Establishment of realistic patient-derived preclinical models for prostate cancer bone metastasis

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Introduction

Bone metastases are frequent and fatal outcome of advanced prostate cancer. Many of the currently used preclinical models lack typical characteristics of the heterogenic human disease. We improved existing methodology by using fresh patient-derived tissues.

Patient-derived xenografts of prostate cancer

Clinical prostate tumor specimens were collected from robotic-assisted laparoscopic radical prostatectomy operations in Turku University Hospital (Turku, Finland). These aggressive tumors (Gleason score 7–9) were cut into small pieces and used in two separate experiments to generate patient-derived xenograft (PDX) models.

In the first experiment, the tumor fragments were implanted subcutaneously to nude mice bearing testosterone pellets. The original Gleason scores were retained in the first passage but were lost in the following passages (Figure 1).

In the second experiment, the tumor fragments were digested and inoculated intratibially into the bone marrow cavity of nude mice (Figure 2). The passaging was performed via intratibial inoculation to preserve the typical microenvironment-related characteristics. Thus far, these intratibial PDXs have been grown for four passages. Osteosclerotic tumor growth was observed in bone (Figure 3) and subsequent metastasis to lungs was detected in several mice (Figure 4).

Tumor take rate was approximately 50% in both models as detected by X-ray radiography and histology (Figure 1 and 3), and it correlated with the aggressiveness of the original tumor.

FIGURE 1. Two representative examples of subcutaneous PDXs. PDXs retained their original Gleason grade 4+5 during first subcutaneous passage. However, after following passages, mouse fibroblasts invaded to PDX and human characteristics were lost (data not shown). Bar 200 µm.

FIGURE 2. A. Tissue from prostate cancer patient (Gleason grade 4+5) was cut and digested (B) overnight. Cells were inoculated intratibially into nude mice (C). After 4 months, osteosclerotic tumor was collected, digested and reinculcated.

A. Pathologist drilled tissue from prostate
B. Tissue was cut and digested
C. Cells were inoculated intratibially

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REFERENCES


FIGURE 3. A) Intratibial PDX formed osteosclerotic tumors in bone. X-ray radiography of tumor-bearing and healthy mouse. B) Bone metastasis (white arrow) and healthy bone marrow. Bar 100 µm.

FIGURE 4. Representative figures of PDXs that have metastasized to lungs. Lungs of mice were stained using H&E (A) and immunohistochemically with androgen receptor (AR) (B) and PSA (C) antibodies. Metastases had negative AR and PSA expression. Bar 200 µm.

A. H&E-staining
B. AR-staining
C. PSA-staining

Withdrawn