Advances in mechanisms of asthma, allergy, and immunology in 2010

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2010 was marked by rapid progress in our understanding of the cellular and molecular mechanisms involved in the pathogenesis of allergic inflammation and asthma. Studies published in the *Journal of Allergy and Clinical Immunology* described advances in our knowledge of cells associated with allergic inflammation (mast cells, eosinophils, dendritic cells, and T cells), as well as IgE, cytokines, receptors, signaling molecules, and pathways. Studies used animal models, as well as human cells and tissues, to advance our understanding of mechanisms of asthma, eosinophilic esophagitis, food allergy, anaphylaxis and immediate hypersensitivity, mast cells and their disorders, atopic dermatitis, nasal polyposis, and hypereosinophilic syndromes. Additional studies provided novel information about the induction and regulation of allergic inflammation and the genetic contribution to allergic inflammation. Critical features of these studies and their potential effects on human atopic disorders are summarized here. (J Allergy Clin Immunol 2011;127:689-95.)

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2010 was marked by rapid progress in understanding the cellular and molecular 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 are now provided.

Abbreviations used
CSS: Churg-Strauss syndrome
cysLT: Cysteinyl leukotriene
DC: Dendritic cell
FOXP3: Forkhead box protein 3
HES: Hypereosinophilic syndrome
IPEX: Immune dysregulation, polyendocrinopathy, X-linked
ITIM: Immunoreceptor tyrosine-based inhibitory motif
LT: Leukotriene
NO: Nitric oxide
PAF: Platelet-activating factor
PG: Prostaglandin
SNP: Single nucleotide polymorphism
TSLP: Thymic stromal lymphopoietin

EOSINOPHILS AND INFLAMMATION

Cellular activation

Cell-free eosinophil granules are present extracellularly as intact membrane-bound organelles in sites associated with eosinophil infiltration, including asthma, but have unknown functional capabilities. Neves et al[1] reported that receptors for cysteinyl leukotrienes (cysLTs), cysLT1R, cysLT2 receptor, and the purinergic P2Y12 receptor, are expressed on eosinophil granule membranes. Notably, leukotriene (LT) C_4 and extracellularly generated LTD_4 and LTE_4 stimulated isolated eosinophil granules to secrete eosinophil cationic protein. Inhibitors of the P2Y12 receptor and cysLT1R inhibited these effects. These studies identify previously unrecognized sites of localization, the membranes of intracellular eosinophil granule organelles, and the function for cysLT-responsive receptors that mediate cysLT-stimulated secretion from within eosinophil granules, including those present extracellularly.

Migration

Although much progress has been made with understanding eosinophil recruitment into tissues, relatively little is known about mechanisms that inhibit eosinophil migration. Konya et al[2] reported the role of endothelial cell–derived prostaglandin (PG) I_2. PGI_2 markedly attenuated the migration of eosinophils *in vitro*, and this effect was inhibited by a PGI_2 receptor antagonist, as well as the adenylyl cyclase inhibitor SQ22536. Furthermore, when endothelial cells were treated with a COX inhibitor, eosinophil

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adhesion and migration were blocked. Inhibition of PGI_2 biosynthesis decreased the electrical resistance of endothelial monolayers and compromised the texture of adherent junctions. As such, these findings demonstrate that endothelium-derived PGI_2 might be fundamental for the maintenance of endothelial barrier function against infiltrating cells. These results suggest that selective PGI_2 receptor agonists might have beneficial effects in allergic inflammation.

Extending the role of endothelial cells in regulating eosinophil responses, Asosingh et al[3] examined the ability of endothelial progenitor cells to induce eosinophil recruitment. They showed that circulating endothelial cell progenitors of asthmatic patients and mice with experimental asthma secreted high levels of eotaxin-1 and promoted eosinophil recruitment *in vivo*.

Diseases

Hypereosinophilic syndromes (HESs) are a heterogeneous group of disorders that have received recent attention because of active advances in understanding disease pathology and new approaches to therapy. Crane et al[4] reported the crude incidence of HES as 0.035 cases per 100,000 and an age-adjusted rate of 0.036 per 100,000 person-years. These findings are likely underestimates and mainly limited to the more malignant variants of HES, such as the myeloproliferative types. In another article Helbig et al[5] reported the characteristics and molecular causes of 88 patients with HES from Poland. They found marked patient heterogeneity, with 18% having molecular rearrangement involving the imatinib-inhibited activated tyrosine kinase fusion protein FIP1L1–PDGFRA.

Eosinophilic asthma has been proposed to be associated with asthma severity and represents a phenotype that is likely amenable to therapy with anti–IL-5 therapeutics. Al-Samri et al[6] reported variability of sputum inflammatory cells in asthmatic patients receiving corticosteroid therapy using a prospective study. The investigators found substantial fractions of patients with moderate and severe asthma with sputum eosinophilia, neutrophilia, or both and noted that the inflammatory cells were not stable in nearly two thirds of the subjects over a 1-year period.

Nair et al[7] were able to dissociate sputum eosinophilia from exhaled nitric oxide (NO). They reported the lack of correlation between sputum eosinophil percentages and exhaled NO levels in patients with prednisone-dependent asthma and sputum eosinophilia who participated in a clinical trial of anti–IL-5 mAb (mepolizumab).

Kahn et al[8] reported a novel approach to treating Churg-Strauss syndrome (CSS) by studying a single patient with antineutrophil cytoplasmic antigen–negative disease treated with mepolizumab. They found a remarkable improvement in asthma symptoms, eosinophilia, and chest computed axial tomographic scan findings, highlighting the potential pivotal role of IL-5 and eosinophils in patients with CSS. Extending these findings, Kim et al[9] reported that mepolizumab was effective in reducing steroid doses and eosinophil levels in 7 patients with CSS.

Furthering the focus on mepolizumab, Conus et al[10] examined its effect on duodenal eosinophils in patients with eosinophilic esophagitis. The treatment had no effect on the duodenal infiltration of eosinophils, T cells, and mast cells in subjects participating in a small placebo-controlled clinical study.

Although typically associated with eosinophils, Abonia et al[11] demonstrated the presence of mastocytosis and mast cell degranulation in patients with eosinophilic esophagitis. In addition, the investigators identified an esophageal mast cell–associated transcriptome that was significantly divergent from the eosinophil-associated transcriptome, with carboxypeptidase A3 mRNA levels serving as the best mast cell surrogate marker, and provided evidence for the involvement of KIT ligand in the pathogenesis of eosinophilic esophagitis. Extending the involvement of mast cells in eosinophilic esophagitis, Aceves et al[12] reported selective accumulation of mast cells in the esophageal smooth muscle. Furthermore, these investigators demonstrated that these mast cells produced TGF-β, which had the potential to induce smooth muscle contractility *in vitro*.

Swallowed glucocorticoids are known to be effective for the treatment of eosinophilic esophagitis, but the mechanism of their action has not been tested. Now Caldwell et al[13] have presented evidence that swallowed steroids induce local effects in the esophagus based on the identification of corticosteroid-induced genes in the esophagus after treatment. Focusing on one steroid-induced transcript, the authors distinguish fluticasone responders from untreated patients with active eosinophilic esophagitis and patients without eosinophilic esophagitis. In addition, they determine that one steroid-induced transcript, FK506-binding protein 5 (FKBP51), reduces glucocorticoid-mediated inhibition of IL-13 signaling in epithelial cells *in vitro*, suggesting that FKBP51 might influence fluticasone propionate responsiveness. Additionally, they propose that esophageal FKBP51 levels have diagnostic and prognostic significance in patients with eosinophilic esophagitis.

DENDRITIC CELLS AND T LYMPHOCYTES

Dendritic cell promotion of inflammation

Comparison of inflammatory ($CD11c^+CD1c^-$) and resident ($CD11c^+CD1c^+$) skin dendritic cells (DCs) from patients with psoriasis by Zaba et al[14] demonstrated increased expression of inflammation-related proteins, including TRAIL, Toll-like receptors 1 and 2, S100A12/ENRAGE, and CD32 by the $CD1c^-$ DC population. These molecules, which are ligands for keratinocyte receptors, could allow inflammatory DCs to promote inflammatory disease through direct effects on keratinocytes. Esser et al[15] demonstrated that nanovesicles (exosomes) released from human macrophages and DCs can contribute to inflammation by producing eicosanoids in response to appropriate stimuli and can synthesize LTC_4 from LTA_4.

Association of DC subpopulations with inflammation

Dua et al[16] demonstrated that allergen challenge of asthmatic subjects increases the sputum numbers of both inflammation-associated myeloid DCs and tolerance-associated plasmacytoid DCs. Because DC expression of the $\alpha\gamma_2$ form of FcεRI facilitates DC allergen uptake and presentation, Chand et al[17] evaluated the effects of 12 weeks of omalizumab (anti-IgE antibody) treatment on myeloid and plasmacytoid DCs in bronchial tissue of asthmatic subjects. They demonstrated that this treatment induced a selective decrease in airway myeloid DCs, with no decrease in plasmacytoid DC numbers.

Schroeder et al[18] demonstrated that treatment of subjects with cat allergy with omalizumab (anti-IgE mAb) for 3.5 months decreased DC IgE and FcεRI expression and the ability of