TP8: Influence of myostatin on bone metastasis formation in breast cancer and multiple myeloma

Scientific staff

Berno Dankbar, Dr. rer. nat. principal investigator
Dr. Corinna Wehmeyer, Postdoc
Julia Reinhard, PhD student
Peter Paruzel, technician

Project description

Bone metastases from breast cancer affect 65% to 80% of patients and more than 80% of patients with multiple myeloma (MM) develop bone metastases. Both breast cancer and MM-derived bone metastases are osteolytic and generation of metastases is mediated by the formation and activation of mature osteoclasts from precursor cells of the myeloid lineage. It appears that there is a complex crosstalk between tumor cells and the bone microenvironment providing a variety of growth factors for cancer cells and osteoclastic factors, which are either secreted by the cells of the microenvironment or released from the bone matrix as a consequence of osteoclast-mediated bone resorption. In this regard, inhibition of TGF-ß and Activin A, both members of the TGF-ß superfamily, suppress osteoclastic bone resorption in mouse models of multiple myeloma and breast cancer, indicating an important role of these factors in bone metastases. In this context, we have recently discovered that myostatin, another member of the TGF-ß superfamily, strongly enhances osteoclast development and that deficiency or inhibition of myostatin highly ameliorates disease severity and in particular bone erosion in arthritic mice**. We hypothesize, that myostatin participates in the interactions of tumor cells with the bone microenvironment, promoting osteoclast development and thereby bone lesions.** To investigate the role of myostatin in bone metastases, myostatin will be inhibited in two syngeneic and two xenograft models for both breast cancer and MM and the formation of bone lesions will be evaluated. In addition to the *in vivo* analyses, the role of myostatin in tumor/stromal/bone cell interactions will be investigated in coculture experiments and direct/ indirect effects of tumor cells on osteoclast differentiation and activity will be examined. This project will provide new insights into the formation of tumor-induced bone lesions and may facilitate the development of novel treatment strategies to prevent the development of osteolytic lesions in myeloma and breast cancer metastases.

Expertise

In vivo quantification of osteoclasts and bone erosion by TRAP staining, µCT and histomorphological analyses.
Assays for quantitative analysis of osteoclast development and activity *in vitro* (TRAP, Live cell Imaging, pit formation).
Quantification of osteoclast markers and signaling pathway analyses during osteoclastogenesis (Smad, MAPK, NFAT, NFκB).

Project-related publications

Wehmeyer C, Frank S, Beckmann D, Böttcher M, Cromme C, König U, Fennen M, Held A, Paruzel P, Hartmann C, Stratis A, Korb-Pap A, Kamradt T, Kramer I, van den Berg W, Kneissel M, Pap T, Dankbar B (2016). Sclerostin inhibition promotes inflammatory joint destruction through enhanced activation of TNFR-mediated signaling. Sci Transl Med. 8: 330ra34.

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Wunrau C, Schnaeker EM, Freyth K, Pundt N, Wendholt D, Neugebauer K, Hansen U, Pap T, Dankbar B (2009). Establishment of a Matrix-Associated Transepithelial Resistance

Invasion (MATRIN) Assay to Precisely Measure the Invasive Potential of Synovial Fibroblasts. Arthritis Rheum. 60: 2606-11.

de Gorter DJJ, Reijmers RM, Beuling EA, Naber HP, Kuil A, Kersten MJ, Pals ST, Spaargaren M (2008). The small GTPase Ral mediates SDF-1-induced migration of B cells and multiple myeloma cells. Blood 111: 3364-72.

Derksen PW, de Gorter DJJ, Meijer HP, Bende RJ, van Dijk M, Lokhorst HM, Bloem AC, Spaargaren M, Pals ST (2003). The hepatocyte growth factor/Met pathway controls proliferation and apoptosis in multiple myeloma. Leukemia 17(4):764-74.

Dankbar B, Padró T, Leo R, Feldmann B, Kropff M, Mesters RM, Serve H, Berdel WE, Kienast J (2000). Vascular endothelial growth factor and interleukin-6 in paracrine tumor-stromal cell interactions in multiple myeloma. Blood 95:2630-6.

Further information:
https://www.medizin.uni-muenster.de/imm