TP13: Molecular and functional characterization of the normal and malignant plasma cell / bone interface – from single cell mutual interaction to clinical implications in angiogenesis, bone disease and survival

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Project description

Multiple Myeloma is a disease of malignant plasma cells spreading and accumulating in the bone marrow with subsequent induction of disseminated (osteoporosis) and localized (osteolytic lesions) bone disease. Myeloma cell interaction with mature bone cells and skeletal precursors confers bone resorption and inhibition of bone regeneration. Single cells may also reside and survive in protected niches in the bone marrow as a source for residual disease and relapse. Our main hypotheses are that physical interaction between skeletal precursors and myeloma cells creates niches and educates bone cells (MSC, OB), and that we can characterize the mutual interaction of tumor and bone in the niche using single cell harvesting and OMICs analyses. Our main **objectives** are to **molecularly and functionally characterize the bone marrow niche of normal vs. malignant plasma cells, to relate niche constitution and interaction factors to large cohorts of patient's malignant plasma cells characterized by molecular profiling, whole-body imaging and clinical outcome, and to functionally validate these findings *in vitro* and *in vivo*** (CRISPR/CAS9, adherence assays, U266-myeloma mouse model). Building on previous complementary and synergistic experience of our groups and network, dissecting this molecular crosstalk using single cell analyses will reveal targets to identify, mobilize and eradicate niche-protected dormant myeloma cells in order to cure residual disease and reconstitute bone regeneration. This project will contribute to a collaborative network within and beyond µBone to unravel myeloma dissemination, bone disease and angiogenesis.

Expertise

We have established coculture systems to study the mutual interactions of tumor and cells of the bone microenvironment and already characterized several relevant targets that are associated with the clinical outcome. In cooperation with the chair of the department of Material Sciences in Würzburg (Prof. Jürgen Groll) we physically and biochemically characterize and pick single tumor cells on a layer of skeletal precursors using a Fluid Atomic Force Microscope. Our groups are experienced in single cell analysis and array / RNAseq evaluation. Further experience comes from collaboration with the SPP partner Prof. Christoph Klein in Regensburg. We have access to large databases of patient derived myeloma cell populations for molecular profiling as well as their clinical data to correlate these data with the clinical outcome (profiled MMC (MGUS/ AMM/MM) by GEP (n=642), RNA-seq (n=356), WES (n=242), pairs AMM/MM (n=28), osteolyses/iliac crest (n=21) with wb-imaging, wbCT (n=324, bone lesions), wbMRI (PCI focal / diffuse, n=318), functional imaging, dceMRI (n=244) dwiMRI (cellularity, angiogenesis, n=220). We have also established mouse models and CRISPR/CAS9 techniques to evaluate candidate molecules for their functional relevance.

Project-related publications

1. Solimando AG, Brandl A, Mattenheimer K, Graf C, Ritz M, Ruckdeschel A, Stühmer T, Mokhtari Z, Rudelius M, Dotterweich J, Bittrich M, Desantis V, Ebert R, Trerotoli P, Frassanito MA, Rosenwald A, Vacca A, Einsele H, Jakob F, Beilhack A. JAM-A as a

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2. 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. 9;11(5):e0155087. doi: 10.1371/journal.pone.0155087. eCollection 2016. PubMed PMID: 27158817; PubMed Central PMCID: PMC4861277.
3. Dotterweich J, Schlegelmilch K, Keller A, Geyer B, Schneider D, Zeck S, Tower RJ, Ebert R, Jakob F, Schütze N. Contact of myeloma cells induces a characteristic transcriptome signature in skeletal precursor cells -Implications for myeloma bone disease. Bone. 2016 Dec;93:155-166. doi:10.1016/j.bone.2016.08.006. Epub 2016 Aug 9. PubMed PMID: 27519972.2016.
4. Seckinger A, Meißner T, Moreaux J, Depeweg D, Hillengass J, Hose K, Rème T, Rösen-Wolff A, Jauch A, Schnettler R, Ewerbeck V, Goldschmidt H, Klein B, Hose D. Clinical and Prognostic Role of Annexin A2 in Multiple Myeloma. Blood, 2012.
5. Neben K, Jauch A, Hielscher T, Hillengass J, Lehners N, Seckinger A, Granzow M, Raab MS, Ho AD, Goldschmidt H, Hose D. Progression in smoldering myeloma is independently determined by the chromosomal abnormalities del(17p), t(4;14), gain1q, hyperdiploidy, and tumor load. J Clin Oncol. 2013 Dec 1;31(34):4325-32. doi: 10.1200/JCO.2012.48.4923. Epub 2013 Oct 21. PubMed PMID: 24145347.
6. Seckinger A, Delgado JA, Moser S, Moreno L, Neuber B, Grab A, Lipp S, Merino J, Prosper F, Emde M, Delon C, Latzko M, Gianotti R, Lüoend R, Murr R, Hosse RJ, Harnisch LJ, Bacac M, Fauti T, Klein C, Zabaleta A, Hillengass J, Cavalcanti-Adam EA, Ho AD, Hundemer M, San Miguel JF, Strein K, Umaña P, Hose D, Paiva B, Vu MD. Target Expression, Generation, Preclinical Activity, and Pharmacokinetics of the BCMA-T Cell Bispecific Antibody EM801 for Multiple Myeloma Treatment. Cancer Cell. 2017 Mar 13;31(3):396-410. doi: 10.1016/j.ccell.2017.02.002. Epub 2017 Mar 2. PubMed PMID: 28262554.

Further information:
https://www.med.uni-wuerzburg.de/orthopaedie/startseite/
https://www.klinikum.uni-heidelberg.de/Research-Group-Hose-Seckinger.143456.0.html