Nikolaus-Fiebiger-Center of Molecular Medicine

Chair of Experimental Medicine I (Molecular Pathogenesis Research)

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Research focus

- Cellular plasticity as driving force of metastasis
- EMT-activators in cancer-associated fibroblasts (CAF) and macrophages (CAM)
- Nuclear co-factors of the tumorigenic EMT-activator ZEB1
- Role of the EMT-activator ZEB1 in pancreas development und homeostasis
- Role of the EMT-activator ZEB1 in skeletal development and osteosarcoma
- Dual pathways to endochondral osteoblasts: A novel chondrocyte derived osteoprogenitor cell identified in hypertrophic cartilage

Structure of the Chair

Professorship: 1
Personnel: 17

- Doctor (of Medicine): 1
- Scientists: 5
  (thereof funded externally: 3)
- Graduate students: 6

Special structural feature
Managing Director of the Nikolaus-Fiebiger Center (NFZ), alternating biannually with the Chair of Experimental Medicine II

Research

Our research is focused on the development and malignant progression of solid cancers, particularly on the molecular mechanisms of tumor invasion and metastasis. The aim is to develop novel therapeutic concepts to fight these processes. We integrate cell-/molecular-biological, epigenetic, and genetic methods, *in vitro* and *in vivo* model systems, as well as analyses of human tumor samples and patient data.

Cellular plasticity as driving force of metastasis

PI: Dr. M. Stemmler, Dr. S. Brabletz, Prof. Dr. T. Brabletz

We have shown that the ability of cancer cells to adapt to changing conditions und demands is a major determinant of malignant progression towards a therapy-resistant, metastatic disease. This ability is termed aberrant cellular plasticity. The molecular basis in many cases is a molecular motor which we identified, i.e. the ZEB1/miR200 feedback loop. By this molecular motor, the transient expression of ZEB1 in cancer cells activates stemness properties and a partial epithelial-mesenchymal transition (EMT), which stimulates invasion, therapy resistance dissemination, and finally metastasis in solid cancer types. The central role of ZEB1 in tumorigenicity, plasticity, and metastasis was proven by us by a conditional knockout of ZEB1 in a genetic mouse model of pancreatic cancer.

EMT-activators in cancer-associated fibroblasts (CAF) and macrophages (CAM)

PI: Dr. M. Stemmler, Dr. S. Brabletz, Dr. H. Schuhwerk, Prof. Dr. T. Brabletz

The observed high plasticity in cancer cells implies that not only genetic alterations, but also regulatory inputs from the tumor environment are major driving forces of tumor progression. Thereby the interaction of cancer cells with cancer associated fibbroblasts (CAF) and macrophages (CAM) plays an important role. We could show that the EMT activator ZEB1 is highly upregulated in CAFs and CAMs as compared to their normal counterparts and regulates the expression of central genes of these cell types. By using conditional ZEB1 knockout mice, we investigate the effect of a ZEB1 depletion on development and progression of gastrointestinal tumors.

Nuclear co-factors of the tumorigenic EMT-activator ZEB1

PI: Dr. S. Brabletz, Dr. M. Stemmler, Dr. R. Eccles, Prof. Dr. T. Brabletz

We demonstrated that ZEB1 is an important tumorigenic factor. ZEB1 is a transcription factor and by unknown mechanisms it can switch from a transcriptional repressor to an activator. We postulated the recruitment of unknown nuclear co-factors as underlying mechanism and identified a number of potential binding partners by mass spectrometric analyses. In this project we validate and characterize their binding to ZEB1. In addition we investigate their mutual functional effects. Thereby we also determine changes in whole genome expression patterns and epigenetics by applying ChIPSeq analyses. On the basis of the results, the long term aim is to develop inhibitors of ZEB1 function also for potential therapeutic usage.

Role of the EMT-activator ZEB1 in pancreas development und homeostasis

PI: Dr. M. Stemmler

Based on the data that ZEB1 is crucial for the pathogenesis of pancreatic cancer, we hypothesized that it also regulates normal pancreas development and adult pancreas homeostasis. This is investigated in a conditional ZEB1 knockout mouse model. First results showed no strong effect of ZEB1 on pancreatic development, but indicate a role of ZEB1 in pancreatic homeostasis under stress conditions. We now investigate this by applying different stress conditions (high fat, high glucose, pancreatitis, etc.).

Role of the EMT-activator ZEB1 in skeletal development and osteosarcoma

PI: Dr. S. Brabletz, Dr. M. Ruh, Prof. Dr. T. Brabletz

In a conditional ZEB1 knockout mouse model we identified, besides other affects, strong defects in embryonic bone development. We subsequently demonstrated that mesenchymal stem cells (MSC) need ZEB1 to maintain their stemness state. Consequently ZEB1 had to be downregulated to allow differentiation to osteoblasts. This regulatory mechanism also affects the generation of osteosarcoma. We could show that the expression of ZEB1 correlates with a particular aggressiveness of osteosarcomas. Depletion of ZEB1 in osteosarcoma cells reduces their stemness competence, tumorigenicity, and aggressiveness.

Dual pathways to endochondral osteoblasts: A novel chondrocyte derived osteoprogenitor cell identified in hypertrophic cartilage

PI: Prof. Dr. K. von der Mark

This research has been focusing on the molecular and cellular events in the cartilaginous growth plate of long bones and vertebrae involved in the control of growth and development of the skeleton. A number of transgenic mouse lines were developed which allowed deciphering the specific role of growth factors, hormones, and transcription factors of hypertrophic chondrocytes in the regulation of cartilage-bone turnover. According to the general

understanding, the chondrocyte lineage terminates with the elimination of late hypertrophic cells by apoptosis in the growth plate. However, in recent genetic lineage tracing experiments using mouse lines, which express reporter genes under the collagen 10 promotor, the group challenged this concept and demonstrated that murine hypertrophic chondrocytes can survive beyond ''terminal'' differentiation and gives rise to a progeny of osteoblasts participating in endochondral bone formation.

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. Bachelor's and Master's theses are supervised.

Selected publications

Krebs AM, Mitschke J, Losada ML, Schmalhofer O, Boerries B, Busch H, Boettcher M, Mougiakakos D, Reichardt W, Bronsert P, Brunton VG, Winkler TH, Brabletz S, Stemmler MP, Brabletz T. The EMT activator ZEB1 is a key factor for cellular plasticity and promotes metastasis in pancreatic cancer. Nat Cell Biol, 2017, 19: 518-29

Ye X, Brabletz T, Kang Y, Longmore GD, Nieto MA, Stanger BZ, Yang J, Weinberg RA. Upholding a role for EMT in breast cancer metastasis. Nature 2017, 547: E1-E3

Aiello NM, Brabletz T, Kang Y, Nieto MA, Weinberg RA, Stanger BZ. Upholding a role for EMT in pancreatic cancer metastasis. Nature 2017, 547: E7-E8

Schwab A et al. Polyol Pathway Links Glucose Metabolism to the Aggressiveness of Cancer Cells. Cancer Res 2018, 78: 1604-18

Lafita-Navarro MC, Kim M, Borenstein-Auerbach N, Venkateswaran N, Hao YH, Ray R, Brabletz T, Scaglioni PP, Shay JW, Conacci-Sorrell M. The aryl hydrocarbon receptor regulates nucleolar activity and protein synthesis in MYC-expressing cells. Genes Dev 2018, 32: 1303-1308

Brabletz T, Kalluri R, Nieto MA, Weinberg RA. EMT in cancer. Nat Rev Cancer 2018, 18: 128-34

International cooperations

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

Dr. M. Conacci-Sorrell, UT Southwestern Medical Center, Dallas: USA

Prof. A. Ben Ze'ev, Weizman Institute, Rehovot: Israel

Dr. F. Siebzehnrübl, Stem Cell Institute, Cardiff: UK

Prof. Dr. A. Puisieux, Cancer Research Center, Lyon: France