



Comment on "Abscopal effect in the radio and immunotherapy"

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See the article "Abscopal effect in the radio and immunotherapy" in Volume 39 on page 247.

We first want to congratulate Pevzner et al. [1] for providing a complete yet succinct overview of the general understanding of the abscopal effect. As mentioned by the authors, while this phenomenon has been described for decades, the underlying molecular mechanisms allowing localized radiation to exert a disseminated anti-tumoral effect remains profoundly opaque. Although a multiplicity of pathways, effectors and mediators have been described, little work yielded results which could allow the clinical instrumentalization of this effect.

In this review, the authors report the proposed unifying mechanism allowing distant effect of localized radiation therapy, which hinges on the activation of local CD⁸⁺ T lymphocytes. These effector cells are exposed and primed to tumoral antigens and then exported to distant lesion sites, where they operate their cytolytic effect. The authors also mention that the generation of a large amount of de novo tumor antigens is responsible for robust immunogenicity, which is required to achieve potent activation of local leukocytes, as confirmed by others [2].

We do agree that tumor mutational burden (TMB) is usually considered as the primary predictor of neoantigen load, which is itself ontologically associated with tumoral immunoreactivity [3]. However, as underlined in pancreatic cancer [4] as well as other organ systems, distinct orthogonal signatures, like chemokine expression, can be used as robust, complementary proxies of the degree of tumoral T-cell infiltration and activation, even in the absence of high TMB or neoantigens. Alternatively, a variety of molecular signatures characteristic of T cell-inflamed phenotypes have been identified, with high T-cell infiltration generally predictive of good immunotherapeutic response. This, in turn, provides a plausibly robust prognosticator of response to immune checkpoint inhibitors [5]. In essence, it is suggested that tumoral immunogenicity, and response to immunotherapy, are not solely contingent on neoantigens and, by extension, TMB. Indeed, recent analysis of the phase 2 pan-cancer study (CA209-538) demonstrated no predictive value of TMB to response to combined PD-1/CTLA-4 (programmed cell death protein-1/cytotoxic T lymphocyte antigen-4) checkpoint inhibition [6]. Rather, tumor infiltration by competent lymphocytes, which appears to be associated with different immunobiologically relevant signatures, could be a complementary, powerful metric of predicted therapeutic sensitivity to both radio and immunotherapies.

We agree with the authors that identifying lesions most likely to generate systemic response to lo-

calized radiotherapy, either when used singly or in combination with immune checkpoint inhibitors, is a crucial endeavour for radiotherapeutic research. Therefore, we'd like to suggest that tumors with T cell-inflamed phenotypes could, potentially, be good candidates for abscopal investigations. Additionally, we believe that these tumors should not be identified only on the basis of their TMB, but also by using specific signatures indicative of tumor lymphocytic infiltration. Such characterization efforts should be undertaken in the context of radiotherapy in order to better identify tumors that would benefit from synergistic interventions integrating both radiations and immune checkpoint inhibitors. Considerate investigations of the molecular underpinning of these phenomena will potentially allow clinicians to effectively leverage the abscopal effect, allowing systemic efficacy of a fundamentally localized therapeutic strategy.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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