CCL2/CCR2-driven monocyte recruitment to the tumor following radiotherapy influences the outcome of the treatment of head and neck cancer

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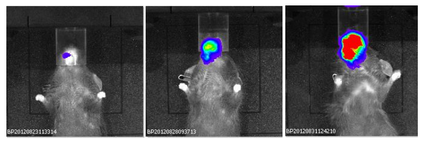
INTRODUCTION

We hypothesized that monocytes recruited to tumor sites affects the response to radiotherapy (RT). Local RT is the major treatment to control locally advanced head and neck (H&N) cancer. Several findings suggest that immuno-modulatory agents may synergize with RT. The role of monocytes/macrophages in the response to RT is under extensive investigation. Among the many factors secreted by tumor cells, **the chemokine CCL2 and its receptor CCR2 are involved in inflammatory monocyte recruitment** from bone marrow to the inflammatory site. We have recently developed a **model of human papillomavirus (HPV)-related H&N cancer using immunocompetent mice** and validated its usefulness to evaluate the tumor response to the combination of a cancer vaccine and RT [1]. Here we exploit the same model to analyze the role of myeloid cells in the response to local RT.

METHODS

TC1/luciferase cells were injected at a sub-mucosal site in the inner lip of C57Bl/6 mice to mimic a head and neck cancer. Tumor growth was followed by *in vivo* imaging.



Days after tumor challenge

4 **8** **14**

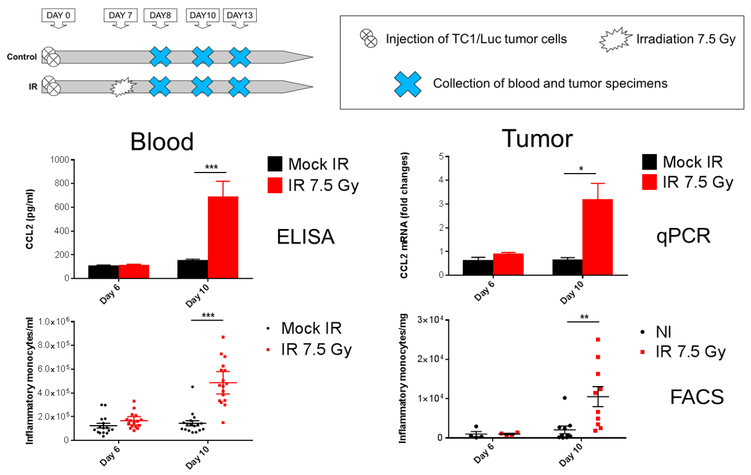
Local irradiation to the head and neck region was performed using a 200 kV Varian X-ray irradiator at a dose rate of 1,08 Gy/min

Multiparametric flow cytometry analysis was performed to characterize the immune infiltrate, using the following markers: CD45, CD11b, CD11c, CD64, Siglec-F, Ly6C, Ly6G, F4/80

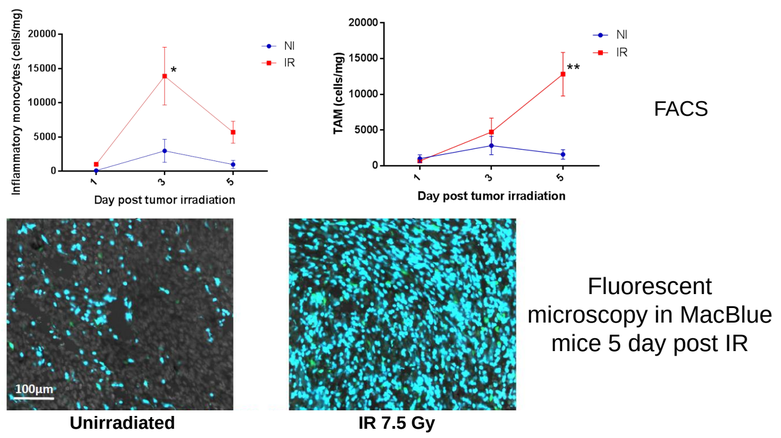
Fluorescent imaging was performed on tumor-bearing MacBlue mice, expressing ECFP from a truncated colony stimulating factor 1 receptor (Csf1r) promoter

RESULTS

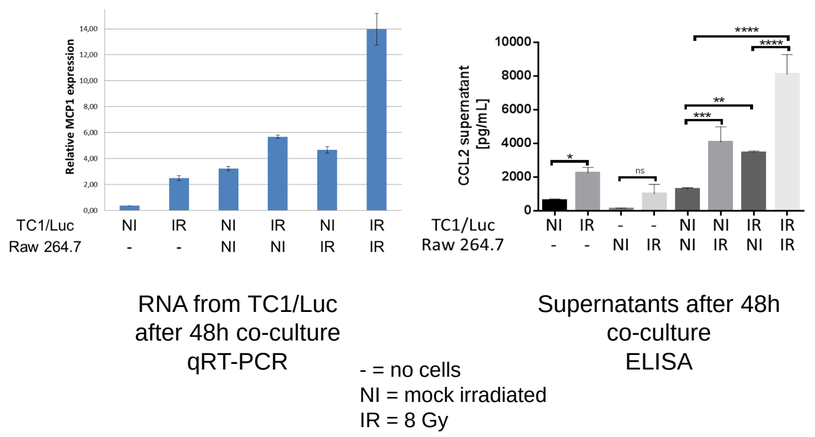
Local radiotherapy increases CCL2 levels and monocyte infiltration



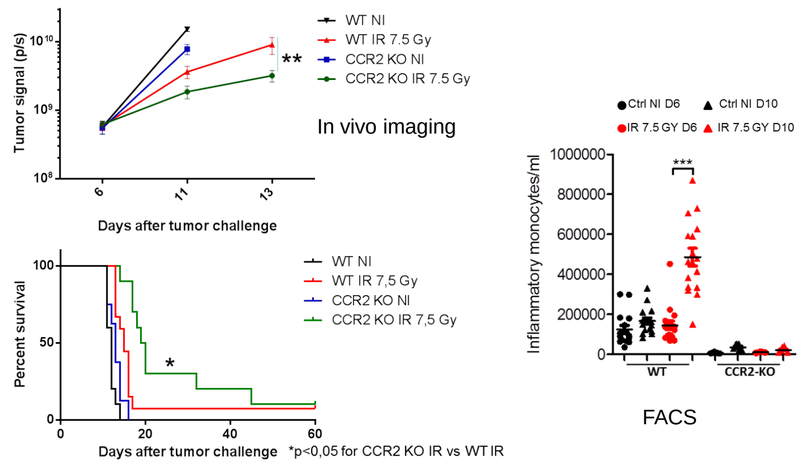
TAM are upregulated at later time points



Irradiation-induced CCL2 in tumor cells is increased by co-culture with monocytes



CCR2 KO mice have a better tumor response and a better survival



Similar results were obtained in CCL2 KO mice

CONCLUSIONS

Our data suggest interplay between tumor and monocytes/macrophages that can amplify the effects of radiotherapy on the immune system. We propose that **reducing radiation-induced monocyte recruitment yields improved results in the treatment of HPV-related head and neck cancer by radiotherapy**, in line with observations made in other cancer types [2,3]. Immunologically-augmented radiotherapy could allow reduction of the delivered radiation dose, thus minimizing the risk of treatment sequelae while maintaining optimal tumor control.

REFERENCES

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3. Connolly KA et al., Oncotarget. 2016

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