Establishment of patient-derived prostate cancer models for drug development and personalized medicine studying fibroblast growth factor receptor (FGFR) inhibitors as investigational drugs

Tuomela Johanna1, Yu Lan2, Tuomala Mikka1, Taimen Pekka2, Boström Peter1, Halleen Jussi1 and Härkönen Pirkko1
1Pharmatest Services Ltd, Turku, Finland; 2Institute of Biomedicine, Department Cell of Biology and Anatomy, University of Turku, Turku, Finland

Introduction

FGF-signaling pathway seems to have an important role in the progression of metastatic prostate cancer, and FGFR inhibitors have provided interesting preliminary results in preclinical studies. However, many of the currently used preclinical tumor models lack typical microenvironment and characteristics of human disease. The aim of this study was to establish patient-derived prostate cancer models (PDX) and study FGFR inhibitors as potential investigational drugs.

Materials and methods

Clinical prostate tumor specimens were collected from robotic-assisted laparoscopic radical prostatectomy operations in Turku University Hospital, Turku, Finland (Figure 1). Patient-derived tissues of Gleason grade 7-9 were cut into 1-2 mm\(^3\) pieces and cultured in vitro for 6 days with androgen supplementation. FGFR inhibitors Dovitinib and AZD4547 were administered into the tissue culture medium (Figure 2). Viability and differentiation of cultured tissues were examined immunohistochemically by the expression of Ki-67, androgen receptor (AR) and PSA. PDX in vivo models were developed by implanting tissue pieces either subcutaneously or subrenally, or by digesting and then inoculating intratibially into the bone marrow cavity of Balb/c nude mice. Mice were supplemented with testosterone pellets.

Conflict of interest

Johanna Tuomela and Jussi Halleen are employees of Pharmatest Service Ltd. Authors claim no conflict of interest.

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References


Results

In vitro

Non-cultured Dovitinib AZD4547

In vivo

H&E

A) Original tumor B) 1st passage C) 2nd passage D) 3rd passage

FIGURE 6. Intratibial model. Tumor pieces were digested and inoculated intratibially or subrenally. Tumor growth was followed by x-ray and ultrasound.

FIGURE 7. A) Tissue from s.c. PDX (originally Gleason grade 4 + 5) was digested, and the cells were inoculated intratibially. After 4 months, osteoblastic tumour was collected, digested and reinoculated. Tumor cells formed metastases to lungs. However, they have lost many original characteristics. Bar 200 µm.

Conclusion

FGFR inhibitors demonstrated anti-proliferative effects on patient-derived models in vitro. Challenging PDX prostate cancer in vivo models were successfully established utilizing various tumor microenvironments. These models provide a personalized medicine tool that could be used to test the individual prostate cancer patients’ responses to therapy in the future.