Commentary

Optimizing radiation for cancer immunotherapy

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Various protocols are under investigation for the purpose of optimizing radiotherapy for cancer treatment. Due to recent advances in image guidance and radiation delivery, a new option is to treat tumors with a single intense dose of radiation, 30 Gy or more (1,2). Alternatively, radiation doses can be "fractionated" over multiple treatment periods. Radiotherapy kills tumor cells and their associated stromal and vascular cells, and in some instances can induce T cell-mediated immunity that is effective at killing tumors outside the radiated area, a phenomenon called the "abscopal effect" (3,4). Since complete tumor remission usually depends on an effective anti-tumor immune response, it is important to determine how different radiation regimens influence anti-tumor immune responses. Filatenkov and coworkers (5) investigated the effect of radiation delivery protocols on the numbers and properties of immune cells in the microenvironments of colon cancer cells in mice. Weakly immunogenic ectopic CT26 colon tumors grown in syngeneic Balb/c mice usually responded to a single 30 Gy dose of intense radiation with durable tumor remissions due to T cell-mediated tumor killing. Fractionated radiation regimens were not as effective at stimulating T cells responses or durable remissions. The authors conclude that an examination of the tumor immune response may be useful for optimizing radiation regimens applied to various tumors.

A critical role for myeloid cells in tumor immunosuppression following radiation

Solid tumors produce factors that normally evoke an immune response, but tumors also create an immunosuppressive microenvironment by producing additional anti-inflammatory factors such as adenosine (6), TGFβ (7) and nitric oxide (8). Tumor cells also express indoleamine 2,3-dioxygenase (IDO) that converts *L*-tryptophan to *L*-kynurenine (9). Tryptophan depletion and kynurenine accumulation inhibit immune effector cell proliferation. These factors also stimulate the production of immunosuppressive cells such as myeloid-derived suppressor cells (MDSCs), tolerogenic (M2) tumor-associated macrophages (TAMs), and T regulatory (Treg) cells. These suppressor cell populations influence T cells to express additional inhibitory signaling molecules (PD-1, CTLA-4, and Tim-3). Filatenkov and coworkers (5) found that high intensity radiation of tumors, as opposed to fractionated radiation, resulted in tumor remissions that were associated with an increase in tumor-associated $CD8^+$ T cells and a reduction in $CD11b^+/Gr1^+$ MDSCs over 14 days following radiation. These responses were dependent on $CD8^+$ dendritic cells (DCs), $CD4^+/CD40L^+$ T helper cells, $CD8^+$ cytotoxic T cells and IFNγ (*Figure 1*). Tumor remission in response to intense radiation was not observed in $Batf3^{-/-}$ mice that lack $CD8^+$ DCs (10). The findings implicate the minor $CD8^+$ DC subset, as important for tumor antigen cross presentation and $CD8^+$ T cell expansion in tumors and/or tumor-draining lymph nodes. They also suggest that radiation, together with T cells activation and IFNγ, cooperate to reduce MDSCs in tumors, to enhance the ratio of $CD8^+$ DCs/MDSCs and thereby produce anti-tumor immunity.

Effects of chemotherapeutic agents on tumor immunity

As with intense radiation, the antitumor activity of some

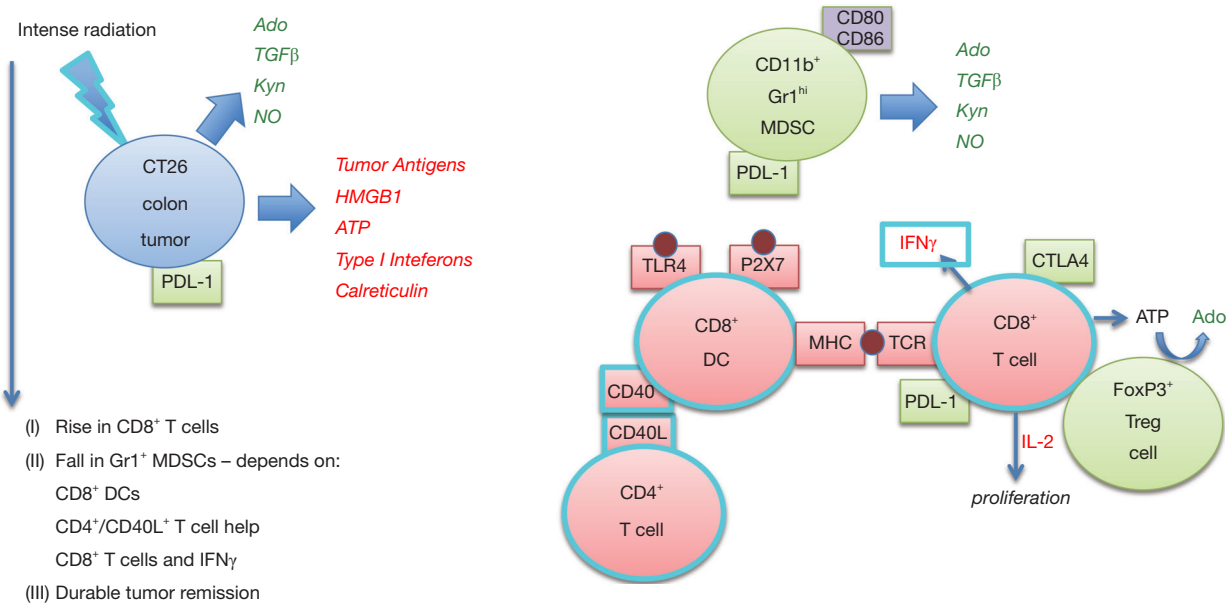

Figure 1 Factors that influence immune responses in tumors following intense radiation. In response to a single exposure to intense radiation (30 Gy) CT26 colon tumors rapidly release pro-inflammatory factors that stimulate the accumulation of pro-inflammatory cells shown in red. Tumors also release anti-inflammatory factors and stimulate accumulation of immunosuppressive cells or T cell exhaustion factors shown in green. Over 14 days following intense radiation there is an increase in tumor-associated $CD8^+$ T cells, a decrease in myeloid-derived suppressor cells (MDSCs), and T cell dependent tumor remission. Cells and factors that are required for optimal T cell mediated tumor killing are outlined in blue. HMGB1, High mobility group box 1; NO, nitric oxide; Kyn, *L*-kynurenine.

chemotherapeutic agents is mediated in part by activation of host immunity. Gemcitabin (11) and 5-fluouracil (12) are cytotoxic to MDSCs and activate tumor T cells. Cisplatin was found to increase numbers of tumor-associated DCs, decrease MDSCs, and enhance the immune response in melanoma-bearing mice (13). Paclitaxel (14) and docetaxel (15) were also found to reduce numbers of tumor-associated MDSCs. It will be of interest to determine if these responses depend on $CD8^+$ DCs, as is the case with intense radiation.

Effects of adenosine triphosphate (ATP) and adenosine of tumor immunity

ATP released from stressed or apoptotic tumor cells in response to radiation is acutely excitatory to the immune system by activating pro-inflammatory ATP-receptors (P2X and P2Y receptors) found on myeloid and lymphoid cells (16). However, certain tumors and tumor-associated suppressor cells express CD73 or CD39, which are ecto-enzymes that rapidly convert pro-inflammatory ATP into anti-inflammatory adenosine (17). Myeloid-selective deletion of immunosuppressive adenosine A2A receptors (A2AR) was recently found to change the phenotype of MDSCs by greatly reducing their IL-10 production, and to suppress the growth and metastasis of 4T1-12B breast cancer cells (6). A2AR blockers in tumors stimulate the activation of T cells, much like "check point inhibitors" such as anti-PD-1 and anti-CTLA4. In fact, A2AR blockade and anti-PD-1 synergistically inhibit the growth of breast and colon cancer cells (18). Since intense radiation causes tumor cell necrosis and apoptosis, rapidly released ATP can be degraded to adenosine. It will be of interest in future studies to determine if the combination of intense radiation and adenosine receptor blockade robustly stimulates anti-tumor immunity, and the roles for $CD8^+$ DCs and MDSCs in these responses.

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Footnote

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Conflicts of Interest: The author owns equity in Lewis and Clark, Pharmaceuticals, a company developing drugs targeting adenosine receptors.

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