

News and commentaries

Immunology highlights at high altitude: review of the fourth EAACI-GA²LEN Davos Meeting

The field of allergy is moving fast. To keep pace with the underlying immunologic mechanisms, the 4th EAACI-GA²LEN Davos meeting on 'Basic Immunology Research in Allergy and Clinical Immunology' was organized in Grainau, Germany, February 16th–19th, 2006 by the Immunology Section of the European Academy of Allergy and Clinical Immunology and the ZAUM – Center for Allergy and Environment, Technical University Munich, with generous support from GA²LEN. Recent advances and new insights on innate and adaptive immunity, environmental factors influencing immune responses, immune regulation and allergic inflammation were presented by keynote speakers and selected participants.

**J. Gutermuth, G. Köllisch,
M. Bewersdorff, A. Braun,
F. Alessandrini, T. Jakob**

Division of Environmental Dermatology and Allergy
GSF/TUM, ZAUM – Center for Allergy and
Environment, Technical University Munich, Munich,
Germany

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PD Dr Thilo Jakob
Division of Environmental Dermatology and Allergy
GSF/TUM
ZAUM – Center for Allergy and Environment
Technical University Munich
Biedersteinerstr. 29
80802 Munich
Germany

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In order to promote high level basic immunology research in the field of allergy and clinical immunology, the Immunology Section of the European Academy of Allergy and Immunology (EAACI) set up a biannual meeting on 'Basic Immunology Research in Allergy and Clinical Immunology' in 2001. Three successful meetings took place in Davos, Switzerland, which coined the term 'EAACI Davos Meeting'. Because of generous support from the Global Allergy and Asthma European Network of Excellence (GA²LEN), it was now possible to have the 4th meeting already 1 year earlier. Six symposia started with a keynote lecture followed by presentations of participants, covering three main areas of allergy research: (i) innate immunity, (ii) adaptive immunity and regulation and (iii) allergic inflammation. Goal of the meeting was to create an engaging scientific environment in which allergy and asthma related immunologic concepts were covered with ample time for discussion during which young scientists had the opportunity to directly interact with known capacities in the field.

Adjuvants and lymphocytes

Philippa Marrack from the Howard Hughes Institute in Denver, CO, USA, raised the question how alum, which

has been used as an adjuvant for the last 50 years, stimulates the immune system: alum injections primed B cells in the presence of a GR1+ cell population, that was induced after alum injection and produced high amounts of interleukin (IL)-4 (1). Alum did not work through Toll-like receptors (TLRs) and complete Freund's adjuvant did not induce the GR1+ cell population or priming of B cells. As potential natural counterpart to alum, *Schistosoma* eggs exerted similar activation properties: induction of a IL-4-producing GR1+ cell population, B cell priming via IL-4 and induction of Th2 responses. Interestingly, also pollen grains are likely to act via the same pathway. In search of the responsible ligands and receptors, Lewis X sugar of *Schistosoma* eggs, which induced Th2 like responses, was identified as potential candidate.

Not all is toll in innate immunity

Hermann Wagner from the Department of Medical Microbiology, Hygiene and Immunology, Technical University Munich, Munich, Germany, gave insight in the role of TLRs in the recognition of exogenous/endogenous ligands, and pathogen vs sterile driven inflammation. He was pointing out, that other recently

discovered receptors, like RIG-I and NALP3 also can recognize viral RNA independent of TLRs (2). Some TLR ligands, like RNA or DNA occur in the host organism itself and a crucial question is how the discrimination between self and nonself RNA or DNA is achieved. Wagner reported that phosphothioate oligodeoxynucleotides (ODN) complexed to liposomes induce TLR9 dependent activation, whereas phosphodiester ODN induce TLR9 dependent and independent activation. Moreover noncanonical DNA sequences or calf thymus DNA together with liposomes can induce TLR9 independent activation. Biacore binding experiments of CpG DNA or DNA to TLR9 showed, that at low concentrations, bacterial CpG DNA binds to TLR9 whereas host DNA does not. With increasing concentrations of host DNA, it can also bind to TLR9. This offers an explanation how self and nonself DNA can be discriminated: low concentrations of pathogenic DNA are enough to activate the immune system, whereas naturally occurring host DNA is only active via TLR9, if concentrations are abnormally high (e.g. diseased cells).

Adaptive immunity and regulation

Ron Germain, Potomac MD, head of the Lymphocyte Biology Section at the NIH in Bethesda, MD, USA, challenged a number of immunological concepts* including the dogma of cross presentation and the role of dendritic cells (DC) in maintaining tolerance to self antigens. In addition, he proposed that priming and activation of T cells does not follow an 'analog' model with a linear dose dependent increase of activation in every individual T cell. Rather, naïve T cells achieve a state of activation when a certain threshold level is reached in a particular cell. In this 'digital model' increasing activating stimuli lead to a larger absolute number of T cells which differentiate into effector memory T cells. Finally, Germain proposed a stochastic model of the initial pathophysiology of autoimmune disease. As every T cell has to reach a threshold level of activation before it can differentiate, a reduced threshold level of autoreactive T cells could initiate and perpetuate the development of autoimmune disease. In susceptible individuals, a very low dose therapy with immunosuppressives might prevent the activation of autoreactive T cells and subsequent disease processes.

Ulrich von Andrian from the Department of Pathology at Harvard Medical School Boston, USA, visualized immune cell interactions by *in vivo* two-photon microscopy (3): transient serial DC – T cell encounters during the first 8 h were followed by 12 h with stable contacts and production of IL-2 and interferon- γ (IFN- γ) by T cells.

*This talk was prepared by Ronald N. Germain in his personal capacity. The views expressed herein do not necessarily represent the views of NIH, DHHS, or the USA.

On day 2, rapid T-cell motility and proliferation was observed. Furthermore, antigen specific cytotoxicity was visualized in CD8 cells with specificity for hemagglutinin (HA) and B cells expressing HA. Killing of HA-positive B cells took 4 h and was preceded by loss of target cell motility. Transforming growth factor- β (TGF- β) secreting Treg cells abolished cytotoxicity. The third aspect covered by von Andrian was the recruitment of effector cells into inflamed tissue in a contact hypersensitivity model. Surprisingly, the model worked in T-cell deficient Rag^{-/-} mice, which challenged the dogma that only T cells confer hapten specific memory: also hepatic natural killer (NK) cells of T-cell deficient Rag^{-/-} mice were able to transfer hapten specific sensitization to naïve mice (4).

Richard Flavell from the Section of Immunobiology at the Howard Hughes Institute/ Yale University, New Haven, CT, USA, reviewed the role of TGF- β in innate and adaptive immune responses (5). NK cells responded to regulation by TGF- β : BALB/c mice with transgenic (tg) NK cells, which carry a TGF- β dominant negative receptor (dnTGF β R2), displayed defective TGF- β -signaling in NK cells, but showed increased NK cell number and NK cell activation. At the same time a reduced control of Th1 adaptive immune responses was observed. Furthermore, mice with dnTGF β R2 tg T cells displayed normal T cell development, but exhibited spontaneous T cell activation, autoantibody production and development of lethal multifocal inflammatory disease. Additionally, TGF- β induced CD4 + CD25+ T cell expansion *in vivo* and FOXP3 positive T cells with regulatory properties *in vitro*. Furthermore, TGF- β promoted splenic Treg cell maintenance and prevented activation of T effector cells. As the critical source for TGF- β in regulating T cell responses, autocrine TGF- β derived from T cells was identified in conditional TGF- β knock-out mice.

Novel players in allergic inflammation

Dale Umetsu from the Department of Immunology at the Children's Hospital Boston, USA, gave new insights on the emerging role of natural killer T (NKT) cells in inflammatory diseases: NKT cells are to date believed to link innate and adaptive immunity by early production of cytokines and are found in various diseases such as cancer, inflammatory and infectious diseases. Bronchial asthma is regarded as a mainly CD4 T-cell mediated disease. Opposing to this classical model, Umetsu showed that NKT-cell activation by synthetic or natural glycolipid-ligands of the NKT-cell receptor alone was sufficient to induce airway hyperreactivity and inflammatory bronchoalveolar lavage (BAL) infiltrate. These hallmarks of asthma were not observed in CD1d^{-/-} deficient mice and effects were dramatically reduced in IL-4^{-/-} and IL-13^{-/-} deficient mice. Furthermore, glycolipids induced AHR in mice lacking conventional CD4 T cells. Moreover, in the BAL of human asthmatic patients 45–86% of

CD4 cells were identified as NKT cells, whereas in lung biopsies from sarcoidosis patients (a Th1-mediated disease) no increase of NKT cells was observed. The overall view of these observations led to the identification of NKT cells as important players in the pathogenesis of asthma and as potential targets for future therapies (6, 7).

Keynote lectures were followed by oral presentations selected from the abstracts (published at <http://www.eaaci.net/media/PDF/D/801.pdf>) which covered a wide range of basic immunology topics related to allergy. Among the many excellent contributions Schmidt-Weber et al. (Davos, Switzerland) identified a Treg 'regulon' which negatively regulates transcription of FOXP3, the master transcription factor of Treg cells by binding the Th2-transcription factor GATA-3 (8). Schäkel et al. (9) (Dresden, Germany) described a mechanism by which erythrocytes in a CD47/SIRP- α dependent fashion inhibit the maturation of M-DC8+ cells in peripheral blood. Studies by Ruland et al. (Munich, Germany) demonstra-

ted that Bcl10/Malt1 complexes are essential positive regulators of Fc ϵ RI-dependent mast cell activation, leading to production of proinflammatory cytokines, while leaving degranulation and leukotriene synthesis unaffected (10). Ruprecht et al. (11) (Bellinzona, Switzerland) described TLR ligands as the third pivotal signal for activation of naïve B cells and Bruhns et al. (Paris, France) identified a novel Fc receptor, Fc γ RIV, on murine neutrophils and monocytes/macrophages that bound IgE-complexes, suggesting a new role for IgE in allergic immune reactions by directly triggering myeloid cells.

To conclude, 74 doctoral and postdoctoral scientists from 20 different countries enjoyed a fantastic meeting in the Bavarian Alps, where high level scientific education and exchange were offered in a familiar and most friendly atmosphere. We will continue this tradition with the next EAACI-GA²LEN Davos Meeting which is scheduled for February 2007 in Davos (for details see <http://www.eaaci.net>).

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