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RADIATION-INDUCED ABSCOPAL EFFECTS ON CARDIOVASCULAR SYSTEM

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Abstract

Radiotherapy is widely employed in the curative or palliative treatment of practically all cancers which mainly exerts infield cytotoxic effects by direct physical DNA damage or indirect insults from reactive oxygen species, contingent upon the radiation source being utilized. In contrary, first defined by Mole in 1953 'radiation-induced abscopal effect (RIAE)' refers to the distant non-targeted actions of radiation on organ basis or the whole body that may be either beneficial or detrimental. Although it is challenging to comment on exact mechanisms of RIAE, it is widely acknowledged that the non-targeted distant effects of RIAE are mainly mediated by the cytokines released from the tumor or bystander cells into the circulation, or radiation-induced systemic immunity. The present review focuses mainly on the rarely addressed potential impacts of RIAE on the cardiovascular system and tries to provide evidence for suggested mechanisms.

Introduction

Short after the Wilhelm Conrad Röntgen's discovery of X-ray in 1895, ionizing radiation has been rapidly implemented to diagnostic and therapeutic medical applications. The main target of therapeutic radiation is to produce double-strand DNA breaks with the ultimate goal of cell cycle arrest or cell death during the subsequent mitosis as a result of misrepaired or unrepaired DNA damages. As widely adopted by the radiation protection agencies, the established radiobiological doctrine suspects no impacts in cells not crossed by the incoming radiation or more specifically the non-targeted cells located outside the radiation field. However, over several decades, it was realized that the radiation effects were also evident in unirradiated distant metastatic destinations and normal tissues in the forms of antitumor or abnormal inflammatory responses, respectively. Further challenging the traditional doctrine, the same phenomenon has also been exemplified by the occurrence of genetic changes in non-irradiated cells in a partially irradiated cell population in preclinical studies (1-4). This unpredicted action of radiation on tissues outside the radiation field was first defined by Mole in 1953 and named as the abscopal effect (AE), which is the combination of the Latin prefix 'ab' denoting 'position away' and 'scopus' as a target shooting at (5). In English literature, the 'abscopal' and 'bystander effect' are interchangeably used expressions of the same phenomenon, although abscopal and bystander refer for distant and nearby effects of radiation, respectively.

Mechanisms of Actions of Radiation-induced Abscopal Effects

Radiation-induced AE (RIAE) has been exhibited to produce an extensive variety of biological effects on the genetic material including the micronucleus production, gene locus mutations, sister chromatid exchanges, gross genome rearrangements, chromosome aberrations, deletions, duplications, gene amplification and mutations, and activation of the carcinogenesis (6). Many signaling pathways have been postulated to play roles on RIAE induction including the direct intercellular interactions via gap junctions or through diffusion of the secreted signals in the same medium and extracellular distant actions produced by the nitric oxide (NO), reactive oxygen species (ROS) including long-lived hydrogen peroxide, growth factors, transforming factor beta1 (TGF-β1), tumor necrosis factor alfa (TNF-α), interleukin 1 (IL-1) and IL-8 (6,7). As a result, all these factors generate chronic systemic inflammation, genomic instability, and radiation susceptibility in surrounding and nan-targeted distant healthy tissues (7).

Clinical information of RIAE originates from many tumor types as recently reviewed by Aboudeh et al in a case by case manner (8). Accessible data proposes the radiation-induced immune activation as the dominant mechanism

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underlying the RIAE which can be detected at neighboring tissues or distant sites soon after the therapeutic irradiation, such as a couple of minutes to 1-2 hours interim. To explain the mechanism of emergence of RIAE in non-targeted distant healthy tissues, in 1968 Hollowell et al hypothesized that exposure to radiation can result in the release of soluble factors into the peripheral circulation, leading to chromosomal damage in cultured cells not directly exposed to irradiation (9). Conceptually analogous to the soluble cytokines and chemokines that are thought to induce nausea and fatigue secondary to clinical radiation therapy, these factors were able to create messenger effects at remote organ sites, which were later called chromosome breaking- or clastogenic factors by Emerit et al in 1994 (10).

Potential Influences of RIAE on Cardiovascular System

Some deliberately designed animal studies proved the presence of RIAE in totally shielded organs receiving almost no radiation dose (11-13). Results of these preclinical investigations support the hematologic propagation of a local immune-inflammatory response to distant organs through locally manufactured cytokines. Nonetheless, in either conventional or modern radiotherapy the whole body is unavoidably exposed to very low but significant radiation doses via leakage from the head of the therapy unit, scattering from the shielding blocks, flattening filters and the beam collimators resulting incident scatter in the treatment room, and the internal scatter from the directly irradiated part of the patient. In absence of total shielding of the non-targeted body parts, as in the case of routine radiotherapy practice, patient's whole body becomes the biologic penumbra as receives some more or less radiation dose depending on the distance from the irradiation field. Therefore, it may not be easy to discriminate the extensively studied low-dose cardiovascular effects from the chemokine-/cytokine-mediated RIAE.

It is hard to talk about the potential impacts of RAIE on cardiac and vascular tissues in absence of particular preclinical and/or clinical investigations. However, reasonable anticipations should still be made considering the regularity of the same cytokines secreted by the irradiated tissue to circulation and those playing role in cardiovascular diseases manifesting in unirradiated populations (Figure 1). The unique study investigating the RAIE on heart tissue was reported by Aravindan et al. (14) and demonstrated that the radiation significantly induced the DNA binding capacity of nuclear factor kappa B (NF-kB) in non targeted cardiac tissue after the lower abdominal irradiation of mice. Independent of the fractionation the 22 of 88 genes were upregulated while this expanded up to 56 depending on the fractionation schedule, with resultant DNA fragmentation in the non-targeted heart. The authors of this study further proposed the NF-kB as the orchestrator of the transduction of various abscopal signals.

The NF-kB activated by RAIE is capable of stimulation of many targeted late response genes, such as those related to cell growth, cell cycle, proliferation, differentiation, inflammation, and apoptosis. Also, 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 close commonness between these factors and those responsible from the development and progression of atherosclerosis, and coronary vascular and muscular heart disease (especially the inflammatory cardiovascular diseases such as those induced by rheumatoid arthritis), it is reasonable to anticipate that RIAE may cause serious cardiovascular diseases including the coronary artery heart disease and myocardial infarction.

Accessible evidence unequivocally proposes that the distant antitumor effect induced by RIAE is an immune-mediated phenomenon. However, only a small proportion of the systemic immunity originated by the tumor cells are tumor-specific while most of the immunity inducing cancer antigens are common for both the tumor and normal tissue cells with or without slight modifications. The same antigens may further initiate an autoimmune reaction against the normal tissues with no exceptions for cardiovascular tissues (15). Therefore, in the era of radioimmunotherapy, it is imperative to keep in mind that the RIAE may further be enhanced with the more common utilization of immunotherapeutics concurrent with radiotherapy, which may potentially increase the cardiovascular manifestations of RIAE in conjunction with other non-targeted sites.

Conclusions

The RIAE is mainly mediated through the cytokines and immune factors causing inflammatory and immune responses at the distant non-targeted tumor or healthy tissues including the cardiovascular system. Although not

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studied extensively, yet, accessible limited evidence proposed that the principal drivers of the RIAE are the NF-kB and factors induced by its activation via local irradiation. The similarities between the factors playing key roles in the development of cardiovascular diseases and those secreted by the irradiated tumor cells suggest that RAIE may itself induce serious cardiovascular diseases, which may further be enhanced with tumor-induced nonspecific immunity or with the more common use of **immunotherapeutic** agents concurrent with radiotherapy. In this manner, the future research should concentrate on both the unrevealed components of RIAE and countermeasures against its unintended complications on the non-targeted distant organs including the cardiovascular system, at least as much as the research on the direct actions of medium to high dose radiation on irradiated tissues.

References

1. H. Zhou, M. Suzuki, G. Randers-Pehrson, D. Vannais, G. Chen, J.E. Trosko, C.A. Waldren, T.K. Hei, Radiation risk to low fluences of a particles may be greater than we thought, Proc. Natl. Acad. Sci. USA 98 (2001) 14410-5.
2. K. Prise, Studies of bystander effects in human fibroblasts using a charged particle microbeam, Int. J. Radiat. Biol. 74 (1998) 793-798.
3. E.I. Azzam, S.M. De Toledo, J.B. Little, 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. USA 98 (2001) 473-478.
4. H. Nagasawa, J.B. Little, Induction of sister chromatid exchanges by extremely low doses of α-particles, Cancer Res. 52 (1992) 6394-6396.
5. Mole RH. Whole body irradiation; radiobiology or medicine? Br J Radiol. 1953;26(305): 234-41.
6. 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.
7. 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.
8. Abuodeh Y, Venkat P, Kim S. Systematic review of case reports on the abscopal effect. Curr Probl Cancer. 2016;40(1):25-37.
9. 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, NY), Royal Society of Medicine, 1968, pp. 240-4.
10. 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.
11. 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.
12. 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.
13. Koturbash I, Loree J, Kutanzi K, et al. 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.
14. Aravindan S, Natarajan M, Ramraj SK. 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.
15. 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.