Department of Medicine 1 – Gastroenterology, Pneumology, and Endocrinology

Chair of Internal Medicine I

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Research focus
- Intestinal diseases
- Experimental hepatology
- Therapeutic targets for treatment of IBD
- Division of clinical and experimental pulmonology
- Molecular gastroenterology
- Molecular hepatology and GI-oncology
- Molecular neuro-gastroenterology
- Patient-oriented research and innovative therapeutic strategies in IBD
- Cell trafficking and T cells in IBD
- Cytokines and transcription factors in IBD and carcinoma

Structure of the Department

Professorships: 9
Personnel: 329
- Doctors (of Medicine): 66
- Scientists: 19 (thereof funded externally: 13)
- Graduate students: 61

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

Research

The Department of Medicine 1 focuses on studying the functions and interactions of genes and proteins that are associated with the pathogenesis of gut, lung, and liver diseases. Beside the well established immunological, molecular biological and cell biological techniques, also innovative and interdisciplinary detection methods are developed.

In July 2018 the DFG funded SFB/Transregio 241 (TRR 241) "Immune-Epithelial Communication in Inflammatory Bowel Diseases" started (compare own report).

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. S. Wirtz, PD 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 the interferon-dependent induction of hepatocellular necrosis contributes to gradual accumulation of extracellular matrix components and hepatic tissue remodeling.

Therapeutic targets for treatment of IBD

PI: Dr. I. Atreya, Dr. R. Lopez-Posadas
We try to achieve improved insights into the immunopathogenesis of chronic inflammatory diseases of the intestine (IBD) or lung. In this context, we in particular focus on T lymphocytes and innate lymphoid cells and their capacity to accumulate in inflammatory tissue sites and interact locally with epithelial cells or other tissue-resident cell types. 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 intend to identify new therapeutic target structures for an improved treatment of inflammatory diseases.

Division of clinical and experimental pulmonology

PI: PD Dr. F. Fuchs, Prof. Dr. K. Hildner
Our clinical research unit attempts to test innovative imaging technologies during clinical routine. Our experimental research attempts focus on the role and function of immune cell subpopulations in the pathogenesis of pulmonary diseases. The lung biobank established and located at our Department allows us to study the immunological micromilieu of the lung in great detail. For example, the presence and functionality of innate immune cell subpopulations in the broncho-alveolar lavage is assessed in current research projects.

Molecular gastroenterology

PI: Prof. Dr. C. Becker
This group focuses on the immunological and molecular mechanisms that lead to the development of infection, IBD, and cancer within the gut. During the reporting period, the working group carried out various studies on the role of cell death in the development and resolution of inflammation and colon cancer. The researchers were able to show that necroptosis can play an important role for the therapy of colorectal cancer. Important objectives in the research of necroptosis were not only the elucidation of the cellular signaling pathways and the investigation of the importance of necroptosis in various diseases, but also the development of specific and simple detection methods for necroptosis and for the delineation of necroptosis from other forms of cell death.

Molecular hepatology and GI-oncology

PI: Dr. Dr. P. Dietrich
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 mi-

croenvironment and important neuro-immunologic interactions driving cancer progression and metastasis.

Molecular neuro-gastroenterology

PI: PD Dr. M. Engel

The main focus of this group is the elucidation of novel neuro-immunological mechanisms in the pathogenesis of IBD. Several studies about the role of neuropeptides and TRP-channels in colonic inflammation were conducted during the reporting period. We could show that ongoing activation and consecutive desensitization of nociceptive and peptidergic neurons expressing TRP channels led to anti-inflammatory and hypolagesic effects not only in the intestine, but rather in the whole organism of the mouse. In addition to their ability to release immuno-regulatory neuropeptides from peptidergic neurons, TRP channels are also functionally expressed in non-neuronal cells. For the first time we discovered the functional role of TRPM8 in several populations of murine macrophages. TRPM8 in macrophages was essential for anti-inflammatory action in the context of DSS colitis, which was mediated through a balance shift of pro- and anti-inflammatory cytokine expression.

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. During the reporting period, the researchers characterized the role of so-called tissue-resident memory T cells in chronic colitis. They were able to demonstrate a key role of these cells in the orchestration of intestinal inflammation in pre-clinical models and human patient samples. Moreover, the group explored the importance of different gut homing pathways for several immune cell populations. The superordinate objective of these investigations was to generate new insights for the optimization of existent and the development of novel therapeutic approaches in IBD.

Cytokines and transcription factors in IBD and carcinoma

PI: PD Dr. B. Weigmann

The research focus of the work group are specific proteins, so-called transcription factors and immunologically important cytokines, which are produced by T cells. The NFAT transcription factors are important for the activation of Th2 cells and have been previously associated with ulcerative colitis (UC). Another focus of the work group is interleukin-9, which was identified in association with UC and is produced by a specific T-cell population, Th9 cells. The regulation of GATA-3 by the use of blocking antisense Oligonukteotide, so-called DNAzyme, could serve as a basis for a new effective therapy concept for UC. Furthermore, the effect of cyclosporin A (CsA), which is used in UC, is the subject of current studies. Here, the mechanism of action should be elucidated because CsA cannot be used in Crohn's disease and is only effective in acute UC.

Teaching

The Department of Medicine 1 is involved in the curricular teaching of human and dental 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

He GW, Günther C, Kremer AE, Thonn V, Amann K, Poremba C, Neurath MF, Wirtz S, Becker C. PGAM5-mediated programmed necrosis of hepatocytes drives acute liver injury. Gut. 2017 Apr;66(4):716-723

Zundler S, Schillinger D, Fischer A, Atreya R, López-Posadas R, Watson A, Neufert C, Atreya I, Neurath MF. Blockade of αEβ7 integrin suppresses accumulation of CD8+ and Th9 lymphocytes from patients with IBD in the inflamed gut in vivo. Gut. 2017 Nov;66(11):1936-1948

Pavel ME et al. Health-related quality of life for everolimus versus placebo in patients with advanced, non-functional, well-differentiated gastrointestinal or lung neuroendocrine tumours (RADIANT-4): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 18.10 (2017): 1411-1422

Knieling F, Gonzales Menezes J, Claussen J, Schwarz M, Neufert C, Fahlbusch FB, Rath T, Thoma OM, Kramer V, Menchicchi B, Kersten C, Scheibe K, Schürmann S, Carlé B, Rascher W, Neurath MF, Ntziachristos V, Waldner MJ. Raster-Scanning Optoacoustic Mesoscopy for Gastrointestinal Imaging at High Resolution. Gastroenterology 154.4 (2018): 807-809

Dietrich P, Koch A, Fritz V, Hartmann A, Bosserhoff AK, Hellerbrand C. Wild type Kirsten rat sarcoma is a novel microRNA-622-regulated therapeutic target for hepatocellular carcinoma and contributes to sorafenib resistance. Gut 67.7 (2018): 1328-1341

Atreya R, Neurath MF. Mechanisms of molecular resistance and predictors of response to biological therapy in inflammatory bowel disease. Lancet Gastroenterol Hepatol. 2018 Nov;3(11):790-802

International cooperations

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