Institute of Pathology

Division of Nephropathology

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Research focus

- Afferent renal innervation
- Complement-mediated cross-talk between tubular and interstitial cells in renal transplantation.
- Analysis of the pathological effects of light chains and AL protein forms
- The role of DPP4 in crescentic glomerulonephritis
- Chronic kidney disease of unknown etiology (CKDu)
- SriKid H_2O – Investigation of correlations between localized chronic kidney diseases and water quality in Sri Lanka
- Pathology work-up of GvL and GvHD in mice and man
- Role of the receptor GPR126 in heart and kidney development
- Establishment and function of non-centrosomal MTOCs in striated muscle
- Heart regeneration
- Cardiac tissue engineering
- Zebrafish as cancer model

Structure of the Division

Professorships: 2
Personnel: 32

- Doctors (of Medicine): 4
- Scientists: 4 (thereof funded externally: 0)
- Graduate students: 18

Clinical focus areas

- Diagnosis on kidney biopsies
- Diagnosis on peritoneal biopsies
- Diagnosis on iliac crest
- Diagnosis of heart diseases
- Lightmicroscopy, immunohistology, electron microscopy

Research

Clinical and experimental cooperations are well established with clinical partners and research groups of UK Erlangen and FAU as well as external cooperators, working in the field of nephrology. Main focus of the Division of Nephropathology is to test molecular hypotheses on experimental and human kidney biopsy material.

Afferent renal innervation
PI: Prof. Dr. K. Amann
In spite of clear evidence of its importance, a basic feature of renal innervation – the regulation of sympathetic activity by afferent renal nerves – is not yet understood. It is particularly unclear whether renal afferents, i.e. the dorsal root ganglion neurons with renal projections, stimulate or inhibit sympathetic activity. We want to demonstrate in a model of experimental hypertension that afferent renal nerve activity acts rather sympathoinhibitory, but not sympathoexcitatory. This project will be done in collaboration with Prof. Dr. R. Veelken (Department of Medicine 4). Funding: IZKF

Complement-mediated cross-talk between tubular and interstitial cells in renal transplantation
PI: Prof. Dr. M. Büttner Herold, Prof. Dr. C. Daniel, Prof. Dr. K. Amann
In this project the activation of the complement pathway, in particular the lectin signaling pathway, during renal transplantation and thereby the interaction with renal tubular epithelial and inflammatory cells will be investigated. Human renal biopsies and kidney tissue from experimental studies in rats will be used for this purpose. Using an inhibitory antibody directed against the activator of the lectin-activated complement pathway MASP-2 or a C5 blocker inhibiting the terminal pathway of all complement pathways, we aim to prevent graft deterioration and graft loss. In addition, the interaction of different complement factors with renal tubule cells will be investigated in vitro. Funding: SFB 1350

Analysis of the pathological effects of light chains and AL protein forms
PI: Prof. Dr. K. Amann
In this project we investigate the cellular response of amyloidosis light chain (AL) peptides in the heart and kidney, which are important for understanding tissue pathology. Attempts will be made to separate the effect of the various AL peptides themselves from environmental factors, i.e., changes in the milieu or differentiation of cells. In addition, these in vitro data will be the basis for subsequent in vivo analyses in animal models. The work is embedded in a research group consisting of researchers in Kiel, Heidelberg, Ulm and Munich. Funding: FOR 2969

The role of DPP4 in crescentic glomerulonephritis
PI: Prof. Dr. C. Daniel
In this project, we investigate the role of dipeptidyl peptidase IV (DPP4) in pathogenesis of crescentic glomerulonephritis. DPP4 is an exoprotease cleaving incretins as well as different chemokines, but can also act as a co-receptor for cell-cell recognition. Therefore, we induce an anti-GBM model in rats and compare disease propagation in DPP4-inhibitor treated animals with untreated controls. Analysis will focus on the role of DPP4 in crescent formation and changes in kidney function. Funding: Boehringer Ingelheim GmbH

SriKid H_2O – Investigation of correlations between localized chronic kidney diseases and water quality in Sri Lanka
PI: Prof. Dr. K. Amann
Together with nephrologists (Dr. N. Nanayakkara, Prof. Dr. K.-U. Eckardt), hydrogeologists (Prof. J. Barth, Prof. R. Chandrajith) and toxicologists (Prof. C. Zwiener) from Germany and Sri Lanka, we investigate in this interdisciplinary project causes and pathogenesis of chronic kidney dis- ease of unknown etiology (CKDu) that is restricted to dry areas in tropical regions. Beside histopathological characterization of renal biopsies using immunohistology and electron microscopy, comprehensive analysis of drinking water will be done. The aim of this project is to uncover the causes and pathogenesis of this life- threatening disease. Funding: BMBF

Pathology work-up of GvL and GvHD in mice and man
PI: Prof. Dr. M. Büttner-Herold
Diagnosis of GvHD is challenging due to its high variability of clinical and histopathological manifestations and insufficient validation of diagnostic criteria, even for experienced transplant pathologists. Therefore this project aims to better define diagnostic criteria of GvHD by using a round robin test with participation of four different institutes of pathology focusing on GvDH in colon. In addition, together with Prof. Dr. M. Evert (Regensburg) and Prof. Dr. A. Rosenwald (Würzburg) this project will support other sub-projects of the SFB/TRR 221 (compare own report) by production and evaluation of immune-histological sample analysis including human as well as murine GvDH. Funding: DFG, IZKF A84

Role of the receptor GPR126 in heart and kidney development
PI: Prof. Dr. F.B. Engel
Adhesion GPCRs are characterized by large N-termini and a GPS motif at which they are autoproteolytically cleaved into a C-terminal and N-terminal fragment (CTF and NTF, respecttively). Following the discovery that the adhesion GPCR Gpr126 is essential for trabeculation during heart development, Gpr126 was shown to play a critical role in the organization of the endocardium and its differentiation. Analysis of various zebrafish mutants has further shown that the CTF and NTF have distinct roles regulating separate cellular processes during trabeculation. Analysis of Gpr126 zebrafish mutants has also shown that Gpr126 plays a role in kidney development. Funding: DFG, IZKF

Establishment and function of non-centrosomal MTOCs in striated muscle
PI: Prof. Dr. F.B. Engel
Microtubule organization plays a pivotal role in cellular architecture and biological processes such as intracellular transport, signal transduction, mitotic spindle assembly, and organelle positioning. Recently, we have shown that the centrosome - the dominant microtubule organizing center (MTOC) in most proliferating vertebrate

cells - is disassembled in cardiomyocytes during development and that the nuclear envelope adopts the MTOC function. This relocalization of the MTOC was associated with a decline of cardiomyocyte proliferative capacity. MTOC relocalization to non-centrosomal (nc) sites has been described in a wide variety of differentiated cell types. Yet, despite this phenomenon is well known and mutations in related genes cause severe human disease, the formation and function of ncMTOCs are poorly understood. We have now elucidated the molecular mechanism underlying the establishment of nuclear MTOC in muscle cells. Furthermore, we could show that this mechanism is also used by osteoclasts. In rat cardiomyocytes, AKAP6 anchors centrosomal proteins to the nuclear envelope through its spectrin repeats, acting as an adaptor between nesprin-1α and Pcnt or AKAP9. In addition, AKAP6 and AKAP9 form a protein platform tethering the Golgi to the nucleus. Both Golgi and nuclear envelope exhibit MTOC activity utilizing either AKAP9, or Pcnt-AKAP9, respectively. AKAP6 is also required for formation and activity of the nuclear envelope MTOC in human osteoclasts. Moreover, ectopic expression of AKAP6 in epithelial cells is sufficient to recruit endogenous centrosomal proteins. Finally, AKAP6 is required for cardiomyocyte hypertrophy and osteoclast bone resorption activity. Collectively, we decipher the MTOC at the nuclear envelope as a bi-layered structure generating two pools of microtubules with AKAP6 as a key organizer. Funding: DFG

Heart Regeneration
PI: Prof. Dr. F.B. Engel
The loss of cardiomyocytes after heart injury cannot be corrected by conventional treatment methods. Mammalian cardiomyocytes establish a cell cycle arrest after birth and the final cell cycle results in binucleation or polyploidization. In contrast, cardiomyocytes of zebrafish and amphibians maintain their ability to proliferate and can regenerate their hearts by inducing cell division of existing cardiac muscle cells. The research group has recently developed new methods to distinguish cell division and binucleation (failure of cytokinesis) in cardiomyocytes. In addition, we have characterized these processes and demonstrated that also binucleated cardiomyocytes can be induced to proliferate. Our results indicate that postnatal binucleated cardiomyocytes upon stimulation can enter mitosis, cope with their multiple and/or unpaired centrioles by forming pseudo-bipolar spindles, and divide. Funding: DFG, ELAN

Cardiac tissue engineering
PI: Prof. Dr. F.B. Engel
Materials for the generation of artificial heart tissue are tested for tissue replacement therapy. In close collaboration with Prof. Dr. A.R. Boccaccini (Department of Biomaterials, Faculty of Engineering) and Prof. T. Scheibel (Bayreuth Materialzentrum, University of Bayreuth), we cur- rently focus on the analysis of electroconductive materials, collagen, and recombinantly produced silk. We are now able to produce beating heart tissue from human pluripotent stem cells that beat for weeks without external stimulation and respond to various pharmaceuticals. In addition, we have started to integrate endothelial cells into our fabrication strategy to pre-vascularize the tissues. Funding: DFG, TRR 225, Foundation Medicine

The zebrafish as cancer model
PI: Prof. Dr. F.B. Engel
Since cardiomyocytes establish a strict cell cycle arrest after birth – and thus cardiac tumors are very rare - cardiomyocyte differentiation appears to be an excellent model to identify new potential targets for cancer treatment. To determine the role of candidate genes such as IQGAP3 in cancer cell proliferation and migration, a zebrafish xenograft model will be used and live cell imaging will be performed. We study IQGAP3 in colorectal cancer as: 1) IQGAP3 is downregulated during heart development and mis-localized during the last cell cycle resulting in binucleation. 2) It is expressed in proliferating transit-amplifying cells in crypts and is upregulated in colorectal cancer; one of the most common and lethal cancers. During the last decade the zebrafish model has been established as a powerful tool for cancer biology. In addition to its general advantages, the embryonic zebrafish is an excellent xenograft model as its adaptive immune system matures not before 4 weeks post-fertilization. Therefore, injection of mouse or human cells will not cause an immune rejection. Moreover, xenografts can be performed in zebrafish 48 hours post-fertilization and results will be obtained 4 days later at 6 days post-fertilization. Funding: Wilhelm Sander Foundation

Teaching

The Division of Nephropathology participates in the teaching of the Institute of Pathology and acts as "Advanced Training Center for Nephropathology" of the European Society of Pathology.
Bachelor's and Master's theses as well as MD and PhD theses are supervised.

Selected publications

Daniel C, Leppkes M, Munoz LE, Schley G, Schett G, Herrmann M. Extracellular DNA traps in inflammation, injury and healing. Nature reviews Nephrology. 2019; 15(9):559-575.

Balasooriya S, Munasinghe H, Herath AT, Diyabalanage S, Ileperuma OA, Manthrithilake H, et al. Possible links between groundwater geochemistry and chronic kidney disease of unknown etiology (CKDu): an investigation from the Ginnoruwa region in Sri Lanka. Exposure and Health. 2020; 12(4):823-834.

Rodionova K, Veelken R, Hilgers KF, Paulus EM, Linz P, Fischer MJM, et al. Afferent renal innervation in anti-Thy1.1 nephritis in rats. American journal of physiology Renal physiology. 2020;319(5):F822-f832.

Rodionova K, Hilgers KF, Paulus EM, Tiegs G, Ott C, Schmieder R, et al. Neurogenic tachykinin mechanisms in experimental nephritis of rats. Pflugers Archiv : European journal of physiology. 2020;472(12):1705-1717.

Vergarajauregui S, Becker R, Steffen U, Sharkova M, Esser T, Petzold J, Billing F, Kapiloff MS, Schett G, Thievessen I, Engel FB. AKAP6 orchestrates the nuclear envelope microtubule-organizing center by linking golgi and nucleus via AKAP9. Elife. 2020; 9:e61669.

Roshanbinfar K, Vogt L, Ruther F, Roether JA, Boccaccini AR, Engel FB. Nanofibrous Composite with Tailorable Electrical and Mechanical Properties for Cardiac Tissue Engineering Adv Funct Mater. 2020; 30(7): 1908612.

Musa G, Srivastava S, Petzold J, Cazorla-Vázquez S, Engel FB. miR-27a/b is a post-transcriptional regulator of Gpr126 (Adgrg6). Ann N Y Acad Sci. 2019; 1456(1):109-121.

Leone M, Engel FB. Pseudo-bipolar spindle formation and cell division in postnatal binucleated cardiomyocytes. J Mol Cell Cardiol. 2019; 134:69-73.

Roshanbinfar K, Mohammadi Z, Mesgar AS, Dehghan MM, Oommen OP, Hilborn J, Engel FB. Carbon nanotube doped pericardial matrix derived electroconductive biohybrid hydrogel for cardiac tissue engineering. Biomater Sci. 2019; 7(9):3906-3917.

International cooperations
Prof. S. Shankland, Department of Nephrology, University of Washington, Seattle: USA

Dr. N. Nanayakkara, Kandy University Hospital, Kandy: Sri Lanka

Prof. M. van den Hoff, Department of Anatomy, Academic Medical Center Amsterdam, Amsterdam: The Netherlands

Prof. M. Kapiloff, Stanford Cardiovascular Institute, Stanford University: USA

Prof. J. Hilborn, Department of Chemistry, Angstrom Laboratory, Uppsala University: Sweden