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Immuno-oncology: Allying forces of radio- and immuno-therapy to enhance cancer cell killing

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Contents

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ABSTRACT

Besides the local effects of ionizing radiation at the cellular and molecular levels in tumor tissues, the interactions of radiotherapy with the host's immune system are nowadays at the center of many investigations. In some cases, these interactions can be strong enough to immunize the patient against the tumor, leading to a rejection by the host of both the irradiated tumor and distant metastases. In this latter case, the rejection mechanism is called "abscopal effect". Over the last two decades, increasing attention has also been paid to the combination of various forms of immunotherapies with radiation, as an attempt to boost cancer cell killing mechanisms. In particular, a significant number of translational and clinical studies are now investigating both the effects of immune checkpoint blockade strategies and adoptive immunotherapies in combination with radiation. A better understanding of the mechanisms driving the interactions between ionizing radiation and the immune system help us envision the advantages that may be offered by the adjunction of immunotherapy to radiotherapy in various clinical models.

1. Introduction

A pillar of oncology, radiotherapy (RT) plays a central role in the local-regional control of solid malignancies. While the use of RT as sole therapeutic modality has been so far articulated around the effects of ionizing radiation (IR) to cancer cells and their microenvironment, its interactions with the host's immune system are nowadays at the center of many investigations: in some cases, these interactions can immunize the patient against the tumor, leading to a rejection by the host of both the irradiated tumor and metastases (Frey et al., 2012; Park et al., 2014). In this latter case, the rejection mechanism is called "abscopal effect" (Mole, 1953). To optimize the management of locally advanced diseases, RT has nevertheless to be combined to surgery and systemic treatments. Till the turn of the century, concomitant chemo-radiotherapy (CRT; also denoted here as "chemoradiation") was considered as the privileged approach to treat more efficiently stage III–IV tumors of epithelial origin (Bartelink et al., 1997; Bernier et al., 2004).

In recent years, the advent of immune checkpoint inhibitors (ICI) generated encouraging clinical results for various malignan-

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cies (Salama et al., 2016; Schoenhals et al., 2016). A significant number of translational and clinical studies are nowadays investigating both immune checkpoint–based strategies and adoptive immunotherapies in combination with IR (Sharabi et al., 2015a; Finkel et al., 2016; Friedman et al., 2016; Kim et al., 2016; Popp et al., 2016). The objective of this review article is to both revisit some of the links established so far between the immune system and response to IR, and emphasize how a better understanding of interactions between adoptive immunotherapies and RT will help develop innovative strategies.

The analysis will be articulated around three main axes, namely a) cancer, radiation and host's immune system; b) the mechanistic background behind radio- and immunotherapy in cancer cells; and c) the development of vaccines in immuno-radiotherapy. We used search strings on studies addressing the issue of interactions between IR and the host's immune system, as well as combination of immuno-therapeutic agents- and radiotherapy, via the following search terms: immune system, radiation, radiotherapy, immunotherapy, radio-sensitization, immune checkpoints inhibitors, immune activation. This review is essentially based on full articles published since 2000 and retrieved from the Pubmed search engine (http://www.ncbi.nlm.nih.gov/pubmed).

2. Response of the tumor cells and their micro-environment to radiation and interactions with host's immune system

2.1. From the tumor cells to their microenvironment

Both innate and adaptive immune systems are able to detect the presence of cancer cells and kill them. To proliferate, tumor tissues must therefore have evaded host's immune-surveillance (Formenti and Demaria, 2013). For many years, it was thought that there were only few synergies between the immune system and RT-induced tumor response. Recently, several reports provided convincing clues that RT actually does interact with the immune system with an order of magnitude higher than expected from previous observations (Derer et al., 2015; Multhoff et al., 2012; Vatner et al., 2014). When IR targets malignant cells, it can modulate tumor immunogenicity and enhance both antigen presentation and cytokines production (Bernstein et al., 2016).

Irradiating tumor tissues can both induce a form of cancer cell death, called "immunogenic", and release various "danger" signals sensed by the host's immune system to reject the tumor (Demaria and Formenti, 2007).

In terms of immuno-suppressive effects, IR down-regulates some co-stimulatory molecules such as CD80 and CD86 on immature dendritic cells (DCs) (Cao et al., 2004). While IR also enhances the expression of other co-stimulatory molecules in antigen-presenting cells (APCs), T cells, and stromal cells (Lugade et al., 2005), its cytotoxic effects can also induce the production of inflammatory cytokines, which enhance antigen uptake by DCs (Multhoff et al., 2012). Promising synergies between anti-cytotoxic T lymphocyte antigen-4 (CTLA4) and anti-programmed cell death-ligand 1 (PD-L1) antibodies in inducing an immune-mediated response have been observed in animal models (Vatner et al., 2014; Kaminski et al., 2005). Through the expression of new antigens and their immune adjuvant-like effects, IR converts the tumor tissue into an *in situ* vaccine eliciting tumor-specific T cells and endowing the host with immune memory. Both synchronous malignant cell deposits distant from the tumor exposed to radiation and those emerging months or years later from dormancy can be potentially rejected via this immune memory (Demaria and Formenti, 2007).

Throughout the twentieth century, boosting biological effects of IR has been considered as a main key to success to enhance cancer cell radiosensitivity (Sakai and Okada, 1984). In a recent past, increasing attention was paid to potential correlations between biological IR effects on the tumor microenvironment and treatment outcome. It has indeed been repeatedly substantiated that IR not only impacts on malignant cells viability but also triggers multiple immune-modulatory effects within their micro-environment (Lehnert, 2000). The potential role of IR in enhancing immune activity against cancer cells finds its source in the release of signals acting as pro-inflammatory modifiers (Demaria and Formenti, 2007; Sakai and Okada, 1984; Lehnert, 2000). For example, IR induces chemokines such as CXCL9, CXCL10, and CXCL16, which promote recruitment of effector CD8 and T-helper 1 CD4T cells in melanoma (Lugade et al., 2005) and breast cancer cells (McBride et al., 2004). In addition, interleukin 1β, tumor necrosis factor α and type 1 and 2 interferons are among the pro-inflammatory cytokines known to be induced by IR (Demaria and Formenti, 2007; McBride et al., 2004; Matsumura and Demaria, 2010; Hallahan et al., 1989; Ishihara et al., 1993).

Beyond the increased production of immune-stimulatory cytokines mentioned above, IR effects on the tumor microenvironment also include increases in natural killer (NK) cell activity, antigen presentation to dendritic cells, and CD8+ T-cell infiltration (Lugade et al., 2005). As for this latter effect, a single dose of 20 Gy, but not fractionated RT, to a B16 melanoma model resulted in increased T cells present in the microenvironment, significant tumor regression, and increased T-cell priming in lymph nodes (Lee et al., 2009). In addition RT was shown to enhance major histocompatibility complex (MHC) class I expression (Reits et al., 2006) and down-regulate inhibitory immune signals from myeloid-derived suppressor cells (Formenti and Demaria, 2013; Drake, 2012).

In addition, IR up-regulates the expression of immune checkpoint ligands, including PD-L1, not only on the tumor cell surface but also in immune cells within tumor microenvironment (Dovedi et al., 2016; Deng et al., 2014a; Parikh et al., 2014), thereby preventing auto-immune responses against both normal and malignant cells. After irradiation, PD-L1 up-regulation on tumor cell surface is dependent on interferon γ released from CD8+ T cells (Dovedi et al., 2016). However, in some models, IR can have an opposite effect, since it was shown to reduce checkpoint expression on malignant cells (Bernstein et al., 2014). Differences in tumor histo-types and microenvironment conditions, in addition to IR dose- and time-factors, might account to some extent for such discrepancies.

IR is also known to increase, possibly through TGFβ secretion, the infiltration of regulatory T cell (Treg) populations (Kachikwu et al., 2011; Wirsdorfer et al., 2014). Sharabi et al. indeed reported that stereotactic radiation to B16-OVA or 4T1-HA tumors increased the number of CD4+ CD25hiFoxp3+ Treg cells in their microenvironment (Sharabi et al., 2015b). Since Treg cells down-regulate both adaptive and induced immune responses, this increase in cell density counterbalances radiation-induced immune activation (Sakaguchi et al., 2008). This approach could optimize regimens of RT combined with immunotherapy, for strategies depleting Treg populations were shown to enhance the efficacy of radiation in preclinical models (Sharabi et al., 2015b): for instance, Kachikwu et al., using the TRAMP C1 prostate cancer model, reported that systemic elimination of Treg populations enhanced tumor regression after IR (Kachikwu et al., 2011). When IR was combined with PC61 antibody-mediated Treg depletion, local tumor control improved, and antigen-specific anti-tumor immune responses were enhanced.

Regulating pro-tumor factors is another potential target when considering the potential impact of tumor micro-environment on treatment outcome after RT. Among these pro-tumor factors, Interleukin 6 (IL-6) and Transforming Growth Factor-β1 (TGF-β1) are key factors in Th17 cells differentiation. Up-regulation of pro-tumor cytokine interleukin-17A (IL-17A) contributes to enhance tumor