TP2: Functional characterization of bone metastasis-initiating and radioresistant prostate tumor cells

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Project description

Metastatic tumors are the cause of more than 90% of cancer related deaths due to the fact that current therapies frequently fail to provide durable curative response if tumor is spread. It is becoming commonly accepted that tumor metastases are driven by the evolved populations of cancer stem cells (CSC) at their worst. We discovered that some common molecular pathways regulate prostate CSC as well as tumor cell radioresistance. Furthermore, previous observations elucidated a possible association between the development of radioresistant and metastatic cancer cell phenotypes during tumor progression. On the other hand, prostate tumor metastases have heterogeneous response to radiotherapy. Our assumption is that activation of certain signaling pathways detected on the genomic and transcriptomic levels in bone-marrow disseminated tumor cells (DTC), circulating tumor cells (CTC) or even primary tumors can be prognostic for bone metastasis development and additionally can be involved in the response of metastases to radiotherapy. **We hypothesize that bone microenvironment plays a role in the maintenance and propagation of the cell populations with metastatic and radioresistant features.**
To test this hypothesis we will perform an unbiased and systematic analysis of genomic and transcriptomic profiling of prostate tumor cells representing different levels of metastatic process (primary tumors, CTC and DTC from prostate cancer patients with and without bone metastases, isogenic metastatic prostate cancer cell lines with different levels of radiosensitivity) to validate activation of CSC-related signaling pathways and to understand the role of bone microenvironment in the maintenance and propagation of prostate cancer cells with metastasis-initiating and radioresistant features. These mechanisms and phenotypes will be validated by using CRISPR/Cas9 mediated knockout of candidate genes, 3D primary cell cultures, mouse metastatic models, monitoring of bone turnover *in vivo*, and correlation of candidate genes to clinical data and patients' response to therapy.
This study will identify **the phenotypes and mechanisms which are regulating bone metastasis initiating cells and their survival after radiotherapy, and are associated with bone microenvironment.**

Expertise

OncoRay infrastructure includes a state-of-the-art animal facility with small animal imaging devices (e.g. micro-CT, small animal PET/MRI, small animal ultrasound and optical imaging). Our groups established different *in vitro* (e.g. sphere formation, marker analysis) and *in vivo* (limiting dilution assay) analyses for prostate CSC populations. We characterized prostate CSC populations and established radioresistant prostate cancer cell lines by multi- omics approaches including whole genome gene expression analysis, miRNA profiling,

comparative genome hybridization (CGH) array, proteomic analysis, metabolomics analysis as well as *in vivo* tumorigenicity analysis in xenografts mouse models. In collaboration with the Department of Pathology and Department of Urology, University Hospital Carl Gustav Carus in Dresden we established different 2D and 3D models for prostate primary cell cultures based on freshly dissociated prostate cancer tissue biopsies. Currently, we are optimizing this culture system in collaboration with B CUBE – Center for Molecular Bioengineering, Dresden and applying a defined biomatrix containing bone-derived peptides for the CSC maintenance and propagation. We performed comparative analysis of the global gene expression and radiobiological clonogenic survival for a panel of primary cell cultures and matched benign tissues. We also established the CRISPR/Cas9 gene editing technology to analyze the role of individual genes in prostate cancer metastatic and tumor initiating phenotype.

Project-related publications

Peitzsch C, Tyutyunnykova A, Pantel K, **Dubrovska A**. Cancer stem cells: The root of tumor recurrence and metastases. Semin Cancer Biol. 2017, 44:10-24.

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Linge A, Lock S, Gudziol V, Nowak A, Lohaus F, von Neubeck C, Jutz M, Abdollahi A, Debus J, Tinhofer I, Budach V, Sak A, Stuschke M, Balermpas P, Rodel C, Avlar M, Grosu AL, Bayer C, Belka C, Pigorsch S, Combs SE, Welz S, Zips D, Buchholz F, Aust DE, Baretton GB, Thames H, **Dubrovska A**, Alsner J, Overgaard J, **Baumann M, Krause M**. Low CSC marker expression and low hypoxia identify good prognosis subgroups in HPV(-)HNSCC after postoperative radiochemotherapy: a multicenter study of the DKTK-ROG. Clin Cancer Res. 2016, 22(11):2639-49.

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https://www.oncoray.de/