

# Characterization of local and systemic effects of radiotherapy in a breast cancer mouse model

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Radiotherapy, the standard of care therapy for breast cancer patients, can induce systemic phenomena which lead to regression and rejection of non-irradiated, distant tumor lesions (abscopal effect). The 4T1 breast cancer model was used in immunocompetent BALB/c mice to study this abscopal effect that is linked to the immune system. The modulation of stromal cells after radiotherapy in bone marrow, blood and lungs was monitored by flow cytometry. Expression of different genes including c-Kit, CCN1, ZEB2, arginase II and IL-1 $\beta$  was modulated in the blood and bone marrow by local radiotherapy, confirming an inflammatory systemic effect induced by radiotherapy. Interestingly, radiotherapy treatment induced a strong cellular immune response particularly in the blood, involving both natural killer cells and pro-inflammatory myeloid cells. Moreover, the systemic effects of radiotherapy were also observed at protein level. Indeed, several growth factors (M-CSF, FGF, IGF1), angiogenic factors (angiopoietin, endostatin) and metalloproteases were affected by radiotherapy. An upregulation of anti-metastatic factors including RAGE, PAI-1 and TPO was detected in irradiated mice. Furthermore, systemic anti-tumor effects of radiotherapy were also confirmed in the lungs where an increased percentage of pro-inflammatory myeloid cells and c-Kit<sup>+</sup> immune cells was detected in the lungs of irradiated mice. Finally, splenomegaly and lymphadenopathy were observed in the 4T1 BALB/c model and lymphadenopathy seems to be associated with no effect of radiotherapy. Further experiments need to be performed in order to establish the link between radiotherapy response, development of lymph node ganglia and splenomegaly.

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