TP6: Characterization of the impact of bone-seeking tumors on the osteocyte network and the osteocyte-mediated regulation of bone turnover

Scientific staff

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Project description

Recent studies demonstrate that the bone composition is altered by migrating cancer cells and that tissue mechanical properties are crucial for metastatic process. Osteocytes, being the most prevalent cells in bone, reside in lacunae and span their protrusions over an area of 1200 m². With this intricate network, osteocytes orchestrate skeletal adaptation to mechanical stimuli and regulate bone homeostasis through intense communication with osteoblasts and osteoclasts. However, little is known about the characteristics of the osteocyte-lacunar network in bone affected by metastatic process and how they influence tumor cell behavior**. The central hypothesis is that the osteocyte network and functionality are altered by skeletal metastasis and these alterations contribute to pathological behavior of bone-residing cells and the resulting bone fragility.** To test this hypothesis, we will: i. characterize morphological features of the osteocyte network, evaluate local mechanical properties of the matrix, and determine bone ultrastructure using 2D/3D imaging/microanalysis during bone metastases formation in mouse models; ii. using the same *in-vivo* models, analyze the impact of osteocyte functionality status on the bone metastatic process; iii. assess the bidirectional communication between osteocytes and tumor cells, and the impact of mechanical stimulation on tumor cell invasion *in vitro*; iv. establish the adhesion molecule profile of naïve osteocytes and tumor-primed osteocytes to identify targets modulating osteocyte-tumor cell interactions. Key findings will be validated in bone biopsies with metastases obtained from breast- and prostate cancer patients using the Hamburg bone registry. **This project will provide novel and detailed insights into the interaction between osteocytes and tumor cells, and will give a direction towards new therapeutic strategies inhibiting bone metastases via modulation of osteocyte-tumor cell cross-talks.**

Expertise

Strong expertise in bone imaging (µCT) and bone histomorphometry. Bone cell analyses ex vivo.

Osteocyte network visualization (Electron Microscopy) and osteocyte functional imaging (Confocal Microscopy).

We have expertise in multimodal and multiscale techniques for bone tissue characterization, including acoustic microscopy, synchrotron micro- and nanotomography, optical spectroscopy and numerical modeling, aimed at development of multiscale structure-functional models of mineralized musculoskeletal tissues. Focused Low-Intensity Pulsed Ultrasound (FLIPUS) set-up is at our disposal for geometry- and acoustic dose-controlled mechanical cell stimulation.

Project-related publications

1. Milovanovic P, Zimmermann EA, Vom Scheidt A, Hoffmann B, Sarau G, Yorgan T, Schweizer M, Amling M, Christiansen S, **Busse B**. The Formation of Calcified Nanospherites during Micropetrosis Represents a Unique Mineralization Mechanism in Aged Human Bone. Small. 2017;13(3).
2. Milovanovic P, Zimmermann EA, Riedel C, vom Scheidt A, Herzog L, Krause M, Djonic D, Djuric M, Püschel K, Amling M, Ritchie RO, **Busse B**. Multi-level characterization of human femoral cortices and their underlying osteocyte network reveal trends in quality of young, aged, osteoporotic and antiresorptive-treated bone. Biomaterials. 2015;45:46-55
3. **Busse B**, Bale HA, Zimmermann EA, Panganiban B, Barth HD, Carriero A, Vettorazzi E, Zustin J, Hahn M, Ager JW 3rd, Püschel K, Amling M, Ritchie RO. Vitamin D deficiency induces early signs of aging in human bone, increasing the risk of fracture. Sci Transl Med. 2013;5(193):193ra88
4. Thiele S, Göbel A, Rachner TD, Fuessel S, Froehner M, Muders MH, Baretton GB, Bernhardt R, Jakob F, Glüer CC, Bornhäuser M, **Rauner M**, Hofbauer LC. WNT5A has anti-prostate cancer effects in vitro and reduces tumor growth in the skeleton in vivo. J Bone Miner Res. 2015;30(3):471-80.
5. Browne AJ, Göbel A, Thiele S, Hofbauer LC, **Rauner M**, Rachner TD. p38 MAPK regulates the Wnt inhibitor Dickkopf-1 in osteotropic prostate cancer cells. Cell Death Dis. 2016 25;7:e2119.
6. Puts R, Rikeit P, Ruschke K, Kadow-Romacker A, Hwang S, Jenderka KV, Knaus P, **Raum K**. Activation of Mechanosensitive Transcription Factors in Murine C2C12 Mesenchymal Precursors by Focused Low-Intensity Pulsed Ultrasound (FLIPUS). IEEE Trans Ultrason Ferroelectr Freq Control. 2016;63(10):1505-1513.

Further information:

https://www.bone-lab.de