Introduction

Tumor cell invasion is traditionally studied in three-dimensional (3D) models composed of rat or mouse extracellular matrix (ECM) proteins such as type I collagen and laminin (1). However, there is an urgent need for more predictive fully human 3D models to be utilized in drug discovery and development.

As both molecular and cellular components of tumor microenvironment (TME) play critical roles in tumor progression, special attention should be paid to the growth environment in 3D cultures (2).

Myoma tissue consists of cellular components (endothelial cells, smooth muscle cells, lymphocytes, macrophages, fibroblasts, myofibroblasts, etc.) and various extracellular matrix proteins and glycoproteins (such as collagen types I, II and III, and laminins). It is therefore an ideal platform for tumor cell invasion (3).

The aim of this study was to characterize a novel fully human organotypic model using uterine leiomyoma tissue and various cancer cell lines to be used for testing efficacy of potential new cancer drugs in preclinical phases of drug development.

Materials and Methods

• 3–4 × 10^5 tumor cells were added on top of macroscopically heterogeneous 8-mm biopsy discs. The cells were attached overnight and the myoma discs were transferred onto nylon discs resting on curved steel grids in 12-well plates with sufficient volume of media as described earlier (3). After 10 days of culture myomas were fixed and embedded into paraffin and sectioned.

Organotypic sections were examined by histological (HE) staining and immunohistochemical stainings against cytokeratin and GFP. The invasion was analyzed microscopically where maximal invasion depth per microscopic field was measured.

Doxycycline (10 µM; in cell culture media) was used as a test compound.

Criteria for the selection of myomas were size, location (intramural, submucous), medication (hormonal treatment), menstrual cycle, age of donor (premenopausal, perimenopausal, postmenopausal). The myoma tissues were obtained after informed consent of the patients from routine surgery at the Department of Obstetrics and Gynaecology, Oulu University Hospital. Each experiment was performed using discs from the same dissected myoma.

Conclusions

We conclude that the established fully human organotypic 3D model provides a remarkable advantage to screen potential new therapeutic options for cancer. It provides a totally new commercially useful testing platform for identifying innovative treatment approaches targeting cancer cells and/or TME components.

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References


Organotypic 3D invasion platform: Tumor cells, grown on the top of myomas were allowed to invade the tissue. Myomas were collected, fixed, embedded to paraffin and sectioned. Stains were stained by either histological or immunohistochemical methods.

Tumor cells (arrows) in myoma tissue. Representative Hematoxylin and eosin (H&E), immunohistochemical GFP (G) and peroxidase (D) stainings. The difference in invasion between cell lines was quantified as maximal invasion depth. Photochromic noninvasive cell layer and any artificial invasion were excluded from the analyses. Doxycycline inhibited invasion of HSC-3 cells (F).

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