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Review

Integration of radiation and immunotherapy in breast cancer - Treatment implications

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ABSTRACT

Radiation therapy (RT) has been successfully used in the treatment of breast cancer (BC) for over a century. While historically thought to be immunosuppressive, new data have shown that RT can work together with the immune system to eliminate cancer. It can cause immunogenic cell death and facilitate tumor neoantigen presentation and cross-priming of tumor-specific T-lymphocytes, turning irradiated tumor into an in-situ vaccine. Unfortunately, due to various immune escape mechanism put in place by the tumor, RT alone rarely results in a systemic response of metastatic disease sites (known as the abscopal effect). Immunotherapy, a series of agents designed to stimulate the immune system in order to generate tumor-specific immune response, is showing promise in treatment of various cancers, including BC, and can be an ideal complement to RT in stimulating a systemic immune response to reject the tumor cells. This review discusses the mechanisms in which RT can trigger an immune response for tumor rejection, and provide emerging preclinical and clinical data of combination immunoradiotherapy, and its potential in treating BC.

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Contents

1. Introduction

Immunotherapy has been increasingly gaining an important role in cancer treatment due to its potential to recover the individual patient's immune recognition of cancer and develop an acquired immune response against malignant cells in the entire body. In order to grow and spread, cancer cells develop mutations that allow them to escape recognition and elimination by the host's immune system. Available immunotherapy agents either re-activate the immune system or release its brakes to allow recognition of cancer cells as non-self, and successfully reject

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them. Rapidly established as a main treatment in melanoma, non-small cell lung cancer, and certain genitourinary malignancies [1–7], immunotherapy is more recently being tested on breast cancer (BC) [8–11].

Even in malignancies where the current immunotherapy has demonstrated efficacy, response rates remain low, highlighting the need for more effective agents or combined modalities. Radiation therapy (RT), using accelerated high-energy particles (photons, electrons, protons, neutrons etc.), has been used for treatment of cancer for over a century. Originally discovered by a successful treatment of a woman with locally advanced BC, radiation has played a central role in this disease [12,13]. For instance, RT has permitted the implementation of breast conservation in most patients, and multiple meta-analyses of clinical trials comparing the outcome of irradiated versus non irradiated patients have demonstrated superior loco-regional control, metastasis free survival, and overall survival in irradiated patients [14].

The classical mechanism of action of RT consists of damaging the DNA of the irradiated cells, preventing their replication, and leading to cell death [15]. The effect of RT has long thought to be restricted to the local area targeted by the beam. Furthermore, due to the exquisite radiosensitivity of lymphocytes, total body irradiation is used to eradicate the immune system prior to stem cell transplant, conveying RT a characterization of powerful immunosuppressive therapy [16–18]. Localized radiotherapy, however, has drastically different effects from total body irradiation, much more limited to the tissue targeted by the radiation beam. It is in the setting of localized RT that a role as an immune-stimulant has been recently recognized, since its associated local and systemic effects were discovered to be sensed by the immune system [19,20].

Throughout the time, rare reports of regression of tumors outside of radiation field have attracted the attention to a potential systemic effect of RT. This phenomenon is termed "abscopal effect" (Latin: 'ab' - away from, 'scopus' – target) [21]. Abscopal effects are extremely rare and a recent review was only able to identify 46 reported case in the literature from 1969 to 2014 [22]. The rarity of abscopal effects of RT reflects the fact that, once metastases are detected, a sustained cancer-related immunosuppression has already been established. In order to elicit the abscopal effects of RT in metastatic disease, or in preclinical models mimicking metastatic disease, some of this concurrent immune suppression must be relieved. This concept was initially tested by Demaria et al. in a syngeneic model of murine mammary carcinoma, in a series of experiments that first linked the abscopal effects to an immune mediated mechanism [23]. The preclinical findings were confirmed in a clinical trial, where 41 patients with metastatic cancer treated with combination of local RT and administration of granulocyte-macrophage colony-stimulating factor produced objective abscopal response in a remarkable 26.8% of the patients [24]. It is now known that radiation causes multiple immunostimulatory effects [25].

Radiation induces "immunogenic cell death" (ICD); a process of cell death that involves release of various cytokines and signals that modify the microenvironment of tumors and stimulate influx of immune cells to recognize tumor-specific antigens released by dying cells [26]. RT thus possesses the potential to convert tumor into an in-situ vaccine to provide systemic, long-lasting protection against cancer [27]. This more recently recognized property of RT makes it an ideal modality to combine with immunotherapy, as already successfully demonstrated in multiple animal and human studies [11,28–42]. This article provides a review of some of the various mechanisms through which immunotherapy can work to eliminate cancer, and how its effect can be boosted by combining it with the use of RT, specifically with respect to treatment of BC.

2. Cancer and the immune system

Induction of anti-tumor immunity is a complex, multi-step process regulated by positive and negative regulatory signals [43]. First, tumor-specific antigens must be released and up-taken by activated antigen-presenting cells (APCs), such as dendritic cells (DCs). DCs migrate to draining nodes where they present the processed epitopes as part of the major histocompatibility complex (MHC) molecules to T-cells, resulting in their activation and proliferation. Once activated, tumor-specific T-cells need to migrate to the tumor where, if the existing immunosuppressive microenvironment is overcome, they can reject the tumor. Other T-lymphocytes can differentiate into memory T-cells, capable of preventing future recurrence of the same tumor [44,45].

In order to grow and metastasize, tumor cells must first find ways to escape elimination by the immune system. One common mechanism of escape by tumors, similar to what is used by many viruses, is down-regulation or inactivation of the MHC class I antigen processing and presentation machinery [46,47]. Interestingly, Newcomb et al. showed the recovery of MHC class I expression after radiotherapy in a murine model of glioma [48].

In addition, the continuous cross talk of tumors with the immune system results in elimination of some transformed cancer cells and selection through the process of "immunoediting" of cells with least immunogenic antigens, capable to survive in their immunocompetent hosts [49,50]. For instance, in a BC model, it has been suggested that disease recurrence can be due to $CD8^+$ T-cell induced epithelial to mesenchymal transition, with the resulting cells having acquired characteristics consistent with BC stem cells [51]. While tumor-infiltrating $CD8^+$ T-cells are generally thought to be involved in immune rejection and portend to better outcomes, the above study shows that through immunoediting, they can also participate in selecting more invasive and metastatic cell clones [52,53].

Not only do tumors evolve by gradually escaping immune rejection, they can also develop an immunosuppressive microenvironment that favors their growth. Cancer growth and invasion is associated with signaling to recruit regulatory T-cells (Tregs) and myeloid elements such as primarily tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs), which are responsible for the production of anti-inflammatory cytokines, including Transforming Growth Factor-Beta (TGF-β) and IL-10, further blunting anti-tumor immunity by inhibiting the cytolytic activity of cytotoxic T-cell (CTL) [54,55]. Furthermore, tumor vascular endothelium can directly kill or dysregulate CTLs through engagement of the Programed Cell Death Protein-1 (PD-1) receptor by expressing PD-1 ligand (PD-L1) [56,57].

Through genomic instability and under immunoediting pressure, tumor cells evolve to evade immune recognition despite a plethora of mutated neoantigens that are potentially more immunogenic are generated in the process of acquiring such mutations [58,59]. In fact, tumors with the highest degree of genomic instability are often found to have a more prominent lymphocytic infiltrate [60,61]. Nevertheless, mechanisms that regulate immune rejection (and protect from autoimmune diseases) counterbalance cancer elimination, including those mediated by immune checkpoints, which function like brakes for the immune system. Thus, interference with these brakes aiming at releasing pre-existing immunity against heavily mutated tumor cells loaded with a variety of neoantigens can potentially recover immune recognition of tumors as foreign. Most of the currently used and ongoing trials of

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