TP11: Role of Tgif1 in breast cancer-induced pathological bone remodeling

Scientific staff

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Project description

In the bone microenvironment, breast cancer cells severely alter the balanced osteoblast-dependent bone formation and osteoclast-mediated bone resorption. Although the vicious cycle of bone metastasis is an established interaction between the cancer cells, osteoblasts and osteoclasts, more insights into the cellular and molecular mechanisms of the interaction between breast cancer cells and bone cells within the bone microenvironment and the process of cancer cell colonization into bone are needed. In this project, we aim to explore novel mechanisms of breast cancer colonization into bone and intend to further characterize the interactions of circulating tumor cells (CTCs) and disseminated tumor cells (DTCs) with the bone microenvironment. In addition, the emerging mechanistic data may provide the opportunity to establish a novel approach for targeting bone metastases. The project is based on our preliminary work demonstrating that the homeodomain protein TG-interacting factor 1 (Tgif1) is a novel regulator of osteoclast function and bone resorption. The underlying hypothesis of this project is that Tgif1 affects the cellular cross talk in breast cancer-induced pathological bone remodeling and may serve as a therapeutic target to reduce osteolytic bone disease. By combining *in vitro* experiments, innovative *in vivo* studies and patient samples we aim to investigate the role of Tgif1 in cancer-induced bone destruction *in vitro* and *in vivo*. Furthermore, we propose to target Tgif1 by microRNA (miRNA) replacement therapy and to analyze the miRNA-Tgif1 signaling in breast cancer patients. The results of this research project will expand our knowledge on the mechanisms of breast cancer metastases to bone and disease progression.

Expertise

We have established various syngeneic and xenograft models to investigate breast cancer growth, metastasis and cancer-induced bone destruction. In addition, we have profound expertise in bone histology, histomorphometry and bone imaging using *in vivo* and *ex vivo* uCT (viva80, Scanco).

Project-related publications

Haider MT, **Taipaleenmäki H**. Targeting the Metastatic Bone Microenvironment by MicroRNAs. *Front Endocrinol*. 9:202, 2018.

Taipaleenmäki H., Farina NH, van Wijnen, AJ, Stein, JL, **Hesse, E***, Stein, GS*, Lian, J.B*. Antagonizing miRNA-218-5p attenuates Wnt signaling and reduces metastatic bone disease of triple negative breast cancer cells. *Oncotarget*, 7:79032-79046, 2016. *equal contributors

Taipaleenmäki H, Browne G, Akech J, Zustin J, van Wijnen AJ, Stein JL, **Hesse E***, Stein GS*, Lian JB*. Targeting of Runx2 by miR-135 and miR-203 impairs progression breast cancer and metastatic bone disease. *Cancer Res.* 75:1433-44, 2015. *equal contributors

van der Deen M*, **Taipaleenmäki H***, Zhang Y, Teplyuk NM, Gupta A, Cinghu S, Shogren K, Maran A, Yaszemski MJ, Ling L, Cool SM, Leong DT, Dierkes C, Zustin J, Salto-Tellez M, Ito Y, Bae SC, Zielenska M, Squire JA, Lian JB, Stein JL, Zambetti GP, Jones SN, Galindo M, **Hesse E***, Stein GS*, van Wijnen AJ*. MicroRNA-34c inversely couples the biological functions of the runt-related transcription factor RUNX2 and the tumor suppressor p53 in osteosarcoma. *J Biol Chem.* 288:21307-19, 2013. *equal contributors

Browne G*, **Taipaleenmäki H***, Stein GS, Stein JL, Lian JB. MicroRNAs in the control of metastatic bone disease. *Trends Endocrinol Metab*. 25:320-7, 2014. *equal contributors

Hesse E, Saito H, Kiviranta R, Correa D, Yamana K, Neff L, Toben D, Duda D, Atfi A, Geoffroy V, Horne W.C, Baron R. Zfp521 controls bone mass by HDAC3-dependent attenuation of Runx2 activity. *J Cell Biol*. 191, 1271-1283, 2010.