

# Radiation-Induced Bystander Effect Research: Literature Review

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The aim of the present study is to review literature on radiation-induced bystander effect research. The radiation-induced bystander effect concerns a plethora of biological phenomena occurring in non-irradiated cells as a result of signal transmission from irradiated cells. This paper discusses many radiation-induced bystander effect *in vitro* experiments, e.g., for numerous types of cell lines or tumor cells. The influence of nanomaterials on the radiation-induced bystander effect is analyzed. Moreover, the relationship between the radiation-induced bystander effect and the radiation-induced senescence, inflammatory pathways and endothelial cells is discussed. The authors have tried to explore as many mechanisms accompanying the radiation-induced bystander effect as possible. The in-depth mechanism research on cell proliferation influenced by the bystander effect of radiation will be useful to understand the biological effects of radiation.

topics: radiation-induced bystander effect (RIBE), tumor cells, radiobiology, radiotherapy

## 1. Introduction

According to the classical theory of radiobiology, the radiation genetic effect originates from a direct reaction of energetic particles and reactive free radicals with DNA molecules. Therefore, the biological effects of ionizing radiation were believed to be restricted to tissues within the treatment field due to direct targeting at the nucleus leading to DNA damage. Radiobiological research has recently been expanded to include non-targeted effects for adjacent tissues surrounding the targeted area. A response of non-irradiated cells to radiation exposure is known as the radiation-induced bystander effect (RIBE) [1]. These are biological changes in non-irradiated cells occurring by transmitting signals from the irradiated bystander cells [2]. Cells exposed to irradiation can induce different biological effects in non-irradiated cells due to cell-cell interactions. As a result, the cells are killed or show chromosomal instability and other abnormalities [3].

RIBE in cells has been widely observed in radiobiology. For decades, many investigations have demonstrated that RIBE occurs not only for very low-dose but also for large-dose irradiation and not only in the cultured cells but also in the partially irradiated organisms. In some ways, RIBE is a deterministic rather than a stochastic effect of radiation and it must happen once a radiation dose is high enough to trigger cell responses. Moreover, evidence shows that biological consequences of RIBE can be observed in offsprings of partially irradiated organisms, indicating that RIBE is not just an apparent phenomenon occurring within the irradiated individual but can also induce genetic and

epigenetic effects on the offspring. On the other hand, most of direct radiation damages are generated by radiation-induced free radicals such as  $\bullet\text{OH}$  through a series of chemical reactions.

Some authors [4] are of the opinion that the majority of bystander effects are induced by biochemical molecules because RIBE is induced by soluble factors including cytokines and free radicals released from directly irradiated cells, which is a biological process that occurs after physicochemical reactions of radiation. Therefore, RIBE belongs to the domain of radiation responses although it happens later than the acute radiation response and, accordingly, it is time to incorporate RIBE into the concept of the “classical” radiation effect.

Although the bystander effect is generally attributed to ionizing radiation, it also occurs with other stressors such as UVR, chemotherapy and photodynamic therapy [5]. The bystander effect involves a wide range of biological processes such as DNA damage, chromosomal abnormalities, malignant transformation, cell death, apoptosis, adaptive response [6], cell viability reduction, formation of micronuclei, delay and premature mutations [7].

## 2. Materials and methods

### 2.1. *In vitro* studies of RIBE

For decades, the evidence of RIBE has been obtained in many types of cell lines including fibroblasts [8–10], lymphocytes [11, 12] and endothelial cells [13, 14] as well as in different tumor cells including human bone-marrow mesenchymal stem cells (hMSC) and embryonic stem cells (hESC) [15], human glioblastoma cells (DBTRG-05MG) [16],

lung carcinoma cell line (A549) [17], human breast cancer cell line (MDA-MB-231) [18] and Chinese hamster ovary (CHO-K1) cells [19].

Kulcenty et al. [20] assumed that surgical wound fluids (WF) collected from patients after a breast-conserving surgery would activate RIBE in treated cells, thus altering the tumor microenvironment. To confirm this hypothesis, WF collected from patients after a breast-conserving surgery (BCS) alone, after a BCS followed by an intraoperative radiation therapy (IORT) treatment and WF from BCS patients together with the RIBE medium were incubated with human breast cancer (MCF-7) and human breast carcinoma MDA-MB-468 cell lines. Shortly, MDA-MB-468 cells were irradiated in suspension. A total dose of 10 Gy was administered at approximately 2.5 Gy/min applying GammaCell®1000 Elite (BestTheratronics Ltd., Ottawa, Canada), using a  $^{137}\text{Cs}$  source. After irradiation, the cells were cultured for 24 h and then the RIBE medium was collected, sterile-filtered and stored at  $-80^{\circ}\text{C}$ .

In order to analyze the effect of RIBE without any perturbing factor, we decided to perform the analysis on the medium collected from the corresponding cells. Investigation findings show that WF stimulate the CSC phenotype and epithelial-to-mesenchymal transition (EMT) program in breast cancer cell lines. This effect was partially abrogated when the cells were incubated in WF collected from patients after a breast-conserving surgery followed by IORT. Additionally, the role of RIBE in altering the properties of WF to induce the CSC phenotype and EMT program is indicated. RIBE significantly modifies the tumor microenvironment and although this effect is most commonly observed at low and medium doses, it may also play a significant role in high-dose irradiation [21].

Chen et al. [22] investigated the bystander effect of different types of irradiation including gamma irradiation (GR) and lithium heavy ion irradiation (LR) on a model human neuroblastoma cell line (SH-SY5Y). The gamma and lithium ion irradiation induced different bystander effects on the SH-SY5Y cell line. RIBE induced by gamma irradiation promoted cell proliferation through activating the ERK and AKT signaling pathways but it could only slightly influence the cell cycle of non-irradiated SH-SY5Y cells. In turn, RIBE induced by the lithium heavy ion irradiation inhibited cell proliferation, arrested the cell cycle and activated the process of pro-apoptosis.

Kaźmierczak et al. [23] investigated the radiation-induced bystander effect in Chinese hamster ovary (CHO-K1) cells. CHO-K1 were irradiated in the dose range of 0.1–4 Gy of high linear energy transfer (LET)  $^{12}\text{C}$  ions and X-rays. The system allowed for homogeneous irradiation of all biological samples and the schematic view was presented in [24]. Quantitative analysis of the results confirmed the proper functioning of the dosimetric system used in the tested setup. To examine the bystander effect,

irradiated and non-irradiated cells were co-cultured in special Petri dishes with inserts. The cells shared the medium but could not touch each other. In the analysis, two complementary radiobiology tests were used: the micronucleus assay and the clonogenic assay. Summarizing, the survival fraction of CHO-K1 cells co-cultured with cells irradiated with different doses of  $^{12}\text{C}$  ions and X-rays was not reduced regardless of the absorbed dose and density of irradiated cells plated on inserts. The authors failed to find any evidence for the bystander effect in experiments. These results are in conflict with a number of published results [25, 26]. However, there are also data in the literature showing no evidence of the bystander effect in a variety of cell lines, including clonogenic survival, induction of chromatid breaks and micronuclei [27–29].

It is unclear why the bystander effect was not observed in the experiments reported. One possible explanation for these results may be the fact that the CHO-K1 cells do not produce a bystander signal or they do not respond to the bystander signal produced under experimental conditions. The dependence of the bystander effect on a cell type and experimental conditions was reported in the literature [30–32]. Johnson et al. [33] demonstrated that cell density influences experimental conditions by depriving cells of serum, glucose or oxygen which have a variable influence on their growth and survival. Depriving cells of serum as well as a specific serum batch may inhibit/ elicit the production of, or response to, the bystander signal. It was presented in [34] that the use of a growth medium supplemented with a specific lot of calf serum was capable of increasing the number of cells undergoing radiation-induced transformation. Alternative explanations for the observed lack of evidence for RIBE response in this study can be seen in the included dependence on radiation quality, dose and/or LET, interaction effects between RIBE and radioadaptive responses [26, 32]. Experiments designed specifically to test these hypotheses would be necessary to evaluate such suppositions.

A lot of work has been done in the research of molecular signaling transduction factors related to RIBE. Many bystander signaling factors have been identified so far, namely reactive oxygen species (ROS) [35–37], nitric oxide (NO) [38–40], transforming growth factors- $\beta$ 1 (TGF- $\beta$ 1) [41], cyclooxygenase-2 (COX-2) [42], tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) [43] and interleukin-8 (CXCL8) [44, 45]. It has recently been reported that cytochrome-c (heme protein) was also an important regulator of RIBE [46, 47]. Moreover, using a multi-cell line co-culture system, it was found that macrophages could play a role as a signaling-transmitter between irradiated cells and non-irradiated cells and thus mediated the secondary bystander effect [48, 49]. It is easy to imagine that these soluble molecules released from irradiated cells could transfer through a culture medium to

impact distant bystander cells. But when the irradiated cells are linked to non-irradiated cells with a smooth gap junction intercellular communication (GJIC), some small signaling molecules can transfer through GJIC and further induce bystander responses including chromosome damage, genomic instability, mutations and malignant transformation [50–54].

It was found that RIBE could be affected by adjusting GJIC. In malignant cells, there is a frequent reduction in the transcription level of connexin genes in GJIC. Rescuing GJIC among tumor cells by transferring the connexin gene could reduce tumor malignancy [55]. Shao et al. [56] found that, when human salivary gland (HSG) adenocarcinoma cells were treated with cell-permeable 8-Br-cAMP to enhance GJIC between cells, the radiation-induced bystander MN formation and G2/M-phase arrest were reduced and the survival fraction was correspondingly increased. Moreover, they found that NO molecule was involved in GJIC-mediated radioprotection of HSG cells. In addition, He et al. [57] found that, when human macrophage (U937) cells were irradiated, cAMP was released from bystander normal liver cells (HL-7702) through a p53-dependent signaling pathway, and then this secondary message molecule compensated into the irradiated U937 cells and promoted cell survival of U937 macrophages.

## 2.2. RIBE and nanomaterials

The effect of nanomaterials on cells is highly related to the internalization of particles inside cells. It is important to take into consideration the compatibility of the nanoparticles towards the treated cells [58]. Rostami et al. [59] reported that different RIBE responses were observed in MCF-7 and lung cancer cells (QUDB) after treating them with glucose-coated gold NPs (Glu-GNPs). Glu-GNPs increased RIBE in QUDB cells, while no effects on RIBE were observed in MCF-7 cells. This observation may suggest that the cell type is one of the factors which determine the impact of nanomaterials on RIBE. Analyzing the induction of RIBE in cancer and normal cells is particularly important because if NPs delivered to tumor cells are able to increase the RIBE responses in normal cells, they may neutralize the therapeutic ratio. According to a study of Abudayyak et al. [60], the cytotoxicity of nanoparticles could be related to many different factors, such as oxidative stress that results in biological systems' damage. It should be highlighted that the biocompatibility and toxicity of nanoparticles could be dependent on cell types and sensitivity which must be taken into consideration.

Ahamed et al. reported in [61] that bismuth oxide nanoparticles ( $\text{Bi}_2\text{O}_3$  NPs) below  $50 \mu\text{g/ml}$  concentration were non-cytotoxic to MCF-7 cells. The application of a radiosensitizer during treatment raises the issue if they could contribute to RIBE in non-irradiated cells.

Zainudin et al. [62] in an *in vitro* study intended to examine the possibility of increment in RIBE as a result of  $\text{Bi}_2\text{O}_3$  NPs application as a radiosensitizer (to enhance the effectiveness of radiation treatment) during radiotherapy for a 10 MV photon beam. The MCF-7 and human fetal osteoblast (hFOB 1.19) cell lines were incubated with and without  $\text{Bi}_2\text{O}_3$  NPs prior to irradiation. The treated cells were irradiated with radiation doses of 0 to 12 Gy using a 10 MV photon beam in a single exposure. The RIBE responses between the normal and cancerous cells after the incubation with an irradiated cell conditioned medium (ICCM) were also investigated. This work provided the first *in vitro* study of the  $\text{Bi}_2\text{O}_3$  NPs on the bystander effects in the non-targeted cells through the medium transfer technique. To ensure that the presence of a radiosensitizer does not neutralize the therapeutic ratio, it is necessary to analyze the effect of  $\text{Bi}_2\text{O}_3$  NPs on RIBE. Interestingly, the study demonstrates that the  $\text{Bi}_2\text{O}_3$  NPs do not contribute and enhance RIBE in both the cancer and normal cells. This observation is consistent with the results obtained by previous studies regarding the dose independence of the bystander effect induced by a conditioned medium harvested from irradiated cells [10, 59, 63]. This result shows an insignificant increase in the RIBE response by any increase in the dose.

Previous studies show that every cell within a population has a potential to release a bystander signal but the sensitivity of cells in responding to a bystander signal may depend on intrinsic cell characteristics [59]. These results reveal a constant RIBE response in the dose range from 0.5–10 Gy, but beyond 10 Gy (at 12 Gy), the RIBE responses are increased. Different biological effects at high doses may induce different responses towards the bystander effect in non-targeted cells. RIBE may occur through the transmitted signals from irradiated cells either by direct cell-to-cell contacts or by the secretion of soluble factors into the medium [59]. Several bystander signaling factors have been considered in RIBE responses. It has been reported that the growth medium, inflammatory cytokines, ROS and nitric oxide (NO) are involved in the bystander responses caused by the conditioned medium harvested from irradiated cells [59, 64, 65]. The findings indicate that the  $\text{Bi}_2\text{O}_3$  NPs do not significantly increase RIBE in both MCF-7 and hFOB 1.19 cells as the cells can continue their proliferation and clonogenic survival for a long term after treatment with ICCM treated with  $\text{Bi}_2\text{O}_3$  NPs [62].

## 3. Discussion

### 3.1. RIBE and radiation-induced senescence

Radiation-induced cell cycle effects, such as the G2 DNA damage block, result in both a depression of growth rate and entry of cells into an observable senescent state. Nelson et al. [66] found that

senescent human fibroblast cells can induce RIBE, spreading senescence in intact neighboring fibroblasts *in vitro*. Details of the passaging procedure, which includes the dilution of both senescent and non-senescent cells followed by the division of only the non-senescent cells to repopulate culture flasks, also affect the proportions of senescent and non-senescent cells observed at each passage.

Exosomes were found to convey a senescence-inducing signal, much as they do in the other bystander effects of radiation [67]. However, the experiments do not rule out other means for conveying the signal between cells such as passing through gap junctions, being transported within non-exosomal extracellular vesicles (EV) or by diffusion of unencapsulated molecules after a release into the extracellular medium.

Borghesan et al. [68] have found that the soluble fraction and small extracellular vesicles from senescent cells are responsible for mediating paracrine senescence to nearby cells.

The induction of bystander senescence by low radiation doses has implications for radiation risk assessment [69]. Accumulation of senescent cells in normal tissue is thought to be a key driver of aging.

Radiation-induced senescence, whether through direct irradiation or a bystander mechanism, has the potential to increase the burden of senescent cells and accelerate the aging process. This type of risk has yet to be evaluated. There may also be medical implications of bystander senescence for patients undergoing radiotherapy. These include a beneficial contribution to the tumor sterilizing effect of radiation or to the suppression of replication and division of damaged cells within the tumor or in the tumor margin. However, there is a risk that organ performance may decrease as a result of an increase in senescent cells [70]. Further research will be required to elucidate the mechanisms of bystander senescence as well as its impact on human health.

### 3.2. RIBE and inflammatory pathways

Genes involved in the creation of RIBE and the inflammatory pathways are often the same. The most important of these genes are COX-2, inducible nitric oxide synthase (iNOS), the nuclear factor of kappa B (NF $\kappa$ B) and mitogen-activated protein kinases (MAPKs/P38 $\alpha$ ). An overexpression of these genes occurs by various factors and leads to an inflammation and NO production as oxidative stress's increased results. UVR causes the production of macrophages to produce cytokines such as interleukin (IL)-1, IL-2, IL-8, tumor necrosis factor alpha (TNF- $\alpha$ ) and transforming the growth factor beta (TGF- $\beta$ ). These factors stimulate the cytokine receptors that are located on the cell surface and facilitate gene expression. These changes are the main factors in tissue inflammation that it is irradiated directly. The observed cytokines during a stimulation of gene expression of NF $\kappa$ B or

MAPKs genes such as extracellular signal-related kinase (ERK), JUN gene (protein coding) and P38 gene lead to COX-2 and iNOS transcription activation. COX-2 is not expressed in all tissues; in contrast, its expression level is also very low. The smallest increase in the expression of this gene is clear. COX-2 is the main factor in the production of prostaglandines like PGE<sub>2</sub>, PG-I<sub>2</sub> which causes blood vessels dilation as well as inflammation. iNOS produces NO as well; thus, it increases the oxidative stress level. The overexpression of these genes is often associated with an increase in the COX-2.

According to the studies mentioned above, it is expected that the radiation doses cause the cytokines production through stimulating macrophages activities, which leads to increasing COX-2 and iNOS expression in non-irradiated cells. *In vitro* studies have shown that RIBE could have a threefold increase in COX-2, near the irradiated cells. *In vivo* studies have shown that a severalfold increase in the expression of these genes occurred during 72 h after radiation exposure [5, 71].

### 3.3. RIBE and endothelial cells

Angiogenesis, i.e., the formation of new blood vessels from a pre-existing vascular network, is a critical step in tumor growth as well as metastasis. It is well established that angiogenesis is a regulated process and various molecules contribute to promote angiogenesis, both during physiological and pathological conditions [72].

Molecules or factors released from irradiated cells may promote tumor growth through inducing angiogenic responses in endothelial cells [73]. Additionally, irradiated cancer cells are capable of releasing angiogenic factors such as a glycosylated mitogen protein (VEGF) [74] and matrix metalloproteinases (MMPs) [75] into extracellular milieu. Irradiated tumor cells relay their bystander effects on non-tumoral cells, which promote secondary tumorigenesis in the vicinity [76, 77], including the induction of angiogenesis which favor cell survival and invasion [78].

Oh et al. [79] found that ionizing radiation inhibited angiogenesis in endothelial cells obtained from tumorous breast tissues, whereas it promoted angiogenesis in endothelial cells of normal ones. Parthymou et al. [80] demonstrated that conditioned media (CM) from irradiated C6 glioma cells enhance the survival and migration of human umbilical vein endothelial cells (HUVECs) *in vitro*. Reports have shown, however, that irradiated endothelial cells exhibit angiogenic responses [81, 82] but bystander effects of irradiated cells on endothelial cells have not been fully known.

## 4. Conclusions

The radiation-induced bystander effect is a destructive reaction in non-irradiated cells and it is the primary factor in determining the efficacy and success of radiation therapy in cancer treatment.

Despite some promising investigations on RIBE, there are still gaps in understanding the mechanism and responses between the irradiated cells and adjacent healthy cells when a radiosensitizer is applied during radiation treatment.

More studies could help to establish early interventions against RIBE while improving the efficacy of tumor cells treatment. Measures that could alleviate or even inhibit RIBE may be proposed in the near future.

Furthermore, the in-depth mechanism research on cell proliferation influenced by the bystander effect of radiation will also be useful in understanding the biological effects of radiation.

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