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Combined Effect of Metallic Pollutant Lead And Radiation on Body Defense-Immunity

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ABSTRACT: At present, the opinions about the interaction between ionizing radiation and the immune system are largely controversial. For long, high-dose ionizing radiation was considered as net immune suppressing mainly due to the exquisite radiosensitivity of the lymphoid system. While this increased radiosensitivity cannot be contested, a rapidly growing number of scientific publications have demonstrated a very heterogeneous quantitative and functional response of the different components of the immune system to radiation⁽¹⁻³⁾. A major milestone was achieved in the field of onco-immunology, where it has been shown that local tumor irradiation could modulate the immunogenicity of tumor cells and also the antitumor immune responsiveness both locally in the tumor microenvironment and at a systemic level⁽⁴⁻⁶⁾. This latter observation opened the gate for studies exploring optimal combinations of radiotherapy (RT) and immunotherapy in order to achieve a synergistic effect.

It was additionally recognized that some of the radiation-induced late side effects are of immune and inflammatory nature. At present, one of the most studied fields of research in radiation biology is focused around the biological effects of low doses, where the observed pathophysiological endpoints are due to mechanisms other than radiation-induced direct cell killing. Such mechanisms are for example radiation-induced bystander effects or abscopal effects, which by sharing common mediators with various immunological signaling processes, are most probably immune-mediated.

The multitude of studies investigating the interactions between ionizing radiation and the immune system lead to the emergence of a new, highly interdisciplinary scientific field called radio immunobiology, with the potential to induce a paradigm change in this area and to achieve direct clinical applications within a relatively short term.

I. INTRODUCTION

Radiotherapy is one of the cornerstone treatment modalities for cancer. It is also the most commonly used cancer treatment strategy, with approximately 60% of patients with solid tumors receiving curative or palliative irradiation as part of their treatment¹.

High precision techniques are currently available, making treatment delivery more safe and effective, while sparing adjacent normal tissue².

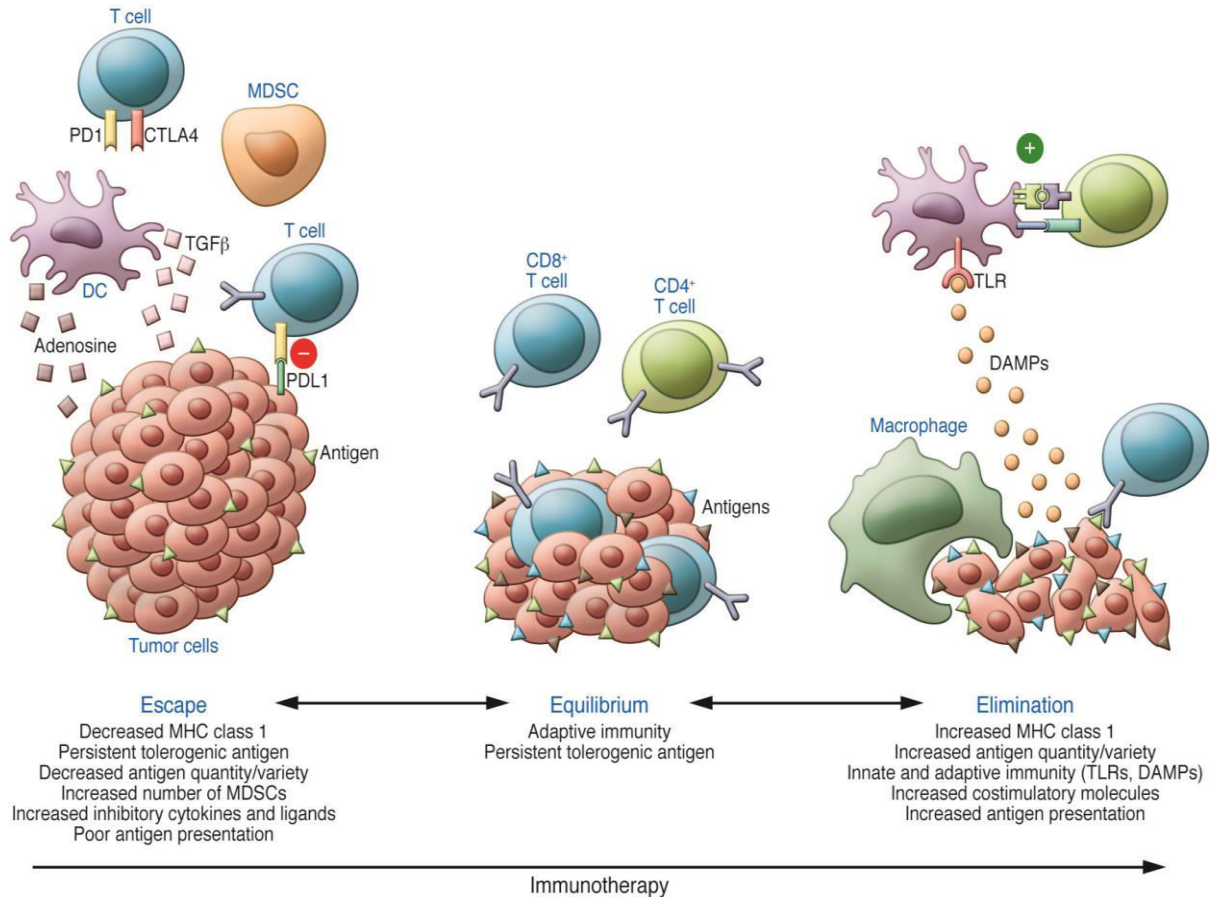
Radiation-induced cell death is modulated by several factors related to the molecular physicochemical effects that induce cellular stress. Depending on the dose and irradiation schedules used, cellular senescence or death will occur as a result of the disequilibrium caused by the stress³.

The tumor microenvironment, especially the degree of oxygenation, has also long been known to influence the response to radiation. This has broadened the studies on radiobiology that currently include the effects of radiation on tumor vasculature, fibroblasts and immune cells⁴.

There is growing interest in research on immunotherapies based on the critical role of the immune system in cancer development and dissemination⁵. The anticancer immune response may also be activated by ionizing radiation, and a combination of different treatment strategies is promising in this field^{3,6}.

The objective of this manuscript was to provide a brief update about the role of radiotherapy in cell death and the activation of the antitumor immune system from the perspective of clinical applications in oncologic treatment.

Immunotherapy and the cancer immunoediting hypothesis.



In the immunoediting hypothesis, the tumor immune system balance shifts among tumor escape (to mutation-specific antigens), equilibrium, and elimination. Tumor escape (left) occurs in cases with poor antigenic expression, immunosuppressive cytokines, MDSCs, and expression of negative regulatory receptors on T cells (which engage cognate ligands on the tumor). In the equilibrium phase (middle), the tumor and the adaptive immune system coexist. Here, the immune system creates a growth-inhibitory environment and antigenic tumor outgrowths are kept in check. In tumor elimination (right), which often occurs in early tumor development, highly antigenic tumor clones are recognized and eliminated by both innate and adaptive immune systems. Various forms of immunotherapy (e.g., vaccines, adoptive cell transfer, targeted immune therapeutics) aim to shift the balance from escape and equilibrium to elimination.⁷

II. REVIEW OF LITERATURE

There is increasing evidence that radiation can work to produce quantitatively superior results with immunotherapy for local tumor control at the site of irradiation, but much excitement is focused on a completely different qualitative responses than can emerge between radiation and immunotherapy, systemic abscopal cancer eradication. While the optimal radiation dose, fractionation, and modality to be used in combination with immunotherapy remain to be determined, some preclinical evidence suggests that higher doses of radiation such as those delivered during hypofractionated regimens generate more immunologic responses. Recent technologic advances in clinical radiation therapy have now made it possible to deliver ablative radiation doses precisely to tumors using stereotactic radiation techniques such as SBRT/SABR. Thus, stereotactic radiation in combination with immunotherapy agents represents an exciting and potentially fruitful new space for improving cancer therapeutic responses.



To date, radiobiological models have been primarily focused on improving the therapeutic ratio of radiation treatment by enabling a toxic dose of radiation to tumor cells while sparing normal tissue. The linear quadratic (LQ) model of radiobiology is based on differential DNA repair in normal and tumor tissues. The LQ model predicts single-strand lethal damage (α parameter in LQ equation) and double-strand lethal damage (β parameter in the LQ equation) induced by ionizing radiation. Subsequent sublethal damage repair can also be modeled. The LQ model predicts that delivery of radiation dose in small fractions induces maximum tumor cell death compared with single-dose delivery, with minimal effects on normal tissue.¹

Traditionally, delivery of doses of 50 to 70 Gy using multiple fractions of 1.8 to 2 Gy per fraction in the curative setting of solid tumors is preferred to deliver the best therapeutic ratio. Recent technological advances in planning and delivery of external beam radiotherapy such as 3-dimensional image guidance, modulation of beam intensity and multileaf collimators, and 4-dimensional tumor tracking have allowed conformal delivery of larger doses per fraction while minimizing dose to normal tissues with higher precision. Thus, hypofractionated and extreme hypofractionated delivery schedules have been employed in treatment of many tumor types to increase tumor cell death while maintaining the therapeutic ratio.⁴

III. DISCUSSION

Besides the direct effects of radiation in reducing viable cancer cells, RT may induce modifications on the local microenvironment that can affect tumor development (5). Most tumor cells do not express major histocompatibility complex (MHC) class II. As a consequence, they cannot directly activate the specific CD4+ T cell-mediated tumor immunity, which is essential for the development of adaptive immune responses. Tumor cells develop multiple and complex mechanisms to fully escape immune surveillance. These cells can produce immunosuppressive cytokines and the recruitment of inhibitory and regulatory cell types, decrease expression of antigens, lose expression of MHC class I molecules, have an aberrant antigen processing, cause anergy or deletion of T cells, and generate the dysfunction of dendritic cells (DCs) (5-8). The interaction of all these factors could lead to cancer cells escaping the immune system (6).

It has been shown that RT may contribute to making tumors visible to the immune system (9-14). After RT treatment, there is an increase pool of peptides for antigen presentation displayed by MHC-I molecules (6). The tumor-associated derived antigens (TAAs) released to the tumor periphery can be captured by DCs. These DCs become active via toll-like receptors (TLRs) recognition, in which endogenous danger signals emitted by dying tumor cells are identified. The activation of DCs is characterized by the upregulation of cell surface molecules involved in antigen presentation and costimulation (e.g., CD80, CD86) and the release of pro-inflammatory cytokines. Thus, activated DCs migrate to secondary lymphoid organs where TAAs will be presented to CD4+ Th cells in the context of MHC-II. Active, effector, T cells may recirculate through the body and generate a tumor-specific immune response in distant areas. By means of this mechanism, adaptive immune responses may help to eradicate metastasis of tumors that do not express MHC-II. CD4+ T cells may help to kill tumor cells by several mechanisms. One such is enabling the development of tumor specific CD8+ T cells which recognize tumor peptides by MHC-I (Figure 1). CD4+ T cells, particularly Th1 cells, secrete interferon (IFN)- γ , which induces MHC-I expression in tumor cells. IFN- γ may also collaborate to control tumor growth by inhibiting angiogenesis. In addition, tumors treated with RT increase the IFN- γ -production, which in turn upregulates MHC-I expression. Despite the central role of CD4+ T cells on anti-tumor adaptive immunity, exogenous antigens such as TAAs, may be presented by DCs via cross-priming to CD8+ T cells in the context of MHC-I; this process could take place without a previous CD4+ T cell helping. This would support the hypothesis that radiation may enhance the tumor immunogenicity by promoting cross-priming and stimulating the effector phase of the anti-tumor immune response (1,10,15). In addition, RT can induce the secretion of a wide range of cytokines and other mediators by RT-targeted tumor cells and surrounding cells (such as endothelial cells of tumor stroma and infiltrating tumor cells).⁸

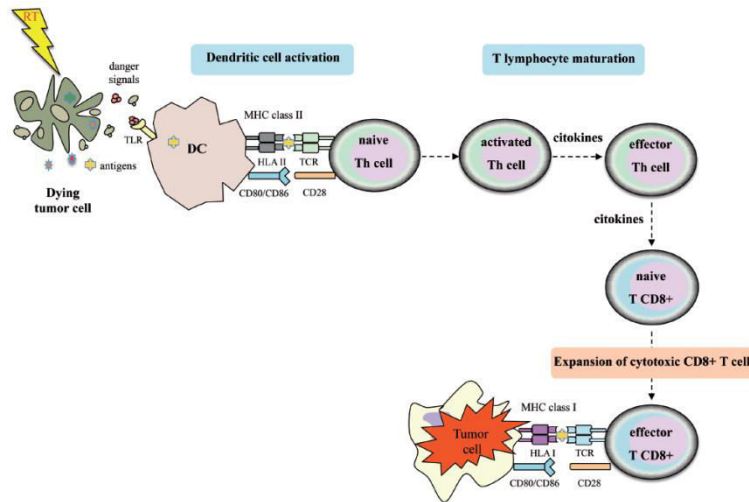


Figure 1 Mechanism of removal tumor cells. In presence of appropriate “danger signals”, immature DCs become active and mature. DCs migrate to secondary lymphoid organs where the antigens, released by dying cells, are captured in the periphery, processed into peptides and presented to CD4+ Th cells in the context of MHC-II. Once activated, effector T cells may help to generate an effective immune response through the activation of cytotoxic CD8+ T cells that can eradicate tumor cells by recognizing peptides presented in the context of MHC-I. Abbreviations: DC, dendritic cell; HLA: human leukocyte antigen; MHC: major histocompatibility complex; RT: radiation therapy; TCR: T cell receptor; Th: T helper; TLR: Toll-like receptor.

IV. CONCLUSION

Lead (Pb) is a ubiquitous environmental pollutant. High-dose exposure as well as chronic exposure leads to increased blood and tissue Pb levels; these elevated levels of Pb are known to affect many systems, primarily the hematopoietic, renal, and central nervous systems, especially in growing children and pregnant women¹⁰. One form of subclinical Pb toxicity ($\leq 10 \mu\text{g Pb/dl}$) affects heme synthesis by inhibiting δ -aminolevulinic acid dehydratase, a key enzyme in heme synthesis. These changes in heme status could result in reduced Hb production, microcytic hypochromic anemia associated with reticulocytosis, and basophilic stippling of erythrocytes¹⁰. As a result, it would seem plausible that Pb could act to amplify any toxicities in hosts associated with Fe-deficiencies such as changes in erythropoiesis, immune function and host defense, as well as essential cellular activities such as DNA replication and repair. To date, potential additive/synergistic effects from sub-clinical Pb toxicities on anemia-derived changes in immune parameters have not been well-studied in humans or animal models.⁹

Understanding the differential effects of conventional fractionation versus SBRT and SRS on the TME may help to inform choice and improve response to combination therapies.¹² Likewise, improved knowledge of the effects of radiation dose and fractionation on the TME may help to optimize treatment planning of radiation delivery. Although hypofractionation may promote enhanced CD8⁺ T-cell responses, efficacy may be diminished by death of infiltrating lymphocytes (particularly in irradiated lymph nodes) and other microenvironmental changes such as increased tumor hypoxia and polarization of M2 macrophages. Dose modulation with heterogeneous high- and low-dose regions within the tumor may provide a hybrid form of radiation delivery that may promote the antitumor effects of both high-dose and conventional fractionation regimens.¹¹



REFERENCES

1. Cell survival curves . In: Hall, EJ, Giaccia, AJ, eds. Radiobiology for the Radiologist. 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2012:35–23.
Google Scholar
2. Mahajan, A, Ahmed, S, McAleer, MF. Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial. *Lancet Oncol.* 2017;18:1040–1048.
Google Scholar | Crossref | Medline | ISI
3. Aridgides, P, Bogart, J. Stereotactic body radiation therapy for stage I non-small cell lung cancer. *Thorac Surg Clin.* 2016;26:261–269.
Google Scholar | Crossref | ISI
4. Qiu, H, Moravan, MJ, Milano, MT, Usuki, KY, Katz, AW. SBRT for hepatocellular carcinoma: 8-year experience from a regional transplant center [published online ahead of print July 14, 2017]. *J Gastrointest Cancer.* doi:10.1007/s12029-017-9990-1.
Google Scholar | Crossref
5. Kishan, AU, King, CR. Stereotactic body radiotherapy for low- and intermediate-risk prostate cancer. *Semin Radiat Oncol.* 2017;27:268–278.
Google Scholar | Crossref | ISI
6. Baliga, S, Kabarriti, R, Ohri, N. Stereotactic body radiotherapy for recurrent head and neck cancer: a critical review. *Head Neck.* 2017;39:595–601.
Google Scholar | Crossref | ISI
7. Kim, MS, Kim, W, Park, IH. Radiobiological mechanisms of stereotactic body radiation therapy and stereotactic radiation surgery. *Radiat Oncol J.* 2015;33:265–275.
Google Scholar | Crossref | Medline | ISI
8. Song, CW, Lee, YJ, Griffin, RJ. Indirect tumor cell death after high-dose hypofractionated irradiation: implications for stereotactic body radiation therapy and stereotactic radiation surgery. *Int J Radiat Oncol Biol Phys.* 2015;93:166–172.
Google Scholar | Crossref | Medline | ISI
9. Park, HJ, Griffin, RJ, Hui, S, Levitt, SH, Song, CW. Radiation-induced vascular damage in tumors: implications of vascular damage in ablative hypofractionated radiotherapy (SBRT and SRS). *Radiat Res.* 2012;177:311–327.
Google Scholar | Crossref | Medline | ISI
10. Brown, JM, Carlson, DJ, Brenner, DJ. The tumor radiobiology of SRS and SBRT: are more than the 5 R's involved? *Int J Radiat Oncol Biol Phys.* 2014;88:254–262.
Google Scholar | Crossref | Medline | ISI
11. Mole, RH. Whole body irradiation; radiobiology or medicine? *Br J Radiol.* 1953;26:234–241.
Google Scholar | Crossref | Medline | ISI
12. Reynders, K, Illidge, T, Siva, S, Chang, JY, De Ruysscher, D. The abscopal effect of local radiotherapy: using immunotherapy to make a rare event clinically relevant. *Cancer Treat Rev.* 2015;41:503–510.
Google Scholar | Crossref | Medline | ISI



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