

MSc DEFENCE Thursday, March 2nd, 2017

Student: Ada Young

Title: CLINICALLY RELEVANT CONVENTIONAL DOSE OF IONIZING RADIATION ENHANCES TUMOUR CELL MIGRATION IN HUMAN BREAST CANCER CELL LINES

Time and location: 9:30am PDT; 2nd Floor Meeting Room, BC Cancer Research Centre, 675 West 10th Avenue, Vancouver, BC

Supervisor: Kevin Bennewith

ABSTRACT

It is estimated that >90% of cancer-related deaths are associated with the development and growth of tumour metastases. While tumour cell migration can be enhanced by high doses of ionizing radiation (IR) *in vitro*, the effect of lower, clinically relevant conventional IR doses on tumour cell migration and metastasis is unclear. We hypothesize that tumour cells that survive radiation therapy have a higher propensity to migrate, invade and eventually metastasize to secondary sites, independent from radiation-induced changes in the solid tumour microenvironment.

Breast cancer cell lines treated with 2.3Gy IR were imaged in real-time over 72h to quantify changes in single cell migration. EMT statuses of cell lines were determined using Western blot and flow cytometry. We used conditioned medium from irradiated cells to determine whether cellular migration was influenced by secreted factors. TGF- β ELISAs were used to elucidate its possible role in enhancing cell migration after IR. Human chemokine antibody array was used to identify radiation-induced secreted factors. Pre-irradiated and sham treated breast tumour cells were IV-injected or orthotopically implanted into mice to examine changes in lung extravasation and local invasion respectively.

The mesenchymal MDA-MB-231 and LM2-4 cell lines treated with 2.3Gy of IR migrated a greater total distance and/or displaced further from the point of origin compared to untreated cells. We did not observe induction of EMT by 2.3Gy irradiation, although MCF-7 cells migrated further from the point of origin after IR. Conditioned media from 2.3Gy treated tumour cells enhanced migration and displacement of untreated tumour cells. TGF- β ELISA analysis of supernatants from sham and 2.3Gy treated MDA-MB-231 cells revealed an almost two-fold increase in TGF- β 1 in 72h post irradiated samples compared to sham controls. Chemokine antibody arrays revealed a number of up-regulated proteins after 2.3Gy treatment. 8 hours after IV injection, 2.3Gy pre-irradiated tumour cells observed enhanced lung extravasation compared to sham controls. There was no significant difference in local invasion between orthotopically implanted sham and 2.3Gy treated MDA-MB-231 cells.

IR dose of 2.3Gy are sufficient to enhance migration of both non-metastatic and metastatic breast cancer cell lines independent of EMT. By quantifying changes in the metastatic ability of tumour cells treated with a clinically relevant dose of radiation, our findings will help to determine whether there is a need for additional administration of targeted secondary therapy to minimize tumour cell dissemination.