Advances in mechanisms of allergy and clinical immunology in 2012

Bruce S. Bochner, MD,[a] Marc E. Rothenberg, MD, PhD,[b] Joshua A. Boyce, MD,[c] and Fred Finkelman, PhD[b] *Baltimore, Md, Cincinnati, Ohio, and Boston, Mass*

Manuscripts published in the "Mechanisms of allergy and clinical immunology" section of the *Journal of Allergy and Clinical Immunology* during 2012 enhanced our knowledge of the involvement of cytokines and other mediators in allergic disorders and described novel approaches for understanding mechanisms of allergic and immunologic diseases. Also published were articles focused on mechanisms of allergen-specific immunotherapy and the development of novel antiallergic treatments, as well as strategies to achieve tolerance to allergens. The highlights of these studies and their potential clinical implications are summarized in this review. (J Allergy Clin Immunol 2013;131:661-7.)

Key words: *Dendritic cells, cytokines, immunotherapy, mast cell, basophil, eosinophil, T cells, regulatory T cells*

Since its inception in 2003, initially as "Advances in mechanisms of allergy" covering articles published in 2001 and 2002 in the "Mechanisms of allergy and clinical immunology" section (formerly "Mechanisms of allergy") of the *Journal of Allergy and Clinical Immunology*,[1] these annual reviews have become a popular mainstay of the *Journal*. This year's version should be no exception and summarizes articles that represent advances in mechanisms of allergy and clinical immunology published in the *Journal* during 2012 (Table I). Although the topics covered by this review, like the articles themselves, are quite diverse, particularly prominent features among these articles include those involving dendritic cell (DC) and regulatory T (Treg) cell biology; IL-1/IL-33 family, T_H1, T_H2, and T_H17 cytokines; new forms of therapies relevant to the practice of allergy and immunology; the latest insights into how allergen-specific therapies might be working; and original animal models, including so-called "humanized" models in which human cell xenografts are established in mice to allow the study of human biology and cell-based therapeutics in a preclinical animal setting. In addition to summarizing key findings, when possible, the potential clinical implications are also included.

Abbreviations used

AHR:	Airway hyperresponsiveness
CIITA:	MHC class II transactivator
CRTH2:	Chemoattractant receptor homologous molecule expressed on T_H2 cells (also called DP2 and CD294)
CysLT:	Cysteinyl leukotriene
DC:	Dendritic cell
EMT:	Epithelial mesenchymal transition
EPF:	Eosinophilic pustular folliculitis
Foxp3:	Forkhead box protein 3
HDE:	House dust extract
HDM:	House dust mite
IRAK-M:	IL-1 receptor–associated kinase M
MITF:	Microphthalmia transcription factor
MSC:	Mesenchymal stem cell
α-MSH:	α-Melanocyte stimulating hormone
NLRP3:	Nucleotide-binding domain and leucine-rich repeat protein 3
OVA:	Ovalbumin
OX40L:	OX40 ligand
PAR:	Protease-activated receptor
PG:	Prostaglandin
SLIT:	Sublingual immunotherapy
SPT:	Skin prick test
TFE3:	Transcription factor E3
TLR:	Toll-like receptor
Treg:	Regulatory T
TSLP:	Thymic stromal lymphopoietin

INVOLVEMENT OF CYTOKINES AND OTHER MEDIATORS IN ALLERGIC DISORDERS

Barlow et al[2] demonstrated that IL-25/IL-33–responsive innate type 2 lymphoid cells (nuocytes) are an important source of IL-13

From [a]the Division of Allergy and Clinical Immunology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore; [b]the Division of Allergy and Immunology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center; and [c]the Division of Rheumatology, Immunology and Allergy, Department of Medicine, Brigham and Women's Hospital, Boston.

Disclosure of potential conflict of interest: B. S. Bochner is a Scientific Advisory Board member for Allakos and Merck; has consultancy arrangements with TEVA, Sanofi-Aventis, United States Diagnostic Standards, Medicis, Pharmacyclics, Hoffman–La Roche, and Tarsa Therapeutics; is employed by Johns Hopkins University; has received one or more grants from or has one or more grants pending with the National Institutes of Health (NIH) and the Dana Foundation; has received royalties from Elsevier and from UpToDate; and owns stock/stock options in Allakos and in Glycomimetics. M. E. Rothenberg is a Board member for the International Eosinophil Society and for the American Partnership for Eosinophilic Disorders; serves as Consultant and Director of the Scientific Advisory Board of, owns stock/stock options in, and has received one or more payments for travel/accommodations/meeting expenses from Immune Pharm; has received one or more grants from or has one or more grants pending with the NIH and the Department of Defense (DOD); is the inventor of patents that are owned by CCHMC; and has received royalties from Teva Pharmaceuticals. J. A. Boyce has been supported by one or more grants from, has received one or more consulting fees or honoraria from, and has received one or more payments for lecturing from or is on the speakers' bureau for Merck and has consultancy arrangements with Calcimedica. F. Finkelman has received one or more grants from or has one or more grants pending with the NIH, the Veterans Administration, and the DOD and has a pending patent for desensitization.

Received for publication December 6, 2012; revised December 11, 2012; accepted for publication December 12, 2012.

Available online January 23, 2013.

Corresponding author: Bruce S. Bochner, MD, Division of Allergy and Clinical Immunology, Johns Hopkins Asthma and Allergy Center, 5501 Hopkins Bayview Circle, Rm 2B.71, Baltimore, MD 21224-6821. E-mail: bbochner@jhmi.edu.

0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2012.12.676

TABLE I. Key advances in our understanding of the mechanisms of asthma, allergy, and immunology as reported in 2012 in the *Journal of Allergy and Clinical Immunology*

Topic	Advances and observations
IL-33 biology	Production of nuocytes; role in rhinitis and mast cell activation
DC biology	Role of MHC class II expression; tissue recruitment by diesel exhaust particles and allergens mediated by specific chemokines and their receptors; role in mediating IL-13–dependent inflammation
PAR2	Roles in allergenicity and nasal hypersecretion
Predicting allergic disease and development of tolerance	Using personal home dust extracts to predict sensitization; use of DC biomarkers to predict efficacy roles for Treg cells and DCs
Mechanisms of immunotherapy	Understanding the IgG_4 response; use of allergen-specific tetramers to track allergen-specific T cells and changes during immunotherapy
Novel therapies	Cotargeting IgE and FcγRIIb; use of fullerene derivatives

in a mouse model of allergic airway disease and can produce sufficient IL-13 in response to IL-25 to induce airway hyperresponsiveness (AHR) and allergic lung inflammation. A difference between $CD4^+$ T-cell secretion of IL-13 and the related cytokine IL-4 was also demonstrated: IL-13 was secreted by lung $CD4^+$ T cells, whereas IL-4 was secreted by lymph node but not lung $CD4^+$ T cells.

Haenuki et al[3] evaluated the role of IL-33, a cytokine that is known to promote allergic responses by stimulating T_H2 cytokine secretion through effects on multiple cell types, in patients with allergic rhinitis. Increased serum IL-33 and decreased nasal epithelial cell IL-33 levels were demonstrated in patients with allergic rhinitis, and ragweed extract stimulated release of IL-33 by nasal epithelial cells in a mouse model of this disorder. Furthermore, allergic rhinitis was considerably more severe in wild-type than in IL-33–deficient mice. In addition to promoting T_H2 cytokine secretion, IL-33 promoted mast cell histamine release and basophil-active chemokine secretion. Consequently, IL-33 antagonists might suppress the development of allergic rhinitis.

Wu et al[4] evaluated IL-1 receptor–associated kinase M (IRAK-M), which negatively regulates Toll-like receptor (TLR) 2 function, and demonstrated that its expression is increased in airway epithelium from asthmatic patients. In addition, IRAK-M was shown to be upregulated *in vitro* in human primary airway epithelial cell cultures by IL-13 through a pathway dependent on phosphatidyl inositol 3-kinase activation of c-Jun, which binds to the IRAK-M promoter. This suggests a mechanism through which increased IL-13 levels in asthmatic patients can impair TLR2-dependent airway host defense against bacterial pathogens.

Parmentier et al[5] demonstrated that human T_H2 cells express considerably more *CYSLTR1* mRNA (which encodes the cysteinyl leukotriene [CysLT] receptor 1 [CysLT1]) than T_H1 cells and respond more than T_H1 cells to CysLTs. CysLT1 signaling in T_H2 cells is mediated by $G\alpha_q$ and $G\alpha_i$ proteins and is responsible for the chemotactic effect of leukotriene D_4 on T_H2 cells. These observations might account for some of the anti-inflammatory effects of CysLT1 antagonists in asthmatic patients. Brand et al[6] showed that induction of allergic airway disease in mice was associated with methylation of the promoter of the gene for IFN-γ in $CD4^+$ T cells, which decreases IFN-γ expression. Reversal of IFN-γ promoter methylation in $CD4^+$ T cells inhibited T_H2 polarization and allergic airway inflammation. These observations suggest the importance and potential usefulness of epigenetic modification as a therapy for allergic disorders.

Hsia et al[7] used a mouse model to show that the absence of surfactant protein A allows increased macrophage and neutrophil TNF-α production. A further increase in TNF-α production in response to *Mycoplasma* species infection enhances mast cell secretion of mediators that contribute to AHR. Thus surfactant protein A can inhibit AHR during *Mycoplasma* species infection by suppressing TNF-α production.

Finally, using adoptive transfer of CD8 ovalbumin (OVA) transgenic (OT-I) cells in mice, Tang et al[8] examined the role of CD8 T cell–derived IFN-γ in their effector function. They report that wild-type effector CD8 OT-I cells, but not IFN-$\gamma^{-/-}$ effector OT-I CD8 T cells, attenuated T_H2 inflammation induced in sensitized mice by OVA challenge. In contrast, the IFN-$\gamma^{-/-}$ effector OT-I CD8 T cells were able to both induce and exacerbate lung inflammation due in part to effects on lung DCs. A main conclusion of their work is that IFN-γ, specifically that derived from CD8 T cells, can be important for controlling T_H2 pulmonary inflammation in their murine model.

NOVEL APPROACHES FOR UNDERSTANDING MECHANISMS OF ALLERGIC AND IMMUNOLOGIC DISEASES

Massoud et al[9] demonstrated that intraperitoneal administration of intravenous immunoglobulin activates DCs to induce a highly suppressive, antigen-specific, forkhead box protein 3 (Foxp3)–positive Treg cell population that homes to the lungs and thoracic lymph nodes of mice that had been immunized intranasally with OVA or ragweed. Consequently, the anti-inflammatory effects of intravenous immunoglobulin might be partially explained by suppression through Treg cells of allergic airway inflammation and AHR.

Sedej et al[10] explored crosstalk between 2 receptors for prostaglandin (PG) D_2, chemoattractant receptor homologous molecule expressed on T_H2 cells (CRTH2; also called DP2 and CD294) and DP_1, through *in vitro* studies with human eosinophils. Heterodimerization of these 2 receptors was shown to suppress calcium signaling by means of ligation of DP_1 but to amplify calcium signaling through ligation of CRTH2. Consequently, targeting of the DP_1/CRTH2 heterodimer can suppress the inflammatory effects of PGD_2 mediated by CRTH2 in allergic disorders.

Liang et al[11] demonstrated that the highly allergenic cysteine protease papain acts directly on naive T cells through protease-activated receptor (PAR) 2 to stimulate secretion of IL-4 and the chemokines CCL17 and CCL22, which induce basophil