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The Immunology of Ablative Radiation

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Radiation has been a staple of cancer therapy since the early 20th century and is implemented in nearly half of current cancer treatment plans. Originally, the genotoxic function of radiation led to a focus on damage and repair pathways associated with deoxyribonucleic acid as important therapeutic targets to augment radiation efficacy. However, in recent decades, the participation of endogenous immune responses in modifying radiation effects have been widely documented and exploited in both preclinical and clinical settings. In particular, preclinical studies have highlighted the capacity of hypofractionated–radiation dose schedules to modify endogenous immune responses raising interest in the use of hypofractionation in the clinical setting to harness the indirect immune effects of radiation and improve clinical responses. We review the current literature regarding the immunomodulatory effects of hypofractionated "ablative" radiation with a primary focus on the preclinical literature but also highlight examples from the clinical literature.
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Introduction

Radiation has been a staple of cancer therapy since the early 20th century and is implemented in nearly half of current cancer treatment plans. Originally, the genotoxic function of radiation led to a focus on damage and repair pathways associated with deoxyribonucleic acid as important therapeutic targets to augment radiation efficacy. However, in recent decades, the participation of endogenous immune responses in modifying radiation effects has been widely documented and exploited in both preclinical and clinical settings. In particular, an early study by Stone et al[1] was the first to document the effect of immune status (sufficient or deficient due to experimental manipulation) on tumor dose responses in syngeneic mouse fibrosarcoma. This observation was largely ignored until substantial work during the last decade expanded our understanding of how the immune system, and in particular T lymphocytes (T cells), participate in the host response to tumor radiation.[2-5]

Given the well-known sensitivity of lymphocytes to radiation-mediated apoptosis and potential for unintended immunosuppression arising from suboptimal dose and fractionation schedules, application of local radiation in hypofractionated ablative doses has been pursued as a means to capture both the direct cytotoxic and indirect immune-activating effects of radiation. Regarding immunostimulation, there is still a paucity of data on the specific dose and fractionation schedules. The effects of dose and fractionation on tumor-specific immune responses have been reviewed elsewhere[6] and are outside the scope of this review; however, we review some of the basic applications of stereotactic body radiation therapy (SBRT) and the preclinical data that support SBRT as an immune modifier. The reader is directed to reviews published in this issue and elsewhere for more comprehensive discussion of some of the basic immunologic mechanisms highlighted in this article.[7-9] In addition, for the purposes of this review and for lack of sufficient preclinical and clinical data for a rigorous comparison, we draw little distinction between the varying hypofractionated or single high-dose radiation treatment approaches, such as intensity-modulated radiation therapy, image-guided radiation therapy, and SBRT, despite acknowledgment of the important differences in clinical application.

General Remarks About Preclinical Animal Models of SBRT

Most of what we know about the immunomodulation of hypofractionated radiation doses (sometimes referred to "ablative" doses) characteristic of SBRT comes from preclinical animal models that use subcutaneous inoculation of tumor cell

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lines in syngeneic mice. The strategic advantage of this experimental setup is the ability to achieve relatively complete systemic shielding of the animal with a stationary, single radiation source. The tumor is usually exposed to the beam path by passing the tissue (skin and enclosed tumor) through a narrow orifice in the shielding that is oriented perpendicular to the beam path, thus eliminating all but the small amount of side scatter that can pass into the directly adjacent normal tissue traversing the orifice. It is worth noting that this experimental system, while a close approximation, does not replicate the extent of normal tissue exposure that occurs during the execution of a typical multi-beam SBRT treatment plan.

More importantly, considering the translational relevance of these studies, it is prudent to discuss the well-known, but rarely discussed, fact that inoculation of tumor cells lines in syngeneic animals results in the induction of innate and adaptive immune responses. For tumors that are capable of progressive growth in syngeneic animals, the immune response that is induced on inoculation fails to eliminate the deposited cancer cells, thereby resulting in rapid death of the host, usually within 3-6 weeks because of excessive tumor burden. The failure of the immune system to successfully combat the initial tumor challenge results from the formation of a well-documented immunosuppressive tumor microenvironment that thwarts immune-mediated attack during initial adaptation of the tumor cells to in vivo growth.

This localized suppression is followed closely by systemic immune suppression accompanying progressive tumor growth. Studies published by Paul Ehrlich in 1906 and Ernest Bashford[10] in 1908 demonstrated that the immune response generated from transplantable tumor challenge could successfully reject a second inoculum of the same tumor that was given within a short window following the primary inoculum. Rejection of the secondary challenge despite continued growth of the primary inoculum was a seemingly paradoxical observation that Bashford termed concomitant immunity and demonstrated the vaccine-like function of tumor challenge and the importance of local and systemic immune suppression in syngeneic "progressor" tumors. The time-dependent erosion of concomitant immunity with tumor progression was demonstrated to result from the induction of a systemic suppressor T-cell population[11] that was later demonstrated to be regulatory T cells.[12]

Importantly, as noted by Vaage,[13] "once immune resistance is evoked the resistance factors are never absent but may be depressed and not revealed, depending upon the conditions of the tests and strength of the antigens." Experimental demonstration of the preservation of immune resistance despite systemic suppression comes from studies that "unmasked" antitumor immunity to established tumors by systemic[11,12] or local[14] depletion of regulatory T cells. Considering these longstanding historical observations, it is fair to say that experimental systems using transplantable tumor cell lines are probably a more appropriate model for how hypofractionated or ablative radiation might augment existing T-cell immunity rather than initiating (or priming) de novo T-cell responses. This conceptual framework bears relevance when considering the widely popularized notion that local radiation of an established tumor can function as an in situ vaccine through the induction of immunogenic cell death and activation and maturation of antigen-presenting cells.[7-9] In this review, we focus mainly on the experimental data regarding immunomodulation of ablative radiation in the setting of existing T-cell responses and discuss the potential application and relevance to several clinical treatment scenarios involving SBRT.

Effects of Ablative Radiation Within the Target Volume

Direct Sensitization of Tumor Cells to T-cell–Mediated Killing

To date, many studies have documented the myriad mechanisms through which ablative radiation doses can increase the sensitivity of tumor cells to direct T-cell–mediated killing. These mechanisms include upregulation of the antigen-presentation machinery through increased expression and cell surface localization of major histocompatibility complex proteins,[3,15,16] increased expression of immunogenic tumor antigens,[17,18] upregulation of T-cell co-activating ligands,[19] and even sensitization of tumor cells to antigen-independent cell death through the Fas receptor.[20] These and other mechanisms have been reviewed elsewhere.[21] More importantly, an emerging trend in the most current research has been an understanding of the mechanisms through which the tumor stroma modulates ablative radiation and vice versa. The tumor stroma is a relatively loosely defined term that encompasses all cells within the tumor mass that are not neoplastic, including vascular endothelial cells, fibroblasts, hematopoietic cells of lymphoid and myeloid origin, and acellular components such as the extracellular matrix.

Pioneering work by Hans Schreiber and Rolf Zinkernagel established the importance of the tumor stroma in immunologic rejection of immunogenic tumors, demonstrating that inoculation of tumor cells with tumor stroma could drastically enhance their tumorigenicity and in some cases facilitate the growth of tumors normally rejected as cell suspensions in syngeneic mice.[22,23] Further studies by Spiotto and Schreiber[25] demonstrated that presentation of tumor antigens by both cancer cells and the stroma was required for complete elimination of antigenic tumors and tumors harboring antigen-negative clones (antigen-loss variants).[24] Given the importance of stromal antigen presentation, Zhang et al[26] demonstrated that a single dose of 10 Gy of local radiation was sufficient to sensitize antigenic tumors to T-cell–mediated rejection through "loading" of the tumor stroma with tumor antigens. Studies from our group demonstrated a similar phenomenon, wherein local radiation of established B16 melanoma tumors with a single ablative dose of 20 Gy facilitated cross-presentation of tumor antigens by dendritic cells in the tumor stroma.[27]

From the standpoint of local radiation, it is unclear what pathways control the transfer of antigen from tumor cells to the