TP1: Influence of the skeletal remodeling status on tumor cell dissemination and metastatic outgrowth

Scientific staff

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Project description

The bone matrix is continuously remodeled through the balanced activities of two substantially different cell types, bone-forming osteoblasts and bone-resorbing osteoclasts. In our project we wiill address the question, **if and how an impaired bone remodeling status affects tumor cell dissemination and metastatic outgrowth *in vivo***. For that purpose we will inject human and murine breast cancer cells into mice to study skeletal metastasis formation as well as changes in the bone microenvironment In contrast to the majority of previously published studies, **we do not aim at modifying the seed (i.e. the tumor cells), but the soil (i.e. the recipient mouse).** To achieve our goals we have backcrossed different mouse models into genetic backgrounds (BALB/c and NSG) allowing xenotransplantation or syngeneic transplantation of cancer cells. While three of the models (*Calca*$^{-/-}$, *Calcr*$^{-/-}$ and *Notch2*$^{+/HCS}$) display specific disturbances of the coupling mechanisms required to synchronize bone formation and bone resoprtion, the other four models (*Lrp5*$^{+/HBM}$, *Col1a1-Sost, Col1a1-Krm2 and Col1a1-tTA;pTet-Wnt1*) display selective changes in osteoblast activity. Since all these genetically modified mouse models have been previously analyzed to define not only their bone remodeling status, but also the molecular causes of the observed phenotypes, **we expect that our results will clearly identify, which bone remodeling cell type is primarily involved in the suggested detrimental crosstalk between bone and tumor cells**.

Expertise

Our Institute of Osteology and Biomechanics (IOBM) has a long expertise in bone-specific cellular and molecular characterization of genetically modified mouse models and osteologic patient assessment. In the last years we have identified several key mechanisms controlling skeletal remodeling and we have constantly improved our scientific infrastructure to allow deep phenotypic analysis of mouse models and patients. Our equipment contains a Faxitron contact-x-ray cabinet, a µCT40 (Scanco), a Nano-CT (Skyscan), two Zwick-material testing devices for biomechanical assessment of mouse bones, tissue infiltration devices, heavy duty microtomes, microscopes, as well as histomorphometry stations, including two Osteomeasure Histomorphometry units (Osteometrix, Atlanta, GA, USA) and one BioquantOsteo Histomorphometry unit (Bioquant USA).

Project-related publications

Luther J, Yorgan TA, Rolvien T, Ulsamer L, Koehne T, Liao N, Keller D, Vollersen N, Teufel S, Neven M, Peters S, Schweizer M, Trumpp A, Rosigkeit S, Bockamp E, Mundlos S, Kornak U, Oheim R, Amling M, Schinke T, David JP. Wnt1 is an Lrp5-independent bone-anabolic Wnt ligand. Sci Transl Med. 2018;10:eaau7137.

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Keller J, Catala-Lehnen P, Huebner AK, Jeschke A, Heckt T, Lueth A, Krause M, Koehne T, Albers J, Schulze J, Schilling S, Haberland M, Denninger H, Neven M, Hermans-Borgmeyer I, Streichert T, Breer S, Barvencik F, Levkau B, Rathkolb B, Wolf E, Calzada-Wack J, Neff F, Gailus-Durner V, Fuchs H, de Angelis MH, Klutmann S, Tsourdi E, Hofbauer LC, Kleuser B, Chun J, Schinke T, Amling M. Calcitonin controls bone formation by inhibiting the release of sphingosine 1-phosphate from osteoclasts. Nat Commun. 2014;5:5215.

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Further information:
https://www.uke.de/kliniken-institute/institute/osteologie-und-biomechanik/index.html