Nikolaus-Fiebiger-Center of Molecular Medicine

Chair of Experimental Medicine I (Molecular Pathogenesis Research)

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Research Focus
- Cellular Plasticity: a driving force for cancer progression and other disease processes
- The role of fibulin-4 in the mechanostability of the musculoskeletal connective tissue
- Molecular mechanisms of endochondral ossification and skeletal development

Structure of the Institute

The Chair of Experimental Medicine I is located at the NFZ and is, together with the Chair of Experimental Medicine II, responsible for the organization and administration of the Center. In 2013 – 2014, about seven scientists and technical staff were involved in research and teaching at the Chair of Experimental Medicine I, three of them supported by grants. Prof. Dr. D.N. Müller held the Chair from April 2011 until October 2012. Prof. Dr. J. Behrens acted as temporary chairman after Prof. Dr. D.N. Müller left until April 2014. Since May 2014, Prof. Dr. T. Brabletz has been holding the Chair of Experimental Medicine I. Until the end of 2014, there was an increase in staff members with the result that eight persons are presently working in Prof. Dr. T. Brabletz' group. In addition, Prof. Dr. K. von der Mark (retired) continued to lead a research group financed by grants and participated in teaching molecular medicine. In a translational approach, the Brabletz lab focuses on cancer research with the aim to develop new diagnostic and prognostic tools as well as novel therapeutic strategies.

Research

Cellular Plasticity: a driving force for cancer progression and other disease processes

Project managers: Dr. M. Stemmler, Dr. S. Brabletz, Prof. Dr. T. Brabletz

It became evident that cancer cells are highly adaptive to the demanding environmental conditions – a property which can be summarized as aberrant cellular plasticity. In addition to accumulation of genetic alterations, aberrant cellular plasticity is now considered as a major driving force for cancer progression towards a therapy resistant, metastatic disease, as well as for the pathogenesis of other diseases. Our group has discovered one underlying molecular mechanism controlling cellular plasticity: A phenotypic switch between a stemness/EMT state and a differentiated state which is exerted by a double-negative feedback loop between the EMT-activator ZEB1 and the miR-200 family of microRNAS, the so-called ZEB1/miR-200 feedback loop. Future work will address the role of cellular plasticity in cancer and other diseases and explore it as a target of therapeutic intervention. We will:
- investigate the role of the ZEB1/miR-200 feedback loop in cancer initiation and metastasis;
- investigate the microenvironment as a modulator of cellular plasticity in cancer;
- identify novel mechanisms underlying cellular plasticity;
- explore the translational and clinical relevance by developing novel treatment strategies;
- investigate the role of cellular plasticity in other disease processes, such as organ fibrosis, kidney diseases, inflammation.

To address our research questions, we use molecular, epigenetic, and genetic in vitro approaches, cell, and animal models (e.g. mouse tumor models and conditional knockout and transgenic models of plasticity-related genes), as well as human tumor material and patients' data.

The role of fibulin-4 in the mechanostability of the musculoskeletal connective tissue

Project managers: Dr. T. Sasaki, Prof. Dr. K. von der Mark

Fibulin-4 is a 50 kDa extracellular matrix protein which is essential – together with elastin and fibrillin – for assembly and function of elastic fibers of the cardiovascular, musculoskeletal, and lung elastic tissues. Patients with a recessive missense mutation in fibulin-4 display not only defects in elastogenesis resulting in cutis laxa and aneurisms, but also in multiple bone fractures at birth; two patients showed arachnodactyly. Fibulin-4 deficiency in mice is perinatally lethal due to cardiovascular and lung abnormalities and leads to joint contractures during fetal development. The goal of this DFG-funded project was to clarify the role of fibulin-4 in connective tissue development and homeostasis. The skeletal phenotype of fibulin-4 deficient mouse embryos was analyzed using morphological, immunohistochemical, and in situ hybridization techniques. Surprisingly, in fibulin4 deficient mice the size of collagen fibrils and collagen crosslinking was affected, explaining the joint contracture on fibulin-4 null mice. In order to clarify the genotype-phenotype relation of fibulin-4 mutations, several mutagenized recombinant proteins with clinically relevant fibulin-4 mutations were prepared. Most mutations, in particular those affecting calcium binding sites, affected secretion, matrix assembly and enhanced resistance against proteinases, resulting in fibulin deficiency. Furthermore, multiple interactions with collagens, fibrillin and elastin, as well as with lysyloxidases and LTBP were impaired, explaining the defect in collagen crosslinks in fibulin4 null mice. Molecular dynamic simulations were performed which provided new insight into the structure of the fibulin molecule and the conformational instability of mutations affecting the calcium binding site.
The proposed studies will provide novel insights into the role of fibulin-4 in the assembly and stability of elastic fibers as well as in the development and homeostasis of cardiovascular tissue.

Molecular mechanisms of endochondral ossification and skeletal development

Project manager: Prof. Dr. K. von der Mark

During development of the vertebral skeleton, chondrocytes shape the cartilage models of the subsequent bony elements of the extremities, ribs and the spine. Chondrocytes grow and differentiate rapidly and are replaced by bone cells in a complex process called "endochondral ossification". For reproducible skeletal growth, a precise spatially and temporally coordinated control of endochondral ossification is an absolute requirement. Similar processes also occur during fracture callus healing and development of osteophytes in osteoarthritic joints. Therefore, elucidation of factors and mechanisms involved in endochondral ossification is essential not only for our understanding of the regulation of normal skeletal growth and skeletal dysplasias, but also for the development of new tools in the diagnosis and therapy of joint degeneration, fracture healing, and cartilage and bone repair. The analysis of these factors by means of molecular biological techniques, cell and organ culture systems, and transgenic mouse models is currently the major focus of a DFG-funded research project.

The development of a collagen10-specific targeting vector for recombination into BAC (bacterial artificial chromosomes) allowed the specific overexpression or deletion of genes in hypertrophic chondrocytes. Mating BACCol10-Cre deleter mice to conditional β-catenin knockout mice (Prof. Dr. R. Kemler, Max-Planck-Institute Freiburg) resulted in transgenic mice lacking trabecular bone in the subchondral zone of the diaphysis. This deficiency was due to enhanced RANKL activity stimulating osteoclast differentiation in β-catenin deficient chondrocytes.

An unexpected finding resulting from genetic lineage tracing studies with BACCol10;Cre induced YFP-reporter gene expression in transgenic mice provided new insight into the mechanism of cartilage – bone conversion in endochondral ossification. According to general understanding, the chondrocyte lineage terminates with the elimination of late hypertrophic cells by apoptosis in the growth plate. In our cell tracking studies, however, we demonstrated that hypertrophic chondrocytes can survive beyond "terminal" differentiation and give rise to a progeny of osteoblasts participating in endochondral bone formation. In searching for transitory cells between hypertrophic chondrocytes and trabecular osteoblasts, we identified by confocal microscopy a novel, small reporter gene positive cell type with mitotic activity in the lower hypertrophic zone at the chondro-osseous junction. We propose that these cells mark the initiation point of a second pathway giving rise to endochondral osteoblasts, alternatively to perichondrium derived osteoprogenitor cells. These findings add to current concepts of chondrocyte-osteocyte lineages and give new insight into the complex cartilage-bone transition process in the growth plate.

Teaching

The Chairs of Experimental Medicine I and II organize lectures, seminars, and experimental classes in cell, molecular, and developmental biology at basic and advanced levels for students of Molecular Medicine, Medicine, and Biology. Special lectures, including tumor biology and oncology, molecular mechanism of cell differentiation, and development, cell-cell and cell-extracellular matrix interactions, are given.

Selected Publications

Brabletz T, Lyden D, Steeg PS, Werb Z. Roadblocks to translational challenges on metastasis. Nat Med 2013, 19: 1104-9

Siebzehnrübl F, Silver DJ, Tugertimur B, Deleyrolle LP, Siebzehnrübl D, Sarkisian MR, Devers KG, Yachnis AT, Kupper MD, Neal D, Nabilsi NH, Kladde MP, Suslov O, Brabletz, S, Brabletz T Reynolds BA, Steindler DA. The ZEB1 pathway links glioblastoma initiation, invasion and chemoresistance. EMBO Mol Med 2013, 5: 1196-212

Vannier C, Mock C, Brabletz T, Driever W. ZEB1 regulates E-Cadherin and Epcam expression to control cell behavior in early zebrafish development. J Biol Chem 2013, 288: 18643-59

Golovchenko S, Hattori T, Hartmann C, Gebhardt M, Gebhard S, Hess A, Pausch F, Schlund B, von der Mark K. Deletion of beta catenin in hypertrophic growth plate chondrocytes impairs trabecular bone formation. Bone 2013, 55(1): 102-12

Puisieux A, Brabletz T, Caramel J. Oncogenic roles of EMT-inducing transcription factors. Nat Cell Biol 2014, 16: 488-94

Zhou X, von der Mark K, Henry S, Norton W, Adams H, de Crombrugghe B. Chondrocytes transdifferentiate into osteoblasts in endochondral bone during development, postnatal growth and fracture healing in mice. PLoS Genet 2014, 10(12): e1004820

International Cooperations

Prof. Dr. G. Goodall, University of Adelaide: Australia

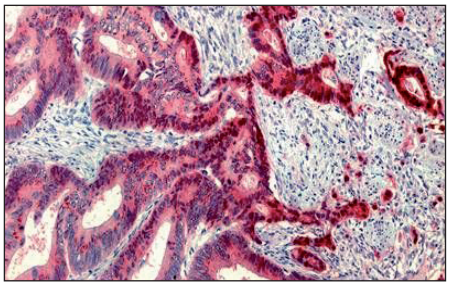
Prof. Dr. R. Fodde, Erasmus University, Rotterdam: The Netherlands

Prof. Dr. G. Berx, VIB and University of Ghent: Belgium

Prof. Dr. C. Hartmann, Institute of Molecular Pathology, IMP, Vienna: Austria

Prof. T. Hattori, Graduate School of Dentistry and Medicine, Okayama University, Okayama: Japan

Prof. B. de Crombrugghe, MD, Anderson Cancer Center, Texas University, Houston: USA



Plasticity of tumor cells in colon cancer.