Theoretical Bases of the Influence of Radiation-induced Abscopal Effects on the Cardiovascular System

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SUMMARY
Radiation therapy (RT) has been recognized as an efficient treatment modality commonly utilized in the curative or palliative management of many cancers for more than a century. Cytotoxic effects of RT are principally eventuated by its direct infield physical DNA damage or indirect insults from reactive oxygen species, dependent on the radiation source in use. On the contrary, radiation-induced abscopal effect (RIAE) refers to the distant non-targeted either profitable anti-tumoral or deleterious actions of radiation on a particular tissue, organ system, or the entire body. Although it is quite challenging to comment robustly on the precise RIAE mechanisms, yet, it is broadly acknowledged that the non-targeted distant effects of RIAE are chiefly mediated by the cytokines secreted from the tumor or bystander cells into the blood circulation or by the radiation-induced systemic immunity. The present brief review focuses principally on the rarely addressed, but likely, consequences of RIAE on the cardiovascular system in the light of accessible proof for the proposed RIAE mechanisms.

Keywords: Abscopal effect; cardiovascular system; radiotherapy.

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Introduction
Ionizing radiation has been hastily implemented into the diagnostic and palliative/curative therapeutic medical interventions soon after its revelation by Wilhelm Conrad Röntgen in 1895. Ionizing radiation is a well-established persuasive anti-cancer agent because of its capability to kill cancer cells chiefly as a consequence of DNA damage provoked by the high energy bestowed by the traversing radiation. The primary objective of therapeutic radiation is to produce double-strand DNA breaks with the specific goal of cell cycle arrest or cell death during the imminent mitosis as a result of mispaired or unpaired lethal double-strand DNA damage. Conventionally, radiobiology investigations have exclusively concentrated on the nuclear DNA as the unique target of ionizing radiation-induced damage, and the established radiobiological doctrine suspects no radiation effects on the non-targeted cells situated outside the radiation field. Nevertheless, the commendable recent radiobiology research convincingly demonstrated that the radiation effects were not confined wholly to the irradiated cells but were also spreading to the unirradiated neighboring cells, distant metastatic destinations, and remotely located normal healthy tissues either in the form of antitumor or abnormal inflammatory re-
sponses. This phenomenon has also been pre-clinically established by the demonstration of the development of genetic changes in neighboring non-irradiated cells in partially irradiated cell populations.[1-4] Such unpredicted radiation-induced effects outside the irradiated area were first called as "Abscopal effect (AE)" by Mole in 1953.[5] Although the AE and bystander effect are interchangeably used expressions of the same process, yet, they refer to the respective distant and nearby effects of radiation, which are quite distinct by induction mechanisms and differential spatial body locations relative to the index irradiated field.

In spite of the fact that the radiation-induced AE (RIAE) may essentially influence the cardiovascular system, yet, the information about the involved mechanisms and the potential consequences are scant. Therefore, the present brief review tended to address these issues on a hypothetical premise in a lack of convincing clinical proof.

**Mechanisms of Actions of RIAEs**

The United Nations Scientific Committee on the Effects of Atomic Radiation 2006 report defines the bystander effect as “the ability of irradiated cells to convey manifestations of damage to neighboring cells not directly irradiated,” and AE as “a significant response in a tissue that is physically separate from the region of the body exposed to radiation.”[6] Similarly, the International Commission on Radiological Protection describes the bystander effect of radiation as the transmission of signals from irradiated to non-irradiated cells in a cell population, leading to biological changes in the recipient cells.[7] As illustrated in Figure 1, albeit the two phenomena typically emerge from the same irradiation process, yet the bystander effect and AE represent significantly different processes carefully considering the effective mechanisms underneath.

Supporting the hypothesis of the bewildering interdependence of all body cells, the RIAE describes the “off-target” or “away from the target” influences of a localized irradiation process, which essentially implies that harm to one cell will unavoidably influence the body in general as proposed by Mole.[5] This theory was principally founded on the observation that the thyroid hormone synthesis in the rat thyroid was reduced to one-fourth of its typical levels just 3 days after a partial abdominal irradiation dose of 6-10 Gy in the absence of any direct irradiation to the thyroid gland or the hypophysis.[5] Considering the possible mechanisms of actions, RIAE has been shown to deliver a broad assortment of biological effects on the genetic material through micronucleus production, gene locus mutations, sister chromatid exchanges, gross genome rearrangements, chromosome aberrations, deletions, duplications, gene amplification/mutations, and activation of the carcinogenesis.[8] Various signaling pathways have been hypothesized to assume critical roles in RIAE induction, including the direct intercellular interactions through gap junctions or through the diffusion of the secreted signals in the same medium and extracellular distant actions generated by the nitric oxide, reactive oxygen species including long-lived hydrogen peroxide, growth factors, transforming factor beta-1 (TGF-β1), TGF-β2 tumor necrosis factor alfa (TNF-α), interleukin 1 (IL-1), IL-8, IL-10, eotaxins, tissue inhibitor matrix metalloproteinase 1, vascular endothelial growth factor, as well as changes in the tissue proportion of macrophages, neutrophils, and T-lymphocytes.[8,9] In consequence, every one of these factors contributes to the likely development of chronic systemic inflammation, induced immunity, genomic instability, and radiation susceptibility in surrounding and non-targeted distant healthy tissues.[9,10]

As reviewed by Siva et al. and Abuodeh et al.[9,11] on a case-by-case ground, RIAE may clinically originate from many irradiated tumor types. At present, the accumulated information overwhelmingly counsels the radiation-induced immune activation as the preeminent mechanism underlying the RIAE development after local irradiation, which can be distinguished at neighboring tissues or remote sites as soon as just a few minutes to 1-2 h after the therapeutic or experimental irradiation. In 1968, Hollowell and Littlefield[12] hypothetically proposed that any focalized radiation exposure can provoke secretion and release of soluble factors into the growth medium with ensuant chromosomal damage in cultured cells not directly exposed to the radiation. These factors were later shown to be able to incite messenger effects at remote organ sites by Emerit in 1994, namely, the chromosome breaking or clastogenic factors,[13] which were conceptually analogous to the soluble cytokines and chemokines deemed to instigate nausea and fatigue after clinical radiation therapy (RT). Landing support, the honorable respective investigations by Demaria et al.[14] and Formenti and Demaria[15] further exhibited that the RIAE process was most likely mediated by the immune system. Such that, tumor cells undergo immunogenic death, wherein many specialized immune cells are involved as mediators. Consequently, it has been hy-
pothesized that local RT can produce a consistent and robust immune-mediated AE in the proper settings. [14-16] Considering the impact of RIAE on widespread cancer cells, although the local RT can stimulate both pro-immunogenic and immunosuppressive (like the programmed cell death ligand-1) pathways, yet the net effect usually favors the anti-tumor immune activity.

The clinical proof backing the presence of RIAE in the scenario of therapeutic RT is still scarce. In 1995, one of the first clinical evidence of RIAE was portrayed in a 77-year-old male patient with chronic lymphocytic leukemia who received 32.4 Gy fractionated radiotherapy restricted to the neck and supraclavicular area. Other than encountering a quick improvement of the local symptoms, his spleen size and WBC count were returned to normal limits just 3 weeks after the completion of the radiotherapy.[17] This finding was also asserted in another woman with chronic lymphocytic leukemia who received local field 24 Gy (2 Gy/fraction) radiotherapy to the axilla.[18] The unirradiated neck lymph nodes started to regress by 2 weeks of radiotherapy, which regressed completely during the follow-up. Very recently, Kareff et al.[19] announced a case of a 69-year-old woman with metastatic typical pulmonary carcinoid with multiple lung nodules who experienced a notable reduction in the size of an untreated left upper lobe nodule after the stereotactic body RT to an oligoprogressive left lower lobe lesion. Such observational data scientifically prove both the possible emergence of ARIE either after conventionally fractionated RT or stereotactic RT, and its beneficial actions on the non-targeted lesions, which might be designated “abscopal efficacy.”

RIAE and Cardiovascular System

The cardiovascular system, also called the circulatory system, is the transport system of the body composed of the heart, the blood vessels, and the circulating nearly 5 L of blood. The cardiovascular system bears vital functions such as the transportation of nutrients, oxygen, carbon dioxide, hormones, cytokines, chemokines, and blood cells that provide nourishment, regulation of the temperature and pH, and fighting against pathogens. Several carefully designed animal studies convincingly confirmed the presence of RIAE in completely protected organs receiving practically no radiation dose.[20-22] Such preclinical research outcomes established the hematologic propagation of a local immune inflammatory response to remotely located organs through locally manufactured cytokines, including the cardiovascular system. In any case, either
with the conventional or modern radiotherapy, the entire body is unavoidably exposed to very low but significant radiation doses through leakage from the head of the therapy unit, scattering from the shielding blocks, flattening filters and the beam collimators resulting in the incident scatter in the treatment room, and the internal scatter from the directly irradiated part of the patient. In a lack of complete shielding of the non-targeted body parts, as in the case of routine radiotherapy practice, the patient’s entire body inadvertently becomes the biologic penumbra as receives relatively low doses of radiation depending on the distance from the irradiation field. Thusly, it might be formidable to distinguish the extensively studied low-dose cardiovascular effects from that of the chemokine-/cytokine-mediated RIAE.

In the apparent lack of explicitly planned preclinical and clinical examinations exploring the presence and direct consequences of the RIAE on the cardiovascular framework, it gets inconvenient to solidly remark on the conceivably existing RIAE in this vital organ system. However, prudent propositions should still be made thoughtfully respecting the commonness of the cytokines secreted by the irradiated tissue to circulation and those naturally assuming vital roles in cardiovascular diseases manifested in unirradiated populations (Fig. 2). Until now, the sole study directly exploring the RAIE on the cardiovascular system was published by Aravindan et al.[23] which demonstrated that the DNA binding capacity of nuclear factor kappa B (NF-κB) in non-targeted cardiac tissue of mice was notably enhanced after the low-dose abdominal irradiation. Regardless of the fractionation, 22 of 88 specific genes were upregulated, while this rate increased to 56 relying on the fractionation schedule, with resultant DNA fragmentation in the non-targeted heart. The researchers moreover counseled the NF-κB as the orchestrator of the transduction of discrete abscopal signals that influence diverse tissues and organ systems, including the cardiovascular system, in particular the heart.

The NF-κB enacted by RAIE is capable of inciting many targeted late response genes, such as those related to cell growth, cell cycle, proliferation, differentiation, inflammation, and apoptosis. Exhibiting the logical connection among the inflammation process and DNA damage response/repair, successful experiments also showed that NF-κB was involved in inducible nitric oxide synthetase and cyclooxygenase activity, as well as the stimulated production of cytokines and chemokines, such as IL-1α and β, IL-6, TNFa, chemokine (C-X-C motif) ligand 1 (CXCL1), CXCL2, and CXCL8 after the irradiation procedure. [24,25] This selective activation may typically occur within a few hours following irradiation and might be ataxia-telangiectasia mutated dependent. A subsequent activation wave can be observed within 24 h, which might be related to receptor binding by secreted cytokines, like TNFa.[26] As a result, NF-κB could modulate the response of directly irradiated cells and also alert neighboring non-irradiated cells through autocrine and paracrine pathways leading to the further secretion of cytokines and chemokines with significant functions on RIAE.[27] Therefore, as the bystander/abscopal and inflammatory responses share homologies, the increased levels of NF-κB might be of utmost importance in the induction of the non-targeted cardiovascular toxicity of focal irradiation procedure, which might be named “abscopal toxicity.”

Another proposed protein with abscopal toxicity is the monocyte chemoattractant protein 1, or chemokine ligand 2 (CCL2), which is a member of the C-C chemokine cytokine family. The CCL2 assumes critical roles in activation and migration of leukocytes through binding the C-C motif chemokine receptor 2

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**Fig. 2.** Proposed common pathways among the development of non-targeted radiation-induced abscopal and radiation unrelated cardiovascular diseases.

ROS: Reactive oxygen species, NO: Nitric oxide, NF-κB: Nuclear factor kappa B, TNF-α: Tumor necrosis factor alpha, TGF-β: Transforming growth factor beta, IL-1: Interleukin-1, IL-6: Interleukin-6, IL-8: Interleukin-8.
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Likewise the other non-targeted body parts. Landing boost the abscopal toxicity in the cardiovascular system, concurrent with radiotherapy, which may conceivably with the more common usage of immune therapeutics that the RIAE may more substantially be enhanced dioimmunotherapy, it is compulsory to bear in mind focal lung irradiation.[35,36] Thusly, in the era of ra-

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In this manner, like the NF-κB, CCL2 has all the earmarks of being another equivalently important mediator of tumor- and radiation-induced non-targeted cardiac effects.

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In this manner, the subsequent research should concentrate fiercely on both the concealed components of RIAE and effective countermeasures against its un-

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