such as *K. pneumoniae* (20), and viral agents such as H1N1 influenza (21). This early IL-17 response is dominated by γδ T cells (21–23) and to a lesser extent by invariant natural killer T (iNKT) cells in the LPS model (24). It has also been shown that ozone exposure can also rapidly induce

IL-17 iNKT cells in the lung (25). IL-17–producing γδ T cells express IL-23 receptor and IL-1 receptor type 1 and can respond directly to IL-23 and IL-1b (26, 27). IL-17 can then signal to both fibroblasts and lung epithelium that express IL-17 receptor A and IL-17 receptor C to induce CXCR2 ligands such as CXCL1, CXCL2, and CXCL5 as well as the granulopoietic growth factor granulocyte colony-stimulating factor. Both *in vitro* and *in vivo* studies show that the presence of tumor necrosis factor-α can greatly augment the effect of IL-17 on these responses (28, 29). A major effect of IL-17 is stabilization of mRNA stability for CXCR2 ligands such as CXCL1 (30). In the setting of experimental *K. pneumoniae* infection the majority of IL-17–producing cells are γδ T cells. However, after mucosal immunization with heat-killed *K. pneumoniae*, by 14–21 days this response is replaced by Th17 cells (23). These Th17 cells show broad specificity as they are capable of recognizing other Enterobacteriaceae family members and proliferate in a class II MHC–restricted fashion. One potential group of antigens that may explain this are outer membrane proteins (23). This broad reactivity has also been demonstrated for fungal-specific Th17 cells (31). For example, Th17 cells that were generated in response to *Blastomyces dermatitidis* also proliferate in response to *Histoplasma capsulatum* and *Coccidioides immitis* (31). These cells can confer serotype-independent immunity against these fungal pathogens (31). In addition, IL-17–producing cells have also been shown to mediate serotype-independent immunity to *Streptococcus pneumoniae* pulmonary infection (32).

Another source of IL-17 in the gastrointestinal tract is innate lymphoid cells (ILC3 cells) (33), but their frequency in the lung is still unclear. It has been reported that ILC3 cells are present in the lungs of obese patients with asthma as well as in obese mice and that these cells contribute to exacerbation (34).

IL-22 and Mucosal Immunity

The IL-22 receptor is expressed on the conducting airways in the healthy lung in both club cells (Clara cells) as well as ciliated cells (35, 36). Blocking IL-22 during experimental *K. pneumoniae* infection results in bacteremia and enhanced mortality (35). Moreover, recombinant IL-22 applied in the lung improves bacterial clearance (35). IL-22 has also been shown in a model of ventilator-induced lung injury to have potential therapeutic benefit (37). It has been shown that the lack of IL-22 is associated with reduced epithelial repair (38) and increased fibrosis (36) in experimental influenza infection. IL-22 can activate STAT3 in airway epithelium and thus can augment the expression of antimicrobial genes as well as aid in epithelial repair (39). The cellular sources of IL-22 in these models have yet to be determined but likely include γδ T cells, $CD4^+$ T cells, as well as potentially NK cells. In the gastrointestinal tract it has been shown that a critical source of IL-22 is innate lymphoid cells (ILC3 cells), but it remains unclear whether this population is important in the lung. Patients with cystic fibrosis (CF) have large numbers of IL-22 cells, and the vast majority of these cells at the time of lung transplantation are $CD4^+$ cells (40). In the setting of CF, these cells may be important in maintaining mucosal immunity against CF pathogens. Although the IL-22 receptor is expressed in the conducting airway in the healthy lung, after influenza infection, regenerative pods (36) express high levels of IL-22 receptor and thus the receptor appears to be up-regulated at foci of airway repair. IL-22 has also been shown to be proinflammatory in the lung when combined with IL-17 (41).

IL-22 can be antagonized by a decoy receptor IL-22–binding protein. The lack of IL-22–binding protein in mice leads to increased epithelial STAT3 activation and enhanced carcinogenesis in a colon cancer model (42). IL-22 is in phase 1 clinical trials (registration number ACTRN12612000713897), and based on what we know of its current biology may have therapeutic potential in lung disease. However, the field needs to proceed cautiously and keep in mind the potential of IL-22 to augment epithelial carcinogenesis. However, this concern may be mitigated by short-term use of this novel cytokine.

Conclusions

IL-17 can mediate both neutrophil and macrophage recruitment in the lung (14), and this can have beneficial effects on host immunity to both extracellular pathogens but also augment vaccine-induced immunity against intracellular pathogens such as *Mycobacteria tuberculosis* (43). However, IL-17 has been associated with certain forms of severe asthma (34), CF (40), and chronic obstructive pulmonary disease (44), and in these chronic lung diseases IL-17 may contribute to pathology. The role of IL-22 and IL-22–binding protein in these diseases needs to be defined. In addition, the role of IL-17 and IL-22 in carcinogenesis in the lung needs to be further defined in future research. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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