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 and adaptive lymphoid cells in leishmaniasis
- Molecular biology of malaria
- Molecular mycology

Structure of the Chair

Professorships: 4
Personnel: 92
- Doctors (of Medicine): 10
- Scientists: 9 (thereof funded externally: 1)
- Graduate students: 22

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 Coxiella, Listeria, Mycobacteria, Leishmania, Plasmodia and Aspergillus. The Institute is fully equipped with laboratories, hypoxia chambers for *in vitro* and *in vivo* analyses, fluorescence and confocal laser scanning microscopes, real-time PCR machines, analytical fluorescence activated cell sorters (FACS) for flow cytometry, and imaging systems.

Regulation of innate immunity in infection and inflammation

PI: Prof. Dr. R. Lang

Our research aims at elucidating how the immune system generates resistance to infection without causing excessive inflammation. The group discovered that the cord factor, a mycobacterial cell wall glycolipid, is a ligand of the C-type lectin receptor Mincle. We have characterized the activation of macrophages and the induction of Th1/Th17 responses by Mincle. In ongoing work, we are addressing macrophage reprogramming by the cord factor as a mycobacterial evasion strategy. In a second research project, we focus on the functional analysis of the "dual-specificity phosphatases" (DUSP), which inhibit signal transmissions of receptors for pathogen recognition as well as cytokines. A third project aims at identifying the immunological factors involved in the chronification during *Coxiella burnetii* infection *in vivo*.

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 both enzymes use the same substrate. In tumor necrosis factor (TNF)-deficient mice, an overexpression of host cell arginase 1 can be observed correlating with a reduced ability to control the NO-sensitive parasite *Leishmania (L.) major*. The group aims to elucidate the molecular mechanisms by which TNF prevents an upregulation of host cell arginase 1. Furthermore, the group investigates whether the host or parasite arginase are critical for the resolution of cutaneous leishmaniasis and for the lifelong survival of Leishmania *in vivo*. In another project, the group analyses the interaction between iNOS/NO and iron metabolism and the antimicrobial and immunoregulatory function of reactive chlorine intermediates. Finally, the group studies the interaction between iNOS/NO and the iron metabolism.

Genetic and bacterial factors in chronic inflammation

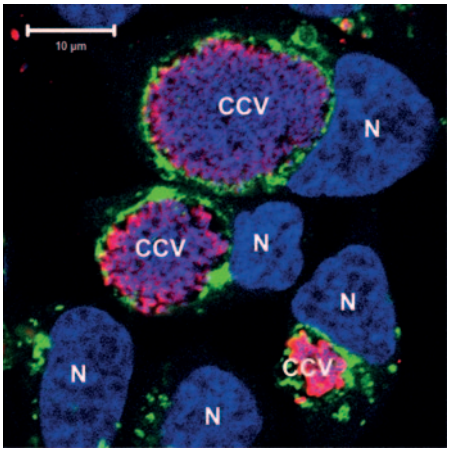
PI: Prof. Dr. J. Mattner

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 (i.e. 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 mechanisms of action of *C. burnetii* virulence factors, in particular those with anti-apoptotic activities, i.e. AnkG.



HeLa229 cells, infected with Coxiella burnetii for 60 h The nucleus (N) was stained with DAPI (blue), C. burnetii with specific antibodies (red) and the lysosomal membrane protein LAMP-1 with an anti-LAMP-1 antibody. C. burnetii can replicate to high numbers in the LAMP-1 positive C. burnetii-containing vacuole (CCV), which can reach the size of the nucleus.

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 lymphoid cells in leishmaniasis

PI: PD Dr. U. Schleicher

Both innate and adaptive 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. In another project, the group analyzes how B cells regulate the immune response in visceral leishmaniasis and affect the course of infection.

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 which 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.

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 newly established teaching modules within the elite master degree program Integrated Immunology (which started in the winter term 2018/2019) 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 PhD theses.

Selected publications

Mattner J, Wirtz S. Friend or Foe? The Ambiguous Role of Innate Lymphoid Cells in Cancer Development. Trends Immunol. 2017 Jan;38(1): 29-38

Friedrich A, Pechstein J, Berens C, Lührmann A. Modulation of host cell apoptotic pathways by intracellular pathogens. Curr Opin Microbiol 2017, 35: 88-99

Ostrop J, Lang R. Contact, Collaboration, and Conflict: Signal Integration of Syk-Coupled C-Type Lectin Receptors. J Immunol 2017, 198: 14035

Leitherer S, Clos J, Liebler-Tenorio EM, Schleicher U, Bogdan C, Soulat D. Characterization of the Protein Tyrosine Phosphatase LmPRL-1 Secreted by Leishmania major via the Exosome Pathway. Infect Immun. 2017, Jul 19;85(8): pii: e00084-17

Messlinger H, Sebald H, Heger L, Dudziak D, Bogdan C, Schleicher U. Monocyte-Derived Signals Activate Human Natural Killer Cells in Response to Leishmania Parasites. Front Immunol 2018, 9: 24

Yu Y, Blachowicz A, Will C, Szewczyk E, Glenn S, Gensberger-Reigl S, Nowrousian M, Wang CCC, Krappmann S. Mating-type factor-specific regulation of the fumagillin/pseurotin secondary metabolite supercluster in Aspergillus fumigatus. Mol Microbiol 2018, 10: 1045-1065

International cooperations

Prof. R. Ostuni, San Raffaele Telethon Institute for Gene Therapy, Milano: Italy

Prof. M. Trost, Faculty of Medical Sciences, Newcastle University, Newcastle: UK

Prof. C. C.C. Wang, Department of Pharmacology and Pharmaceutical Sciences, University of Southern California, Los Angeles, CA: USA

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

Prof. L. Wicker, University of Cambridge, Cambridge: UK