Defining the Roles of IL-33, Thymic Stromal Lymphopoietin, and IL-25 in Human Asthma

It is clear that a hyperactive type 2 immune response contributes to the pathogenesis of asthma in at least a subgroup of patients. Blood, sputum, and airway biomarkers of increased IL-13 activity (CLCA1, periostin, serpinB2, and MUC5AC) and IL-5 activity (eosinophilia) can identify those with a so-called "Th2-high" type of disease. The utility of molecular subtyping in asthma is buoyed by recent clinical trials demonstrating that some "TH2-high" asthmatics may respond favorably to therapies that block these pathways (1, 2). However, asthma is much more than a T cell–mediated disease, and innate epithelial and immune cell functions are critical in its pathogenesis (3). A better approach may to distinguish asthma subtypes based on the upstream innate factors that drive IL-13 and IL-5 production. In this context, three leading candidates have been identified in mouse models of airway disease (IL-33, thymic stromal lymphopoietin [TSLP], and IL-25), but their importance in the pathogenesis of human asthma has only recently been explored.

The case for IL-33 is bolstered by observations that genetic polymorphisms near the *IL33* and *IL1RL1* loci are strongly linked to asthma (4, 5). This genetic association of the IL-33–IL-33R pathway appears stronger in children (6), and increased levels of IL-33 and the soluble form of IL-33R, sST2, can be found in the sputum and blood specimens in children with asthma (7). Two small studies have reported an increase in the levels of IL-33 protein in the airways from adults with asthma (8, 9). Respiratory virus infections may also induce epithelial production of IL-33 (10), potentially impacting acute exacerbations. However, detection of this IL-1–like cytokine in airway samples can be difficult due to its rapid proteolytic degradation, consistent with its potent functions as an extracellular alarmin and intracellular transcriptional regulator. On the receptor side, expression levels of *ST2L* were increased in the airway brushings from severe asthmatics and correlated with *CLCA1*, *Eotaxin-3*, and airway eosinophilia (11). However, the utility of ST2L or sST2, which are expressed by airway epithelial and immune cells, as asthma biomarkers still remains to be confirmed.

In the case of TSLP, genetic associations and biomarker analyses have also linked this epithelial-derived IL-7–like cytokine to asthma. Polymorphic variants of *TSLP* locus have been observed in adult subjects with asthma of European, North and Central American, and Japanese descent (4, 5, 12). Several groups have found an increase in TSLP in the endobronchial biopsies and lavage samples from patients with asthma (13, 14). The number of TSLP-positive cells was highest in patients with severe disease, yet *TSLP* mRNA expression was only weakly correlated with eosinophilia and the type 2 immune signature, possibly due to the use of inhaled corticosteroids at the time of sample collection in this study (14). The most compelling argument for TSLP's role in allergic asthma was demonstrated in a recent multicenter, placebo-controlled trial in which AMG157, an anti-TSLP monoclonal antibody, attenuated eosinophilic inflammation and bronchoconstriction after allergen exposure (15).

In the September 15 issue of the *Journal*, Cheng and colleagues presented the strongest case for IL-25, an IL-17–like cytokine, in the pathogenesis of "Th2-high" allergic asthma in adults (16), Remarkably, the investigators were able to collect blood, sputum, bronchoalveolar lavage, endobronchial biopsies, and airway brushings in 43 symptomatic, recently diagnosed patients with asthma who had never been treated with steroids (and in 21 control subjects without asthma). Using results from the bronchial brushings as the platform for the rest of their study, the investigators found that *IL25* mRNA expression was significantly increased in a subgroup of subjects with asthma, whereas *IL33* and *TSLP* expression were not. The increase in *IL25* mRNA in endobronchial brushings correlated with the number of IL-25–positive epithelial cells, as well as levels of *IL25R* mRNA expression and numbers of IL-25R–positive cells in the endobronchial biopsies, consistent with IL-25–IL-25R pathway activation. Based on the *IL25* mRNA levels in the brushings, the asthma cohort was divided into "IL-25–high" and "IL-25–low" subgroups. It should be noted that the "IL-25–high" subgroup was also highly allergic, based on reactivity to a panel of allergens and serum IgE. Thus not surprisingly, the "IL-25–high" subgroup also displayed a "Th2-high" phenotype, with evidence of eosinophil activation, increased expression of IL-13 pathway biomarkers, and greater methacholine bronchoreactivity compared with the "IL-25–low" subgroup and control subjects without asthma. An increase of IL-25 was also detectable in the plasma, suggesting that a minimally invasive blood test could be used to stratify patients for treatment. The patients in the "IL-25–high" subgroup responded better to inhaled corticosteroids, with a more dramatic improvement in lung function compared with the "IL-25–low" patients with asthma, and corresponding decrease of plasma IL-25 after 4 weeks of inhaled corticosteroid treatment. In summary, this study supports a role for IL-25 in the pathogenesis of "Th2-high," steroid-responsive, allergic asthma and proposes a new approach to phenotyping based on the innate mediator that may actually drive the type 2 immune responses found in these patients.

One cannot assert that IL-25 is the sole driver of type 2 immune responses in "Th2-high" individuals with asthma, nor can one conclude that IL-25 is more important than IL-33 or TSLP in disease pathogenesis. First, the expression patterns of these cytokines vary between the epithelial layers, such that IL-25 expression is found throughout the airway epithelium, whereas IL-33 expression is highest in the cells along the base (10). Airway brushings may not provide the representative portion of cells that express the highest levels of IL-33. Second, the relative abundance of these cytokines likely depends on the mechanism

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of asthma development. Thus, IL-25 may be higher in patients with allergen-induced asthma, whereas IL-33 may be higher in virus-associated disease and TSLP may be higher in toxin-associated disease (such as cigarette smoke). Third, genetic polymorphisms in these pathways clearly influence the development of asthma. How the genetic susceptibility traits translate at the molecular level into chronic airway disease is unknown. Future head-to-head comparisons of IL-33, TSLP, and IL-25, like Cheng and colleagues', should help to define their relative importance in the pathogenesis of all subtypes of asthma. ■

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Bridging Genetics, Epidemiology, and Respiratory Medicine

One of my patients at our Pediatric Lung and Allergy Unit had a tough start in life. He was born a few weeks prematurely and suffered early from respiratory syncytial virus bronchiolitis. At the age of 10 years, he presented with rather severe asthma. His mother, who'd had a diagnosis of asthma since childhood, expressed concerns about the boy's future health and whether he would outgrow his symptoms and lung function impairment. "Are hereditary factors of importance for his lung development?" she asked. This is a highly relevant question that few research groups have comprehensively addressed to date, and we eagerly await new findings that could be of importance in our daily clinical practice. In the September 15 issue of the *Journal*, Wu and colleagues precisely addressed the question about genetic determinants influencing lung function growth in children with asthma, and their findings bring us one step closer in our understanding of the mechanisms involved (1).

The genetics of respiratory diseases and lung function have been evaluated in numerous studies, most recently in several

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