29.+ 30. August 2019
Berlin Brandenburgische Akademie der Wissenschaften
Markgrafenstraße 38, 10117 Berlin

Leibniz Association

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Leopoldina-Symposium

Environmental Education of the Immune System in Health and Disease

Abstract Book

A Symposium of the Leibniz-Network Immune Mediated Diseases and the Leibniz ScienceCampus Chronic Inflammation

Supported by:

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financial support: 1.000 €

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Thursday, August 29

	Welcome and Opening Remarks: Andreas Radbruch	
Session I	**The Immune System in Context of its Body** ***Chairs: Anja Hauser, Thomas Kamradt***	
9:00-9:25	Irmgard Förster	Environmental control of immune homeostasis and cellular metabolism by the AhR/AhRR pathway
9:25-9:50	Claudia Waskow	Cross communication of hematopoietic cells of adult and embryonic origin
9:50-10:15	Sander Bekeschus	ROS as immunomodulatory agents
10:15-10:40	Andreas Diefenbach	The role of the innate immune system in the adaptation of barrier organs to the environment
10:40-11:15	Coffee Break	
Session II Part I	**Immune Imprinting by Nutrition and Lifestyle** ***Chairs: Reinhold Schmidt, Jean Krutmann***	
11:15-11:40	Tilman Grune	Immune System and Nutrition
11:40-12:05	Julia Polansky- Biskup	Epigenetics in T cell differentiation: From genome-wide signatures to local regulators and their targeted manipulation
12:05-12:30	Charlotte Esser	Skin barrier and nutrition – role of the aryl hydrocarbon receptor
12:30-12:55	Dietmar Krautwurst	Nutrition-related immune cell priming
12:55-14:30	Lunch Break	
Session II Part II	**Immune Imprinting by Nutrition and Lifestyle** ***Chairs: Antigoni Triantafyllopoulou, Klaus Rajewsky***	
14:30-14:55	Carsten Watzl	The effect of acute and sustained beta2-adrenergic receptor stimulation on the function of natural killer cells
14:55-15:20	Susanne Krauss-Etschmann	Early life environment in shaping risk for respiratory disease and potential dietary intervention
15:20-15:45	Christoph Scheiermann	Circadian rhythms in the immune response
15:45-16:15	Coffee Break	
Session III	**Education of the Immune System by Microbiota** ***Chairs: Chiara Romagnani, Heribert Hofer***	
16:15-16:40	Ivaylo I. Ivanov	Microbiota-epithelium interactions educate host adaptive immunity
16:40-17:05	Hyun-Dong Chang	Microbiota controlling TGF-β and IgA expression in the intestinal mucosa

17:05-17:30	Andrew Macpherson/ Stephanie Ganal-Vonarburg	Distinct mucosal or systemic responses to non-pathogenic intestinal microbes build the B cell repertoire and its functional responsiveness
17:30-17:55	Alexander Scheffold	Shaping of the human T cell repertoire by the microbial environment: mind the "-myces"!
18:00-18:45	**Science Slam** ***Moderators: Dimitrios L. Wagner, Lennard Ostendorf***	
18:45-21:00	**Postersession and Get Together** ***Chairs: Chiara Romagnani, Andrey Kruglov***	

Friday, August 30

	Keynote Lecture ***Chair: Andreas Radbruch***	
8:30-9:30	Lorenzo Moretta	NK cells in the therapy of acute, high-risk leukemia: KIR/HLA-I mismatch and more
Session IV	**Pathogens and Chronicity** ***Chairs: Stefan Ehlers, Bimba Hoyer***	
9:30-9:55	Marcus Altfeld	Sex differences in inflammation during chronic HIV-1 infection
9:55-10:20	Christoph Hölscher	Inflammation in tuberculosis: friend or foe of whom?
10:20-10:45	Dietmar Zehn	In**TOX**ication causes T-cell exhaustion in chronic infection
10:45-11:30	Coffee Break	
Session V	**Therapies - One Health** ***Chairs: Kristina Lorenz, Angela Zink***	
11:30-11:55	Falk Hiepe	Memory plasma cells as therapeutic target in antibody-mediated diseases
11:55-12:20	Gülsah Gabriel	Current challenges for science and healthcare posed by emerging influenza viruses
12:20-12:45	Nils Blüthgen	Modelling signalling in the intestine and colon cancer, cell by cell
12:45-13:00	**Lessons learned and poster award** ***Andreas Radbruch***	
	Farewell Soup	
13:30-15:30	**General Assembly** ***ScienceCampus Chronic Inflammation + Leibniz-Network Immune Mediated Diseases***	

Abstracts Invited Speakers

Environmental control of immune homeostasis and cellular metabolism by the AhR/AhRR pathway

Imgard Förster

Immunology and Environment, Life & Medical Sciences (LIMES) Institute, University of Bonn

The increasing prevalence of metabolic syndrome is a characteristic of industrialized countries. Besides the consumption of a high caloric diet, an additional risk factor may lie in the enhanced uptake of anthropogenic chemicals. The aryl hydrocarbon receptor (AhR) pathway regulates important functions in cellular detoxification, immune cell differentiation and intestinal homeostasis. AhR activation by environmental pollutants causes liver pathology and affects lipid metabolism. On the other hand, consumption of natural, plant-derived AhR ligands contained in food was shown to strengthen the intestinal barrier. The AhR repressor (AhRR) is mainly expressed in immune cells of barrier organs and controls AhR signaling in a cell type-specific manner.

AhR-deficient mice were previously described to resist high fat diet (HFD)-induced obesity and liver steatosis. We now investigated the role of the AhRR in comparison to AhR in the context of global and myeloid cell-specific energy metabolism. Unexpectedly, AhRR knockout mice also exhibited resistance to HFD-induced obesity similar to AhRKO mice, accompanied by a strongly enhanced energy expenditure, increased oxygen consumption and enhanced lipolysis in brown adipose tissue. This phenotype was partly recapitulated in conditional myeloid cell-specific AhRR-knockout mice, indicating that deregulation of AhR signaling in immune cells causes alterations in systemic metabolism. Further, we could demonstrate that long-term fetal-liver-derived macrophage (FLiM) cell lines and primary macrophages with AhRR-deficiency have an increased capacity for mitochondrial oxidative phosphorylation as well as glycolysis compared to wild-type cells as determined by extracellular flux analysis. Transcriptome and lipidome analyses revealed that expression of metabolism-associated genes and the presence of specific lipid classes were significantly altered in AhRR-/- compared to WT macrophages, suggesting that these cells may have defects in lipid and glucose metabolism.

Taken together, we show that AhRR, similarly to AhR, contributes to diet-induced obesity and associated pathology presumably through dysregulation of cellular metabolism in myeloid cells. We hypothesize that AhRR and AhR may both promote the development of metabolic syndrome by differential action in hematopoietic versus non-hematopoietic cell-types.

Cross communication of hematopoietic cells of adult and embryonic origin

Claudia Waskow

Regeneration in Hematopoiesis, Leibniz-Institute on Aging, Fritz-Lipmann-Institute (FLI), Jena

Embryo-derived macrophages persist in many tissues throughout life but their turn-over kinetic, precise function and importance for adult hematopoiesis and tissue integrity

over time is underexplored.

It remained unclear how the differentiation of dendritic cells (DCs) is regulated *in vivo*. We show that Csf1r-mediated signals control the spleen DC pool size in Flk2-deficient animals by a cell-extrinsic and non-hematopoietic mechanism engaging embryo-derived tissue-resident red pulp macrophages (RP-Mp), providing a novel regulatory option to control the differentiation of mature blood cells from adult hematopoietic stem cells. The RP-Mp – DC interaction axis remains physiologically of great importance during the regeneration of DCs after activation-induced depletion in adult mice *in vivo*. Further, we show that osteoclasts, which are bone-resorbing cells important for bone integrity, tooth eruption and bone cavity formation are of embryonic origin and their maintenance depends on iterative fusion of circulating monocytes with long-lived osteoclast syncytia. Consequently, monocyte transfusion results in gene transfer that can be exploited to rescue adult-onset osteoclast pathologies such as osteopetrosis mediated by cathepsin K-deficiency.

Thus, evidence is presented that a cross-talk between hematopoietic cell types of distinct origins is required for steady-state hematopoiesis throughout life, implying existence of a novel layer of complexity for the understanding and potentially manipulation of hematopoietic differentiation processes *in vivo*.

ROS as immunomodulatory agents

Sander Bekeschus

ZIK plasmatis, Leibniz Institute for Plasma Science and Technology (INP), Greifswald, Germany

Reactive oxygen species (ROS) are generated endogenously and exogenously in health and disease. Especially inflammation is characterized by their ubiquitous presence. Upon stimulus, myeloid cells are potent producers of several kinds of ROS, for instance, superoxide anion generated via the nicotinamide adenine dinucleotide phosphate oxidase systems (NOXs) including dual oxidases (DUOXs), hydrogen peroxide dismutating from superoxide anion either spontaneously or via superoxide dismutases (SODs), nitric oxide being generated via nitric oxide synthases (NOSs), peroxynitrite being formed in the reaction between nitric oxide and superoxide anion, and myeloperoxidase (MPO) forming hypochlorous and hypobromous acid as well as tyrosyl radical by harnessing hydrogen peroxide. While the antimicrobial efficacy and dose-dependent cytotoxic effects of these ROS is reasonably well understood, the role of ROS as immunomodulatory agents is less clear. At the same time, ROS perform also redox-signaling functions and are therefore vital for a number of physiological responses. Both aspects motivate, in principle, the use of ROS as therapeutic agents. By generating a partially ionized gas, called cold physical plasma, multiple ROS can be produced in the gas phase at high concentrations to be subsequently transferred to biological targets such as cells and tissue. Promising results have been obtained with the treatment of chronic wounds and recently also cancer *in vitro*, *in vivo* and in patients. The mechanistic basis of these findings with therapeutic ROS is far from understand but evidence will be presented that immunomodulation plays at least in part a role in the responses observed.

The role of the innate immune system in the adaptation of barrier organs to the environment

Andreas Diefenbach

Department of Microbiology, Infectious Diseases and Immunology, Charité - Universitätsmedizin Berlin and German Rheumatism Research Centre (DRFZ), A Leibniz Institute

Environmental genotoxic factors pose a serious and constant peril to the genomic integrity of cells at barrier surfaces with the environment. They can induce mutations that, if they occur in epithelial stem cells, contribute to malignant transformation and cancer development. Genome integrity in epithelial stem cells is closely guarded by an evolutionary conserved, cellular response pathway, the DNA damage response (DDR). The DDR culminates in either transient cell cycle arrest and DNA repair or elimination of damaged cells by apoptosis. Here we show, that the cytokine interleukin (IL-)22 produced by group 3 innate lymphoid cells (ILC3) and γδ T cells is an important rheostat of the DDR machinery in intestinal epithelial stem cells. Using a new mouse model allowing for the sporadic inactivation of the IL-22 receptor in colon epithelial stem cells, we demonstrate that IL-22 is required for an effective initiation of the DDR following DNA damage. In consequence, stem cells deprived of IL-22 signals and exposed to carcinogens escaped DDR-controlled apoptosis, contained more mutations, and were more likely to give rise to colon cancer. We identified metabolites of glucosinolates, a group of phytochemicals contained in cruciferous vegetables, to be an commonplace source of genotoxic stress in intestinal epithelial cells. Glucosinolate metabolites are ligands of the aryl hydrocarbon receptor (AhR) and AhR signaling in ILC3 and γδ T cells controlled their production of IL-22. Mice fed with diets deprived of glucosinolates produced only very low levels of IL-22 and, consequently, the DDR in epithelial cells of mice on a glucosinolate-free diet was crippled. Collectively, we identify a homeostatic network protecting stem cells against perils to their genome integrity by AhR-mediated "sensing" of genotoxic components contained in diets. AhR signaling in turn ensures on-demand production of IL-22 by innate lymphocytes directly regulating components of the DDR in epithelial stem cells.

Immune System and Nutrition

Tilmann Grune

German Institute of Human Nutrition, Department of Toxicology, DIfE, Potsdam

Besides genetic setup, nutrition is the major factor influencing our metabolism and, therefore, the aging process and the development of chronic diseases. Such an effect might be indirectly mediated via epigenetic regulations or due to a direct influence on hormonal homeostasis or cellular metabolism. Cells need nutrients for energy production, proliferation, synthesis or other processes.

Numerous links are established connecting the function of the immune system with the nutritional status. This concerns both the different cells of the immune system and the humoral immune system with its multiple factors. Nutrition influences immunological functions from early childhood to oldest age.

Besides the effect of macronutrients, e. g. PUFA, research focused especially on several micronutrients such as the vitamins A, C, D, E, B6, B12, and folate, or the trace elements zinc, iron, or selenium. So today, it seems generally accepted that a poor diet is compromising immune function. Furthermore, a diet rich in low-molecular weight carbohydrates and saturated fat is stimulating a pro-inflammatory state.

The effect of the pro-inflammatory factors chemerin, omentin, and others on the development of age-related diseases, such as colorectal cancer and heart failure, as well as their relation to diet is recently a focus of research. Higher circulating chemerin levels were positively associated with colorectal cancer and heart failure. Interestingly, the level of chemerin can be modified by dietary intervention, such as a high-protein diet.

In general, plant and/or protein based diets seem to be associated with a reduction of the pro-inflammatory state. Once, the methodological requirements for a stable measurement of selected cytokines are established, further epidemiological studies will emphasize the relevant relationship between nutrition, pro-inflammatory mediators and metabolic diseases.

Epigenetics in T cell differentiation: From genome-wide signatures to local regulators and their targeted manipulation

Julia Polansky-Biskup

Charité - Universitätsmedizin Berlin, BCRT - Berlin Institute of Health Center for Regenerative Therapies and Deutsches Rheuma-Forschungszentrum – DRFZ, ein Institut der Leibniz-Gemeinschaft

CD4+ T cells shape the type, intensity and duration of most effective adaptive immune responses and contribute significantly to protective immunity. These features make them promising effectors for adoptive T cell therapies in various clinical settings such as chronic viral infections, and cancer. At the same time, CD4+ T cells are key effectors in chronic (auto-immune) inflammatory diseases when the physiological immune-regulation fails. It is therefore of utmost importance to understand the normal, but also the disease-associated altered differentiation pathways and survival requirements for human CD4+ T cells. Such insights will highlight new promising points of therapeutic intervention and will allow optimization of T cell products for adoptive T cell therapy.

We are interested in the regulatory impact of epigenetics on T cell differentiation. Therefore, we are generating genome-wide epigenetic maps of human T cell populations and use these data for the identification of key epigenetic regulators, which are functionally involved in T cell differentiation, function and survival. In parallel, we are developing tools for the targeted manipulation of such epigenetic elements ('epigenetic editing'), which might be used for the fine-tuning of therapeutic T cell products in the future.

Skin barrier and nutrition – role of the aryl hydrocarbon receptor

Charlotte Esser

Leibniz Research Institute for Environmental Medicine (IUF), Düsseldorf

Environmental influences by chemicals on living organisms can be beneficial or adverse. We get exposed to small molecular weight chemicals via air, water, and food, both from natural and anthropogenic sources. Some small molecular weight chemicals are important nutrients, providing anti-inflammatory or anti-oxidant benefits. It is worth understanding mechanisms of chemical interactions with the body in order to interpolate toxic effects, to provide dietary recommendations, or to develop drugs on a more rational basis. My research focusses on the aryl hydrocarbon receptor (AHR), an evolutionary old latent cytoplasmic transcription factor. Ligand binding results in conformational change of AHR, its translocation to the nucleus and eventually the start of cell-specific transcriptional programs. AHR functions are diverse, including the control of chemical-degrading enzymes, cell differentiation, immune functions. AHR is especially abundant in the barrier tissues, congruent with their proximity to the environment. We have tested the role of AHR in (i) skin barrier homeostasis and (ii) for skin-resident γδ T cells in mice. AHR-/- mice or their AHR+/+ (WT) littermates were mechanically stressed by tape stripping, and then analysed for barrier stability and repair capacity. Deficiency of AHR in the skin keratinocytes resulted in higher transepidermal water loss, i.e. an impaired barrier, and lower repair kinetics than in WT littermates. Importantly, feeding young mice an AHR-ligand deficient chow, for several weeks mimicked this phenotype. The effect was reversible: re-introducing ligands to the diet improved skin barrier again. On a transcriptional level, AHR controlled many genes related to barrier stability1. In another line of research, we looked at the role of AHR for the inflammatory default setting of the immunosurveillant murine skin resident γδ T cells, also known as "dendritic epidermal T cells" (DETC). We found that AHR is mandatory for the establishment of DETC in the murine skin after birth, and that AHR presence keeps a brake on their inflammatory potential. Regarding DETC abundance in the skin, dietary lack of AHR ligands, phenocopied genetic AHR knock-out. Ablating AHR from DETC cells in adults also reduced DETC frequency. Data regarding a possible anti-inflammatory outcome on DETC by dietary interventions are not conclusive yet, and further research is under way.

In conclusion, AHR is an important regulator for skin homeostasis and diet-derived ligands appear relevant to achieve physiological levels of AHR activity for skin health.

1Haas et al. J. Invest. Dermatol. (2016) 136:2260

This work was supported by the Deutsche Forschungsgemeinschaft, grant ES103/7-1

Nutrition-related immune cell priming

Dietmar Krautwurst

Chemoreception & Biosignaling, Leibniz-Institute for Food Systems Biology (LSB) at the Technical University of Munich, Freising

To meet consumers' demands and the challenge of a continuous supply of high quality nutrition, today's food is highly processed and contains an increasing number of compounds. Here, artificial sweeteners are of particular importance, since a reaction to the obesity epidemic entails broad substitution of sugars in order to reduce calorie intake. Our research revealed that consumption of food-typical sweetener concentrations modulated the transcriptional profile of their taste receptors and immune mediators related to priming of circulating neutrophils. We hypothesize that taste receptors of immune cells are sensors for food-borne stimuli involved in establishing a post-prandial, reversible alertness of our immune system, to balance homeostasis and immunity.

The effect of acute and sustained beta2-adrenergic receptor stimulation on the function of Natural Killer cells

Carsten Watzl

Leibniz Research Centre for Working Environment and Human Factors at Technical Univerity Dortmund (IfADo)

It is well established that stress can interfere with normal immune function. The neurotransmitter epinephrine plays a crucial role during acute stress in the so-called fight-or-flight response. It is already established that epinephrine can act on cells of the immune system. The number of lymphocytes in peripheral blood increases after exposure to epinephrine. More importantly, the outcome of cancer therapies and major surgery can be influenced by epinephrine-mediated effects on the immune system.

Here we studied the effect of epinephrine on the function of Natural Killer (NK) cells in an *in vitro* setting. NK cells are innate lymphoid cells that are involved in the control of viral infection and tumors. NK cells respond to epinephrine mainly through beta2-adrenergic receptor (beta2AR) signaling, which leads to increased cAMP levels in the cytoplasm. Our data show that beta2AR stimulation affects signal transduction of activating NK cell receptors. As a result, acute exposure of NK cells to epinephrine reduces NK cell cytotoxicity and production of interferon-gamma. More importantly, epinephrine blocks the affinity increase of the adhesion protein LFA-1, which is induced through the stimulation of NK cell activating receptors. The beta2-AR mediated inhibition can be reverted by the PKA inhibitor H89. This suggests that PKA signaling after beta2AR stimulation interferes with LFA-1 mediated NK cell adhesion. Interestingly, chronic beta2AR exposure completely prevented the inhibitory effects of acute epinephrine stimulation on NK cell functions. Therefore, acute and chronic exposure to epinephrine can have very different effects on the function of immune cells, which may explain some effects of acute and chronic stress on the immune system.

Early life environment in shaping risk for respiratory disease and potential dietary intervention

Susanne Krauss-Etschmann

Research Center Borstel (FZB), Leibniz Lung Center

Background
Epidemiological studies support the developmental origin of chronic immune related diseases such as asthma or chronic obstructive pulmonary disease (COPD). Maternal smoking during pregnancy is one of the strongest environmental risk factors for developing asthma in later life and affects the offspring microbiome. Understanding how in utero exposure to cigarette smoke affects immunity should help to develop primary prevention strategies, e.g. through dietary intervention.

Summary of presentation
Exposure of pregnant mice to mild cigarette smoking alters numbers of CD4 and CD8 T cells both in the periphery and in the thymus in offspring at three weeks of age. NGS sequencing of isolated thymocytes revealed changes in immune related canonical pathways in CD8 single positive cells. At present it is unclear, if mild maternal smoking affects asthma risk in offspring, but altered T cell development could be a risk factor for immune related diseases.

To develop potential dietary intervention strategies for prevention of allergic asthma, we searched for immune modulatory compounds in supernatants from probiotic bacteria and identified D-tryptophan, which is a non-proteinogenic amino acid. Oral supplementation of mice with D-tryptophan before experimental asthma induction, led to lessened airway inflammation and eosinophilia as well as reduced airway hyperreactivity. In addition, pulmonary Th2-responses were diminished, while Helios+ Treg were increased. Furthermore, gut microbial β-diversity which is reduced in experimental asthma was partly maintained. Single, defined bacterial products can be immune-modulatory in the host & might be exploited for future development of preventive strategies for chronic inflammatory disorders.

Circadian rhythms in the immune response

Christoph Scheiermann

University of Geneva and Ludwig-Maximilians-Universität München

The number of leukocytes circulating in blood is under circadian, i.e. ~24h, control. This talk will summarize latest findings on the mechanisms governing leukocyte migration from the blood into various organs, focusing on the distinct leukocyte subtype- and organ vascular-specific molecules involved. A focus will be on the oscillatory expression patterns of adhesion molecules, chemokines and their receptors, expressed on endothelial cells and leukocytes, which are critical regulators of rhythmic leukocyte recruitment. Furthermore, the relevance of clock genes in endothelial cells and leukocytes for leukocyte function and migration will be discussed.

Microbiota-epithelium interactions educate host adaptive immunity

Ivaylo I. Ivanov

Columbia University, New York, USA

Understanding how microbes interact with eukaryotic organisms is crucial for understanding fundamental processes in biology. Most of the underlying cellular and molecular mechanisms of these interactions have been studied in the context of invasive pathogens. In contrast, how microbiota interact with host cells and engage host immunity has remained largely unexplored. Commensal microbes play crucial roles in host physiology and immunity and, therefore, whether they possess novel mechanisms of communication with the host is of considerable interest.

We examined the mechanism of interaction between epithelium-associated segmented filamentous bacteria (SFB) and the intestinal immune system. In contrast to other commensals, SFB induce an antigen-specific CD4 T cell response that consists almost entirely of Th17 cells. We showed that this occurs through a novel antigen presentation pathway involving communication between different subsets of innate immune cells. We also characterized the mechanism of communication between SFB and intestinal epithelial cells and identified a novel mode of host-microbe interaction. I will discuss how these mechanisms can specifically control induction of CD4 T cell responses to resident microbes.

Microbiota controlling TGF-β and IgA expression in the intestinal mucosa

Hyun-Dong Chang

Deutsches Rheuma-Forschungszentrum – DRFZ, ein Institut der Leibniz-Gemeinschaft

Recent evidence shows that distinct bacteria of the microbiota can imprint the immune system of their host decisively impacting on protective and pathological immunity.

In the physiological state, bacteria of the microbiota are exposed to the immune system, but regulatory mechanisms maintain tolerance and prevent overt inflammation. Physiological tolerance of the mucosal immune system is maintained by T helper cells expressing the cytokines interleukin-10 and/or transforming growth factor beta (TGF-β). TGF-β is also the cytokine targeting antibody class switch recombination to immunoglobulin A (IgA) in activated B lymphocytes, the predominant class of mucosal antibodies. IgA is actively transported into the gut lumen and there shapes and controls the microbiota composition. By serendipity, we have identified a distinct bacterial genus of the murine microbiota, which induces TGF-β in intestinal T follicular helper cells, and IgA secreting plasma cells in the lamina propria of the small intestine, resulting in significantly increased mucosal IgA production. These potentially anti-inflammatory bacteria are also present in the microbiota of humans, and its presence correlates to levels of mucosal IgA there.
In a personalized approach to profile the individual microbiota from feces patients

with inflammatory bowel disease, we have developed "High-Resolution Microbiota Cytometry" as a non-invasive diagnostic tool, which will allow us to visualize dramatic changes of the microbiota composition fast and efficiently, and to isolate distinct bacteria for functional and molecular analyses.

Distinct mucosal or systemic responses to non-pathogenic intestinal microbes build the B cell repertoire and its functional responsiveness

Andrew Macpherson / Stephanie Ganal- Vonarburg

Department for BioMedical Research (DBMR), University of Bern, Switzerland

Microbiota colonization causes profound B cell stimulation and immunoglobulin induction. To understand how the B cell repertoire develops in the earliest phases of microbial colonization we have used transient reversible microbial exposures in germ-free mice. Distinct oligoclonal responses to all isotypes after intestinal mucosal exposure differ from those after intravenous systemic exposure or germ-free controls. The selective IgA repertoire after intestinal dose escalation becomes progressively restricted and clonally related, whereas the systemic IgG repertoire can be broadened to a range of microbial cytoplasmic as well as cell-surface antigens. There are hierarchical repertoires during different stages of B cell development which are dominantly shaped by microbial exposure at memory and plasma cell stages, with clonal overlaps generated between earlier transitional states. Whereas sequential systemic exposure to different taxa broadens the IgG repertoire and multiplies specific responses, sequential mucosal exposure produces limited overlapping repertoires and attrition of initial IgA binding specificities. This shows a contrast between a flexible response to systemic exposure consistent with the need to avoid fatal sepsis and a restricted response to mucosal exposure reflecting the generic nature of mucosal microbial mutualism.

Shaping of the human T cell repertoire by the microbial environment: mind the "-myces" !

Alexander Scheffold

Institut für Immunologie, Christian-Albrechts-Universität zu Kiel und Universitätsklinikum Schleswig-Holstein

Our body is permanently exposed to environmental antigens, impacting on various local but also systemic physiological processes. The immune system has a pivotal role to regulate this chronic encounter - promoting tolerance, ranging from ignorance to active tolerance and control of microbial colonization to prevention of invasive infections. Dysregulated immune responses against distinct environmental antigens may underlie various types of immune-related diseases both, locally as well as systemically. How this control is specifically achieved for individual microbes and how local versus systemic effects are regulated is currently poorly understood. Analysis of human T cell responses against ubiquitous environmental antigens surprisingly identified two members of the mycobiome as major targets of prototypic human T cell responses, mediating tolerance, commensalism and systemic immune modulation and affecting essentially all human individuals. The ubiquitous airborne fungus *A. fumigatus*, is a main inducer of antigen-specific regulatory T cells, which mainly seem to prevent allergies. In contrast, the intestinal commensal *C. albicans* is a major inducer of human Th17 responses. In fact, among 30 tested fungal species, Candida is the sole direct inducer of Th17 cells. Against all other fungi, including A. fumigatus only minor and variable fractions of Th17 cells were detected. Surprisingly, these Th17 cells, but not Th1 cells against the same fungal species, were strongly and selectively cross-reactive against *C. albicans*. Strikingly, patients with chronic respiratory diseases such as asthma, COPD and cystic fibrosis show increased frequencies of these cross-reactive *A. fumigatus*-stimulated Th17 cells. This is particularly evident in acute allergic bronchopulmonary Aspergillosis (ABPA), suggesting their active contribution to lung inflammatory disease.

Our data identify the mycobiome, which are currently mostly neglected by microbiota analyses as major modulators of the human T cell repertoire. We also provide a unique example how protective intestinal Th17 immunity may simultaneously promote immune pathology when deviated to different target antigens and tissues via inter-species cross-reactivity. Modulation of human T cell responses by cross-reactivity to the microbiota may have a general impact on human T cell immunity and represents a specific mechanism for systemic modulation of antigen-specific immunopathology by locally resident members of the microbiota.

Keynote Lecture

NK cells in the therapy of acute, high-risk leukemia: KIR/HLA-I mismatch and more

Lorenzo Moretta

Ospedale Pediatrico Bambino Gesù, Roma

Natural Killer (NK) cells play a central role in innate defenses against viruses and tumors. They belong to a family of innate lymphoid cells (ILC) that do not express receptors encoded by rearranging genes. NK cell function is regulated by inhibitory and activating receptors most of which identified by Alessandro Moretta. The inhibitory receptors most relevant in the control of NK cell function recognize HLA-cl I molecules. Importantly, killer Ig-like receptors (KIR) recognize allotypic determinants shared by different HLA-cl I alleles, while CD94/NKG2A recognizes the non-classical HLA-E. The need of the NK cell inactivation, implied the existence of activating receptors. The prototypes and the most important in tumor cell killing were discovered our labs. Named NKp46, NKp44, NKp30 according to their molecular weight, they were collectively called natural cytotoxicity receptors (NCR). While in an autologous setting all NK cells express one or more receptors for self HLA-class I, in an allogeneic setting it is possible that KIRs present on a subset of NK cells do not recognize alleles expressed by allogeneic cells ("alloreactive" NK cells). Although NK cells display a potent anti-tumor activity *in vitro* and are thought to participate in the immunosurveillance against tumors, the tumor microenvironment may sharply inhibit their effector function, primarily by downregulating the surface expression of activating receptors. NK cell cytotoxicity has been exploited in the haploidentical haemopoietic stem cells transplantation (HSCT) setting to cure high-risk leukemias (applied when no HLA-compatible donors are available, i.e. approximately 35% of patients). The infusion of mega-doses of T-depleted CD34+ HSC allows an efficient engraftment with unfrequent, mild grade, GvHD. In the T-depleted, haplo-HSCT, in the absence of donor T lymphocytes, NK cells play a central role in the anti-leukemia effect. A more recent evolution of the manipulation strategy of haplo-HSCT, based on the infusion of TCRαβ- and CD19-depleted mononuclear cells (including mature donor NK cells and TCRγδ+ T cells in addition to CD34+ cells) results in a prompt availability of effector cells resulting in a better protection against early leukemia relapses and GvHD. Indeed, this strategy, successfully applied by Franco Locatelli and our groups, led to a further improvement of the clinical outcome of pediatric patients, with a 70% 5 years survival probability in both ALL and AML pediatric patients. Overall, the haplo-HSCT, now applied in numerous centers in the world, has allowed to safe thousands of lives. This success, in otherwise lethal leukemias, are largely based on the discovery of NK receptors. The recent finding by our group that, in tumor patients, NK cells may express PD1, extends to HLA-Class-I- tumors (undetectable by T cells) the efficacy of therapies based on the use of checkpoint inhibitors disrupting the PD-1/PD-L axis. Moreover, while CAR-T cell therapy revealed efficacious in various hematologic malignancies, it requires a personalized approach using patient-derived autologous T cells to prevent GvHD. Recently developed CAR-NK cell platforms may overcome this limitation and represent a novel, excellent off-the-shelf tool. In addition, both homing properties and function of CAR-NK may be complementary to CAR-T cells possibly representing a better mean to treat solid tumors.

Sex differences in inflammation during chronic HIV-1 infection

Marcus Altfeld

Research Department Virus Immunology, Heinrich Pette Institute(HPI), Hamburg

Our immune system defends us from environmental threats, such as bacterial and viral infections, and detects and removes abnormal cells that potentially lead to malignancies. Optimal immunological homeostasis is achieved when the threat (e.g. pathogen) is removed with the highest efficiency whilst avoiding collateral tissue damage for the host. Increasing scientific evidence suggests that this immunological balance is different between women and men. It has been shown that women mount stronger immune responses against pathogens compared to men, leading to more rapid control or clearance of infections. Enhanced immune responsiveness in females, however, comes at a cost, including aggravated tissue damage, higher immune activation, persistent inflammation and significantly higher incidences of autoimmune diseases. These differences in immune responses between the sexes are reflected in sex differences in the manifestations of HIV-1 infection. Women can better control initial HIV-1 replication, resulting in lower viral loads during primary infection; however, during chronic persistent infection continuous exposure to antigen results in higher levels of inflammation and faster HIV-1 disease progression in women. Work by our group and others has demonstrated a critical role of differences in the Type I IFN pathway between women and men in mediating these sex differences in HIV-1-induced immune activation and inflammation. Increasing data show that immune regulatory genes encoded by the X chromosome escape X chromosome inactivation (XCI), resulting in higher mRNA levels of their gene products in immune cells from women compared to men. I will present novel data demonstrating that escape from XCI of genes involved in the Type I IFN response of pDCs contribute to the sex differences in immune responses observed during HIV-1 infection.

Inflammation in tuberculosis: friend or foe of whom?

Christoph Hölscher

Research Center Borstel (FZB), Leibniz Lung Center

Mycobacterium tuberculosis (Mtb) has the capacity to remain viable within the host although the latter mounts an adequate immune response. This gives rise to a chronic inflammatory response aimed at restraining harmful effects of the persisting microorganism. This response in tuberculosis (TB) follows the characteristic pathophysiological pattern of granuloma formation and entails significant tissue damage in patients with active disease. In most infected individuals, the inflammatory immune response is able to keep Mtb in check but in active TB, inflammation is captured by the pathogen to resume growing, induce granuloma necrosis and to eventually leave the host. Nevertheless, the interplay of inflammation, host protection, mycobacterial replication and disease progression still remains elusive. This lecture outlines the salient features of inflammation associated with TB and discusses strategies to modulate the hosts immune response as adjunct to antibiotic treatment.

In**TOX**ication causes T-cell exhaustion in chronic infection

Dietmar Zehn

Technical University of Munich

Persisting exposure to viral antigen in chronic infection and cancer can induce a T cell phenotype known as “exhaustion”. This phenotype is characterized by low cytokine production and up-regulated expression of inhibitory receptors, resulting in a less potent effector response than T cells found in acute infections. From a therapeutic perspective, it is critically important to understand and overcome the transcriptional networks that induce and maintain the “exhausted” phenotype. Several molecules have been proposed to impact the differentiation of T cells in chronic infection, none of which act exclusively in chronic infection as they also impact T cell differentiation in acute infection. However, by performing well-defined side by side comparisons of T cells with or without an exhausted phenotype in chronic infection, we have identified that the thymocyte selection-associated high mobility group-box protein (Tox) serves an exclusive role in inducing the exhausted phenotype. In fact, while the absence of Tox did not cause major impairments in activation, expansion, and memory-formation of T cells in acute infection, Tox deficient T cells retained an acute phenotype in chronic infections. This involved decreased levels of inhibitory receptor expression, more effective virus control, and a significantly augmented level of immunopathology compared to chronic infection in T cells with Tox. Moreover, Tox is critical for maintaining the Tcf-1 positive progenitor T cell pool. Tcf-1+ T cells declined rapidly without Tox and, as a consequence, the entire population was rapidly depleted. Overall, we have established that Tox is a key transcription factor that reinforces the phenotype and longevity of exhausted T-cells in chronic viral infection.

Memory plasma cells as therapeutic target in antibody-mediated diseases

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Plasma cells represent a final stage of B cell differentiation after its activation. They are specialized in the generation and secretion of high amounts of antibodies. We distinguish between newly generated proliferating plasmablasts, which are migratory and sessile nonproliferating mature plasma cells. The latter reside as long-lived plasma cells in survival niches in the bone marrow for years or lifetime. They can be also present in inflamed tissues as long as inflammation occurs. Long-lived plasma cells are usually the result of a secondary immune response. In particular, long-lived plasma cells are crucial for the maintenance of humoral memory. They secrete antibodies independently of B cell activation, antigen contact and T cell help. That is why we call them memory plasma cells. Because of their resistance to conventional immunosuppressive drugs or therapies targeting B cells, memory plasma cells secreting pathogenic antibodies present a therapeutic challenge in antibody-mediated diseases such as autoimmune disorders, allergies or transplanted organ rejection. So far, only immunoablative regimens including anti-thymocyte globulin (ATG) followed by autologous stem cell transplantation or proteasome inhibitors, which are approved in the treatment of the malignant plasma cell disease multiple myeloma are able to deplete memory plasma cells. But these approaches impair the protective humoral immunity resulting in immunodeficiency. Consequently, our group has been working on a therapeutic strategy leading to a selective depletion of autoreactive memory plasma cells sparing the protective memory plasma cells. The basic principle of this approach is that after plasma cells are labeled *in vivo* with the antigen-of-interest using an antibody recognizing plasma cells (e.g. anti-CD138), those secreting specific antibodies are targeted by their own antibodies via antibody-mediated ablative effector mechanisms, such as complement lysis and antibody-mediated cellular cytotoxicity. In a murine model bearing memory plasma cells secreting anti-ovalbumin (OVA) and -chicken gamma globulin (CGG) antibodies we used for the first time an antigen-antibody (OVA/anti-CD138 antibody) conjugate for *in vivo* labeling and selective ablation of plasma cells that secrete antibodies specific for the antigen OVA. The selective depletion also led to a stable reduction of the corresponding serum anti-OVA antibody levels. In contrast, CGG-specific plasma cells and circulating anti-CGG antibody levels remained unchanged. This technology offers unique and entirely new options for assessing the pathogenic role of a specific antibody in a given disease, and for the development of causative therapies for antibody-mediated diseases.

Current challenges for science and healthcare posed by emerging influenza viruses

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Zoonotic virus infections may lead to major economic losses and disease burden in animals and man. Herein, particularly emerging viruses, such as avian H5N1 and H7N9 influenza viruses, MERS-CoV and ZIKV challenge current surveillance and health care systems. Moreover, evolving avian influenza viruses pose a major pandemic threat. This highlights the urgent need for network collaborations involving scientists, clinicians and public health experts working at the animal-human interface. As a major global health challenge, pandemic preparedness plans need to consider the holistic One Health concept. In this presentation, current challenges posed by emerging influenza viruses to animal and human health will be presented.

Modelling signalling in the intestine and colon cancer, cell by cell

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The intestinal epithelium is organised by complex signalling networks that are deregulated in cancer by oncogenic mutations. The network is highly nonlinear and involves strong feerback regulation, making it difficult to understand quantitatively However, it remains unclear how cell hierarchies in this tissue are distorted by these mutations, how much of the original hierarchy is preserved in tumours, and how targeted drugs interfering with these signalling networks act within this hierarchical tissue.

NK cell receptor NKG2D enforces pro-inflammatory features and pathogenicity of Th1 and Th17 cells

1

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Introduction

The effector functions of T helper (Th) cells can be shaped not only by receiving the T cell receptor and costimulatory signal but also through signals transmitted via cytokine receptors or a myriad of activating receptors. NKG2D is a molecular sensor of stressed cells expressed on different subsets of innate and adaptive lymphocytes. Despite its established role as potent stimulator of the immune system, particularly as an activating receptor on NK cells and costimulatory molecule on CD8+ T cells, NKG2D-driven regulation of CD4+ T helper (Th) cell-mediated immunity remains unclear.

Methods and Results

We identified a population of T-bet expressing NKG2D+CD4+ T cells in spleen and bone marrow of C57BL/6 mice, whereas a significant portion of NKG2D+CD4+ T cells derived from the small intestine lamina propria expressed RORγt. In line with this, the de novo expression of NKG2D could be induced on naïve CD4+ T cells both under Th1 and Th17 polarizing conditions. While NKG2D was mildly impacting the expression of IFNγ in fully polarized Th1 cells, the *in vitro* expression of NKG2D was associated with GM-CSF+IFNγ+ Th17 cells. Global gene expression analysis further confirmed enforced expression of type 1 signature genes in Th17 cells by NKG2D and we could show a direct effect of NKG2D triggering in enhancing the production of IFNγ and GM-CSF in Th17 cells. By fate mapping of Il17a-expressing cells *in vivo* in a mouse model of antigen-induced arthritis, we could show that under inflammatory conditions, NKG2D highly enriched the population of T-bet-expressing Th17 cells. Indeed, during arthritis, NKG2D was associated with modulated expression of GM-CSF and IFNγ in antigen-specific Th1 and T-bet+ Th17 cells, which was in line with our *in vitro* data. Most importantly, T cell specific deletion of NKG2D impaired the ability of antigen-specific CD4+ T cells to promote inflammation *in vivo* during antigen-induced arthritis, resulting in significantly reduced knee swelling and tissue immunopathology and improved disease score.

Conclusions

Altogether, our results indicate that the triggering of NKG2D by stress-ligands induced during inflammation modulates the effector functions of both Th1 and Th17 cells *in vitro* and *in vivo*. Our data demonstrate that conditional deletion of NKG2D in T cells has a clear impact *in vivo* in an inflammatory disease model and imply that NKG2D might serve as an important target for the amelioration of chronic inflammatory diseases mediated by a mixed Th1 and Th17 response.

A High glucose diet controls IgA levels via TLR4-dependent mechanism

2

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Intestinal microbiota controls multiple aspects of the body homeostasis including the development of many diseases. Microbiota composition is known to be regulated by the host immune system as well as by environmental factors, such as diet. However, interplay between microbiota, host immune system and diet remain understudied. Patients with type II diabetes (T2D) are characterized by microbiota dysbiosis and enhanced amount of IgA antibodies in blood. Since one of the major mechanisms of microbiota composition control is IgA production, we hypothesized that high-glucose supplementation modulates IgA production and subsequently composition of microbiota. Here we found that high-glucose diet lead to the increased levels of dimeric IgA in serum, but not in the gut. At the same time, glucose did not affect neither IgA+ plasma cell frequencies in different compartments of the body, nor IgA transport into the lumen. Next, we revealed that increased serum IgA production during the high glucose supplementation is mediated by TLR4, since increased IgA were abrogated in TLR4 KO upon high glucose diet. Finally, glucose supplementation modified IgA-coating of microbiota in WT mice. Altogether, our data reveal that high glucose diet leads to increased dimeric serum IgA production that is dependent on TLR4 and altered recognition of microbiota by IgA.

This research was supported from the Russian Science Foundation (Project No. 17-74-20059).

Antibiotic use during pregnancy increases murine offspring asthma severity in a dose dependent manner.

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Background:
The use of antibiotics during pregnancy is associated with increased allergic asthma risk in the offspring, and given that approximately 25% of pregnant women are prescribed antibiotics, it is important to understand the mechanisms contributing to this phenomenon. Currently, there are no studies that directly test this association experimentally. Our objective was to develop a mouse model in which antibiotic treatment during pregnancy results in increased offspring asthma susceptibility.

Methods:
Pregnant mice were treated daily from gestation day 8 to 17 with an oral solution of the antibiotic vancomycin, and three concentrations were tested. At weaning offspring were subjected to an adjuvant-free experimental asthma protocol using ovalbumin as an allergen. A kinetic analysis of the gut microbiota was performed in mothers and offspring with samples collected from five different time points; short chain fatty acids were also analyzed in allergic offspring.

Results:
We found that maternal antibiotic treatment during pregnancy was associated with increased offspring asthma severity in a dose dependent manner. Furthermore, maternal vancomycin treatment during pregnancy caused marked changes in the gut microbiota composition in both dams and pups at several different time points. The increased asthma severity and intestinal microbiota changes in pups were also associated with significantly decreased cecal short chain fatty acid concentrations.

Conclusion:
Consistent with the "Developmental Origins Hypothesis", our results confirm that exposure to antibiotics during pregnancy shapes the neonatal intestinal environment and increases offspring allergic lung inflammation.

Mild maternal smoking influences lung T cell populations and gene expression in CD8SP thymocytes after intrauterine CS exposure in murine offspring

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Introduction:
Epidemiological studies have demonstrated that smoking during pregnancy induces lower birth weight, decreases lung function and impairs lung development in children, thereby increasing the susceptibility to develop asthma and COPD. Due to underreporting of smoking, mild maternal smoking might be concealed. We hypothesize that mild maternal smoking could alter the immune development after intrauterine exposure, even in the absence of low birth weight and lung function deficits.
Objective: To investigate immune cells in lung, spleen and thymus in mice from infancy to adulthood after mild *in utero* smoking.

Methods:
Female C57Bl/6 mice were exposed to

mainstream cigarette smoke (CS) four days before mating. Thereafter, dams were exposed to CS or room air (RA) until delivery 1/day for 1h (1 puff/min = 6 research cigarettes (3R4F, University of Kentucky, USA)); inExpose exposure system (SCIREQ, Canada). Lung and thymic T cells were analyzed by FACS on postnatal day (PND) 3, 21 and 56. At PND21, CD4+ and CD8+ single-positive (SP) thymocytes were FACS sorted and analyzed by next-generation sequencing (NGS) (Illumina NextSeq500, USA) followed by pathway analyses (Ingenuity Pathway Analysis (IPA), Qiagen, The Netherlands).

Results:
At PND21, lungs of prenatally CS-exposed offspring showed lower CD3+ T cells with increased CD4+ T cells and a prominent decrease of CD8+ T cells. Similar changes were observed in the spleen and thymus. NGS revealed 92 up- and 36 downregulated genes in CD8SP thymocytes, with no significant regulation in thymic CD4SP. In silico pathway analyses suggested altered gene expression in the network analysis including hematological system development and function, developmental disorders and immune cell trafficking. In this network, immune related genes were upregulated (interleukin 4 receptor (IL4R), runt-related transcription factor 3 (RUNX3), forkhead box protein P1 (Foxp1), IL10RB) with a concomitant downregulation of phasphoinositide-3-kinase (PI3K).

Conclusion:
Our data revealed altered T cell populations in lung, spleen and thymus of PND21 offspring after mild intrauterine CS exposure. IL-4 is involved in the differentiation of innate memory-like CD8+ thymocytes, which supports the immune defense in neonates and infants before peripheral memory CD8+ T cells are established. The identity of CS modulated cells being innate memory-like CD8+ thymocytes needs further confirmation.

Obesity, biomarkers of inflammation and distal sensorimotor polyneuropathy

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Obesity and inflammatory processes have been implicated in the development of distal sensorimotor polyneuropathy (DSPN). However, prospective analyses on the relationship between biomarkers of inflammation, measures of obesity and DSPN are scarce. Therefore, we aimed to assess associations of different measures of obesity and biomarkers reflecting multiple aspects of immune activation with incident DSPN. Additionally, we investigated if biomarkers of inflammation may mediate the link between obesity and incident DSPN.

The study was based on data from the population-based Cooperative Health Research in the Region of Augsburg (KORA) F4/FF4 cohort (follow-up 6.5 years). Serum levels of biomarkers of inflammation were measured using proximity extension assay technology.

Twenty-six out of 71 biomarkers were associated with incident DSPN. After

adjustment for multiple testing, higher levels of six biomarkers remained related to incident DSPN. Three of these proteins (MCP-3/CCL7, MIG/CXCL9, IP-10/CXCL10) were chemokines, while the other three (DNER, CD40, TNFRSF9) were soluble forms of transmembrane receptors. Pathway analyses indicated that multiple cell types from innate and adaptive immunity may be involved in the development of DSPN. Moreover, both general and abdominal obesity were associated with development of DSPN. Three of the aforementioned biomarkers (CCL7, CXCL10, DNER) were found as potential mediators in these associations. Thus, we identified novel associations between biomarkers of inflammation and incident DSPN pointing to a complex cross-talk between innate and adaptive immunity in the pathogenesis of the disease. Biomarkers of subclinical inflammation partly mediated the association between obesity and DSPN. Importantly, obesity and subclinical inflammation are modifiable risk factors for DSPN, and thus recommendations regarding the prevention of DSPN should include the adherence to a healthy body weight with a normal BMI and waist circumference.

Human CD34$^+$ hematopoietic progenitors from various compartments give rise to all innate lymphoid cell subsets in vitro

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Rising as critical effectors of innate immunity, innate lymphoid cells (ILCs) are chiefly tissue resident sentinels which play pivotal roles in the initiation, regulation, and resolution of inflammation, particularly at mucosal surfaces. Besides fetal lymphoid tissue inducer (LTi) cells, post-natal ILCs can be classified based on their effector functions and transcriptional requirements into ILC1, ILC2, ILC3, which parallel T helper (Th) cell lineages, and Natural Killer (NK) cells, which parallel T cytotoxic cells. While *in vitro* generation of Th lineages has dramatically expanded our understanding of their functional requirements for both differentiation and effector functions in response to inflammatory signals, generation of ILC lineages has not been systematically explored. Previous studies investigating ILC differentiation from committed precursors have relied on analyses based on the expression of few markers or cytokines, which are suboptimal to assign lineage identity. In this study we established an *in vitro* platform to reliably engender human ILCs from CD34$^+$ hematopoietic progenitor cells (HPCs) from different tissue compartments, namely umbilical cord blood, peripheral blood, bone marrow and tonsils. With a systematic approach, we phenotypically, functionally, and transcriptionally characterized the *in vitro* generated ILC lineages, validating their identity by global comparison to ex vivo isolated ILCs. Similar to the T cell generation systems of the 90s, having such a resource precludes the leaps and bounds of advances in the field, can aid in clarifying and unifying ILC semantics, and boost exploration of homeostatic mechanisms underlying inflammation.

Identification of pro- and anti-inflammatory Th cells regulating chronic inflammation in juvenile idiopathic arthritis

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The macrophage tetraspan MS4A4A enhances Dectin-1-dependent NK cell-mediated resistance to metastasis.

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MS4A4A is a tetraspan surface molecule with unknown expression pattern, immune receptor partners and function.

We demonstrated that MS4A4A is selectively expressed by macrophage (but not by dendritic cells) and that its expression is gained during the differentiation from monocyte to macrophage. Human tissue-resident macrophages, macrophages infiltrating the synovium of rheumatoid arthritis patients and tumor-associated macrophages are all positive for MS4A4A. MS4A4A is highly expressed by alternatively activated macrophages (IL-4 and glucocorticoids) and MS4A4A expression is also induced in monocytes from patients treated with methylprednisolone.

By a split-ubiquitin two hybrid analysis, FLIM-FRET and immunofluorescence (STED) we identified for the first time Dectin-1 as a partner of MS4A4A. We demonstrated that MS4A4A colocalizes with the β-glucan receptor Dectin-1 in the lipid rafts after Zymosan engagement. MS4A4A is essential for full activation of the Syk pathway downstream Dectin-1, both

upon the stimulation of macrophages with fungal compounds or with tumor cells bearing specific Dectin-1-activating glycans. MS4A4A deficiency in macrophages has no impact on primary tumor growth, but compromises Dectin-1-driven NK cell-mediated resistance to metastasis. Indeed, in the absence of MS4A4A macrophages produce less NK cell-activating cytokines (IL-15 and IL-18) and express lower levels of NK cell-activating receptors (INAM). This impairment of the macrophage-mediated activation of NK cells leads to inefficient NK cell antitumoral functions (decrease of IFN-γ production and cytolytic granule release) and then to the uncontrolled spread of Dectin-1-dependent metastasis.

Thus, MS4A4A is a tetraspan molecule expressed during macrophage differentiation and polarization that functionally interacts with Dectin-1 and is essential for full response by this innate immunity receptor, including NK cell-mediated resistance to metastasis.

TNF hampers intestinal tissue repair in colitis by restricting IL-22 bioavailability

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Successful treatment of chronic inflammatory diseases integrates both cessation of inflammation and induction of adequate tissue repair processes. One of the examples of such therapy is Tumor Necrosis Factor (TNF) inhibition in IBD patients. However, molecular mechanisms of intestinal repair upon TNF blockade during IBD remain not understood. Here, by the usage of human TNF Knock-in mice (hTNFKI) in a model of adoptive T cell transfer, we revealed that TNF interferes with tissue repair program via induction of soluble natural antagonist of IL-22 (IL-22Ra2; IL-22BP) in the colon and abrogates IL-22, STAT3-mediated mucosal repair during colitis. Pharmacological T-TNF blockade reduced IL-22BP expression in the colon leading to the increased IL-22 levels, colonic epithelial cell proliferation and restoration of colonic epithelium functions. Thus, our data revealed the mechanism of how anti-TNF therapy induces mucosal healing and provides novel potential targets for IBD treatment in humans.
This work was funded by the DFG (NE1466/2-1).

A murine model to study the development of COPD pathogenesis in smokers with viral infections

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Background

Cigarette smoking is the main risk factor for chronic obstructive pulmonary disease (COPD). On the other hand, not every smoker develops COPD. Therefore, additional triggers must exist. Smokers experience more severe and frequent viral infections. Therefore, we hypothesized that viral infections in smokers trigger pathways that enhance susceptibility to COPD.

Aim

To assess if a viral trigger enhances the release of mediators related to COPD pathology in smoke-exposed mice.

Methods

Female C57Bl6/J mice were exposed to cigarette smoke (CS, total particle matter 7600 mg/m3) or room air daily for one hour for 24 days. One hour after the last exposure, the viral dsRNA mimic 10 µg poly (I:C) (control: PBS) was applied intranasally. 24 hours later bronchoalveolar lavage (BAL) was collected. Cell free fluid was used for cytokine quantification and 2D protein gels. Mass spectrometry was used to identify proteins regulated by CS & poly (I:C).

Results

GM-CSF, IL-1, IL-6, INF-, KC/GRO, TNF- and VEGF-A were elevated in smoked mice exposed to poly (I:C) compared to mice exposed to CS or poly (I:C) only. 2D protein gel analysis revealed 906 regulated spots, in mice treated with CS and poly (IC) versus CS or poly (I:C) alone. Based on intensity of regulation and statistical differences among the groups, six spots were chosen for mass spectrometry, which yielded 53 proteins. For further prioritization of future functional analyses, data were intersected with BALF cell transcriptomes of COPD patients. Jointly regulated proteins were lipocalin-2, alpha-1-antitrypsin (serpin A1) prolactin-inducible protein (PIP), haptoglobin, Protein T4-A (serpin B3) and Leupin (serpin B4).

Conclusion

In “smoking” mice, the TLR3 ligand poly (I:C), induces a synergistic inflammatory response. Further regulated proteins were shown in an unbiased proteomic approach and confirmed in COPD patients. We suggest that our model can be used to investigate pathways for the development of COPD by virus-induced inflammation in smokers.

Funded by the BMBF (FKZ 13N13857).

Phytoestrogen Supplementation and Intermediate Cardiovascular Disease Risk Factors among Postmenopausal Women: a Meta-analysis of Randomized Controlled Trials

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Background

Phytoestrogens are becoming popular constituents of human diets and are increasingly used by postmenopausal women.

Objective

Our study aimed to determine the association of phytoestrogen supplementation with intermediate cardiovascular disease (CVD) risk factors in postmenopausal women.

METHODS: Five electronic databases (Medline, EMBASE, Web of Science, Cochrane CENTRAL, Google Scholar) were systematically searched to identify randomized controlled trials (RCTs) that assessed the association of phytoestrogen supplementation with CVD risk factors (serum lipids, inflammation markers, homocysteine, fibrinogen, markers of endothelial function, carotid intima media thickness (CIMT)) in postmenopausal women. Data were extracted by two independent reviewers using a pre-defined data collection form.

Results

In total, 50 RCTs were identified, including 3,599 individual postmenopausal women. There was substantial heterogeneity in quality across studies and 23 RCTs showed poor quality. Results are reported in pooled mean difference [95% CI] of changes. Use of phytoestrogens was associated with a decrease in serum total cholesterol (–0.27 mmol/L [–0.42 to –0.12]), low density lipoprotein (–0.24 mmol/L [–0.36 to –0.13]), triglycerides (–0.18 mmol/L [–0.27 to –0.09]) and apolipoprotein B (–0.12 g/L [–0.19 to –0.06]) and with an increase in serum apolipoprotein A-1 (0.05 g/L [0.01 to 0.10]). Also, phytoestrogen supplementation was associated with a decrease in serum intercellular adhesion molecule 1 (–18.86 ng/mL [–30.06 to -7.65]) and E-selectin (–2.32 ng/mL [–4.05 to –0.59]). There was no association observed between phytoestrogen supplementation and inflammatory markers, fibrinogen, homocysteine or other endothelial function markers. In contrast, use of phytoestrogens was associated with an increase in CIMT (9.34 µm [95% CI, 0.39 to 18.29]).

Conclusion

Phytoestrogen supplementation seems to modestly improve the CVD risk profile of postmenopausal women by influencing blood lipids and parameters of endothelial function. In high risk women, although modest, a harmful effect on CIMT progression may be present. However, because of limited quality and the heterogeneous nature of the current evidence, additional rigorous studies shall explore the role of phytoestrogens in menopausal cardiovascular health.

Leopoldina-Symposium Environmental Education of the Immune System in Health and Inflammation
August, 29 - 30, 2019

A Symposium of the Leibniz-Network Immune Mediated Diseases and the Leibniz ScienceCampus Chronic Inflammation

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