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Review

Can immunostimulatory agents enhance the abscopal effect of radiotherapy?

Antonin Levy [a,b,c], Cyrus Chargari [a,b,c,d], Aurelien Marabelle [e], Jean-Luc Perfettini [b,c,f], Nicolas Magné [g], Eric Deutsch [a,b,c,e,*]

[a] *Department of Radiation Oncology, SIRIC SOCRATES Gustave Roussy Cancer Campus, 114 rue E. Vaillant, 94800 Villejuif, France*
[b] *Université Paris-Saclay, Faculté de Médecine, 94270 Kremlin Bicêtre, France*
[c] *INSERM U1030, Molecular Radiotherapy, Gustave Roussy Cancer Campus, Villejuif, France*
[d] *Institut de Recherche Biomédicale des Armées, Brétigny sur Orge, France*
[e] *DITEP, Gustave Roussy Cancer Campus, 114 rue E. Vaillant, 94800 Villejuif, France*
[f] *Cell death and Aging team, Gustave Roussy Cancer Campus, 114 rue E. Vaillant, 94800 Villejuif, France*
[g] *Institut de Cancérologie Lucien Neuwirth, Saint Priest en Jarez, France*

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Abstract Ionising radiation (IR) may harm cancer cells through a rare indirect out-of-field phenomenon described as the abscopal effect. Increasing evidence demonstrates that radiotherapy could be capable of generating tumour-specific immune responses. On the other hand, effects of IR also include inhibitory immune signals on the tumour microenvironment. Following these observations, and in the context of newly available immunostimulatory agents in metastatic cancers (anti-cytotoxic T lymphocyte-associated antigen 4 and programmed cell death protein-1 or -ligand 1 [PD1 or PDL-1]), there is a remarkable potential for synergistic combinations of IR with such agents that act through the reactivation of immune surveillance. Here, we present and discuss the pre-clinical and clinical rationale supporting the enhancement of the abscopal effect of IR on the blockade of immune checkpoints and discuss the evolving potential of immunoradiotherapy.

* *Corresponding author*: Department of Radiation Oncology, Gustave Roussy, 114 rue Edouard Vaillant, 94850 Villejuif, France. Tel.: + 33 1 42 11 65 73; fax: + 33 1 42 11 52 53.
E-mail address: Eric.DEUTSCH@gustaveroussy.fr (E. Deutsch).

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1. Introduction

Radiation therapy (RT) is a pivotal treatment in oncology. It is estimated that more than half of patients will receive RT during the course of their disease. The therapeutic potential of RT has long been exclusively ascribed to its ability to mediate antiproliferative and cytotoxic effects. In fact, after exposure to ionising radiation (IR), various macromolecules in tumour cells sustain multiple injuries, notably DNA which is the main target for RT. This damage is prominently consecutive to the undirected establishment of oxidative stress within the tumour cells or to direct interaction between IR and chromosomes.

During the past two decades, the accumulated preclinical data suggest that the clinical efficacy of RT also involves mechanisms of interaction between the tumour cell and the stroma. Tumour cells exposed to IR and on the verge of dying release a wide panel of mediators with biological effects that are also involved in cell signalling or inflammation. They include reactive oxygen species, as well as several cytotoxic cytokines, such as transforming growth factor (TGF) β1 and also tumour necrosis factor (TNF) α. Our understanding of the death mechanisms involved in the anti-tumour effect of RT has significantly improved over the last few years. It has now become clear that upon lethal stimulation (such as apoptotic or necrotic signals), irradiated cancer cells can release immunostimulatory molecules leading to a phenomenon called immunogenic cell death (ICD) [1,2]. Indeed, these molecules, also called damage-associated molecular patterns (DAMPs), give rise to the recruitment of antigen-presenting cells in the tumour bed, and the elicitation of a general adaptive anti-tumour immune response. Still, although RT is used routinely as a local treatment in numerous clinical situations, only a few distant responses in unirradiated sites have been reported [3,4].

This phenomenon, described as the "abscopal effect," purports that RT exerts out-of-field activity. New insights into the mechanism of action of RT brought to the light the fact that exposure to RT induces antigen release from the tumour, thereby activating both the host's innate and adaptive immune system. Consequently, RT might help reverse the tolerance to weakly immunogenic tumour-associated antigens in order to elicit an anticancer immune response [5,6]. However, the abscopal effect has remained a rare clinical event when RT is used alone. Indeed, the frequency of in-field and distant relapses in locally advanced tumours treated with irradiation alone suggests that this radiation-induced anti-tumour immunity is inadequate or at least remains to be improved in order to maintain a long-term anti-tumour effect.

Within the last 5 years, immune checkpoint inhibitors have demonstrated impressive efficacy in various advanced tumour locations [7–9]. Interestingly, there is now rationale that RT can positively interact with immunotherapies in inducing a sustained abscopal effect. We review here the preclinical and clinical evidence for the abscopal effect and highlight the therapeutic prospects of combining RT with immune-modulating agents, with special emphasis on immune checkpoint inhibitors.

2. Immune effects of RT: preclinical and clinical evidence

2.1. The immune response as part of the local and distant effect of RT

The primary objective of RT is to achieve local tumour control, which ultimately may translate into enhanced survival [10]. Beyond its direct local effects, RT also amplifies tumour immunogenicity by inducing tumour cell death and the subsequent release of pro-inflammatory cytokines. Since the early 2000s, irradiation has been shown to be capable of inducing or potentiating a systemic anti-tumour immune response culminating in ICD. Schematically, RT triggers tumour antigen release and modulates the tumour cell phenotype, activating immune responses and increasing immune recognition [11,12]. The adaptive and innate immune response induced by RT is part of the anti-tumour effect in irradiated volumes but also out of field.

When the local efficacy of RT is examined, there appears to be intratumour activation of the immune response, characterised by the recruitment of T lymphocytes and the secretion of T_h1 cytokines. Furthermore, there is a positive correlation between the intensity of this response and patient outcomes [13,14]. Thus, the short-term ablation of CD4+CD25+FOXP3+ regulatory T(reg) cells was shown to increase the therapeutic effect of RT [15]. The leukaemia inhibitory factor, which is involved in the terminal differentiation of immunological cells, may also be another key factor that has been observed during the acquisition of a radioresistant phenotype in nasopharyngeal cancer models [16].

The biological mechanisms of the abscopal effect are thought to rely on the ability of RT to elicit an immune response. This was more thoroughly reviewed elsewhere [17]. Briefly, irradiated tumours release danger signals (DAMPs; e.g. heat shock proteins or high-mobility group protein B1 [HMGB1] alarmin protein detected by the toll-like receptor (TLR) 4 on dendritic cells [DC]) that lead to DC activation. RT can also induce a dose-dependent increase in MHC class I presentation in human tumour cells leading to tumour recognition. Activated DCs can then prime T cells and cause an appropriate level of CD8+ T lymphocyte cytotoxicity [18,19]. The Fms-like tyrosine kinase receptor 3 ligand (Flt3-L), which activates the production of DC, induced abscopal effects on a moderately immunogenic syngeneic tumour (mouse mammary carcinoma 67NR) in a T-cell-dependent manner [20]. Lee *et al.* also proposed