**TP5:** Junctional adhesion molecule interactions at the multiple myeloma interface

**Scientific staff**

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**Project description**

This project aims to explore the interaction of multiple myeloma (MM) cells with other cell types within the bone marrow (BM) niche. MM is a B-cell malignancy of clonally expanding antibody producing plasma cells that ultimately leads to osteolytic bone lesions, bone destruction, hypercalcemia, kidney failure, anemia and infections. MM is characterized by dissemination of multiple tumor cells throughout the BM. To date, MM remains a largely incurable and highly fatal hematologic disease. MM progression depends on interactions with the local microenvironment in the BM. MM cells in contact with BM-stromal cells and extracellular matrix (ECM) components escape the effects of therapy through cell adhesion-mediated drug resistance (CAM-DR) which is one of the major challenges in treating MM. It still remains elusive what mechanisms or interactions within the MM-BM-compartment encourage one or several malignant clones to leave their initial niche and start disseminating. The cell adhesion/migration system in the MM microenvironment has been recognized as a major mechanism of MM cell survival and the development of drug resistance and therefore became a promising target in MM treatment. Recent work and publications have demonstrated that tight junction molecules, including junctional adhesion molecule (JAM)-family members, are crucial components of signaling pathways that regulate cell polarity and vascular permeability, and have a vast potential to both repress and promote tumorigenesis. We identified members of the JAM-family as promising candidates to target MM – stroma/endothelium-interactions. **The central hypothesis for this proposal is that JAM-molecules are involved in mediating the contact between MM clones and the endothelium/stroma and that deregulation of these molecules leads subsequently to a different signal transduction within heterogeneous subclones.** To test this hypothesis we will visualize MM cell interactions with the BM endothelium/stroma regarding the involvement of JAM-molecules in direct and indirect co-culture experiments using fluorescence microscopy, flow cytometry and state-of-the-art light sheet fluorescence microscopy (LSFM) of intact bones as read out systems. Additionally we will determine the mRNA-expression profile of different MM cell populations after having physical contact with BM cells using our syngeneic MM mouse model.

The results of this project will yield **novel insights into the role of JAM-molecules and associated pathways in MM interactions with the bone microenvironment regarding survival, migration and dissemination.** Ultimately, we envision that a better understanding of the pathophysiology of JAMs in MM will result in optimal combinatorial treatment strategies to overcome drug resistance in patients suffering from MM and help to establish semi-personalized anti-MM strategies

**Expertise**

We have an established syngeneic orthotopic MM mouse model of non-invasive imaging that presents all the cardinal features of MM for intravenous and intratibial injections of luciferase-positive MM cell lines. The luciferase in the MM cells allows in vivo monitoring before and after drug treatment with bioluminescence imaging (BLI). This facilitates convenient, reliable, and sensitive tracking of MM cells within living animals. This model is highly suitable for monitoring the effects of different treatment regimens in immunocompetent mice. The microscopy technique that particularly enriches our toolbox to study MM – MM niche –

interactions is light-sheet fluorescence microscopy (LSFM). When combined with tissue clearing methods LSFM provides optical sectioning with multiple-view imaging of large specimen like intact bones with cellular resolution and low levels of photobleaching.

**Project-related publications**

Solimando AG\*, Brandl A\*, Mattenheimer K, Graf C, Ritz M, Ruckdeschel, Stühmer T, Mokhtari Z, Rudelius M, Dotterweich J, Bittrich M, Desanti V, Ebert R, Trerotoli P, Frassanito MA, Rosenwald A, Vacca A, Einsele H, Jakob F, Beilhack A. (2017). JAM-A as a prognostic factor and new therapeutic target in multiple myeloma. *Leukemia*, doi; 32(3):736-743.

Stegner D, Eeuwijk JMM, Angay O, Gorelashvili M, Pinnecker J, Schmitthausen P, Semeniak D, Friedrich M, Brede C, Beilhack A, Schulze H, Nieswandt B, Heinze KG. (2017). Thrombopoiesis is spatially regulated by the bone marrow vasculature. *Nature Communications*, 8:127.

Müller E, Bauer S, Stühmer T, Mottok A, Scholz CJ, Steinbrunn T, Brünnert D, Brandl A, Schraud H, Kreßmann S, Beilhack A, Rosenwald A, Bargou RC, Chatterjee M. Pan-Raf co-operates with PI3K-dependent signalling and critically contributes to myeloma cell survival independently of mutated RAS. Leukemia. 2016 Sep 30. doi: 10.1038/leu.2016.264.

Dotterweich J, Tower RJ, Brandl A, Müller M, Hofbauer LC, Beilhack A, Ebert R, Glüer CC, Tiwari S, Schütze N, Jakob F. The KISS1 Receptor as an In Vivo Microenvironment Imaging Biomarker of Multiple Myeloma Bone Disease. PLoS One. 2016 May 9;11(5):e0155087. doi: 10.1371/journal.pone.0155087. eCollection 2016.

**Further information:**
http://www.beilhack.org/