TP21: Hypoxia pathway proteins during homing and propagation of bone metastasis in mice

Scientific staff

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Project description

Sufficient oxygen pressure is required for our organs to function properly. Conversely, insufficient oxygen supply (**hypoxia**) is a prominent feature in various pathological processes, including tumor development and metastasis. The central mediators during hypoxia are **hypoxia inducible factors (HIF)** whereas their downstream effects are tightly regulated by **oxygen-dependent HIF prolyl hydroxylases (PHDs)**. Previously, we and others revealed that PHD2 plays a central role during different stages of tumor development, whilst this oxygen sensor is also essential during **bone mineralization,** and **normalization of the endothelial barrier** in the bone (marrow) after stress.

With this project, we aim to dissect the different roles of PHD2 in (prostate/breast) cancer bone metastasis models, including in transgenic mouse models (e.g. Flk1:cre-, Osx:cre-PHD2$^{f/f}$). We will focus on tumor cell **homing**, **colonization** and the **bone** microenvironment. This will allow us to evaluate the cell-intrinsic effects of the hypoxia pathway proteins as well as the impact of **bi-directional tumor/stroma cross-talk** in the bone/bone marrow.

Expertise

Expertise and methods for Hypoxia pathway proteins (HIF/PHD) and transgenic mouse lines (floxed lines: PHDs, HIFs, HIF-related proteins – various bone cell cre lines)

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

Xenograft models (PC3-Luc, C4-2B-Luc, MDA-MB-231) and syngeneic models (B16-F10, EO177, TRAMP-C1, RM1-BM, 4T1)

Project-related publications

Grinenko T, Eugster A, Thielecke L, Ramasz B, Krüger A, Dietz S, Glauche I, Gerbaulet A, von Bonin M, Basak O, Clevers H, Chavakis T, **Wielockx B**. Hematopoietic stem cells can differentiate into restricted myeloid progenitors before cell division in mice. Nat. Commun.,15;9(1):1898, 2018.

Rauner M, Franke K, Murray M, Singh RP, Hiram-Bab S, Platzbecker U, Gassmann M, Socolovsky M, Neumann D, Gabet Y, Chavakis, T, Hofbauer L, **Wielockx B.** Increased EPO Levels Are Associated with Bone Loss in Mice Lacking PHD2 in EPO-Producing Cells. *J Bone Miner Res.* 2016; (10):1877-1887.

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;30:471-80.

Mamlouk, S., J. Kalucka, R. P. Singh, K. Franke, A. Muschter, A. Langer, C. Jakob, M. Gassmann, G. B. Baretton and **Wielockx, B**. Loss of prolyl hydroxylase-2 in myeloid cells and T-lymphocytes impairs tumor development. *Int J Cancer,* 2014; 15;134(4):849-58.

Rachner TD, Göbel A, Thiele S, **Rauner M**, Benad-Mehner P, Hadji P, Bauer T, Muders MH, Baretton GB, Jakob F, Ebert R, Bornhäuser M, Schem C, Hofbauer LC. Dickkopf-1 is regulated by the mevalonate pathway in breast cancer. *Breast Cancer Research* 2014;16:R20.

Franke K, Kalucka J, Mamlouk S, Singh RP, Muschter A, Weidemann A, Iyengar V, Jahn S, Wieczorek K, Geiger K, Muders M, Sykes AM, Poitz DM, Ripich T, Otto T, Bergmann S, Breier G, Baretton G, Fong GH, Greaves DR, Bornstein S, Chavakis T, Fandrey J, Gassmann M, **Wielockx B**. HIF-1alpha is a protective factor in conditional PHD2-deficient mice suffering from severe HIF-2alpha-induced excessive erythropoiesis. *Blood* 2013;121(8):1436-45.

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