TP4: Dissecting the role of TAM receptors in myeloma-induced osteoclast activation and their immune-modulatory function

## Scientific staff

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## Project description

A hallmark of multiple myeloma (MM) is the reciprocal "vicious" interaction between PC and osteoclasts (OC). This cross-talk leads to disease progression, immunosuppression and osteolytic bone disease. Despite significant advances in the treatment of MM the disease remains incurable in the majority of patients. Therefore, the discovery of novel mechanisms promoting myeloma and its associated bone disease are still urgently needed. In this context, the development of an increased understanding of the interaction between myeloma cells, immune cells and bone cells is of special interest because immune cells hold great potential to destroy malignant cells. However, the regulation and therapeutic activation of anti-myeloma immune responses in the bone marrow is understudied. Our preliminary data show that Protein S (ProS) promotes the proliferation and survival of MM cells. At the same time, it fosters the activation of OC via the receptor Mer, which belongs to the TAM receptor family. Genetic blockade of ProS reduces myeloma burden and prolongs the survival of mice bearing a systemic MM model. Importantly, MM-induced bone disease is almost completely abrogated upon neutralization of ProS. Thus, the blockade of the ProS-Mer axis holds potential to reduce myeloma burden and decrease MM-induced OC activation. In addition, we found that ProS induces an immunosuppressive phenotype of OC.
Based on these data we propose a detailed functional investigation of the underlying molecular mechanisms and of the therapeutic potential of the clinically applicable small molecule Mer inhibitor R992 for treatment of MM with a special focus on bone disease. In addition, we will dissect the role of the two alternative TAM receptors Axl and Tyro 3 in osteoclastogenesis. For this purpose, we will use co-cultures and mouse models of MM with OC-specific blockade of TAMR by genetic approaches. Furthermore, we will evaluate the therapeutic effect of TAMR blockade on MM progression as well as on its associated bone disease and immunosuppression. Ultimately, we will translate our findings from the bench to the bedside by analyzing the association of ProS and TAMR with prognosis and MM-induced bone disease.

## Expertise

We established different systemic syngeneic and xenograft MM models eliciting osteolytic bone disease. In these models we monitor disease progression and survival. Furthermore, we analyze the interactions between the tumor cells and different cell populations within the bone microenvironment including osteoclasts and osteoblasts. In addition, in cooperation with E. Hesse (Hamburg) bone disease can be tracked by µCT analysis. We developed significant expertise in isolation and differentiation of osteoblasts, osteoclasts and immune cells including T cells. We perform co-culture of different cell populations in vitro in order to study the cross-talk between bone and immune cells. In addition, we have access to primary samples (PB and BM) from MM patients.

Project-related publications

Bauer R*, Udonta F*, Wroblewski M, Ben-Batalla I, Santos IM, Taverna F, Kuhlencord M, Gensch V, Päsler S, Vinckier S, Brandner JM, Pantel K, Bokemeyer C, Vogl T, Roth J, Carmeliet P, Loges S. Blockade of Myeloid-Derived Suppressor Cell Expansion with All-Trans Retinoic Acid Increases the Efficacy of Antiangiogenic Therapy. Cancer Res. 2018;78(12):3220-3232. (*equal contribution)

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Waizenegger JS*, Ben-Batalla I*, Weinhold N, Meissner T, Wroblewski M, Janning M, Riecken K, Binder M, Atanackovic D, Taipaleenmaeki H, Schewe D, Sawall S, Gensch V, Cubas-Cordova M, Seckinger A, Fiedler W, Hesse E, Kröger N, Fehse B, Hose D, Klein B, Raab MS, Pantel K, Bokemeyer C, Loges S. Role of Growth arrest-specific gene 6 - Mer axis in multiple myeloma. Leukemia. 2015;29(3):696-704. (*equal contribution)

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Further information:
https://www.uke.de/kliniken-institute/institute/institut-f%C3%BCr-tumorbiologie/forschung/arbeitsgruppen/index.html