UNIVERSITY HOSPITAL

Department of Medicine 1 – Gastroenterology, Pneumology and Endocrinology

Chair of Internal Medicine I

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Forschungsschwerpunkte

- Intestinal diseases
- Experimental hepatology
- Epithelial cytoskeleton dynamics in the gut
- Therapeutic targets for treatment of IBD and colorectal cancer
- Division of clinical and experimental pulmonology
- Molecular gastroenterology
- Molecular hepatology and GI-oncology
- Patient-oriented research and innovative therapeutic strategies in IBD
- Cell trafficking and T cells in IBD
- Cytokines and transcription factors in IBD and CAC
- Clinical and experimental nutritional and sports medicine – Hector-Center

Structure of the Department

Professorships: 10
Personnel: 478

- Doctors (of Medicine): 69
- Scientists: 23
  (thereof funded externally: 14)
- Graduate students: 61

Clinical focus areas

- Gastroenterology
- Pneumology
- Endocrinology and diabetology
- Hepatology
- Nutritional medicine
- Intensive care
- Emergency reception

Research

The research focus of the Medical Clinic 1 is a better understanding of the physiology and pathophysiology of the gut, liver and lung. In particular, we are investigating how cells and their functions contribute to the development of diseases such as inflammation and cancer, and which molecular targets may be suitable for therapeutic intervention. In addition to established immunological, molecular biological and cell biological techniques, innovative and interdisciplinary detection methods are being developed.

Intestinal diseases
PI: PD Dr. Dr. C. Neufert, Prof. Dr. M. Waldner
Our research focus is on the pathogenesis of intestinal inflammation and colorectal cancer. Herein, we evaluate molecular mechanisms promoting disease development. Current investigations address the role of the intestinal immune system and its interaction with other gut cell populations. Through an increasing knowledge about these processes, our studies could help to improve the therapeutic options for patients suffering from intestinal inflammation and colorectal cancer.

Experimental hepatology
PI: PD Dr. Wirtz, Prof. Dr. C. Günther, PD Dr. A. Kremer
We work on pathophysiological processes that drive the initiation and progression of acute and chronic liver disorders and their attendant symptoms such as pruritus and fatigue. We are particularly interested in novel signal transduction pathways that trigger the occurrence of massive hepatocyte death, which is a common feature of acute hepatic inflammation and toxin-dependent liver injury. In this context, we could demonstrate that besides apoptotic cell death, programmed necrosis substantially contributes to hepatocellular death during liver inflammation. Therefore, we currently evaluate in preclinical studies and patient cohorts how regulated necrosis contributes to gradual accumulation of extracellular matrix components and hepatic tissue remodeling.

Epithelial cytoskeleton dynamics in the gut
PI: Dr. R. Lopez-Posadas
This group aims at the description of cytoskeleton-dependent molecular mechanisms regulating epithelial integrity in the gut. This knowledge might be exploited in order to develop innovative diagnostic and therapy strategies for the benefit of IBD and CRC patients, and contribute to current efforts in the context of epithelial restitution for the clinical management of chronic intestinal diseases.

Therapeutic targets for treatment of IBD and colorectal cancer
PI: PD Dr. I. Atreya
We intend to achieve improved insights into the imunopathogenesis of inflammatory bowel diseases (IBD) and the antitumor immune response in colorectal cancer. In this context, we in particular focus on T lymphocytes and innate lymphoid cells in the peripheral blood, inflamed intestinal mucosa or tumor tissue and their capacity to interact locally with epithelial cells, different types of mucosal immune cells or other tissue-resident cells. Supported by innovative experimental settings, we are able to perform detailed functional analyses and advanced imaging of primary human immune cells derived from the peripheral blood or tissue biopsies of affected patients. Overall, our investigations aim on the identification of new therapeutic target structures for an improved treatment of IBD and colorectal cancer.

Division of clinical and experimental pulmonology
PI: Dr. F. Fuchs, Prof. Dr. K. Hildner
The lung tissue bank established and located at our Department allows us to study the immunological micromilieu of the lung in greater detail. For example, the presence and functionality of innate immune cell subpopulations in the broncho-alveolar lavage is assessed in current research projects. Our clinical research unit currently focusses on the state-wide establishment of the infrastructure for a research data network to study lung cancer within the Bavarian cancer research centre (BZKF). Clinical studies within this network are under way.

Molecular gastroenterology
PI: Prof. Dr. C. Becker
The research group focuses on immunological and molecular mechanisms in the development of gastrointestinal infections, inflammation and cancer. During the reporting period, several studies were performed on the role of cell death in the development and resolution of intestinal inflammation and colon cancer. It has been shown that necroptosis in the intestinal epithelium plays a crucial role in the development of intestinal inflammation and that necroptosis can be regulated by the immune system. Important goals in the research of necroptosis were not only the elucidation of cellular signaling pathways and the study of the significance of necroptosis in various diseases, but also the development of specific detection methods for necroptosis and for the differentiation of necroptosis from other forms of cell death.

Molecular hepatology and GI-oncology
PI: PD Dr. Dr. P. Dieterich
The group addresses molecular mechanisms of acquired therapy resistance in hepatocellular carcinoma (HCC). HCC mostly develops in cirrhotic livers. During the reporting period, the group also investigated underlying molecular mechanisms of liver metastasis of gastrointestinal (GI) tumors such as colon cancer. Liver metastasis majorly contribute to the poor prognosis of GI-cancers. The group focused on small RNA molecules that strongly affect main cancer- and therapy resistance-associated signaling pathways like the RAS-RAF-ERK-pathway. Moreover, the group revealed novel cellular cross-talk mechanisms mediated by neuropeptide-signaling in GI-cancer types that affect the tumor microenvironment and important neuro-immunologic interactions driving cancer progression and metastasis.

Patient-oriented research and innovative therapeutic strategies in IBD
PI: Prof. Dr. R. Atreya
This group aims at characterizing the molecular mechanism of action of anti-inflammatory therapies in IBD and the identification of biomarkers for the prediction of therapeutic response. The translational identification and characterization of immunological resistance mechanisms against biologics is another research

focus of the group. The clinical application of molecular endoscopy for the individual prediction of therapeutic response in IBD represents another field of our group.

Cell trafficking and T cells in IBD

PI: Dr. S. Zundler

The main interest of this group is to understand processes of cell trafficking in intestinal immunology with special focus to IBD and related translational applications. Moreover, the team examines the impact of cell trafficking originating from the gut for inter-organ communication, e.g. with the joints or the brain and explores the modulation of the intestinal microbiome by chemotactic peptides. During the reporting period, the researchers characterized the role of α4β7 integrin-mediated gut homing of monocyte subpopulations for intestinal wound healing, which is clinically relevant in the context of therapeutic integrin blockade in IBD. Another focus was the analysis of cell type-specific dose response profiles of anti-integrin antibodies, which could serve as the basis for optimized treatment protocols.

Cytokines and transcription factors in IBD and CAC

PI: PDDr. Dr. B. Weigmann

The main research areas of the working group are T-cell-specific transcription factors and the associated cytokines. Transcription factors of the NFAT family in particular are important modulators of Th2 cells and are closely related to ulcerative colitis (UC). They are the subject of studies with intestinal inflammation models. Another focus of the working group is the cytokine interleukin-9, which was identified a few years ago in connection with UC and which is produced by Th9 cells. IL-9 is being investigated as a mediator for CAC (colitis-associated colon carcinoma) in the working group. Furthermore, the fabrication of stimuli sensitive, bio-functionalized PLGA nanocarriers incorporating surface attached bio-molecules for more specific targeting of inflamed colon tissue through active/passive mechanisms is the aim of another research area of the working group. Finally, the effect of cyclosporine A, which is used in UC, is the focus of current studies. Our data indicate that by specifically switching off the Tec-Kinase, Itk, the activation of T cells can be prevented and thus the resolution of the inflammatory reaction in the intestine can be induced.

Clinical and experimental nutritional and sports medicine – Hector-Center

PI: Prof. Dr. Y. Zopf

The working group examines the influence of nutrition and sports on body composition, performance, muscular metabolism, and the molecular mechanisms of inflammation in oncological and obese patients. We could show that even patients with advanced cancer profit from a high-protein nutrition and sports. In our experimental model, we demonstrated that myokines activate muscular metabolism, reduce the proliferation of tumor cells and induce their cell death. We could further show that our innovative sports and nutritional interventions reduce the systemic inflammation in obese patients, increase the physical performance, and improve the metabolic risk profile. In the field of food intolerance, we examine the influence of food on mucosal integrity. We focus on the detection of molecular pathomechanisms of mucosal inflammation and on the effects of anti-inflammatory food.

Teaching

The Department of Medicine 1 is involved in the curricular teaching of human medicine with compulsory and elective courses. Particularly noteworthy is the interdisciplinary teaching within the cross section lectures together with the Departments of Medicine 2 and 5 as well as the Institutes of Clinical Microbiology, Immunology, and Hygiene and of Clinical and Molecular Virology, respectively. The Department of Medicine 1 offers a student ultrasound training with exclusive devices for this propose. MD and PhD doctorates are supervised.

Selected publications

Kreiß L, Thoma O, Dilipkumar A, Carlé B, Longequeue P, Kunert T, Rath T, Hildner K, Neufert C, Vieth M, Neurath MF, Friedrich O, Schürmann S, Waldner MJ. Label-Free In Vivo Histopathology of Experimental Colitis via 3-Channel Multiphoton Endomicroscopy. Gastroenterology. 2020 Sep;159(3):832-834.

Heichler C, Scheibe K, Schmied A, Geppert A, Schmid B, Wirtz S, Thoma O, Kramer V, Waldner MJ, Büttner C, Farin HF, Pešić M, Knieling F, Merkel S, Grüneboom A, Gunzer M, Grützmann R, Rose-John S, Koralov SB, Kollias G, Vieth M, Hartmann A, Greten FR, Neurath MF, Neufert C. STAT3 activation through IL-6/IL-11 in cancer-associated fibroblasts promotes colorectal tumour development and correlates with poor prognosis. Gut. 2020 Jul;69(7):1269-1282.

Schleier L, Wiendl M, Heidbreder K, Binder M, Atreya R, Rath T, Becker E, Schulz-Kuhnt A, Stahl A, Schulze L, Ullrich K, Merz SF, Bornemann L, Gunzer M, Watson AJM, Neufert C, Atreya I, Neurath MF, Zundler S. Non-classical monocyte homing to the gut via α4β7 integrin mediates macrophage-dependent intestinal wound healing. Gut. 2020 Feb;69(2):252-263.

Zundler S, Becker E, Spocinska M, Slawik M, Parga-Vidal L, Stark R, Wiendl M, Atreya R, Rath T, Leppkes M, Hildner K, López-Posadas R, Lukassen S, Ekici AB, Neufert C, Atreya I, van Gisbergen KPJM, Neurath MF. Hobit- and Blimp-1-driven CD4 + tissue-resident memory T cells control chronic intestinal inflammation. Nat Immunol. 2019 Mar;20(3):288-300.

Schmitt H, Billmeier U, Dieterich W, Rath T, Sonnewald S, Reid S, Hirschmann S, Hildner K, Waldner MJ, Mudter J, Hartmann A, Grützmann R, Neufert C, Münster T, Neurath MF, Atreya R. Expansion of IL-23 receptor bearing TNFR2+ T cells is associated with molecular resistance to anti-TNF therapy in Crohn's disease. Gut. 2019 May;68(5):814-828.

Günther C, Ruder B, Stolzer I, Dorner H, He GW, Chiriac MT, Aden K, Strigli A, Bittel M, Zeissig S, Rosenstiel P, Atreya R, Neurath MF, Wirtz S, Becker C. Interferon Lambda Promotes Paneth Cell Death Via STAT1 Signaling in Mice and Is Increased in Inflamed Ileal Tissues of Patients With Crohn's Disease. Gastroenterology. 2019 Nov;157(5):1310-1322.e13.

International cooperations

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