New preclinical model for immuno-oncology: combination of tumor, bone microenvironment and immune system

Tiina E. Kähkönen1, Mari I. Suominen1, Jenni Mäki-Jouppila1, Jussi M. Halleen1, Azusa Tanaka2, Michael Seller2 and Jenni Bernoulli1

1Pharmatest Services Ltd., Finland – Email: Correspondence to tiina.kahkanen@pharmatest.com
2Taconic Biosciences, Hudson, NY, USA

Breast and other solid tumors commonly metastasize to bone. Bone marrow microenvironment regulates hematopoietic stem cells and thereby immune cell differentiation. Therefore, a system with functional interaction between bone, immune system and cancer is a prerequisite in development and preclinical testing of novel immunotherapies against osseous tumors.

Aim of the Study

To establish a model where tumor, bone microenvironment and immune system would be combined to a functional entity, to characterize the tumor-induced bone changes, and to establish a validated platform for preclinical testing of immunotherapies.

Materials and Methods

An intratrautal injection of 1x10^6 of BT-474 (ER+, PR+, HER2+, ATCC) human breast cancer cells was given to female NOG and huNOG mice (HSCT-NOG-F, provided by Taconic Biosciences). These humanized mice were produced through engrafting HCD34+ hematopoietic stem cells (HSC) into C57BL/6J nude mice (NOG.Cg-PtK1r+/+Tcl/JcTac; Taconic Biosciences). Tumor-induced bone changes were followed by radiography at 4, 6 and 8 weeks. Bone mineral density (BMD) was quantified by dual-energy x-ray absorptiometry (DXA), and bone volume and three-dimensional architecture was studied by micro computed tomography (μCT). Spleen, thymus, lymph nodes and hind limbs were collected and tumor and bone areas, as well as the expression of human CD3 (BSR10, Nordic Biosite), CD4 (B594, Nordic Biosite), CD8 (B56, Nordic Biosite), CD45 (2B11/PD27/26, Nordic Biosite), CTLA-4 (B568, BioSB) and PD-L1 (P03, Diza Corporation) in immune cells was analyzed.

huNOG mice support mainly the differentiation of T- and B-cells. If differentiation towards lineage X is desired, transgenic NOG mice can be used for engraftment: hIL6-NOG: monocytes, hIL2-NOG, hIL15-NOG: NK-cells and huNOG-EXL: all lineages.

Conclusions

To our knowledge, this study describes establishment of the first humanized mouse model of tumor growth in bone. The model is characterized by tumor growth and extensive tumor-induced osteoblastic changes and tumor-infiltrating human immune cells in bone, and it mimics the late stage of breast cancer metastasized to bone. This humanized mouse model provides a completely new platform for preclinical testing of cancer immunotherapies, particularly therapies targeting cancers metastasizing to or growing in bone.

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