INTRODUCTION

Immunobiology of Radiotherapy: New Paradigms

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It has been well demonstrated that irradiated dying cancer cells release tumor antigens. The extracellular antigens and dying tumor cells are engulfed by circulating bone marrow-derived antigen-presenting cells (APCs). After antigen uptake, APCs migrate to lymph nodes, where they engage with helper T cells for post-stimulation and APC activation. Induction of Th1 response and the activation of APCs further stimulate the induction of tumor specific cytotoxic T lymphocytes (CTLs) that could potentially clear tumor cells both at primary and metastatic sites (Fig. 1).

Radiation-induced immune modulation happens in two important phases. First, radiation induces damage-associated molecular pattern (DAMP) molecules. In this event, radiation normalizes tumor vasculature, modulates tumor cell phenotype and increases immune recognition of the tumor cell. Radiation treatment can cause: a. upregulation of chemokines and adhesion molecules, providing signals for T cells to be attracted to the tumor; and b. upregulation of MHC molecules and tumor-associated antigens, making it easier for endogenous or immunotherapy-induced T cells to recognize and kill tumor (immunogenic modulation). Second, amplification by abrogating immune checkpoint factors with simultaneous costimulation of effector factors can ultimately lead to the induction of multiple unique T-cell populations (antigen cascade) that can kill antigen disparate tumor cells at metastatic sites (systemic effect) (Fig. 2).

Radiation-Induced Immunomodulation

This issue highlights novel findings and concepts on the immunobiology of radiation therapy coupled with translational concepts. Wattenberg et al. (1) reported on several cases where radiation modulates tumor cells to undergo immunogenic cell death or immunogenic modulation and this immune response is directly proportional to radiation dose. Current clinical radiotherapy regimens involve both hypofractionated and hyperfractionated treatments. Therefore, it is important to understand how immune genes respond to survival adaptation of irradiated tumor cells (during multifractionation as well as after single high-dose fraction) to best exploit radiation for combined immunotherapy approaches. Aryankalayil et al. (2) demonstrated that both multifractionated as well single-dose radiation induced DAMPs and positively modulated the cytokine environment, with more observed in multifractionated radiotherapy. Kanagavelu et al. (3) demonstrated the presence of immune modulation in partially irradiated contralateral syngeneic lung tumors. Interestingly, partial tumor volume irradiation of the primary tumor led to an increased presence of infiltrating lymphocytes in both primary and distant tumors, unlike total tumor volume irradiation, suggesting that there is depletion of T cells in total tumor volume high-dose irradiation. To interrogate T-cell sensitivity, Filatenkov et al. (4) demonstrated that autologous T-cell infusion with high-dose hypofractionated radiation could compensate the lymphodeplevtive conditions for a more effective outcome than high-dose hypofractionated radiotherapy alone. These findings emphasize the need to combine radiation therapy with immune augmenting strategies for better outcomes. Along similar lines, there is an argument that radiation therapy alone does not have the intensity to generate enough proinflammatory signals to help overcome radiation-induced immune suppressive factors (5). Therefore, a partnership of radiation with targeted immunotherapy agents appears to be important to achieve therapeutically effective antitumor immune response and this partnership has shown some promising outcomes in preclinical and clinical settings (5).

Myeloid Cells in Radiation-Induced Immunomodulation

Macrophages and dendritic cells (DCs) play important roles in radiation-induced immune modulation. Adaptive immune response triggered by radiation therapy for tumor control can be negated by several factors activated through tumor myeloid cells (6). One such factor is Arginase I, which was shown to have a role in improving radiation-treated tumor control, although targeting multiple pathways in macrophage differentiation maybe a more effective tumor control strategy (6). Dendritic cells are important for