UNIVERSITY HOSPITAL

Department of Surgery

Chair of Surgery

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Research focus
- Evaluation of prognosis of gastrointestinal tumors
- Randomized trials for gastrointestinal tumors
- Outcomes research of complex surgery with hospital discharge data
- Pathophysiologic role of vascular effects of IFN-γ in gastrointestinal diseases
- Tumor-micromilieu induced plasticity of tumor endothelial cells in colorectal carcinoma
- Genome editing of pancreatic tumor models
- Organoid models in pancreatic cancer
- Immunepathophysiology of acute (sepsis) and chronic (colitis) inflammation
- Immunephenotyping and liquid biopsy analysis of gastrointestinal tumors

Structure of the Chair

Professorships: 4
Personnel: 308
- Doctors (of Medicine): 38
- Scientists: 10 (thereof funded externally: 6)
- Graduate students: 44

Clinical focus areas
- Oncological surgery
- Surgery of the gastrointestinal tract
- Metabolic and bariatric surgery
- Endocrinological surgery
- Minimally invasive surgery
- Transplantation
- Outpatient surgery
- Surgical emergency

Research

Clinical research at the Department of Surgery mainly consists of the clinical cancer registry, randomized trials of gastrointestinal tumors and evaluation of nationwide hospital discharge data. The translational research is focused on colorectal cancers/inflammatory bowel diseases and pancreatic cancer. Groups of investigators focusing on tumor micromilieu and sepsis are connecting the main research topics.

Evaluation of prognosis of gastrointestinal tumors
PI: Prof. Dr. R. Grützmann, Prof. Dr. S. Merkel
Since 1978, a clinical cancer registry has been prospectively maintained for organ specific tumor documentation. At present, more than 30,000 patients are registered. Main foci are on colorectal cancer with over 13,000 and pancreatic cancer with over 2,700 documented cases. Patients are followed for life with only 1% of patients lost to follow-up. The scientific evaluation of this data focuses on health services research, quality management, the improvement of tumor classification, the identification of prognostic factors, the definition of quality indicators, and quality of life research. The documentation of specific diagnostics and multimodal treatment strategies results from an interdisciplinary cooperation of numerous departments and institutes at the Faculty of Medicine.

Randomized trials for gastrointestinal tumors
PI: Prof. Dr. R. Grützmann, Dr. H. Golcher
The Department of Surgery respectively the interdisciplinary Colorectal Cancer Center/ Modul Pancreas Cancer took part in different multicenter trials about gastrointestinal tumors, inter alia " Pancreatoduodenectomy with or without pro- phylactic Ligamentum teres hepatis wrap around the gastroduodenal artery stump for prevention of pancreatectomy hemorrhage" or "International Prospective Observational Cohort Study for Optimal Bowel Resection Extent and Central Radicality for Colon Cancer (T-REX)". The "Prospective trial for comparison of hepaticojejunostomy as interrupted versus continuous suture" was initiated the department of surgery. Patients were screened during the interdisciplinary tumor board for gastrointestinal tumors, assigned to the studies and further attended. The surgical second opinion ("panel of surgeons") for the CONKO-007-trial (patients with non resectable pancreatic carcinoma) is organized by the study team, too, and evaluation takes place in the daily tumor conference.

Outcomes research of complex surgery with hospital discharge data
PI: PD Dr. C. Krautz
A variety of surgical procedures in general surgery are associated with varying perioperative outcomes due to their complexity. Analyses of nationwide hospital discharge data provide the possibility to examine the underlying causes. Currently, we are assessing the effects of volume-based referral on perioperative outcomes in complex surgery in order to give recommendations for the future hospital market structure in Germany.

The interferon-γ pathway in the immune evasion of colorectal cancer
PI: PD Dr. N. Britzen-Laurent, Prof. Dr. Dr. M. Stürzl
Interferon-γ (IFN-γ) is a pleiotropic cytokine, which plays an important role in the immunosurveillance of colorectal cancer (CRC). Here we investigated the impact of IFN-γ-resistance in tumor cell lines on tumor progression. Colon tumorigenesis increased in mice with an inactivated IFN-γ pathway in intestinal cells. In human CRC, a decreased expression of the IFN-γ receptor (IFNγRα) correlated with reduced cancer-related survival and increased metastasis. At the molecular level, IFN-γ-resistance was due to a decreased stability of IFNγRα, which was attributed to a defective N-glycosylation. Expression of the glycosyl-tranferase MGAT3 could reinstate IFNγRα expression and signaling activity. These data suggest that IFN-γ resistance is a common evasion mechanism of CRC tumor cells that is regulated by protein N-glycosylation.

The role of vascular plasticity in gastrointestinal diseases
PI: Prof. Dr. E. Naschberger, PD. Dr. N. Britzen-Laurent, Prof. Dr. Dr. M. Stürzl.
The importance of vascular plasticity for the development of gastrointestinal diseases is investigated in colorectal carcinoma and inflammatory bowel disease. An important finding of these studies was that tumor vessels in colorectal carcinoma release soluble mediators that counteract tumor development in prognostically favorable tumors. In addition, we found that interferon-induced vascular permeability is a critical driver in the development of inflammatory bowel disease. Both findings open up new approaches for the treatment of gastrointestinal diseases and are currently being validated in different experimental models and tested with regard to their translational applicability for the treatment of the diseases.

Cellular memory processes in the pathogenesis of colorectal carcinoma
PI: Prof. Dr. Dr. M. Stürzl, Prof. Dr. E. Naschberger
The tumor microenvironment is established by the interplay of tumor cells with stromal cells (e.g. endothelial cells, fibroblasts) and immune cells and controls the course of the disease. The hypothesis of this research area is that stromal cells in colorectal carcinoma are shaped by different microenvironments and retain certain "memory functions" to the environment in the tumor also in culture. Cellular memory processes are exploited to gain new insights into the pathogenesis. To this end, we established novel methods for isolating fibroblasts and endothelial cells from colorectal carcinomas with different microenvironments and identified via the differential characterization of the isolated cells at the genome, transcriptome, and epigenome levels novel mediators that control metastasis. The approach confirms that cultured stromal cells can serve as cell spies for the intra-tumoral microenvironment and it provides new approaches to treat the disease.

Genome editing of pancreatic tumor models
PI: Prof. Dr. C. Pilarsky
Pancreatic cancer is the fourth most frequent cause of cancer in the western world with a five

year survival rate of 10%. This is caused by late detection and chemoresistance of the tumor. In this project we are trying to understand more precisely which mechanisms influence tumor development. Based on the well-known changes in the tumor genome, we are targeting specific genes, especially gene involved in DNA repair, with CRISPR/Cas9 technology and are testing whether our tumor models become more sensitive to the application of chemotherapeutic agents. This allows an adaptation of chemotherapeutic regimens to the mutation pattern of the individual tumor within the framework of modern precision medicine. In the second part of this approach we identify genes associated with metastasis and invasion to identify metastasis associated targets for pharmacological intervention.

Organoid models in pancreatic cancer
PI: Prof. Dr. C. Pilarsky
In this project we will test the influence of the culture conditions on the chemosensitivity of pancreatic carcinomas. For this purpose, pancreas tumor cells are grown as a special tissue culture, the organoid culture, and treated with chemotherapeutic agents. This allows us to examine how the individual models can be treated in a tissue. This allows a better understanding of the necessary dosage of chemotherapeutic agents and a possible better preclinical testing of new chemotherapies.

Immunepathophysiology of acute (sepsis) and chronic (colitis) inflammation
PI: PD Dr. G. Weber, Dr. A. Bénard
The immune system consists of innate and adaptive components that operate in close proximity to protect the host against infections. During infection the host can be at risk due to imbalanced immune responses. A major therapeutic goal, then, is to establish an equilibrium between controlling infection and controlling inflammation. One promising strategy is to harness the endogenous immune system to augment processes that are beneficial and curb processes that cause harm. Such strategies, however, require understanding of the diseases pathophysiology. Currently, we are focusing on the role of interleukin-3 as central regulator for acute and chronic inflammation.

Immunephenotyping and liquid biopsy analysis of gastrointestinal tumors
PI: PD Dr. G. Weber
Successful treatment of cancer disease is based on the in-depth understanding of the involved mechanisms leading to cancer development and progression. Thus, precise knowledge of the immunogenicity of the individual tumor as well as early and precise diagnosis is required. Within this project, we will develop non-invasive alternative techniques – so called liquid biopsies - to diagnose cancer disease, predict and monitor disease progression, and finally to improve patient selection for established treatment strategies. In addition, we are immunologically phenotyping the individual cancer disease to evaluate immune therapeutic strategies.

Teaching

The Department of Surgery is offering courses for students of Medicine, Dentistry, Molecular Medicine, and biology. The Dr. House colloquium is an interdisciplinary lecture with the internal medicine. By the implementation of a surgical skills lab, surgical residents as well as medical students benefit from learning different surgical approaches and may acquire basic surgical skills using modern laparoscopic simulators. MD and PhD theses are supervised.

Selected publications

Merkel S, Weber K, Brunner M, Baecker J, Agaimy A, Göhl J, Hohenberger W, Schellerer V, Grützmann R. Prognostic subdivision of pT2 rectal carcinomas. Int J Colorectal Dis. 2019 Mar;34(3):409-415.

Beck C, Weber K, Brunner M, Agaimy A, Semrau S, Grützmann R, Schellerer V, Merkel S. The influence of postoperative complications on long-term prognosis in patients with colorectal carcinoma. Int J Colorectal Dis 2020;35(6):1055-1066.

Consensus in determining the resectability of locally progressed pancreatic ductal adenocarcinoma - results of the Conko-007 multicenter trial. Wittel UA, Lubgan D, Ghadimi M, Belyaev O, Uhl W, Bechstein WO, Grützmann R, Hohenberger WM, Schmid A, Jacobasch L, Croner RS, Reinacher-Schick A, Hopt UT, Pirkl A, Oettle H, Fietkau R, Golcher H. BMC Cancer. 2019 Oct 22;19(1):979.

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Wohlfahrt T, Rauber S, Uebe S, Luber M, Soare A, Ekici A, Weber S, Matei AE, Chen CW, Maier C, Karouzakis E, Kiener HP, Pachera E, Dees C, Beyer C, Daniel C, Gelse K, Kremer AE, Naschberger E, Stürzl M, Butter F, Sticherling M, Finotto S, Kreuter A, Kaplan MH, Jüngel A, Gay S, Nutt SL, Boykin DW, Poon GMK, Distler O, Schett G, Distler JHW, Ramming A. PU.1 controls fibroblast polarization and tissue fibrosis. Nature 2019 Feb;566(7744):344-349. doi: 10.1038/s41586-019-0896-x.

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International cooperations
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