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REVIEW

# 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.



## 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 misrepaired or unrepaired 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-

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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-

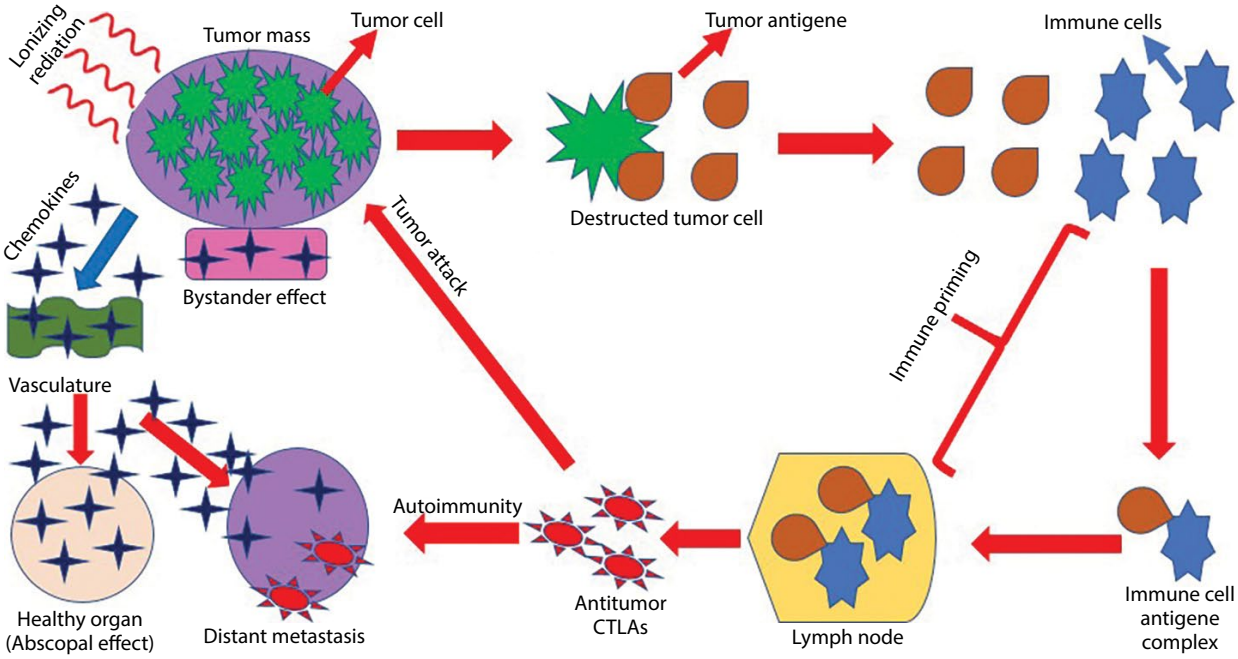


**Fig. 1.** Schematic presentation of the recommended pathways for the radiation-induced abscopal and bystander effects. CTLAs: Cytotoxic T-lymphocyte-associated proteins.

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

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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-kB 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, TNFα, chemokine (C-X-C motif) ligand 1 (CXCL1),

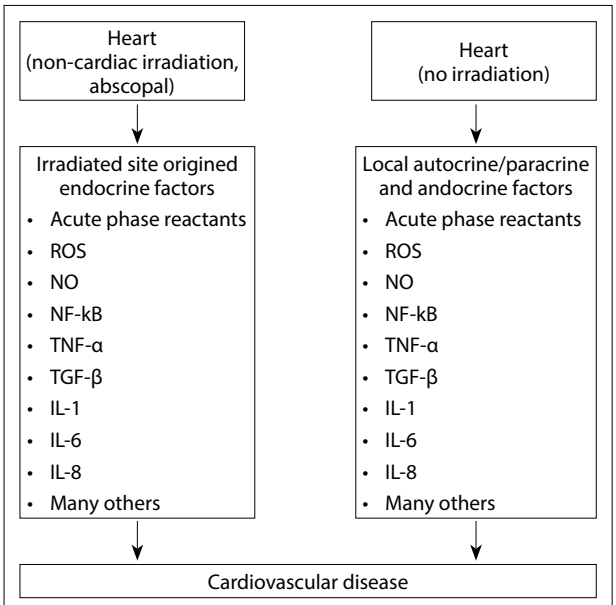


**Fig. 2.** Proposed common pathways among the development of non-targeted radiation-induced abscopal and radiation unrelated cardiovascular diseases.
ROS: Reactive oxygen species, NO: Nitric oxide, NF-κB: Nuclear factor kappa B, TNF-α: Tumor necrosis factor alpha, TGF-β: Transforming growth factor beta, IL-1: Interleukin-1, IL-6: Interleukin-6, IL-8: Interleukin-8.

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 TNFα.[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

(CCR2) and CCR4 receptors that result in the recruitment of monocytes, memory T-cells, and dendritic cells to the inflammation sites.[28,29] The CCL2 and IL-8 mediate the inflammatory reactions[30] and are further involved in the pathogenesis of immunological diseases accompanied by monocytic infiltrates, such as the psoriasis, rheumatoid arthritis, and atherosclerosis.[31] In addition, the CCL2 levels increase in irradiated tissues and cells after 2–9 Gy irradiation or in serum after fractionated low-dose radiation exposure in a dose-dependent manner.[32,33] It has been demonstrated that the increased CCL2 serum levels after low-dose radiation were related to the excess risk of cardiovascular disease.[34] 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.

Furthermore, local irradiation itself increases the endocrine secretion of death receptors and ligands, cytokines, chemokines, and reactive oxygen and nitrogen species. Considering these facts together with the apparent similarities between these factors and those responsible for the initiation, development, and progression of atherosclerosis, coronary heart diseases, and myocardial heart diseases (particularly the inflammatory cardiovascular diseases, such as the rheumatoid arthritis-related ones), it is reasonable to anticipate that RIAE may cause serious cardiovascular diseases including the coronary artery heart disease and myocardial infarction.

Moreover, open proof unequivocally advocates that the distant anti-tumor effects induced by RIAE represent an immune-mediated phenomenon, which gained generous agreement by the radiation oncology society as the dominant mechanism of RIAE. However, only a modest proportion of the systemic immunity originated by the tumor cells is tumor specific, while larger part of the cancer antigens instigating immune response is basic for both the tumor and typical tissue cells with or without slight alterations. Soundly, with no specific exemption for any organ or tissue, similar antigens may further initiate an autoimmune reaction against the normal tissues, such as the radiation pneumonitis experienced in the contralateral non-targeted lung after focal lung irradiation.[35,36] Thusly, in the era of radioimmunotherapy, it is compulsory to bear in mind that the RIAE may more substantially be enhanced with the more common usage of immune therapeutics concurrent with radiotherapy, which may conceivably boost the abscopal toxicity in the cardiovascular system, likewise the other non-targeted body parts. Landing support to this rational forethought, it has been shown that the expression change of multiple chemokine receptors enhances T-cells functions after the administration of immune checkpoint inhibitors (ICIs), which promote the increased overexpression and secretion of the pro-inflammatory TNF-α, granzyme B, and interferon-γ by the activated T-cells that might contribute to or enhance the ARIE-related cardiac injury.[37,38]

## Conclusion

To our current understanding, the RIAE is predominantly mediated through the cytokines and immune factors secreted by the irradiated tumor cells or neighboring unirradiated bystander cells, prompting inflammatory and immune responses at the distant non-targeted tumor, or healthy tissues including the cardiovascular system. Albeit not searched extensively to date, yet, limited open proof proposed that the foremost drivers of the RIAE are the NF-κB, CCL2, and factors induced by their activation through local irradiation. The similarities between the factors assuming key actions in the development of cardiovascular diseases and those secreted by the irradiated tumor cells or bystander cells recommend that RAIE may itself induce serious cardiovascular diseases, which may further be enhanced with tumor-actuated non-specific immunity or with the more common use of immunotherapeutic agents concurrent with radiotherapy, such as the novel ICIs. In this manner, the subsequent research should concentrate fiercely on both the concealed components of RIAE and effective countermeasures against its unintended complications on the non-targeted remote organ systems including the cardiovascular system.

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## References

1. Zhou H, Suzuki M, Randers-Pehrson G, Vannais D, Chen G, Trosko JE, et al. Radiation risk to low fluences of α-particles may be greater than we thought. Proc Natl Acad Sci U S A 2001;98(25):14410–5.
2. Prise K, Belyakov OV, Folkard M, Michael BD. Studies of bystander effects in human fibroblasts using a charged particle microbeam. Int J Radiat Biol

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doi: 10.5505/tjo.2022.S1003

1998;74(6):793–8.
3. Azzam EI, De Toledo SM, Little JB. Direct evidence for the participation of gap junction-mediated intercellular communication in the transmission of damage signals from α -particle irradiated to nonirradiated cells. Proc Natl Acad Sci U S A 2001;98(2):473–8.
4. Nagasawa H, Little JB. Induction of sister chromatid exchanges by extremely low doses of α-particles. Cancer Res 1992;52(22):6394–6.
5. Mole RH. Whole body irradiation; radiobiology or medicine? Br J Radiol 1953;26(305):234–41.
6. UNSCEAR. Effects of ionizing radiation. New York: United Nations Publication Sales No. E.10.XI.3; 2008.
7. The International Commission on Radiological Protection. Low-dose extrapolation of radiation-related cancer risk. ICRP publication 99. Amsterdam, Netherlands: Elsevier, International Commission on Radiological Protection; 2006.
8. Wang H, Yu KN, Hou J, Liu Q, Han W. radiation-induced bystander effect: Early process and rapid assessment. Cancer Lett 2015;356(1):137–44.
9. Siva S, MacManus MP, Martin RF, Martin OA. Abscopal effects of radiation therapy: A clinical review for the radiobiologist. Cancer Lett 2015;356(1):82–90.
10. Pouget JP, Georgakilas AG, Ravanat JL. Targeted and off-target (bystander and abscopal) effects of radiation therapy: Redox mechanisms and risk/benefit analysis. Antioxid Redox Signal 2018;29(15):1447–87.
11. Abuodeh Y, Venkat P, Kim S. systematic review of case reports on the abscopal effect. Curr Probl Cancer 2016;40(1):25–37.
12. Hollowell JG, Littlefield LG. Chromosome damage induced by plasma of X rayed patients an indirect effect of X-ray. In: Proceedings of the society for experimental biology and medicine. Society for experimental biology and medicine. New York: Royal Society of Medicine; 1968. p. 240–4.
13. Emerit I. Reactive oxygen species, chromosome mutation, and cancer: Possible role of clastogenic factors in carcinogenesis. Free Radic Biol Med 1994;16(1):99–109.
14. Demaria S, Ng B, Devitt ML, Babb JS, Kawashima N, Liebes L, et al. Ionizing radiation inhibition of distant untreated tumors (abscopal effect) is immune mediated. Int J Radiat Oncol Biol Phys 2004;58(3):862–70.
15. Formenti SC, Demaria S. Systemic effects of local radiotherapy. Lancet Oncol 2009;10(7):718–26.
16. Kepp O, Senovilla L, Vitale I, Vacchelli E, Adjemian S, Agostinis P, et al. Consensus guidelines for the detection of immunogenic cell death. Oncoimmunology 2014;3(9):e955691.
17. Sham RL. The abscopal effect and chronic lymphocytic leukemia. Am J Med 1995;98(3):307–8.
18. Lakshmanagowda PB, Viswanath L, Thimmaiah N, Dasappa L, Supe SS, Kallur P. Abscopal effect in a patient with chronic lymphocytic leukemia during radiation therapy: A case report. Cases J 2009;2:204.
19. Kareff SA, Lischalk JW, Krochmal R, Kim C. Abscopal effect in pulmonary carcinoid tumor following ablative stereotactic body radiation therapy: A case report. J Med Case Rep 2020;14(1):177.
20. Croizat H, Frindel E, Tubiana M. Abscopal Effect of irradiation on haemopoietic stem cells of shielded bone marrow--role of migration. Int J Radiat Biol Relat Stud Phys Chem Med 1976;30(4):347–58.
21. Mohye El-Din AA, Abdelrazzak AB, Ahmed MT, El-Missiry MA. radiation induced bystander effects in the spleen of cranially-irradiated rats. Br J Radiol 2017;90(1080):20170278.
22. Koturbash I, Loree J, Kutanzi K, Koganow C, Pogribny I, Kovalchuk O. *In Vivo* Bystander effect: Cranial X-irradiation leads to elevated DNA damage, altered cellular proliferation and apoptosis, and increased p53 levels in shielded spleen. Int J Radiat Oncol Biol Phys 2008;70(2):554–62.
23. Aravindan S, Natarajan M, Ramraj SK, Pandian V, Khan FH, Herman TS, et al. Abscopal effect of low-LET γ-Radiation mediated through rel protein signal transduction in a mouse model of nontargeted radiation response. Cancer Gene Ther 2014;21(2):54–9.
24. Hellweg CE. The nuclear factor kB pathway: A link to the immune system in the radiation response. Cancer Lett 2015;368(2): 275–89.
25. Lam RK, Han W, Yu KN. Unirradiated cells rescue cells exposed to ionizing radiation: Activation of NF-kappa B pathway in irradiated cells. Mutat Res 2015;782:23–33.
26. Wu ZH, Shi Y, Tibbetts RS, Miyamoto S. Molecular linkage between the kinase ATM and NF-kappa B signaling in response to genotoxic stimuli. Science 2006;311(5764):1141–6.
27. Biton S. and Ashkenazi A. NEMO and rip1 control cell fate in response to extensive DNA damage via TNF-alpha feed forward signaling. Cell 2011;145(1):92–103.
28. Carr MW, Roth SJ, Luther E, Rose SS, Springer TA. Monocyte chemoattractant protein 1 acts as a T-lymphocyte chemoattractant. Proc Natl Acad Sci U S A 1994;91(9):3652–6.
29. Xu LL, Warren MK, Rose WL, Gong W, Wang JM. Human recombinant monocyte chemotactic protein and other C-C chemokines bind and induce directional migration of dendritic cells *in vitro*. J Leukoc Biol 1996;60(3):365–71.
30. Rodemann HP, Bamberg M. cellular basis of radiation-induced fibrosis. Radiother Oncol 1995;35(2):83–90.

31. Xia M, Sui Z. Recent developments in CCR2 antagonists. Expert Opin Ther Pat 2009;19(3):295–303.
32. Kim TD, Li G, Song KS, Kim JM, Kim JS, Yun EJ, et al. Radiation-induced thymidine phosphorylase upregulation in rectal cancer is mediated by tumor-associated macrophages by monocyte chemoattractant protein-1 from cancer cells. Int J Radiat Oncol Biol Phys 2009;73(3):853–60.
33. Wolff HA, Rolke D, Rave-Frank M, Schirmer M, Eicheler W, Doerfler A, et al. Analysis of chemokine and chemokine receptor expression in squamous cell carcinoma of the head and neck (SCCHN) cell lines. Radiat Environ Biophys 2011;50(1):145–54.
34. Little MP, Gola A, Tzoulaki I. A model of cardiovascular disease giving a plausible mechanism for the effect of fractionated low-dose ionizing radiation exposure. PLoS Comput Biol 2009;5(10):e1000539.
35. Rödel F, Frey B, Multhoff G, Gaipl U. Contribution of the immune system to bystander and non-targeted effects of ionizing radiation. Cancer Lett 2015;356(1):105–13.
36. Morgan GW, Breit SN. Radiation and the lung: A reevaluation of the mechanisms mediating pulmonary injury. Int J Radiat Oncol Biol Phys 1995;31(2):361–9.
37. Tocchetti CG, Galdiero MR, Varricchi G. Cardiac toxicity in patients treated with immune checkpoint inhibitors: It is now time for cardio-immuno-oncology. J Am Coll Cardiol 2018;71(16):1765–7.
38. Varricchi G, Galdiero MR, Marone G, Criscuolo G, Triassi M, Bonaduce D, et al. Cardiotoxicity of immune checkpoint inhibitors. ESMO Open 2017;2(4):e000247.