P64 Radiosensitivity of patient-derived xenograft tissue slices versus organoids in prostate cancer

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Introduction & Objectives: Radiation therapy (RT), usually combined with androgen deprivation therapy, is a standard treatment option for localised and locally advanced prostate cancer (PC). However, tumors might recur after RT and new combination strategies aiming to enhance RT effect are under investigation. Unfortunately, traditional cell line models may not adequately recapitulate in vivo irradiation effects. Novel 3D culture technologies might circumvent this disadvantage while preserving the suitability for semi-high throughput screening approaches. Here, we evaluate the radiosensitivity of PC organoids, in order to use them as a representative preclinical model for the testing of radiotherapy-drug combinations.

Materials & Methods: Tissue slices and organoids from 2 androgen-dependent and androgen receptor (AR) positive patient derived xenografts (PDX; *Navone et al. Prostate 2018*) were tested and compared for their sensitivity to RT. PC310 harbors a homozygous deletion in the breast cancer associated two (*BRCA2*) gene, while PC82 is a *BRCA2*-wild type tumor. Tissue slices were produced and cultured as reported previously (*Zhang et al. Prostate 2019*). Organoids were established by plating small cell clumps from fresh PDX tumors into synthetic hydrogel (Noviogel, NovioCell, Oss, The Netherlands). They were passaged and cultured until sufficient volumes were reached. Tissue slices and organoids were irradiated with a dosage of 2Gy using an Xstrahl Cabinet Irradiator RS320 (Xstrahl Ltd., Camberley, UK). Cell proliferation, apoptosis and DNA damage response were evaluated immediately, 24 and 72 hours after RT by EdU incorporation/Click-iT™ reaction, TUNEL assay and detection of 53BP1 foci as a marker of DNA double-strand breaks (DSBs), respectively.

Results: Directly post-RT, no effect on cell proliferation and apoptosis was observed, neither in tissue slices nor organoids. In both models, a significant drop in cell proliferation was observed after 24 and 72 hours, while a significant increase in the apoptotic cell fraction occurred after 72 hours. In PC82 organoids, this increase was already observed after 24 hours. These organoids seem to be highly sensitive to RT, with no proliferating cells at 24 hours after irradiation. In both tissue slices and organoid cultures, DSBs, evaluated by the number of 53BP1 foci per nucleus, were repaired at 72 hours post-RT in PC82 while this was not the case in the PC310 model. However, repair kinetics in PC82 might be biased due to RT-induced high cell apoptosis levels.

Conclusions: We show a comparable response to RT between PDX derived organoids and their matched tissue slices, making PC organoids an interesting preclinical model for testing radiotherapy-drug combinations and allowing semi-high throughput screening. Whether PC82 carries mutations which lead to high radiosensitivity warrants further investigation.