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
- EMT-transcription factors as regulators of cell-metabolism and DNA-repair
- EMT-dependent transcriptional enhancers in cancer metastasis

Structure of the Chair

Professorship: 1
Personnel: 15

- Doctor (of Medicine): 1
- Scientists: 5
- (thereof funded externally: 4)
- Graduate students: 4

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 fibroblasts (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.

EMT-transcription factors as regulators of cell-metabolism and DNA-repair
PIs: Prof. Dr. T. Brabletz, PD Dr. S. Brabletz, PD Dr. M. Stemmler, Dr. H. Schuhwerk, Dr. J. Kleemann
A new project is dedicated to our recently discovered relationship between the expression of EMT transcription factors and the regulation of cellular metabolism, in particular fatty acid metabolism, and DNA replication or associated DNA repair mechanisms. Both subfields aim to define EMT-dependent bottleneck factors for cancer cell survival, which then serve as targets for therapeutic attacks.

EMT-dependent transcriptional enhancers in cancer metastasis
PIs: PD Dr. S. Brabletz, Dr. Nora Feldker.
Phenotypic plasticity enables tumor cells to metastasize. The EMT transcription factor Zeb1 mediates this plasticity and drives metastasis, which is accompanied by substantial enhancer reprogramming. Because Zeb1 functions as a transcriptional coactivator in putative enhancer regions, we are examining the enhancer landscape in metastatic cell lines to determine Zeb1-dependent enhancers, their target genes, and their relevance to metastasis development. The results will be validated in human cell lines and organoids. This will allow us to understand the molecular context of metastasis and use it as a basis for new prognostic and therapeutic approaches.

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
Feldker N, Ferrazzi F, Widholz SA, Guenther K, Lukassen S, Kleemann J, Riegel D, Bönisch U, Eccles RL, Schmidl C, Stemmler MP, Brabletz T*, Brabletz S*. Genome-wide cooperation of the EMT-activator ZEB1 with YAP and AP-1 factors in breast cancer. EMBO J, 39(17):e103209 (2020). * joint senior authors.

Stemmler MP, Eccles RL, Brabletz S, Brabletz T. Non-redundant functions of EMT-transcription factors. (invited review) Nat Cell Biol, 21: 102-112 (2019)

Liu M, Zhang Y, Yang J, Cui X, Zhou Z, Zhan H, Ding K, Tian X, Yang Z, Fung KA, Edil BH, Postier RG, Bronze MS, Fernandez-Zapico ME, Stemmler MP, Brabletz T, Li YP, Houchen CW, Li M. ZIP4 Increases Expression of Transcription Factor ZEB1 to Promote Integrin α3β1 Signaling and Inhibit Expression of the Gemcitabine Transporter ENT1 in Pancreatic Cancer Cells. Gastroenterology. 2020 Feb; 158(3): 679-692.

Haensel D, Sun P, MacLean AL, Ma X, Zhou Y, Stemmler MP, Brabletz S, Berx G, Plikus MV, Nie Q, Brabletz T, Dai X. An Ovol2-Zeb1 transcriptional circuit regulates epithelial directional migration and proliferation. EMBO Rep. 2019 Jan;20(1): e46273.

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