Genetic and metabolic control of radiotherapy-induced breast cancer metastasis

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Abstract

While radiotherapy is standard clinical practice for women with breast cancer (BC), the consequences surrounding low-dose ionizing radiation (LDIR) are much less understood. Due to uneven dose distribution, the tumor core, margins and diffusive infiltrates can receive LDIR as a byproduct of primary tumor irradiation. This would generate subcytotoxic effects, among which mitochondrial defects could be relevant based on the consideration that mitochondrial DNA (mtDNA) is a primary target of radiation. Recently, our lab has reported a link between mitochondrial defects and the promotion of cancer cell migration, invasion and metastasis, where subcytotoxic levels of mitochondrial ROS (mtROS) activate the transforming growth factor β (TGFβ) pathway at the level of src kinase directly within mitochondria (1). Therefore, we hypothesize that BC cells receiving LDIR could also display an increased capacity to migrate, invade and metastasize.

Here, using human MCF-7 and MDA-MB-231 breast cancer cells, we report that a single dose of LDIR elicits maximal migration below the conventionnal clinical dose of 2 Gy (0.5 Gy and 0.125 Gy, respectively). In MCF-7 cells, maximal migration was accompanied by a peak in basal respiration and ATP production detected by Seahorse oximetry, and a concomitant increase in mtROS production via dihydroethidium (DHE) and MitoSox staining. In MDA-MB-231 cells, maximal migration was accompanied by a decrease in basal respiration and ATP production, however still associated with an increase in ROS production. In MCF-7, the general ROS inhibitor N-acetyl-L-cysteine, but also specific mtROS inhibitors MitoQ, SOD2 overxpression and mitochondrial-targeted catalase overexpression all abolished LDIR-induced metastasis. In MDA-MB-231, pharmacalogical and transgenic ROS inhibitor experiments are currently ongoing.

Collectively, our data indicate that BC cell migration and therefore possibly also invasion and metastasis could be a side effect of radiotherapy when the cytotoxic dose is not reached. This study provides an incentive to evaluate mitochondria-targeted pharmacological agents as inhibitors of LDRI-induced prometastatic responses and to elucidate targetable mtROS-induced pathways that contribute to these responses.

References

1. Porporato PE, et al. Cell Reports 2014;8:754-766.