TP09: Examination of the pleiotropic effects of Dickkopf-1 in osteotropic metastasis formation ("homing") and the colonization of breast cancer cells in bone

Scientific staff

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Project description

Dickkopf-1 (DKK-1) is best known for its role as a Wnt-Inhibitor that promotes osteolytic bone lesions by inhibiting osteoblast function. Our data indicate that DKK-1 has pleiotropic, context dependent effects during the steps of establishing bone metastases secondary to breast cancer. While direct anti-tumor effects were observed following DKK-1 knockout, vital steps of the metastatic process like migration or the potential to form colonies were unaltered or even increased. In our project, we aim at deciphering these effects in detail, explaining the underlying molecular mechanisms, and helping to define the therapeutic and prognostic potential of DKK-1 in the complex processes occurring from cancer cells homing to bone and their survival in the bone microenvironment to the establishment of overt bone lesions. Our central hypothesis is that **DKK-1 has complex and in part opposing effects during different stages of breast cancer homing to bone and the establishment of overt metastases within the bone microenvironment.**

Expertise

We have established human and murine osteotropic cancer cell lines with knocked out DKK-1 expression. These and further cell lines are used *in vitro* to analyze different aspects of metabolism, including vitality, proliferation, adhesion, migration, the clonogenic potential, and apoptosis using a broad panel of assays, western blot, ELISAs, and quantitative realtime-PCR. To assess the interactions of bone and tumor cells, we use murine osteoblastic and osteoclastic cell lines and *ex vivo* differentiation protocols. Furthermore, we are using established animal models with subcutaneous and intracardiac injections of different bone-homing tumor cell lines. Tumor formation and growth within bone can be imaged by bioluminescence. In addition we are able to comprehensively characterize the bone phenotype of mice and patients.

Project-related publications

Rachner TD, Kasimir-Bauer S, Göbel A, Erdmann K, Hoffmann O, Browne AJ, Wimberger P, Rauner M, Hofbauer LC, Kimmig R, Bittner AK. Prognostic value of RANKL/OPG serum levels and disseminated tumor cells in non-metastatic breast cancer. Clin Cancer Res. 2018

Rachner TD, Coleman R, Hadji P, Hofbauer LC. Bone health during endocrine therapy for cancer. Lancet Diabetes & Endocrinology. 2018;6:901-10.

Göbel, A., Kuhlmann, J.D., Link, T., Wimberger, P., Browne, A.J., Rauner, M., Hofbauer, L.C., and Rachner, T.D. (2017). Adjuvant tamoxifen but not aromatase inhibitor therapy decreases serum levels of the Wnt inhibitor dickkopf-1 while not affecting sclerostin in breast cancer patients. Breast Cancer Res. Treat. 164, 737–743.

Browne, A.J., Göbel, A., Thiele, S., Hofbauer, L.C., Rauner, M., and Rachner, T.D. (2016). p38 MAPK regulates the Wnt inhibitor Dickkopf-1 in osteotropic prostate cancer cells. Cell Death Dis. 7, 1–11.

Göbel, A., Browne, A.J., Thiele, S., Rauner, M., Hofbauer, L.C., and Rachner, T.D. (2015). Potentiated suppression of Dickkopf-1 in breast cancer by combined administration of the mevalonate pathway inhibitors zoledronic acid and statins. Breast Cancer Res. Treat. 623–631.

Rachner, T.D., Göbel, A., Thiele, S., Rauner, M., Benad-Mehner, P., Hadji, P., Bauer, T., Muders, M.H., Baretton, G.B., Jakob, F., et al. (2014c). Dickkopf-1 is regulated by the mevalonate pathway in breast cancer. Breast Cancer Res. 16, R20.

Further information: https://www.bone-lab.de