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Review article

Combining radiation therapy and cancer immune therapies: From preclinical findings to clinical applications

Associer la radiothérapie à l'immunotherapie : des découvertes précliniques aux applications cliniques

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ABSTRACT

Besides its direct cytotoxic effect on the tumor cells, radiation therapy is also able to elicit an immune-mediated systemic anti-tumor response, resulting in tumor regression in irradiated sites but also within distant out of field secondary lesions and providing a long-term anti-tumor response. It is now clear that associating ionizing radiation with immune therapies can enhance radio-induced anti-tumor immune responses. Over the last decade, such a combination aroused considerable interest among the scientific community, with many preclinical models and clinical trials, using many types of immune therapies and radiation regimens. In this article, we summarize the main mechanisms underlying radio-induced anti-tumor responses. We will then present an extended overview of the recent preclinical and clinical research built on this background of combined radiation and immune therapy, shedding light on what we know so far about such a promising strategy.

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RÉSUMÉ

Outre ses effets cytotoxiques directs, la radiothérapie peut engendrer une réponse systémique antitumorale, grâce à l'activation du système immunitaire, et ainsi provoquer une régression tumorale aussi bien au niveau des sites irradiés qu'en dehors des volumes irradiés, au niveau des tissus tumoraux à distance. Par cette stimulation du système immunitaire, une réponse prolongée peut être observée, la radiothérapie agissant comme une vaccination antitumorale in situ. Depuis l'arrivée de l'immunothérapie dans la prise en charge du cancer, il est maintenant établi que l'association de la radiothérapie à de tels traitements peut favoriser l'apparition d'une immunité anti tumorale radio-induite. Par conséquent, cette combinaison a suscité un intérêt grandissant dans la communauté scientifique au cours des dernières années, et est étudiée dans un grand nombre de modèles précliniques, mais également mise en pratique dans de nombreux essais cliniques. Dans cette revue de la littérature, nous revenons sur les mécanismes biologiques sous-tendant cette réponse immunitaire anti tumorale induite par les radiations ionisantes. Nous allons ensuite dresser un panorama détaillé des essais précliniques et cliniques récents et en cours, associant la radiothérapie aux diverses stratégies d'immunothérapie, mettant en lumière ce que nous savons actuellement de cette combinaison prometteuse.

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1. Introduction

Traditionally, radiobiological explanation of radiation tumor cell kill was mostly represented by a direct cytotoxic effect, including the induction of irreparable DNA damage, through double-strand break, leading to cell-cycle arrest and cell death [1]. Ionizing radiations are known to lead to cell death by many lethal mechanisms, including mitotic catastrophe, apoptosis, necrosis, autophagy and senescence and radiation induced DNA damages are classically explained by the 5R's of radiobiology: radio sensitivity, repopulation, re oxygenation, redistribution within the cell cycle and repair of sub lethal damages [2]. Over the past decade, a significant growing body of evidence has shown that radiotherapy has immune modulatory effects, leading to redefine the classical vision of radiobiology [3–5]. Indeed, radiation therapy (RT) is able to stimulate the immune response through various mechanisms, inducing cellular expression of immune factors on both tumor cells and within the tumor microenvironment [6–8]. This activation of the immune system through RT can, in rare isolated cases, lead to an abscopal effect, where tumor regression occurs in distant out of field tumor/metastatic sites [4,9]. Since its first description by Mole et al. in 1953, several clinical examples have reported this phenomenon [10]. With the advent of cancer immunotherapies over the last past years, clinical cases of abscopal responses are more frequent when RT is associated to such therapies [8,10]. Nevertheless, if abscopal effect is one reflection of anti-tumor radio-induced immunity, it is not sufficient to fully evaluate the efficacy of these associations. Indeed, many preclinical and clinical trials are now testing this combination, with various types of immune therapies, such as checkpoint inhibitors, cytokines, vaccines, etc., and the objectives of these trials are not only the occurrence of abscopal effect, but also primary tumor response, progression free survival and overall survival.

The present review will first focus on the understanding biological rationale behind immune effects of RT. Then, we will review preclinical and clinical studies evaluating the combination between RT and immunotherapy, with the objective of providing an extensive overview of on what we know so far regarding this association.

2. Radiation therapy and the immune system

By its cytotoxic effects over tumor cells, RT can generate tumor-associated antigens (TAAs), which will be recognized and captured by antigen presenting cells (APC), such as dendritic cells (DCs), or by tumor cells themselves. These antigens are processed and presented to T cells, resulting in the priming and activation of T cell response against TAAs [11]. Not all radiation induced tumor cell deaths can lead to the exposure of TAAs, and only cell death which are sensed by the immune system as dangerous can trigger an antitumor immune response. These so-called immunogenic cell deaths are not only accompanied by exposure of TAAs, but also by a release of damage-associated molecular patterns (DAMPs), such as heat shock proteins (HSPs), high mobility group box 1 molecules (HMGB1), nucleotides or uric acid [12,13]. These DAMPs are recognized by toll-like receptors (TLRs), expressed at the surface of DCs, and play a pivotal role in the activation and maturation of the DCs [14]. By this phenomenon, DAMPs facilitate the uptake of TAAs and their presentation via the major histocompatibility complex class 1 (MHC-1) to tumor-specific cytotoxic T lymphocytes CD8+ [15]. Moreover, RT can induce the translocation of calreticulin (CRT) to the tumor cells' surface membrane, increasing tumor cell sensitivity to cytotoxic T lymphocytes [16]. CRT can bind to CD91 on APCs, such as DCs and macrophages, stimulating receptor phagocytosis of TAAs and their presentation on MHC-1 [17] (Fig. 1).

RT is not just able to induce the expression of MHC-1 at the surface of T lymphocytes CD8+, but also the death receptor Fas/CD95 and NKG2D ligand at the surface of T lymphocytes CD8+ and Natural Killers (NK) lymphocytes, enabling tumor cells recognition, and hence their destruction, by these immune cells [18,19].

Radiation can activate both innate and adaptive immune system to trigger anti-tumor responses, not only at irradiated site, but also at distant out of field metastatic sites, consisting in the abscopal effect [4,9]. Besides the mechanisms exposed earlier to explain this phenomenon, RT induce an intra-tumor cascade of type I and type II interferons (IFNs), through the Stimulator of Interferon Genes (STING)-mediated DNA-sensing pathway [20] (Fig. 2). After phagocytosis of dying irradiated tumor, tumor derived fragment of DNA enter CDs cytoplasm. This cytosolic DNA is detected, leading to the production of cyclic GMP-AMP (cGAMP) by the cyclic GMP-AMP synthase (cGAS). cGAMP activates STING to up regulate the transcription of type I IFN genes, through a STING-TBK-IRF3-NFkB signaling pathway [20–22]. Type I IFNs can stimulate TAAs presentation by DCs to T cells, and thus their activation, both within irradiated site and in lymph nodes, enhancing an irradiation-induced tumor-specific T-cell response. When activated, T cells and NK lymphocytes will be able to secrete type II IFNs, such as IFNγ. IFNγ can, in turn, trigger MHC-1 expression at tumor cells surface [23]. Hence, through this cascade, RT enhances the recruitment and activation of T cells and CDs.

Moreover, RT can enhance the secretion of other cytokines, such as CXCL-10 and CXCL-16, which receptor CXCR-6 is located at the surface of activated T CD8+ and CD4+ lymphocytes, allowing their recruitment towards tumor sites [24,25].

Besides, these cellular effects over tumor sites, RT can also modify the tumor microenvironment: by up regulating adhesion molecules, such as vascular cell adhesion protein 1 (VCAM-1) and intracellular cell adhesion protein 1 (ICAM-1), RT promotes the recruitment of anti-tumor T lymphocytes and other leukocyte into the tumor microenvironment [26].

Paradoxically, ionizing radiation can also have immunosuppressive effects and enforce immunological tolerance, compromising its anti-tumor activity (Fig. 3). For example, RT can also induce the down regulation of co stimulatory surface markers, such as CD86 and CD80, known to be expressed at the surface of immature dendritic cells (DCs), thus hampering T-cell activation [27]. Also, RT has been described to be able to inactivate NK lymphocytes [28]. Moreover, RT can lead to the recruitment of myeloid derived suppressor cells (MDSC) and regulatory T (Treg) lymphocytes in the tumor microenvironment, contributing to the immune tolerance of the immune system towards tumor cells [29,30]. Notably, irradiation has been shown to induce monocyte/macrophage infiltration in tumors. These recruited macrophages, described as tumor associated macrophages (TAMs), can adopt an M2-like pro-tumoral and anti-inflammatory phenotype, often leading to tumor recurrence and treatment failure [31].

Finally, contributing to immune tolerance, RT can enhance production of TGF-B, an anti-inflammatory and immunosuppressive cytokine [32,33].

If RT can act like an "in situ vaccine", by inducing a systemic immune response against tumor epitopes shared by the primary and metastatic tumor sites, its immunosuppressive effects can compromise its efficacy. Therefore, combining RT with immunotherapies seems to be a logical solution to overcome both radio-induced immunosuppression and tumor immune tolerance. Thus far, many pre-clinical and some clinical studies have demonstrated the synergistic effect of immune therapy and RT on tumor control [34–36].

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