ESF-JSPS Frontier Science Conference Series
for Young Researchers

Cutting Edge Immunology and its Clinical Application

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BOOKLET OF ABSTRACTS

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In order of appearance in the programme

Plenary Lectures

ESF-JSPS Frontier Science Conference Series for Young Researchers
Cutting Edge Immunology and its Clinical Application

Name: Jean-François BACH
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Title:
Infections, immunoregulation and autoimmune diseases

Abstract:

Most autoimmune diseases are polygenic and multifactorial. The disease concordance rate between monozygotic twins varies according to diseases. It is often high (20-40 %) demonstrating the importance of genetic factors. However, the existence of a large percentage of discordant twins argues in favour of an important role of environmental factors.

The study of predisposing genetic factors is complicated by the multiplicity of genes in question and the low risk factor associated with this exception of HLA genes. Progress has been made in some autoimmune diseases, notably in insulino-dependent diabetes mellitus (IDDM) for the identification of some predisposing genes but the number of clearly recognised genes remains very limited. The role of epigenetic marks is still elusive.

Concerning the role of environment, major attention has been drawn to bacteria and viruses. The etiologic role of *campylobacter jejuni* in Guilain-Barré syndrome is well established as well as that of group A streptococci in rheumatic fever. Additionally the role of various viruses has been suggested in multiple sclerosis and IDDM but no definite virus has yet been clearly identified. Various drugs induce autoimmune diseases, notably systemic lupus erythematosus and myasthenia gravis, but drug-induced autoimmune diseases do not appear to be necessarily identical to idiopatic autoimmune diseases.

Paradoxically, the environment may prevent the onset of autoimmune diseases. There is now compelling evidence suggesting that the decline of infections in industrialized countries is at the origin of the increase of most autoimmune diseases. The evidence is based on epidemiologic data but also relies on animal models. Underlying mechanisms are diverse. They include homeostatic factors, regulatory T cells and Toll-like receptors. The role of the various regulatory T cell subsets will be discuss in detail.

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Cutting Edge Immunology and its Clinical Application

Name: Tadamitsu Kishimoto
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Title:
IL-6: From its discovery to medicine and back again

Abstract:
IL-6 was originally identified as a T cell-derived cytokine, which induces antibody production in B cells. A series of subsequent studies have revealed that IL-6 has a pleiotropic activity in various tissues and cells and its deregulated expression is responsible for several chronic inflammations and hemopoietic malignancies.

Humanized antibody against 80kd IL-6R (Tocilizumab) has shown significant therapeutic effect in RA, JIA and Castleman's diseases. The antibody is effective even on anti-TNF unresponsive inflammatory diseases. Recently, TH17 is shown to be responsible for the pathogenesis of autoimmune diseases and IL-6 together with TGF-β are essential for the induction of TH17. We identified a new transcription factor required for Th-17 cell induction, which is induced by IL-6 and TGF-β. This molecule, aryl hydrocarbon receptor (Ahr) interacts with Stat1 and Stat5 and abrogate their negative activity in the induction of Th-17 cell differentiation. Experimental arthritis is completely abrogated in Ahr-KO mice as well as T cell-specific Ahr-deficient mice. In contrast, Ahr is shown to negatively requlate LPS-induced inflammatory cytokines production in macrophages by interacting with STAT-1. Thus, Ahr-KO mice become hyper-sensitive to LPS-induced septic shock. I will discuss here a novel pathways of the regulation of inflammation through the regulation of STAT1 with Ahr.

Lectures by Speakers

Session 1

Name: Toshiaki Ohteki
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Title:
Regulatory role for interferon in HSC homeostasis - an old cytokine with a new function

Abstract:
Hematopoietic stem cells (HSCs) are pluripotent cells with the capacity for the life-long production of the entire lineage of mature hematopoietic cells. Under steady-state conditions, most HSCs are quiescent residents of the BM niche, a state that preserves their capacity to self-renew. Type I interferons (IFNs) are essential for establishing the host antiviral state, their role in hematopoietic homeostasis remains unstudied. We found that type I IFNs induce activation and exhaustion in HSCs, and that IRF2, a transcriptional suppressor of type I IFN signaling, preserves the self-renewal and multi-lineage differentiation capacity of HSCs. As virus infection stimulates host immune cells to induce type I IFNs, we also consider the importance of viral infection-induced type I IFNs in the activation of HSCs. Interestingly, we found that acute infection with both RNA and DNA viruses stimulates HSC activation in WT mice, mice lacking type I IFN- or type II IFN-signaling, whereas such HSC activation is completely impaired in mice lacking both type I and type II IFN-signaling, suggesting stringent requirements of either type-I or -II IFN signaling, but not others, for HSC activation in viral infection. Our findings may lead to improvements for BM-transplantation and type-I IFN-based therapies for viral infections and cancer.

References: Sato T et al. Nat Med 15, 696-700 (2009); Essers MA et al. Nature 458, 904-908 (2009). Baldridge MT et al. Nature 465, 793-797 (2010)

Session 1

Name: Yousuke Takahama
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Title:
Thymic microenvironments that shape T lymphocyte repertoire

Abstract:
During T cell development in the thymus, a virgin repertoire of diverse TCR-ab recognition specificities in immature thymocytes is selected through positive and negative selection to form an immunocompetent and self-tolerant repertoire of mature T cells. Positive selection supports the survival of thymocytes that receive weak signals of low-avidity TCR engagement, whereas negative selection deletes potentially harmful self-reactive thymocytes upon high-avidity TCR engagement. Recent advances in the biology of thymic stromal cells have indicated that intimate crosstalk between developing thymocytes and thymic medullary epithelial cells that promiscuously express genes encoding tissue-specific self-antigens is essential for the establishment of a self-tolerant TCR repertoire. It has also been indicated that the formation of an immunocompetent TCR repertoire requires positive selection by thymic cortical epithelial cells expressing a unique protein degradation machinery. These results suggest the role of self-peptide repertoires specifically expressed by multiple thymic microenvironments in the development of the adaptive immune system.

J Exp Med 208:383-394, 2011; Immunity 32:29-40, 2010; PNAS 106:17129-17133, 2009; Immunity 29:438-450, 2008; Science 316:1349-1353, 2007.

Session 2

Name: Maria Yazdanbakhsh
Affiliation: Leiden University Medical Center, Leiden, The Netherlands

Title:
Immune regulation and chronic helminth infections

Abstract:
Helminth infections induce strong Th2 and Treg responses and chronic helminth infections have been shown to be negatively associated with inflammatory diseases. There are even number of clinical trials using helminth infections to cure inflammatory bowl disease, multiple sclerosis or allergies.
Studies in populations residing in areas where helminth infections are highly endemic have allowed us to show that IL4 producing and GATA-3+ CD4+ cells are highly abundant in increasing gradient from Europe, Urban Africa to rural Africa where chronic helminth infections are highly endemic. Using field applicable assays, we it has been possible to study functional Treg activity in areas where helminth infections are endemic, showing that presence of helminths is associated with strong regulatory activity of CD4+CD25++Foxp3+ cells.
To understand the immune modulatory role that these infections exert, effort has been put into identification of signature molecules derived from helminths that are capable of inducing Th2 or regulatory T cell responses. Using in vitro assays based on human dendritic cell and T cell interaction, we have identified novel molecules that can condition dendritic cells to instruct naïve T cells into developing into Th2 and Treg.
We will discuss one of these molecules, Omega-1, which is excreted from *Schistosoma mansoni* eggs and is capable of enhancing Th2 and the characteristics of Omega-1 that are needed for a so called “Th2 danger” signals.

Session 2

Name: Yoshinori Fukui
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Title: Immune regulatory functions of DOCK2 in health and disease

Abstract:
Tissue infiltration of activated T cells is a hallmark of allograft rejection and organ-specific autoimmune diseases. This process involves a complex cascade of molecular interactions and cellular responses, including chemokine-dependent T cell migration, the recognition by T cell receptors of undefined peptides bound to MHC molecules, the engagement of costimulation and adhesion molecules with their ligands, and the activation of multiple intracellular signal transduction pathways leading to the release of cytokines which are the key to T cell expansion and tissue destruction. However, since migration and activation of T cells are both critically dependent on remodeling of the actin cytoskeleton, inhibition of the cytoskeletal reorganization in leukocytes would be a novel approach to attenuate allograft rejection and autoimmune diseases.

DOCK2 is a mammalian homologue of *Caenorhabditis elegans* CED-5 and *Drosophila melanogaster* Myoblast City, and is predominantly expressed in hematopoietic cells. Although DOCK2 does not contain the Dbl homology domain and the pleckstrin homology domain that are typically found in guanine nucleotide exchange factors (GEFs), DOCK2 catalyzes the GTP–GDP exchange reaction for Rac via its DHR-2 domain. We had earlier reported that DOCK2 plays a critical role in migration and activation of T cells by regulating the actin cytoskeleton through Rac activation. In addition, we recently found that DOCK2 also regulates innate immune responses. In my talk, I will discuss immune regulatory functions of DOCK2 and refer to the possibility of using DOCK2 as a molecular target controlling allograft rejection and autoimmune diseases.

Session 3

Name: Kiyoshi Takeda
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Title:
Regulation of intestinal homeostasis by innate immunity

Abstract:
Innate immunity has been shown to control antigen-specific adaptive immune responses. In addition, abnormal activation of innate immunity, due to the breakdown of negative regulatory mechanisms, causes several inflammatory disorders, including inflammatory bowel diseases. Therefore, activity of innate immunity is finely regulated at the intestinal mucosal surfaces. Intestinal mucosa is a unique site, where many numbers of symbiotic microflora exist. In the intestinal mucosa, there are several unique subsets of innate immune cells, which orchestrate a peculiar immune response. For example, CD103-positive dendritic cells have been shown to instruct development of regulatory T cells in the mesenteric lymph nodes and the lamina propria. We identified CD70-positive (CX3CR1-positive) dendritic cells that show microbiota-dependent induction of Th17 cells in the lamina propria. In addition, we recently identified a novel subset of innate immune cells that prevent intestinal inflammation through suppression of T cell proliferation. The function of these regulatory myeloid cells is defective in the absence of IL-10/Stat3 signaling pathway. Thus, activity of several unique subsets of innate immune cells is responsible for maintenance of intestinal homeostasis.

Session 4

Name: Kazuo Sugamura
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Title:
Regulation of memory T cell development bu OX40 costimulatory signals

Abstract:
Homeostatic proliferation of T cells is critically involved in the generation and maintenance of memory T cells. Recent studies have focused much attention on the crucial roles of MHC-TCR interaction and γc cytokines, such as IL-7 and IL-15, in the homeostatic control of memory $CD4^+$ T cells. However, the role for costimulatory signals on the homeostatic proliferation of $CD4^+$ T cells remains controversial although costimulatory signals contribute to the optimal proliferation and survival of T cells.

Costimulatory signals through OX40, a TNF receptor family member are essential for the optimal activation of T cells, and involved in the pathogenesis of T cell-mediated inflammatory diseases, such as inflammatory bowel disease and interstitial pneumonia. However, the detailed relationship between OX40 signaling and homeostatic proliferation of T cells is still unclear.

To address this, we have set up several experimental settings, in which polyclonal effector memory ($CD44^{high}CD62L^{low}$) $CD4^+$ T cells were transferred into lymphopenic recipient mice. We found that homeostatic proliferation of donor effector memory CD4 T cells was divided into two types in terms of cell division times (slow (≤ 3) and fast (≥ 8)). In addition, treatment with blocking antit-OX40L mAb during homeostatic proliferation of effector memory $CD4^+$ T cells specifically suppressed the fast-proliferating cells. In contrast, inhibition of IL-7 signals by administration of blocking anti-IL-7Rα mAb during homeostatic proliferation demonstrated a preferential reduction of the slow-proliferating population. Furthermore, simultaneous blockade of both OX40 and IL-7 signals completely inhibited the homeostatic proliferation of effector memory $CD4^+$ T cells by suppressing both the fast and slow homeostatic proliferation. Collectively, OX40 signals contribute to the homeostasis of effector memory $CD4^+$ T cells in an IL-7-independent manner.

Session 4

Name: Ed Palmer
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Title:
affinity thresholds in T cell tolerance

Abstract:
T cell tolerance is established in the thymus (central tolerance) and maintained in the body (peripheral tolerance). In both compartments, developing thymocytes or peripheral T cells are able to measure and 'interpret' antigen affinity, allowing them to make an appropriate response. The lecture will try to explain some elements of the principle of affinity, the initiation of TCR signaling and the cellular mechanisms required for a differentiated T cell response.

Session 5

Name: Hajime Karasuyama
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Title:
Emerging roles of basophils in protective and pathological immune responses

Abstract:
Basophils are the least abundant granulocytes and represent less than 1% of peripheral blood leukocytes. Although they are evolutionarily conserved in many animal species, their functional significance remained uncertain, and they were erroneously considered as a lesser relative or precursor of mast cells. Basophil research was long hampered by their rarity and the lack of useful analytical tools, but recent studies have defined previously-unrecognized roles for basophils, which are distinct from those played by mast cells. We have recently developed powerful tools suitable for *in vivo* analysis of basophil function, a basophil-depleting CD200R3-specific mAb and engineered mice deficient only in basophils. Taking advantage of these novel tools, we demonstrated that basophils play critical roles in the initiation of acute and chronic allergic responses, namely IgG-mediated systemic anaphylaxis and IgE-mediated chronic cutaneous allergic inflammation, independently of mast cells. We next explored whether basophils have any host-beneficial function *in vivo*, and identified their essential role in acquired protective immunity against ticks. Ticks are blood-feeding ectoparasites and transmit a variety of microorganisms, many of which can cause serious infectious diseases such as Lyme disease. Basophils are recruited to the tick-feeding site in mice during the second (but not first) infestation, concomitant with the manifestation of acquired resistance to tick feeding. Depletion of basophils before the second tick infestation completely abolished the tick resistance. Collectively, basophils play nonredundant roles in both protective and pathological immune responses.

Session 5

Name: Toshio Hirano
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Title:
Interleukin 6 amplifier and autoimmune diseases: a four step model

Abstract: It is thought that the recognition of specific antigens by autoreactive CD4+ T cells contributes to the tissue specificity of autoimmune diseases. In many cases, however, causative, tissue-specific antigens have not been established, even for diseases associated with class II MHC alleles. Rheumatoid arthritis (RA) and arthritis in F759 knock-in mouse line (F759 arthritis) are such examples. Several evidences support a pathogenic role for $CD4^+$ T cells in both diseases: associations with class II MHC and CD4 molecules; increased numbers of memory/activated $CD4^+$ T cells; and improved outcomes in response to suppressions and/or deficiencies in class II MHC molecules, $CD4^+$ T cells, and the T cell survival cytokine IL-7. IL-7 further increases the homeostatic proliferation of $CD4^+$ T cells, which exasperates the development of arthritis in F759 mice. While we postulated that recognition of tissue antigen by $CD4^+$T cells is a cause of F759 arthritis, we found an accumulation of activated $CD4^+$ T cells in a manner independent of tissue antigen-recognitions in the joint is critical for F759 arthritis. We observed that local microbleeding-mediated CCL20 expression induced such an accumulation, causing arthritis via chronic activation of an IL-17A-dependent IL-6 signaling amplification loop in type 1 collagen+ cells that is triggered by $CD4^+$ T cell-derived cytokine(s) such as IL-17A. We named this loop the IL-6 amplifier. Thus, certain class II MHC–associated, tissue-specific autoimmune diseases could be induced by local events that cause an antigen-independent accumulation of effector $CD4^+$ T cells followed by the induction of the IL-6 amplifier in the affected tissue. We

have proposed a Four Step Model for MHC class II associated autoimmune disease: 1) T cell activation regardless of antigen specificity; 2) local events inducing a tissue-specific accumulation of activated T cells; 3) transient activation of the IL-6 amplifier; and 4) enhanced sensitivity to cytokines in the target tissue. The interaction of these events results in the chronic activation of IL-6 amplifier leading to the manifestation of autoimmune diseases and chronic inflammatory proliferative diseases.

References

T.Hirano. Interleukin 6 in autoimmune and inflammatory diseases: a personal memoir. Proc. Jpn. Acad., Ser. B. 86(7); 717-730. 2010

M.Murakami et al., Local microbleeding facilitates IL-6– and IL-17–dependent arthritis in the absence of tissue antigen recognition by activated T cells. J. Exp. Med. 208: 103-114, 2011

Session 5

Name: Antonio Lanzavecchia
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Title:
Dissecting the human immune response to pathogens

Abstract:
Memory T and B lymphocytes and long lived plasma cells represent a repository of the antigenic experience of an individual. By analyzing the specificity and function of these cells we can gain insights into the human immune response and identify correlates of protection. We have developed methods to dissect the functional heterogeneity and antigenic repertoire of human T, B and plasma cells. These methods are used: i) to identify subsets of effector and memory T cells with distinct role in immune surveillance and protection in different tissues against different classes of pathogens, and ii) to dissect the relative role of plasma cells and memory B cells in the humoral response to pathogens and to isolate broadly neutralizing antibodies. A better understanding of the class and specificity of the human immune response will be instrumental to guide the design of effective vaccines

Session 7

Name: Hiroshi Kiyono, D.D.S., Ph.D.
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Title:
Spick-and-Span for the Development of Mucosal Vaccine:
Transgenic-Rice (MucoRice)- and Nanogel Chaperon-based Vaccine
for the induction of Protective Immunity

Abstract:
The aero-digestive tract (ADT) is equipped with the mucosal immune system (MIS) which is capable of inducing a prompt and robust antigen-specific mucosal immune response at the entry of pathogens for the prevention of their invasion. Further, oral or nasal administration of vaccine via the ADT resulted in the induction of systemic immunity, leading to the double layers of protection at both mucosal and systemic compartments. The delivery of vaccine antigen to the MIS is thus logical and known to be effective and non-invasive for the induction of antigen-specific mucosal and systemic immune responses against emerging and re-emerging pathogens. To achieve our common goal for the creation of most attractive, effective and safe mucosal vaccine, our laboratory has been developing two novel mucosal vaccine systems, rice-based vaccine (MucoRice) and nanogel-based vaccine (Chaperon vaccine). MucoRice, a seed of transgenic rice plant expressing vaccine antigen, is a cold-chain- and needle-free vaccine which offers long-term stability of vaccine antigen for more than 3 years without any refrigeration storage and resistance to digestive enzyme. These unique characteristics qualify MucoRice system as a new generation of oral vaccine production, preservation, and delivery system. Oral vaccination of MucoRice expressing B subunit of cholera toxin(CT-B) thus resulted in the induction of antigen-specific protective immunity in both mucosal and systemic compartments without any major adverse events. Further, Nanogel-based vaccine (or Chaperon Vaccine) holds vaccine antigen in the nanoparticles formed by cationic cholesteryl group-bearing pullulan (CHP) and

functions as an artificial chaperon for the delivery of native form of vaccine antigen to the MIS for the induction of antigen-specific immune response. The adaptation of chaperonging nanogel technology led to the creation of an adjuvant- and needle-free nasal vaccine. Nanogel-based vaccine containing Hc portion of *Clostridium botulium* type-A neurotoxin (BoHc/A) is effective in the delivery of vaccine antigen to the upper respiratory MIS including nasophalynx-associated lymphoid tissue (NALT) and nasal epithelium leading to the induction of BoHc/A-pecific protective immunity in both mucosal and systemic compartments. These new generation of mucosal vaccines will lead to the innovative vaccination strategy against emerging and re-emerging infectious diseases.

Session 7

Name: Åke Lernmark
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Title:
Immunotherapy of type 1 diabetes.

Abstract:
Type 1 diabetes is strongly associated with autoimmunity against the pancreatic islet beta cells. The genetic etiology is strongly associated with HLA-DQ and GWAS indicated that more than 40 additional genetic factors, mostly related to lymphocyte function might contribute. The disease is increasing worldwide. Persistent islet autoimmunity may be triggered as early as about 12 months of age. The clinical onset may occur at any age. The warning signals are autoantibodies against insulin, GAD65, IA-2 or the ZnT8 transporter. The autoantibodies are heralding subclinical symptomless islet autoimmunity. The time to clinical onset is related to HLA risk and the number of islet autoantibodies. High risk HLA and all four autoantibodies tend to predict an early age at onset. At the time of clinical onset the patients are given insulin as a replacement therapy to sustain life. Primary prevention trials have or are attempted in high-risk HLA subjects with gluten free diet (failed), hydrolyzed casein (TRIGR study), oral omega-3 DHA (NIP study), Vitamin D as well as oral or nasal insulin (Pre-POINT study). Secondary prevention clinical trials have included nicotinamide (failed), cyclosporine (failed), BCG vaccine (failed), ketotifen (failed). Antigen-specific secondary clinical trials have included parenteral insulin (failed), oral insulin (a possible effect in subjects with high titer insulin autoantibodies, intranasal insulin (failed). Ongoing secondary prevention clinical trials include anti-CD3 (TrialNet), nasal or oral insulin, and alum-formulated GAD65 (DIAPPREV-IT). Non-antigen specific intervention clinical trials include anti-CD3 (several trials, transient protection of residual beta-cell function), ATG (Immune Tolerance Network), Rituximab (TrialNet; transient protection), Abatacept (TrialNet – CTLA4-Ig), HrINFalpha (no effect) and Anakinra (JDRF). Antigen-specific clinical trials include DiaPep77 (no effect in young adults), alum-GAD65 (DIAMYD – prolonged protection of residual beta-cell function), Altered peptide ligand (no effect) and proinsulin-based DNA vaccine (BHT-3021). Novel approaches to antigen-specific immunotherapy may be needed to successfully prevent the disease or preserve beta cells at the clinical onset.

Short Talks & Posters by Participants

Short Talk (Session 1)

Name: Olympe Chazara
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Title:
Immunogenetics of killer cell immunoglobulin-like receptors (KIR) and HLA-C in pregnancy

Abstract:

Olympe Chazara[1], Susan E. Hiby[1], Hugo H. Hilton[2], Paul J. Norman[2], Lydia E. Farrell[1], Peter Parham[2], Ashley Moffett[1]
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Natural Killer cells (NK) are the major leukocyte population in the decidua during the first trimester of pregnancy, and are thought to have a role in mediating trophoblast invasion. They express a number of receptors capable of recognizing MHC class I expressed by trophoblast, including two-domain Killer Immunoglobulin-like Receptors (KIR), which recognize HLA-C. Genetic analysis of pregnancies complicated by pre-eclampsia, fetal growth restriction or recurrent miscarriage have shown that those disorders of pregnancies are associated with an increase frequency of the maternal KIR AA genotype and this is mainly associated with HLA-C2 in the fetus. We are now combining new cohorts, especially pre-eclamptic pregnancies in order to perform more detailed analysis, at the allele level, of the KIR genes previously identified, including *KIR2DL1* and *KIR2DS1*, and of the *HLA-C* alleles implicated. Preliminary allele typing results in our Caucasian cohorts (936 individuals studied with healthy pregnancy controls and pregnancies complicated with pre-eclampsia or recurrent miscarriage) show that *KIR2DL1* is polymorphic, with 11 alleles observed whereas *KIR2DS1* is monomorphic, with only one allele, *KIR2DS1*002* reported. One of the *KIR2DL1* alleles found at a high frequency seems to be associated, when present in both copies, with recurrent miscarriage. Functional properties of the different *KIR2DL1* alleles are under investigation in uNK cells, in order to be able to determine how KIR allelic variations can affect subsets of uNK cells and to what extent the maternal HLA-C might influence her response to the fetal HLA-C.

Short Talk (Session 1)

Name: Maaike Joerink[1], Gisela Slaats[1], Merel Oortveld[1], Erika Rindsjö[1], Fredrik Stenius[2], Johan Alm[2], Annika Scheynius[1]

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Title:
The role of epigenetics in fetal programming of allergic diseases

Abstract:
Fetal programming of adult disease describes the hypothesis that intrauterine exposures can increase the risk for an individual to develop disease later in life. It has been suggested that fetal programming also contributes to the later development of allergic diseases and that this is mediated via epigenetic regulation. The placenta is an essential part of the intrauterine environment and its functioning crucial for the proper development of the fetus. Gene expression within the placenta is influenced by the maternal environment. Changes in gene expression can influence the development of the fetal immune system, and thus the risk for later allergy development. In a previous publication we analyzed the gene expression of 17 immune relevant genes in 36 placentas (Joerink *et. al.* 2010). The placentas were selected based on the allergen-sensitization status of both parents, their lifestyle and if they were living on a farm or not. We identified CD14, IL-12(p40), STAT4 and GATA3 to be differentially expressed in the placenta depending on maternal environment (living on a farm and parental allergen-sensitization). Currently we are analyzing the DNA methylation levels of the promoter regions of the above mentioned genes and in addition of TLR2 and TLR4 by means of high resolution melt analysis (HRM). Preliminary data suggest that in general the DNA methylation levels in placenta are low and that the promoter regions of CD14 and TLR4 might be differentially regulated. Whether this DNA methylation differences correlate to gene expression, the maternal environment (lifestyle, living on a farm and parental allergen-sensitization), or later development of allergy remains to be analyzed. Analyzing the intrauterine environment at the level of gene expression and DNA methylation might reveal new markers which could help identifying the individuals at risk to develop allergic diseases and help defining preventive strategies.

Short Talk (Session 2)

Name: Keisuke Nagao
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Title:
Regulation of dendritic cell trafficking by hair follicles

Abstract:
The Langerhans cells (LC) are enigmatic dendritic cells that reside in the epidermis. LCs are reported to self-renew in steady state and differentiate from Gr-1^{high} monocytes under inflammation, but how LCs are recruited and enter the epidermis is unknown. Herein, we report that LCs repopulate the epidermis via hair follicles (HF) in two distinct modes. One is the slow repopulation of langerin^{+} Epcam^{+} MHC II^{+} LCs that occur in clusters, and the other is the rapid infiltration of langerin^{-} EpCAM^{-} MHC II^{+} LC precursors. The latter is enhanced by inflammation and occurs rapidly within a few days. Interestingly, repopulation of both cell types occurs via HFs. LC precursors first appear to accumulate to HF bulge area, an important structure that houses keratinocyte and melanocyte stem cells, prior to entering epidermis. A unique mechanism that attracts LC precursors to epidermis was defined by utilizing bone marrow transplantation experiments, as well as by in vivo observations using multi-photon microscopy. Defining processes and mechanisms of leukocyte-epithelial interactions should provide implications to better understand and ultimately control percutaneous immunity

Short Talk (Session 2) and Poster Session I, No. 13

Name: Masahiro Kitano
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Title:
BCL6 Protein Expression Shapes Pre-Germinal Center B Cell Dynamics and Follicular Helper T Cell Heterogeneity

Abstract:
The transcription factor BCL6 is essential for the development of germinal center (GC) B cells and follicular helper T (Tfh) cells. However, little is known about in vivo dynamics of BCL6 protein expression during and after development of these cells. By using a novel BCL6 reporter mouse strain, we found that antigen-engaged B cells upregulated BCL6 before clustering in GCs. Two-photon microscopic analysis indicated that BCL6 upregulation in pre-GC B cells contributed to sustaining their interactions with helper T cells and was required for their entry to GC clusters. Our data also suggested that Tfh cells gradually downmodulated BCL6 protein over weeks after development. The BCL6-low Tfh cells were promoted to acquire proliferative quiescence and upregulated IL-7 receptor. These results clarify the role of BCL6 in pre-GC B cell dynamics, and highlight the modulation of BCL6 expression in Tfh cells that persist in the late phase of the antibody response.

Short Talk (Session2) and Poster Session II, No. 1

Name: Akihiko Muto
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Title:
The repression of plasma cell differentiation by Bach2 allows activated B cells to execute class switch recombination

Abstract:

Two transcription factors, Pax5 and Blimp-1, form a gene regulatory network (GRN) with a double negative loop, which defines either B cell (Pax5-high) or plasma cell (Blimp-1-high) status as a binary switch. However, a subcircuit that adds on class switch DNA recombination (CSR) in activated B cells is not clear. Here we reveal that Bach2, a transcription factor required for CSR, represses the expression of Blimp-1 in activated B cells to enable CSR. In the absence of Bach2, mouse splenic B cells more frequently expressed Blimp-1 upon polyclonal activation by lipopolysaccharide (LPS). Concurrently with Blimp-1 expression, $Bach2^{-/-}$ B cells differentiated to IgM antibody secreting cells (ASCs) more rapidly than control wild-type cells. Preclusion of plasma cell differentiation by genetic loss of Blimp-1 expression in $Bach2^{-/-}$ B cells was sufficient to restore CSR in vitro. These data, together with mathematical modelling of the GRN, indicate that Bach2 supports differentiation of isotype switched plasma cells by transiently repressing Blimp-1 expression upon B cell activation and thus limiting differentiation to IgM secreting plasma cell. We propose that the response of GRN dynamics to Bach2 is critical in diversifying B cell fates.

Short Talk (Session 2) and Poster Session II, No. 17

Name: Tomoyoshi Yamano
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Title:
Ex-vivo expanded DC induce donor- specific central and peripheral tolerance and prolong the acceptance of donor skin allografts

Abstract:
Dendritic cells (DC) are known to regulate immune responses by inducing both central and peripheral tolerance. DC play a vital role in negative selection of developing thymocytes by deleting T cells with high-affinity for self-peptide-MHC complexes. In the periphery, DC mediate peripheral tolerance by promoting regulatory T cell development, induction of T cell unresponsiveness, and deletion of activated T cells. We studied whether allogeneic DC obtained from bone marrow cultured either with Flt3L (FLDC) or GM-CSF (GMDC) could induce allo-specific central and peripheral tolerance after i.v. injection; B cells were used as a control. The results showed that only FLDC reached the thymus after injection, and these cells induced both central and peripheral tolerance to donor MHC. For central tolerance, injection of FLDC induced antigen-specific clonal deletion of both CD8 and CD4 single-positive thymocytes. For peripheral tolerance, injection of FLDC induced donor-specific T cell unresponsiveness and prolonged survival of donor-derived skin grafts. Tolerance induction by adoptive transfer of Flt3L-induced DC could be a useful approach for promoting graft acceptance after organ transplantation.

Short Talk (Session 3) and Poster Session II, No. 10

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Title:

Toll-like receptor 3 is up-regulated by p53 and is induced by anti-cancer drugs to potentiate poly I:C-induced tumor cell apoptosis.

Abstract:

Toll-like receptors (TLRs) are important sensors of microbial pathogens and mediators of innate immune responses. However, the basal regulation of TLRs is largely unexplored. We recently found that the tumor suppressor p53 positively regulates the transcription of TLR3, a receptor for viral dsRNA and poly I:C, by binding to the p53 site in TLR3 promoter. Activation of p53 by 5-fluorouracil (5-FU) increased the TLR3 mRNA in epithelial cells with wild type p53 but not in cells harboring mutant p53. Moreover, induction of cytokines regulated by TLR3, such as IL-8 and IFN-β, after poly I:C stimulation was impaired in HCT116 $p53^{-/-}$ cells. These results suggest that p53 influences TLR3 expression and function. TLR3 has also gained recognition as a novel molecular target for cancer therapy because TLR3 activation by poly I:C directly causes tumor cell death. Based on our findings that p53 increases TLR3 expression and on another study showing that interferon-α(IFN-α) also up-regulates TLR3, we hypothesized that p53-activating reagents and IFNs may potentiate poly I:C-induced tumor cell death. Screening of several anti-cancer drugs together with poly I:C revealed that 5-FU increased TLR3 mRNA and potentiated poly I:C-induced apoptosis in HCT116 $p53^{+/+}$ cells. On the other hand, IFN-α increased poly I:C-induced apoptosis and TLR3 mRNA in HCT116 $p53^{+/+}$ and $p53^{-/-}$ cells. Furthermore, the combination of poly I:C, 5-FU and IFN-α induced the highest apoptosis in $p53^{+/+}$ and $p53^{-/-}$ cells. Taken together, these data suggest that anti-cancer drugs up-regulate TLR3 expression and subsequently potentiate poly I:C-induced apoptosis.

Short Talk (Session 3) and Poster Session II, No. 19

Name: Ryusuke Yoshimi
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Title:
Autoantigen TRIM21 as a therapeutic target for systemic lupus erythematosus and Sjogren's syndrome

Abstract:
TRIM21/Ro52/SS-A1, a member of the tripartite motif (TRIM) family, has long been known as an autoantigen recognized by antibodies in sera of patients with systemic lupus erythematosus (SLE) and Sjogren's syndrome (SS), systemic autoimmune inflammatory diseases of unknown cause. TRIM21 is comprised of RING, B-box, coiled-coil and PRY/SPRY domains and has a ubiquitin E3 ligase activity by the RING domain. Despite increasing understanding of molecular aspects of TRIM21, its physiological role *in vivo* has remained unclear. To elucidate the *in vivo* function of TRIM21, we generated *Trim21*$^{-/-}$ mice with the *Trim21* gene replaced by an EGFP reporter. EGFP expression analyses showed that *Trim21* was widely expressed in many tissues, with the highest levels in immune cells. Studies of *Trim21*$^{-/-}$ embryonic fibroblasts demonstrated that TLR-mediated induction of proinflammatory cytokines, including IL-1beta, IL-6, TNFalpha and CXCL10, was consistently upregulated relative to wild-type cells. Reporter analyses demonstrated that TLR-mediated NF-kappaB activation was higher in *Trim21*$^{-/-}$ cells than in wild-type cells, accounting for their enhanced cytokine expression. In contrast, functional analyses of immune cells from *Trim21*$^{-/-}$ mice revealed no abnormalities in their composition or function, even though ubiquitylation of IRF3 and IRF8 was impaired. These results suggested possible redundancies in activities mediated by TRIM21. Consistent with this concept, we found that a number of TRIM family members were upregulated in *Trim21*$^{-/-}$ cells. Taken together, these findings demonstrated that TRIM21 plays an important role in the negative regulation of NF-kappaB-dependent proinflammatory cytokine responses, and suggest that multiple TRIM proteins contribute to the maintenance of functional equilibrium in inflammatory responses in part through functional redundancy. Here we present the analyses of the phenotype of *Trim21*$^{-/-}$ mice and discuss the possibility of TRIM21 as a target for therapy of SLE and SS.

Short Talk (Session 3)

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Title:
Acute-phase Trypanosomiasis: Role of parasite surface glycoprotein and DNA in immune response dysregulation

Abstract:
Trypanosomiasis due to *Trypanosoma brucei* and *Trypanosoma congolense* remains a threat to human and animal lives in tsetse-infested pockets of Sub-Saharan Africa. The fundamental hallmark of the disease is immune dysregulation owing to severe inflammation and overstimulation of antibody responses in the acute phase and immunosuppression in the subsequent chronic stage. Three mouse strains A/J, Balb/c and C57BL/6 varying in genetic susceptibility to Trypanosomiasis have been identified as appropriate animal models.

Gene expression dynamics in the host during the acute phase of *Trypanosoma congolense* infection were investigated by transcriptional profiling of tolerant (C57BL/6), moderately susceptible (Balb/c) and susceptible (A/J) mice over a 17-day timecourse. Pathway analysis of differentially-expressed genes revealed significant perturbation of the antigen processing and presentation, toll-like receptor and inflammatory pathways with an expression signature akin to the endotoxic shock response elicited by the bacterial endotoxin, lipopolysaccharide (LPS). This observation was suggestive of *T.congolense*-specific pathogen associated molecular patterns (PAMPs) that mimicked bacterial LPS in induction of an inflammatory immune response in the acute phase of infection.

Follow-up studies in an immunologically naïve mouse macrophage culture system using *E.coli* LPS as a positive control showed that *T.congolense* variant surface glycoprotein (VSG) and DNA activated macrophages to a classical phenotype characterized by increased secretion of pro-inflammatory cytokines

and chemokines, particularly by macrophages from the tolerant mouse model, C57BL/6.

This LPS-like inflammatory response may be beneficial to the host for effective parasite clearance but also sets stage for severe pathologies as anaemia and cachexia. The results also provide insights on management of the acute phase of Trypanosomiasis drawing from known therapeutic interventions against bacterial sepsis in order to influence favorable disease outcomes. Additionally, confirmation of *T.congolense* VSG as the causative factor presents new opportunities for the exploration of GPI-based therapy for the control of inflammation and infection-associated pathologies. Further characterization of the conserved GPI anchor of *T.congolense* VSG coupled with advances on carbohydrate-based vaccines presents a fresh perspective in the quest for a vaccine for African Trypanosomiasis.

Short Talk (Session 4)

Name: Georg Pongratz, Judith Anthofer, Madlen Melzer and Rainer H Straub
Affiliation: Department of Internal Medicine I, University Hospital Center, Regensburg

Title:
The sympathetic neurotransmitter norepinephrine inhibits proinflammatory IL-7R^{+} B cells in arthritis

Abstract:
Background: Recent data show higher concentrations of IL-7 in synovial fluid of patients with rheumatoid arthritis (RA) as compared to osteoarthritis (OA). Among other cells in the inflamed synovium, IL-7 Receptor (IL7R) is expressed on synovial B cells but the role of these cells in arthritis is unclear.

Results: Activation of naïve splenic murine B cells with CD40L and IL-4 in vitro increases IL7R expression on these cells. To determine the role of IL-7R+ B cells in arthritis we treated arthritic mice with B cells that have been activated and stimulated with IL-7. Mice treated with IL-7 stimulated B cells developed more severe arthritis than controls. We know from former experiments that norepinephrine treated B cells show anti-inflammatory potential in arthritis. Therefore, B cells were activated in the presence of norepinehphrine and then stimulated with IL-7. Treatment of mice with these B cells did not show different severity of arthritis as compared to controls.
As possible explanation for this observation we show that proper IL-7 signaling via STAT5 is inhibited in B cells pretreated with norepinephrine.

Conclusion: Taken together, these data indicate that IL7R+ B cells have a proinflammatory role in arthritis, which can be inhibited by the sympathetic neurotransmitter norepinephrine via inhibition of IL-7R signaling.

Short Talk (Session 4)

Name: Ahmad Jalili M.D, PhD
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Title:
Induction of targeted cell migration by cutaneous administration of a DNA vector encoding a biologically active chemokine CCL21

Abstract:
Skin inflammation can induce local expression of CCL21, which is subsequently drained to lymph nodes (LNs) influencing their cellular composition. To determine whether the same can be achieved by dermal administration of a plasmid DNA (pDNA) encoding CCL21, we generated a pDNA-based gene construct allowing high-level expression of CCL21. Expression and secretion of biologically active CCL21 were confirmed in vitro by immunohistochemistry, western blot analysis, ELISA, and transwell chemotactic assays. In vivo experiments showed cellular expression of transgenic CCL21 after particle-mediated gene gun delivery of pDNA into skin. CCL21 was expressed in the epidermis, consequently secreted into the upper dermis, and transported into the draining LNs, which resulted in increased CCL21 concentration, total cell number, and frequencies of CD11c(+) DCs and CD4(+)/CD62L(+) naïve, CD4(+)/CD62L(-), and CD8(+)/CD62L(-) effector memory T-cells (expressing CCL21 receptors CCR7 or CXCR3), as well as retention of adoptively transferred T-lymphocytes, in the draining LNs of plt/plt mice (lacking endogenous expression of CCL21). Our studies show that biologically active CCL21 can be overexpressed by genetic means in vitro and in vivo. This strategy allows reconstitution of a genetic defect and colocalization of different cell types in the secondary lymphoid organs, an important prerequisite for targeted cell migration.

Short Talk (Session 5)

Name: Anette Wolff
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Title:

Revealing mechanisms behind pathological autoimmunity by studying the monogenic disease APS I

Abstract:

Autoimmune polyendocrine syndrome type I (APS I) is a monogenic disease caused by mutations in the autoimmune regulator (AIRE) gene. Patients have a variety of manifestations in different organs, both endocrine and ectodermal tissues, and in addition mucocutaneous candidiasis. An important diagnostic tool for APS I is the finding of circulating autoantibodies against key enzymes in the affected organs. In addition, we have recently discovered that patients also have antibodies towards type I interferons and Th17-associated cytokines. The previously hypothesis that candidiasis in APS I patients is a result of immunodeficiency is now challenged, and we believe that also this feature has an autoimmune ethiology. Autoimmunity towards the immune system itself is also found in other patients, for instance thymoma patients. We here present the identification of IL17F and IL22 as targets for autoantibodies in APS I patients and the search for the mechanisms behind this phenomenon. We also draw parallels to other autoimmune diseases and aim to describe mechanisms behind chronic candidiasis in APS I patients.

Short Talk (Session 6) and Poster Session I, No. 12

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Title:
The role of Syk in activation of B cell subsets and its relevance to SLE

Abstract:
BACKGROUND B cells play a pivotal role in systemic lupus erythematosus (SLE) pathology. Spleen tyrosine kinase (Syk) functions as a key molecule in BCR-mediated signaling, although underlying mechanisms of Syk in autoimmune diseases such as SLE remains unclear.
OBJECTVES; To clarify the molecular mechanisms of Syk in B cell activation and to document its relevance to SLE and its treatment.
RESULTS; A combinatorial stimulation with BCR-crosslinking, soluble CD40L, and CpG efficiently induced DNA synthesis with cell cycle progression, co-stimulatory molecule expression, TNF-α, IL-6 and IgG production with expression of *AICDA*, *blimp-1* and *xbp-1*. The activation was observed predominantly in memory B cells especially in the presence of CpG, whereas the addition of Syk inhibitor completely abrogated a sequence of processes shown above. It is of note that BCR-crosslinking markedly induced expression of TLR9 and the following TRAF-6. Furthermore, BCR-crosslinking with soluble CD40L and CpG most strongly induced expression of TRAF-6 and phosphorylation of NF-kB in B cells. Intriguingly, a Syk inhibitor significantly inhibited not only expression of TLR9 and TRAF-6 but also NF-κB phosphorylation. Such inhibition by a Syk-inhibitor was also observed in Raji cells, which exhibited high basal activated signals. Furthermore, B cells from SLE patients showed strong Syk phosphorylation and TRAF6 expression in active SLE, whereas only a slight phosphorylation was observed in B cells in inactive patients and healthy donors. As predicted, preparation with a Syk inhibitor *in vitro* abrogated phosphorylation

of Syk and TRAF-6 expression.

CONCLUSIONS; Syk-mediated BCR-signaling is prerequisite for optimal induction of TLR9 and TRAF-6, thereby allowing efficient propagation of CD40 and TLR9-signaling in human B cells. Robust B cell activation by CpG indicates the importance of TLR9 and TRAF-6 expression induced by BCR/Syk signals especially in human memory B cells. Additionally, results from B cells of SLE patients underscore the potential role of Syk in B-cell-mediated pathological processes in SLE.

Short Talk (Session 6) and Poster Session I, No. 8

Name: Hiroshi Fujii
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Title:
hTERT insufficiency in rheumatoid arthritis causes PUMA-mediated T-cell apoptosis

Abstract:
Background : T cells of rheumatoid arthritis have several abnormalities, one of which is premature telomere shortening. In this study, we examined the mechanism of telomere shortening and the effect of low telomerase activity on cellular behavior.
Methods : After stimulation of CD4 T cells from RA patients and healthy control with anti-CD3/CD28 antibody, cell numbers, cell division, cell death and telomerase activity were measured. hTERT, the catalytic component of telomerase was knocked down by RNA interference or over-expressed by nucleofection of hTERT-IRES-GFP construct. Expression of p53 and the BH3-only proteins PUMA, BIM, NOXA was measured by qPCR and Western blotting.
Results : After stimulation, cell division of naïve CD4 T cells were similar in patients and controls. However, the cell recovery was lower and cell death rate was higher in RA T cells. TCR-induced telomerase activity was significantly decreased in RA naïve CD4 T cells. Knocking down of telomerase activity significantly inhibited cell recovery. Conversely, aberrant expression of hTERT rescued RA CD4 T cells from apoptotic death. Insufficient telomerase activity induced apoptotic cell death via p53 and PUMA in T cells of rheumatoid arthritis.
Conclusion : The enzyme telomerase directly regulates naïve CD4 T cell survival. In RA patients, such naïve CD4 T cells have a selective defect in induction of telomerase activity during the priming response, rendering them highly susceptible to apoptosis. Deficient repopulation of peripheral T cells imposes proliferative stress on the T-cell pool, including premature immunosenescence.

Short Talk (Session 6)

Name: Mayumi Ueta, M.D., Ph.D.
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Title:

Regulation of Ocular Surface Inflammation by Prostaglandin E Receptor Subtype EP3

Abstract:

In this study, we first investigated whether the prostaglandin (PG) E_2-EP3 pathway regulates the development of murine experimental allergic conjunctivitis (EAC), since it has been reported that the PGE_2-EP3 pathway negatively regulates allergic reactions in a murine allergic asthma model. Our findings showed that EP3 was constitutively expressed in mice ocular surface (cornea and conjunctiva) epithelium. EP3KO mice demonstrated significantly increased eosinophil infiltration in conjunctiva after RW-challenge compared to wild-type mice. Conversely, treatment of wild-type mice with an EP3-selective agonist resulted in significant decrease in eosinophil infiltration, which was blunted in EP3KO mice. These data suggest that PGE_2 acts on EP3 in conjunctival epithelium and down-regulates the progression of EAC.

Second, we examined the expression of EP3 in human conjunctival epithelium and compared it with conjunctiva from devastating ocular surface inflammatory diseases such as Stevens-Johnson Syndrome (SJS) or Ocular Cicatricial Pemphigoid (OCP) patients. Normal human conjunctival epithelium expressed EP3-specific mRNA and EP3 protein, however we could not find the positive signal in conjunctival epithelium from SJS or OCP patients, suggesting that EP3 is strongly down-regulated in the conjunctival epithelium of devastating ocular surface inflammatory diseases.

In summary, EP3 in conjunctival epithelium might down-regulate ocular surface inflammation. Thus, the findings of our study offer-up the possibility of epithelial cells as a target for anti-inflammatory treatment.

Short Talk (Session 7) and Poster Session II, No. 9

Name: Hidetoshi Takedatsu
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Title:
The new therapeutic approach for inflammatory bowel disease using an oligonucleotide delivery system, antisense Macrophage-migration inhibitory factor (MIF) / Schizophyllan (SPG) complex

Abstract:
Background and Aim: Schizophyllan (SPG), a polysaccharide that belongs to beta-(1-3) glucan family, adopts a triple helix formation. The triple helix formation of SPG is dissociated to three single chains of SPG (s-SPG) by dimethyl sulfoxide (DMSO) or alkali solution. These s-SPGs re-form triple helix formation in normal condition (renaturation). Interestingly, we found that a macromolecular complex was formed consisting of two s-SPG chains and one polynucleotide chain, during this renaturation process was carried out in a mixture containing s-SPG and a single-stranded polynucleotide (Figure 1). We applied to this complex to deliver functional oligonucleotides as antisense DNA to treat the inflammation of intestine. The pathogenesis role of Macrophage-migration inhibitory factor (MIF) mainly produced by macrophages has been shown in the inflammatory bowel disease, such as Crohn's disease and ulcerative colitis. Here, we examined the biological function and the therapeutic effect of antisense MIF/SPG complex against colitis.
Method: C57BL/6 mice were given 2 % dextran sodium sulfate (DSS) drinking water for 5 days. Severity of colitis and MIF expression was evaluated on day 14. The function of CD11b+ macrophages isolated from DSS-treated mice was analyzed. Immunofluorescence was performed to confirm whether CD11b+ macrophages uptake this complex. The inhibitory effect of antisense MIF/SPG complex was evaluated in vitro. In addition, antisense MIF/SPG complex was intraperitoneally administered in DSS treated mice, and the severity of colitis was evaluated.
Result: By 2% DSS administration, severe colitis was induced, and the expression of MIF was increased in the serum, colon, and MLN. MIF was mainly produced from CD11b+ macrophages in DSS-treated mice. Immunofluorescence showed that antisense MIF/SPG

complex but not antisense MIF alone was uptake into macrophage. Further, Dectin-1, which was known as a receptor of SPG, was significantly increased in CD11b+ macrophages of DSS-treated mice compared with control mice by FACS analysis. MIF production both in vitro and in vivo was significantly suppressed by antisense MIF/SPG complex. Administration of antisense MIF/SPG complex ameliorated intestinal inflammation.

Conclusion: Administration of antisense MIF/SPG complex effectively suppressed MIF production and significantly ameliorated the inflammation of colon. Our result demonstrated the possibility of new therapeutic approach against the inflammatory bowel disease.

Short Talk (Session 7) and Poster Session II, No. 4

Name: Yoko Oyama
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Title:
High-mobility group box-1 protein promotes granulomatous nephritis in a cycle involving monocyte chemoattractant protein - 1

Abstract:
Granulomatous nephritis can be triggered by diverse factors and results in kidney failure. However, despite accumulating data about granulomatous inflammation, pathogenetic mechanisms in nephritis remain unclear. In this study, we demonstrated elevated HMGB1 expression in renal granulomas in rats with crystal-induced granulomatous nephritis caused by feeding an adenine-rich diet. HMGB1 levels were also raised in urine and serum, as well as monocyte chemoattractant protein-1 (MCP-1), a mediator of granulomatous inflammation.

Injection of HMGB1 worsened renal function and upregulated MCP-1 in rats with crystal-induced granulomatous nephritis. HMGB1 also induced MCP-1 secretion in rat renal tubular epithelial cells *in vitro*. *Hmgb1*$^{+/-}$ mice with crystal-induced nephritis displayed reduced MCP-1 expression in the kidneys and in urine and the number of macrophages in the kidneys was significantly decreased. We conclude that HMGB1 is a new mediator involved in crystal-induced nephritis that amplifies granulomatous inflammation in a cycle where MCP-1 attracts activated macrophages, resulting in excessive and sustained HMGB1 release. HMGB1 could be a novel target for inhibiting chronic granulomatous diseases.

Short Talk (Session 7)

Name: Chantal Hargreaves
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Title:
Anti-TSHR autoantibodies in Graves' disease develop from non-autoreactive precursors

Abstract:
Introduction: Graves' disease (GD) is an antibody driven autoimmune disease, where antibody to thyroid stimulating hormone receptor (TSHR), stimulate the gland to produce excessive thyroid hormone resulting in hyperthyroidism. Knowledge of factors responsible for production of antibody to TSHR with thyroid stimulating activity is fundamental to gaining a deeper insight into the molecular basis of the condition.
We have recently described two monoclonal antibodies (mAbs), KSAb1 (IgG2b, k) and KSAb21 (IgG2a, k), derived from the same mouse with powerful thyroid stimulating antibody (TSAb) properties. V-region sequence analysis showed that both were derived from the same rearranged H- and L-genes. This gave us an opportunity to study the antigenic specificity of the rearranged genes that predispose to the generation of TSAbs.
Methods: To study the binding properties of the rearranged germline (RG) sequence of these antibodies, we synthesised the germline variable region light and heavy genes of KSAb1 and KSAb2. The synthetic RG construct was cloned in pAK19 vector for bacterial expression as recombinant Fab (rFab) preparations and purified to homogeneity by metal chelation. As controls, rFab preparation of KSAb1 and an irrelevant control, rFab 96/3 were expressed and purified in a similar manner.
Reactivity of rFab RG to TSHR was examined by a variety of experimental parameters, including: competitive inhibition of radiolabelled thyroid stimulating hormone (TSH) binding to immobilised TSHR, stimulation of the TSHR second messenger cAMP in CHO cells transfected with full-length TSHR and by flow cytometry.

Results: rFab RG did not inhibit radiolabelled TSH from binding TSHR, did not stimulate cAMP and did not display measurable binding in flow cytometry assays.

Conclusion: This data suggests anti-TSHR autoantibodies develop from non-reactive precursor B cells and this pathogenicity may develop through the process of somatic hypermutation in the periphery. Experiments are currently underway to further define when pathogenicity arises and whether it is an environmental agent that first drives the clonal expansion of such rogue B cells.

Poster Session I, No. 1

Name: Akihiko Murata
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Title:
Function of a Notch ligand, Delta-like 1 as an adhesion molecule

Abstract:

Mast cells (MCs) accumulate in sites of chronic inflammatory diseases. But it is unclear which adhesion molecules are involved in this process. The expression of Notch ligands are known to be up-regulated in inflammatory sites where MCs accumulate. Although Notch is known as signaling molecule that can activate integrins, the contribution of Notch receptor-ligand interactions to the adhesion of MCs has not been studied.

In this study, we showed that mouse bone marrow-derived cultured MCs adhered to OP9 stromal cells forced to express a Notch ligand, Delta-like 1 (Dll1) (OP9-DL1) more efficiently than to OP9-control. Surprisingly, Notch signaling in either MCs or stromal cells did not account for the efficient adhesion of MCs to OP9-DL1. Metabolically inactive MCs were still adhesive to OP9-DL1. The efficient adhesion was blocked only by inhibiting the Notch receptor(s)-Dll1 interactions with recombinant DLL1 or antagonistic antibodies against Dll1 or Notch2. These results indicate that Notch receptor(s) and Dll1 themselves promote the adhesion of MCs by functioning as adhesion molecules. This new appreciation provides an important clue to molecular basis of cell accumulation in inflammatory sites.

We are investigating the contribution of Notch ligands to the adhesion of other hematopoietic cell lineages, and found that Dll1 promoted the adhesion of broad cell lineages. Interestingly, another Notch ligand, JAGGED2 promoted the adhesion of MCs but not T lineage cells. It might suggest that there is a mechanism that directs the specific adhesion of T cells mediated by Dll1.

Poster Session I, No. 2

Name: Tomohisa Baba
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Title:
Thymic Sirpα+ conventional dendritic cells orchestrate central tolerance system against blood-borne antigens

Abstract:

Intrathymic negative selection and differentiation of regulatory T (Treg) cells are a cardinal event in central tolerance system. Thymic dendritic cells (DCs) are presumed to be capable of inducing the apoptosis of autoreactive T progenitor cells and of alternatively differentiating them into Treg cells. In spite of the presence of heterogenous DC subsets in thymus, similarly observed on other lymphoid organs such as lymph nodes and spleen, the role of each intrathymic DC subset in the central tolerance is still unclear. Recently, we demonstrated that mice deficient in a CC chemokine receptor, CCR2, exhibited a selective diminution in $CD11c^{+}CD11b^{+}CD8^{-}Sirp\alpha^{+}$ conventional DC (cDC) subset in the thymus with an accumulation of T cells with reactivity against serum self-antigen in the periphery. Here, we further revealed that $Sirp\alpha^{+}$ cDCs in the thymus can selectively capture blood-borne antigens due to their unique intrathymic localization nearby small vessels and inside perivascular regions, and then induce the antigen-specific Treg cells and subsequent clonal deletion to an intravenously injected antigen, depending on the intensity of antigen presentation.

Poster Session I, No. 4

Name: Femke Broere
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Title:
Heat shock protein (HSP)70-specific regulatory T cells suppress established chronic inflammation.

Abstract
Stress proteins or heat-shock proteins (HSP) are evolutionary conserved proteins which are present in every prokaryotic and eukaryotic cell. Their main function is to protect cells from lethal damage under stressful circumstances such as inflammation. Stress proteins are up-regulated during inflammation and can therefore be considered as 'biomarkers' of inflammation. Interestingly, elution studies have shown Hsp70 (-derived) peptides to be the major MHC class II ligands presented by cells under stress. Since stress enhanced presentation of Hsp70-derived peptides may lead to activation of anti-inflammatory T cells, we hypothesized that T cell epitopes of Hsp70-derived peptides can be targets for epitope-specific immunotherapy in inflammatory diseases. By epitope mapping, we identified the highly conserved B29 peptide as a dominant T cell epitope of *Mycobacterium tuberculosis* (Mt) Hsp70 in BALB/c mice. B29-specific T cells were found cross-reactive with the mouse homologue peptides, mB29a and mB29b. Peptide elution studies in humans and mice showed that the B29 homologue peptides are present in MHC-II. In addition, previously we have shown up-regulation of endogenous Hsp70 in antigen presenting cells enhanced T cell activation of a $CD4^+$ T cell hybridoma recognizing mB29b. Together these data emphasized that the mB29b peptide was processed and presented from the endogenous Hsp70 under physiological conditions. Nasal application of B29 and its mouse homologues suppressed the induction of proteoglycan induced arthritis (PGIA) in BALB/c mice, demonstrating the immunoregulatory potential of the peptides. Moreover, both nasal application and parenteral vaccination with B29 induced activation of a potent $CD4^+CD25^+$ regulatory T cell (Treg) population that reduced arthritis in recipient mice after transfer of only 3.10^5 T cells. $CD4^+CD25^+$ T cells from B29 treated mice could suppress effector T cell proliferation in an antigen specific manner. Depletion of the $CD25^+$ population prior to vaccination reduced the suppressive potential of the transferred population indicating

that natural occurring Tregs were involved in B29 induced protection in murine arthritis. Interestingly, transfer of HSP70-specific Tregs suppressed established PGIA. Control OVA-specific Tregs were not able to suppress inflammation in any transfer.
Since (m)B29 peptides have been frequently found in human MHC class II molecules and in our study were recognized by human $CD4^+$ T cells it is attractive to speculate that these peptides can be used to amplify the naturally existing Hsp-specific Treg response in patients with chronic inflammatory disease.

Poster Session I, No. 5

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Title:

Intraclonal diversification and stereotyped IGHV-D-J gene rearrangements in MZ B cells from human spleens.

Abstract:

The IGH V-D-J repertoire of marginal zone (MZ) from four spleens was analysed and compared to that of germinal center (GC) and follicular mantle (FM) B cells. We selectively investigated the MZ B cells with an IgM^{high}, IgD^{low}, CD38neg phenotype, naive B cells (FM) with IgD^{high}, IgM^{high}, CD38neg phenotype and IgDneg, CD38pos, IgMpos expressing GC B cells. More than 70% of IGH V-D-J molecular clones from MZ and GC exhibited somatic mutations, with similar frequency. Sequence analyses showed in GC and MZ B cell subset, the presence of sequences repeated more than once, that were classified as members of the same clonal family. Moreover, some of these expanded sequences showed a different number of mutations on the IGH V gene thus indicating the presence of an ongoing process of diversification. Finally, ''stereotyped'' sequences sharing the same IGH V-D-J genes and very similar or identical HCDR3 were found in MZ from different spleens. Besides providing information on the immunoglobulin gene repertoire and the potential of the MZ B cells to diversify in situ, these studies may be useful for tracing the cell of origin of certain B cell lymphoproliferative disorders.

Poster Session I, No. 6

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Title:

Antibodies with induced polyreactivity improve survival in experimental sepsis.

Abstract:

The in vitro exposure of IgG to protein-modifying agents (low and high pH buffers, high salt solutions, etc.) is known to induce a strong antigen-binding polyreactivity. The exposure of some monoclonal and polyclonal IgG to these pro-oxidative molecules resulted in an irreversible enlargement of the spectrum of recognized antigens. Naturally polyreactive antibodies are known to play a role of a first-line defense against invading pathogens. Induced antigen-binding polyreactivity may represent an additional innate-type defense mechanism. The modified immunoglobulins have a therapeutic potential as the passive immunotherapy with the Fe(II)-exposed, but not with the native pooled IgG (IVIg), improved significantly animal survival in three experimental sepsis models used - induced by the injection of bacterial lipopolysaccharide, by the colon puncture and ligation (CLP) technique or by the intraperitoneal administration of zymosan. The therapeutic effect of Fe(II)-exposed IVIg was still present when it was administered as late as 6 hours after the LPS injection and was not dependent on the levels of residual Fe(II) ions in the preparation. Our data strongly suggest that modified therapeutic IVIg preparations are promising agents for the passive immunotherapy of sepsis and related inflammatory syndromes.

Poster Session I, No. 9

Name: Stefan M. Gold
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Title:
Dynamic development of glucocorticoid resistance in experimental autoimmune encephalomyelitis and multiple sclerosis

Abstract:

Glucocorticoids (GC) are powerful endogenous and therapeutic modulators of inflammation and play a critical role in control of autoimmunity. GC resistance can be seen in patients with cell-mediated autoimmune disorders and poses major problems for the clinical management of these diseases but the underlying mechanisms are not well understood. In this study, we demonstrate that GC resistance of T cell responses develops dynamically in a mouse model of cell-mediated autoimmunity, experimental autoimmune encephalomyelitis (EAE). GC resistance was seen in both autoantigen-specific and nonspecific responses and preceded clinical symptoms and infiltration of T cells and monocytes into the central nervous system. GC resistance affected apoptotic and non-apoptotic pathways, and was linked to downregulation of glucocorticoid receptor alpha (GR α) expression. GC resistance in T cells was also seen in multiple sclerosis (MS) patients with radiological evidence of ongoing inflammation. GC resistance was absent in MS patients during pregnancy, when relapse risk is decreased, and present post partum, a time of increased relapse risk. These data demonstrate for the first time that GC resistance during autoimmune inflammation is dynamically regulated. This has implications for the timing of steroid treatments for exacerbations as well as the possibility to target GC resistance therapeutically. In addition, this study provides a putative pathway to explain the observed association between psychological stress and exacerbation of autoimmune diseases.

Poster Session I, No. 10

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Title:
Antigenicity and Immunogenicity of Hepatitis B Surface Antigen Displayed on pIII Protein of Filamentous Bacteriophage M13

Abstract:
Despite the presence of an effective vaccine for about thirty years, hepatitis B infection still remains a serious health problem worldwide, causing acute and chronic hepatitis, cirrhosis and hepatocellular carcinoma. HBV vaccine is prepared with aluminum hydroxide and effective in healhy subjects after three immunization but, has less effect in HBV carriers, immunocompromised adults, patients with organ transplant and chronic renal failure. Since its discovery, aluminum compounds are the most commonly used adjuvants in human immunization, but they mostly induce humoral immunity and is not effective in raising cellular immunity. Several adjuvants have been tested to induce a strong immune response to HBV vaccine in all subjects and one of the alternative is the use of phage particles as a carrier or adjuvant. Phage particules are antigenic themselves and capable of inducing both humoral and cellular immunity. Because of this unique properties especially for the last two decades, various antigens including HBV have been displayed on phages.
In the present study, full-length Hepatitis B virus surface antigen was cloned into phagemid vector (pCANTAB5E) and transformed into E.coli. Positive clones were then infected with M13 helper phage to obtain phages displaying HBsAg-pIII as fusion protein on their surface (recombinant phage). BALB/c and BALB/j mice were immunized with various amount of recombinant phages and antibody response was detected. After obtaining an unexpected anti-HBs response in mice immunized with wild type phage, recombinant phages was complexed with anti-phage monoclonal antibody to overcome the non-specific polyclonal antibody response. The effect of recombinant phages to overcome the tolerance and to induce specific anti-HBs antibody response in HBV transgenic mice is also under investigation.

Poster Session I, No.14

Name: Evgenia Korotkova
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Title:
Autoimmune processes in microbial pathology

Abstract:
In recent years there has been a growth of protracted and chronic processes in microbial diseases. The purpose of this study was to assess the impact of autoimmunity on the flow of microbial diseases. For this 85 people were surveyed, including 45 women with bacterial vaginosis, 10 patients with chronic atrophic gastritis, 10 – with prolonged unhealed gastric ulcer, 10 – with immunodeficiency and 10 – with undiagnosed pathology. Autoimmune antibodies – antinuclear antibodies (ANA), antimitochondrial antibodies (AMA), anti-smooth muscle antibodies (ASMA) and anti-gastric parietal cells antibodies (AGPA) were identified in all groups of patients. Autoantibodies were determined in serum by indirect immunofluorescence test in mouse kidney/stomach substrate using the Autoantibody test system IMMCO Diagnostics. This test system allows to identify the autoimmune reaction in the tissues of specific biotopes and not in biological fluids.
ANA were detected in 7% of patients: 5 of them with the immunodeficiency and 1 woman with bacterial vaginosis. AMA detected in 7% of patients: 1 of them with chronic atrophic gastritis, 3 – with immunodeficiency and 2 – with bacterial vaginosis. 23.5% of people (2 – with chronic atrophic gastritis, 3 – with prolonged unhealed gastric ulcer, 4 – with immunodeficiency and 11 – with bacterial vaginosis) had a titre of ASMA 1:20-1:40, which is a variant of the norm. AGPA were identified in 3 patients with chronic atrophic gastritis, 5 – with prolonged unhealed gastric ulcer, 3 – with immunodeficiency, 13 – with bacterial vaginosis and a healthy person (29,4% of total surveyed). The greatest number of sera with positive results on the AGPA appeared in women with bacterial vaginosis. This indicates that asymptomatic chronic atrophic gastritis, which could the cause dysbiotic processes in the body with the dominant manifestation

in the genital system. Autoantibodies were not detected in 49.4% of tested patients.

Thus, autoimmune antibodies are markers not only autoimmunity but also of microbial pathology. Autoimmunity develops during protracted and chronic course of microbial diseases. The correlation between the increased content of AGPA and combined lesion of vaginal mucosa, stomach and intestines.

Poster Session I, No. 15

Name: Kubelkova Klara
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Title:
Irradiated Mice and Passive Transfer of Immunity against *Francisella tularensis.*

Abstract:

We investigated the immune response induced by the *Francisella tularensis* (*F. tularensis*) strain 15L and *F. tularensis* live vaccine strain (LVS). Before infection, Balb/c or C3H/CBi mice were intraperitoneally (i.p.) injected with serum obtained from immunized mice with *F. tularensis* LVS (resp. 15L) or heat-killed *F. tularensis* LVS (resp. 15L). Both serum LVS (resp. 15L) and heat-killed LVS (resp. 15L) from immune mice transfer protection to naive recipient. Thus immunized mice were infected with sublethal or lethal doses of *F. tularensis* LVS (rep. 15L). Our findings clearly demonstrate that *F. tularensis* specific antibodies produced in immunized mice with both live and heat-killed *F. tularensis* LVS (resp. 15L) were completely protective in passive transfer experiments and likewise in subsequent highly-virulent strain infection. Here we also characterize and acknowledge immunogenic repertoire of *F. tularensis LVS* for the purpose of finding potential target molecules that can activate the host immune system using general immunoproteomic approach.

Seeing that the contributory role of specific antibodies in the host defence still remains unclear, we used irradiated mice to elucidate and characterize the humoral role of antibodies during immune response. Moreover using irradiated mice, we partly sought to disprove the crucial role of T cell-mediated protective immunity and the role of Th1/Th2 cytokines.

Poster Session I, No. 18

Name: Akiko Maekawa
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Title:
GPR17 Regulates Immune Pulmonary Inflammation Induced By House Dust Mite

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Abstract:
The cysteinyl leukotrienes elicit bronchoconstriction in asthmatic humans through the type 1 receptor, $CysLT_1R$. We previously found that GPR17, a 7-transmembrane receptor, negatively regulates the function of $CysLT_1R$ in the mouse ear microvasculature. We postulated that complex $CysLT_1R$-mediated inflammatory responses would be augmented in *Gpr17*$^{-/-}$ mice and reduced in *Cysltr1*$^{-/-}$ and *Gpr17*/*Cysltr1*$^{-/-}$ mice as compared to WT mice. Using a protocol of intranasal sensitization and challenge with house dust mite (*Df*), we show a markedly increased accumulation of inflammatory cells in the bronchoalveolar lavage fluid and lung sections, induced expression of $CysLT_1R$ by inflammatory cells, and significantly increased total IgE and *Df*-specific IgG1 in *Gpr17*$^{-/-}$ mice as compared to WT mice, and the absence of such changes in *Cysltr1*$^{-/-}$ or *Gpr17*/*Cysltr1*$^{-/-}$ mice. Sensitization by adoptive transfer of *Df*-pulsed BMDCs of each genotype into naïve WT recipients or of *Df*-pulsed WT BMDCs into naïve recipients of each genotype and *Df* challenge revealed markedly increased pulmonary inflammatory and serum IgE responses for the *Gpr17*$^{-/-}$ as compared to WT and significant loss of responses in the genotypes lacking $CysLT_1R$. The aggregate findings reveal a marked role for $CysLT_1R$ in both the afferent and efferent phases of allergic pulmonary inflammation and a critical negative regulation of that potential by GPR17.

Poster Session I, No. 19

Name: Kazufumi Matsushita
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Title:
Zc3h12a is an RNase essential for controlling immune responses by regulating mRNA decay

Abstract:
Toll-like receptors (TLRs) recognize microbial components, and evoke inflammation and immune responses. TLR stimulation activates complex gene expression networks that regulate the magnitude and duration of the immune reaction. Here we identify the TLR-inducible gene *Zc3h12a* as an immune response modifier that plays an essential role in preventing immune disorders. *Zc3h12a*-deficient (-/-) mice suffered from severe anemia, and most died within 12 weeks. *Zc3h12a*$^{-/-}$ mice also showed highly elevated serum immunoglobulin levels and autoantibody production together with a greatly increased number of plasma cells, as well as infiltration of plasma cells to the lung. Most *Zc3h12a*$^{-/-}$ splenic T cells showed effecter/memory characteristics and produced interferon-γ in response to T cell receptor stimulation. Macrophages from *Zc3h12a*$^{-/-}$ mice showed highly elevated production of IL-6 and IL-12p40, but not TNF, in response to TLR ligands. Although activation of TLR signaling pathways was normal, *Il6* mRNA decay was severely impaired in Zc3h12a$^{-/-}$ macrophages. Overexpression of Zc3h12a accelerated *Il6* mRNA degradation via its 3'-untranslated region (UTR) and destabilized RNAs with 3'-UTRs for genes including IL-6, IL-12p40 and the Calcitonin receptor. Zc3h12a harbors a putative N-terminal nuclease domain, and the expressed protein exhibited ribonuclease activity, consistent with a role in the decay of IL-6 mRNA. Together, these results indicate that Zc3h12a is an essential ribonuclease that prevents immune disorders by directly controlling the stability of a set of inflammatory genes.

Poster Session I, No. 20

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Title:
Characterization of human trophoblast as immunomodulators

Abstract:
The fetus is regarded as a semi-allograft since it expresses genes of paternal origin. Thus, the maternal immune system recognizes the fetus as “non-self” and should therefore, according to immunological principles, reject the fetus. It has been increasingly acknowledged that there are bi-directional interactions at the fetal-maternal interface, and that this cross talk indeed has important regulatory functions in normal pregnancy and delivery. From the fetus side, trophoblast cells are involved in the cross talk. Besides their role in spiral artery formation and acting as a barrier, they also show a tremendous capability in production of hormones, growth factors and also immunomodulatory proteins. Epstein-Barr virus-induced gene 3 (EBI3) and interleukin-12 alpha (IL-12α/p35), members of the IL-12 heterodimeric cytokine family, associate together to form the cytokine interleukin-35 (IL-35). In mice, IL-35 has been identified as an inhibitory cytokine produced by regulatory T cells (Treg) for maximal suppressive activity. While IL-35 in humans so far has not been convincingly associated with Treg cells, this cytokine seems to be produced by human trophoblast cells, as shown by previous studies demonstrating EBI3 and p35 expression by both syncytiotrophoblast and extravillous trophoblast cells. The aim of the current study is to validate the expression and explore the functional status of IL-35 in human trophoblasts. For this purpose, an immortalized first trimester (first 12 weeks of pregnancy) human extravillous trophoblast cell line, HTR-8/SVneo, is being used. Preliminary studies using quantitative real time polymerase chain reaction and a commercially available IL-35 ELISA kit have shown that the IL-12 family members p35 and EBI3 are expressed by the cell line and associate to secrete IL-35, a cytokine that may have a hitherto unrecognized role in the immune tolerance in pregnancy. Functional studies using siRNA and blocking antibodies are underway, aiming at elucidating how trophoblast-derived IL-35 affects human macrophage and lymphocyte function.

Poster Session I, No. 21

Name: Nikolina Mihaylova Mihaylova
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Title:
Target silencing of disease-associated B-lymphocytes by chimeric molecules in SCID model of pristane-induced autoimmunity

Abstract:
Systemic lupus erythemathosus (SLE) is a polygenic autoimmune disease characterized by B cell hyperactivity that leads to the generation of autoantibodies, formation of immune complexes, and clinical involvement of multiple organs. The current therapies of the disease are non-specific and more precise approaches targeting the disease-associated B lymphocytes, are urgently needed for clinical practice.
Experimental therapy in humans is limited by technical and ethical restrictions. In contrast, studies in humanized mouse models can circumvent some of these limitations. SCID mice, which lack both T and B lymphocytes and readily accept xenogenic cells, have been used widely for transfer of lymphocytes from SLE patients or from lupus-prone mice.
Autoreactive B cells have a prominent role in the pathogenesis of autoimmune diseases, not only as forerunners of autoantibody producing plasma cells, but also as antigen presenting cells. The co-ligation of FcγRIIb with BCR inhibits the BCR-induced cellular proliferation and other downstream biological responses. These functions make FcγRIIb an attractive target for downregulation of autoimmune B cell activity.
We constructed a chimeric antibody by coupling the dsDNA-mimicking peptides to a rat anti-mouse FcγRIIb monoclonal antibody to target disease-associated B lymphocytes only. Intravenous immunoglobulin (IVIg) preparations are known to modulate autoimmune diseases via several $F(ab')_2$- and Fc-dependent mechanisms. In the present study we test the effect of treatment with IVIg to pristane-induced autoreactive B cells and how this treatment affects the FcγRIIb expression. This study describes also a newly developed pristane-induced

transferred SCID model of autoimmunity. This model allows the combination of pristane-induced autoimmune B or T cells from Balb/c mice with normal B or T cells from the same strain and modulation of the generated autoimmune response by a protein-engineered antibody.

Using the chimeric molecules in B (pristane) + T (pristane) transferred SCID model resulted in low level of IgG anti-DNA antibodies and of proteinuria during the treatment. In contrast, an increase in the urine protein concentration, anti-DNA antibodies and deposition of IgG-containing immune complexes in the glomeruli were observed in the PBS-injected controls during the same period. No pathologic kidney histology was detected in DNA-like chimera injected animals.

The treatment of autoimmune-prone and healthy mice with therapeutic IVIg has been shown to up-regulate the expression of the FcgammaIIb inhibitory B cell receptors. In contrast of lupus-prone mice pristane-induced autoimmunity is a result of different regulatory mechanism which acts opposite and the administration of IVIg down-regulated FcgammaIIb B cell expression.

In the present study we report a possible way to limit the interaction between autoimmune B and T cells, resulting in suppression of the lupus syndrome in pristane-induced cell-transferred SCID mice. The elimination of autoantigen-specific B cells could leave autoreactive T cells without potency of prolonged pathogenetic effects and restricts the progress of lupus disease in pristan-induced SCID model of autoimmunity.

Poster Session II, No. 2

Name: MINH-HUE NGUYEN
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Title:
Phosphorylation and Activation of Cell Division Cycle Associated 5 by Mitogen-Activated Protein Kinase Play a Crucial Role in Human Lung Carcinogenesis

Abstract:
We analyzed the gene expression profiles of clinical lung carcinomas using a cDNA microarray containing 27,648 genes or expressed sequence tags, and identified *CDCA5* (cell division cycle associated 5) to be upregulated in the majority of lung cancers. Tumor tissue microarray analysis of 262 non–small cell lung cancer patients revealed that CDCA5 positivity was an independent prognostic factor for lung cancer patients. Suppression of CDCA5 expression with siRNAs inhibited the growth of lung cancer cells; concordantly, induction of exogenous expression of CDCA5 conferred growth-promoting activity in mammalian cells. We also found that extracellular signal-regulated kinase (ERK) kinase phosphorylated CDCA5 at Ser79 and Ser209 *in vivo*. Exogenous expression of phospho-mimicking CDCA5 protein whose Ser209 residue was replaced with glutamine acid further enhanced the growth of cancer cells. In addition, functional inhibition of the interaction between CDCA5 and ERK kinase by a cell-permeable peptide corresponding to a 20-amino-acid sequence part of CDCA5, which included the Ser209 phosphorylation site by ERK, significantly reduced phosphorylation of CDCA5 and resulted in growth suppression of lung cancer cells. Our data suggest that transactivation of CDCA5 and its phosphorylation at Ser209 by ERK play an important role in lung cancer proliferation, and that the selective suppression of the ERK-CDCA5 pathway could be a promising strategy for cancer therapy.

Poster Session II, No. 3

Name: Yumiko Nishikawa
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Title:
Aire-dependent organization of thymic microenvironment for the establishment of self-tolerance

Abstract:
The roles of Aire in organization of the thymic microenvironment for establishing self-tolerance remain enigmatic. We previously suggested that Aire controls the differentiation program of medullary thymic epithelial cells (mTECs), thereby organizing the global mTEC integrity that enables tissue-restricted self-Ag (TRA) gene expression from terminally differentiated mTECs (JEM 2008). Based on this finding, we assumed that the effect of Aire-dependent mTEC differentiation should have broader impact so that the developmental process of thymocytes might be also affected in Aire-deficient mice. Here, we show that, besides the control of TRA gene expression, Aire in thymic stroma regulates T-cell maturation process, thereby determining the fate of autoreactive T-cells upon engagement with the corresponding auto-Ags. We have also studied Aire-dependent clonal deletion process with a mouse model in which neo-self Ag expression was targeted to Aire-expressing mTECs.

Poster Session II, No. 6

Name: Yuichi Sekine, Tadashi Matsuda
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Title:
STAP-2 modulates activation-induced cell death by influencing caspase-8 activation

Abstract:
In the present study, we found that an adaptor protein, STAP-2, is a new member of the Fas-death-inducing signaling complex (Fas-DISC) and participates in activation-induced cell death (AICD) in T-cells. Expression of STAP-2 enhanced Fas-mediated apoptosis and caspase-8 aggregation/activation in Jurkat T-cells. Regarding the molecular mechanisms, STAP-2 directly interacted with caspase-8 and enhanced the interactions between caspase-8 and FADD in the Fas-DISC. In addition, STAP-2 protein has a consensus caspase-8 cleavage sequence, VEAD, in its C-terminal domain, and the processing of STAP-2 by caspase-8 was crucial for Fas-induced apoptosis. Physiological roles of STAP-2 were confirmed by observations that STAP-2-deficient mice displayed ACID impairment as well as superantigen-induced T-cell depletion. Therefore, STAP-2 is a novel participant in the regulation of T-cell apoptosis through the control of Fas-mediated caspase-8 activation.

Poster Session II, No. 7

Name: Souichi Shiratori1,2, Sumio Hayakawa1, Hiroaki Yamato1,3, Takeshi Kameyama1, Chihiro Kitatsuji1, Masahiro Imamura2 & Akinori Takaoka1

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Title:

Identification of ZAPS as a new regulator of RIG-I-mediated antiviral response

Abstract:

The poly(ADP-ribose) polymerase (PARP) superfamily currently constitutes various key regulators that are involved in not only cell survival and cell death in response to noxious stimuli, but also other diverse biological processes and pathogeneses of diseases in a manner dependent on or independent of their PARP activity. However, no interaction of the PARPs with host innate immune responses has been defined. Here we report that the PARP-13 shorter isoform (ZAPS; zinc-finger CCCH-type antiviral protein 1, short form), rather than the full-length protein (ZAP), was selectively induced by 5′-triphosphate–modified RNA (3pRNA) and functioned as a potent stimulator of interferon responses in human cells mediated by the RNA helicase retinoic acid-inducible gene I (RIG-I). ZAPS associated with RIG-I to promote the oligomerization, which led to robust activation of IRF3 and NF-κB transcription factors. Knockdown of ZAPS by RNA interference approach resulted in impaired induction of interferon (IFN)-α, IFN-β and other cytokines and inhibited viral replication after infection with RNA viruses that involve RIG-I, including influenza virus and Newcastle disease virus. These results indicate that ZAPS is a key regulator of RIG-I signaling during the innate antiviral immune response, which suggests its possible use as a therapeutic target for viral control.

Poster Session II, No. 8

Name: Ibrahim Sogut, Ibrahim Hatipoglu, Aylin Ozdemir Bahadir, B. Koray Balcioglu, K. Serkan Uzyol, Berrin Erdag, Aynur Basalp
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Title:
Development of Monoclonal Antibodies to Hepatitis B Core Antigen Displayed on Filamentous Bacteriophage

Abstract:

Adjuvants are the molecules activating and directing innate and adaptive immune response to antigens in vaccine formulation. One of the main function of adjuvants is to stimulate antibody production against to antigens. Although aluminum compounds and mineral oil adjuvants are the most commonly used adjuvants in human and animal immunization respectively, there has been intensive research on the development, isolation and synthesis of new alternative adjuvant. It has been shown that phages are immunogenic molecules capable of inducing both humoral and cellular immune response. Hepatitis B infection is still a serious global health problem causing acute and chronic hepatitis, liver cirrhosis and hepatocellular carcinoma. The immunological markers of hepatitis B infection are the surface antigen (HBsAg), the core antigen (HBcAg) and the e antigen (HBeAg). The Hepatitis B virus core gene codes for two different proteins; HBc and HBe antigen and HBcAg takes role in viral packaging and nucleocapsid formation and is also important in determining the presence of replicating Hepatitis B virus.

In the present study, the full-length Hepatit B core antigen (HBcAg) was expressed as HBcAg-pIII fusion protein on M13 phage and the efficiacy of recombinant phage on the generation of monoclonal antibodies was studied in BALB/c mice. Mice were immunized three times with the recombinant phage expressing HBcAg and after boosting, the mouse with high antibody titer was selected for fusion. Fusion was performed by some modification of classical fusion protocols. After successful fusion, four monoclonal antibodies to HBc antigen were developed. The specificity and immunglobulin type of antibodies were determined. The results have sown that M13 phage can be effectively used as alternative adjuvants for the development of monoclonal antibodies to hepatitis B core antigen.

Poster Session II, No. 13

Name: Hiroto Tsuboi
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Title:
Analysis of epitopes and function of anti-M3 muscarinic acetylcholine receptor antibodies in patients with Sjögren's syndrome

Abstract:
<Background>
M3 muscarinic acetylcholine receptor (M3R) plays a crucial role in the secretion of saliva from salivary glands. It is reported that some patients with Sjögren's syndrome (SS) carried inhibitory auto-antibodies against M3R.
<Objective>
To clarify the epitopes and function of anti-M3R antibodies in SS.
<Methods>
1) We synthesized peptides encoding the extracellular domains of human-M3R including the N-terminal region, first, second, and third extracellular loops. Antibodies against these regions were examined by ELISA in sera from 42 SS and 42 healthy controls.
2) Human salivary gland (HSG) cells were pre-incubated with IgG separated from sera of anti-M3R antibodies-positive SS, -negative SS, and controls for 12 hr. After loading with Fluo-3, HSG cells were stimulated with cevimeline hydrochloride, and intracellular Ca^{2+} concentrations ($[Ca^{2+}]i$) were measured.
<Results>
1) Antibodies to the N-terminal, first, second and third loop were detected in 42.9% (18/42), 47.6% (20/42), 54.8% (23/42), and 45.2% (19/42) of SS, while in 4.8% (2/42), 7.1% (3/42), 2.4% (1/42), and 2.4% (1/42) of controls, respectively.
2) Antibodies to the second loop positive SS-IgG inhibited the increase of $[Ca^{2+}]i$ induced by cevimeline hydrochloride. Antibodies to the N-terminal positive SS-IgG and antibodies to the first loop positive SS-IgG enhanced it, whereas antibodies to the third loop positive SS-IgG showed no effect on $[Ca^{2+}]i$ as well as anti-M3R antibodies negative SS-IgG.
<Conclusion>
Our results indicated the presence of several B cell epitopes on M3R in SS. The influence of anti-M3R antibodies on salivary secretion might differ based on these epitopes.

Poster Session II, No. 14

Name: Mayumi Ueta,[1,2] Toshiyuki Matsuoka,[3] Norihiko Yokoi[1], Chie Sotozono[1], Shuh Narumiya,[3] Shigeru Kinoshita.[1]

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Title:

Regulation of Ocular Surface Inflammation by Prostaglandin E Receptor Subtype EP3

Abstract:

In this study, we first investigated whether the prostaglandin (PG) E_2-EP3 pathway regulates the development of murine experimental allergic conjunctivitis (EAC), since it has been reported that the PGE_2-EP3 pathway negatively regulates allergic reactions in a murine allergic asthma model. Our findings showed that EP3 was constitutively expressed in mice conjunctival epithelium. EP3KO mice demonstrated significantly increased eosinophil infiltration in conjunctiva after RW-challenge compared to wild-type mice. Consistently, significantly higher expression of eotaxin-1 mRNA was observed in EP3KO mice. Conversely, treatment of wild-type mice with an EP3-selective agonist resulted in significant decrease in eosinophil infiltration, which was blunted in EP3KO mice. Expression of cyclooxygenase (COX-2) and prostaglandin E synthases (PGESs) was up-regulated and PGE_2 content was increased in the eyelids after RW challenge. These data suggest that PGE_2 acts on EP3 in conjunctival epithelium and down-regulates the progression of EAC.

Second, we examined the expression of EP3 in human conjunctival epithelium and investigated the function of human conjunctival epithelial cells. Normal human conjunctival epithelium expressed EP3-specific mRNA and EP3 protein. In primary human conjunctival epithelial cells stimulated with polyI:C, pre-treatment by the EP3 agonist significantly suppressed the production of CXCL10, CXCL11, RANTES, IL-6. Furthermore, we compared the EP3 expression with conjunctiva from devastating ocular surface inflammatory diseases such as Stevens-Johnson Syndrome (SJS) or Ocular Cicatricial

Pemphigoid (OCP) patients and we could not find the positive signal in conjunctival epithelium from SJS or OCP patients, suggesting that EP3 is strongly down-regulated in the conjunctival epithelium of devastating ocular surface inflammatory diseases.

In summary, EP3 in conjunctival epithelium might down-regulate ocular surface inflammation. Thus, the findings of our study offer-up the possibility of epithelial cells as a target for anti-inflammatory treatment.

Poster Session II, No. 16

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Title:
Suppression of host immunity by a *Toxoplasma* virulence factor ROP18

Abstract:

The ROP18 kinase has been identified as a key virulence determinant conferring a high-mortality phenotype characteristic of type I *Toxoplasma gondii* strains. This major effector molecule is secreted by the rhoptries into the host cells during invasion; however, the molecular mechanisms by which this kinase exerts its pathogenic action remain poorly understood. Here we show that ROP18 targets a host factor named ROP18 binding protein 1 (ROP18BP1). Disruption of the *ROP18* gene severely impairs acute toxoplasmosis by the type I RH strain. Because another virulence factor ROP16 kinase modulates immune responses through its N-terminal portion, we focus on the role of the N-terminus of ROP18 in the subversion of host cellular functions. The N-terminal extension of ROP18 contributes to ROP18BP1-dependent pathogenicity by interacting with ROP18BP1 and destabilising it. The kinase activity of ROP18 is essential for proteasome-dependent degradation of ROP18BP1 and for parasite virulence. Consistent with a key role for ROP18BP1 in resistance against this intracellular pathogen, ROP18BP1-deficient mice exhibit a high susceptibility to infection by ROP18-deficient parasites. The results reveal that interference with ROP18BP1-dependent immune responses is a novel pathogenic mechanism induced by ROP18.

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Title:
Influence of *HLA* class I and *HLA-KIR* compound genotypes on HIV-2 infection

Abstract:
Overall, the time to AIDS after HIV-2 infection is longer than with HIV-1 and many individuals infected with HIV-2 virus remain healthy throughout their lives. Multiple *HLA* and *KIR* gene products have been implicated in the control of HIV-1 but the effect of variation at these loci on HIV-2 disease is unknown. Here we show for the first time that *HLA-B*1503* associates significantly with poor prognosis after HIV-2 infection and *HLA-B*0801* associates with susceptibility to infection. Interestingly, previous data indicate that *HLA-B*1503* associates with low viral loads in HIV-1 clade B-infection, but has no significant effect on viral load in clade C infection. In general, alleles strongly associated with HIV-1 disease showed no effect in HIV-2 disease. These data emphasize the unique nature of the effects of *HLA* and *HLA/KIR* combinations on HIV-2 immune responses relative to HIV-1, which could be related to their distinct clinical course.