in nonatopic individuals. Genomic phenotypic predictive modeling significantly predicted asthma cases, but demonstrated poor discriminative ability. Finally, associations between asthma and other immune diseases were noted.

CONCLUSIONS. Two novel loci (1q21.3 and 11q13.5) significantly associate with asthma risk with the use of large genome-wide discovery and replication cohorts.

REVIEWER COMMENTS. In a “big data” world, sifting reality from statistical chaff presents a significant challenge. By the use of genome-wide association study on several independent cohorts, the researchers give weight to their novel candidate loci. Although not previously associated with asthma risk, IL6R’s feasible mechanistic connection to asthma encourages further investigation. Without a known function and with only loose atopy and Crohn associations, the proposed 11q13.5 locus carries much less biological heft. Despite the inclusion of known, novel, and associations, the proposed 11q13.5 locus carries much less biological heft. Despite the inclusion of known, novel, and genetically significant genetic variances, the study’s phenotypic predictive models lack discrimination value, likely because of data imprecision, missing environmental covariates, and other unappreciated asthma risk variables. Even so, more refined phenotypic predictive modeling holds great promise in translating ever-expanding data into improved patient care.

The Alarmin Interleukin-33 Drives Protective Antiviral CD8+ T Cell Responses

PURPOSE OF THE STUDY. Pathogen-associated molecular patterns decisively influence antiviral immune responses, whereas there is less known about how endogenous signals of tissue damage (known as alarmins) are involved in antiviral defenses.

METHODS. Mice were infected with lymphocytic choriomeningitis virus (LCMV), a single-stranded RNA virus, and a genome-wide cDNA expression analysis of total spleen tissue was performed and compared with the uninfected mouse. From a large panel of interleukins and inflammatory cytokines, interferon-γ and interleukin (IL)-33 (along with its receptor ST2) were the most highly upregulated. Infection with LCMV, as well as a murine herpesvirus (MHV-68), was performed in wild-type mice, mice deficient in IL-33 (IL-33−/−), and mice in which IL-33 effects were blocked with a soluble decoy receptor (III-rII-Fc). Proliferative responses of cytotoxic lymphocytes (CTLs) specific for LCMV were measured.

RESULTS. Levels of IL-33 peaked at 3 to 5 days after infection, mirroring levels of LCMV mRNA. After infection with LCMV, proliferative responses of virus-specific CD8+ T cells were 90% lower in IL-33−/− mice and in mice with IL-33 decoy receptors, and CTL responses were absent. Productive viral replication was necessary for IL-33–mediated CTL proliferation. Additionally, recombinant IL-33 significantly augmented CTL responses to other viruses (vaccinia-based vectors), and CTLs appeared to respond to IL-33 directly. Last, the authors provided evidence that IL-33 expression was produced by fibroblastic reticular cells, a stromal cell population of the T-cell zone of the spleen and an important target of LCMV infection.

CONCLUSIONS. These findings suggest that the alarmin IL-33 provides a molecular link to understand how viral replication can enhance CTL responses to infection. IL-33 also serves as a signal from nonhematopoietic cells that acts directly on CTLs to augment protective responses.

REVIEWER COMMENTS. IL-33 has attracted attention as a link between nonhematopoietic cells and the immune system. For example, it appears to be important in the developing airway as an inducer of a Th-2–dominated phenotype. This article shows a different role for IL-33 as an important inducer of CD8+ T cells in response to viral infection in the murine model. Children with asthma and other allergic diseases express higher levels of IL-33 and may thus have a stronger CTL-mediated response to viral infection.

High Environmental Relative Moldiness Index During Infancy as a Predictor of Asthma at 7 Years of Age

PURPOSE OF THE STUDY. To further assess a cohort of children examining the relationship between mold exposures at 1 and 7 years of age and asthma at age 7 years.

STUDY POPULATION. The sample included 176 children with at least 1 atopic parent followed from birth to age 7 years.

METHODS. Home assessments, inspections, and floor dust sampling were done at age 1 and 7 years. Clinical examinations were performed at 1, 2, 3, 4, and 7 years of age and included history and skin testing to Aeroallergens. At 7 years of age, spirometry pre- and postbronchodilator were performed, and, if negative, a methacholine challenge was undertaken. Children were defined as asthmatic if they had asthma symptoms and objective confirmation...
of airway reversibility or a positive methacholine challenge. Homes were examined for mold damage, and floor dust samples were collected. A standardized and validated methodology for mold exposure called the Environmental Relative Moldiness Index (ERMI) was used. Children from homes with mold contamination were compared with those from homes without.

RESULTS. Thirty-two percent of the parents of the study children had asthma. Asthma at age 7 years was associated with parental history of asthma (odds ratio [OR] 3.9), allergic sensitization to dust mite (OR 3.3), African American race (OR 3.2), and high ERMI (OR 2.4) by multivariate analysis. Air-conditioning was associated with a decreased risk of asthma (OR 0.3). Mold exposure at age 7 years was not associated with an increased risk of asthma. There was no difference in mold sensitization between groups with high ERMI or low ERMI. The odds of having a home with a high ERMI was associated with African American race (OR 3.0) and negatively associated with air-conditioning use (OR 0.4).

CONCLUSIONS. High ERMI value in a home during infancy is associated with an asthma diagnosis at age 7 years.

REVIEWER COMMENTS. There are several interesting points from this study, the strength of which lies in the use of a standardized mold assessment technique. As we look for ways to prevent asthma, focusing on exposures in infancy and early childhood are likely to be important. This study identifies mold exposure as one of the risk factors for the development of asthma in at-risk children. It also demonstrates that the effect of exposure does not require allergic sensitization to molds, although the number of molds that were evaluated by skin testing was small and may have missed some sensitization. Regardless, remediation of mold damage in a home during infancy may result in the reduction of asthma, although this needs to be confirmed with prospective studies. This study also supports the association of early dust-mite sensitization and the development of asthma. Dampness in the home is associated with both mold and dust-mite growth; in this study, however, the dust-mite sensitization was not a confounder of the ERMI-asthma relationship, suggesting an independent effect. This study also sheds light on previous studies that have failed to confirm the relationship between mold exposure and asthma. Because the ERMI depends on the quantitative evaluation of mold DNA in floor dust samples, the authors were able to note that visual and olfactory assessment, even by inspectors, missed significant mold problems ~50% of the time.

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Relationship Between Serum Vitamin D, Disease Severity, and Airway Remodeling in Children With Asthma

PURPOSE OF THE STUDY. To evaluate the relationship between serum vitamin D, lung function, and airway remodeling pathology in pediatric severe, therapy-resistant asthmatics (STRA).

STUDY POPULATION. Studied were 86 children, aged 6 to 16 years, 36 with STRA, 26 with moderate asthma (MA), and 24 without asthma (control). STRA was defined as those receiving at least 800 μg of inhaled steroids (beclomethasone equivalent) per day and additional controller medications. MA was defined as well-controlled asthma on <800 μg of beclomethasone equivalent per day.

METHODS. Serum 25-hydroxyvitamin D [25(OH)D₃] was measured. Symptom control was assessed by the childhood asthma control test (ACT). Acute asthma exacerbations were defined as requiring high-dose oral steroids for at least 3 days in the past 6 months. Spirometry was performed in accordance with ATS guidelines. Bronchoscopy, bronchoalveolar lavage, and endobronchial biopsy was performed in 22 children with STRA, and nonasthmatic controls were included (bronchoscopy for other reasons). Differences between the 3 groups were assessed by using one-way analysis of variance or Kruskal-Wallis test.

RESULTS. Levels of 25(OH)D₃ were significantly lower in STRA than in MA and control subjects (P < .001) and were positively associated with lung function, indicated by percent predicted forced expiratory volume in 1 second (P < .001) and forced vital capacity (P = .002), and with ACT scores (P < .001). An inverse relationship was noted between 25(OH)D₃ levels and asthma-related exacerbation (P < .001), as well as inhaled steroid dose used (P = .001) in the MA and STRA groups. Finally, there was an inverse relationship between 25(OH)D₃ and airway smooth muscle (ASM) mass (P = .008), although study did not indicate a relationship between 25(OH)D₃ and tissue eosinophils, neutrophils, or mast cells. Additional assessment of ASM mass showed an inverse correlation with ACT score (P < .001) and a positive correlation with bronchodilator reversibility (P = .009).

CONCLUSIONS. This study demonstrates that lower serum 25(OH)D₃ levels are associated with increased asthma severity, increased asthma-related exacerbations, and higher inhaled glucocorticoid requirements. Furthermore, decreased serum 25(OH)D₃ levels resulted in worse lung function and poorer asthma control. Within the STRA group, low serum 25(OH)D₃ levels were associated with increased ASM mass but not with other parameters of airway remodeling or airway inflammation.

REVIEWER COMMENTS. This study provides additional data to support the association between vitamin D status and
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