The abscopal effect: modeling and predicting the effect of radiation therapy on non-irradiated tumors when combined with immune-checkpoint blockers

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Introduction

We have developed preclinical and clinical 'Virtual Tumor' ('VT') models that can predict how a tumor will respond to drug exposure. The agent-based method we employ is particularly suitable for modeling not only tumor cells, but also entities involved in the adaptive immune response, and the interactions between these species[1-3]. The purpose of this study was to extend the VT platform to model simultaneously: i) the response of a tumor treated with ionizing radiation (IR) only or in combination with immune-checkpoint blockers; ii) the tumor response in lesions where radiation has not been performed, in the absence/presence of an immune-checkpoint blocker. Building on previous work, in which the VT platform was extended by the addition of a module that captures the synergy of PD(L)-1 blockade with conventional anticancer therapies[1], we have further expanded the model to integrate the immune-checkpoint blocker module with immune species activated by irradiation of the target tumor – in particular circulating cytotoxic T cells – in order to mimic the systemic abscopal effect. Ultimately, this expansion enables us to simulate the effect of tumor growth control on out-of-field lesions when delivered in combination with an immune-checkpoint blocker.

Extension of the Virtual Tumor immuno-oncology model to include the abscopal effect

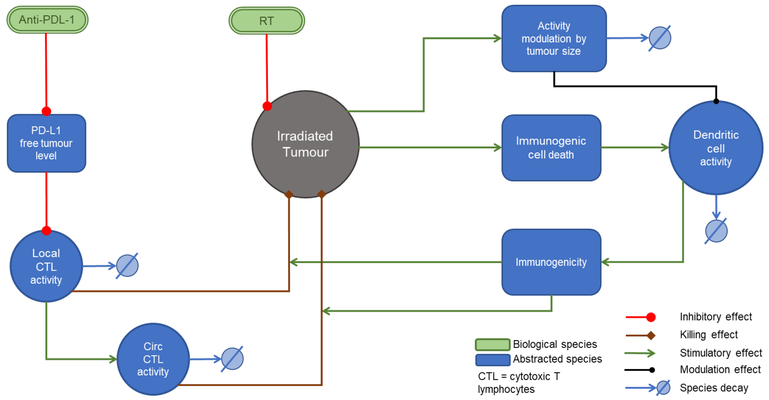

Figure 1. Schematic of the Virtual Tumor model for the irradiated tumor. IR treatment results in immunogenic cell death (ICD), which (via dendritic cell function) increases the immunogenicity of the tumor and amplifies the anti-tumor activity of cytotoxic T cells (CTLs). Anti-PD-L1 therapy releases the suppression of CTL activity by PD-L1.

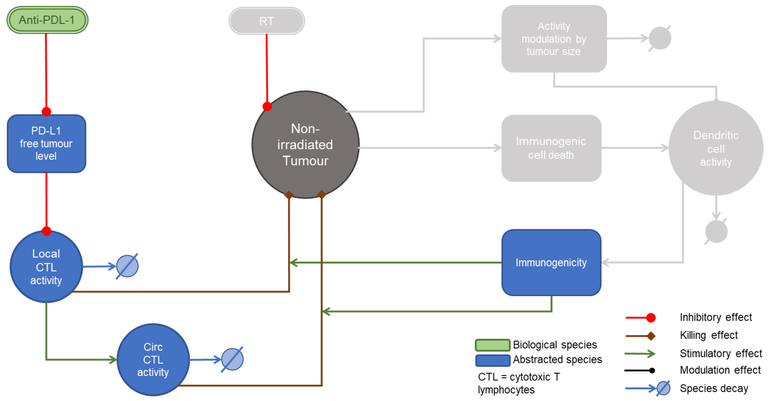

Figure 2. Schematic of the Virtual Tumor model for the non-irradiated tumor. There is no direct effect of IR on the untreated tumor. Instead, the abscopal anti-tumor effect is mediated by the enhanced tumor immunogenicity and systemic CTL activity.

Application of the model to a literature case study

We evaluated the capability of the VT to model the efficacy of IR in combination with an anti-PD-L1 antibody, through a preclinical case study derived from the literature[4]. The VT model was first calibrated for the control and the monotherapies. Since no PK data were available for the anti-PD-L1 antibody used in the experimental study, we took the anti-PD-L1 antibody avelumab as a proxy. The calibrated model was then used to simulate the combination efficacy in irradiated and non-irradiated lesions, capturing the abscopal effect.

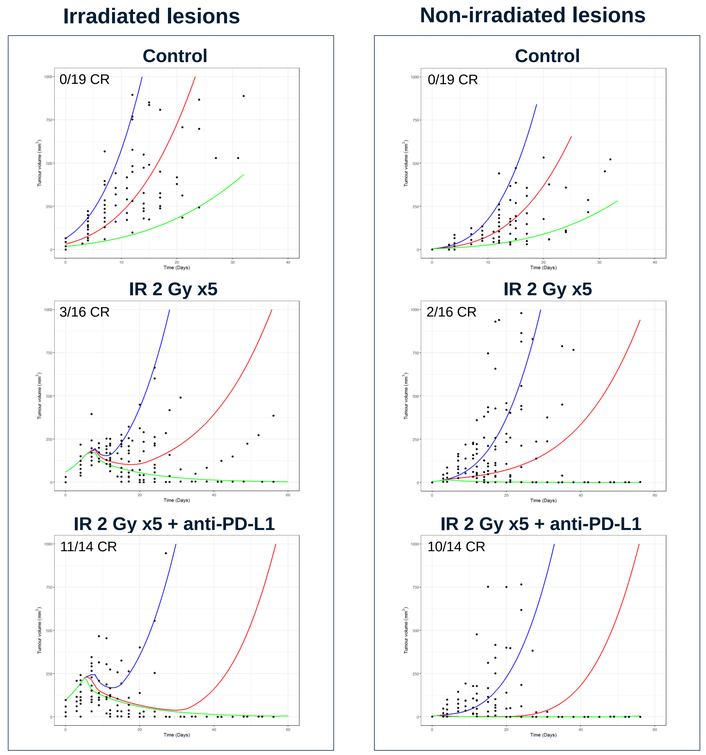

Figure 3. Simulation of tumor growth over time. Experimental data were taken from ref. 4. Black symbols correspond to the experimental data points. Red lines show the mean simulation by the VT model. Green and blue lines show simulation of the extremes of tumor growth dynamics (corresponding to a range of cellular doubling times) in the case of the controls, or the variability in response to treatment (corresponding to a range of immune response magnitudes).

- The variability observed in the control arms of the study can be explained by variation in the cellular doubling time (in these simulations the cellular doubling time is varied across a range of values).
- Most of the variability in treatment response can be explained by variation in the magnitude of the immune response induced by the IR treatment. (In these simulations the cellular doubling time is fixed, while the magnitude of the immune response is modulated across a range of values.)
- The simulations reflect the increase in efficacy obtained from the combination at both irradiated and non-irradiated sites.
- The model also indicates that substantial combination efficacy can be achieved with modest immune responses.
- The therapeutic response observed in the non-irradiated secondary tumor can be explained by the systemic immune response induced by irradiation of the primary tumor.

Using the model to explore mechanisms of interaction in immuno-oncology combinations

The model also enables tracking of species other than tumor volume, in order to the better understand the processes that lead to cellular death and tumor growth inhibition (TGI).

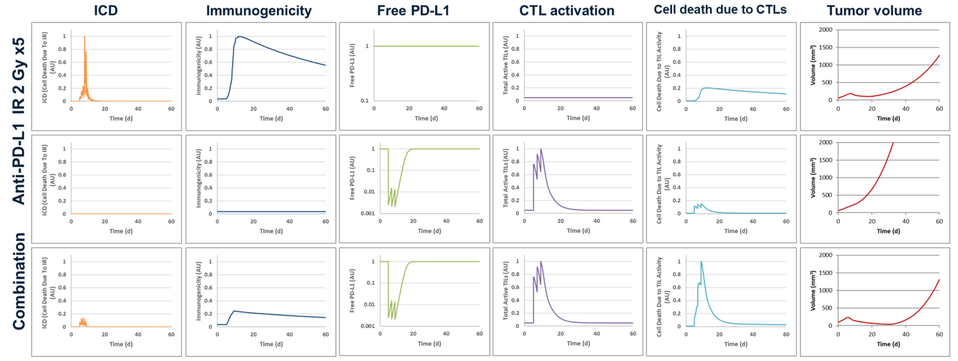

Figure 4. Example time-course profiles for key model species following treatment with IR and anti-PD-L1 (fixed cellular doubling time and immune response magnitude).

IR treatment induces ICD and an increase in tumor immunogenicity, but due to the suppression of CTL activity by PD-L1, cell death caused by CTLs is relatively low. Anti-PD-L1 therapy increases CTL activity by releasing PD-L1 inhibition, but tumor immunogenicity remains low and so cell death due to CTLs is minimal. In the combination, a modest increase in tumor immunogenicity coupled with release of PD-L1 inhibition triggers significant cell death due to CTLs. (Immunogenicity is reduced when IR and anti-PD-L1 are given concurrently, because cell death due to CTLs, which exceeds ICD, is not considered to be immunogenic.)

Evaluating efficacy of various IR schedules

We performed simulations to estimate the efficacy that different IR dose/schedules in combination with anti-PD-L1 therapy have on the irradiated and non-irradiated tumors. Table 1 and Table 2 show the efficacy of IR only and the combination, respectively.

Table 1. TGI for IR treatment only and Table 2. TGI for combination treatment with IR and anti-PD-L1. Simulations were performed using the same parameters values utilized in Figure 3 (red line), assuming that irradiated and non-irradiated tumors have identical initial size.

IR Treatment	TGI (%) Irradiated	TGI (%) Non-irradiated
2Gy qd x5 (10Gy)	92	72
1 Gy bid x5 (10Gy)	81	71
2Gy bid x3 (12Gy)	65	56
2Gy bid x3 alt (12Gy)	77	70
4Gy qd x3 (12Gy)	72	55
7Gy qd x1 (7Gy)	54	43

IR Treatment	aPD-L1 (del., d)	TGI (%) Irradiated	TGI (%) Non-irradiated	aPD-L1 (del., d)	TGI (%) Irradiated	TGI (%) Non-irradiated
2Gy qd x5	0	100	96	3	100	100
1 Gy bid x5	0	99	94	3	100	100
2Gy bid x3	0	96	92	3	100	100
2Gy bid x3 alt	0	92	88	3	100	100
4Gy qd x3	0	100	98	3	100	100
7Gy qd x1	0	98	95	3	100	100

Table 1 shows that IR treatments achieve different levels of tumor regression in irradiated and non-irradiated tumors. The combination improves TGI, and efficacy is maximized when the administration of anti-PD-L1 is delayed by 72 hours with respect to IR start, since this allows ICD and immunogenicity to peak before T cell activation.

Conclusions

A model has been developed integrating the interactions between IR-induced DNA damage, the adaptive immune response and tumor growth in irradiated and non-irradiated tumors. We find that most of the variability observed experimentally can be explained by the magnitude of the immune response elicited by IR treatment. We also show that the combination is more efficacious when anti-PD-L1 is given with a delay of 72 hours, which it is consistent with findings reported in the literature[5-7]. In addition, the model suggests that the efficacy achieved is robust to changes in IR schedule and total dose.

***References*:**
[1] Brightman, FA et al., Abstract 680. Cancer Res 75, 4866-66 (2015). [2] Ortega, F et al., Abstract 4866. Cancer Res 79, (13 Suppl) (2019). [3] Orrell, DA et al., Abstract 4918. Cancer Res 71, (8 Suppl) (2011). [4] Dovedi, S et al., Clin Cancer Res 23(18); 5514–26 (2017). [5] Kosinsky, Y et al. J. Immunother. Cancer 6, (2018). [6] Dovedi, SJ et al. Cancer Res. 74, 5458–5468 (2014). [7] Antonia, SJ et al. N. Engl. J. Med. (2018).

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