Institute of Clinical Microbiology, Immunology, and Hygiene

Division of Infection Biology

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Research focus

- Immune response against helminths and allergens
- Role of dendritic cells for maintenance of immunological tolerance
- Identification of STAT6-regulated genes and proteins in B cells
- Regulation of protective immunity against helminths by STAT6 in gastrointestinal epithelial cells

Structure of the Division

Professorship: 1
Personnel: 13

- Scientists: 2 (thereof funded externally: 2)
- Graduate students: 9

Research

The research focus at the Division of Infection Biology aims at characterizing the immune responses against helminths and viruses. In addition, the regulation of immunological tolerance against self-antigens and resolution of inflammation are investigated. We use a variety of infection models and genetically modified mouse strains to dissect the mechanisms that regulate protective immunity and tolerance.

Immune response against helminths and allergens

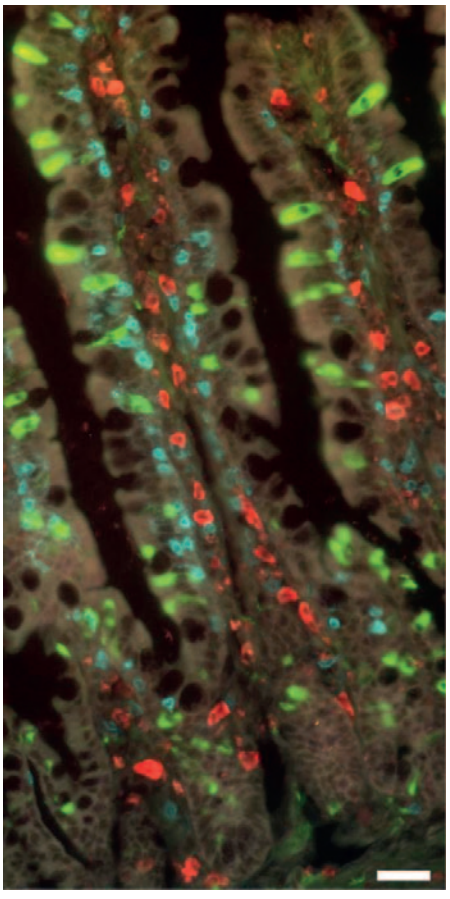
Main focus of the research activities is the characterization of type 2 immune responses which are elicited by parasitic worms (helminths) and allergens. In both situations, the immune system reacts with an increase in Th2 cells, mast cells, eosinophils, basophils, and production of IgE. Infection of genetically modified mice with helminths can be used as a model to study the complex interaction between different cell types that orchestrate and execute type 2 immune responses. Work at the Division of Infection Biology could demonstrate that release of IL-4/IL-13 from basophils plays an important role for protective immunity against different gastrointestinal helminths. These results are based on studies with mixed bone marrow chimeras. We observed that basophils play an important role for protective immunity against helminths especially during secondary infections. Basophils can be efficiently activated by Fc receptors to which helminths-specific antibodies bind. These helminths-specific antibodies are probably generated by long-lived plasma cells that were induced by the primary infection and constitute the immunological memory function. It further became apparent that basophils are essential for chronic allergic inflammation of the skin. This pathologic condition can be induced by passively sensitizing basophils with haptenspecific IgE, followed by antigen-mediated IgE crosslinking. As shown by others before, mast cells are not required for this inflammatory response. The mechanisms that regulate protective and pathological functions of basophils are subject of our current investigations.

Role of dendritic cells for maintenance of immunological tolerance

Dendritic cells (DC) play an important role as antigen-presenting cells for activation of naive T cells. They can further promote immunological tolerance by deletion of autoreactive T cells from the thymus or by inhibiting the activation of peripheral T cells. We generated mice that constitutively lack DC and noticed that these mice develop spontaneous systemic autoimmune inflammation. The pathology is characterized by increased levels of activated T cells, high serum immunoglobulin levels, formation of autoantibodies, weight loss, and infiltration of leukocytes into various tissues. Using this model, we studied whether regulatory T cells are affected by the absence of DC, whether autoantibodies are causative for the disease, and whether impaired negative selection of autoreactive T cells could account for the loss of immunological tolerance in these mice.

Identification of STAT6-regulated genes and proteins in B cells

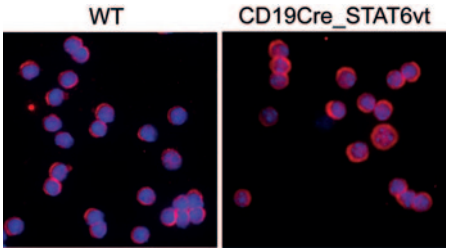
We recently demonstrated that the transcription factor STAT6 in B cells plays an important role for the germinal center reaction. Following up on this result we performed comparative transcriptome and proteome analysis of wild-type and STAT6-deficient B cells. We observed that more than 200 mRNAs were up-regulated more than 3-fold in a STAT6-dependent manner, and 149 mRNAs were more than 3-fold down-regulated. In collaboration with Prof. Dr. B. Warscheid (University of Freiburg) we demonstrated that expression of most of the STAT6-dependent proteins is regulated at the transcriptional level. We currently work on the functional characterization of some of the genes identified in this screening.
In addition, we generated transgenic mice that express a constitutively active form of STAT6 in B cells. We currently characterize these CD19Cre_STAT6vt mice to gain a better understanding of the function of STAT6 in B cells. B cells of CD19Cre_STAT6vt mice express more CD23 (low-affinity IgE receptor) on the cell surface and a higher frequency of germinal center B cells expresses IgG1. These mice will now be analyzed after infection with Lymphocytic Choriomeningitis Virus (LCMV) to determine whether constitutively active STAT6 can promote class switch recombination to IgG1 and IgE in this viral infection model.



Histological staining from the small intestine of a N. brasiliensis-infected mouse to detect tuft cells (green), ILC2s (red), and CD4 T cells (blue)

Regulation of protective immunity against helminths by STAT6 in gastrointestinal epithelial cells

The role of intestinal epithelial cells for expulsion of helminths is poorly understood. Infection of mice with the gastrointestinal helminth Nippostrongylus brasiliensis results in a STAT6-dependent increase of goblet cells, tuft cells, and Paneth cells in the small intestine. To investigate whether expression of activated STAT6 in intestinal epithelial cells is sufficient for protective immunity against helminths, we generated Villini-Cre_STAT6vt mice that express constitutively active STAT6 in intestinal epithelial cells. These mice show a very efficient immune response even in the absence of T cells. Based on these results we will identify and characterize STAT6-regulated genes in intestinal epithelial cells.



Detection of STAT6 in the nucleus of B cells from CD19Cre_STAT6vt mice
B cells from the spleen of wild-type (WT) and CD19Cre_STAT6vt mice were stained with anti-STAT6 antibodies (red) and DAPI (blue). The pictures demonstrate that STAT6 is more abundant in the nucleus (blue) of CD19Cre_STAT6vt as compared to control mice.

Teaching

The Division of Infection Biology offers lectures, seminars, and teaching courses for students of Medicine and Molecular Medicine as well as various teaching modules of the Faculty of Sciences.
Bachelor's and Master's theses are supervised as well as PhD theses.

Selected publications

Lehmann B, Biburger M, Brückner C, Ipsen-Escobedo A, Gordan A, Lehmann C, Voehringer D, Winkler T, Schaft N, Dudziak D, Sirbu H, Weber GF, Nimmerjahn F. Tumor location determines tissue-specific recruitment of tumor-associated macrophages and antibody-dependent immunotherapy response. Sci Immunol 2017, Jan 6;2(7). pii: eaah6413

Symowski C, Voehringer D. Interactions between Innate Lymphoid Cells and Cells of the Innate and Adaptive Immune System. Front. Immunol. 2017, 8:1422

Mokada-Gopal L, Boeser A, Lehmann CHK, Drepper F, Dudziak D, Warscheid B, Voehringer D. Identification of novel STAT6-regulated proteins in mouse B cells by comparative transcriptome and proteome analysis. J Immunol 2017, 198:3737-3745

Uderhardt S et al. Enzymatic lipid oxidation by eosinophils propagates coagulation, hemostasis and thrombotic disease. J Exp Med. 2017, 214:2121-2138

Reitz M, Brunn ML, Rodewald HR, Feyerabend TB, Roers A, Dudeck A, Voehringer D, Jönsson F, Kühl AA, Breloer M. Mucosal mast cells are indispensable for the timely termination of Strongyloides ratti infection. Mucosal Immunol. 2017 Mar;10(2):481-492

Willebrand R, Dietschmann A, Nitschke L, Krappmann S, Voehringer D. Murine eosinophil development and allergic lung eosinophilia are largely dependent on the signaling adaptor GRB2. Eur J Immunol. 2018, 48:1786-1795

International cooperations

Dr. J.S. Silvestre, Paris Cardiovascular Research Center, INSERM UMR-S 970, Paris: France

Prof. Dr. D. Finke, University of Basel, Basel: Switzerland

Dr. J. Kitaura, The University of Tokyo, Tokyo: Japan

Dr. S. Bedoui, The University of Melbourne at the Peter Doherty Institute for Infection and Immunity, Melbourne: Australia