Review

Highlights in Cellular and Molecular Mechanisms of Allergic Diseases

XXVth Congress of the European Academy of Allergology and Clinical Immunology in Vienna

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Key Words

Abstract

This year, the annual congress of the European Academy of Allergology and Clinical Immunology was held on 10–14 June in Vienna. More than 6,000 delegates, practicing bench or bedside work or both, gathered from over 50 countries throughout the world. Health professionals, basic scientists and fellows in training could choose between a variety of activities in plenary, main, educational and workshop sessions, highlights of the past year, pros and cons, and oral abstract and poster sessions, and met with experts. A total of 1,713 abstracts, 31 symposia, and 54 workshops were presented, ranging from basic science to clinical trials and modern treatment of allergic diseases. Here, we summarize the highlights of cellular and molecular mechanisms of allergic disease.

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T Cell, B Cell, and Dendritic Cell Interactions in Innate and Adaptive Immune Responses

T Cells

A large proportion of the annual congress of the European Academy of Allergology and Clinical Immunology (held on June 10–14, 2006, in Vienna) was devoted to understanding the paradigm of the suppressive functions of regulatory T (T_{reg}) cells and the role of a novel subpopulation of T cells, Th17 cells. T_{reg} cells appear to keep the immune response under control, in many aspects, because dysfunction of these cells has been demonstrated in different autoimmune diseases, tumor growth, transplant rejection, chronic infections, allergy and asthma [1–4]. Therefore, targeting T_{reg} cells may have a great potential in the treatment of these diseases. In this context, it was shown that rapamycin selectively expands CD4+CD25+FoxP3+ T cells in vitro [5]. These cells suppress proliferation of syngeneic T cells in vitro and prevent allograft rejection in vivo. A recently published study by Coenen et al. [6] also showed that rapamycin may increase the suppressive potential of human CD4+CD25+ T cells in autoimmune responses in vitro. An original

lecture was delivered by Akbar, who stressed the need to better understand the influence of T cell homeostasis and senescence in young and elderly humans. It is especially important in the light of the fact that the human average lifespan in the developed countries has significantly increased over the last hundred years [7]. Using a sophisticated method with deuterium-labeled glucose, the lifespan of different T cell subsets was estimated, namely 198 days for naive CD4+CD25–RA+ T cells; 24 days for memory CD4+CD25+RO+ T cells and 8 days for T_{reg}.

M. Akdis elaborated on the regulation of the B cell isotype switch by IL-10-producing as well as CD4+CD25+ T_{reg} cell subsets. Antibody isotype regulation by Th1 and Th2 cells has been reported previously, whereas antibody regulation in T_{reg} cell-B cell interaction has not been known yet. She presented interesting results showing that IL-10-producing T_{reg} cells induced IgG_4 and IgA production and additionally IL-10, TGF-β, Tr1 cells, and CD4+CD25+T_{reg} cells inhibit IgE synthesis by B cells.

The role of T_{reg} cells in allergy and health was further discussed by Kapsenberg [8], who reviewed the existing data on the role of dendritic cells (DC) in the induction of peripheral tolerance. He suggested that different probiotics may have different immunomodulatory properties and promote mucosal tolerance, which is in part mediated by T_{reg} cells. It is probable that probiotics act via pattern recognition receptors on DC to induce DC subsets, which promote the generation of T_{reg} cells. The protective and therapeutic effect of microbial products in atopy was also the subject of a presentation by Di Felice et al. [9, 10]. They used a mouse model of allergen sensitization to the major pollen allergen of *Parietaria judaica* (rPar j 1) to study the immunomodulatory activity of a mixture of different probiotics. The prophylactic treatment with probiotics induced a significant reduction in serum total and specific IgE as well as specific IgG_1. It was accompanied by a significant increase in the production of IFN-γ and a significant reduction in splenic IL-4 secretion. They also showed an increase in IL-10 and IFN-γ in bronchoalveolar lavage (BAL) fluid analysis. Their results point to an immunomodulatory role of probiotics, especially through IL-10 and IFN-γ, and thus a role in IgE suppression.

Another highlight of the meeting was a newly described subpopulation of Th cells, the Th17 cells, that are characterized by the secretion of IL-17 and to lesser extend IL-8 and GM-CSF [11, 12]. Th17 cells are distinct from the Th1, Th2 or T_{reg} and have potent proinflammatory properties. IL-17 promotes granulopoiesis and neutrophil accumulation at the site of inflammation, playing a crucial role in the protection against bacterial infections. In mice, in the presence of the proinflammatory cytokine IL-6, TGF-β induces differentiation of Th17 cells. IL-23, both an IL-2 receptor γ chain and IL-12 cytokine family member, has been shown to be involved in the survival and expansion of Th17 cells [13, 14]. Transcription factors responsible for Th17 lineage commitment have not been identified until present. Sallusto in her talk reviewed current knowledge on Th17 cells and emphasized their key role, together with Th1, Th2 and T_{reg} cells, in specific immune response. She also provided new insights into the role of zymosan, an insoluble cell wall polysaccharide of the yeast *Saccharomyces cerevisiae* in Th17 cells lineage commitment. She showed that zymosan, that acts through Toll-like receptor (TLR)-2, selectively induces IL-23 secretion, but not IL-12 by DCs. In an attempt to identify a specific marker for Th17 cells, Sallusto et al. demonstrated the chemokine receptor CCR6. However, this chemokine receptor is not only specific for Th17, it is also expressed on memory T cells and T cells secreting IFN-γ and IL-10. Nonetheless, measurement of CCR6 expression allows to exclude Th2 cells. Furthermore, her group identified human Th17 clones against Candida, suggesting a role for Th17 in the immune response against fungi. The theme of Th17 cells and innate immune response was continued by de Jong. She presented data on priming human monocyte-derived DCs in vitro on their ability to promote the development of Th17 cells. Among different TLR agonists, her group identified peptidoglycan as a key bacterial constituent in terms of induction of IL-17 secretion by memory T cells and promotion of Th17 cell development. Peptidoglycan acts via TLR2 and the nucleotide-binding oligomerization domain modulating TLR2 signaling, which leads to the production of high levels of IL-23 by primed DCs. Interestingly, several viruses which they tested were not able to prime DCs to induce Th17 cell differentiation [15].

Allergic inflammation is not only localized to allergen-affected tissues, it might also influence the entire body. Bossios et al. [16] generated data in support of the concept that the body distribution of newly produced T cells upon allergen exposure is changed. They used intraperitoneally given bromodeoxyuridine in ovalbumin-sensitized BALB/c mice to label newly produced cells upon ovalbumin challenge. CD3+ and bromodeoxyuridine-positive cells from various organs and BAL fluid were determined by flow cytometry. Significant increases in the proportion of newly produced CD3+ cells were found in the bone marrow, lung and BAL fluid. Interest-

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ingly, there was no change in the distribution of cell populations in the lymph nodes, blood and spleen. The above results indicate that airway inflammation alters the distribution of CD3+ cells in the body, supporting the hypothesis that it is a systemic disease.

Dendritic Cells

Depending on the microbial information they encounter in peripheral tissues, DCs promote the development of different specific T cell responses. It is also known that a tryptophan-degrading enzyme, indoleamine 2,3-dioxygenase (IDO), can be a potent inducer of immunosuppression and tolerance in vivo and in vitro. It is expressed by some antigen-presenting cells upon inflammatory stimuli, and it has been shown that allergic asthma can be abrogated by IDO-expressing epithelial cells in the lung. TLR9 ligand-induced pulmonary IDO activity by epithelial cells of the lung inhibits Th2-driven experimental asthma [17]. von Bubnoff et al. showed that tryptophan deprivation affects the T cell-stimulatory capacity of DCs. As determined by flow cytometry, human monocyte-derived DCs generated in the absence of tryptophan demonstrated altered expression of surface antigens related to antigen presentation and costimulatory activities and were weak inducers of T cell stimulation. In conclusion, IDO may in part regulate tolerance induction by its modulatory effect on DCs [18].

The innate immune system serves as a sensor in the identification of the invading pathogens and modulates the type of adaptive immune response. IL-12 produced by DCs leads to the differentiation of naive CD4+ T cells into Th1 cells, mounting an effective immune response against pathogens, but may also lead to autoimmune diseases and chronic forms of allergic inflammation. The cells providing this initial IL-12 remain to be elucidated. Schäkel in his talk described a subset of DCs, which is the principal and primary source of IL-12p70, when blood leukocytes are either stimulated with TLR4-ligand lipopolysaccharide or CD40-ligand. These so-called slanDCs are characterized by the 6-sulfo LacNAc, an O-linked carbohydrate modification of P-selectin glycoprotein ligand-1, and by the expression of the following markers: CD162, CD1c–, CD11c+, CD16+, CD14–, C5aR+ and CD45RA+. They account for the majority of DCs in human blood (0.6–2% of PBMCs). Interestingly, the IL-12 response and maturation of slanDCs are completely blocked in coculture with erythrocytes. This inhibition of maturation depends on the expression of CD47 on erythrocytes and of its ligand signal-regulatory protein-α on DCs. Although slanDCs are potent cells secreting

IL-12 and TNF-α, inhibition of their maturation by erythrocytes might prevent overreaction of slanDCs in the circulation [19].

Matricardi in his presentation pointed out the discrepancy of promising results of mycobacteria in mouse models and lack of such data in human studies. He concluded that it may still be worthwhile to investigate whether T_{reg} cells are induced in response to different mycobacterial strains, as demonstrated in humans [20, 21]. Fuchs presented interesting results on the preventive effect of the *Mycoplasma fermentans*-derived lipopeptide MALP-2 derivate bisacyloxypropylcystein (BPPcysPEG) on asthma in a mouse model. BPPcysPEG is a synthetic TLR2/TLR6 agonist and is thought to mimic bacterial infection. Fuchs et al. [22] studied five treatment groups; BPPcysPEG, IFN-γ, BPPcysPEG/IFN-γ and dexamethasone in mice. They found that eosinophil numbers were significantly diminished in BAL fluid after treatment with either dexamethasone or BPPcysPEG/IFN-γ compared to vehicle control. They did not observe any induction of neutrophils. Response to methacholine was also improved. Their findings suggested that treatment with BBPcysPEG and IFN-γ could shield from asthma symptoms, and the combination might be used as an adjuvant in allergen-specific immunotherapy and for allergy prevention [22].

B Cells and IgE Regulation

The theme of the innate immune system was continued by Sackesen. She presented captivating data on the effect of suppressive oligonucleotides, which are repetitive TTAGGG sequences as expressed in mammalian telomeric DNA, on human B cells. Her investigation revealed the effects of suppressive oligonucleotides on human B cell activation and antibody production. Purified B cells were stimulated with specific ligands for TLR2–TLR 9 in the presence or absence of suppressive oligonucleotides. B cell differentiation, proliferation and antibody production were determined. Circulating B cells proliferated and turned into antibody-secreting cells in response to TLR3, TLR7 and TLR9 ligands. All three TLR ligands similarly induced a program of B cell activation leading to blast formation with increased expression of CD27, CD38, CD86, B cell maturation antigen, CD19 and CD20. Determination of the frequency of antibody-producing cells revealed that only a fraction of activated B cells turned into IgA. Some of the cells became IgG_1- and IgG_4-producing plasma cells, whereas a high percentage remained as memory B cells. Suppressive oligonucleotides significantly inhibited all of the mentioned fea-

tures of B cells demonstrating a natural mechanism for the control of B cell memory. Her group concluded that host-derived telomere oligonucleotides can downregulate B cell maturation and antibody responses [23].

The theme of IgE regulation was the subject of several other presentations. Marth presented evidence for a stable repertoire of allergen-specific IgE in allergic individuals [24]. Her group analyzed variable regions of major birch pollen allergen (Bet v1)-specific IgE in patients with seasonal allergy. They found more limited numbers of sequences coding for variable regions for Bet v1-specific IgE. Experiments repeated after three birch pollen seasons showed almost no change in the Bet v1-specific IgE-variable region repertoire, indicating that the repertoire of allergen-specific IgE is derived from a pre-established pool of IgE-producing cells.

Vercelli gave a talk on the results of the ALEX study. One of the aims of this study was to analyze allergen-specific immune responses in 9-year-old children that had grown up in city or countryside environments. In support of the hygiene hypothesis, the study indicated that serum levels of allergen-specific IgG_1, IgG_4 and IgE were reduced in children living on farms. At the same time, the levels of allergen-specific IgG_2 and IgG_3 were unchanged. It was emphasized that different allergens may generate specific humoral immune responses in terms of types of antibody classes due to a sequential process of immunoglobulin isotype switching. Because the IgG_1 gene is upstream of the immunoglobulin locus, its expression is a prerequisite for downstream locus switching. She also presented data indicating the absence of IgG_1 was associated with low IgE and IgG_4 for many types of allergen. In line with Vercelli's talk was a lecture given by Launer. He summarized different aspects of the role of microbial components on the modulation of immune responses [25–27]. Low doses of lipopolysaccharide cause eosinophilia, high secretion of IL-5 and IL-13 and high IgE production. On the other hand, high doses of lipopolysaccharide are responsible for increases in IFN-γ and IgG_{2a}. TLR ligands for TLR2 and TLR8 can activate T_{reg} cells, but interestingly TLR signaling reverses the suppressive effect of T_{reg} cells. High-dose endotoxin, the best-known farm exposure product, induces high expression of suppressor of cytokine signaling-1, which has inhibitory function on TLR signaling, leading to less IFN-γ production.

It is well known that a subset of food-allergic patients responds clinically not only with symptoms in the gastrointestinal tract, but also with asthmatic reactions [28]. Ozdemir et al. [29] studied the role of intestinal mesenteric CD4+ T cells on food-induced immediate-type hypersensitivity in the development of asthma. They described a food-induced intestinal immediate-type hypersensitivity model in ovalbumin-sensitized BALB/c mice after intragastric challenges. In their model, they demonstrated eosinophilic infiltration in small intestinal specimens, as well as goblet cell hyperplasia and shortened villus height/crypt depth ratios, representative findings of food allergy. After various aerosol ovalbumin challenges, they demonstrated airway hyperreactivity and eosinophilic airway inflammation in CD4+ cell-transferred naive mice.

Effector Cells and Mechanisms of Allergic Inflammation

Mast cells are major effector cells in IgE-mediated allergic diseases. Essential signals for mast cell activation occur after the cross-linking of the IgE receptor, FcεRI, which then leads to the secretion of preformed mediators and de novo synthesis of proinflammatory leukotrienes and cytokines. Gutermuth presented a novel signaling pathway in mast cells. He showed that mice deficient in Bcl-10 or Malt1 are severely impaired in terms of IgE-dependent late-phase anaphylactic reactions. Even though proximal signaling and degranulation are normal in these animals, mast cells cannot produce TNF-α and IL-6 upon FcεRI ligation, due to impaired activation of NF-κB [30]. Another regulatory pathway of the mast cells was discussed by Maurer. He reminded that despite their unwanted IgE-associated effects, mast cells contribute to host defense against invading bacteria [31]. His group used Kit^w/Kit^{w-v} mice deficient in mast cells. Mast cell-deficient mice infected to develop septic peritonitis succumbed to sepsis, indicating a critical role of mast cells as a source of TNF-α, which stimulates neutrophils in an early immune response. When an infected mouse mast cell population was increased via administration of stem cell factor, these mice were less susceptible to septic peritonitis. Another example was the process of effective wound healing, which is positively influenced by mast cells. The processes were not related to IgE and FcεIIR, because blocking of IgE does not prevent the observed effects.

Other important cells involved in allergic inflammation are basophils. The activation of these cells via cross-linking of IgE and a role of histamine receptor 2 (HR2) in this process has been investigated by Mete et al. [32]. Purified basophils from whole blood, which are known

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to express HR2, were stimulated by the HR2 agonist dimaprit. Stimulation with dimaprit significantly suppressed basophil activation after surface IgE cross-linking, which was determined by CD203c expression on the cells. Since it is known that HR2 induces cAMP, they used forskolin and were able to suppress activation of basophils upon anti-IgE cross-linking. Release of sulfidoleukotrienes by activated basophils was also diminished by both dimaprit and forskolin. HR2 expressed on human basophils represents a novel target for the treatment of allergic inflammation, because of its ability to rapidly suppress basophil degranulation and activation upon surface IgE cross-linking.

The role of the complement cascade in allergic disease has been confusing and controversial [33, 34]. Wang presented interesting results on the use of anti-mouse and anti-human C5 antibodies (mAbs) to block intrapulmonary activation of C5 via nebulization [35]. Ovalbumin-sensitized and -challenged mice developed airway inflammation with significantly elevated intrapulmonary C5 activity and transepithelial infiltration of inflammatory cells. Nebulization of anti-C5 mAb inhibited C5 in the lungs in a dose-dependent manner without affecting serum C5 activity. Repeated chronic aerosol administrations of anti-mouse C5 mAb did not cause detectable changes in the airways of normal BALB/c mice. Yi Wang's group demonstrated that a single nebulization of either anti-mouse C5 mAb or dexamethasone significantly blocked methacholine-induced airway hyperresponsiveness in mice with established airway inflammation. The nebulization of a combined dose of corticosteroid and anti-C5 mAb had better efficacy than monotherapy.

Neutrophins, including nerve growth factor, brain-derived neutrophic factor, neutrophin-3 and neutrophin-4, seem to be another important regulator of allergic asthma. Neutrophins have been shown to play an important role in the development of allergic asthma by increasing airway inflammation and hyperreactivity [36]. In order to identify the potential target cells of neutrophins, Nassenstein et al. [37] analyzed the expression of high-affinity neutrophin receptors (Trk), namely TrkA, TrkB, and TrkC, in a murine model of asthma. They observed that all Trk receptors were constitutively expressed in large nerve bundles as well as in small nerve fibers surrounding the airways. Moreover, TrkA and TrkC were expressed in airway smooth muscle cells. After allergen provocation, there was a marked increase in infiltrating Trk+ cells, notably TrkB+ and TrkC+ cells. Further investigations revealed that Trk+ cells belong to a heteroge-

neous group of CD45+ leukocytes. Infiltrating CD19+ B cells, CD4+ T cells, and DEC205+ (membrane glycoprotein, DCs and epithelial cells, 205 kDa), CD11c+ and MHC class II antigen-presenting cells expressed those receptors. They suggested that allergen contact may lead to an enhanced infiltration with Trk+ cells and/or to an upregulation of Trk receptor expression. Therefore, they hypothesized that neurotrophins might affect allergic airway inflammation by influencing different immune cell populations.

The correlation between allergy development and natural killer (NK) cell phenotypes in childhood was presented by Sundstrom [38]. Mononuclear cells collected from cord and peripheral blood of 2- and 5-year-old allergic and non-allergic children were compared by flow cytometry. NK cells, isolated from cord blood of children that later developed allergy, expressed more NKp30 receptors and less of the activating NKG2C/CD94 receptor complex compared to non-allergic children. Cord blood from children that later developed allergy contained also smaller populations of CD56bright NK cells. At 2 years of age, NK cells from allergic children showed a reduced capacity to produce IFN-γ in response to stimulation with IL-2 and IL-12. Sundstrom's group stated that differences in the NK cell phenotype in the cord blood may suggest a predisposition towards allergy.

The novel pathogenic link between T cells and pruritus in atopic skin inflammation was the subject of a talk by Sonkoly [39]. Using real-time RT-PCR, Sonkoly demonstrated that IL-31 was significantly overexpressed in 'pruritic' atopic compared to 'non-pruritic' psoriatic skin lesions. Moreover, in vivo, staphylococcal superantigen, enterotoxin B, was shown to rapidly induce IL-31 expression in atopic individuals. Furthermore, activated leukocytes expressed significantly higher IL-31 levels in atopic dermatitis patients compared to control subjects. Their findings provide a new link between staphylococcal colonization, subsequent T cell recruitment/activation and pruritus in atopic dermatitis patients, and emphasize that IL-31 may represent a novel target for antipruritic drug development.

It has recently been demonstrated that epithelial activation and apoptosis play an important role in the pathogenesis of eczematous dermatitis and asthma [40]. Tomasz Basinski et al. [41] presented new data on the mechanisms of activation-induced cell death of human sinus epithelial cells (HSEC) in the pathogenesis of chronic rhinosinusitis. They showed that IFN-γ is a major factor which induces the activation of HSECs by upregulation of MHC class II molecules and sensitizes HSECs to the apop-

tosis induction by TNF-related apoptosis-inducing ligand (TRAIL) and Fas ligand (FasL). Interestingly, TRAIL and FasL alone did not induce apoptosis of HSEC. T cells infiltrating sinus epithelium from chronic rhinosinusitis individuals were found to express more TRAIL compared to healthy individuals. Coculture experiments of HSEC with activated sinus-infiltrating T cells followed by blocking of IFN-γ demonstrated that IFN-γ is an effector factor, which increases susceptibility of HSEC to the apoptosis induced by TRAIL and FasL secreted by T cells.

Transcription Factors in Allergic Inflammation

Th2 cells play a central role in allergic inflammation. Since GATA-3 is a transcription factor playing a decisive role in the development of the Th2 phenotype, it is a promising target for the treatment of allergic diseases [42]. Garn presented captivating data on GATA-3-specific DNAzyme, a molecule that combined the specificity of antisense molecules with an inherent enzymatic activity. Garn et al. [43] compared the anti-allergic capacity of that DNAzyme with GATA-3-specific antisense-DNA and small interfering RNA using preventive and therapeutic strategies in a mouse model of experimental asthma. The intranasal application of DNAzyme showed the most pronounced effects in eosinophil numbers in the BAL fluid, on local IL-5/IFN-γ ratios, in histopathology demonstrating reduced airway goblet cell numbers and reduced tissue inflammation. Airway hyperreactivity to methacholine was also reduced in comparison to the untreated group. Notably, effects were only observed after intranasal application [43].

The theme of T_{reg} cells was expanded by Schmidt-Weber who demonstrated transcription factors responsible for the regulation of Foxp3, which is in turn decisive on T_{reg} cell lineage commitment [44]. The same group (Mantel et al. [44]) indicated that naive T cells activated in the presence of TGF-β and IL-4 do not have the potential to upregulate FOXP3. Transgenic mice overexpressing GATA-3 in CD4+ T cells had a decreased number of CD4+CD25+FoxP3+ T cells. On the other hand, CD4+CDC25– T cells from these transgenic mice were unable to express FoxP3. The differentiation of naive T cells into Th2 cells is dependent mainly on IL-4, which induces GATA-3 and GATA-3-suppressed FOXP3 expression. Thus, cytokines present at the time of priming of naive T cells play a major role in the lineage commitment decision, not only for Th1 and Th2, but also for T_{reg} cells [45].

T-bet, STAT1, STAT4, GATA-3, and STAT6 are known to be responsible for lineage commitment into Th1 and Th2 T cell subsets, respectively. Nouri-Aria presented data on the contribution of T-bet and STAT6 to the regulation of Th1 and Th2 cytokine profiles at the transcriptional level [46]. The group analyzed cutaneous CD3 and T-bet expression compared to CD3 and STAT6 expression on T cells after intradermal injection of grass pollen allergen, *Phleum pratense*, and tuberculin (purified protein derivatives) in humans. Computerized double immunofluorescence microscopy results showed that antigen challenge caused an increase in the number of CD3+STAT6+ T cells in skin biopsies from atopics, but not in skin biopsies from non-atopic individuals. In contrast, skin challenge with purified protein derivatives led to a significant increase in CD3+T-bet+ cells in non-atopics and to a lesser extent in atopics. Their results support the role of T-bet and STAT6 in the expression of Th1 and Th2 responses in humans, respectively.

In conclusion, we must objectively admit that the meeting was a great success, thanks to the organizers and all of the professionals who actively participated in the activities of the congress of the European Academy of Allergology and Clinical Immunology. We look forward to next years' meeting in Gothenburg. We hope that it will again give an excellent opportunity to come together to discuss new findings and disseminate ideas for a better prevention and treatment of allergic diseases.

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