

Intravital Microscopy of Prostate Cancer Lesions in Bone: Kinetics of Osteolysis and Therapy Response

E. Dondossola¹, Stephanie Alexander¹, Steve Alexander¹, B. Holzapfel², Christopher J Logothetis¹, D. Hutmacher² and P. Friedl^{1,3,4}

¹ David H. Koch Center for Applied Research of Genitourinary Cancers, The University of Texas MD Anderson Cancer Center, Houston, TX

² Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Australia

³ Radboud University Medical Center, Nijmegen, The Netherlands

⁴ Cancer Genomics Centre, The Netherlands

Background. Bone metastases are the initial site of progression and account for many of the complications experienced by men with metastatic prostate cancer (PCa), including therapy resistance. Besides cell intrinsic mechanisms, the interaction between PCa cells and the bone microenvironment critically contributes to lesion expansion and drug sensitivity.

Methods. We here developed a mouse model amenable to intravital multiphoton microscopy (iMPM) to longitudinally study PCa-stromal cell interactions and therapy response in a partially humanized neobone, established in the dermis of the mouse.

Results. Tissue engineered bone constructs, TEBCs, were generated by functionalizing polymeric polycaprolactone scaffolds with human mesenchymal stem cells (hMSCs) differentiated to osteoblasts followed by cell-derived calcification of the inter-scaffold space. 30 days after implantation of functionalized scaffolds under the skin of the mouse, bone and bone marrow maturation resulted in a 30mm³ cavity surrounded by optically transparent cortical bone of 50-60 mm thickness, as monitored by microCT and iMPM. Intra-bone tumor growth and osteolysis dynamics caused by human fluorescent PCa cells (PC3) were three-dimensionally reconstructed by multi-parameter detection through a body window, including collagen and bone matrix (SHG), calcified bone (fluorescent bisphosphonates), osteoclasts (cathepsin K), bone surface (THG), blood vessels and stromal phagocytes (fluorescent dextran), and PC3 cells (nuclear H2B/eGFP, cytoplasmatic DsRed2). As a proof of concept, the efficacy to halt bone remodeling during bisphosphonate therapy was detected, revealing the composition and kinetics of the bone-tumor interface.

Conclusions. Combining engineered neobone with an optical window is suited to detail the 3D organization and dynamics of cancer lesions in bone and provides mechanistic insight and efficacy predictions for therapy response. Thus, this strategy will be implied to dissect the therapeutic effect of radium 223, a radioisotope with bone seeking properties, and the first agent that improves the duration and quality of life of advanced metastatic PCa patients. By using this model we will test the hypothesis that ²²³Ra alters stromal niches, structurally and molecularly, in a manner that accounts for the clinical observations in established macroscopic lesions.

Conflicts of interest: None

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