Institute of Clinical Microbiology, Immunology and Hygiene

Chair of Microbiology and Immunology of Infection

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Research focus
- Regulation of innate immunity in infection and inflammation
- Innate immunity, macrophages, arginase, and NO synthase
- Genetic and bacterial factors in chronic inflammation
- Pathogenicity of Coxiella burnetii
- Microbial phosphatases
- Innate lymphocytes and tumor necrosis factor in leishmaniasis
- Molecular biology of malaria
- Molecular mycology
- Innate checkpoints of T cell regulation
- Pathogenicity of Salmonella and microbiome analyses

Structure of the Chair

Professorships: 4
Personnel: 93
- Doctors (of Medicine): 10
- Scientists: 12 (thereof funded externally: 1)
- Graduate students: 15

Clinical focus areas
- Accredited clinical-microbiological diagnostics division
- Around the clock microbiological on-call service and emergency diagnostic testing
- Clinical infection related ward rounds for critical cases on the wards of the UK Erlangen
- Accredited hygiene laboratory
- Hospital hygiene related consultation and assistance of the UK Erlangen
- University outpatients' clinic for vaccination and travel medicine

Research

The different research groups of the Institute of Clinical Microbiology, Immunology, and Hygiene study the innate and adaptive immune response during infectious diseases, investigate mechanisms of microbial virulence, and analyze the regulation of basic inflammatory processes, using immunological, cell-biological, and molecular techniques. Various infectious disease models are studied which include infections with bacteria (Coxiella, Listeria, Mycobacteria, Salmonella), protozoa (Leishmania, Plasmodia) and fungi (Aspergillus). The Institute is fully equipped with laboratories, a hypoxia chamber for *in vitro* analyses, fluorescence and confocal laser scanning microscopes, real-time PCR machines, analytical fluorescence activated cell sorters (FACS) for flow cytometry, imaging systems and a next generation sequencing machine.

Regulation of innate immunity in infection and inflammation
PI: Prof. Dr. R. Lang
The question driving our research is how the immune system generates resistance to infection without causing excessive inflammation. We recently showed a pivotal role of TLR-MyD88 in sensing of *Coxiella burnetii* and established a mouse model for studying Q fever in vivo. *Mycobacterium tuberculosis* is another important intracellular pathogen. We have discovered that the cord factor of the mycobacterial cell wall activates macrophages through the MINCLE-SYK-CARD9 pathway, leading to strong Th17 immunity. Dissecting Mincle activation by microbial glycolipids and identification of signaling and transcription factors involved has been a focus of the lab. We are now investigating the functional consequences of CLR regulation by the cytokines IL-4 and TNF. In addition, the role of TDM-Mincle signaling in immune evasion by mycobacteria is addressed in ongoing work.

Innate immunity, macrophages, arginase, and NO synthase
PI: Prof. Dr. C. Bogdan
Nitric oxide (NO), which is synthesized from the amino acid L-arginine by the interferon (IFN)-γ inducible NO synthase (iNOS) in macrophages and other cells, is essential for the defense against intracellular pathogens and a central regulator of the immune system. The enzyme arginase can inhibit the enzymatic activity of iNOS because it competes for the same substrate. Additionally, the arginase reaction allows the synthesis of polyamines that are crucial for cellular growth and differentiation. Ongoing research work of the group focuses on the questions, by which mechanisms host cell and/or parasite arginase contribute to disease development in cutaneous leishmaniasis (*L. major, L. mexicana*) and to the lifelong persistence of *Leishmania* and thereby prevent resolution of the infection. In another project, the group analyses the interaction between iNOS/arginase and iron metabolism and the antimicrobial and immunoregulatory function of reactive chlorine intermediates.

Genetic and bacterial factors in chronic inflammation
PI: Prof. Dr. J. Mattner
Autoimmune responses and inflammatory processes in the intestine and the liver result from complex interactions of genetic, predisposing factors, and distinct environmental cues. Although the autoantigens targeted by the immune system are often ubiquitously expressed in the body, the inflammatory processes are frequently tissue-specific. In this context, the group investigates the genetic and immunological factors (e.g., CD101, Arginase 1 and 2) that govern the immune responses in the intestine and the liver. Furthermore, we analyze the role of microbial antigens in the development of autoimmune responses by applying targeted gene deletion strategies.

Pathogenicity of *Coxiella burnetii*
PI: PD Dr. A. Lührmann
The obligate intracellular bacterium *Coxiella burnetii* is causing Q fever in humans. This zoonotic disease is characterized by a flu-like illness, but can progress to an atypical pneumonia. In rare cases, this disease can become chronic, which mainly manifests itself as endocarditis. The research group aims to clarify how *C. burnetii* infection develops into chronic inflammation. To obtain insights into the pathogenicity of *C. burnetii*, we are analyzing host cell factors and bacterial virulence factors that are necessary for the establishment of the replicative *C. burnetii*-containing vacuole. Additionally, we are investigating the molecular activity of *C. burnetii* virulence factors, in particular those with anti-apoptotic activities, i.e. AnkG.

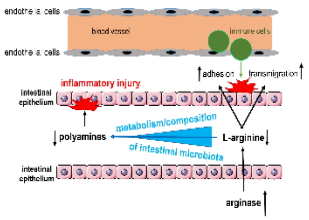

Figure: Overview over the pathological changes in the gut induced by arginase expression and subsequent L-arginine deficiency. The consumption of L-arginine by arginase lowers the diversity of the intestinal microbiota and the production of polyamines resulting in an augmented adhesion and extravasation of inflammatory immune cells and accelerated intestinal epithelial injury. (Adapted from Baier et al., JCI 2020)

Microbial phosphatases
PI: Dr. D. Soulat
Human pathogens have developed numerous strategies to invade their host cell targets. One important virulence mechanism is the secretion of proteins that interfere with host cell signaling (e.g. microbial phosphatases). Pathogen-secreted phosphatases are able to hijack the cellular immune response in a manner that leads to the creation of a pathogen-friendly environment inside the infected host. The research group currently works with two human pathogens: (a) the bacterium *Listeria monocytogenes* causing food-borne disease

and (b) the causative agent of cutaneous leishmaniasis, *Leishmania major*.

Innate lymphocytes and tumor necrosis factor in leishmaniasis
PI: PD Dr. U. Schleicher
Innate lymphocytes contribute to the immune response against Leishmania parasites. In the mouse models of cutaneous and visceral leishmaniasis, the group investigates which of the different subpopulations of the so-called innate lymphoid cells (ILC) is relevant for the defense against Leishmania and by which signals effector functions of ILC are activated and regulated. The prevalence and activation of these cells by Leishmania is also studied in the human system. Furthermore, the group is interested in understanding which protective mechanisms mediated by the cytokine tumor necrosis factor are crucially involved in the healing process of *Leishmania major* infections. Particularly, the role of non-hematopoietic cells is addressed.

Molecular biology of malaria
PI: Dr. M. Petter
Malaria pathogenesis relies on various cellular processes in the life cycle of malaria parasites that each represent promising targets for therapeutic interventions and vaccine development. These include host cell invasion, the expression of virulence factors, and the differentiation of sexual stages that are transmitted by the vector, the Anopheles mosquito. The research group is interested in understanding the molecular mechanisms governing the transcriptional control of these vital processes, focusing on the functional and mechanistic characterization of chromatin-associated proteins such as the bromodomain protein PfBDP1, which contributes to epigenetic gene regulation in malaria parasites by binding to acetylated histones.

Molecular mycology
PI: Prof. Dr. S. Krappmann
Infections with the omnipresent molds of the genus *Aspergillus* and especially with *A. fumigatus* represent a life-threatening complication for immunocompromised patients. Research efforts in this group aim at the characterization of fungal-specific virulence determinants, such as its metabolic versatility or secreted effectors that support infection of a susceptible host by A. fumigatus. Furthermore, the sexual cycle of this ascomycete and its impact on fungal secondary metabolism is investigated. Most recent research efforts in collaboration with Prof. Dr. D. Vöhringer (Division of Infection Biology) aim to elucidate the interplay of *A. fumigatus* with eosinophils, which are relevant in the context of allergic reactions to this fungus.

Innate checkpoints of T cell regulation
PI: Dr. Christian Schwartz
Innate immune cells initiate and shape adaptive immune responses to infections and inflammatory stimuli. Programmed death ligand 1 (PD-L1) is a major regulator of T cell responses – with both inhibitory and activating properties. Different innate immune cells including dendritic cells, macrophages, and type 2 innate lymphoid cells, express PD-L1 and interact with T helper cells. We are investigating the cell-specific function of this immune checkpoint molecule during type 2-biased immune responses found in adipose tissue homeostasis and helminth infections. Furthermore, we study the microbial factors that regulate PD-L1 expression on innate cells during inflammation.

Pathogenicity of Salmonella and microbiome analyses
PI: Dr. R. Gerlach
Salmonellosis is one of the most common bacterial infectious diseases worldwide and in Germany. The research group investigates molecular mechanisms underlying the pathogenicity of Salmonella enterica. In particular, bacterial secretion systems are in focus. Secretion systems play a crucial role in pathogenicity, as Salmonella uses these structures and their substrates to interact with host cells and other bacteria. Furthermore, the research group investigates the influence of host-specific environmental factors on the regulation and function of Salmonella virulence factors. Environmental signals, such as decreased oxygen, play a crucial role in host cell recognition as well as successful adaptation of bacteria to different habitats within the host. For successful colonization, Salmonella and other pathogens must also overcome the barrier function established by the host microbiota. Therefore, another focus of the research group is the analysis of the microbiota composition of humans and using animal models in health and infectious disease.

Teaching

The Institute offers lectures and teaching courses for students of Medicine, Dental Medicine, Molecular Medicine, Biology, and Pharmacy. Particularly noteworthy is the main lecture on immunology within the master degree program Molecular Medicine, the teaching modules within the elite master degree program "Integrated Immunology" and the teaching of the interdisciplinary subject "Infectious Diseases and Immunology" within the clinical part of the training of medical students. In cooperation with the Institute of Clinical and Molecular Virology, our Institute organizes continuous medical education lectures on various infectious diseases for local physicians.
We supervise Bachelor's and Master's theses as well as MD and doctoral theses.

Selected publications
Hayek I, Fischer F, Schulze-Lührmann J, Dettmer K, Sobotta K, Schatz V, Kohl L, Boden K, Lang R, Oefner PJ, Wirtz S, Jantsch J, Lührmann A. (2019) Limitation of TCA-cycle intermediates represents an oxygen-independent nutritional antibacterial effector mechanism of macrophages. Cell Reports 26: 3502-3510.

Saunders SP, Floudas A, Moran T, Byrne CM, Rooney MD, Fahy CMR, Geoghegan JA, Iwakura Y, Fallon PG, Schwartz C. Dysregulated skin barrier function in Tmem79 mutant mice promotes IL-17A-dependent spontaneous skin and lung inflammation. Allergy. 2020 Jul 9;75(12): 3216-3227.

Paduch K, Debus A, Rai B, Schleicher U*, and Bogdan C*. (2019). Resolution of Cutaneous Leishmaniasis and Persistence of Leishmania major in the Absence of Arginase 1. J Immunol 202(5):1453-1464

Binder J, Shadkchan Y, Osherov N, Krappmann S. The essential thioredoxin reductase of the human pathogenic mould Aspergillus fumigatus is a promising antifungal target. Front Microbiol 2020, 11: 1383

Tang J., Chisholm S.A., Yeoh L.M., Gilson P.R., Papenfuss A.T., Day K.P., Petter M. and Duffy M.F. 2020. Histone modifications associated with gene expression and genome accessibility are dynamically enriched at Plasmodium falciparum regulatory sequences. Epigenetics Chromatin. 13. 1: 50

Schick, J., J. Schafer, C. Alexander, S. Dichtl, P. J. Murray, D. Christensen, U. Sorg, K. Pfeffer, U. Schleicher, and R. Lang. 2020. Cutting Edge: TNF Is Essential for Mycobacteria-Induced MINCLE Expression, Macrophage Activation, and Th17 Adjuvanticity. Journal of immunology 205: 323-328

International cooperations
Dr. R. Ostuni, San Raffaele Telethon Institute for Gene Therapy, Milano: Italy

Paul A. Beare (Coxiella Pathogenesis Section, Rocky Mountain Laboratories, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Hamilton, Montana, USA

Prof. N. Osherov, Sackler School of Medicine, Tel-Aviv University: Israel

Prof. G. Weiss, University of Innsbruck, Innsbruck: Austria

Prof. Dr. L. Wicker, University of Oxford – Medical Sciences Division, UK

Dr. G. Superti-Furga, Research Center for Molecular Medicine or the Austrian Academy of Science, Vienna, Austria.

Prof. P. Fallon, Trinity Biomedical Sciences Institute, School of Medicine, Trinity College Dublin, Dublin, Ireland

Dr. M. Duffy, University of Melbourne

Prof. P. Andersen, Statens Serum Institut, Copenhagen, Denmark