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Editorial

# The Potential Roles of Radiation-Induced Bystander Effects in Radiation Therapy

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Radiation-induced bystander effects (RIBEs) refer to the biological changes in unirradiated cells or tissues when the neighboring cells or tissues are traversed by ionizing radiation, such as changes in gene expression, DNA damage, cell killing, malignant transformation, epigenetic alterations et al. In spite of the reports on RIBEs in earlier time [1-4], this phenomenon did not attract much interest until 1992, when Nagasawa and Little provided the direct evidence for the occurrence of RIBE [5]. Since then, RIBEs have been demonstrated in a variety of cell types (including normal and cancer cells), tissue models and *in vivo* [6-9]. So far, the concept of bystander effects has been broadened, containing not only bystander responses in cell culture, but also long-range effects occurring within or between tissues or organs called abscopal, out-of-field or distant bystander response [10]. Along with other non-targeted effects such as adaptive response, genetic instability, et al., RIBEs challenge conventional radiation dogmas such as the DNA targeted theory and linear no-threshold (LNT) model so that they may have an impact on estimation of radiation cancer risk, particular at low doses [11], and outcomes of radiation therapy (RT) as well [10].

RIBE was once thought a low dose effect, meaning that it makes an important contribution to the overall effects at low doses, but plays little role in the biological responses at high doses [12]. However, more and more studies suggest that RIBE is one of the important factors that should be taken into consideration in the evaluation of protocols for cancer radiotherapy. RIBEs have been found to occur in the scenarios of intensity-modulated radiotherapy (IMRT) and spatially fractionated radiation (GRID) treatment [13-16]. They can take place from irradiated to unirradiated cells and other way around [13]. And cellular communication between differentially irradiated cell populations plays an important role [15]. The maximum cell death produced by the bystander effect could be calculated through a biophysical model, suggesting that it should not be ignored [17]. As a matter of fact, it is suggested that bystander effects may be essential in producing a robust decrease in cancer cell survival in directly irradiated populations [18]. And the abscopal effect induced by RT that sterilized non-irradiated tumor cells was through bystander signals in xenograft mouse mode [19]. In addition, acquired tumor cell radiation resistance at the treatment site was found to be strongly related to radiation-orchestrated intercellular communication [20]. Moreover, since irradiation can promote the invasiveness of both irradiated and bystander cancer cells [21], RIBEs may play an important role in cancer metastasis. A novel concept [22] has been proposed that RT-caused damage in various organs can upregualte some factors such as chemokines, growth factors, alarmines, and bioactive phosphosphingolipids in “bystander” tissues, which provide chemotactic signals to cancer cells that survived the initial treatment resulting to metastasis. All of these studies indicate that RIBEs can not only play an

important role in low dose effects, but also affect the overall biological effects in the scenario of RT where high doses apply, thus affecting the efficacy of RT.

Besides to the benefits of RT for cancer patients, RT often causes side effects. It has been found that the side effects of RT and bystander cell signaling may have a larger impact than previously acknowledged [23]. Additionally, ionizing radiation is a well-known carcinogen. Almost 1 in 10 cancer diagnoses are second malignancies. It is critical to understand the contribution of RT to second cancer induction [24]. Although most of second cancers occur within the irradiation field of original tumor, some second cancers develop in the organs relatively far from the radiation field [25,26]. The results from these clinical studies not only indicate that radiation is an important cause of the incidence of second cancer, but also suggest that RIBEs may contribute to this. The finding that radiation can induce genomic instability through bystander effects or increased mutation rates in the progeny of surviving irradiated cells *in vitro* suggests that RT-induced second primary cancer can arise from radiation-induced somatic genomic instability [24,27]. However, direct evidence for the involvement of RIBEs in the occurrence of second cancer post-RT is still limited. This warrants further studies on the roles of RIBEs in the process of second cancer incidence.

RIBE is a manifestation of intercellular signal transduction in nature. The majority of studies on RIBEs have been carried out in normal cells. Although the mechanisms underlying RIBEs are still poorly understood, gap junction intercellular communication (GJIC) [6], reactive oxygen species (ROS) [28] and soluble signaling molecules such as inflammatory cytokines [29] have been demonstrated to be involved in bystander signaling of normal cells. So far, it appears that normal or cancer cells share some common bystander signaling. For example, Transformation Growth Factor β1 (TGF-β1) has been demonstrated to be an important signaling of RIBEs in normal [30] and cancer cells [31,32]. Similarly, nitric oxide plays an important mediating role in RIBEs in both normal [33] and cancer cells [34]. Very recently, exosomes, specialized membranous nano-sized vesicles secreted by a variety of cells such as cancer cells, has been shown to be one kind of signal carriers between irradiated and bystander cancer cells [35] and human kerotinocytes [36]. Besides the signalings between irradiated and bystander cells, ATM, cyclooxygenase-2, ERK, JNK, MAPK, NF-κB, TGF-β1 pathways in irradiated and bystander cells have been found to mediate bystander effects in cancer cells [29]. Recent studies have also found that radiation promotes the invasion of the non-irradiated, surrounding breast cancer cells through metabolic alterations [37], and autophagy plays a negative role in RIBEs in breast cancer cells involving the activation of the CSF2-JAK2 pathway [38]. Additionally, the data on RIBEs also suggest the possible cell type dependence of bystander signaling pathways. While Dickey et al. [39] reported that miRNAs did not seem to be the primary signaling factor associated with bystander DNA damage in human colon carcinoma cell lines; we found that miR-21 acted as an important mediator of RIBEs in H1299 non-small-cell lung cancer cells [31].

The occurrence of RIBEs is out of question by now, but their potential importance in RT still needs to be determined. In addition to acquiring more data on RIBEs in animal systems and humans, sophisticated theoretical models taking non-targeted effects into consideration should be developed with the cooperation of radiation biologists, physicists and system biologists. With this kind of models, it is possible that the efficacy, side effects and the risk of second cancer of RT may be predetermined more accurately. Moreover, the underlying mechanisms of RIBEs *in vivo* need to be elucidated. With clear understanding of the mechanisms involving some specific signaling pathways, it may be doable to develop novel radiosensitizers to amplify deleterious RIBEs in cancer cells or protective agents to decrease side effects and second cancer risk in normal tissues or organs, thus increasing the therapeutic gains.

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