Key advances in mechanisms of asthma, allergy, and immunology in 2009

Fred D. Finkelman, MD,[a,b,c] Joshua A. Boyce, MD,[d] Donata Vercelli, MD,[e,f,g] and Marc E. Rothenberg, MD, PhD[h] *Cincinnati, Ohio, Boston, Mass, and Tucson, Ariz*

The year 2009 was marked by rapid progress in understanding cellular and chemical mechanisms in the pathogenesis of asthma and other allergic disorders. Studies published in the *Journal of Allergy and Clinical Immunology* described advances in our knowledge of signaling molecules and pathways, cytokines, and activation and tolerance in asthma and murine models of this disease; food allergy; anaphylaxis and immediate hypersensitivity; mast cells and their disorders; atopic dermatitis; allergic conjunctivitis; nasal polyposis; and hypereosinophilic syndromes. Additional studies provided novel information about the induction and regulation of allergic inflammation and the genetic determinants of asthma and responsiveness to asthma therapy. Critical features of these studies and their potential effect on human atopic disorders are summarized here. (J Allergy Clin Immunol 2010;125:312-8.)

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Abbreviations used

AAD:	Allergic airway disease
AD:	Atopic dermatitis
ADEH:	Atopic dermatitis eczema herpeticum
AHR:	Airway hyperresponsiveness
DC:	Dendritic cell
FLG:	Filaggrin gene
HES:	Hypereosinophilic syndrome
HLX1:	H.20-like homeobox 1
LT:	Leukotriene
mDC:	Monocytoid dendritic cell
OR:	Odds ratio
PAF:	Platelet-activating factor
PG:	Prostaglandin
PLAUR:	Plasma urokinase plasminogen activator receptor gene
PPI:	Proton pump inhibitor
RSV:	Respiratory syncytial virus
SNP:	Single nucleotide polymorphism
SphK1:	Sphingosine kinase 1
$sPLA_2$:	Secreted phospholipases A_2
STIP1:	Stress-inducible protein 1 gene
T-bet:	T-box transcription factor
TBX21:	T-box 21 gene
TLR:	Toll-like receptor
VEGF:	Vascular endothelial growth factor

The year 2009 was marked by rapid progress in understanding cellular and chemical mechanisms in the pathogenesis of asthma and other allergic disorders, as reflected by a large number of excellent articles published in the *Journal of Allergy and Clinical Immunology*. Many of the observations described in these articles have potentially important clinical implications. Brief descriptions of some of the most important of these articles follows, grouped according to the disease, mechanism, or both that was studied.

ASTHMA MODELS AND ASTHMA

Although there are substantial differences between human asthma and murine models of allergic airway disease (AAD), important similarities between human asthma and murine AAD make the models useful for investigating mechanisms that are likely to be important in human asthma.[1]

Signaling

Several studies evaluated the importance of signaling molecules and pathways. Shao et al[2] reported that administration of Fms-like tyrosine kinase 3 ligand, a dendritic cell (DC) growth factor, prevents and reverses allergic airway inflammation and airway hyperresponsiveness (AHR) in murine ovalbumin-induced AAD. This suppressive effect is associated with increased number and suppressive activity of a pulmonary DC population

From [a]the Cincinnati Veterans Affairs Medical Center; [b]the Division of Immunology, University of Cincinnati College of Medicine; the Divisions of [c]Immunobiology and [h]Allergy and Clinical Immunology, Cincinnati Children's Hospital Medical Center; [d]the Department of Medicine, Harvard Medical School, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital; [e]the Functional Genomics Laboratory, Arizona Respiratory Center, and [f]the Department of Cell Biology, College of Medicine, University of Arizona, Tucson; and [g]the Arizona Center for the Biology of Complex Diseases (ABCD), University of Arizona.

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Reprint requests: Fred D. Finkelman, MD, Division of Immunology, Department of Medicine, University of Cincinnati College of Medicine, 231 Albert Sabin Way, Cincinnati, OH 45267-0563. E-mail: ffinkelman@pol.net.

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that is characterized by surface molecule expression as $CD11c^{high}CD11b^{low}$ and has higher expression of CD8a, B220, CD19, Programmed Death Ligand-1 (PDL1), PDL2, CD80, and CD89 and lower expression of F4/80, CD40, and CCR7 than a stimulatory pulmonary DC population that is $CD11c^{low}CD11b^{high}$.

Raymond et al[3] identified $CD11b^{high}CD107^{-}$Signal-regulatory protein α (SIRP-α)$^{+}$ DCs as the myeloid DC subset most responsible for promoting a pulmonary T_H2 response and AAD. An interaction between CD47 and SIRP-1α on these cells was shown to be important in their trafficking to thoracic lymph nodes and the induction of AAD.

Takeda et al[4] found the γ isoform of the signaling enzyme phosphoinositide 3–kinase to be important in the development of some features of ovalbumin-induced murine AAD (airway eosinophilia, AHR, and airway remodeling) but not for the development of ovalbumin-specific IgE and IgG1 antibody responses. Phosphoinositide 3–kinase γ appeared to be involved in the challenge/effector phase of allergic responses, suggesting that it might be a therapeutic target for bronchial asthma.

Ohnishi et al[5] reported that leukotriene (LT) B_4 ligation of LTB_4 receptor 1 on $CD8^{+}$ effector memory T cells that secrete IL-13 is important for recruitment of these cells to the airways and the consequent development of allergic inflammation and AHR in some murine models of asthma. Suppression of extracellular signal-regulated kinase 1/2 signaling pathways in these cells suppressed AHR, airway eosinophilia, goblet cell hyperplasia, and T_H2 cytokine production in these models. This suggests that extracellular signal-regulated kinase 1/2 signaling might be an attractive target for suppression of $CD8^{+}$ T cell–mediated AHR.

Haberberger et al[6] studied sphingosine kinase 1 (SphK1), the critical pulmonary enzyme for synthesis of the signaling molecule sphingosine-1-phosphate, which has been considered as a target for asthma therapy. SphK1-deficient C57BL/6 mice had less airway eosinophilia and AHR than seen in SphK1-sufficient C57BL/6 mice in response to airway ovalbumin administration. However, SphK1-deficient mice had pulmonary vascular hyperresponsiveness to the same extent as SphK1-sufficient mice in response to a relatively short course of ovalbumin and more severe pulmonary vascular hyperresponsiveness after chronic ovalbumin immunization. These observations suggest that inhibiting SphK1 or sphingosine-1-phosphate in patients with asthma might have the detrimental side effect of inducing or exacerbating pulmonary artery hypertension.

Mikhak et al[7] performed adoptive transfer studies that used an ovalbumin model of AAD in T-cell receptor transgenic C57BL/6 mice to investigate the importance of specific chemokine receptors in AAD pathogenesis. These studies demonstrated the importance of the chemokine receptor CCR4, but not CCR8 or CXCR3, for the migration of antigen-specific T_H2 cells to the lungs. CCR4 disruption decreased airway T_H2 cytokine levels and reduced airway eosinophilia and mucus production. Consequently, CCR4 blockade might have a use in asthma therapy.

Park et al[8] built on previous studies that showed that mice deficient in T-box transcription factor (T-bet), a transcription factor critical for the induction of T_H1 cytokine responses, overproduce T_H2 cytokines and develop spontaneous AAD. T cell–specific T-bet expression was shown to suppress AAD, even when induced late in AAD development. This suggests the potential usefulness of molecules that promote T-bet expression and activity and asthma therapeutics.

Cytokines

Several studies evaluated relationships between specific cytokines and asthma. Lewis et al[9] sought to clarify the roles of IL-4 and IL-13 in asthma pathogenesis. DNA Affymetrix microarrays were used to profile pulmonary gene expression in BALB/c mice inoculated intratracheally with ragweed pollen or house dust mite extracts, IL-4, IL-13, or both cytokines. In the dust mite–inoculated animals genes dependent on IL-13 for induction were verified by comparing pulmonary gene expression in house dust mite–inoculated wild-type and *IL13* knockout mice. A signature gene expression profile consisting of 23 genes was commonly induced by means of inoculation with house dust mite, ragweed pollen, or IL-4 plus IL-13. Among the 21 genes induced uniquely by IL-4, roughly half were interferon response genes, and half were genes important in immunoregulation. In contrast, genes unique to IL-13 primarily encoded proteins produced by epithelial cells. These data imply that although both IL-4 and IL-13 are involved in the induction of experimental pulmonary inflammation, IL-4, but not IL-13, induces genes that negatively regulate allergic inflammation.

He et al[10] evaluated the importance of IL-17 in AAD initiated by priming BALB/c mice to ovalbumin by means of epicutaneous sensitization. Epicutaneous sensitization of BALB/c background mice deficient for both IL-4 and IL-13 led to dermal infiltration with $CD4^{+}$ T cells. The response differed from that in IL-4/IL-13–sufficient mice by the absence of eosinophils and IgE production and the increased production of IL-17A. Ovalbumin airway challenge of the ovalbumin-sensitized IL-4/IL-13–deficient mice resulted in IL-17–dependent neutrophilic inflammation with AHR but decreased eosinophilia and goblet cell hyperplasia compared with IL-4/IL-13–sufficient mice. IL-17A overproduction was promoted by selective IL-4, but not IL-13, deficiency. These observations raise the concern that suppression of atopy with IL-4 or combined IL-4/IL-13 antagonists might induce nonatopic, IL-17–dependent airway inflammation and hyperresponsiveness.

Activation and tolerance were also investigated in murine AAD. Goplen et al[11] found that BALB/c mice immunized intranasally with dust mite, ragweed, or *Aspergillus* species allergen eventually had tolerance to the immunogen, with decreased AHR and allergic airway inflammation. However, immunization with 2 or all 3 allergens prevented tolerance induction and led to chronic allergic airway inflammation and AHR. This suggests that T_H2 responses to multiple allergens can reinforce each other and inhibit regulatory mechanisms that lead to tolerance.

Dakhama et al[12] reported that mice infected with respiratory syncytial virus (RSV) as neonates produced IgE anti-RSV antibodies. RSV reinfection induced AAD with AHR that was IgE, FcεRI, and mast cell dependent to develop in these mice. This suggests that RSV-specific IgE might contribute to wheezing that develops in children after RSV infection and raises the possibility that therapeutics that block IgE or FcεRI might be useful for treating patients with post-RSV wheezing.

Kanda et al[13] reported a surprising relationship between eosinophils and IFN-γ in a murine AAD model. Although others have found that eosinophils are not required to induce AHR or allergic airway inflammation in BALB/c mice and that IFN-γ can suppress AHR and allergic inflammation, Kanda et al reported that