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Imaging of Tumor Growth and Metastasis In a Pancreatic Cancer Mouse Model

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Introduction

Mouse models have been developed for use in cancer research to investigate antitumor response and its role in disease progression, as well as to predict efficacy and find toxicities for cancer chemotherapeutic agents prior to beginning a clinical test. Among mouse models, human tumor xenograft has become the most common. In this model, human tumor cells are transplanted into immunocompromised mice which do not reject human cells, either under the skin or directly into the organ in which the tumor originated[1]. Depending upon the number of cells injected or the size of the tumor transplanted, the tumor will develop over several weeks or months and the response to appropriate therapeutic regimes can be studied *in vivo*.

Here, we used the UVP iBox® Scientia™ Imaging System (UVP, LLC, Upland, CA) to visualize the tumor in a pancreatic cancer model *in vivo*. Tumor growth is then measured using the Area Density functionality of the UVP VisionWorks®LS Acquisition and Analysis Software.

Materials & Methods

Vector, Cell Line and Animal

The human pancreatic cancer cell line MIA-PaCa-2 was transduced with Red Fluorescent Protein (RFP)-tagged plasmid. Cell culture and selection of MIA-PaCa-2 cells stably expressing RFP were conducted. Male nude mice (BALB/c-nu/nu) were purchased from Beijing HFK Bio-Technology Co. Ltd., China. The nude mice were acclimated for one week prior to the experiment.

Orthotopic Transplantation Tumor Model

MIA-PaCa-2 cells stably expressing RFP were grown in RPMI-1640 medium supplemented with 10% fetal calf serum (FCS) until harvested. The mice were anesthetized with isoflurane. Cells (1×10^7 cells in 0.1 mL PBS) were subcutaneously injected into the nude mice. The mice were observed regularly after tumor cell injection and monitored for signs of wound healing disturbance, evidence of tumor development and decreased physical activity.

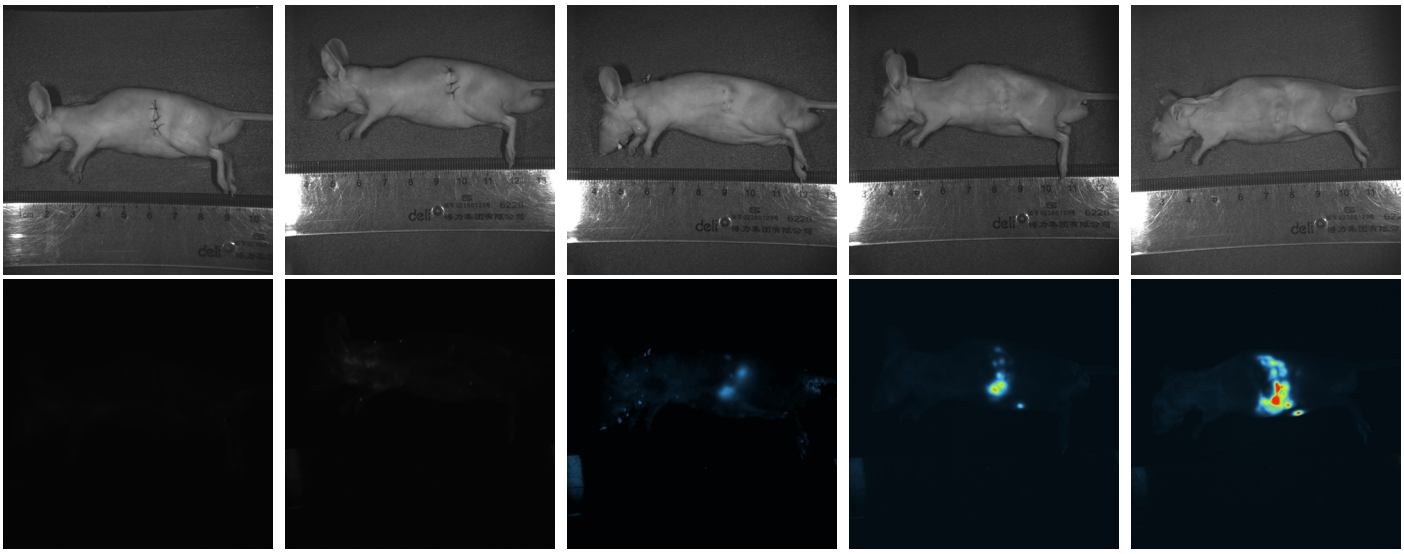

Figure 1. Tumor growth in nude mice at 1, 7, 14, 21 and 28 days after transplantation. The upper row shows mouse images captured at the aforementioned time periods under white light. The lower row shows the correponding RFP signal detected images using the RFP filter set, including excitation filter (525 BP45) and emission filter (650 BP50).

The mice with tumor growth were selected and used for orthotropic transplantation. Tumor tissues were harvested and cut into pieces under aseptic conditions. Tumor pieces were orthotopically implanted into new mice, and the mice were then placed back into their cages and raised.

Fluorescent Imaging

The mice were observed each week following tumor transplantation. Mice were anesthetized and images of the animals were captured each week with the iBox Scientia configured with the RFP excitation filter (525 BP45) and emission filter (650 BP50).

Image Processing and Analysis

UVP's VisionWorksLS Acquisition and Analysis Software was used to measure the optical fluorescence density of the tumor's RFP signals and for data presentation. Identical region of interest (ROI) windows were used during analysis to ensure repeatable, consistent quantification of the fluorescence signal in different images.

Results & Discussion

During the course of the experiment, the mice demonstrated evident weight loss after transplantation (Figure 1, upper row). The tumor was developed quickly after transplantation in mouse body. On the day of transplantation (Day 1), the implanted tumor tissue was small and covered by other tissues, no RFP signal was visible. Even at day 7, there was no obvious RFP signal at the tumor site. At 14 days after transplantation, weak RFP signal was observed at the primary site, indicating that the tumor cells were growing. 21 days after the transplantation, a dramatic increase in RFP signal was observed from the primary site. In addition, strong signal was seen in the abdominal cavity, indicating that the pancreatic tumor cells had broken off from the primary tumor site and metastasized to other organs. At 28 days post transplantation, the RFP signal continued to increase in size, indicating that further tumor metastasis was formed in mouse body.

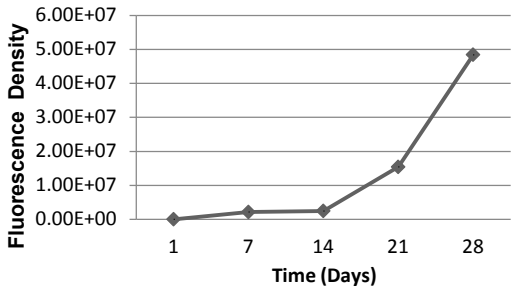

Figure 2. Tumor growth curve. Mice were imaged each week from day 1 to day 28 post implantation. Quantification (fluorescence density) of the RFP fluorescent signal from the tumor regions was performed using VisionWorksLS software.

Quantification data (Figure 2) confirmed our observation that the tumor cells were continuously growing during the entire length of the experiment. The RFP signal density at 28 days was approximately 18 fold higher compare to that shown on day 14.

In our study, the pancreatic cell line MIA PaCa-2, established by A. Yunis, et al. in 1975 from pancreatic tumor tissue obtained from a 65-year-old Caucasian male, was used[2]. This cancer cell line was selected as it has a high potential to form metastases. The RFP-tagged MIA PaCa-2 mouse model permits easy tracking and quantification of fluorescent signal from tumor growth *in vivo*. Furthermore, it is an efficient method for real time evaluation of therapeutic efficacy.

The UVP iBox Scientia Imaging System (Figure 3), together with VisionWorksLS Acquisition and Analysis Software, provided reliable imaging and data analysis tools for studying tumor matastasis in a mouse model.

References

1. Richmond, A, Su, Y. Mouse xenograft models vs GEM models for human cancer therapeutics. Dis Model Mech, 1(2-3), 78-82, 2008.
2. http://www.atcc.org/~/ps/CRM-CRL-1420.ashx

Figure 3. iBox Scientia Imaging System