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Synergistic antitumor activity of immune strategies combined with radiation

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1. ABSTRACT

Since its discovery more than a hundred years ago, radiation has been used to treat cancer. In recent decades, advances in radiation technology have expanded the role and value of radiation in imaging and treating many forms of cancer. Currently, there is a growing interest in combining radiation with other modalities, such as immunotherapy, to treat a broad range of malignancies. This article reviews the use of standard and novel combinations of radiation therapy and immunotherapy to eradicate tumor cells. The combination of radiation therapy and immunotherapy holds particular promise as a strategy for cancer therapeutics for a variety of reasons. First, there is evidence that immunotherapy is most beneficial when employed early in the disease process and in combination with standard therapies. In addition, radiation may act synergistically with immunotherapy to enhance immune responses, inhibit immunosuppression, and/or alter the phenotype of tumor cells, thus rendering them more susceptible to immune-mediated killing. Finally, as monotherapies, both immunotherapy and radiation may be insufficient to eliminate tumor masses. However, following immunization with a cancer vaccine, the destruction of even a small percentage of tumor cells by radiation could result in cross-priming and presentation of tumor antigens to the immune system, thereby potentiating antitumor responses.

2. INTRODUCTION

Radiation is often considered immunosuppressive (1), an activity that is most likely a result of the complex interplay of hormesis and the abscopal effect. Hormesis is a dose-regulated response to toxins or other stressors that is characterized by low-dose stimulation and high-dose inhibition (2). The phenomenon was recognized in the late 19th century in yeast and bacteria, and termed hormesis in 1948 by Southam and Erhlich (2, 3). According to this theory, radiation causes mutations within the cell while simultaneously accelerating the mechanisms within the cell that recognize and repair such mutations. Hormesis may explain why low-level radiation leads to a decline in the rate of cell death and, in some cases, improved overall health (4-6). The abscopal effect is another paradoxical effect of radiation on cellular systems. Also called the "distant bystander" effect (7), it describes the phenomenon whereby local radiation may have an antitumor effect on tumors distant from the site of radiation. More recently, ionizing radiation's ability to enhance distinct immune responses by inducing a danger signal that excites and activates the immune system has come under investigation (8, 9). Immunomodulators and immunosuppressors appear to operate on a continuum, so that at low doses, ionizing radiation may stimulate and modulate immune response, while at higher doses, destruction of hematologic cells and mediators may abrogate entire immune functions. In a

report on the synergistic combination of radiation and immunotherapy in cancer treatment, Friedman describes a "danger model" of immunity wherein ionizing radiation generates an inflammatory microenvironment filled with apoptotic and necrotic cells, cytokines, chemokines, inflammatory mediators, and acute-phase reactant proteins (10). This milieu of immune modulators allows antigen-presenting cells (APCs), such as dendritic cells (DCs) and macrophages, to process newly exposed antigens and potentially generate antigen-specific immunity (10-12). APCs migrate to the location of radiation-induced cellular injury, undergo maturation, and present postirradiation cellular debris and antigens to T cells, creating the functional link between radiation and increased immune response (11). The creation of novel combination cancer treatments is a direct result of exploiting this radiation-induced danger signal and harnessing the antigen specificity of the immune system.

The goal of tumor immunotherapy is to overcome tolerance to weakly immunogenic tumor-associated antigens (TAAs) and stimulate an immune response to tumor cells (10, 13, 14). The rationale for combining radiation and immunotherapy lies in the growing evidence that ionizing radiation induces cellular death in tumor cells, thereby releasing the multiple novel tumor antigens required to overcome tolerance, and igniting the "danger signals" needed to stimulate an immune response (15-17). Radiation ignites a "danger" zone filled with DCs, DC growth factors, T cells, and tumor antigens, exposing the immune system to sufficient numbers of cumulatively immunogenic TAAs to develop a therapeutic immune response (18-23). This is not the only mechanism by which radiation is able to augment tumor immunity. Radiation-induced upregulation of MHC class I, death receptors (Fas/CD95), and the costimulatory molecules B7-1, intercellular adhesion molecule-1 (ICAM-1), and lymphocyte function-associated antigen-3 (LFA-3) (together called TRICOM) sensitizes tumor cells to immune-mediated killing (24-27). In addition, radiation has been shown to alter the tumor microenvironment by affecting extracellular matrix proteins and the expression of adhesion molecules. These radiation-facilitated changes lead to increased APC and effector T-cell populations at the tumor site (28-32). The growing evidence of ionizing radiation's effects on cellular processes and antigen presentation increases the likelihood that combining radiation and immunotherapy will result in clinical benefit for cancer patients.

3. EXTERNAL BEAM RADIATION AND CANCER IMMUNOTHERAPY

Early efforts to combine radiation and immunotherapy employed whole-body irradiation, on the theory that it would eliminate resident T cells and thereby make room for the tumor-specific T cells generated by adoptive transfer to grow and expand. However, recent studies suggest that local external beam radiation can stimulate an effective antigen-specific immune response. *In vivo* studies have demonstrated that the combination of tumor-focused external beam radiation and immunotherapy can facilitate antitumor immunity better than either modality alone. Cameron *et al.* (33) reported increased survival using local tumor irradiation combined with adoptive transfer of tumor-infiltrating lymphocytes and IL-2 to treat multiple established (≥ 7 days) hepatic metastases in mice. Younes *et al.* (34) studied renal carcinoma with bilateral pulmonary metastases in a murine model. They observed that local irradiation to the left lung in combination with systemic IL-2 therapy led to greater tumor reduction in both lungs than was achieved by either modality alone, suggesting that radiation enhanced the systemic effect of immunotherapy. Other investigators employing this combination strategy in mice have reported similarly positive effects in murine lymphoma and mammary carcinoma tumors induced subcutaneously (s.c.) on both flanks (35). Treatment of one of the tumors with combined radiation and immunotherapy with IL-2 resulted in regression of the contralateral untreated tumor. Another study combined external beam radiation and anti-CD40L monoclonal antibody to treat a B-cell lymphoma model (36). CD40 ligation can activate APCs, allowing them to maximally and appropriately stimulate cytotoxic T-cells. Anti-CD40 treatment and 5 Gy irradiation were ineffective when employed singly, but the combination resulted in long-term survival of the mice.

In addition to IL-2 and immunomodulatory antibodies, therapeutic vaccines are being actively investigated as immunotherapy for cancer. TAAs such as carcinoembryonic antigen (CEA) and mucin-1 (MUC1), which are overexpressed on a wide variety of tumor cells *in vivo* (27), are being studied as targets for vaccine-mediated immunotherapies (37-41). Chakraborty *et al.* (22) have focused on the combination of low-dose radiation (8 Gy) delivered directly to the tumor, and active therapeutic vaccination for the treatment of s.c. murine tumors. The vaccine is composed of poxviral vectors that express TRICOM and CEA. Although either modality alone was ineffective, the combination of radiation and vaccine was not only curative in 50% of mice bearing CEA^+ tumors (Figure 1), but also imparted protection from subsequent tumor challenge. Interestingly, the combination strategy was not curative for mice bearing CEA^- tumors, suggesting that an antigen-specific immune response mechanism was responsible. Because these studies used local external beam radiation and not whole-body irradiation, the enhanced antitumor effect is probably attributable to radiation-induced changes within the tumor itself.

Studies investigating the mechanism by which local tumor irradiation enhances therapeutic response to immunotherapy have established that neoplastic cells may evade the adaptive immune system by altering expression of specific molecules, and that nonlethal doses of radiation may alter the phenotype of target tissue by upregulating some gene products and making tumor cells more susceptible to T cell-mediated immune attack. MHC class I is responsible for direct presentation of tumor antigen peptides to cytotoxic T lymphocytes (CTLs) via peptide-MHC complexes. ICAM-1 and other cell adhesion molecules enhance T cells' ability to kill target cells by improving cell-to-cell adhesion (42, 43). Preliminary findings have demonstrated that nonlethal doses of

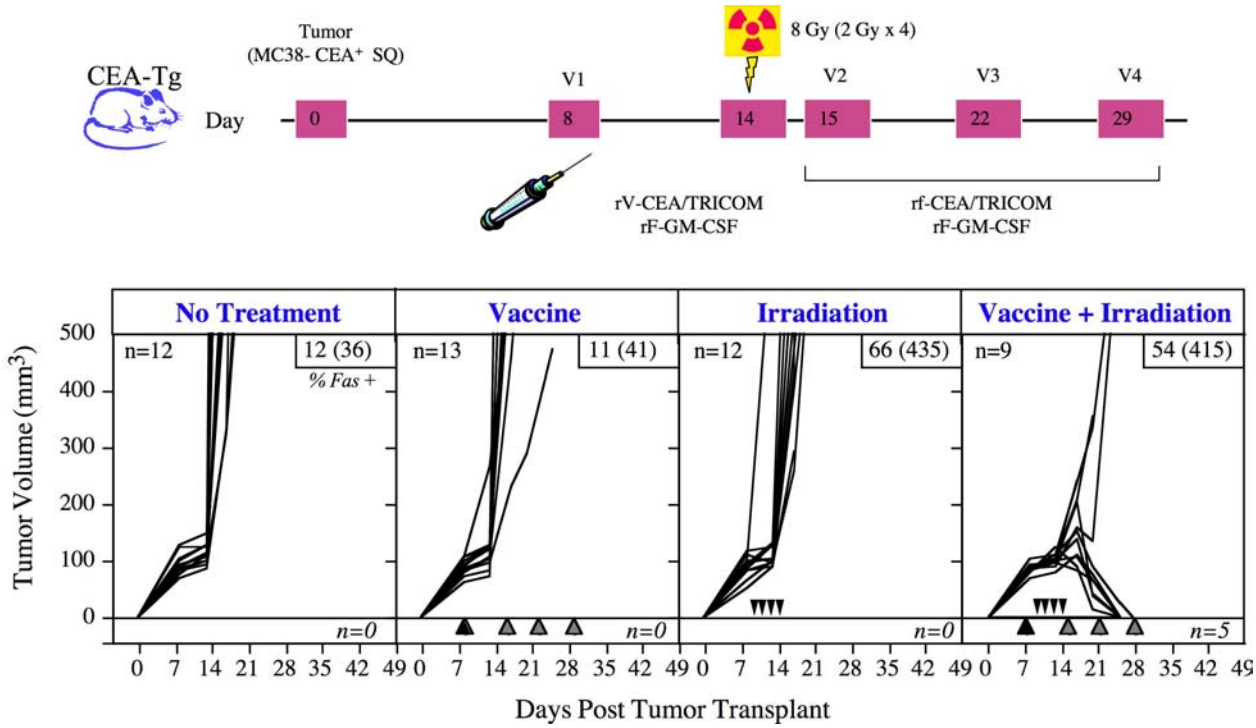

Figure 1. Combination of vaccine and radiation therapy (22). The vaccine consisted of poxviral vectors expressing TRICOM and CEA. Neither modality was effective alone, but the combination was curative in 55% of tumor-bearing mice and conferred protection from subsequent tumor challenge. Adapted from (22).

radiation induce a 2-phase, dose-dependent increase in MHC class I presentation in human tumor cells (Figure 2) (44). MHC class I molecules present endogenous peptides to CTLs. Many of these peptides are generated by the proteasome from newly synthesized but rapidly degraded proteins (RDPs). Within 4 hours after exposure, the protein degradation triggered by radiation damage leads to a peptide pool. Because peptides limit MHC class I assembly, the increased peptide pool gives rise to increased antigen presentation. Later, repair responses create an upregulation of DNA repair proteins, which leads to an increase in specific peptides. During the late cellular effects of ionizing radiation (> 4 hours after exposure) the mTOR pathway is activated, resulting in translation of proteins and increased generation of peptides from the RDPs of these new proteins. At each of these stages, unique proteins are expressed and upregulated in response to ionizing radiation, resulting in novel peptide presentation (44). Various proteins may be selectively upregulated and/or degraded in response to irradiation, including DNA repair proteins such as proliferating cell nuclear antigen, and proteins involved in cell cycle checkpoints, apoptosis, and protein degradation (44, 45).

The effect of radiation on Fas (CD95) and its associated cell-death mechanisms has recently been investigated. Activated Fas ligand-expressing CTLs often use Fas expression on tumors to directly kill tumor targets (46). In murine studies, radiation increased Fas gene expression in CEA-expressing tumor cells, enhancing the cells' susceptibility to CEA-specific CTL-mediated killing (27). In one study, after irradiation with 8 Gy, MC38-CEA$^+$ tumor cells showed an upregulation of Fas for > 11 days (22) (Figure 3). Fas ligand displays a complex pattern of inducible and constitutive expression associated with a number of different functions as a death factor or a costimulatory molecule in lymphocyte activation (44). Activated CTLs express cell-surface Fas ligand, which binds to Fas molecules on the target cell surface. This interaction sends signals to the target cell to undergo apoptosis (22, 23, 44).

In the study conducted by Chakraborty *et al.* (22), mice transgenic for human CEA (CEA-Tg mice) were injected s.c. with MC38-CEA$^+$ tumor cells, and 8 days later were divided into 4 groups (Figure 1). In the first group, which received no treatment, progressive tumor growth killed all the mice by day 30. The second group received vaccine alone in a diversified prime-and-boost regimen. The mice were primed on day 8 with recombinant vaccinia (rV)-CEA/TRICOM admixed with recombinant fowlpox (rF)-GM-CSF, followed by boosts with rF-CEA/TRICOM admixed with rF-GM-CSF on days 15, 22, and 29. This vaccine regimen alone did not significantly inhibit tumor growth. The third group of mice received radiation therapy alone. Beginning on day 14, tumors were irradiated with 2 Gy/day x 4 days (total 8 Gy). This therapy, too, had no significant impact on tumor growth. In the fourth group, mice were treated with a combination of the vaccine and radiation regimens described above, which resulted in a significant decrease in both tumor volume and the rate of tumor growth. Furthermore, 40% of mice receiving the

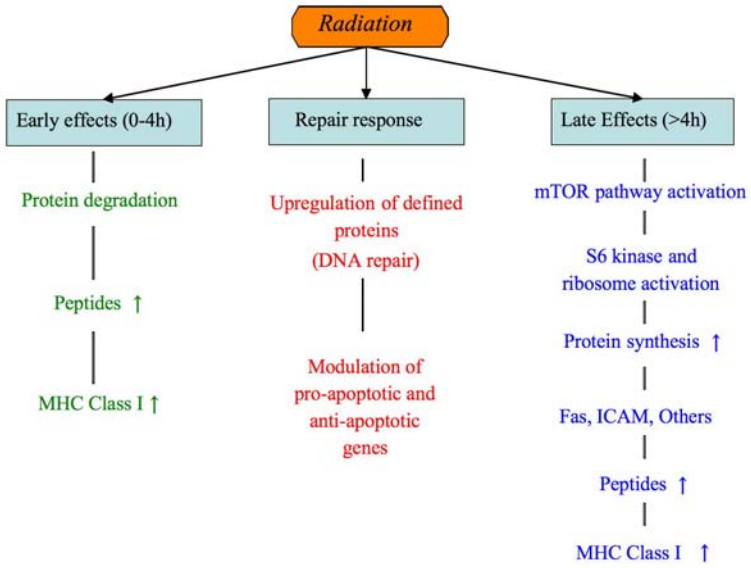

Figure 2. Summary of the effects of ionizing radiation on MHC class I antigen presentation. Early effects are caused by degradation of proteins that may be triggered or damaged by irradiation. Later effects are caused by activation of the mTOR pathway, which results in increased translation of proteins and increased generation of peptides from the RDPs of these new proteins. The increased peptide pool enhances MHC class I assembly because peptides are the limiting factor. In addition, unique proteins are expressed/upregulated in response to ionizing radiation, resulting in novel peptides presented by MHC class I molecules. Adapted from (44).

combination therapy showed a complete resolution of tumor mass and remained tumor-free for the duration of the study (180 days). This result was strictly dependent on Fas expression, as CEA-specific CTLs did not kill tumors expressing a dominant-negative version of the Fas gene.

Phenotypic modulation of tumors by radiation does not appear to be limited to Fas for all tumor types. Garnett *et al.* (23) examined 23 human carcinoma cell lines (12 colon, 7 lung, and 4 prostate) for their response to nonlytic doses of radiation (10 or 20 Gy). They examined changes in surface expression of Fas and other molecules involved in T cell-mediated immune attack, such as ICAM-1, MUC-1, CEA and MHC class I, and found that T cell-mediated immune killing was increased even in cells deficient in functional Fas. Radiation upregulated at least one of these surface molecules in 21 of 23 (91%) cell lines studied. Furthermore, all 5 irradiated $CEA^+/A2^+$ colon tumor cell lines demonstrated significantly enhanced killing by CEA-specific HLA-A2-restricted $CD8^+$ CTLs compared to nonirradiated cell lines (Figure 4). Microarray analysis of gene expression changes revealed that many additional genes had been modulated by irradiation. These upregulated gene products may further enhance the tumor cells' susceptibility to T cell-mediated immune attack or serve as additional targets for immunotherapy. Overall, the results of this study suggest that nonlethal doses of radiation render human tumor cells more amenable to immune system recognition and attack. Ongoing studies are investigating whether these effects are the result of a radiation-induced local inflammatory response, which could cause an influx of T cells to the region or a reduction in the number of regulatory T cells within the tumor microenvironment.

In vitro and *in vivo* preclinical use of local tumor irradiation in combination with various forms of immunotherapy has provided the rationale for the clinical use of this strategy in cancer patients. Recent clinical trials have combined radiation with TRICOM-based poxviral vector vaccines, and a recently completed clinical study (21) employed external beam radiation and prostate-specific antigen (PSA)-based vaccines in patients with clinically localized prostate cancer. Results of this trial indicated that the combination of vaccine and radiation was safe, and that it effectively generated a PSA-specific immune response in these patients. Another clinical study currently underway combines CEA-expressing TRICOM-based vaccines and low-dose external beam radiation delivered directly to liver metastases in patients with CEA^+ solid tumors (47). Other clinical trials are being planned to further assess the clinical benefit of combining external beam radiation and therapeutic vaccines, some of which will examine tumor tissue biopsies before and after radiation to see if TAAs are upregulated.

4. BONE-SEEKING RADIONUCLIDE AND CANCER IMMUNOTHERAPY

In advanced stages, many primary human carcinomas such as thyroid, breast, kidney, prostate, and multiple myeloma typically involve painful bone metastases that require palliative therapy. Strontium-89 (^{89}Sr) and samarium^{153} (^{153}Sm) are bone-seeking radionuclide-chelated radiopharmaceuticals used to relieve

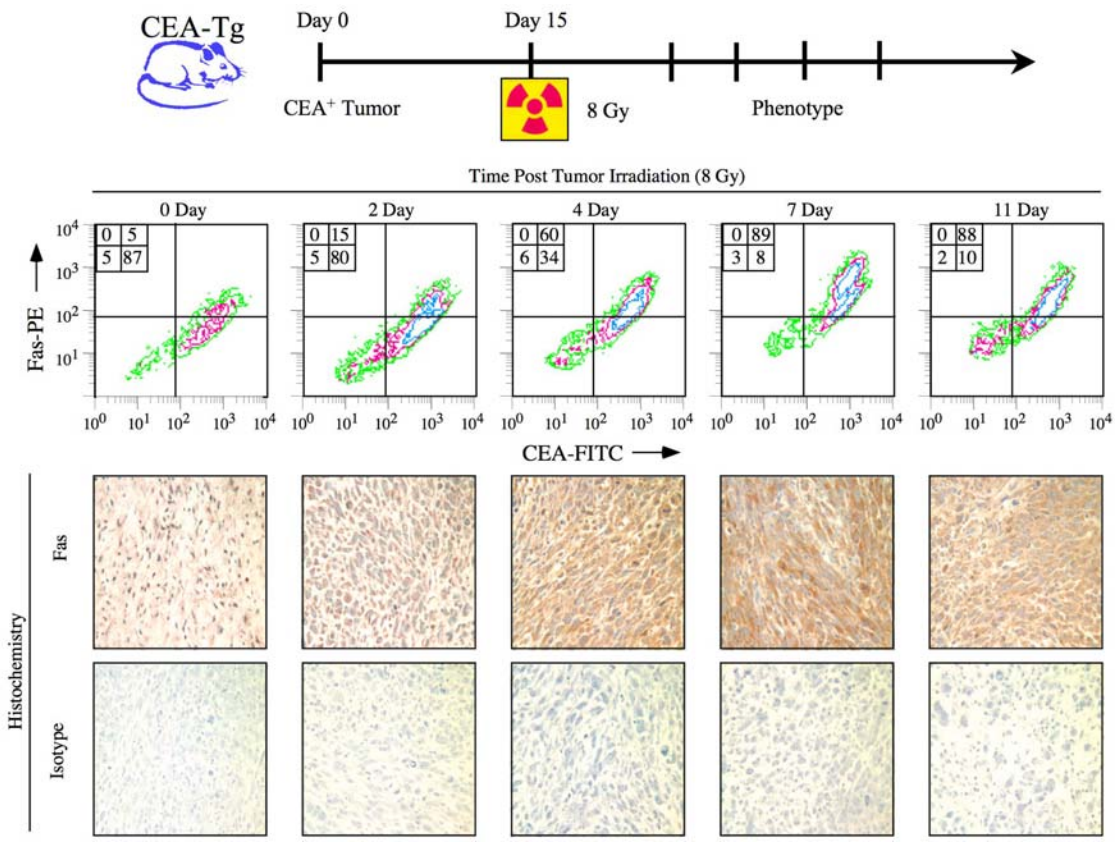

Figure 3. Expression of radiation-induced upregulated Fas on tumor cells is maintained for > 11 days. C57BL/6 mice were injected s.c. with $3x10^5$ MC38-CEA$^+$ tumor cells. After 14 days, tumors were subjected to 8 Gy external beam radiation. Tumors were surgically removed at indicated times after radiation, costained with CEA and Fas antibodies, and analyzed for Fas expression by flow cytometry and immunohistochemistry. Insets show percentage of positive cells for each quadrant. To confirm Fas expression, tumors were harvested at the corresponding times after irradiation and immunostained with anti-Fas mAb or an isotype control antibody. Adapted from (22).

the pain of metastasis to bone. In the case of ^{153}Sm, it is believed that chelation to ethylenediaminetetramethylenephosphonate (EDTMP) forms a complex that can bind avidly to hydroxyapatite in bone, especially in areas of high turnover such as metastatic lesions (48). ^{153}Sm is FDA-approved as a single agent in this setting, but there is increasing interest in using it in conjunction with immunotherapy for the treatment of a variety of solid tumors. Several factors make ^{153}Sm a superior candidate than ^{89}Sr for use in combination therapies. At 46 hours, the half-life of ^{153}Sm is significantly shorter than the 50.6-day half-life of ^{89}Sr, allowing for repeated administration and faster recovery from pancytopenia (the main toxicity of both is myelosuppression) (49-53). In addition, ^{153}Sm emits both beta particles and gamma rays, a characteristic that offers more imaging options.

The calculated dose of palliative radiation delivered to bone metastases by chelated ^{153}Sm is between 18 and 80 Gy (48, 54), which may be just below the dose required for a therapeutic effect. A clinical trial employing multiple doses of ^{153}Sm showed PSA declines in prostate cancer patients with metastatic bone lesions (52), and a phase II study reported increased survival in metastatic breast cancer patients receiving ^{153}Sm (55). Ongoing studies are examining the effect of ^{153}Sm on phenotypic modulation of human tumor cells. In one study, 10 tumor cell lines of prostate, breast, and lung origin were exposed to clinically relevant palliative levels of ^{153}Sm for 4 days, then examined by flow cytometry for modulation of several cell surface molecules. Of the 10 cell lines, 100% upregulated Fas and CEA, 70% upregulated MUC-1, 40% upregulated MHC class I, and 30% upregulated ICAM-1. Upregulation of any of these surface molecules could potentially render tumor cells more susceptible to killing by CTLs (56). Exposure of the human prostate cancer cell line LNCaP to ^{153}Sm resulted in the upregulation not only of Fas, ICAM-1, CEA and MUC-1, but also of PSA, prostate-specific membrane antigen, and prostatic acid phosphatase. When incubated with PSA-specific CTLs, LNCaP cells treated with ^{153}Sm were killed significantly better than untreated tumor cells. This result was also seen when ^{153}Sm-treated cells were incubated with MUC-1- or CEA-specific CTLs, showing that exposure of human tumor cells to ^{153}Sm rendered them more susceptible to killing by a variety of antigen-specific CTLs. Further analysis of LNCaP after exposure to ^{153}Sm demonstrated enhanced

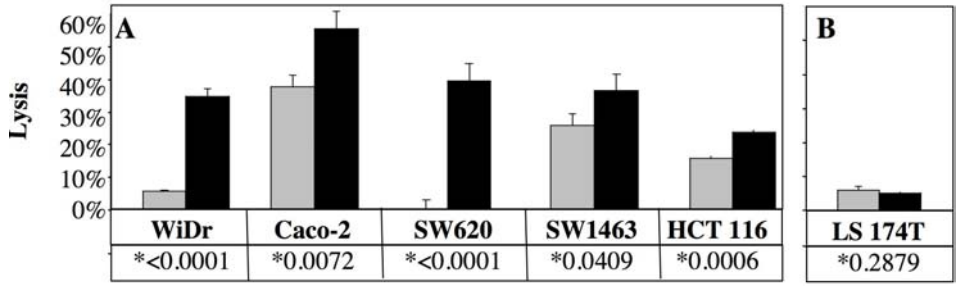

Figure 4. Irradiation increases sensitivity of human tumor cells to Ag-specific cytotoxic T-cell killing. Five $CEA^+HLA\text{-}2^+$ tumor cell lines were mock-irradiated (gray bar) or irradiated with 10 Gy (black bar) and recultured for 72 hours. Cells were then labeled with ^{111}Indium and coincubated with HLA-A2-restricted CEA-specific CTL for 18 hours at an E:T ratio of 30:1. LS 174T, a $CEA^+HLA\text{-}A2^-$ cell line, was used as a negative control. *Statistical significance compared to nonirradiated group. Adapted from (23).

mRNA expression of several prostate tumor antigens, ICAM-1, Fas, and proapoptotic genes, as measured by quantitative PCR. These studies were all conducted *in vitro*; however, work is in progress to establish a bone metastasis model to study the effect of ^{153}Sm treatment *in vivo*. Future studies will combine ^{153}Sm treatment with vaccine to determine whether ^{153}Sm sensitizes tumor cells to CTL-mediated killing *in vivo*.

5. RADIOLABELED MONOCLONAL ANTIBODIES AND CANCER IMMUNOTHERAPY

Systemic radiotherapy, which delivers therapeutic radionuclides to cancer cells via monoclonal antibodies (mAb), is another promising modality for the treatment and management of cancer. Radiolabeled mAb have been shown to target tumor cells precisely and preferentially (57). They can seek out micrometastases that are not observable by current imaging technology and thus cannot be targeted by external beam radiation. Radiolabeled mAb may alter tumor-cell phenotype and render tumor cells more susceptible to vaccine-mediated T-cell killing as effectively as sublethal external beam radiation, while their specificity minimizes damage to normal tissue. Moreover, due to the path length of the attached radionuclide (for example, ^{90}Y has a path length of approximately 100 cell diameters), a single mAb bound to one tumor cell can have a radioactive effect on neighboring tumor cells as well.

The use of radiolabeled mAb has been more successful in the treatment of hematological malignancies than in solid tumors, possibly because solid tumors are less susceptible to radiation-induced cell death (58, 59). Factors that limit solid-tumor sensitivity to radiolabeled mAb include limited vascular supply, elevated interstitial pressure, and heterogeneous uptake of mAb by tumor cells (60, 61). Because uptake of mAb correlates inversely with tumor size, patients with low tumor volume and minimal residual disease may be the best candidates for radioimmunotherapy (RIT) (62). TAAs are key to the efficacy of radiolabeled mAb, alone or in combination with vaccine strategies (63). Modrak *et al.* (64) first demonstrated that low-dose radiation is associated with increased TAAs, which are necessary for immunotargeting, immunodetection, and immunotherapy. Most studies of combination therapies using radiolabeled mAb have focused on the cytotoxic properties of radiation (65, 66), but a recent report (67) cited the ability of radiolabeled mAb to alter tumor-cell phenotype and enhance immunologic targeting of tumor cells, as well as a therapeutic synergy between radiolabeled antibody and vaccine therapy. The model used in this study consisted of CEA-Tg mice and a murine carcinoma cell line transfected with CEA. CEA-Tg mice (68) received a diversified prime-and-boost vaccine regimen of rV-CEA/TRICOM and rF-CEA/TRICOM (69, 70) in combination with systemic RIT using ^{90}Y-COL-1, a high-affinity CEA-specific murine mAb. Mice were injected s.c. with MC38-CEA^+ tumor cells and primed after 8 days with rV-CEA/TRICOM. The mice received a single dose of 100 μCi ^{90}Y-COL-1 on day 14 and a boost of rF-CEA/TRICOM on days 15, 22, and 29. The dose of radiolabeled mAb was noncurative as a monotherapy, and the vaccine regimen alone was insufficient to slow tumor growth. However, the combination resulted in a significant reduction in tumor volume and a statistically significant increase in survival. The therapeutic efficacy of this combination therapy was mediated by the Fas/Fas ligand pathway, as demonstrated by a study in which Ag-bearing tumor cells expressing dominant negative Fas were not susceptible to the combination therapy (71). Further illuminating the mechanism whereby this combination therapy led to enhanced tumor regression, mice treated with radiolabeled antibody and vaccine showed a significant increase in the percentage of tumor-infiltrating CEA-specific $CD8^+$ T cells compared to vaccine alone. In addition, the mice demonstrated $CD4^+$ and $CD8^+$ T-cell responses to TAAs not encoded by the vaccine (gp70 and p53), indicating an antigen cascade (72). Overall, these results showed that targeted tumor irradiation in combination with vaccine promotes effective antitumor response, which may have implications for the design of future clinical trials of mAb and immunotherapy.

6. BRACHYTHERAPY AND CANCER IMMUNOTHERAPY

Brachytherapy is the practice of temporarily or permanently inserting a source of radiation into or near a

malignant tumor (73). Brachytherapy delivers a continuous emission of high-dose radiation to tumor cells, while doing less damage than external beam radiation to surrounding healthy tissue, thus minimizing side effects. In head and neck cancers, brachytherapy can spare impairment of speech, swallowing, and facial appearance (74). There are several early reports of promising outcomes in breast cancer, with few local recurrences, minimum toxic effects, and excellent cosmetic outcomes (75-77). The use of intraluminal brachytherapy for recurrent lung cancer (78, 79), esophageal tumors, and pancreatic carcinomas metastatic to the biliary tract (80-82) is increasing as well, with high-dose-rate brachytherapy delivered via catheter offering increased local control and survival along with substantial palliation (83-85). Soft tissue sarcomas, ocular malignancies, central nervous system neoplasms, gynecological malignancies (86-88) and bladder cancer have all been treated successfully to some degree with brachytherapy (73).

One of the most successful uses of brachytherapy has been in the treatment of early-stage prostate cancer. Treatment modalities such as external beam radiation, radical prostatectomy, and hormone-deprivation therapy are too aggressive for patients with early-stage disease. This, along with their potential for severe side effects and complications, has led to a growing interest in brachytherapy for this patient population. Prostate cancer is an appealing target for immunotherapy as well. Because the prostate is not essential for life, the potential of immunotherapy to induce autoimmune reactions poses little risk.

Most of the murine studies employing brachytherapy have had endpoints of tumor-cell toxicity, survival, or effect on tumor microenvironment (89-94). There have been few clinical studies on the immunologic consequences of brachytherapy. An early study evaluated lymphocytes after the use of intracavitary radium for early-stage cancer of the uterine cervix (95), and a report on treating stage I endometrial cancer with brachytherapy showed that iridium-192 (^{192}Ir) had no influence on cell-mediated immunity and no sustained detrimental effects on lymphocyte function (96). Another study of cervical cancer found that low-dose-rate brachytherapy suppressed T helper cells, T suppressor cells, and cytotoxic T cells. The absolute number of natural killer cells and monocytes remained unchanged, with an increase in the ratio of monocytes to T cells (88). While these observations are interesting, they offer little insight into the potential complexities of combining brachytherapy and immunotherapy. There is an early report on the ability of iodine-125 (^{125}I) and a recombinant poxviral vaccine to modulate phenotype and enhance antigen-specific killing of tumor cells (97), but more such studies are needed on the use of brachytherapy and immunotherapy in multiple disease settings.

7. CONCLUSION

Learning how to exploit radiation-induced changes to tumor-cell antigens, and how to induce effective immune responses to these cumulatively immunogenic stimuli, is an exciting frontier in cancer therapy research. Many clinical trials exploring the use of radiation and vaccines in the treatment of cancer are currently underway. As knowledge of the synergistic effects of radiation and immunotherapy increases, the translational use of this strategy for a variety of carcinomas will become more feasible.

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