Advances in asthma: New understandings of asthma's natural history, risk factors, underlying mechanisms, and clinical management

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The last 2 years yielded a proliferation of high-quality asthma research. These include new understandings of the incidence and natural history of asthma, findings on the effects of exposure to air pollution, allergens, and intake of acetaminophen, soy isoflavones, and polyunsaturated fatty acids, and exposure to microbial products. The past 2 years have benefited from great strides in determining potential mechanisms of asthma development and asthma exacerbations. These novel understandings led to identification and development of exciting new avenues for potential therapeutic intervention. Finally, there has been significant progress made in the development of tools to facilitate the diagnosis of asthma and measurement of airway physiology and in precision diagnostic approaches. Asthma guidelines were updated and new insights into the pharmacologic management of patients, including biologics, were reported. We review the most notable advances in the natural history of asthma, risk factors for the development of asthma, underlying mechanisms, diagnostic approaches, and treatments. Although greater knowledge of the mechanisms underlying responses and nonresponses to novel therapeutics and across asthma phenotypes would be beneficial, the progress over just the past 2 years has been immense and impactful. (J Allergy Clin Immunol 2021;148:1430-41.)

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The last 2 years have yielded a proliferation of high-quality asthma research. Although this is not an exhaustive list of the many achievements over this time period that further our understanding of asthma, we review the most notable advances in the natural history of asthma, risk factors for the development of asthma, underlying mechanisms, novel diagnostic approaches, and treatments.

NATURAL HISTORY OF ASTHMA

Incidence rates (IRs) were delineated for pediatric asthma across the United States from 1980 to 2017 to determine how incidence may change over time by parental history of asthma and across major demographic features. Data were pooled across 9 US birth cohorts from the Children's Respiratory and Environment Workgroup, sponsored by the National Institutes of Health Environmental Influences on Child Health Outcomes program. Age-specific asthma IRs were highest among children aged 0 to 4 years, with a decline in European American and Mexican American children in 2000 to 2004 followed by a decline in African American and Caribbean American children in 2010 to 2014. Parental asthma history was associated with increased IRs. IRs were similar and higher in African American and Caribbean American children. The differential rates by sex resulted from a decline among adolescent males but relatively stable rates among adolescent females.[1] Predictors of pediatric asthma remission by age 18 to 23 years were examined in the Childhood Asthma Management Program. The level of impairment in FEV_1/forced vital capacity ratio was the largest predictor of asthma remission. Additional predictors of remission included lower airways responsiveness and baseline serum eosinophil count.[2]

The natural history of wheeze was examined in several studies. Sordillo et al[3] characterized wheeze from infancy to adolescence in the Massachusetts-based Project Viva birth cohort, with an additional focus on the presence of single nucleotide polymorphisms (SNPs) in 2 asthma candidate genes (gasdermin B/ORMDL3 and CDHR3). Their latent class growth trajectory model showed 4 independent latent trajectories of wheeze: never/infrequent wheeze (62%), midchildhood-onset wheeze (10%), early transient wheeze (22%), and persistent wheeze (6%). Compared with individuals in the never/infrequent wheeze trajectory, those with midchildhood-onset and persistent wheeze trajectories had

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Abbreviations used

ApoE:	Apolipoprotein E
DN:	Double-negative
ErbB2:	Erythroblastic oncogene B receptor B2
HDM:	House dust mite
ICS:	Inhaled corticosteroid
ILC:	Innate lymphoid cell
ILC1:	Type 1 ILC
ILC2:	Type 2 ILC
ILC3:	Type 3 ILC
IR:	Incidence rate
LABA:	Long-acting beta-agonist
MiR-1:	MicroRNA-1
NKT:	Natural killer T
PUFA:	Polyunsaturated fatty acid
RCT:	Randomized controlled trial
RGMb:	Repulsive guidance molecule b
RV:	Rhinovirus
SNP:	Single nucleotide polymorphism
T2:	Type 2
TLR:	Toll-like receptor
3-NT:	3-nitrotyrosine
γ-T:	γ-tocopherol

higher levels of fractional exhaled nitric oxide, total IgE levels, and maternal history of asthma compared with those in the never/infrequent wheeze category. Participants with an early atopic phenotype (diagnosis of eczema in infancy) were more likely to fall into the trajectory for midchildhood-onset wheeze. Bronchiolitis in infancy and acetaminophen use in pregnancy were associated with all 3 wheeze phenotypes. Participants of Black or ''other'' race/ethnicity and for 1 ORMDL3 SNP each were at increased risk for persistent wheeze.[3] Trajectories of asthma and lung function from childhood age 7 to 53 years in the Tasmanian Longitudinal Health Study were analyzed and 5 trajectories were identified: minimal and least asthma and allergies (49%); late-onset hay fever, no asthma (almost 30%); early-onset remitted asthma and allergies (6.5%); late-onset asthma and allergies (almost 9%); and early-onset persistent asthma and allergies (~6%). The late-onset asthma and allergies trajectory was associated predominantly with the multiple disorders profile, whereas the other trajectories were associated only with the dominant mental health disorders profile. The diagnosis of chronic obstructive pulmonary disease was most strongly associated with the early-onset persistent asthma and allergies trajectory.[4]

The Severe Asthma Research Program III pediatric cohort found, after assessment at enrollment, an annual decrease in the proportion meeting the criteria for severe asthma. After 3 years, only 30% of subjects met the criteria for severe asthma, with improvements in symptom scores, exacerbations, and controller medication requirements, but not lung function. The odds ratio in favor of resolution of severe asthma was 2.75 for those with a peripheral eosinophil count greater than 436 cells/mL.[5] Risk factors such as self-reported race and genetic ancestry for exacerbation-prone asthma, defined as worsening of asthma symptoms requiring initiation of treatment with systemic corticosteroids, were determined among 12 Asthma Clinical Research Network and AsthmaNet trials. Chronic sinusitis, allergic rhinitis, and gastroesophageal reflux disease were associated with increased exacerbation risk in Black subjects. Furthermore, in a subset of 161 Black subjects with genetic data, those with African ancestry greater than the median (≥82%) demonstrated a greater risk of exacerbation.[6]

Clinical characteristics and comorbidities were examined among asthmatic and nonasthmatic patients with coronavirus disease 2019 across 10 hospitals affiliated with Northwestern Medicine. Neither asthma nor ongoing use of inhaled corticosteroids (ICSs) was associated with an increased risk of hospitalization after adjusting for age, sex, and comorbidities.[7] Lovinsky-Desir et al[8] examined patients younger than 65 years hospitalized with coronavirus disease 2019 infection and also were unable to find differences in hospital length of stay, need for intubation, length of intubation, tracheostomy tube placement, hospital readmission, or mortality between patients with and without asthma. Observations between patients with and without asthma were similar when stratified by obesity, other comorbid conditions (ie, hypertension, hyperlipidemia, and diabetes), use of controller asthma medication, and absolute eosinophil count.[8]

RISK FACTORS FOR ASTHMA DEVELOPMENT AND EXACERBATIONS

Findings on a number of established and new asthma risk factors, such as air pollutants, allergens, exposure to microbial products, intake of acetaminophen and oral supplements, and obesity, were updated in the last 2 years (Table I). In the field of air pollution, publications continued to elucidate hazards, such as those determined by proximity to major roadways using a composite measure from the school and home address in the School Inner-City Asthma Study. Such proximity elevated the likelihood of students reporting more asthma symptoms, health care utilization, and worse asthma control.[9] Lee et al[10] reported on age-stratified time-series analyses examining short-term effects on asthma exacerbations of multiple outdoor environmental exposures in Seoul Metropolitan City. In their study, diurnal temperature range was associated with high relative risks of exacerbations among pediatric and elderly subjects. Tree and weed pollen, human rhinovirus (RV), and influenza were associated with a higher risk among school-age children, whereas tree pollen and influenza were associated with a higher risk among adults. Outdoor air pollutants that included particulate matter of less than 10 mm in diameter, nitrogen dioxide, ozone, carbon monoxide, and sulfur dioxide increased the relative risk in all age groups.[10]

The Inner City Asthma Consortium focused on component analysis of 8 cockroach allergens to determine the allergens and specific IgE, IgG, and IgG_4 levels associated with asthma and rhinitis among cockroach- sensitized 10-year-old children. Recognition of more cockroach allergens with higher allergen-specific IgE levels was associated with asthma and rhinitis. Also, the sum of allergen-specific IgE levels correlated strongly with the total cockroach IgE levels, especially among children with asthma and rhinitis. No single allergen dominated the response to cockroach.[11] The Mouse Allergen and Asthma Intervention Trial (MAAIT) demonstrated that a reduction in mouse allergen exposure (≥75% from baseline) among mouse-sensitized and mouse-exposed asthmatic children randomized to integrated pest management plus education or education alone was associated with greater increases in FEV_1 and forced expiratory flow between 25% and 75% of forced vital capacity over 1 year.[12] The investigators from the same clinical trial in secondary

TABLE I. Key advances in asthma risk factors

Exposure	Cohort or city	Finding	Reference
Air pollution	School Inner-City Asthma Study	School/home proximity to traffic worsened student asthma outcomes	9
	Seoul Metropolitan City, Korea	Outdoor air pollutants, diurnal temperature range, pollens, RV, and influenza increased exacerbations	10
Allergens	Inner-City Asthma Consortium	Recognition of more cockroach allergens with higher allergen-specific IgE levels was associated with asthma and rhinitis	11
	MAAIT	Reduction in mouse allergen was associated with increases in lung function	12
		Reduction in mouse allergen was not associated with a specific clinical characteristic	13
Microbial products	Childhood Asthma Study	Distinct nasal airway microbiotas of asthmatic children alter likelihood of exacerbation, RV, and respiratory illnesses	14
	AsthmaNet microbiome study	Differences in sputum microbiota associated with T2-low asthma; oral microbiota associated with atopy	15
	Chicago-area, USA	Bacterial and fungal microbiota and their coassociations differed among asthma phenotypes	16
	Childhood Origins of Asthma study	Composition of the infant microbiome during healthy periods (ie, *Staphylococcus*-dominant) and during acute wheezing illnesses (*Moraxella*) associated with subsequent persistent childhood asthma	17
Antibiotics	CHILD	Reduction in asthma incidence was associated with decreasing antibiotic use in infancy. Early increasing α-diversity of the gut microbiota was associated with reduced childhood asthma	18
Acetaminophen	Melbourne Atopy Cohort Study	Among children with GSTM1 null and GSTT1 present, early acetaminophen was associated with reduced lung function at age 18 y	19
PUFA	Conditions Affecting Neurocognitive Development and Learning in Early Childhood study	Higher n-6 PUFA levels were associated with increased risk of childhood asthma; n-3 PUFA levels were associated with lower risk	20
	Project Viva	Prenatal consumption of eicosapentaenoic acid, docosahexaenoic acid, and α-linolenic acid associated with protection from adolescent asthma	21
Tocopherol		Low age 3 y γ-T with higher α-T levels had higher childhood lung function	22
Overweight	Respiratory Health in Northern Europe, Spain and Australia study; European Community Respiratory Health Survey study	Overweight of the father during his puberty was associated with asthma in the child	23
	UK Biobank, DIAbetes Genetics Replication And Meta-analysis consortium, Meta-Analyses of Glucose and Insulin-related traits Consortium, European Network for Genetic and Genomic Epidemiology	8 genetic loci shared between BMI and later-onset asthma and 10 loci shared between BMI and nonatopic asthma	24
	School Inner-City Asthma Study	Childhood obesity may increase susceptibility to asthma symptoms when exposed to classroom NO_2	25

BMI, Body mass index.

analyses were unable to pinpoint a specific clinical characteristic studied (eg, level of atopy, lung function, and mouse IgE level) that predicted improvement in asthma following mouse allergen reduction.[13]

There have been many recent advances on the role of microbial products. McCauley et al[14] examined the nasal microbiota in asthmatic children during the fall season using 16s mRNA profiling. Nasal *Moraxella* species were associated with increased exacerbation risk. *Staphylococcus* or *Corynebacterium* species–dominated microbiotas were associated with reduced respiratory illness and fewer exacerbations, whereas *Streptococcus* species–dominated microbiotas increased the risk of RV infection. *In vitro* experiments using human alveolar epithelial cells showed that *Moraxella catarrhalis* induced greater epithelial damage and expression of IL-33 and IL-8 compared with *Staphylococcus epidermidis, Staphylococcus aureus,* and *Corynebacterium propinquum* isolated from the nasal secretions of children with asthma.[14] Additional work showed that the association with asthma-related outcomes may vary by site of the microbiota examined. For example, Durack et al[15] compared profiles between the sputum and oral wash among mild atopic asthmatic patients before and after 6 weeks of treatment with inhaled fluticasone. The sputum microbiota exhibited a lower bacterial diversity among a distinct cluster of type 2 (T2)-low asthmatic phenotype with elevated levels of IL-6, IL-7, IL-8, and MIP-3a. The sputum microbiota also showed less diversity compared with placebo controls and nonresponders to ICS treatment. The oral microbiota associated more closely with atopic status.[15] Sharma et al[16] compared fungal and bacterial microbiota from endobronchial and bronchoalveolar lavage (BAL) samples among asthmatic patients and healthy controls. Fungal diversity was lower and *Trichoderma* species were enriched in endobronchial samples from patients with T2-high (peripheral blood absolute eosinophil count >300/mL) compared with T2-low inflammation. *Penicillium* species were enriched in patients with atopic asthma versus nonatopic asthma and among asthmatic patients versus healthy controls. In BAL samples, the dominant genera were *Cladosporium, Fusarium, Aspergillus,* and *Alternaria.* Specific fungal exact sequence variants associated (both positively and negatively) with FEV_1, fractional exhaled nitric oxide, BAL cell counts, and corticosteroid use. As reported in previous studies, endobronchial bacterial diversity was lower in the T2-high compared with the T2-low group.[16] Notably, the nasopharyngeal microbiome may predict future asthma-related outcomes. In the Childhood Origins of Asthma study, *Staphylococcus*-dominant microbiome in the first 6 months of life was associated with increased risk of recurrent wheezing by age 3 years and persistent asthma throughout childhood. In addition, during wheezing illnesses, detection of RVs and *Moraxella* was prominent and also associated with persistent asthma throughout later childhood.[17]

Patrick et al[18] from the Canadian Healthy Infant Longitudinal Development (CHILD) prospective birth cohort focused on antibiotic prescription before age 1 year and asthma incidence at age 5 years as a surrogate for altered microbial exposure. These queries were paired with 16S rRNA gene sequencing data from fecal samples collected during infancy. Asthma incidence increased by 24% with each 10% increase in antibiotic prescribing. Increasing α-diversity of the gut microbiota at age 1 year was associated with a 32% reduced risk of asthma at age 5 years, suggesting that gut microbiota at age 1 year may mediate an association between antibiotic exposure and asthma at age 5 years.[18]

Acetaminophen, soy isoflavones, and polyunsaturated fatty acids (PUFAs) also have been implicated in asthma. Children with GSTM1 null and GSTT1 in the Melbourne Atopy Cohort Study who used acetaminophen more frequently through age 2 years for nonrespiratory reasons had reduced lung function at age 18 years. Among children with GSTP1 Ile/Ile, but not other GSTP1 genotypes, more frequent acetaminophen use was associated with asthma at 18 years.[19] Rosa et al[20] examined levels of PUFA intake among second-trimester pregnant women and found that higher n-6 PUFA levels were associated with increased risk of asthma, whereas n-3 PUFA levels were associated with lower risk of asthma among the offspring when they reached age 4 to 6 years. The authors also detected a significant 3-way interaction between child sex, maternal asthma, and n-6/n-3 PUFA that indicated that boys born to women with asthma with a higher PUFA ratio had the highest risk of asthma.[20] Another study from the Project Viva cohort examined the association of fatty acids ingestion in pregnancy and asthma in adolescent offspring.[21] Prenatal consumption of specific PUFAs, namely n-3 PUFAs, eicosapentaenoic acid and docosahexaenoic acid, and α-linolenic acid, was associated with protection from subsequent adolescent asthma. These data suggest the maternal diet may influence the development of asthma in the offspring by adolescence, and that fatty acid composition of the diet may be protective of subsequent disease. Also, in Project Viva, the cohort was stratified by tertile of age 3 years γ-tocopherol (γ-T) level. Those children in the lower tertile of γ-T were those for whom a higher α-T level was associated with better midchildhood lung function. This protective association of higher α-T levels was not observed among those with higher levels of γ-T.[22]

Finally, advances have been made in determining the importance of overweight or obesity in asthma risk. Overweight status of the father but not mother during puberty was associated with asthma in the child.[23] Eight independent genetic loci were found to be shared between body mass index and later-onset asthma and 10 independent loci shared between body mass index and nonatopic asthma. Additional analyses suggested that the shared loci included genes important to cell differentiation, cell proliferation, cell migration, and inflammatory responses.[24] Other research suggests that the presence of childhood obesity may increase susceptibility to classroom levels of ambient NO_2 as indicated by more frequent asthma symptom days and days caregiver changed plans.[25]

MECHANISMS OF DISEASE

Great strides in understanding potential mechanisms of asthma development, as well as asthma exacerbation, have led to the identification and development of exciting new avenues for therapeutic intervention. In this section, we highlight findings from the last 2 years we believe are most interesting and novel, dividing them broadly on the basis of immune components involved in the mechanism/treatment (Fig 1).

Cytokines and antibody treatments

Cytokines are important to the development and exacerbation of asthma, but most studies explore their effects on hematopoietic but not structural cells. In an *in vitro* set of experiments, Manson et al[26] studied the effect of primary T_H2 cytokines on explanted small bronchi smooth muscle cells and human airway smooth muscle cells. IL-13 increased the potency of histamine, carbachol, and leukotriene D_4 as contractile agonists, whereas IL-4 increased the potency of histamine. In the explanted bronchi, IL-13 increased histamine 1 and cysteinyl leukotriene 1 receptor message expression. Interestingly, IL-5 and IL-17A had no effect in either of these cell types.[26] Thus, canonical T_H2 cytokines, IL-4 and IL-13, can modulate the responsiveness of airway cells to mast cell products, potentially identifying a pathway through which increased responsiveness could led to asthma symptoms.

The cytokine IL-10 is thought to be produced by regulatory T cells as well as macrophage subsets. However, this may not be entirely the case, because IL-10–producing effector (Foxp3-negative) T cells were found in the lungs of mice who had been treated with repeated house dust mite (HDM) administration. Interestingly, the IL-10 produced by these effector T cells appeared to signal through CD11c myeloid cells, driving increased IL-13, while reducing IFN-γ and IL-17A production. Blockade of this IL-10 axis led to increased numbers of monocytic dendritic cells and IFN-γ, as well as decreased IL-13 and eosinophilia. Thus, in this mouse model, IL-10 helped to suppress the atypical IFN-γ response to repeated HDM administration but led to increased T_H2 cytokines in response, further supporting the idea that induction of T_H2 disease may result from an attempt to dampen T_H1 responses.[27]

Several recent publications demonstrated novel findings with significant therapeutic potentials. One study examined the presence of tryptase in patients with asthma. Patients with severe asthma were demonstrated to have elevated blood tryptase,

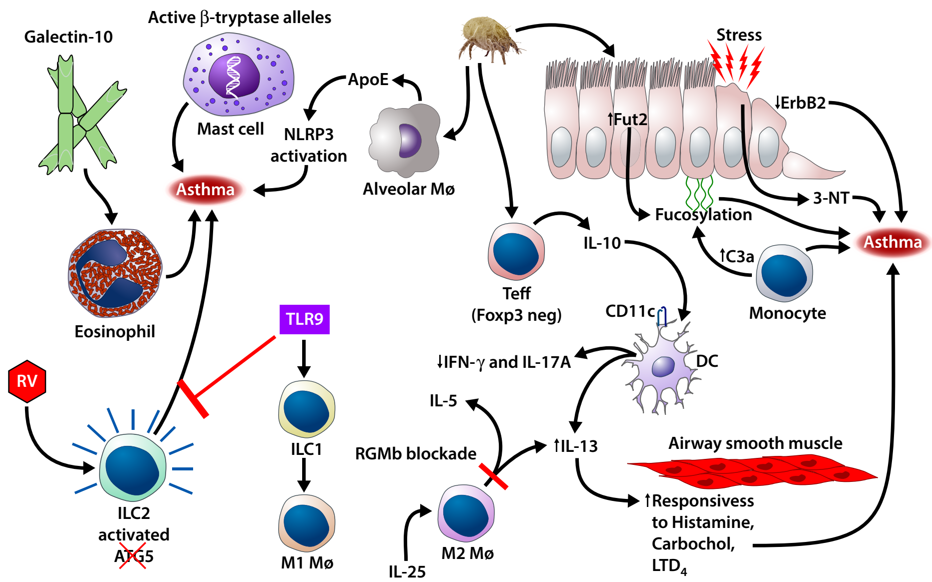

FIG 1. Selected mechanistic advances in asthma research. Galectin-10 crystals and active β-tryptase alleles associated with asthma. RV infection and blockade of ATG5 activated ILC2 cells, whereas TLR9 engagement inhibited activation. IL-25 drove M2 macrophage development; blocking RGMb prevented IL-5 and IL-13 production. HDM increased ApoE from alveolar macrophages and IL-10 from effector T cells; ApoE activated the inflammasome. IL-13 increased smooth muscle responsiveness to various stimuli. HDM increased epithelial cell fucosylation, leading to monocyte recruitment via C3a. Epithelial stress produced 3-NT associated with asthma, as did reduced expression of ErbB2 and impaired wound healing. *ATG5*, Autophagy related 5; *C3a*, complement component 3a; *DC*, dendritic cell; *Fut2*, fucosyltranserase 2; LTD4, leukotriene D_4; *Mø*, macrophage.

regardless of eosinophil status, that correlated with increased expression of active β-tryptase alleles. Patients with asthma in whom blood tryptase was elevated demonstrated reduced responsiveness to anti-IgE therapy compared with those patients with asthma without elevated tryptase levels. The authors hypothesized that the elevated tryptase itself might be exacerbating asthma. They developed an antibody that dissociated tryptase tetramers and demonstrated that it reduced passive IgE anaphylaxis in mice.[28]

The presence of Charcot-Leyden crystals in airways of patients with asthma has been known for more than 150 years. These crystals are composed of galectin-10, an abundant protein found in eosinophil (and basophil) cytoplasm. Using recombinant galectin-10, Persson et al[29] found galectin-10–formed crystals very reminiscent of natural Charcot-Leyden crystals. Administration of galectin-10 crystals in mouse models led to T2 inflammation and many features of asthma. Blocking antibodies against galectin-10 dissolved the crystals *in vitro*, and *in vivo* these antibodies were able to reduce mucous cell metaplasia, IgE production, and airway hyperreactivity in mice.[29] This study suggests that blocking or dissolving galectin-10 crystals may be a potentially useful therapeutic approach to treat asthma.

Innate lymphoid cells

One area of active research in asthma has focused on a set of lymphoid cells that lack antigen receptors. These innate lymphoid cells (ILCs) can be divided into 3 groups: ILC type 1 (ILC1) produce typical T_H1 cytokines such as IFN-γ, whereas ILC type 2 (ILC2) produce T_H2 cytokines, such as IL-4, IL-5, and IL-13, and ILC type 3 (ILC3) produce T_H17-like cytokines (IL-17 and IL-22).[30] Winkler et al[31] looked at the effect of antigen challenge on the frequency and activation of ILC2 cells in the BAL. The authors found that antigen challenge led to increased numbers of ILC2 cells in the BAL but decreased their numbers in the blood. The BAL ILC2 cells were activated and promoting T2 inflammation, whereas the function of the blood ILC2 cells appeared unchanged.[31] Thus, ILC2 cells may be recruited to the airways in asthma, where they become activated and drive T2 inflammation and asthma. ILC2 cells also may be important in viral-induced asthma exacerbations. Using a mouse model, early-life infection (6-day-old Balb/c mice) with RV drove an ILC2-dependent augmented response to a subsequent infection with a different (heterologous) RV strain.[32] Therefore, ILC2 could be the link to explain why RV infection has so strongly correlated with asthma phenotypes.

ILC can have regulatory properties, and a recent publication demonstrated that Toll-like receptor (TLR)9 activation suppressed IL-33 and airway hyperreactivity via inhibition of ILC2, while increasing IFN-α.[33] Interestingly, this IFN-α drove increased IFN-γ production by natural killer cells (another form of ILC1). Thus, TLR9 activation led to increased ILC1 while inhibiting ILC2 function. This may be a useful strategy to reduce ILC2-dependent airway disease, and the authors demonstrated the effectiveness of a microparticle-based delivery system for TLR9 ligands, which could form the basis of this therapy.[33] Metabolic changes in ILC2 cells were found to influence T_H2 cytokine production. Deletion of the autophagy critical gene named autophagy related 5 in ILC2 cells led to impaired use of fatty acid oxidation, while strongly promoting glycolysis. This shift in metabolism associated with increased production of T_H2 cytokines, dysfunctional mitochondria, and excessive reactive oxygen species, demonstrating the potential for metabolic function to define the effect of ILC2 in asthma.[34]

Macrophages/monocytes

M2 macrophages are associated with IL-13 production and are proallergic compared with traditional M1 macrophages. Kim et al[35] explored the relationship between ILC and macrophage differentiation. Comparing induced sputum of patients with asthma to that of controls without asthma, the authors observed that macrophages, ILC1, ILC2, and ILC3 cells were all increased in the induced sputum of patients with asthma.[35] Correlating the numbers of these cell types demonstrated a positive relationship between ILC2 and M2 macrophages, whereas ILC1 and ILC3 cells correlated positively with M1 macrophages. Furthermore, the authors demonstrated that alveolar macrophages cultured with ILC2 cells *in vitro* induced M2 macrophage-related genes; coculture of alveolar macrophages with ILC1 led to expression of M1 macrophage-related genes. Thus, the type of ILC in the airway could skew the airway macrophages and may play an important role in the pathogenesis of asthma.

Macrophages were found to be important in airway disease through expression of the innate molecule repulsive guidance molecule b (RGMb). RGMb is found on various innate cells, such as bronchial epithelial cells, eosinophils, and interstitial macrophages. Using an IL-25–dependent mouse model of allergic asthma, inhibition of RGMb prevented development of airway hyperreactivity and inflammation—even if this blockade occurred only during the challenge phase. Lung interstitial macrophages were noted to express the IL-25 receptor and produced IL-5 and IL-13; therefore, the authors concluded that RGMb blockade may impair the ability of these cells to produce T_H2 cytokines, preventing the development of disease, and speculated that this may be a useful therapy to prevent disease exacerbation.[36]

HDM exposure in a mouse model has been shown to drive NOD-, LRR-, and pyrin domain–containing protein 3 activation, maturation of caspase-1, and IL1-β from alveolar macrophages.[37] Proteases in HDM appear to be most important in driving inflammasome activation, because Gordon et al[38] noted that cysteine and serine proteases found in HDM antigen induced apolipoprotein E (ApoE) secretion from BAL macrophages. This increased ApoE at high-enough concentrations activated NOD-, LRR- and pyrin domain–containing protein 3 and pro–IL-1β expression. In a mouse model, the combination of HDM and polyinosinic-polycytidylic acid led to increased IL-1β in the BAL and NOD-, LRR- and pyrin domain–containing protein 3 inflammasome activation in macrophages in an ApoE-dependent fashion. Thus, proteases in HDM were able to induce an asthma phenotype via elevation of ApoE and subsequent inflammasome activation in alveolar macrophages.[38] Targeted interventions to reduce ApoE might have therapeutic effects in asthma.

T cells

No discussion of research advances in asthma would be complete without covering novel discoveries of the role of T lymphocytes in asthma. We do not normally associate lymphocyte function with the effect of hypoxia; however, exposure of antigen-specific CD8 T cells to hypoxia led to enhanced development of IL-13–expressing T2 cytotoxic T cells. This enhancement occurred through hypoxia induction of hypoxia inducible factor 1α and activation of Janus kinase 1/3 and GATA-3. Adoptive transfer of hypoxia-exposed CD8 T cells into CD8-deficient mice led to increased airway hyperreactivity compared with transfer of normoxia-exposed CD8 T cells.[39] Thus, hypoxia appears to skew CD8 T cells toward an asthma-prone response and may play a role in asthma exacerbations.

Double-negative (DN) natural killer T (NKT) cells do not express CD4 or CD8; a subset of DN NKT cells expresses high levels of CD38. These DN CD38hi NKT cells were found to produce IFN-γ (but not IL-4, IL-13, or IL-17) and in a contact-dependent fashion inhibited CD4 T-cell proliferation and airway hyperreactivity in mice.[40] Furthermore, infection of neonatal mice with influenza drove an increase in DN CD38hi NKT cells, which may be able to inhibit future T-cell proliferation and airway hyperreactivity, providing a mechanism by which prior infection could protect from development of asthma.

Viral infection

Respiratory viral infection early in life associates with the development of asthma, and viral infections later in life drive exacerbations of asthma. There have been important advances in understanding how respiratory viral infections impact development and exacerbation of asthma. One study found bronchial epithelial cells and type II pneumocytes as the major source of IL-33 during RV-induced asthma exacerbations in both humans and mice. Using blocking antibodies, the authors demonstrated that IL-33 suppressed antiviral immune responses leading to decreased IFN-β expression that associated with reduced ability of dendritic cells to promote T_H1-cell development.[41] Therefore, IL-33 could be important in driving viral asthma exacerbations, and targeting IL-33 might be useful not only to reduce asthma but also to improve the respiratory antiviral immune response. Another group, however, found that experimental RV infection led to an amplified antiviral T_H1 response in asthmatic individuals compared with controls. A synchronized bystander expansion of allergen-specific T_H2 cells also was observed but not among those with normal lung function. Regardless of asthma status, an early increase in nasal GCSF, IFN-γ, and TNF, as well as T_H1 cells, correlated with more symptoms, suggesting that the level of the immune response to RV directly related to subsequent airway disease, and even unrelated allergic disease.[42]

Another experimental RV infection study demonstrated that subjects with asthma had an increase in late (days 14-21) upper and lower respiratory tract symptoms compared with subjects without asthma. Treatment with omalizumab in the patients with asthma before RV infection prevented early (first 4 days) changes in lung function and reduced the frequency of subjects having lower respiratory tract symptoms at this time to that seen in nonasthmatic control subjects (from 40%-45% to about 8%-10%).[43] Humans have been shown to make anti-RV IgE, but this study did not assess whether these changes correlated with the presence of antiviral IgE, which could have provided a potential rationale for these findings.[44]

The role of type I IFNs in the antiviral immune response is clear, but how they correlate with disease outcome is opaque. Using biopsy specimens from RV-infected atopic asthmatic patients and nonasthmatic and nonatopic controls, expression of type 1 IFNs was found to be decreased in the bronchial epithelium of patients with asthma. This decreased type 1 IFN response associated with increased viral titers, symptoms, and airway hyperresponsiveness, and correlated with decreased type 1 IFN-producing subepithelial monocytes/macrophages.[45] This study provides additional insight into why patients with asthma might exacerbate when infected with RV.

Epithelium and stress

The airway epithelium plays an important role in immunity and is the site of initial exposure to viruses and allergens, which can drive stress, possibly underlying the development of asthma. One source of redox imbalance and inflammation is nitrosative stress. To determine whether nitrosative stress was associated with asthma outcomes, a recent study reported on the assessment of sputum cells to produce 3-nitrotyrosine (3-NT, a marker of nitrosative stress). Baseline 3-NT levels were increased in the sputum cells from patients with asthma-chronic obstructive pulmonary disease overlap syndrome when compared with cells from patients with asthma alone. Sputum cells from patients with asthma-chronic obstructive pulmonary disease overlap syndrome demonstrated increased production of 3-NT with decreased production of antioxidants. Interestingly, the level of 3-NT correlated with exacerbations and decreased airway function, suggesting that nitrosative stress could be important in the pathogenesis of asthma-chronic obstructive pulmonary disease overlap syndrome.[46]

We often talk about production of cytokines and alarmins from epithelial cells, but inflammatory processes also affect epithelial function in less understood ways. One such way could be glycosylation status of epithelial cells. Using the HDM model, Saku et al[47] found increased expression of the enzyme fucosyltransferase 2 in airway epithelial cells through a signal transducer and activator of transcription 6–dependent fashion. This increased fucosyltransferase 2 expression drove fucosylation of the airway epithelium, and by using mice deficient in fucosyltransferase 2, this fucosylation was shown to associate with complement component 3a production and accumulation of monocytic dendritic cells, as well as development of airway hyperreactivity.[47] Glycosylation (or in this case fucosylation) appears to be important to epithelial function, and the downstream effects on the immune response.

Part of the mechanism of disease in asthma is the repair function of damaged epithelial cells. Epithelial growth factor family members are important in epithelial growth and repair, and one of the epithelial growth factor receptors, erythroblastosis oncogene B2 (ErbB2), has reduced message expression in the airways of patients with asthma. To determine the functional relevance of this finding, Inoue et al[48] examined ErbB2 expression and wound healing in human airway epithelial cells from patients with asthma. Reduced ErbB2 signaling and associated impairment in wound healing correlated with asthma. From these data it appears that impaired ErbB2 signaling may be a hallmark of asthma and a potential therapeutic target for future study.[48]

Many studies have examined ways to phenotype patients with asthma, but few have focused on epithelial-induced signatures to stratify patients. In a recent study from the Unbiased Biomarkers in Prediction of Respiratory Disease Outcomes (U-BIOPRED) cohort, human bronchial epithelial cells were isolated and cultured at air-liquid interface with or without stimulation by IL-6 or a soluble IL-6 receptor. A high IL-6 transsignaling gene signature identified patients with increased exacerbations, blood eosinophils, submucosal T cell and macrophages, and increased TLR pathway–related genes, while cell junction gene expression was reduced. Notably, these transcriptomic pathways were identified in the absence of any T2 airway inflammation; thus, these data suggest a subset of patients with asthma in whom IL-6, but not T2 inflammation, drives airway disease and shows the relevance of phenotyping specific cell responses to inflammatory stimuli.[49]

DIAGNOSIS OF ASTHMA

Scoring systems and diagnostic criteria

Over the past 2 years, significant progress has been made in the development of new scoring systems and tools to facilitate the diagnosis of asthma and to help providers quantify asthma severity. For example, Biagini Myers et al[50] using the Pediatric Asthma Risk Score developed a quantitative tool to predict asthma development in young children. Overall, the Pediatric Asthma Risk Score performed better than the asthma predictive index in children with mild to moderate asthma.[50] Using 4 domains of asthma control, Fitzpatrick et al[51] created a continuous measure of asthma severity called the Asthma Severity Scoring System for adolescents and adults. This tool was found to have acceptable measurement properties and responsiveness to changes in asthma quality of life.[51] Visness et al[52] highlighted the need for consensus guidelines for asthma definitions. In their application comparing 4 different asthma definitions to data from 9 of the Children's Respiratory and Environment Workgroup cohorts, they found substantial differences in asthma prevalence, also suggesting that the diagnosis of asthma on solely a clinical basis can be misleading.[52]

Measures of airway physiology and inflammation

The past 2 years also have led to the development of novel measures of airway physiology, including the use of electronic nose breath prints. Abdel-Aziz et al[53] investigated the ability of noninvasive electronic nose technology to detect atopy in patients with asthma. Using 4 independent asthma cohorts, they found that signals of exhaled volatile organic compounds could classify adequately patients with asthma by atopy.[53] Brinkman et al[54] aimed to identify severe asthma phenotypes using exhaled breath samples from a cohort of adults with severe asthma and electronic nose technology. Samples revealed 3 phenotypes of severe asthma that differed across systemic inflammatory markers and patterns of anti-inflammatory medication use.[54]

Our comprehension of lung ventilation was further expanded by Bell et al[55] who performed the first quantitative functional computed tomography imaging study to understand the spatial determinants of the small airway ventilation heterogeneity markers R5-R20 and Sacin in adult asthmatic patients and healthy volunteers. Asthmatic patients with abnormal small airway ventilation heterogeneity measurements demonstrated small airways disease and reduced ventilation in the inferior regions of the lung, anticipated to affect the effectiveness of inhaled therapies.[55]

Genomic, transcriptomic, methylomic, proteomic, and metabolomic profiling

The past 2 years have brought significant advances within the field of genetics, including those pertaining to specific loci. Among children from the Children's Respiratory and Environment Workgroup consortium, Ober et al[56] performed a genetic association study intended to fine map the most common locus associated with childhood-onset asthma, 17q12-21; they reported that SNPs regulating Gasdermin B expression in airway epithelium may be important in childhood-onset asthma,[56] although whether 17q12-21 genetic variants also are associated with childhood wheezing phenotypes remained poorly explored. Using data from 7 US birth cohorts, Hallmark et al[57] showed that 17q12-21 is a "wheezing locus," and this association may reflect an early-life susceptibility to respiratory viruses common to all wheezing children.

IL-33 SNPs also have been reproducibly associated with asthma, but information about function has not been well understood. Using regression modeling, Ketelaar et al[58] found that genetic signals at the IL-33 locus primarily associated with blood eosinophil counts in the general population and with an eosinophilic asthma phenotype. These signals influenced IL-33 levels in the airway epithelium.[58] Vince et al[59] found that HLA-DRB1*09:01 was associated with higher total IgE levels. This represents the first time an HLA allele has been shown to be associated with total IgE levels in African-ancestry individuals with asthma.

The use of ICS treatment for asthma has long been considered a cornerstone of therapy. The study by Levin et al[60] sought to identify genetic predictors of ICS response in multiple population groups with asthma. They identified a variant, rs3827907, that appeared to influence the response to ICS treatment in multiple population groups and likely mediated its effect through eosinophils.[60]

Additional genetic breakthroughs were made in genome-wide association studies. Shrine et al[61] identified 24 genome-wide signals associated with moderate to severe asthma, including 3 novel signals that regulated mucin production. Pividori et al[62] reported the first large genome-wide association study of both childhood- and adult-onset asthma. They identified 61 independent asthma loci, 23 specific to childhood onset, 1 specific to adult onset, and 37 shared, with larger effect sizes for childhood-onset asthma.[62]

The past 2 years also have brought advancements in transcriptomics, with new information about the nasal and airway epithelium. Kicic et al[63] performed RNA sequencing on upper and lower airway epithelial cells and showed that transcriptional composition was greatly conserved, supporting the notion of a unified airway. Korde et al[64] sought to determine the role of endothelial microRNA-1 in allergic airway inflammation. They found that serum microRNA-1 levels inversely related to sputum eosinophilia, airway obstruction, and number of hospitalizations in asthmatic patients, suggesting that microRNA-1 could have therapeutic potential in patients with asthma.[64]

The field also welcomed advances in DNA methylation profiling. Qi et al[65] identified replicable DNA methylation sites in nasal brushes that may serve as biomarkers of asthma and rhinitis. Methylation of a particular CpG site was positively associated with pet exposure during school.[65] Chen et al[66] showed that early-life undernutrition increased susceptibility to asthma by causing an increase in T_H2 skewing via rapamycin 1–dependent glycolysis upregulation and T_H2 cytokine locus hypomethylation in $CD4^+$ T cells.[66] Reese et al[67] discovered potentially novel biomarkers from the Pregnancy And Childhood Epigenetics consortium. Epigenome-wide meta-analyses of school-age asthma in relation to CpG methylation in blood were determined in newborns, in prospective analyses, or cross-sectionally in school-age children. Pathway analyses found enrichment for asthma-relevant immune processes and overlap in pathways enriched both in newborns and in children.[67]

Finally, progress was made in assessing the utility of airway proteomic signatures, including those measured by the U-BIOPRED study group from sputum supernatants that stratified asthmatic patients according to 10 clusters or proteotypes. These were matched with transcriptomic markers to explore differentially activated underlying mechanisms.[68] Lee-Sarwar et al[69] used a more integrative approach that included metabolomic profiling of fecal and blood samples and intestinal microbiome measures using 16S rRNA sequencing. They found an inverse association between asthma at age 3 years and polyunsaturated fatty acids and other lipids. Specific bacterial taxa, plasma metabolites, and dietary factors, including lack of breast-feeding and meat intake, were associated with asthma-associated metabolites.[69]

TREATMENT

The past 2 years brought updates to asthma guidelines and to the pharmacologic management of patients (Table II). In December 2020, the updated National Asthma Education Prevention Program (NAEPP) guidelines were released, which brought recommendations regarding intermittent use of ICSs and the use of as-needed budesonide-formoterol (ie, single maintenance and reliever therapy).[70] The guidelines included a review of bronchial thermoplasty, for which the long-term efficacy and safety had been previously unknown. A more recent study found, however, that the efficacy of bronchial thermoplasty was sustained for 10 years or more, with an acceptable safety profile for patients.[71]

The past 2 years also brought exciting insights into the unique roles of ICS and long-acting beta-agonist (LABA) therapies. For example, in contrast to African American adolescents and adults who had a superior response to the addition of a LABA, Wechsler et al[72] found that almost half the African American children with poorly controlled asthma had a superior response to an increase in their ICS dose. O'Byrne et al[73] examined as-needed use of budesonide-formoterol (ie, single maintenance and reliever therapy) and found that in mild asthma, as-needed budesonide-formoterol reduced the short-term risk of severe exacerbations after a single day of higher use. Weinstein et al[74] found that addition of formoterol to mometasone furoate maintenance therapy did not increase the risk of serious asthma-related events and reduced the risk of asthma exacerbations. The Palladium study found that once-daily dosing of ICS and LABA improved lung function over ICS monotherapy at week 26; high-dose once-daily dosing was not inferior to traditional twice-daily dosing of ICS-LABA for improvement in trough FEV_1.[75]

In addition, there were multiple gains in the field of biologics. Busse et al[76] showed that benralizumab, when administered for 2 years, had a safety and tolerability profile similar to that observed over 1 year in Efficacy and Safety Study of Benralizumab Added to High-dose Inhaled Corticosteroid Plus LABA in Patients with

TABLE II. Key advances in asthma therapeutics

Pharmacologic advances				
Therapeutic	**Study type**	**Study population**	**Finding**	**Reference**
ICS + LABA	RCT	AA children, adults with poorly controlled asthma	Almost half the children had superior response to increase in ICS and addition of LABA	72
ICS-LABA	*Post hoc* analysis of SYGMA 1	Adolescents and adults with mild persistent asthma	PRN budesonide-formoterol reduced short-term risk of severe exacerbations after single day of use	73
ICS-LABA	RCT	Adolescents and adults with persistent asthma	Adding formoterol to mometasone did not increase the risk of SAEs	74
ICS-LABA	Phase 3 clinical trial	12-75-y-olds with persistent asthma	Once-daily dosing of mometasone-indacaterol improved lung function more than did mometasone	75
Benralizumab	Phase 3 extension trial (1-y results)	Patients who had completed either SIROCCO or CALIMA	No new safety consequences observed in year 2	76
Benralizumab	Safety Extension Study (after 3 y of treatment)	Adolescents and adults with severe asthma who completed SIROCCO or CALIMA	Safe and efficacious	77
Mepolizumab	Open-label extension study	Severe eosinophilic asthmatic patients previously enrolled in DREAM	Safe and efficacious over the long-term	78
Tezepelumab	Phase 3 clinical trial	Severe uncontrolled asthma age 12-80 y	Tezepelumab associated with better lung function, quality of life, and asthma control; fewer exacerbations	79
Fevipiprant	Phase 2 clinical trial	Uncontrolled asthma on dual or triple asthma therapy ≥ 12 y	Reduced sputum eosinophils, improved lung function; decreased exacerbation rates	80
Omalizumab	Prospective observational study	Pregnant asthmatic women exposed to omalizumab	No increased risk of major congenital anomalies	81

Nonpharmacologic advances				
Therapeutic	**Type of study**	**Study population**	**Findings**	**Reference**
BT	Follow-up study of previous RCTs	Patients ≥10 y out from BT	Efficacy sustained ≥10 y; acceptable safety profile	71

BT, Bronchial thermoplasty; *DREAM*, Dose Ranging Efficacy And Safety With Mepolizumab in Severe Asthma; *RCT*, randomized controlled trial; *SAE*, serious asthma-related event; *SYGMA 1*, SYmbicort Given as needed in Mild Asthma.

Uncontrolled Asthma (SIROCCO) and Efficacy and Safety Study of Benralizumab in Adults and Adolescents Inadequately Controlled on Inhaled Corticosteroid Plus Long-acting β2 Agonist (CALIMA) trials. Furthermore, long-term eosinophil depletion by benralizumab did not lead to any new adverse consequences. Improvements in efficacy measures (exacerbation rate, lung function, and asthma symptoms) demonstrated in previous primary randomized controlled trials were maintained. Benralizumab 30 mg every 4 or 8 weeks for 3 years was safe and effective in treating asthma in 86 adolescent patients in the long-term Safety Extension Study to Evaluate the Safety and Tolerability of Benralizumab in Asthmatic Adults and Adolescents on Inhaled Corticosteroid Plus LABA (BORA) trial.[77] The long-term safety and efficacy of mepolizumab in patients with severe eosinophilic asthma was reported by Khatri et al.[78] Mepolizumab maintained clinical effectiveness with a favorable safety profile, with no evidence of inducing neutralizing antibodies.

Although several biologics have been approved by the Food and Drug Administration and are currently in clinical use, research has been ongoing for other potential new therapies. For example, the past 2 years have brought new information about the use of tezepelumab, a human mAb that blocks thymic stromal lymphopoietin. A study by Menzies-Gow et al[79] found that patients with severe, uncontrolled asthma who received tezepelumab had fewer exacerbations and better lung function, asthma control, and quality of life than those who received placebo. Brightling et al[80] showed that therapy with fevipiprant, a prostaglandin D2 receptor antagonist, reduced sputum eosinophils and improved lung function in phase 2 trials of patients with asthma. Neither trial showed a statistically significant reduction in asthma exacerbations after adjusting for multiple testing but did show consistent modest reductions in exacerbations rates.

Lastly, the field of allergy and immunology has continued to gather additional data on the first Food and Drug Administration–approved biologic for the treatment of severe asthma, namely omalizumab. Namazy et al[81] compared outcomes from the Observational Study of the Use and Safety of Xolair (omalizumab) during Pregnancy (EXPECT). In this pregnancy registry those treated with omalizumab were compared with those from a disease-matched population of pregnant women not treated with omalizumab, and no evidence of increased risk of major congenital anomalies among pregnant women exposed to omalizumab was found.[81]

CONCLUSIONS

Over the past 2 years there have been many advances made in the understanding of the natural course, risk factors, mechanisms, and optimal treatment of asthma. As we have noted above, many findings have opened novel avenues for prediction of disease progression and intervention. Mechanistic work has moved the field further from the standard T_H2 paradigm, and demonstrated the complexity of the disease we call "asthma." Future mechanistic research should continue focusing on these pathways and cells that are beyond the standard T_H2 paradigm. This approach should lead to a greater understanding of the variability in the clinical, immune, and multiomic response that underlies this disease. Specific examples of studies in the past 2 years that have the potential to change how we treat and prevent asthma include those that involve antibody therapies against tryptase or galectin-10, agents that target recruitment of ILCs cells to the airways or impact their metabolism, and those that modulate epithelial sugar moieties. Although many of these advancements were made in animal models, it is important that additional research demonstrate the relevance to humans. A greater understanding of the mechanisms underlying responses and nonresponses to novel therapeutics and across asthma phenotypes also would be beneficial. Still, the progress over just the past 2 years has been immense and impactful.

Key advances

- **The differential rates in asthma by sex resulted from a decline among adolescent males but relatively stable rates among adolescent females,[1] and predictors of pediatric asthma remission by age 18 to 23 years included the level of impairment in FEV_1/forced vital capacity, lower airways responsiveness, and baseline serum eosinophil count.[2]**
- **Exposure to air pollution continues to be found to be hazardous and associated with a higher likelihood of students reporting more asthma symptoms, health care utilization, and worse asthma control and asthma exacerbations.[9,10]**
- **Respiratory viral infections impact the development, phenotype, and exacerbation of asthma, new links with ILC2s are apparent, and the airway epithelium has gained prominence as a site for immune processes that underlie how viruses and allergens interact and may drive stress.[32,41-43]**
- **New scoring systems and tools may facilitate the diagnosis of asthma and help providers quantify asthma severity and measure airway physiology.[50,51]**
- **Precision diagnostics feature advances in genomic, transcriptomic, methylomic, proteomic, and metabolomic profiling.**
- **Updates to the NAEPP asthma guidelines and additional studies support novel pharmacologic management of patients.[70]**

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