TP16: Regulation of Tumor Cell Dormancy in Human Prostate Cancer Bone Metastasis

Scientific staff

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Project description

The phenotypic switch of single disseminated tumor cells (DTC) from metastatic latency (dormancy) to re-activation and thus metastatic colonization of the bone marrow (BM) crucially determines the prognosis of prostate cancer (PCa) patients. Therefore, it is of paramount clinical interest to gain insight into the mechanisms that regulate this phenotypic switch. This project is based on the common hypothesis that DTC that enter the BM have undergone the cell biological program of epithelial-to-mesenchymal transition (EMT) already at the primary tumor site, which enabled their detachment from the primary tumor mass. However, if the EMT phenotype is too stable, DTC might remain dormant so that some kind of reversion of the EMT (mesenchymal-to-epithelial transition, MET) might be required to initiate colonization.

We developed xenograft models of human PCa, in which spontaneous metastasis formation to the BM is strongly related to EMT. Accordingly, the only observable type of BM 'metastases' in such models are single DTC, which resembles the aforementioned hypothesis. As a putative driver of EMT we identified Sparc (osteonectin), for which our preliminary findings demonstrate a novel role in regulating protein levels of the Wnt-antagonist Dkk-1. Dkk-1 is a known determinant of metastatic latency in several cancer types. Therefore, we hypothesized that the outgrowth of PCa bone metastases might be suppressed by a paracrine and/or autocrine interplay of Sparc (osteonectin) and Dkk-1 that apparently inhibits BM colonization by fostering EMT.

The first aim of this project will be to investigate whether the BM colonization patterns change upon cDNA- and shRNA-mediated modulation of Sparc or Dkk-1 expression in several cell line-based PCa xenograft models (collaboration with Boris Fehse, Research Dept. Cell and Gene Therapy, UKE). In a second step, we will determine whether Dkk-1 exerts its putative effects on tumor cell dormancy by targeting not only the tumor cells, but also the BM stromal cells. For this purpose, we will use immunodeficient mice with mutation of the Dkk1-binding site of the main receptor Lrp5 (Lrp5-G170V) or with knockout of the co-receptors Krm1, Krm2 or both (collaboration with Thorsten Schinke, Institute of Osteology and Biomechanics, UKE). In addition, we will analyze bone metastasis formation in these mice using a newly established patient-derived xenograft (PDX) model of PCa. Moreover, in order to identify novel markers of metastatic outgrowth in PCa by an unbiased approach, we will use a recently established method of bioluminescence-guided *in situ/ex vivo*-laser ablation of bone metastases and corresponding primary tumors to extract proteins for subsequent differential proteome analysis (collaboration with Hartmut Schlüter, Dept. of Clinical Chemistry, UKE).

Expertise

cell line-based xenograft models, patient-derived xenograft models, *in vivo*-monitoring of spontaneous BM metastases, (in)direct co-culture of human tumor cells and murine Ob/Oc (IOBM, UKE), kinome profiling (Core Facility, UKE), infrared laser ablation of primary tumors and matched BM metastases from mice for subsequent differential proteome analysis (Dept. of Clinical Chemistry, UKE), prostate cancer tissue microarrays with full clinical and laboratory follow-up (Institute of Pathology and Martini-Clinic, UKE)

Project-related publications

Lange T, Oh-Hohenhaus SJ, Joosse SA, Pantel K, Hahn O, Gosau T, et al. Development and characterization of a spontaneously metastatic patient-derived xenograft model of human prostate cancer. Sci Rep, accepted.

Hänel L, Gosau T, Maar H, Valentiner U, Schumacher U, Riecken K, et al. Differential proteome analysis of human neuroblastoma xenograft primary tumors and matched spontaneous distant metastases. Sci Rep 2018;8:13986.

Lange T, Kupfernagel M, Wicklein D, Gebauer F, Maar H, Brugge K, et al. Aberrant presentation of HPA-reactive carbohydrates implies Selectin-independent metastasis formation in human prostate cancer. Clin Cancer Res 2014;20:1791-802.

Lange T, Ullrich S, Muller I, Nentwich MF, Stubke K, Feldhaus S, et al. Human prostate cancer in a clinically relevant xenograft mouse model: identification of beta(1,6)-branched oligosaccharides as a marker of tumor progression. Clin Cancer Res 2012;18:1364-73.

Further information:
https://www.uke.de/kliniken-institute/institute/anatomie-und-experimentelle-morphologie/forschung/projekte_institut_anatomie/