Update in Asthma 2013

Lauren Cohn[1] and Prescott G. Woodruff[2]

[1]Section of Pulmonary, Critical Care, and Sleep Medicine, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut; and [2]Division of Pulmonary, Critical Care, Allergy, and Sleep Medicine, Department of Medicine, and Cardiovascular Research Institute, University of California, San Francisco, San Francisco, California

The year 2013 brought us another step closer to understanding what can drive, influence, and ameliorate asthma. Here, we review all of the primary research in asthma published in 2013 in the *American Journal of Respiratory and Critical Care Medicine* and include other important asthma research focused on immunology and inflammation published in high-impact journals. Our target audience is the general pulmonary practitioner and our goal is to provide a brief annual update on the state of research being published in the *Journal* and how it fits into overall progress in asthma research. Because asthma research encompasses a vast range of disciplines, we review only a fraction of the exciting studies published in 2013.

Overall, these works focused heavily on asthma heterogeneity, using genotypes, biomarkers, and clinical features to expand the characterization of asthma subpopulations. These works also investigated factors that induce and modify disease, such as obesity and environmental exposures, including cigarette smoke, pollution, and stress, and endogenous exposures to the respiratory tract microbiome. Mechanistic studies focused on factors that modify known biological pathways underlying asthma, including both allergic, type 2 inflammation, and nonallergic airway disease. These studies often start with a clinical finding that maps a pathway to the disease. Alternatively, these studies follow the pathways involved in a factor that is elevated in asthma and, later, to its association in different asthma subpopulations.

On the basis of well-defined biological pathways in asthma, in 2013 the scientific community collected more data showing that selected subgroups of patients with asthma respond preferentially to classes of biological agents, and many of those agents continue on the path to U.S. Food and Drug Administration approval. There were also disappointing data suggesting that other therapies, based on impressive preclinical data, were ineffective. Successful clinical trials depend on years of research, and thus the more progress we can make unraveling the complexity of asthma pathogenesis, the more successful we will be in treating disease.

Factors That Modify Disease Development, Progression, and Exacerbation

Divide and Conquer: Cluster Analyses May Define Asthma Subpopulations

Cluster analysis has been used to identify important subpopulations in asthma, and studies in the *Journal* have highlighted both novel applications of cluster analysis and important methodological pitfalls. In a novel approach, Boudier and colleagues applied latent transition analysis to longitudinal data to identify major subgroups among 3,320 adults with asthma and how subgroup membership changed over 10 years (1). Their clusters reflected the presence or absence of atopy and then severity within those groups. In longitudinal analyses they found that patients were unlikely to move between nonatopic and atopic clusters and that nonatopic clusters had a tendency to worsen over time. This study adds to our understanding of the durability of asthma phenotypes and the natural history of the poorly understood nonatopic phenotype. Prosperi and colleagues instead focused on methodological pitfalls of cluster approaches (2). They found that changes in variable definition led to multiple and inconsistent subgroupings of asthma and were more influential than the clustering method. Their results argue for consistency in variable handling in cluster analyses going forward.

Genes

Genetics studies published in the *Journal* in 2013 were largely candidate gene analyses. These studies included a study of P2X7 functional activity in blood and risk for asthma exacerbation (3), a study of glutathione *S*-transferase M1 polymorphisms and response to allergen challenge (4), and a study of Arg16Gly polymorphisms of the β-adrenergic receptor, in patients with exercise-induced bronchoconstriction, which did not show the expected relationship between genotype and loss of bronchoprotection after regular use of salmeterol (5). The study of β-adrenergic receptor polymorphisms highlights the difficulty in translating

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Correspondence and requests for reprints should be addressed to Lauren Cohn, M.D., Section of Pulmonary, Critical Care, and Sleep Medicine, Yale University School of Medicine, 333 Cedar Street, P.O. Box 208057, New Haven, CT 06520-8057. E-mail: lauren.cohn@yale.edu; and Prescott G. Woodruff, M.D., M.P.H., Division of Pulmonary, Critical Care, Allergy, and Sleep Medicine, Department of Medicine and Cardiovascular Research Institute, University of California San Francisco, Box 0130, Room HSE 1305, 514 Parnassus Avenue, San Francisco, CA 94143. E-mail: prescott.woodruff@ucsf.edu

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genetic studies to relevant and actionable guidance for the clinician. Nonetheless, genetic studies in asthma are making some progress in the ever-important area of the functional consequence of asthma-associated single-nucleotide polymorphisms that have been identified by genome-wide association study. For example, in an elegant study published in the *New England Journal of Medicine*, Çalışkan and colleagues found that genetic variants in the 17q21 locus, linked previously to asthma, were associated with wheezing illnesses with human rhinovirus (HRV) infection (6). Furthermore, they found that the expected genetic associations between 17q21 variants and asthma in these cohorts were restricted to children who had HRV-related wheezing, and that HRV induced expression of *ORMDL3* and *GSDMB* in peripheral blood mononuclear cells. This study adds to the emerging evidence that HRV may be an important causal factor in some patients with asthma and provides clues to the functional role that the 17q21 locus may play in asthma, a role that has been difficult to establish.

Obesity

The association of obesity and asthma in children and adults is established. More than one-third of American adults and 17% of children are obese (7), and thus the impact on asthma is immense and potentially treatable. Studies of weight loss in obese patients with asthma indicate that obesity contributes to both inflammation and respiratory mechanics in the development of disease, but those pathways are far from elucidated (8). To investigate the relationship of childhood obesity to disease control Borrell and colleagues examined a large population of African American and Hispanic children and adolescents with asthma (9). In subjects from two clinic-based multicenter asthma case–control studies, the investigators found that obese adolescent boys of both races had a 33% greater chance of having poor asthma control than their normal-weight counterparts. However, for girls this association varied with race and ethnicity. This was the first examination of obesity, age, sex, and race/ethnicity with asthma control in a large population of Hispanic-Latino and African American children and showed that sex and racial factors modify disease activity.

To investigate factors linked to obesity as potential causes of asthma, investigators studied metabolic and hormonal pathways. The metabolic syndrome, a disorder of energy use and storage, which includes abdominal (central) obesity, elevated blood pressure, elevated fasting plasma glucose, and lipid abnormalities and is associated with low-grade inflammation, was hypothesized to be the mediator of asthma in obesity in this investigation by Assad and colleagues (10). In a 25-year longitudinal study, incident asthma was associated with obesity in women, yet body mass index (BMI) was a better predictor of asthma than the metabolic syndrome. Interestingly, using BMI as an index of obesity has been criticized because it underestimates the prevalence of obesity in males, whereas abdominal obesity was a more accurate risk factor for asthma (11, 12). A prospective trial in Norway found that incident asthma was associated with components of the metabolic syndrome, although the greatest effect was large waist circumference (13). Taken together these studies suggest that abdominal obesity is a stronger predictor of asthma and that the effect is independent of the metabolic syndrome. Wright and colleagues investigated the link between maternal obesity and cortisol disruption on repeated childhood wheezing and showed that maternal obesity and cortisol disruption had independent influences on childhood wheezing in a cross-sectional analysis of pregnant mothers (14). Yet, a subgroup of obese mothers with adverse cortisol profiles characterized by abnormally elevated cortisol levels later in the day were most likely to have children with repeated wheeze. These two studies show that hormonal and metabolic pathways thought to influence obesity and hypothesized to be mechanisms of asthma development were not universally associated with asthma. In smaller subgroups of patients with asthma, disturbances in metabolism and cortisol may influence disease, but are not generalizable to larger populations of patients with asthma.

Another feature hypothesized to promote asthma is obesity-induced low-grade systemic inflammation characterized by elevations in cytokines and chemokines, complement proteins, and other hormonal factors that are collectively referred to as adipokines. These include IL-6, tumor necrosis factor-α, vascular endothelial growth factor, and the adipose hormones leptin and adiponectin. In the *Journal* in 2013, three studies provided new insights into how inflammation in obesity may influence asthma. In the Tucson Infant Immune Study, excess maternal weight gain was associated, in their newborn and 3-month-old offspring, with increased tumor necrosis factor-α production from stimulated mononuclear cells, and an increased risk of childhood asthma (15). These studies suggest that the maternal milieu associated with excess pregnancy weight gain shapes immunity in the fetus.

Obese patients with asthma include greater proportions of subjects with both low exhaled nitric oxide (Fe_{NO}) and sputum eosinophils in association with adult-onset, corticosteroid-resistant (CR) disease, when compared with patients with asthma with lower BMIs (16, 17). To define pathways to explain differences in inflammatory patterns in obese patients with asthma, Holguin and colleagues measured the formation of asymmetric dimethyl arginine (ADMA), a product of posttranslational methylation of L-arginine and an L-arginine analog that inhibits both the inducible and constitutive forms of nitric oxide synthases (18). ADMA formation results in uncoupling of nitric oxide synthase, reduced NO synthesis, and increased oxidant production, and ADMA is increased in obesity (19). In patients with moderate to severe, late-onset asthma in the Severe Asthma Research Program (SARP) cohort, obesity correlated with low Fe_{NO} and the L-arginine:ADMA ratio explained part of this reduction. In obese patients with asthma lower NO production may contribute to less allergic airway inflammation, less bronchodilatory NO, and worse lung function, although these complex pathways in asthma are still poorly understood (20). In another study to define why obese subjects with asthma had lower sputum eosinophils, but higher concentrations of IL-5 in the sputum, Desai and colleagues performed transbronchial biopsies and showed higher numbers of eosinophils in the submucosal spaces in obese compared with overweight and normal weight patients with asthma (21). The physiological differences in obese patients with asthma who retained eosinophils in the submucosal compartment, where they were activated, rather than within the airway, may affect

disease activity and the response to therapy. As Peters and Fahy pointed out in their editorial, this eosinophil "high" phenotype in obesity contradicts observations from numerous studies suggesting obese subjects are often not "Th2 high" and raises the possibility that obese subjects may be misclassified based on their low F_{ENO} and sputum eosinophils (22).

Exposures: The "Exposome"

Pollution, dirt, and cigarette smoke. The importance of environmental exposures such as endotoxin, tobacco smoke, and air pollution and the impact of an individual's microbiome remain important areas of research in asthma because these are potentially modifiable factors. Nishimura and colleagues provide evidence that outdoor air pollution may not just exacerbate asthma but may also be a causal factor (23). They analyzed regional data on air pollution levels in two large studies of asthma in Latino and African American children and found that increased levels of NO_2 were associated with incident asthma, particularly in children without a family history of asthma. Two other studies suggest that interactions between environmental exposures may be complex, and not simply additive. Lajunen and colleagues performed a population-based study of incident adult-onset asthma, and found that two factors, that is, (*1*) second-hand smoke exposure and (*2*) having a relative with asthma, had synergistic, dose-related effects on risk of adult-onset asthma (24). By contrast, Matsui and colleagues found a surprising interaction between exposure to endotoxin and concomitant exposure to either tobacco or NO_2. Higher endotoxin exposure was associated with an increased risk of acute events in 146 children and adolescents with asthma when tobacco exposure was detectable but not when tobacco exposure was undetectable (25). Conversely, higher endotoxin exposure was associated with decreased risk of acute asthma events when NO_2 exposure was high but with increased risk when NO_2 exposure was low. These apparent interactions are interesting, but beg confirmation in other studies, given that studies of interactions are akin to subgroup analyses.

Microbiome. Bacterial colonization of the gut and respiratory tract influences the immune system and its modulation can impact disease. In asthma, neonatal asymptomatic colonization of the respiratory tract with pathogenic bacteria was associated with development of asthma in childhood (26). Extending these studies, Følsgaard and colleagues measured inflammatory cytokines in the upper respiratory tract and showed that neonatal colonization with the Proteobacteria, *Haemophilus*, and other pathogenic bacterial species was associated with increased inflammatory cytokines, when compared with the majority of children who were not colonized (27). Thus, airway colonization, previously shown to be similar in the upper and lower airways (28), influences local immunity and may be important in disease development. Goleva and colleagues studied lower airway bacterial colonization in adults with asthma, its influence on the response to corticosteroids, and the relationship to CR asthma characterized by fixed airway obstruction (29). Whereas both corticosteroid-sensitive (CS) and CR patients with asthma had expansions of Proteobacteria microorganisms, there were uniquely expanded gram-negative bacterial profiles in CR compared with CS subjects. Furthermore, *Haemophilus* infection of airway macrophages *in vitro* reduced cellular responses to corticosteroids, suggesting a mechanism for reduced efficacy of corticosteroid treatment in colonized patients. Clearly, bacterial colonization in the respiratory tract modulates local immunity, and may affect disease development and the response to disease. These studies all show increases in *Haemophilus* species among subpopulations of patients with asthma and lay the framework for future studies to define how altered airway bacterial colonization promotes asthma and modulates disease progression and response to therapy.

Social and psychological exposures. Social and psychological factors are exposures that impact the development, control, and reporting of asthma. Thakur and colleagues found that lower socioeconomic status was associated with a higher prevalence of asthma in African Americans, but that lower socioeconomic status was associated with a lower prevalence of asthma in Mexican Americans (30). In Mexican Americans, some of this effect appears to be due to level of acculturation. These data highlight the importance of considering these underrepresented ethnic groups separately when analyzing environmental and cultural factors, which may contribute to asthma.

Investigations have used novel approaches to study the impact of psychological stress in disease. Posttraumatic stress disorder and anxiety were linked to epigenetic and genetic variation in the gene encoding the receptor for adenylate cyclase activating polypeptide 1 (*ADCYAP1R1*) (31). Chen and colleagues conducted an epigenetic analysis in a case–control study of 516 children and found that *ADCYAP1R1* methylation is associated with both asthma and reported exposure to violence (32). In addition, a single nucleotide polymorphism in *ADCYAP1R1* (rs2267735) was associated with asthma. Bahreinian and colleagues also borrowed from the broader field of stress-related research when they studied the relationship between "allostatic load" and asthma in adolescents (33). Allostatic load refers to a set of biological measures thought to reflect a maladaptive response to stress. They studied risk for asthma in 352 adolescents, using seven biomarkers of allostatic load; defined a composite score; and found that high allostatic load was associated with prevalent and incident asthma in boys but not girls after multivariate adjustment.

Psychological disorders may also masquerade as somatic disease. For example, Lavoie and colleagues found that anxiety, mood disorders, and hypochondriasis were common among patients being evaluated for possible occupational asthma (34). Subjects ultimately identified as not having occupational asthma after a structured evaluation were more likely to have hypochondriasis and tended to have more psychiatric disorders overall. These data suggest that psychiatric disorders should be routinely considered in the differential diagnosis of occupational asthma.

Biological Pathways That Influence Disease

Pathways That Augment Th2-driven Asthma

In allergic asthma, Th2 cells and the cytokines they produce lead to eosinophilic

inflammation, mucus hypersecretion, airway hyperresponsiveness, and persistence of disease (35). Clinical trials of anti-cytokine antibodies that block IL-5 or IL-13 showed therapeutic efficacy in selected populations of patients with asthma with evidence of Th2 cytokine–driven disease (36). Mediators that enhance Th2 cell induction and activation, or augment allergen-driven asthma, are important targets to modulate disease, and remained a focus of research in asthma.

Innate lymphoid cells residing in the lung activate early protective immunity in pathogen infection. Human innate lymphoid type 2 (ILC2) cells represent a small population in the human lung that respond to stimulation with IL-25 and IL-33; produce chemokines and cytokines, including IL-13; and recruit appropriate cell populations to the mucosa that enhance Th2 development and Th2 cytokine production (37). Past studies established that ILC2 cells were increased in subjects with asthma and nasal polyposis, compared with subjects without allergic inflammation (38). Shaw and colleagues showed that subjects with chronic rhinosinusitis and nasal polyposis had a higher percentage of ILC2 cells compared with subjects with chronic rhinosinusitis alone, and these cells had the capacity to produce IL-13 in response to IL-33 (39). Thus, ILC2 cells from human nasal polyps have the functional capacity to drive allergy and asthma. In studies published in *Science Translational Medicine*, Barnig and colleagues investigated the regulation of innate lymphocytes in the lung by the counterregulatory lipid lipoxin A_4 (40). Lipoxin A_4, through its receptor ALX/FPR2, caused eosinophil apoptosis and inhibited IL-13 production by ILC2 cells. Because lipoxin A_4 is reduced in asthma (41), the authors suggested that these novel pathways promote persistent eosinophilia and IL-13 production in the lung. These studies identify pathways by which innate lymphoid cells in allergy and asthma may modulate Th2 cytokine production and disease activity.

Various other cell types in the inflammatory environment in the respiratory tract in asthma contribute to disease through release of mediators that increase inflammation. Many of these mediators activate Th2-driven signals specifically, whereas others activate more general inflammatory pathways. Serotonin, a multifunctional neurotransmitter and vasoactive amine with the ability to activate cell adhesion, migration, and cytokine production in T lymphocytes, mast cells, and dendritic cells, and to cause bronchoconstriction, was increased in antigen-challenged subjects with asthma (42). Although past studies showed that serotonin contributes to allergic airway inflammation, Dürk and colleagues showed that serotonin released by platelets, not mast cells, promotes antigen-induced Th2 responses in mice and modulates dendritic cell function, leading to activation of T cells (43). Takyar and colleagues showed that vascular endothelial growth factor stimulates Th2 inflammation through a novel pathway that inhibits expression of microRNA-1 in the lung endothelium, and increases P-selectin that may enhance Th2 cell recruitment to the lung (44). IL-9–producing Th9 cells are proinflammatory and promote mast cell expansion and activation, and thus may play a key role in driving allergic asthma. In comprehensive studies in murine and human cells, Li and colleagues identified cyclooxygenase-2–induced prostaglandin D_2 and prostaglandin E_2 as negative regulators of Th9 development and identified potential negative effects of cyclooxygenase-2 inhibitors in allergic diseases (45). Lysophosphatidic acid (LPA), a biologically active lipid, and autotaxin, the enzyme that generates it, were both elevated in the airways of allergen-challenged subjects with asthma (46). Deficiency of LPA and autotaxin attenuated the development of allergic airway inflammation, and thus these studies show proinflammatory functions of LPA and autotaxin in allergic asthma. In an editorial, Georas suggested a possible role for autotaxin and LPA in obesity-induced disease, because this pathway regulates adipocyte growth and differentiation (47).

Pathways That Regulate Th2-induced Disease

$CD4^+$ regulatory T (Treg) cells comprise subsets of cells that produce IL-10 and/or transforming growth factor-β_1, express the transcription factor FoxP3, and are important in regulating sensitization to allergen and development of Th2 cells. Treg cells were reduced in asthma and allergic disease (48). In the *Journal of Clinical Investigation* in 2013, two articles addressed Treg cells and suppression of Th2 responses in asthma. Jin and colleagues showed that the E3 ubiquitin ligase, Itch, restrains Treg cells from producing Th2 cytokines (49). To define the therapeutic potential of increasing Treg cells in the lung, Mays and colleagues administered to the airways of mice chemically modified FoxP3 mRNA and showed increased Treg cells and reduced allergic airway inflammation, leading to a "rebalancing" of the helper T-cell response (50).

Pathways in Other Asthma Subpopulations

Mechanistic studies in irritant- and exercise-induced asthma indicate that some of the pathways defined in these subpopulations parallel those in allergic disease, whereas other pathways are distinct in the asthma subpopulation. Airway sensory neurons reside in close proximity to immune cells, including eosinophils, dendritic cells, and mast cells. Studies by Hox and colleagues investigated the role of transient receptor potential ankyrin 1 (TRPA-1), the irritant-sensing ion channel expressed in airway chemosensory nerves (51). In a mouse model of irritant-induced, paucigranulocytic asthma, TRPA-1 drives inflammation through release of substance P and activation of mast cells. TRPA-1 was previously shown to play a key role in allergic airway inflammation, serving as a key integrator of interactions between the immune and nervous systems in the airways and driving asthmatic airway inflammation after inhaled allergen challenge (52). Therefore, TRPA-1 likely contributes to airway hyperresponsiveness independent of the characteristics of the airway inflammatory response.

Exercise-induced asthma (EIA) was the focus of studies that investigated levels of secreted phospholipase A_2 (PLA_2) group X (sPLA-X) in subjects with asthma. PLA_2 releases arachidonic acid from membrane phospholipids to initiate eicosanoid biosynthesis. Whereas cytosolic PLA_2s have most commonly been studied, secreted PLA_2s act on phospholipids in the extracellular space. $sPLA_2$-X was increased in the bronchoalveolar lavage of patients

with asthma and highly expressed in airway epithelial cells (53). In subjects with EIA, Hallstrand and colleagues showed that $sPLA_2$-X was increased in the airway epithelium when compared with subjects without EIA. This suggests that in EIA the bronchospastic response to exercise may be due to distinct dysregulated pathways in the airway epithelium (54).

Pathways That Affect Smooth Muscle

Three studies were published in the *Journal* in 2013 that identified new factors that may affect airway smooth muscle contraction and relaxation (55–57). Two of the studies applied multiple modalities to mouse, guinea pig, and human tissues and identified transmembrane protein 16A, a calcium-activated chloride channel, and Toll-like receptor 7, respectively, as factors that modify the response of airway smooth muscle to contractile agents (56, 57). The third study combined laser capture microdissection of human airway biopsies and RNA sequencing to identify two genes (*FAM129A* and *SYNPO2*) that were significantly changed in expression with corticosteroids in asthma and which correlated with degree of airway hyper-responsiveness (55). Although technologically ambitious, that study was relatively small and did not pursue complementary modalities to assess the potential role of these genes. Thus, corroborating studies will be essential.

Pathways That Affect Airway Remodeling and Cause Fixed Airflow Obstruction

Investigations into the prevalence and causes of fixed airflow obstruction in asthma remain a critical area of research, because of its impact on disease severity. Three studies were published in the *Journal* in 2013 that focused on airway remodeling in asthma (58–60). Perret and colleagues followed up a population-based cohort after 35 years and found that those with ongoing asthma had a significant and time-dependent relationship with lack of bronchodilator responsiveness (59). Furthermore, the effects of persistent asthma on fixed airway obstruction were synergistic with smoking, but only in those with atopy. The other studies focused on potential mechanisms of airway remodeling including fibrocytes and their products, connective tissue growth factor, and endothelin-1 (58), and markers of vascular perturbation in asthma, von Willebrand factor propeptide and P-selectin (60). In an interesting study of tissue remodeling in a condition closely related to asthma, Takabayashi and colleagues studied fibrin deposition in chronic rhinosinusitis (61). There was dramatic fibrin deposition in the polyps associated with chronic rhinosinusitis and concomitantly lower levels of D-dimer and tissue plasminogen activator, suggesting that fibrin accumulates, at least in part, because of a defect in fibrinolysis.

New Therapies in Asthma

Several important randomized controlled trials (RCTs) and observational studies investigating therapies for asthma were published in 2013 and proved the concept for a new drug, cast doubt on a novel approach, or identified a novel application of an emerging predictive biomarker.

In a study that cast doubt on a novel approach, Short and colleagues performed an RCT in 18 subjects with asthma to assess the effects of chronic dosing of propranolol in asthma (62). They found no significant effect of propranolol on methacholine or histamine responsiveness, or in asthma control or quality of life.

In an observational study that supports a novel approach to asthma therapy, Tse and colleagues used a large set of health care databases to show that statin use was associated with fewer emergency department visits for asthma and less oral corticosteroid use (63). These data are observational in nature and conflict with small RCTs, but provide some evidence that larger RCTs of statins in asthma may be indicated.

Two novel antiinflammatory approaches were studied in RCTs and yielded largely negative results. Busse and colleagues performed an RCT of IL-17 receptor antagonism, using brodalumab in patients with moderate-to-severe asthma who were not otherwise selected for disease phenotype (64). They found no significant improvement in asthma control (primary outcome) with brodalumab. In secondary analyses, subjects who were more reversible with bronchodilators had a better response to brodalumab. Parulekar and colleagues conducted an RCT of inhibition of T-cell costimulation in allergen-induced airway inflammation (65). In this study, abatacept, a humanized CTLA4 immunoglobulin that blocks T-cell costimulation, did not significantly reduce the percentage of eosinophils in bronchoalveolar lavage induced by segmental allergen challenge, despite some evidence of an effect on the ratio of memory to naive $CD4^+$ T cells in the periphery. This result appears to challenge the orthodoxy that T cells are central to asthma pathogenesis and implies that innate immune cells producing type 2 cytokines play important roles in responses to allergen challenge. However, a more likely explanation is that $CD4^+$ tissue-resident memory T lymphocytes, which do not require costimulation in antigen activation, remain uncontrolled in the lung despite abatacept, as has been shown (66).

Finally, Wenzel and colleagues published an important RCT of dupilumab, an anti–IL-4 receptor antibody, in the *New England Journal of Medicine* in 2013 (67). In a study that sequentially withdrew controller medications, subjects with persistent, moderate-to-severe asthma and elevated eosinophil levels had fewer asthma exacerbations and better lung function with dupilumab. This study strengthens the rationale for Th2-targeted therapy combined with strict subject selection, and points to a new and potentially effective therapeutic agent. In a study specifically designed to test predictive biomarkers of response to a Th2-targeted therapy, Hanania and colleagues performed a 48-week RCT of omalizumab versus placebo in adults with uncontrolled severe persistent allergic asthma and found that high F_{ENO}, high serum eosinophil counts, and high serum periostin levels were all associated with better response to omalizumab (68).

Conclusions

Asthma research in the *Journal* in 2013 examined an extensive range of subjects focused on understanding factors that lead to asthma development, exacerbation, and control. Although these areas of attention in asthma research are not new, a majority of these studies were patient-based investigations of subpopulations of patients with asthma. Through this enhanced understanding of asthma heterogeneity,

there has been much greater progress in defining new pathways of disease. Each article that we have reviewed above advances our insights into how asthma develops and persists in different individuals in various communities. Clinical trials of novel therapeutics indicate that we are making headway in certain subsets of disease. All of this hard-fought ground, the successes and failures, helps to focus future research on pathways amenable to disease modification. The more that we do to unravel the complexity in asthma development, progression, and activity, the better our end game will be. These remain exciting times in asthma research and the payoff is clearly on the horizon. ■

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