There are dramatic demographic shifts occurring in the United States: For the first time, racial/ethnic minorities make up more than half of all the children born in the United States, of which Latinos are the largest and fastest growing group. These facts have significant medical, public health, economic, and political implications. However, the biomedical community has largely adopted the classification and study of Latinos as a single homogenous racial/ethnic group. The results from HCHS/SOL, along with previous studies, provide strong support that environmental and genetic factors for asthma differ by race/ethnicity. The changing U.S. demographics further underscore the significant disease burden asthma carries for the nation, as well as the need to investigate the etiology of the disease in patient cohorts that are more representative of the current, and future, U.S. population.

President Obama made history by announcing the Precision Medicine Initiative during his State of the Union address (12). He proposed a revolutionary shift in patient care that highlighted the necessity of promoting research considering social, environmental, and genetic factors to ensure that all individuals receive the right diagnoses and treatments at the right time. The recognition that many patterns of disease risk are population-specific, and in the case of U.S. Latinos, *ethnic-specific*, presents a significant gain in our knowledge of complex disease. This recognition is likely to be mirrored by an increase in targeted therapies as the growing biotech industry recognizes the “untapped” market potential of tailored therapies. Applied correctly, the Precision Medicine Initiative edict encourages the application of medical care and research efforts in a socially just manner, such that the rising tide of precision medicine lifts *all* boats, including groups disproportionately affected by disease. The study by Barr and colleagues is a step in the right direction. ■

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

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Innate Lymphoid Cells and Acute Respiratory Distress Syndrome

The acute respiratory distress syndrome (ARDS) is a type of hypoxemic respiratory failure that continues to cause significant morbidity and mortality. ARDS is characterized by fluid accumulation in the alveoli in the lungs, which leads to a substantial impairment of gas exchange and reduced lung compliance. The innate

immune response plays a critical role in the pathophysiology of many acute and chronic lung diseases, including ARDS. A variety of immune cells, including neutrophils, macrophages, and dendritic cells, have been shown to contribute to tissue injury in ARDS, with neutrophils being studied extensively (1). Neutrophil influx into the

lungs has been demonstrated to correlate with the severity of ARDS and may directly contribute to the pathogenesis of this disease (2). Several neutrophil chemoattractants, including IL-8 (CXCL8), seem to be central players in recruiting neutrophil and contributing to subsequent tissue damage in both human and preclinical models (3).

IL-17A has been shown to promote the recruitment of neutrophils into the airways through the induction of C-X-C chemokines and granulocyte-colony-stimulating factor production in both murine and rat models (4, 5). IL-17A, often referred to as IL-17, was first cloned in 1993 from a rodent T-cell hybridoma (6). Recent studies have shown that many types of lymphocytes including CD4⁺, CD8⁺, $\gamma\delta$ -T, invariant natural killer T cells, and innate lymphoid cells (ILCs) can produce IL-17 under certain circumstances (7). Elevated IL-17 levels have been observed in the serum of patients with ARDS (8), and IL-17 blockade ameliorates acute lung injury induced by influenza, acid aspiration, or intratracheal endotoxin administration in mice (9–11), indicating a pathological role of the IL-17 pathway in this disease. To fully understand the pathological role of IL-17 in ARDS, a detailed analysis of the cellular sources of this cytokine is required.

In this issue of the *Journal*, Muir and colleagues (pp. 407–416) studied the role of IL-17 in ARDS using mouse models of both LPS-induced lung injury and acute *Pseudomonas aeruginosa* infection (12). The study clearly demonstrated that IL-17A plays a critical role in recruiting neutrophils to the lung during ARDS, as *Il17a*^{−/−} mice had significantly less neutrophil numbers in their airways after LPS-induced lung injury. There was also reduced injury/inflammation in *Il17a*^{−/−} mice after *P. aeruginosa*, whereas the infection burden was similar in wild-type versus knockout animals, which is consistent with previous report suggesting that the IL-17 pathway is dispensable for *P. aeruginosa* clearance, but contributes to tissue inflammation and lung damage (13). The authors went on to identify the cellular sources of IL-17, using flow cytometry analysis in wild-type mice as well as mice with mutations that result in the lack of $\alpha\beta$ -T cells (*Rag2*^{−/−}) or the entire lymphocyte compartment (*Rag2*^{−/−}*Il2rg*^{−/−}). *Il17a* transcripts were undetectable in the *Rag2*^{−/−}*Il2rg*^{−/−} mice (which lack T, B, natural killer, and innate lymphoid cells), excluding the possibility of IL-17 production by neutrophils and macrophages in this model. However, the *Rag2*^{−/−} mice that retain both natural killer cells and innate lymphoid cells expressed a considerable amount of *Il17a* transcripts and developed ARDS with a disease index similar to the wild-type mice, suggesting that non- $\alpha\beta$ T cells are significant sources of IL-17 during acute lung injury. Finally, the authors were able to use multicolor flow cytometry analysis to identify that ILCs are a source of IL-17 during ARDS and appeared to outnumber $\alpha\beta$ -T cells in the lungs after LPS-induced injury in wild-type mice. Group 3 innate lymphoid cells that express IL-17 and IL-22 have been well described in the lamina propria, and these cells can produce IL-17 in response to cytokine stimuli such as IL-23 and IL-1 β in the absence of T-cell receptor signaling, as these cells do not express T-cell receptors (14).

This study further underscored the pathological role of IL-17 in ARDS and suggests that targeting the IL-17 pathway in this disease could be beneficial in reducing neutrophilic inflammation and lung injury. This study also identified ILCs as a cellular source for IL-17 and suggested that perhaps ILCs can be targeted in ARDS. Considering that IL-17 plays fundamental roles in the host defense in the lungs against a variety of pathogens, complete blockage of IL-17 during

ARDS may increase the risk of opportunistic infections. In this regard, blocking subsets of IL-17-producing cells may be beneficial by reducing the disease severity and restoring the homeostatic balance of the IL-17-regulated pathways. For example, the requirement of *Itgb8* expression on CD11c⁺ cells seem to be unique for $\alpha\beta$ -Th17 differentiation (11), although a unique druggable target for ILC3 without affecting Th17 responses has yet to be discovered.

One limitation of this study is the clinical relevance, as the authors only examined the IL-17 cellular sources in mouse models, and not human tissues. A recent human study has found IL-17 producing cells are mainly $\alpha\beta$ -T cells in the BAL of patients with ARDS (15). Others have shown that $\alpha\beta$ -T cells increase alveolar permeability in ARDS, using a unique mouse strain that only lacks $\alpha\beta$ -Th17 cells (11). A potential explanation of this observed discrepancy is that the mice used by most studies are housed in specific pathogen-free environment, and the ILC responses in this setting may be over represented. In contrast, humans encounter pathogen challenges constantly, and harbor a significant number of tissue resident memory T-cells (16), which may be important contributors to acute lung injury. In fact, mice after mucosal immunization harbor memory Th17 cells in the lungs, which highly expresses *Il1r* and *Il23r* (17) and could possibly become potent IL-17 producers once activated in the setting of acute lung injury. Another critical question in the field is whether the location of these IL-17-producing cells matters. However, this is a technical limitation of the flow cytometry analysis, which requires mononuclear cells after enzymatic digestion of the whole lungs. It is possible that the spatial differences in the location of IL-17A-producing cells in the lungs could be more important than the numbers of IL-17A-producing cells during ARDS. Last, the key IL-17 target cells that mediate acute lung injury are currently unknown. Epithelial cells have been proposed to be major IL-17 target cells. Future studies using bone marrow chimeric mice or tissue-specific genetic tools will shed light on the IL-17 target cells in acute lung injury and could provide critical information on the disease pathogenesis, as well as novel drug targets.

Despite these limitations, this study convincingly demonstrated the pathological role of IL-17A in ARDS and identified the cellular sources of IL-17 in preclinical models of ARDS. Future work will need to focus on identifying the cellular sources of IL-17 in humans with ARDS and the development of drugs targeting the IL-17 pathway and IL-17-producing cells in ARDS with minimal adverse effects on compromising host defense. ■

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

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Cystic Fibrosis Transmembrane Conductance Regulator Function in Airway Smooth Muscle

A Novel Role in Cystic Fibrosis Airway Obstruction

The cystic fibrosis transmembrane conductance regulator (CFTR) is a well-established regulator of ion and fluid transport in several epithelia, where it is a chloride and bicarbonate channel that regulates the epithelial sodium channel and other ion transporters controlling the ion and fluid characteristics of epithelial secretions (1). These epithelial functions in the lung have been postulated as the primary cause of CF airway obstruction, producing mucus stasis, infection, and inflammation that ultimately culminate in irreversible airway damage. It has long been observed that approximately half of patients with CF demonstrate reversible airway obstruction, suggesting a contribution of bronchial smooth-muscle tone to the CF airway obstructive phenotype (2, 3). Historically, this has been attributed to the rampant airway inflammation found in the CF airway, producing secondary airway hyperreactivity that is typically treated with bronchodilators as part of routine airway clearance. Teasing out the contribution of CFTR to this airway phenotype has been challenging because of the inability to examine airway smooth-muscle function in CF independent of established lung disease.

In this issue of the *Journal*, Cook and colleagues (pp. 417–426) asked whether CFTR is expressed in airway smooth muscle, and whether the loss of CFTR in airway smooth muscle influences airway muscle tone (4). They used the recently described CFTR knockout pig model to address these questions, which recapitulates many fundamental aspects of CF airway disease

and has shed light on our understanding of important underpinnings of CF lung disease, including susceptibility to infection, mucus obstruction, and structural airway defects (5–8). Capitalizing on the opportunity to study airway function in newborn pigs before established lung infection and inflammation, the team demonstrated that CFTR localizes to the sarcoplasmic reticulum of airway smooth muscle, airway tone is increased in the absence of CFTR expression, and airway smooth muscle from CFTR knockout pigs exhibits delayed calcium reuptake after cholinergic stimulation and increased myosin light-chain phosphorylation. Together, these findings support the hypothesis that defects in CFTR have a direct negative effect on airway smooth muscle tone. Importantly, Cook and colleagues extended these studies and examined the effect of ivacaftor on airway smooth-muscle function (4). Ivacaftor is a recently described potentiator of CFTR that increases the open-channel probability of wild-type CFTR and several clinically relevant CFTR mutations through enhanced channel gating (9, 10). Ivacaftor has received regulatory approval as a monotherapy to treat CF caused by several gating mutations in CFTR and as a combination therapy with lumacaftor (a corrector of the F508del CFTR folding defect) in patients with two copies of the F508del CFTR mutation (11). In the studies highlighted in this issue of the *Journal*, ivacaftor pretreatment decreased cholinergic-stimulated airway