Published in final edited form as:
J Allergy Clin Immunol. 2009 March ; 123(3): 569–574. doi:10.1016/j.jaci.2009.01.041.

Advances in Mechanisms of Asthma, Allergy, and Immunology in 2008

Joshua A. Boyce, MD[1], **David Broide, MD, Ch.B**[2], **Kenji Matsumoto, MD, PhD**[3], and **Bruce S. Bochner, MD**[4]

1*Department of Medicine, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, and Department of Pediatrics, Harvard Medical School, Boston, MA*

2*Department of Medicine, Division of Rheumatology, Allergy and Immunology, University of California San Diego, La Jolla, CA*

3*Department of Allergy and Immunology, National Research Institute for Child Health and Development, Tokyo, Japan*

4*Department of Medicine, Division of Allergy and Clinical Immunology, Johns Hopkins University School of Medicine, Baltimore, MD*

Abstract

This review summarizes selected articles appearing in 2008 in the Journal of Allergy and Clinical Immunology (JACI). Papers chosen include those improving our understanding of mechanisms of allergic diseases by focusing on human basophil, mast cell and eosinophil biology; IgE and its high affinity receptor on various cells; novel properties of omalizumab; airways remodeling; and genetics. Papers from other journals have been included to supplement the topics being presented.

Introduction

The JACI is now one of the premier journals for publication of human cell biology and genetics relevant to asthma and allergic diseases, and this past year was no exception. Studies published in 2008 have advanced our knowledge regarding pathways controlling degranulation of IgE receptor bearing cells and have further elucidated the ability of IgE and anti-IgE therapies to modulate cellular responses. The list of mechanisms by which eosinophils can be activated and kept alive were expanded, as were mechanisms by which viruses, cytokines and other agents may contribute to expression of remodeling genes in the airway. Murine studies explored the potential of immunomodulator therapies to influence airway remodeling. Additional studies furthered our understanding of genes related to atopic disorders including asthma, especially those involved in innate immune responses (see Table I.).

Correspondence and reprint request should be addressed to Dr. Bruce S. Bochner, Johns Hopkins Asthma and Center, 5501 Hopkins Bayview Circle, Room 2B71, Baltimore, MD, 21224, USA; phone: 410-550-2101; fax: 410-550-1733; E-mail: E-mail: bbochner@jhmi.edu.

Mast Cells and Basophils

Spleen-type (Syk) tyrosine kinase is required for the activation of mast cells and basophils occurring in response to FcεRI cross-linkage. Mazuc and colleagues[1] used an ingenious strategy to identify a novel Syk inhibitor. These investigators had previously reported that antibody (termed G4G11) directed against an amino acid sequence that is conserved amongst the Sh2 domains of human, mouse, and rat Syk, introduced into RBL-2H3 cells (a rat mast cell line), blocks FcεRI-mediated activation.[2] The investigators screened an extensive panel of small molecules for their ability to displace G4G11 from its target epitope.[1] They identified 15 molecules that displaced G4G11 binding, and tested one of these (termed C-13) for the ability to block Syk-mediated activation of mast cells. These investigators determined that C-13 binding required Arg68, Glu121, and Glu155 of Syk. C-13 was cell permeable and blocked FcεRI-mediated activation of RBL-2H3 cells by preventing Syk-dependent phosphorylation of Btk and several downstream signaling events. Orally administered C-13 blocked both passive cutaneous and systemic anaphylaxis in mice. This study is an exciting step in the development of Syk-targeted drugs for allergic diseases.

Curcumin (a pigment of curry powder) was previously reported to have “anti-allergic” properties in animal models of allergy.[3] Lee et al. showed that treatment of RBL-2H3 cells with curcumin inhibited their FcεRI-mediated degranulation, production of both TNF-α and IL-4, and activation of mitogen-activated protein kinase.[4] Like C-13, curcumin inhibited Syk enzymatic activity without blocking its FcεRI-mediated phosphorylation. While it is not known whether curcumin targets a region of Syk that is similar to that bound by C-13, this study once again highlights the therapeutic potential of interference with Syk in allergic disease.

Syk is transiently inactivated after FcεRI-mediated cell activation, resulting in a refractory period during which mast cells or basophils are resistant to a second activation after cross-linkage of FcεRI. McGlashan and Udem demonstrated that a Syk inhibitor (NVP-QAB205) completely blocked the release of mediators by mast cells challenged with anti-IgE, but had no effect on Syk inactivation (as indicated by the lack of mediator release in response to a second stimulation with anti-IgE).[5] A similar result was obtained with basophils. An inhibitor of phospatidylinostol-3-phosphate kinase (PI-3K) also completely blocked mediator release by anti-IgE-activated basophils without altering inactivation of Syk. Thus, neither Syk activation nor PI-3K activity is necessary for the transient inactivation of Syk after mast cell or basophil activation. These findings suggest that pharmacologic antagonists that target either Syk or PI-3K should block anaphylactic mediator release without interfering with the potentially desired effect of Syk inactivation during desensitization to antigen.

Sialic acid-binding immunoglobulin-like lectins (Siglecs) are a family of receptors that bind to extracellular glycan structures. Many Siglecs are predicted to have inhibitory functions based on the presence of immunoreceptor tyrosine inhibitory motifs (ITIMs). One member of this family, Siglec-8, is selectively expressed on human eosinophils, basophils, and mast cells. Yokoi et al[5] demonstrated that Siglec-8 engagement inhibited exocytosis of human mast cells in vitro, as well as their production of prostaglandin D_2, but not release of interleukin-8. Siglec-8 engagement also inhibited the contraction of isolated human bronchi in response to stimulation with anti-IgE. The authors generated a series of mutated Siglec-8 constructs, and demonstrated in RBL-2H3 cells that the ITIM domain was crucial for the inhibitory function of Siglec-8. Thus, antibodies or molecules that mimic Siglec-8 ligands could be developed as potential therapeutic agents that prevent mediator generation by mast cells and its physiologic consequences.

Adenosine, a product of neurons and vascular cells released in response to stress, hypoxia, and inflammation, is a known agonist of mast cell activation in vitro, and induce

bronchoconstriction by a mechanism that depends on mast cell-derived mediators. Hua and colleagues[6] studied the potential role of adenosine in mediating airway hyperresponsiveness (AHR) to methacholine. Inhalation of the stable adenosine analogue adenosine-5′ N-ethylcarboxamide (NECA) induced AHR in mice. This feature was absent in mast cell-deficient Wsh/Wsh mice, as well as in mice lacking the A3-type adenosine receptor. The direct role of A3 receptors on mast cells was confirmed by adoptive transfer experiments, in which engraftment of the Wsh/Wsh mice with mast cells derived from wild-type mice, but not with mast cells derived from A3 receptor-deficient mice, restored AHR following inhalation of NECA. The adenosine pathway may thus be an important IgE-independent mechanism by which mast cells contribute to AHR.

Salamon and colleagues[7] used a microarray to identify the profile of mRNA transcripts inducibly expressed by the human LAD2 mast cell line, when these cells were incubated in the presence of membranes derived from activated T cells. This condition induced the expression of 200 transcripts that were not expressed in response to FcεRI cross-linkage. These included several cytokines and chemokines, such as oncostatin M, a cytokine belonging to the IL-6 family with profibrotic properties. LAD2 cells and cord blood-derived mast cells secreted oncostatin M protein when incubated with membranes from activated but not from resting T cells. The production of oncostatin M was sensitive to dexamethasone, and could also be modestly suppressed by curcumin. The quantities of oncostatin M secreted by mast cells were sufficient to induce the proliferation of fibroblasts in vitro. Thus, oncostatin M, produced by mast cells in response to contact with activated T cells, may promote remodeling of the airway and other tissues.

Mast cells and basophils store pre-formed histamine (and mast cells also store serotonin) in secretory granules. Storage of these mediators involves proteoglycans that contain a core peptide termed serglycin. Ringvall et al[8] studied the storage of histamine and serotonin in mast cells from mice lacking serglycin. The granules of the mast cells from the serglycin knockout strain were poorly developed, and contained less histamine and serotonin than did the mast cells from the wild-type strain, particularly in vivo. Although both in vivo- and in vitro-derived mast cells from both strains released histamine and serotonin when activated using calcium ionophore, the quantities released from the cells of the serglycin knockout mice were substantially lower. Interestingly, while histamine release depended entirely on pre-formed stores, some of the serotonin released was synthesized de novo in response to cell activation. The ability of mast cells to generate serotonin, but not histamine, de novo in response to activation suggests a mechanism for the release of this important vasoactive substance that occurs independently of classical degranulation.

Mouse mast cells express two functionally divergent tryptases, termed mouse mast cell protease (MMCP-6) (a homologue of human mast cell tryptase β) and MMCP-7. Human mast cell granules lack a true ortholog of MMCP-7, instead expressing small amounts of tryptase δ, an enzyme that does not exist in mice and that has weak protease activity. Trivedi and co-workers[9] determined how tryptase δ evolved during primate evolution, and why the human enzyme possesses such weak activity. All primates studied (including lemurs, macaque, and great apes) possess genes encoding tryptase δ, which evolved by transformation from an ancestral MMCP-7-like gene. The human tryptase δ gene is truncated, affecting its substrate-binding pocket, resulting in a loss of function. Interestingly, the truncation exists in the tryptase δ genes of the great apes, but not the lemur or macaque genes. Moreover, tryptase δ, and not tryptase β, is the major active tryptase in the monkeys. This study suggests that there were selective environmental pressures that caused the truncation of tryptase δ during the transition to higher primates.

IgE and Anti-IgE

Wang et al[10] compared different clinical laboratory assays by their ability to quantitate allergen-specific IgE levels. They employed three commercial assays to determine whether measurements of IgE were similar and found that there were obvious differences. For example, using the ImmunoCAP assays as the standard for comparison, the Immulite 2000 system tended to overestimate specific IgE levels, whereas the Turbo-MP assay overestimated egg-specific IgE but underestimated dust mite and birch IgE. One important conclusion offered by the authors was that the predicted values previously generated with the ImmunoCAP assay for likelihood of clinical reactivity associated with food-specific IgE levels cannot automatically be applied to results of IgE measurements obtained using other assays.

Christianson et al[11] developed a panel of 31 fully human or mouse-human chimeric recombinant IgEs specific for the house dust mite allergen Der p 2. They then investigated how individual properties of IgE affect biology. They also studied the affinity of these IgEs for Der p 2 and showed that these recombinant IgEs bound nine different Der p 2 epitopes with affinities ranging widely from low pM to mid nM. They discovered that enhanced basophil degranulation occurred with higher total IgE concentrations; with increased ratios of allergen-specific IgE relative to total IgE; with a more even concentration of individual allergen-specific IgE antibody type; with higher IgE affinity for the Der p 2 epitope; and with an increased number of Der p 2 epitopes being recognized by the IgE. This landmark study, as pointed out by the accompanying editorial by Hamilton and Saito[12], showed comprehensively how IgE antibody concentration, IgE antibody clonality, specific activity and affinity all influence degranulation responses and helps us to understand why IgE effects cannot simply be predicted by current specific IgE measurements.

Several papers explored new interesting aspects of omalizumab therapy. Corren and colleagues[13] published work giving two-to-fourfold higher IV doses of omalizumab than currently approved and then reducing the dosing after 28 weeks to see if such step-down dosing would allow beneficial effects to persist. After 14 weeks of administration of the higher dose of omalizumab IV, they observed a >95% suppression of serum free IgE concentrations. Dust mite skin prick tests were also markedly inhibited. When IV dosing was reduced, serum free IgE levels and allergen skin test reactivity increased significantly. Months after discontinuation of therapy, serum free IgE levels and skin test reactivity returned to pre-treatment levels. Two key findings of this study were that 1) six-to-twelve month treatment with omalizumab is unlikely to cause any persistent change in free IgE levels and skin test reactivity off omalizumab, and 2) reductions of omalizumab dosing may allow restoration of IgE-mediated responses.

In a “Letter to the Editor,” Ruppert and co-workers reported on an interesting case in which a 62-year-old male with chronic sinusitis and persistent asthma was treated with omalizumab.[14] His asthma responded favorably, even as he was tapered off prednisolone, but later that year he developed Churg-Strauss Syndrome. The omalizumab was stopped, and he was put back on oral steroids plus cyclophosphamide with improvement. As the authors commented, it is possible that the successful use of omalizumab to control the asthma permitted systemic steroid withdrawal and unmasking of an underlying diagnosis of Churg-Strauss Syndrome. More indisputable in this one case is that omalizumab, in the absence of systemic steroids, was incapable of preventing the extensive tissue eosinophilia that developed in association with Churg-Strauss Syndrome in this individual, even though omalizumab has been shown to reduce airway eosinophilia in asthmatic patients.[15]

Finally, Kaplan et al reported on a study of omalizumab for the treatment of chronic urticaria with autoimmune features.[16] Twelve patients manifesting basophil histamine release and

autologous skin test responses were treated with placebo for four weeks followed by omalizumab for 16 weeks. Marked improvement in urticaria symptom scores was observed, with seven patients achieving complete resolution, four showing improvement and one showing no improvement whatsoever. The treatment was well tolerated. These exciting findings have apparently been confirmed in a slightly larger placebo-controlled trial.[17]

Eosinophils

Cherry et al[18] added to the list of known cytokines capable of activating human eosinophils and prolonging their survival by showing that interleukin-33 (IL-33), a member of the IL-1 cytokine family, can cause production of superoxide anion, eosinophil degranulation and enhanced survival as effectively as IL-5. Receptors for IL-33, namely ST2, were detected on eosinophils, and IL-33-induced survival and production of IL-8 were all blocked with an antibody to ST2. Therefore, IL-33, which is produced by structural cells such as airway epithelium and promotes survival and cytokine production by human mast cells, should gain more attention as a potential contributor to allergic cellular responses.

Adamko and colleagues explored how eosinophil activation may be influenced by cationic charge.[19] They established an in vitro model to mimic cationic-charged deposition of eosinophil proteins in tissues by coating Sepharose beads with cationic or anionic substances. In the presence of eosinophil-activating cytokines, they showed that positively charged beads uniquely caused greater eosinophil degranulation. This release was due to metabolic pathways such as those involving tyrosine phosphorylation and cyclic AMP because pharmacologic inhibitors of these pathways blocked responses. An additional mechanism involved appears to be clustering of β2 integrins on the eosinophils where they adhered to the beads. It was concluded that exposure of eosinophils to positively charged surfaces in the presence of activating cytokines, as might occur in vivo at sites of chronic allergic inflammation, could enhance eosinophil degranulation.

In a “Letter to the Editor,” Simon et al[20] report on a 59-year-old male with FIP1L1-PDGFRA (Fip1-like1-platelet-derived growth factor receptor alpha chain) positive Hypereosinophilic Syndrome, also referred to as chronic eosinophilic leukemia. Unfortunately, he failed to respond to treatment with prednisone, interferon-α, hydroxyurea or imatinib. He had an elevated serum IL-5 level, yet failed to respond to anti-IL-5 antibody (mepolizumab) used alone or in combination with imatinib, and ultimately died of heart failure. When the authors sequenced his FIP1L1-PDGFRA gene, they identified two mutations resulting in two amino acid changes within the kinase domain, which likely caused the imatinib resistance. This case report underscores the need for additional tyrosine kinase inhibitors that may prove effective even when imatinib resistance appears. Indeed, several such tyrosine kinase inhibitors are in advanced clinical trials.[21]

Mechanisms of Airway Remodeling in Asthma

Although the structural features of airway remodeling in asthma are well described, less is known about the mechanism by which environmental stimuli and genes interact to induce airway remodeling, particularly in the subset of asthmatics with more severe airway remodeling and an increased rate of decline in lung function.[22] Rhinovirus infections are the most frequent precipitant of asthma exacerbations triggered by viruses but whether they contribute to airway remodeling is currently unknown. As an increased frequency of asthma exacerbations may contribute to a more rapid decline in lung function[23], studies by Leigh et al[24] investigated potential mechanisms by which rhinovirus infection may contribute to airway remodeling in asthma. They demonstrate that rhinovirus infection induces expression of vascular endothelial growth factor (VEGF), a pro-angiogenic cytokine, by airway epithelial cells in vitro. In addition, in healthy subjects with natural rhinovirus infection levels of VEGF were increased

in nasal lavage fluid at the time of peak symptoms compared to levels observed four weeks after the resolution of symptoms.[24] Although there was an increase in nasal lavage VEGF levels in healthy subjects, further studies are needed to determine whether subjects with asthma and rhinovirus infection have increased levels of VEGF (and possibly other pro-remodeling mediators) in the lower airway, and whether levels of VEGF associate with levels of airway angiogenesis or other features of airway remodeling. Interestingly, over-expression of VEGF in the airways of mice results in both airway angiogenesis as well as other features of airway remodeling[25], suggesting that expression of VEGF in asthma may contribute to more than one feature of airway remodeling in asthma.

Single nucleotide polymorphisms (SNPs) in the metalloprotease A disintegrin and metalloprotease 33 (ADAM33) have been linked with bronchial hyperresponsiveness, poor lung function in early childhood, and a more rapid decline in lung function in COPD as well as a healthy population.[26, 27] Initial studies demonstrated that ADAM33 was expressed by mesenchymal cells such as fibroblasts, myofibroblasts, and smooth muscle cells, but not by epithelial cells, suggesting that these lung cells would mediate the effects of ADAM33 on lung function in asthma. Subsequent studies suggested that airway epithelial cells were a source of ADAM33 in severe asthma.[28, 29] Yang et al[30] therefore investigated whether airway epithelial cells, a source of many pro-remodeling genes and growth factors, also expressed ADAM33. Their studies demonstrated that fibroblasts, but not airway epithelial cells, expressed ADAM33 as assessed by RT-PCR.[30] They demonstrated that the reason for the lack of ADAM33 expression by airway epithelial cells (but not fibroblasts) was due to methylation of CpG dinucleotides in the 5′ region of ADAM33. CpG methylation of genes is a major epigenetic mechanism that regulates gene expression. Incubation of airway epithelial cells with a demethylating agent resulted in expression of ADAM33 by airway epithelial cells[30] underscoring the importance of CpG methylation of ADAM33 in controlling ADAM33 expression in airway epithelial cells. ADAM33, a membrane anchored glycoprotein, also exists as a 55 kDa truncated soluble form (sADAM33) containing the catalytic domain. Puxeddu et al[26] detected sADAM33 in bronchoalveolar lavage fluid of subjects with asthma and demonstrated that TGF-β2 enhanced release of sADAM33 from cells over-expressing full length ADAM33, suggesting a potential regulatory role for TGF-β2 in modulating levels of sADAM33.

Studies also examined the importance of mast cells, located within the airway smooth muscle layer, to AHR[31], and the relationship between the expression of smooth muscle proteins and airway responsiveness.[32] Siddiqui et al[31] studied the relationship of airway remodeling to AHR in subjects with either asthma (who exhibit AHR) or subjects with eosinophilic bronchitis (who do not exhibit AHR). They demonstrated that subjects with asthma and subjects with eosinophilic bronchitis both had a significant increase in airway smooth muscle mass and reticular basement membrane thickness compared to normal controls,[31] suggesting that these features of airway remodeling do not account for the presence of AHR in asthma, and also do not explain the lack of increased AHR in eosinophilic bronchitis. In contrast, mast cell numbers in airway smooth muscle did associate with AHR and airway remodeling with few mast cells present in smooth muscle in eosinophilic bronchitis and increased numbers of mast cells noted in smooth muscle in asthma.[31] Studies by Slats et al[32] demonstrated that AHR in asthma was associated with expression of a particular profile of contractile and structural smooth muscle proteins, in particular α-smooth muscle actin, desmin, and elastin.

Studies in pre-clinical models of asthma examined the potential of novel immunomodulator therapies to influence airway remodeling. Studies by Kearley et al[33] using a mouse model of chronic allergen-induced airway remodeling demonstrated that adoptive transfer of CD4 +CD25+ Tregs reversed established airway inflammation, peribronchial fibrosis, and mucus hypersecretion but did not reverse established AHR suggesting that Tregs affect pathways

related to airway remodeling but not to airway responsiveness. An alternate strategy to Treg administration being investigated is the administration of DCregs. Preliminary studies by Fujita et al[34] demonstrated that administration of DCregs to mice reduced IgE levels, airway inflammation, and AHR in a mouse model of asthma. At present it is not known whether DCregs influence airway remodeling. Leukotrienes are considered to potentially play a role in inducing airway remodeling.[22] Corticosteroids, our current most potent anti-inflammatory therapy in asthma, are not considered to influence the production of CysLTs. Studies by Negri et al[35] suggest that corticosteroids may modulate the expression of CysLT and CysLTR in peripheral blood cells in vitro in the presence of Th2 cytokines such as IL-4. However, further in vivo studies are needed to determine the effect of corticosteroids on these leukotriene pathways in asthma.

Allergy-Related Genes

Allergic diseases, including asthma and atopic dermatitis, are complex genetic disorders that do not conform to a simple Mendelian pattern of inheritance. Most of the inital genes found to be associated with asthma participate in IgE-synthesis, allergic inflammation and/or hyperreactivity of the cells and organs.[36, 37] Yet epidemiological studies strongly suggested that exposure to microbial agents during early infancy protects from allergic diseases.[38, 39] Subsequent studies demonstrated that microbial agents activate innate immune receptors on antigen-presenting cells during concomitant airborne allergen exposure, and induce airborne allergen-specific Th1 (or regulatory T cell) responses as adjuvants to protect the host from allergic sensitization and development of allergic diseases.[40]

Polymorphisms of innate immune molecules were frequently investigated for their association with prevalence of allergic diseases. Polymorphisms of several TLRs and associated molecules have now been reported to be significantly associated with onset of allergic diseases[41, 42], but some studies showed clearly conflicting results.[43] Extensive studies[44] consequently revealed that the susceptibility of environmental microbial exposure depends on the polymorphisms of the receptors or signal transducing molecules of the host; this phenomenon was referred as to “Gene-environment interaction”. Another study showed that such gene-environment interaction still exists in adults[45], suggesting that the adjuvant effect of such innate immune signals may be present even when relatively fewer naive T cells exist.

In contrast to viral upper respiratory infections or endotoxin exposure during early infancy that protect infants from airborne antigen-specific Th2 polarization, it is well-known that infants with “wheezing” caused by common cold viruses such as respiratory syncytial virus (RSV) or rhinovirus (RV) have a very high risk of subsequently developing asthma.[46, 47] These facts seem to conflict with the so-called “Hygiene hypothesis”. Instead, it suggests that individuals who are unable to minimize the viral infection have higher risks for getting asthma. This theory predicts that asthma development is characterized by impaired local immune response to respiratory viruses.[48] Exactly the same line of reasoning for bacterial colonization was reported in that asymptomatic bacterial colonization in the hypopharyngeal region at one-month of age predicts subsequent asthma. [49] These observations may indicate that individuals with defective local innate immune responses to common viruses and bacteria have higher risks for subsequent development of asthma.

Just as with asthma, local innate immune responses in the skin have been shown to play important roles in the onset of atopic dermatitis. Mrabet-Dahbi et al[50] reported that a single nucleotide polymorphism in TLR2 R753Q results in impaired functional properties against *S. aureus*, which can be isolated from 90% of atopic eczema skin lesions.[51] Loss-of-function mutations in filaggrin, a filament-aggregating protein important for the formation of the stratum corneum, have been shown to play critical roles in the onset of atopic sensitization, allergic

rhinitis, asthma and atopic dermatitis.[52] For the development of atopic dermatitis, *S. aureus* secrete proteases and damage skin barrier function; defective production of SPINK5, a protease-inhibiting molecule was shown to be weakly associated with the risk of atopic dermatitis.[53] In addition, superantigens produced by *S. aureus* are known to activate T lymphocytes and facilitate IgE sensitization.[54, 55]

These newly identified genetic defects raise questions regarding how impaired local innate immune response or colonization with *S. aureus* causes allergic sensitization, asthma or atopic dermatitis. It is most likely that weak local innate immune responses may be associated with impaired signals to induce antigen-specific adjuvant effects of the microbial agents to fully stimulate protective Th1 immune responses. If this is the case, then the recent increased prevalence of allergic diseases attributed to improved hygiene conditions will only be found in individuals with susceptible genotypes of innate receptors such as CD14/-159CC.[44] Strategies using innate immunity vaccines targeting TLR4 to prevent allergic diseases may thus only be effective in individuals with this genotype, and not those with CD14/-159TT genotype.

RSV is felt to induce a Th2 type immune response in the lower airways mainly through its F-protein[56], and recently RV has been reported to induce thymic stromal lymphopoietin (TSLP) production[57] and release of several growth factors from bronchial epithelial cells.[24] Pulmonary infection with *Chlamydia pneumoniae* in a mouse model has been shown to induce Th2 type immune memory depending on the severity and timing of infection. Similarly, timing of birth in relationship to winter virus season has been shown to confer a differential risk of developing early childhood asthma.[58] These studies suggest that certain types of infection of the lower airway temporary opens a window of opportunity to establish a detrimental Th2 response when regulatory T cell function is suppressed. In summary, the advances in genetic research of allergic diseases in 2008 shed new light, in particular, on the importance of local immune responses that can play key roles in the regulation of development of allergic sensitization, asthma and atopic dermatitis.

References

1. Mazuc E, Villoutreix BO, Malbec O, Roumier T, Fleury S, Leonetti JP, et al. A novel druglike spleen tyrosine kinase binder prevents anaphylactic shock when administered orally. J Allergy Clin Immunol 2008;122:188–94. [PubMed: 18539317]
2. Dauvillier S, Merida P, Visintin M, Cattaneo A, Bonnerot C, Dariavach P. Intracellular single-chain variable fragments directed to the Src homology 2 domains of Syk partially inhibit Fc epsilon RI signaling in the RBL-2H3 cell line. J Immunol 2002;169:2274–83. [PubMed: 12193692]
3. Ju HR, Wu HY, Nishizono S, Sakono M, Ikeda I, Sugano M, et al. Effects of dietary fats and curcumin on IgE-mediated degranulation of intestinal mast cells in brown Norway rats. Biosci Biotechnol Biochem 1996;60:1856–60. [PubMed: 8987863]
4. Lee JH, Kim JW, Ko NY, Mun SH, Her E, Kim BK, et al. Curcumin, a constituent of curry, suppresses IgE-mediated allergic response and mast cell activation at the level of Syk. J Allergy Clin Immunol 2008;121:1225–31. [PubMed: 18394691]
5. Yokoi H, Choi OH, Hubbard W, Lee HS, Canning BJ, Lee HH, et al. Inhibition of FcepsilonRI-dependent mediator release and calcium flux from human mast cells by sialic acid-binding immunoglobulin-like lectin 8 engagement. J Allergy Clin Immunol 2008;121:499–505. [PubMed: 18036650]
6. Hua X, Chason KD, Fredholm BB, Deshpande DA, Penn RB, Tilley SL. Adenosine induces airway hyperresponsiveness through activation of A3 receptors on mast cells. J Allergy Clin Immunol 2008;122:107–13. [PubMed: 18472152]
7. Salamon P, Shoham NG, Puxeddu I, Paitan Y, Levi-Schaffer F, Mekori YA. Human mast cells release oncostatin M on contact with activated T cells: possible biologic relevance. J Allergy Clin Immunol 2008;121:448–55. [PubMed: 18028996]

8. Ringvall M, Ronnberg E, Wernersson S, Duelli A, Henningsson F, Abrink M, et al. Serotonin and histamine storage in mast cell secretory granules is dependent on serglycin proteoglycan. J Allergy Clin Immunol 2008;121:1020–6. [PubMed: 18234316]
9. Trivedi NN, Raymond WW, Caughey GH. Chimerism, point mutation, and truncation dramatically transformed mast cell delta-tryptases during primate evolution. J Allergy Clin Immunol 2008;121:1262–8. [PubMed: 18325577]
10. Wang J, Godbold JH, Sampson HA. Correlation of serum allergy (IgE) tests performed by different assay systems. J Allergy Clin Immunol 2008;121:1219–24. [PubMed: 18243289]
11. Christensen LH, Holm J, Lund G, Riise E, Lund K. Several distinct properties of the IgE repertoire determine effector cell degranulation in response to allergen challenge. J Allergy Clin Immunol 2008;122:298–304. [PubMed: 18572230]
12. Hamilton RG, Saito H. IgE antibody concentration, specific activity, clonality, and affinity measures from future diagnostic confirmatory tests. J Allergy Clin Immunol 2008;122:305–6. [PubMed: 18571709]
13. Corren J, Shapiro G, Reimann J, Deniz Y, Wong D, Adelman D, et al. Allergen skin tests and free IgE levels during reduction and cessation of omalizumab therapy. J Allergy Clin Immunol 2008;121:506–11. [PubMed: 18269927]
14. Ruppert AM, Averous G, Stanciu D, Deroide N, Riehm S, Poindron V, et al. Development of Churg-Strauss syndrome with controlled asthma during omalizumab treatment. J Allergy Clin Immunol 2008;121:253–4. [PubMed: 18206510]
15. Djukanovic R, Wilson SJ, Kraft M, Jarjour NN, Steel M, Chung KF, et al. Effects of treatment with anti-immunoglobulin E antibody omalizumab on airway inflammation in allergic asthma. Am J Respir Crit Care Med 2004;170:583–93. [PubMed: 15172898]
16. Kaplan AP, Joseph K, Maykut RJ, Geba GP, Zeldin RK. Treatment of chronic autoimmune urticaria with omalizumab. J Allergy Clin Immunol 2008;122:569–73. [PubMed: 18774392]
17. Vonakis BM, Saini SS. New concepts in chronic urticaria. Curr Opin Immunol 2008;20:709–16. [PubMed: 18832031]
18. Cherry WB, Yoon J, Bartemes KR, Iijima K, Kita H. A novel IL-1 family cytokine, IL-33, potently activates human eosinophils. J Allergy Clin Immunol 2008;121:1484–90. [PubMed: 18539196]
19. Adamko DJ, Wu Y, Ajamian F, Ilarraza R, Moqbel R, Gleich GJ. The effect of cationic charge on release of eosinophil mediators. J Allergy Clin Immunol 2008;122:383–90. [PubMed: 18455220]
20. Simon D, Salemi S, Yousefi S, Simon HU. Primary resistance to imatinib in Fip1-like 1-platelet-derived growth factor receptor alpha-positive eosinophilic leukemia. J Allergy Clin Immunol 2008;121:1054–6. [PubMed: 18234315]
21. Simon HU, Cools J. Novel approaches to therapy of hypereosinophilic syndromes. Immunol Allergy Clin North Am 2007;27:519–27. [PubMed: 17868862]
22. Broide DH. Immunologic and inflammatory mechanisms that drive asthma progression to remodeling. J Allergy Clin Immunol 2008;121:560–70. [PubMed: 18328887]
23. O'Byrne PM, Pedersen S, Lamm CJ, Tan WC, Busse WW. Severe exacerbations and decline in lung function in asthma. Am J Respir Crit Care Med 2009;179:19–24. [PubMed: 18990678]
24. Leigh R, Oyelusi W, Wiehler S, Koetzler R, Zaheer RS, Newton R, et al. Human rhinovirus infection enhances airway epithelial cell production of growth factors involved in airway remodeling. J Allergy Clin Immunol 2008;121:1238–45. [PubMed: 18355907]
25. Lee CG, Link H, Baluk P, Homer RJ, Chapoval S, Bhandari V, et al. Vascular endothelial growth factor (VEGF) induces remodeling and enhances TH2-mediated sensitization and inflammation in the lung. Nat Med 2004;10:1095–103. [PubMed: 15378055]
26. Puxeddu I, Pang YY, Harvey A, Haitchi HM, Nicholas B, Yoshisue H, et al. The soluble form of a disintegrin and metalloprotease 33 promotes angiogenesis: implications for airway remodeling in asthma. J Allergy Clin Immunol 2008;121:1400–6. [PubMed: 18410963]
27. Van Eerdewegh P, Little RD, Dupuis J, Del Mastro RG, Falls K, Simon J, et al. Association of the ADAM33 gene with asthma and bronchial hyperresponsiveness. Nature 2002;418:426–30. [PubMed: 12110844]

28. Lee JY, Park SW, Chang HK, Kim HY, Rhim T, Lee JH, et al. A disintegrin and metalloproteinase 33 protein in patients with asthma: Relevance to airflow limitation. Am J Respir Crit Care Med 2006;173:729–35. [PubMed: 16387804]
29. Foley SC, Mogas AK, Olivenstein R, Fiset PO, Chakir J, Bourbeau J, et al. Increased expression of ADAM33 and ADAM8 with disease progression in asthma. J Allergy Clin Immunol 2007;119:863–71. [PubMed: 17339047]
30. Yang Y, Haitchi HM, Cakebread J, Sammut D, Harvey A, Powell RM, et al. Epigenetic mechanisms silence a disintegrin and metalloprotease 33 expression in bronchial epithelial cells. J Allergy Clin Immunol 2008;121:1393–9. [PubMed: 18423563]
31. Siddiqui S, Mistry V, Doe C, Roach K, Morgan A, Wardlaw A, et al. Airway hyperresponsiveness is dissociated from airway wall structural remodeling. J Allergy Clin Immunol 2008;122:335–41. [PubMed: 18572228]
32. Slats AM, Janssen K, van Schadewijk A, van der Plas DT, Schot R, van den Aardweg JG, et al. Expression of smooth muscle and extracellular matrix proteins in relation to airway function in asthma. J Allergy Clin Immunol 2008;121:1196–202. [PubMed: 18405955]
33. Kearley J, Robinson DS, Lloyd CM. CD4+CD25+ regulatory T cells reverse established allergic airway inflammation and prevent airway remodeling. J Allergy Clin Immunol 2008;122:617–24. [PubMed: 18672278]
34. Fujita S, Yamashita N, Ishii Y, Sato Y, Sato K, Eizumi K, et al. Regulatory dendritic cells protect against allergic airway inflammation in a murine asthmatic model. J Allergy Clin Immunol 2008;121:95–104. [PubMed: 17920666]
35. Negri J, Early SB, Steinke JW, Borish L. Corticosteroids as inhibitors of cysteinyl leukotriene metabolic and signaling pathways. J Allergy Clin Immunol 2008;121:1232–7. [PubMed: 18355910]
36. Marsh DG, Neely JD, Breazeale DR, Ghosh B, Freidhoff LR, Ehrlich-Kautzky E, et al. Linkage analysis of IL-4 and other chromosome 5q31.1 markers and total serum immunoglobulin E concentrations. Science 1994;264:1152–6. [PubMed: 8178175]
37. Ober C, Hoffjan S. Asthma genetics 2006: the long and winding road to gene discovery. Genes Immun 2006;7:95–100. [PubMed: 16395390]
38. Strachan DP. Hay fever, hygiene, and household size. BMJ 1989;299:1259–60. [PubMed: 2513902]
39. Braun-Fahrlander C, Riedler J, Herz U, Eder W, Waser M, Grize L, et al. Environmental exposure to endotoxin and its relation to asthma in school-age children. N Engl J Med 2002;347:869–77. [PubMed: 12239255]
40. Kaisho T, Akira S. Toll-like receptors as adjuvant receptors. Biochim Biophys Acta 2002;1589:1–13. [PubMed: 11909637]
41. Kormann MS, Depner M, Hartl D, Klopp N, Illig T, Adamski J, et al. Toll-like receptor heterodimer variants protect from childhood asthma. J Allergy Clin Immunol 2008;122:86–92. [PubMed: 18547625]
42. Nakashima K, Hirota T, Obara K, Shimizu M, Jodo A, Kameda M, et al. An association study of asthma and related phenotypes with polymorphisms in negative regulator molecules of the TLR signaling pathway. J Hum Genet 2006;51:284–91. [PubMed: 16432636]
43. Vercelli D. Learning from discrepancies: CD14 polymorphisms, atopy and the endotoxin switch. Clin Exp Allergy 2003;33:153–5. [PubMed: 12580903]
44. Simpson A, John SL, Jury F, Niven R, Woodcock A, Ollier WE, et al. Endotoxin exposure, CD14, and allergic disease: an interaction between genes and the environment. Am J Respir Crit Care Med 2006;174:386–92. [PubMed: 16614348]
45. Pacheco K, Maier L, Silveira L, Goelz K, Noteware K, Luna B, et al. Association of Toll-like receptor 4 alleles with symptoms and sensitization to laboratory animals. J Allergy Clin Immunol 2008;122:896–902. [PubMed: 18835634]
46. Jackson DJ, Gangnon RE, Evans MD, Roberg KA, Anderson EL, Pappas TE, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. Am J Respir Crit Care Med 2008;178:667–72. [PubMed: 18565953]
47. Lemanske RF Jr, Jackson DJ, Gangnon RE, Evans MD, Li Z, Shult PA, et al. Rhinovirus illnesses during infancy predict subsequent childhood wheezing. J Allergy Clin Immunol 2005;116:571–7. [PubMed: 16159626]

48. Kelly JT, Busse WW. Host immune responses to rhinovirus: mechanisms in asthma. J Allergy Clin Immunol 2008;122:671–82. [PubMed: 19014757]

49. Bisgaard H, Hermansen MN, Buchvald F, Loland L, Halkjaer LB, Bonnelykke K, et al. Childhood asthma after bacterial colonization of the airway in neonates. N Engl J Med 2007;357:1487–95. [PubMed: 17928596]

50. Mrabet-Dahbi S, Dalpke AH, Niebuhr M, Frey M, Draing C, Brand S, et al. The Toll-like receptor 2 R753Q mutation modifies cytokine production and Toll-like receptor expression in atopic dermatitis. J Allergy Clin Immunol 2008;121:1013–9. [PubMed: 18234309]

51. Leyden JJ, Marples RR, Kligman AM. Staphylococcus aureus in the lesions of atopic dermatitis. Br J Dermatol 1974;90:525–30. [PubMed: 4601016]

52. Weidinger S, O'Sullivan M, Illig T, Baurecht H, Depner M, Rodriguez E, et al. Filaggrin mutations, atopic eczema, hay fever, and asthma in children. J Allergy Clin Immunol 2008;121:1203–9. [PubMed: 18396323]

53. Weidinger S, Baurecht H, Wagenpfeil S, Henderson J, Novak N, Sandilands A, et al. Analysis of the individual and aggregate genetic contributions of previously identified serine peptidase inhibitor Kazal type 5 (SPINK5), kallikrein-related peptidase 7 (KLK7), and filaggrin (FLG) polymorphisms to eczema risk. J Allergy Clin Immunol 2008;122:560–8. [PubMed: 18774391]

54. Cardona ID, Cho SH, Leung DY. Role of bacterial superantigens in atopic dermatitis : implications for future therapeutic strategies. Am J Clin Dermatol 2006;7:273–9. [PubMed: 17007538]

55. Semic-Jusufagic A, Bachert C, Gevaert P, Holtappels G, Lowe L, Woodcock A, et al. Staphylococcus aureus sensitization and allergic disease in early childhood: population-based birth cohort study. J Allergy Clin Immunol 2007;119:930–6. [PubMed: 17292957]

56. Legg JP, Hussain IR, Warner JA, Johnston SL, Warner JO. Type 1 and type 2 cytokine imbalance in acute respiratory syncytial virus bronchiolitis. Am J Respir Crit Care Med 2003;168:633–9. [PubMed: 12773328]

57. Kato A, Favoreto S Jr, Avila PC, Schleimer RP. TLR3- and Th2 cytokine-dependent production of thymic stromal lymphopoietin in human airway epithelial cells. J Immunol 2007;179:1080–7. [PubMed: 17617600]

58. Wu P, Dupont WD, Griffin MR, Carroll KN, Mitchel EF, Gebretsadik T, et al. Evidence of a causal role of winter virus infection during infancy in early childhood asthma. Am J Respir Crit Care Med 2008;178:1123–9. [PubMed: 18776151]

Abbreviations

ADAM
A disintegrin and metalloprotease

AHR
Airway hyperresponsiveness

FIP1L1-PDGFRA
Fip1-like1-platelet-derived growth factor receptor alpha chain

IL
Interleukin

ITIM
Immunoreceptor tyrosine inhibitory motifs

MMCP
Mouse mast cell protease

NECA
Adenosine-5′ N-ethylcarboxamide

PI-3K

Phospatidylinostol-3-phosphate kinase

RSV
Respiratory syncytial virus

RV
Rhinovirus

Siglec
Sialic acid-binding immunoglobulin-like lectin

SNP
Single nucleotide polymorphism

SP-D
Surfactant protein-D

Syk kinase
Spleen-type tyrosine kinase

TSLP
Thymic stromal lymphopoietin

VEGF
Vascular endothelial growth factor

Table I

Major advances in mechanisms of asthma, allergy and immunology published in the JACI in 2008

1	Mast cell and basophil biology: involvement and antagonism (by novel molecules and curcurmin) of Syk kinase in FcεRI signaling; inhibition of FcεRI signaling by Siglec-8; role of adenosine A3 receptors and activated T cell surface molecules in mast cell activation; contribution of serglycin to mast cell granule storage function; evolution of mast cell proteases across species.
2	IgE biology: comparison of clinical assays for measuring specific IgE; characterization of multiple functional properties of IgE affecting affinity for ligand and degranulation responses in basophils.
3	Omalizumab: effects on free IgE levels and skin test responses over time; effects on asthma and tissue eosinophilia in a patient developing Churg-Strauss Syndrome while receiving omalizumab; benefits in “autoimmune” urticaria.
4	Eosinophils: activating activity of IL-33 via its receptor ST2; ability of extracellular cationic charges to enhance eosinophil degraulation; report of a patient with chronic eosinophilic leukemia manifesting resistance to imatinib due to mutations in the FIP1L1-PDGFRA kinase domain.
5	Airway remodeling and AHR in asthma: causative contributions of rhinovirus, VEGF, sADAM33, and mast cells within airway smooth muscle; use of DCregs to reduce AHR in mice; inhibitory effect of corticosteroids on cysteinyl leukotriene receptor expression on leukocytes incubated with IL-4.
6	Genetics of allergic diseases: influence of polymorphisms in innate immune receptors including TLRs and filaggrin on asthma and atopic dermatitis by altering both adjuvant effects of microbial agents and local responses to viral and bacterial infections.