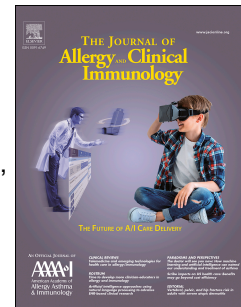


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**Advances in Asthma: New Understandings of Asthma's Natural History, Risk
Factors, Underlying Mechanisms, and Clinical Management**

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Abstract

The last two 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, polyunsaturated fatty acids, and exposure to microbial products. The past two years have benefitted 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 asthma, underlying mechanisms, diagnostic approaches, and treatments. While 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 two years has been immense and impactful.

Key Words:

Asthma, biomarkers, genetics, microbiome, viral infections, cytokines, tryptase, T cells, innate lymphoid cells, macrophages, epithelium, microbiome, asthma scoring systems, airway physiology, biologic therapies

Abbreviations used:

AA: African American

ACO: asthma-chronic obstructive pulmonary disease overlap syndrome

ALSPAC: Avon Longitudinal Study of Parents and Children

ApoE: apolipoprotein E

ASSESS: Asthma Severity Scoring System

ATG5: autophagy related 5

BMI: body mass index

BORA: A Safety Extension Study to Evaluate the Safety and Tolerability of

Benralizumab in Asthmatic Adults and Adolescents on Inhaled Corticosteroid Plus

LABA

C3a: complement component 3a

CALIMA: Efficacy and Safety Study of Benralizumab in Adults and Adolescents

Inadequately Controlled on Inhaled Corticosteroid Plus Long-acting β 2 Agonist

CHILD: Canadian Healthy Infant Longitudinal Development

CREW: Children's Respiratory and Environment Workgroup

CAMP: Childhood Asthma Management Program

CysLT1: Cysteinyl leukotriene 1

DC: Dendritic cell

- 86 DN: Double negative
- 87 DREAM: Dose Ranging Efficacy And Safety With Mepolizumab in Severe Asthma
- 88 ECHO: Environmental Influences on Child Health Outcomes
- 89 ED: Emergency department
- 90 EGF: Epithelial growth factor
- 91 ErbB2: erythroblastic oncogene B receptor B2
- 92 EXPECT: Observation Study of the Use and Safety of Xolair
- 93 FEF25–75: Forced expiratory flow between 25% and 75% of FVC
- 94 FVC: Forced vital capacity
- 95 FEV₁: Forced expiratory volume in one second
- 96 FENO: Fractional exhaled nitric oxide
- 97 Fut2: Fucosyltransferase 2
- 98 GCSF: Granulocyte colony stimulating factor
- 99 GSDMB: Gasdermin B
- 100 GWAS: Genome-wide association studies
- 101 H1: Histamine 1
- 102 HDM: House dust mite
- 103 HIF α : Hypoxia inducible factor 1 α
- 104 IL-6TS: IL-6 trans-signaling gene signature
- 105 ICS: Inhaled corticosteroids
- 106 ILC: Innate lymphoid cell
- 107 ILC1: Type 1 ILC
- 108 ILC2: Type 2 ILC

- 109 ILC3: Type 3 ILC
- 110 IR: Incidence rate
- 111 JAK: Janus kinase
- 112 LABA: Long-Acting Beta-Agonists
- 113 LTD₄: Leukotriene D₄
- 114 MiR-1: MicroRNA-1
- 115 Mø: Macrophage
- 116 NK: Natural killer
- 117 NKT: Natural killer T
- 118 NLRP3: NOD-, LRR- and pyrin domain-containing protein 3
- 119 OR: Odds ratios
- 120 PARS: Pediatric Asthma Risk Score
- 121 PUFA: Polyunsaturated fatty acid
- 122 QOL: Quality of life
- 123 RCT: Randomized Controlled Trial
- 124 RGMb: Repulsive Guidance Molecule b
- 125 RV: Rhinovirus
- 126 SAEs: Serious asthma-related events
- 127 SARP: Severe Asthma Research Program
- 128 sIL-6R: soluble IL-6 receptor
- 129 SIROCCO: Efficacy and Safety Study of Benralizumab Added to High-dose Inhaled
130 Corticosteroid Plus LABA in Patients with Uncontrolled Asthma
- 131 SMART: Single Maintenance and Reliever Therapy

132 SNP: Single nucleotide polymorphism
133 SYGMA 1: SYmbicort Given as needed in Mild Asthma
134 T: Tocopherol
135 T2: Type 2
136 Tc2: Type 2 cytotoxic
137 Th1: T helper 1
138 Th2: T helper 2
139 TLR: Toll like receptor
140 TNF: Tumor necrosis factor
141 U-BIOPRED: Unbiased Biomarkers in Prediction of Respiratory Disease Outcomes
142 VDAART: Vitamin D Antenatal Asthma Reduction Trial
143 VH: Ventilation heterogeneity
144 3-NT: 3-nitrotyrosine
145
146
147

The last two years have yielded a proliferation of high-quality asthma research. While 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 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 (CREW), sponsored by the National Institutes of Health Environmental Influences on Child Health Outcomes (ECHO) 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 18-23 years were examined in the Childhood Asthma Management Program (CAMP). The level of impairment in forced expiratory volume in one second (FEV₁)/forced vital capacity (FVC) 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 and colleagues 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 two asthma candidate genes (GSDMB/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 higher levels of fractional exhaled nitric oxide (FENO), 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 was associated with all three wheeze phenotypes. Participants of Black or “other” race/ethnicity and for one 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 five 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 (approximately 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 COPD was most strongly associated with the early-onset persistent asthma and allergies trajectory.⁴

The Severe Asthma Research Program (SARP) 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 (ORs) 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. Further, in a subset of 161 Black subjects with genetic data, those with African ancestry greater than the median ($\geq 82\%$) demonstrated a greater risk of exacerbation.⁶

Clinical characteristics and comorbidities were examined among asthmatic and nonasthmatic patients with COVID-19 across 10 hospitals affiliated with Northwestern Medicine. Neither asthma nor ongoing use of inhaled corticosteroids (ICS) were associated with an increased risk of hospitalization after adjusting for age, sex, and comorbidities.⁷ Lovinsky-Desir and colleagues examined patients under age 65 years

hospitalized with COVID19 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 two years (Table 1). 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, healthcare utilization and worse asthma control.⁹ Lee and colleagues 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 higher risk among school-aged children, whereas tree pollen and influenza were

associated with higher risk among adults. Outdoor air pollutants that included particulate matter of <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 IgG₄ 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 ($\geq 75\%$ from baseline) among mouse sensitized and exposed asthmatic children randomized to integrated pest management plus education or education alone was associated with greater increases in FEV₁ and FEF_{25–75} over 1 year.¹² The investigators from the same clinical trial in secondary analyses were unable to pinpoint a specific clinical characteristic studied (egs. level of atopy, lung function, 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 and her colleagues 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. compared profiles between the sputum and oral wash among mild atopic asthmatics prior to and following 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 and colleagues compared fungal and bacterial microbiota from endobronchial and bronchoalveolar lavage (BAL) samples among asthmatics 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 asthmatics 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 FEV₁, FENO, 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 Rhinoviruses and *Moraxella* were prominent and also associated with persistent asthma throughout later childhood.¹⁷

Patrick et. al. from the Canadian Healthy Infant Longitudinal Development (CHILD) prospective birth cohort focused on antibiotic prescription prior to age one 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 one year was associated with a 32% reduced risk of asthma at age 5 years, suggesting that gut microbiota at age one 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. 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 4-6 years old. The authors also detected a significant 3-way interaction between child sex, maternal asthma, and n-6/n-3 PUFA that indicated 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, α -linolenic acid, 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 mid-childhood 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 (BMI) and later-onset asthma and 10 independent loci shared between BMI 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 NO₂ 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 two years we believe are most interesting and novel, dividing them broadly based on the immune components involved in the mechanism/treatment (Figure 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 studied the effect of primary T helper 2 (Th2) cytokines on explanted small bronchi smooth muscle cells and human airway smooth muscle cells. IL-13 increased the potency of histamine, carbachol, and leukotriene D₄ (LTD₄) as contractile agonists, while IL-4 increased the potency of histamine. In the explanted bronchi, IL-13 increased histamine 1(H1) and cysteinyl leukotriene 1(CysLT1) receptor message expression. Interestingly, IL-5 and IL-17A had no effect in either of these cell types.²⁶ Thus, canonical Th2 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 lead 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, as 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 Th2 cytokines in response, further supporting the idea that induction of Th2 disease may result from an attempt to dampen Th1 responses.²⁷

Several recent publications demonstrated novel findings with significant therapeutic potentials. One study examined the presence of tryptase in asthma patients. Severe asthma patients were demonstrated to have elevated blood tryptase, 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 to those asthma patients 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 it reduced passive IgE anaphylaxis in mice.²⁸

The presence of Charcot-Leyden crystals in airways of patients with asthma has been known for over 150 years. These crystals are composed of galectin-10, an abundant protein found in eosinophil (and basophil) cytoplasm. Using recombinant

galectin-10, Persson and colleagues found galectin-10 formed crystals very reminiscent of natural Charcot-Leyden crystals. Administration of galectin-10 crystals in mouse models led to type 2 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 hyper-reactivity 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 (ILC) can be divided into 3 groups: ILC type 1 (ILC1) produce typical Th1 cytokines like IFN γ , while ILC type 2 (ILC2) produce Th2 cytokines, such as IL-4, IL-5, and IL-13, and type 3 ILC (ILC3) produce Th17-like cytokines (IL-17 and IL-22).³⁰ Winkler et al looked at the effect of antigen challenge on frequency and activation of ILC2 cells in the bronchoalveolar lavage fluid (BAL). The authors found 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 type 2 inflammation, while 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 type 2 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 toll like receptor (TLR) 9 activation suppressed IL-33 and airway hyper-reactivity via inhibition of ILC2, while increasing IFN α .³³ Interestingly, this IFN α drove increased IFN γ production by natural killer (NK) cells (another form of type 1 ILC). Thus, TLR9 activation led to increased type 1 ILC while inhibiting ILC2 function. This may be a useful strategy to reduce ILC2 dependent airway disease, and the authors demonstrated effectiveness of a microparticle based delivery system for TLR9 ligands, that could form the basis of this therapy.³³ Metabolic changes in ILC2 cells were found to influence Th2 cytokine production. Deletion of the autophagy critical gene named autophagy related 5 (ATG5) in ILC2 cells led to impaired use of fatty acid oxidation, while strongly promoting glycolysis. This shift in metabolism associated with increased production of Th2 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 pro-allergic compared to traditional M1 macrophages. Kim et al explored the relationship between ILC and macrophage differentiation. Comparing induced sputum of patients with asthma to non-asthma controls, the authors observed 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, while ILC1 and ILC3 cells correlated positively with M1 macrophages. Further, the authors demonstrated that alveolar macrophages cultured with ILC2 cells *in vitro* induced M2 macrophage related genes; co-culture of alveolar macrophages with ILC1 lead 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 hyper-reactivity 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 Th2 cytokines, preventing the development of disease, and speculated 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 (NLRP3) activation, maturation of caspase-1, and IL1- β from alveolar macrophages.³⁷ Proteases in HDM appear to be most important in driving inflammasome activation, as Gordon et al 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 NLRP3

and proIL-1 β expression. In a mouse model, the combination of HDM and polyinosinic-polycytidylic acid led to increased IL-1 β in the BAL and NLRP3 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 type 2 cytotoxic T (Tc2) cells. This enhancement occurred through hypoxia induction of hypoxia inducible factor 1 α (HIF1 α) and activation of Janus kinase (JAK) 1/3 and GATA-3. Adoptive transfer of hypoxia exposed CD8 T cells into CD8 deficient mice led to increased airway hyper-reactivity compared to transfer of normoxia exposed CD8 T cells.³⁹ Thus, hypoxia appears to skew CD8 T cells towards 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 express 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 hyper-reactivity in mice.⁴⁰ Further, infection of neonatal mice with influenza drove an increase in DN CD38hi NKT, that may be able

to inhibit future T cell proliferation and airway hyper-reactivity -- 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 IL-33 suppressed anti-viral immune responses leading to decreased IFN- β expression that associated with reduced ability of dendritic cells to promote T helper 1 (Th1) cell development.⁴¹ Therefore, IL-33 could be important in driving viral asthma exacerbations, and targeting IL-33 might be useful to reduce asthma but also to improve the respiratory anti-viral immune response. Another group, however, found that experimental RV infection led to an amplified anti-viral Th1 response in asthmatic individuals compared to controls. A synchronized bystander expansion of allergen specific Th2 cells also was observed – but not among those with normal lung function. Regardless of asthma status, an early increase in nasal granulocyte colony stimulating factor (GCSF), IFN- γ , and tumor necrosis factor (TNF), as well as Th1 cells correlated with more symptoms, suggesting 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 subjects with asthma had an increase in late (days 14-21) upper and lower respiratory symptoms compared to subjects without asthma. Treatment with omalizumab in the asthma patients 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 non-asthmatic control subjects (from 40-45% to about 8-10%).⁴³ Humans have been shown to make anti-rhinovirus 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 anti-viral immune response is clear, but how they correlate with disease outcome is opaque. Using biopsy specimens from RV infected atopic asthmatic patients and non-asthmatic and non-atopic controls, expression of type I IFNs were found to be decreased in the bronchial epithelium of asthma patients. This decreased type I IFN response associated with increased viral titers, symptoms, and airway hyper-responsiveness, and correlated with decreased type I IFN producing sub-epithelial monocytes/macrophages.⁴⁵ This study provides additional insight into why asthma patients might exacerbate when infected with rhinovirus.

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 if nitrosative stress 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 (ACO) when compared to cells from patients with asthma alone. Sputum cells from patients with ACO 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 nitrosative stress could be important in the pathogenesis of ACO.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 found increased expression of the enzyme fucosyltransferase 2 (Fut2) in airway epithelial cells through a STAT6 dependent fashion. This increased Fut2 expression drove fucosylation of the airway epithelium, and by using mice deficient in Fut2, this fucosylation was shown to associate with complement component 3a (C3a) production and accumulation of monocytic dendritic cells, as well as development of airway hyper-reactivity.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 (EGF) family members are important in epithelial growth and repair, and one of the EGF 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 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 asthma patients, but few have focused on epithelial induced signatures to stratify patients. In one recent study from the 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 (sIL-6R). A high IL-6 trans-signaling gene signature (IL-6TS) 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 asthma patients in whom IL-6, but not type 2 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 two years, there has been significant progress 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 using the

Pediatric Asthma Risk Score (PARS) developed a quantitative tool to predict asthma development in young children. Overall, the PARS performed better than the asthma predictive index in children with mild-to-moderate asthma.⁵⁰ Using four domains of asthma control, Fitzpatrick and colleagues created a continuous measure of asthma severity called the Asthma Severity Scoring System (ASSESS) for adolescents and adults. This tool was found to have acceptable measurement properties and responsiveness to changes in asthma quality of life (QOL).⁵¹ Visness and colleagues highlighted the need for consensus guidelines for asthma definitions. In their application comparing four different asthma definitions to data from 9 of the CREW 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 two years also have led to the development of novel measures of airway physiology, including the use of electronic noses (eNose) breath prints. Abdel-Aziz and group investigated the ability of noninvasive eNose technology to detect atopy in patients with asthma. Using four independent asthma cohorts, they found signals of exhaled volatile organic compounds could classify adequately patients with asthma by atopy.⁵³ Brinkman et al aimed to identify severe asthma phenotypes using exhaled breath samples from a cohort of adults with severe asthma and eNose technology. Samples revealed three 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 who performed the first quantitative functional CT imaging study to understand the spatial determinants of the small airway ventilation heterogeneity (VH) markers R5-R20 and Sacin in adult asthmatic patients and healthy volunteers. Asthmatic patients with abnormal small airway VH 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 two years have brought significant advances within the field of genetics, including those pertaining to specific loci. Among children from the CREW consortium, Ober et al 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 (GSDMB) 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 seven U.S. birth cohorts, Hallmark et al 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.⁵⁷

IL-33 SNPs also have been reproducibly associated with asthma, but information about function has not been well understood. Using regression modeling, Ketelaar found 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 found that HLA-DRB1*09:01 was associated with higher total IgE levels.⁵⁹ 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 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 (GWAS). Shrine et al identified 24 genome-wide signals associated with moderate-to-severe asthma, including three novel signals that regulated mucin production.⁶¹ Pividori reported the first large GWAS of both childhood and adult-onset asthma. They identified 61 independent asthma loci, 23 specific to childhood onset, one specific to adult onset, and 37 shared, with larger effect sizes for childhood-onset asthma.⁶²

The past 2 years also has brought advancements in transcriptomics with new information about the nasal and airway epithelium. Kicic et al 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.⁶³ Korde sought to determine the role of endothelial microRNA-1 (miR-1) in allergic airway inflammation. They found that serum miR-1 levels inversely related to sputum

eosinophilia, airway obstruction, and number of hospitalizations in asthmatic patients, suggesting that MiR-1 could have therapeutic potential in asthmatics.⁶⁴

The field also welcomed advances in DNA methylation profiling. Qi et al identified replicable DNA methylation sites in nasal brushes that may serve as biomarkers of asthma and rhinitis. Methylation of one particular CpG site was positively associated with pet exposure during school.⁶⁵ Chen et al showed early-life under-nutrition increased susceptibility to asthma by causing an increase in Th2 skewing via rapamycin 1-dependent glycolysis upregulation and Th2 cytokine locus hypomethylation in CD4+ T cells.⁶⁶ Reese 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 either in newborns, in prospective analyses, or cross-sectionally in school-aged children. Pathway analyses found enrichment for asthma-relevant immune processes and overlap in pathways enriched both in newborns and 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 asthmatics according to 10 clusters or proteotypes. These were matched with transcriptomic markers to explore differentially activated underlying mechanisms.⁶⁸ Lee-Sawar and her colleagues performed 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 breastfeeding and meat intake, associated with asthma-associated metabolites.⁶⁹

Treatment

The past two years brought updates to asthma guidelines and to the pharmacologic management of patients (Table 2). In December 2020, the updated NAEPP guidelines were released, which brought recommendations regarding intermittent use of inhaled corticosteroids and the use of as-needed budesonide–formoterol (i.e. Single Maintenance and Reliever Therapy (SMART)).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 two 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 (AA) adolescents and adults who had a superior response to the addition of a LABA, Wechsler et al found that almost half of AA children with poorly controlled asthma had a superior response to an increase in their ICS dose.⁷² O’Byrne et al examined as-needed use of budesonide-formoterol (i.e. SMART) 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.⁷³ Weinstein et al found that addition of formoterol to mometasone furoate maintenance therapy did not increase the risk of

serious asthma-related events (SAEs) and reduced the risk of asthma exacerbations.⁷⁴
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 FEV₁.⁷⁵

In addition, there were multiple gains in the field of biologics. Busse et al 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 Uncontrolled
Asthma (SIROCCO) and Efficacy and Safety Study of Benralizumab in Adults and
Adolescents Inadequately Controlled on Inhaled Corticosteroid Plus Long-acting β 2
Agonist (CALIMA) trials.⁷⁶ Further, 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 four
or eight 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.⁷⁸ Mepolizumab maintained clinical
effectiveness with a favorable safety profile, with no evidence of inducing neutralizing
antibodies.

While several biologics have been FDA approved and are currently in clinical use,
research has been ongoing for other potential new therapies. For example, the past two

years have brought new information about the use of tezepelumab, a human monoclonal antibody that blocks thymic stromal lymphopoietin. A study by Menzies-Gow et al found that patients with severe, uncontrolled asthma who received tezepelumab had fewer exacerbations and better lung function, asthma control, and QOL than those who received placebo.⁷⁹ Brightling and group showed that therapy with fevipirant, a prostaglandin D2 receptor antagonist, reduced sputum eosinophils and improved lung function in phase 2 trials of patients with asthma.⁸⁰ 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 FDA approved biologic for the treatment of severe asthma, namely omalizumab. Namazy 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

Conclusion

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 Th2 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 Th2 paradigm. This approach should lead to a greater understanding of the variability in the clinical, immune, and multi-omic 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. While 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 18-23 years included the level of impairment in FEV₁/FVC, 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, healthcare 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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Table 1. 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, 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, 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 co-associations differed among asthma phenotypes.	¹⁶
	Childhood Origins of Asthma study	Composition of the infant microbiome during healthy periods (i.e. <i>Staphylococcus</i> -dominant) and during acute wheezing illnesses (<i>Moraxella</i>) associated	¹⁷

		with subsequent persistent childhood asthma.	
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 years.	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, α -linolenic acid, associated with protection from adolescent asthma.	21
	Tocopherol	Low age 3 years 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-	8 genetic loci shared between BMI and later-onset asthma and 10 loci shared between BMI and nonatopic asthma.	24

	Analyses of Glucose and Insulin-related traits Consortium, European Network for Genetic and Genomic Epidemiology		
	School Inner-City Asthma Study	Childhood obesity may increase susceptibility to asthma symptoms when exposed to classroom NO ₂ .	²⁵

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1052 **Table 2: 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 of 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 risk of SAEs.	⁷⁴
ICS-LABA	Phase 3 Clinical Trial	12-75 year olds with persistent asthma	Once daily dosing of mometasone-indacaterol improved lung function more than mometasone.	⁷⁵
Benralizumab	Phase 3 Extension Trial (one year results)	Patients who had completed either SIROCCO or CALIMA	No new safety consequences observed in year 2.	⁷⁶
Benralizumab	Safety Extension Study (after 3 years of treatment)	Adolescents and adults with severe asthma who completed SIROCCO or CALIMA	Safe and efficacious.	⁷⁷
Mepolizumab	Open-label extension study	Severe eosinophilic asthmatics previously enrolled in DREAM	Safe and efficacious over the long-term.	⁷⁸

Tezepelumab	Phase 3 Clinical Trial	Severe uncontrolled asthma age 12-80 years	Tezepelumab associated with better lung function, QOL and asthma control; fewer exacerbations.	79
Fevipirant	Phase 2 Clinical Trial	Uncontrolled asthma on dual or triple asthma therapy ≥ 12 years	Reduced sputum eosinophils, improved lung function; decreased exacerbation rates.	80
Omalizumab	Prospective Observational Study	Pregnant asthmatics exposed to Omalizumab	No increased risk of major congenital anomalies.	81
Non-Pharmacologic Advances				
Therapeutic	Type of Study	Study Population	Findings	Reference
Bronchial Thermoplasty	Follow-up study of previous RCTs	Patients ≥ 10 years out from BT	Efficacy sustained ≥ 10 year; acceptable safety profile.	71

Figure: Selected mechanistic advances in asthma research.

Galectin-10 crystals and active β -tryptase alleles associated with asthma. Rhinovirus infection and blockade of ATG5 activated ILC2 cells, while TLR9 engagement inhibited activation. IL-25 drove M2 macrophage development; blocking RGMb prevented IL-5 and IL-13 production. House dust mite (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-nitrotyrosine associated with asthma, as did reduced expression of ErbB2 and impaired wound healing.

1065 **Abbreviations:** ApoE, apolipoprotein E; ATG5, autophagy related 5; C3a, complement
1066 component 3a; DC, dendritic cell; ErbB2, erythroblastic oncogene B receptor B2; Fut2,
1067 fucosyltransferase 2; ILC, innate lymphoid cell; Mø, macrophage; 3-NT, 3-nitrotyrosine;
1068 RGMb, Repulsive Guidance Molecule b; RV, rhinovirus; TLR9, toll like receptor 9.

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