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Insights on the Radiation-Induced Adaptive Response at the Cellular Level and Its Implications in Cancer Therapy

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Abstract

Background: Development of resistance upon exposure to small doses of ionizing radiation followed by higher doses is known as radiation-induced adaptive response (RIAR). Traditionally, the induction of the RIAR phenomenon at the cellular level has been examined in cell lines, animal models, and epidemiological studies where people live in high natural background radiation. ***Summary:*** The primary intention of the earlier studies was to corroborate the existence of RIAR and the mechanism involved in mediating the response surveyed by exposure to a low dose of radiation (<500 mGy) as priming dose toward the radiation protection point of view. However, the investigation has shifted the focus to understand the relevance of this phenomenon at clinically relevant set-ups (high doses in the order of Gy) and can be exploited during radiotherapy as RIAR is considered a mechanism for the development of radioresistance. Although the knowledge of molecular mechanisms at the cellular level has evolved significantly in multi-fractionated radiotherapy regimes, its relevance in developing radioresistance at low doses remains elusive. The authors recapitulate the existing knowledge on RIAR at cellular levels, specifically after low-dose exposure as an adaptive dose, and discussed its potential implications in clinical radiotherapy outcomes. ***Key Messages:*** Recent studies have contributed to understand the signaling molecules, pathways, and inhibitors to mitigate RIAR-mediated radiation resistance and persistent radio-tolerance at the cellular level. Monitoring the disease progression in tumor samples or liquid biopsies before, during, and after therapy with suitable biomarkers has been proposed as a strategy to translate the phenomena into clinical scenario.

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Introduction

Every organism is exposed to a variety of deoxyribonucleic acid (DNA)-damaging agents, which are generated endogenously, present in the environment (toxicants, ionizing radiation [IR]), and produced due to human activities (industrial chemicals, effluents, and pollutants) [1]. Excitingly, efficient defense mechanisms have evolved in organisms to reduce/nullify the toxic effects caused by those exposures and prevent the health consequences of exposure [2]. The adaptive response (AR) phenomenon is considered one of the existing defense mechanisms where the cells have adapted to cope with higher dose/concentration exposure to DNA-damaging agents [3]. It was presumed that a prerequisite for the phenomena to get activated is the initial DNA damage induced in the system upon exposure to different types of damaging agents. Moreover, AR was not elicited instantaneously but requires a specific time interval between adaptive/priming dose (AD/PD) and challenging dose (CD) to become fully active [4]. Induction of this phenomenon in many organisms, including mammalian cells exposed in vitro and in vivo to physical and chemical agents, has been demonstrated using endpoints such as DNA strand breaks (single or double strand), chromosomal aberrations (CA), formation of micronuclei (MN), sister chromatid exchanges (SCE), apoptosis, cell survival, mutation, and transformation. Because of this broader observation of the AR phenomenon, it has been implicated in radiation protection and cancer radiotherapy (RT).

The application of IR for cancer therapy has increased over the past 2 decades as it focuses on administering radiation safely either as a single dose or multiple fractions (fractionated RT) using different modalities. In addition to those developments in dose delivery, well-studied 5 "R" (repair, re-oxygenation, repopulation, reassortment, and radiation sensitivity) concepts of radiobiology assist in predicting the tumor response as well as enhancing the therapeutic efficacy [5]. As a general rule, tumors show little or no response to a single radiation dose of about 1.5–2.5 Gy of γ- or X-rays, which are used in majority schemes of external beam RT. Meanwhile, upon a multi-fraction radiation regime, many tumors develop a radioresistance, and an AR may contribute to this effect [6]. However, there is an opposite view on the role of the radiation-induced adaptive response (RIAR), as the emerging developments suggest that this phenomenon significantly enhances therapeutic efficacy [7, 8]. These adaptations can be targeted to enhance the cell killing of radioresistant tumor cells [9]. A recent review by Labrie et al. [10] (2022) proposed approaches to exploit the therapeutic stress mitigation involved in AR, such as preventing stress mitigation from inducing cell death, increasing stress to induce cellular catastrophe, and exploiting emergent vulnerabilities in cancer cells and cells of the tumor microenvironment.

Since the first report on these phenomena by Oliver et al. [3] (1984), the existence of this phenomenon has been reported and found to be highly variable depending upon many biological and physical factors. Therefore, in the present review, an attempt was made to summarize the existence of the RIAR phenomenon in various in vitro cultured cell lines (cancer and normal), animal models, clinical samples, and epidemiological studies for a better understanding of the phenomena and its potential relevance in cancer RT. Toward this direction, a literature search was performed using the PubMed database (National Library of Medicine, National Institutes of Health, USA). The strategy to search the literature was based on terms such as RIAR, RIAR and peripheral blood lymphocytes (PBL), RIAR and cell lines, RIAR and animal models, RIAR and epidemiological studies, absence of RIAR, clinical relevance of RIAR, radiotherapy, radiation resistance, and mechanism of RIAR. The authors considered the literature up to 2022, and this evaluation draws mainly on publications from 1984 to 2020. Criteria considered for this review article are adapted from the UNSCEAR report [11], which is predominantly original publication (not editorial, commentary, or correspondence) with experimental evidence indicating that the endpoints described can be linked directly or indirectly to radiation exposure with statistically sound results. In gathering and reviewing the literature, the focus has been on reports considering low-dose and low-dose-rate effects. However, review articles and high-dose studies were considered for context, particularly considering implications for the phenomenon in clinical radiotherapy.

Non-Targeted Effects of IR

The IR interacts with biological matter and deposits its energy using photoelectric interactions, Compton scattering, and pair production [12]. In turn, the transferred energy can induce base/nucleotide damages or strand breaks, leading to many health effects. Such effects were not restricted to irradiated cells alone but also conferred severe biological effects on nonirradiated bystanders or distant cells. Manifestations of those changes have been reported in the cells that are not directly traversed by radiation and modulated levels of DNA damage due to a range and time between the exposures [13–17]. The non-targeted effects of IR are radiation-induced bystander

effect, abscopal effect, RIAR, and genomic instability, which result in alterations in the actual radiation target size and give rise to nonlinear responses in cellular populations and tissues. The present review summarizes the existence of the RIAR phenomenon in various in vitro cultured cell lines (cancer and normal), animal models, clinical samples, and epidemiological studies for a better understanding of its relevance in cancer RT.

Radiation-Induced AR

RIAR is defined as the manifestation of less genetic damage in the cells pre-exposed to a very low dose of AD or PD and later exposed to CD [18]. RIAR develops with a delay of hours, may last from days to months, decreases steadily at doses of about 0.1–0.2 Gy, and is not observed anymore after acute exposures to more than 0.5 Gy [19]. When the cells are given a PD (up to 100 mSv), they induce a mechanism where they fit better to cope with CD (2–4 Gy). This phenomenon has been reported in a range of cell types (human PBL, normal and transformed cell lines, and animal models) following exposures to isotopes of tritium and X-rays, radiofrequency (RF) waves, and high linear energy transfer (LET) particulate radiations.

RIAR in Human PBL

The PBL exposed to either chronic (β-rays from tritiated thymidine) or acute (X-rays) low doses of radiation followed by exposure to relatively CD (150 centi-gray [cGy] of X-rays) showed a 50% reduction in the induced frequency of CA when compared to that of PBL not been exposed to radioisotope/PD of X-rays [3, 20]. It was also found that cross-adaptation occurred; i.e., exposure of lymphocytes to PDs of radiomimetic chemicals, alkylating agents, cross-linking agents, or IR could decrease cell sensitivity to the same agent or any of the others. The adaptation induced by the low radiation dose was ascribed to the induction of a novel, efficient chromosome-break repair mechanism at the time of exposure to a high radiation dose [21]. As induction of DNA damage was suggested to be an initial response/prerequisite for the induction of RIAR, restriction enzymes (*Alu-1*, *DRA-I*, and *Not-I*) were used to induce double-strand break (DSB) in human PBL. The restriction enzymes produce blunt or staggered end types like radiation-induced DSB. When the PBL were pre-treated with *Alu-I* and then with X-rays (150 cGy), the yield of chromosome-type aberrations was reduced to about 60% compared to the sum of the aberrations induced by either *Alu-I* or X-ray alone [22]. These experiments showed that DNA DSBs with either blunt or staggered ends could be the lesions that induce RIAR, whereby cells become less susceptible to the induction of cytogenetic damage by exposure to CDs of IR. Experiments with a mutation in hypoxanthine-guanine phosphoribosyl transferase (*HPRT*) gene locus in human PBL showed that exposure to tritiated thymidine or 1 cGy of X-rays could markedly decrease the number of mutations induced by subsequent CDs of radiation, proving the phenomenon of RIAR [23, 24]. Shadley et al. [25] (1987) did not observe any RIAR when the unstimulated lymphocytes were exposed to radiation. Yet, phytohemagglutinin-stimulated lymphocytes exposed to 2 Gy of X-rays with pre-exposure to PD showed less frequency of CA than those exposed to 2 Gy alone [26]. Sannino et al. [27] (2014) first reported that low-energy RF waves induced AR in human PBL collected, cultured immediately, and analyzed MN frequency.

Conversely, the magnitudes of RIAR measured were not the same among the donors: variability/heterogeneity existed in the response among the donors. Furthermore, it is shown that stage-specific proliferating/cycling cells (G_2/M phase cells-sensitive phase of the cell cycle to elicit RIAR) are required to exhibit this phenomenon and could be elicited only within a relatively small range of radiation dose and dose rate [28]. The PBL isolated from nuclear plant workers received occupational radiation exposure to low doses ranging from 0 to 10 mSv (PD) and was then exposed to a high dose of X-rays (CD) which showed no increase in baseline MN frequency when compared to control [29]. The RIAR examined using PBL as models suggests that with X-rays, beta radiation, and chemicals (radiomimetic agents, restriction enzymes), the magnitude of response is heterogeneous depending upon the stage of lymphocytes at the time of exposure to PD.

RIAR in Normal Cell Lines

Consistent with human PBL, the RIAR phenomenon has been reported in normal cell lines. Ikushima et al. [30] (1987) reported RIAR in V79 Chinese hamster cells using MN formation as the endpoint, i.e., pre-exposure of cells to either tritiated thymidine or 5 cGy of X-rays and then to 1 Gy of γ-rays as CD, attenuated the MN frequency in cells exposed to CD (1 Gy) of radiation alone. Azzam et al. [31] (1994) have also reported the existence of RIAR in γ-irradiated skin fibroblasts (AG1522) using MN formation as the endpoint; in cells pre-exposed to 0.5 Gy as a PD, pre-, and then acute 4 Gy CD, the observed MN frequency was significantly lower than in cells exposed to 4 Gy of γ-rays alone. These results indicated that adapted cells are better protected against DNA damage that leads to chromosomal breaks and the formation of MN. The

transformation frequency of C3H 10T½ cells challenged by acute 4 Gy of γ-rays increased ten-fold over the spontaneous frequency detected in control cells but decreased by 2–3-fold when the cells were pre-exposed to 0.1–1.5 Gy of γ-rays, 3.5 h earlier with PD [32]. Normal human fibroblasts exposed to either ^{60}Co γ-rays or 3H β particles as PDs of either 0.1 mGy at low-dose rates or 500 mGy at high-dose rates showed an absence of RIAR, but it was present at a specific range of PDs between 1 and 500 mGy with the low-dose rate (1–3 mGy/min) and with subsequent exposure of 4 Gy by causing a significant reduction in the MN frequency [33]. Mouse cells (5S) irradiated with 0.02 Gy of γ-rays followed by 3 Gy of X-rays post 5 h showed attenuated expression levels of a protein involved in the mitogen-activated protein kinase (MAPK) pathway than those exposed to CD alone, indicating the existence of RIAR [34]. Mouse spleen cells (C.B-17 ICR severe combined immunodeficiency) pre-irradiated with 1.5 Gy of X-rays (25 h of chronic) followed by CD with 3 Gy of X-rays suppressed the apoptosis when compared to 3 Gy of X-rays acute irradiation alone [35].

Heterogeneity in the induction and magnitude of RIAR was observed among human lymphoblastoid cells; six out of 10 cell lines showed RIAR using MN formation upon exposure to PD of 0.05 Gy and then to 2 Gy of γ-rays with a time gap of 6 h [36]. About 22% increase in cell survival was observed in the chinook salmon embryonic cell line (CHSE-214) with an exposure of 0.5 Gy (PD) of γ-rays followed by exposure to a CD of 10 Gy γ-radiation [37]. Fibroblasts from human (RMP-4 and IMR-90) and mouse embryos were cultured both under monolayer and three-dimensional (3D) conditions and pre-treated with a PD (up to 100 mGy of X-rays) followed by CD (2 Gy of X-rays), which showed an attenuated level of γ-H2AX and p53^{Ser-15} expression than cells exposed to CD alone. Moreover, the percentage of attenuated damage was higher in cells grown in a 3D microenvironment than in a monolayer, implying that the culture conditions/environment influence the RIAR [38]. Observations of RIAR in most studies in normal cells seem advantageous, as the PD exposures followed by CD exposures make the cells adapt and protect them by increasing cell survival [37]. Cell lines from human and animal origin exhibit the RIAR phenomena upon exposure to β-, γ-, and X-rays; moreover, the magnitude depends upon the origin and 2D/3D culture environment.

RIAR in Cancer Cell Lines

Zhou et al. [39] (1993) reported the existence of RIAR in a mouse mammary carcinoma cell line (SR-1) using *HPRT* mutations. SR-1 cells irradiated with PD of 0.01 Gy of X-rays and a CD of 3 Gy of γ-rays showed a 50% reduction in the *HPRT* mutations compared to 3 Gy of X-rays alone. RIAR was observed in leukemic cells (HL-60) exposed to 900 MHz RF fields and doxorubicin (0.125 mg/L); i.e., cells pre-treated with radiation and then to doxorubicin showed significantly increased viability, decreased apoptosis, increased mitochondrial membrane potential, decreased intracellular free Ca^{2+}, increased Ca^{2+}, and Mg^{2+} ATPase activity as compared to the cells exposed to doxorubicin alone [40]. Michigan Cancer Foundation-7 cells exposed to PD of 0.1 Gy of γ-rays followed by CD of 2 Gy of γ-rays showed RIAR, i.e., cells when exposed to 0.1 Gy of γ-rays before 2 Gy of γ-rays as CD resulted in less damage compared to 2 Gy of γ-rays alone [41].

Solanki et al. (2017) investigated the dose rate effects of RIAR; MDA-MB-231 breast cancer cells and V79 Chinese hamster lung fibroblasts were exposed to varying dose rates from 662 keV X-rays and then measured the clonogenic potential of the irradiated cells. An increase in cell survival as a measure of AR was evident with an increase in the dose rate and then a decline to further increase the dose rate [42]. The irradiation condition is related to the conditions of radiopharmaceutical therapy, wherein the dose and dose rate vary depending on the half-life time and uptake of the specific radiopharmaceutical. Similar dose-rate-dependent variation in the magnitude of RIAR has been demonstrated in quiescent normal human fibroblasts exposed to γ-rays [43] and low LET protons [44]. Thus, exponentially increasing radiation dose rates can initiate a cascade of intracellular and extracellular changes that make the tissue more resistant to subsequent exposure to radiation.

Differential RIAR in Normal and Cancer Cell Lines

Studies have documented a differential RIAR phenomenon in normal and tumor cells, i.e., either the tumor cells failed to show RIAR or a differential pattern from normal cells based on the time gap between delivery of PD and CD. Park et al. [45] (1999) first reported the absence of RIAR in cell lines of mouse origin: RIAR was observed by cell survival and apoptosis in normal cells (NL mouse lymphocytes, L929 cells of connective tissue, and PK keratinocytes) and not in tumor cells (skin papilloma cells 308 and X-ray-sensitive L5178Y-S, and EL-4 lymphoma cells). A similar response was demonstrated in cells of human origin; Jiang et al. [46] (2008) reported that PD radiation exposure induces an AR in normal human fibroblast cells (medical research council cell strain 5) but failed to observe the phenomenon when tumor cells (small-cell lung cancer NCIH446 cells, glioblastoma-U251, erythroleukemia-K562, promyelocytic leukemia-HL60 of human origin, and

sarcoma cell line-S180 of mouse origin) were exposed to PD followed by CD. Boyden et al. [47] (1999) examined RIAR in 6 cell lines (two normal fibroblasts and four tumor cells) using survival fraction as an endpoint, i.e., they reported that RIAR neither depends on radiation sensitivity nor the differences between normal and tumor cells. It was postulated that variation in AR reported among different laboratories could be related to several factors such as cell culture conditions, cell cycle effects, types of radiation used as well as dose and dose rates, differences in the test systems, cell strains whether they are derived from normal or tumor tissues, and actual radiation sensitivity of the cell line under investigation [48].

RIAR in Animal Studies

Fritz Niggli et al. (1991) showed that dominant lethal mutations induced in *Drosophila melanogaster* by X-rays exhibited the phenomenon of RIAR. Mature and immature oocytes from strains that differ in their repair ability (repair-proficient yellow white strain and repair-deficient mus-302D1 and mei-41D5 strains) were initially irradiated with 0.02 Gy of X-rays and subsequently with 2 Gy of X-rays at various time intervals; for each strain and stage, the measured dominant lethality was below what was expected based on additive effects of the two irradiations given separately [49]. Yonezawa et al. (1996) reported that PD of X-irradiation 2 months before a second exposure (8 Gy of X-rays) to a sub-lethal dose enhanced the survival rate (30% survived 30 days after irradiation) in mice. They have also reported that in animals pre-irradiated with 5 cGy and then with 8 Gy of X-rays, the survival rate increased to about 70% and was named the Yonezawa effect [50]. It was postulated that PD exposure seems to stimulate the recovery of blood-forming stem cells after the second irradiation and favors a decrease in the incidence of bone marrow death [51]. However, their findings were inconsistent, as they later reported that response depended on the dose and duration between the PD and CD [50]. A similar study with a PD of 0.5 Gy of X-rays followed by CD of 6.5 Gy from carbon ion and neon ion imparted a rescue effect on bone marrow death in a 30-day survival test indicating both X-rays and heavy ions induce RIAR against the detrimental effects of high LET [52].

B6C3F1 mice X-irradiated with PD (0.025–0.5 Gy) and then to CD (1–4 Gy) at different time gaps (1–24 h) showed RIAR with spleen colony-forming assay: it was found that a dose between 0.05 and 0.1 Gy of X-rays was considered as optimum PD for the induction of RIAR [53]. C57BL/6N mice irradiated with 1.5 Gy of X-rays and then with 3 Gy of X-rays with a varying time interval showed RIAR measured as apoptosis in the splenocytes [54]. The induction of RIAR was also observed in transgenic mice, pKZ1 using chromosomal inversion assay after exposure to PDs (0.001–10 cGy of X-rays) followed by 1 Gy of X-rays after 4 h in spleen and prostate cells [55]. Jiang et al. (2012) exposed adult male mice to non-IR (900 MHz at 120 mW/cm^2, RF waves for 4 h/day for 1–14 days) and then subjected them to 3 Gy of γ-radiation: a significant reduction in DNA single-strand breaks measured using comet assay and the incidence of MN in PBL and bone marrow tissues of mice exposed to RF waves and 3 Gy of γ-radiation; thus, proving both genotoxicity endpoints indicated that RF waves induced RIAR [56]. Cao et al. (2014) demonstrated that RF waves induce AR in adult Kunming mice using multiple endpoints [57]. Thus, consistent with cell line models, animal models (drosophila and mouse strains) exhibit the phenomenon of RIAR, which also depends upon the dose and duration between the PD and CD.

RIAR in Epidemiological Studies

Epidemiological studies have shown that an increased level of chronic low-dose radiation (>5.0 mGy/year) seems to act as a PD, resulting in an in vivo RIAR. Kumar et al. [58] (2015) first reported that in vivo chronic low-level natural radiation provides an initial exposure that allows an adaptation to a subsequent challenging radiation exposure using the comet assay. Studies on isolated peripheral blood mononuclear cells exposed to >1 mSv chronic PD followed by 2 and 4 Gy of X-rays revealed the reduced level of comet parameters in the Kerala population. They have reconfirmed the phenomenon using MN formation as an endpoint in the lives of the different populations in the same geographical area. To test the natural background radiation serving as a PD, blood samples of adult individuals aged between 26 and 65 years (low PD group: exposed to 1.5–5.0 mGy/year and high PD group: exposed to >5.0 mGy/year) were collected and then exposed in vitro to 1 and 2 Gy of γ-radiation (CD), the mean frequency of MN remained same in both groups after PD [59]. A similar study was performed using analysis of MN frequency from PBL collected from human volunteers for analyzing the RIAR phenomenon in nonionizing RF (900 MHz RF) equivalent to that used for mobile communication and further challenging exposure to a single dose of mitomycin-C (100 ng/mL): a decrease in MN frequency was observed in samples pre-exposed to RF waves and then to mitomycin-C compared to that induced by mitomycin-C alone, proves that RF PD also induces RIAR [60]. Thus, the RIAR has been reported in humans exposed to low ionizing and non-IR doses.

RIAR Studies in the Relevant Clinical Scenario

Very limited information on RIAR at the dose level practiced during clinical cancer RT is available. Yang et al. (2009) observed a 12.6% increase in cell survival when H460 cells were exposed to 0.05 Gy of X-rays (equivalent to that received during imaging) followed by 2 Gy of X-rays (equivalent to that received during fractionated cancer radiation therapy); it was attributed due to increased cell proliferation and suggested that the delivery of a fraction of therapeutic dose present a potential issue having a negative impact on treatment efficacy owing to low doses, such as RIAR or sub-lethal damage repair that may be initiated during this time [61]. Nonetheless, Hyland et al. (2014) did not see any adverse effect due to the dose received equivalent to that received during imaging (0.05 Gy of X-rays); their results showed that pre-exposure to high doses (1–8 Gy of X-rays) with a time difference of 7.5 and 15 min did not alter the cell survival in irradiated prostate cancer cells DU-145 and H-460 leukemic cells as well as AG1522b normal skin fibroblasts [62]. They have cautioned that the extrapolation of these in vitro and theoretical findings to the clinical context is complicated as two-dimensional monolayer cell culture methods do not replicate the vascular architecture of complex tumors. Hypo-fractionation reduces the therapy sessions, time, and cost, posing a considerable impact and toxic to normal cells. Hence, hyper-fractionation of RT can maximize the probability of resistance in normal cells by making cancer cells sensitive. Molecular mechanisms such as decreased ROS can lead to DNA damage, which increases the DNA repair capacity and thus leads to autophagy or other self-renewal mechanisms contributing to cellular resistance [63]. Hence, challenges remain to minimize or eradicate the resistant tumor sub-population more than the sensitive tumor sub-population.

Absence of RIAR

Several studies on human PBL and cell lines showed an apparent existence of RIAR, but few studies also reported an absence of RIAR. The RIAR was not observed during the stages of prenatal development in utero, in individuals with a genetic predisposition to hyper-radiosensitivity, and in case of high LET radiation exposures [64]. Ueno et al. (1996) demonstrated RIAR in AL human-hamster hybrid cells upon 0.04 Gy of ^{137}Cs γ-irradiation as a PD followed by 4 Gy as CD. The same was abolished upon adding 3-diaminobenzidine or cycloheximide, indicating radio-adaptation to mutagenesis [65]. A study on human U87MG glioma cells showed no RIAR in the clinical range of fractionated or pulsed irradiation [66]. No RIAR in in vitro mouse splenocytes were observed for MN formation upon exposure to a PD of about 20 mGy of γ-rays and CD of about 100 mGy of γ-rays at intervals between 4 and 24 h. Similarly, no RIAR was induced consistently in spleen cells of C57BL/6 or BALB/c mice under in vivo conditions to single or multiple PDs of 20 mGy of γ-rays and subjecting to a CD of 2 Gy of γ-rays post 24 h to that of mouse cells under in vitro conditions [67]. Lowering the dose rate leads to a RIAR as indicated in studies comprising two fibroblasts, two melanoma, and two breast carcinomas, out of which only 3 cell lines (OMB18, HT 144, and T47D) showed RIAR, proving that the differences in the origin of the cell line are one significant parameter [47].

Endpoints and Assays for Evaluation of RIAR

RIAR was measured using many biomarkers. Each marker has advantages and disadvantages in radiation biology studies. Clonogenic survival [37, 68], or yields of CA [3], or SCE [69], or MN [36, 67], or γ-H2AX foci, or HPRT mutations [39], as well as changes in proteins [38] or cell proliferation rate [61] have been extensively used to measure the effect induced after both AD and CD. Table 1 summarizes the various studies that examined the RIAR, the model employed, and the type of radiation used to examine the effect reported in the literature, which are included in this review.

Proposed Mechanisms for RIAR

RIAR is a cellular mechanism observed in response to a low level (PD) of radiation, and several mechanisms have been proposed to explain the phenomena at the cellular level. It has been widely accepted that initiating events to activate the mechanism are the induction of DNA damage response to the DNA damage induced by PD doses, and many signaling molecules and pathways are triggered. At the molecular level, key signaling pathways are DNA damage response, redox to maintain cellular homeostasis, and other effector signaling molecules that mediate either cell survival or eliminate the damaged cell and organelle. They include the DNA repair pathways, de-toxification response pathway (enzymes, molecules help maintain the balance in NF-E2-related 2 [Nrf2] signaling pathway), immune/inflammatory response (pro- and anti-inflammatory signaling molecules), cell

Table 1. Summary of the studies showing the RIAR in different model systems

S. No.	Study type	PD	CD	Endpoints	Observations	Reference
PBL						
1	PBL	Tritiated thymidine	150 cGy of X-rays	CA	50% reduction in the frequency of CA indicating the presence of RIAR	Olivieri et al. [3] (1984)
2		Restriction enzymes: *Alu-1, DRA-I,* and *Not-I*	150 cGy of X-rays	Chromatid aberrations	60% reduction in chromatid aberration frequency indicating the presence of RIAR	Wolff et al. [22] (1998)
3		Tritiated thymidine	1 cGy of X-rays	HPRT mutations	Decrease in the number of HPRT mutations indicating the presence of RIAR	Sanderson et al. [23] (1986); Kelsey et al. [24] (1991)
4		PHA	2 Gy of X-rays	CA	A decrease in the CA frequency indicates the presence of RIAR	Barquinero et al. [26] (1995)
5		0–4 mSv of X-rays	4–10 mSv of X-rays	MN	No increase in baseline MN frequencies in 41 workers temporarily employed at the Nuclear Power Plant Doel (Belgium) proving the presence of RIAR	Thierens et al. [29] (2002)
RIAR in normal cells						
6	V79 (Chinese hamster cells)	Tritiated thymidine/5 cGy of γ-rays	1 Gy of γ-rays	MN	A decrease in MN frequency upon 5 cGy+1 Gy indicates the presence of RIAR	Ikushima et al. [30] (1987)
7	AG1522 (skin fibroblasts cells)	0.5 Gy of γ-rays	4 Gy of γ-rays	MN	A decrease in MN frequency upon 0.5+4 Gy indicates the presence of RIAR as adapted cells are better protected against DNA damage	Azzam et al. [31] (1994)
8	C3H 10T½ (mouse embryonic cells)	0.1–1.5 Gy of γ-rays	4 Gy of γ-rays	Transformation and MN	Transformation frequency decreased by 2–3-fold and MN frequency decreased in primed+challenged cells supporting radio-protective mechanisms against radiation damage in mouse embryo fibroblasts	Azzam et al. [32] (1996)
9	AG1522 or AG1522B (normal human fibroblasts)	0.1–500 mGy of ^{3}H β-particle or ^{60}Co γ-rays	4 Gy of ^{60}Co γ-rays	MN	No decrease in MN frequency indicating the absence of RIAR	Broome et al. [33] (2002)
		1 and 3 mGy of ^{3}H β-particle or ^{60}Co γ-rays	4 Gy of ^{60}Co γ-rays	MN	A decrease in MN frequency indicates the presence of RIAR as the response was not sensitive to DNA damage in this range of doses	
10	5S mouse cells	0.02 Gy of X-rays	3 Gy of X-rays	Protein expression of MAPK	High MAPK levels indicate the presence of RIAR	Shimizu et al. [34] (1999)
11	C. B-17 Icr SCID (mouse spleen cells)	1.5 Gy of γ-rays	3 Gy of X-rays	Apoptosis	Suppression in apoptosis indicating the presence of RIAR	Takahashi et al. [35] (2002)
12	Human lymphoblastoid cells	0.05 Gy of γ-rays	2 Gy of γ-rays	MN	A time gap of 6 h between PD and CD decreased MN frequency in 6 out of 10 human lymphoblastoid cells indicating the presence of RIAR	Sorensen et al. [36] (2002)

Table 1 (continued)

S. No.	Study type	PD	CD	Endpoints	Observations	Reference
13	CHSE-214 (chinook salmon embryonic cells)	0.5 Gy of γ-rays	10 Gy of γ-rays	Cell survival	26.58% protection with a 22% increase in cell survival indicating the presence of RIAR	Kilemade et al. [37] (2008)
14	RMP-4 and IMR-90 (human fibroblasts) MEF	Up to 100 mGy of X-ray	2 Gy of X-rays	DNA damage via γ-H2AX and $p53^{Ser-15}$	More DNA damage; RIAR higher in 3D cells in comparison with 2D cells due to culture conditions	Zhao et al. [38] (2015)
RIAR in cancer cells						
15	SR-1 (mouse mammary carcinoma)	0.01 Gy of γ-rays	3 Gy of γ-rays	HPRT mutations	The presence of RIAR with a time gap of 18/ 24 h between PD and CD caused a 50% reduction in HPRT mutations	Zhou et al. [39] (1993)
16	HL-60 (leukemic cells)	900 MHz of RF fields	Doxorubicin (0.125 mg/L)	Cell viability, apoptosis, mitochondrial membrane potential, intracellular free Ca^{2+} Ca^{2+} and Mg^{2+} ATPase activity	Increased viability, decreased apoptosis, increased mitochondrial membrane potential, decreased intracellular free Ca^{2+}, and increased Ca^{2+} and Mg^{2+} ATPase activity observations indicated the presence of RIAR	Jin et al. [40] (2012)
17	MCF-7 (breast carcinoma)	0.1 Gy of γ-rays	2 Gy of γ-rays	Metabolic viability Apoptosis DNA fragmentation	Reduction in radiation-induced damages in PD + CD with a time gap of 8 h	Gandhi et al. [41] (2018)
Differential RIAR in normal and cancer cell lines						
18	Mouse cells: normal cells (NL lymphocyte, L929 connective tissue cells, and PK keratinocyte) Mouse cells: tumor (308 cells of skin papilloma and L5178y-s and EL-4 lymphoma)	–	–	Apoptosis (ELISA and TUNEL)	RIAR was induced in normal cells due to decreased apoptosis but not in tumor cells with a 0.01 Gy low dose indicating the presence of RIAR in normal cells due to the involvement of the anti-apoptotic pathway proteins	Park et al. [45] (1999)
19	MRC-5 (normal human fibroblast), NCIH446 (small cell lung cancer cells), U251 (glioblastoma), K562 (erythroleukemia), HL60 (promyelocytic leukemia), S180 (mouse sarcoma)	75 mGy of X-rays	4 Gy of X-rays	Expression of apoptotic genes	High expression levels of p53 and Bax and low expression levels of Bcl-2 in tumor cells with primed and challenged doses indicated an absence of RIAR in tumor cells under in vitro and in vivo whereas the presence of RIAR in normal cells	Jiang et al. [46] (2008)
RIAR in animal studies						
20	*Drosophila melanogaster*	0·02 Gy of X-rays	2 Gy of X-rays	DNA Repair	Effects were low for PD + CD compared to separate irradiations in repair-proficient yw strain and repair-deficient mus-302D1 and mei-41D5 strains proving the presence of RIAR	Fritz-Niggli et al. [49] (1991)

Table 1 (continued)

S. No.	Study type	PD	CD	Endpoints	Observations	Reference
21	B6C3F1 mice	0.025–0.5 Gy of X-rays	1–4 Gy of X-rays	Spleen colony-forming assay	A PD in the range of 0.05 and 0.1 Gy for PD + CD with a time gap of 1–24 h induced RIAR	Yoshida et al. [53] (1993)
22	C57BL/6N mice	1.5 Gy of X-rays	3 Gy of X-rays	Apoptosis	Presence of RIAR in mouse splenocytes upon PD + CD	Takahashi et al. [54] (2001)
23	pKZ1 transgenic mice	0.00001, 0.0001, 0.001, and 0.01 Gy of X-rays	1 Gy of X-rays	Chromosomal inversion assay	Presence of RIAR in mouse spleen and prostrate cells upon PD + CD	Day et al. [55] (2007)
24	Peripheral blood and bone marrow tissue of adult male mice	900 MHz of RF	3 Gy of γ-rays	Comet assay MN	RF waves-induced RIAR in mice with a time interval of 4 h/day for 1–14 days	Jiang et al. [56] (2012)
25	Adult Kunming mice	900 MHz of RF	5 Gy of γ-rays	DNA damage, CFU-BM, GM-CSF, *IL-3*	Less damage and an increase in the number of CFU-BM, GM-CSF, and *IL-3* in bone marrow and spleen indicated the presence of RIAR	Cao et al. [57] (2014)
26	ICR mice	5 cGy of X-rays	8 Gy of X-rays	Cell survival	PD + CD with a 2-month interval increased the survival rate by about 70% and decrease the incidence of bone marrow death indicating the presence of RIAR	Yonezawa et al. [51] (1990)
27	ICR mice	0.5 Gy of X-rays	6.5 Gy of carbon/ neon ion	Cell survival	Increase in cell survival and rescue from bone marrow death thus, both X-rays and heavy ions induce RIAR upon PD + CD	Wang et al. [52] (2013)
RIAR in epidemiological studies						
28	PBL (elderly Kerala population)	>1 mSv natural background radiation	2 and 4 Gy of γ-rays	Comet assay	Reduced comet levels upon natural exposures followed by γ-rays thus proving the presence of RIAR in the Kerala population	Kumar et al. [58] (2015)
29	PBL (adult male Kerala population; *n* = 54 of age 26–65 y)	Natural background radiation (1.51–5.0 mGy/ year)	>5.0 mGy/year background radiation 1 and 2 Gy of γ-rays	MN	Decreased MN frequency upon PD + CD proving chronic background radiation induces RIAR in the Kerala population	Ramachandran et al. [59] (2017)
30	PBL-Kerala population (*n* = 5)	Nonionizing RF (900 MHz RF) mobile communication	Mitomycin-C (100 ng/mL)	MN	A decrease in MN frequency upon PD + CD indicating RF PDs also induce RIAR	Sannino et al. [60] (2011)
RIAR studies in relevant clinical scenarios						
31	H460 cells	0.5 Gy of X-rays (imaging dose)	2 Gy of X-rays (therapy dose)	Cell survival	Imaging dose + therapeutic dose induces the repair of sub-lethal damage and RIAR poses a negative impact on therapeutic efficacy	Yang et al. [61] (2009)
32	DU-145 and H-460 (leukemic cells) and AG1522b (normal skin fibroblasts)	0.05 Gy of X-rays	1, 2, 4, and 8 Gy of X-rays	Cell survival	Pre-exposure did not alter the cell survival upon imaging+therapy doses indicating the presence of RIAR in clinical scenarios however the vascular architecture of 2D and 3D cells vary	Hyland et al. [62] (2014)

Table 1 (continued)

S. No.	Study type	PD	CD	Endpoints	Observations	Reference
	Prostate (n = 30) and pelvic node patients (n = 30)				Imaging dose incorporation has no significant impact on cell survival with a time difference between imaging and radiation therapy of 7.5- and 15-min indicating RIAR	
Absence of RIAR						
33	AL (human-hamster hybrid cells)	0.04 Gy of ^{137}Cs-γ-rays	4 Gy of γ-rays	Mutations	Presence of RIAR but upon the addition of 3-aminobenzidine or cycloheximide, RIAR was abolished indicating adaptation to mutagenesis thus RIAR was absent upon the addition of mutagens	Ueno et al. [65] (1996)
34	U-87 MG (human glioma)	0.50–3 Gy of X-rays	0.50–3 Gy of X-rays with a time gap of 6 h	Cell survival	Absence of RIAR in fractionated or pulsed irradiation as only a few DNA breaks were present as a result of the radio-resistant mechanism of human glioma cells	Smith et al. [66] (2003)
35	C57BL/6 or BALB/c mice (splenocytes)	20, 100, and 500 mGy of γ-rays	2 Gy of γ-rays	MN	No RIAR was induced in mouse splenocytes	Bannister et al. [67] (2015)
36	Fibroblasts, melanoma, breast carcinoma	0–4 Gy of X-rays	2–4 Gy of X-rays	Clonogenicity	3 out of 6 cell lines showed RIAR proving variability as one major parameter for the existence of RIAR	Boyden et al. [47] (1999)
37	Fish cell lines CHSE-214 (chinook salmon), RTG-2 (rainbow trout), ZEB-2J (zebrafish)	0.1 Gy of γ-rays	2–5 Gy of γ-rays	Cloning efficiency	RIAR is an inverse phenomenon of bystander effect which varied with time intervals	Ryan et al. [108] (2008)

PBL, peripheral blood lymphocytes; cGy, centi-gray; CA, chromosomal aberrations; RIAR, radiation-induced adaptive response; HPRT, hypoxanthine-guanine phosphoribosyl transferase; PHA, phytohemagglutinin; MN, micronucleus; MAPK, mitogen-activated protein kinase; SCID, severe combined immunodeficiency; PD, priming dose; CD, challenging dose; CHSE, chinook salmon embryonic cells; MEF, mouse embryo fibroblasts; IMR, institute for medical research; H2AX, H2A histone family member X; HL-60, human promyelocytic leukemia cell line; MCF-7, Michigan Cancer Foundation-7; DNA, deoxyribonucleic acid; ELISA, enzyme-linked immunosorbent assay; TUNEL, terminal deoxynucleotidyl transferase biotin-dUTP nick end labeling; MRC-5, medical research council cell strain 5; Bax, Bcl-2-associated X protein; Bcl-2, B-cell leukemia/lymphoma 2 protein; yw, yellow white; MHz, megahertz; CFU-BM, granulocyte-macrophage progenitor; GM-CSF, granulocyte-macrophage colony-stimulating factor; ng, nanogram; Cs, cesium; RTG, rainbow trout; ZEB, zebrafish.

survival/death pathway, endoplasmic response to stress, numerous proteins, and transcription factors involved in mediating/amplifying these stress response pathways [70, 71]. Thus, an altered expression of stress proteins is an essential AR to managing adverse IR conditions.

DNA Damage Response

Cellular recognition upon exposure to IR is by cell cycle sensors and thereby undergoes DNA damage and repair for preserving the genome integrity. A damaged cell activates various molecular pathways in the context of DNA damage and repair mechanisms, thereby leading the cell cycle to either progress, repair, or arrest. DNA damage is sensed by protein products of several genes such as *ATM*, *ATR*, *RAD1*, *RAD9*, and *RAD17* [72]. These proteins act as sensors that arrive at the site of DNA damage, which in turn trigger cell signaling and transduction pathways, thereby identifying cell signals and activating downstream signaling molecules that provide a survival advantage to the damaged cells [73].

DNA Repair

Many repair mechanisms and molecules involved in DNA damage repair have been known to induce RIAR. DNA DSBs are the most common lethal lesions induced upon radiation exposure. It can trigger a series of signal transduction pathways followed by DNA repair mechanisms that integrate as the DNA repair pathways, such as nucleotide excision repair, base-excision repair, nonhomologous end joining (NHEJ), homologous recombination (HR) repair, etc. The DSB induced by PD is predominantly repaired either by HR or by NHEJ pathways [34] via DNA-dependent protein kinase (*DNA-PK*) and *ERCC5* (*XPG*) [74]. In contrast, radioresistance is mediated by single-strand breaks via the elevation of AP-endonuclease levels responsible for base-excision repair [75]. The pathways of HR or NHEJ repair as a basis of the repair mechanism is one of the causal factors for RIAR, as inhibitors of rate-limiting molecules involved in those repair pathways (DNA PKc, PI3K, and $ATM^{-/-}$) did not induce AR in mouse glial cells [72, 76].

Cell Cycle Regulation

The AR can be mediated by feedback signaling pathways of arrest vs. cell cycle proliferation [77]. Levels of cyclins (cyclin D, E, A, and B), cyclin-dependent kinases (CDKN1A and CDKN2A), and kinase inhibitory peptides (p21, p27, p15, and p16) majorly modulate cell cycle proliferation as well as the arrest of cell growth. Ataxia telangiectasia mutated (ATM) protein senses DNA damage and activates DNA damage checkpoint signals by phosphorylating many targets involved in DNA damage pathways. The important downstream targets are the p53, NBS1, RAD9, BRCA1, CHK1, and CHK2 proteins. The target phosphorylation occurs via complexes such as BRCA1-RAD51-BRCA2 and NBS1-MRE11-RAD50 [78]. The phosphorylation of RAD9 activates DNA damage-induced G1/S phase checkpoints. CHK2 protein induces the G1 and G2 arrest via Tp53 and cdc25, respectively. TP53, a tumor suppressor protein involved in DNA damage and apoptosis, is stabilized by phosphorylation by ATM upon irradiation. This intern interacts with the 53BP1 protein to form multiple foci with hundreds of molecules per DSB [79]. Pathways that involve the upregulation of phospholipase C, protein kinase C, and p38 mitogen-activated protein kinase (p38MAPK) upon preexposures to PD with a reverse at high doses, as evident from studies conducted on human and mouse models, suggest that these pathways play an important role in mediating the RIAR [34].

Cell Death

Many molecules and pathways resulting in adaptive processes also occur at the cellular level by eliminating damaged organelles (autophagy) or damaged cells (through apoptosis or necrosis). Autophagy is a housekeeping survival mechanism that promotes programmed cell survival, sustaining homeostasis by maintaining cellular integrity, and favoring efficient cellular or programmed cell death. Autophagy is induced by starvation and various stimuli such as xenobiotics, cytokines, endoplasmic reticulum (ER), and oxidative stress. While autophagy antagonizes apoptosis and promotes cell survival, massive and persistent autophagy has been shown to deplete the cell of organelles and critical proteins and can thus kill extensively damaged cells [80]. Moreover, the cell cycle proliferation is controlled at different steps if the genomes are altered and affect either its repair or apoptosis [81]. Similarly, the Wnt/β-catenin pathway is involved in cellular development, survival, proliferation, etc. Still, the recent finding suggests that the RIAR pathway has been known to provide radioresistance to cancer stem cells [82].

ER Response to Stress

The ER is the primary cell organelle for synthesizing, folding, and sorting proteins. A defect in the organelle and its function resulting in the release of a nonfunctional protein called an "unfolded protein response" is a protective mechanism for adaptation to environmental stress and recovery of normal endoplasmic reticulum functions [83]. The role of bystander effect (expression of biological/biochemical change by a cell or a tissue that is not directly targeted by IR or chemicals) has also been related to the RIAR: that it happens to cells neighboring or even distant from targeted cells [84]. Finally, tissue or organism processes can be implicated in this response by inducing cell proliferation or differentiation, controlling immune/inflammatory reactions, inducing toxic substance excretion through transporters, or activating distant cells through bystander/abscopal effects [85].

Hypoxia

One of the mechanisms to explain RIAR is the activation of the hypoxia-inducible factor. It was proposed that a PD of γ-radiation results in the increased transcription activity of hypoxia-inducible factor and subsequent activation of survival pathways. Therefore, when the cells were primed with PD of radiation, it resulted in the upregulation of survival machinery protecting the cells when they were challenged with high doses of radiation [41].

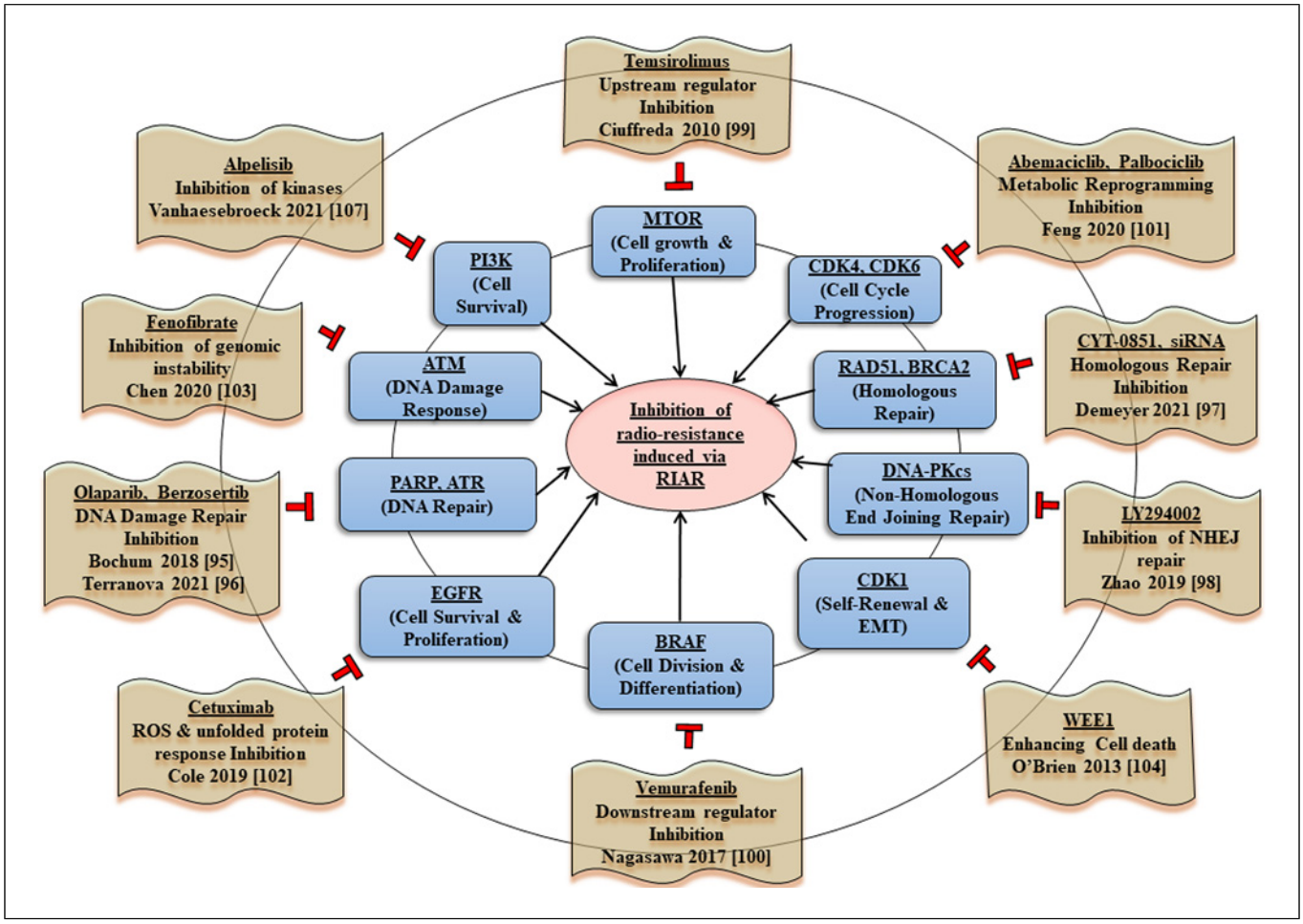

Fig. 1. Overview of inhibitors and their functions against molecules/pathways associated with RIAR. ATM, ataxia telangiectasia mutated; PI3K, phosphatidyl inositol-3 kinase; MTOR, mammalian target of rapamycin; CDK4, cyclin-dependent kinase 4; CDK6, cyclin-dependent kinase 6; RAD51, RAD51 recombinase; BRCA2, breast cancer gene 2; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; CYT-0851, RAD51 inhibitor; siRNA, small interfering RNA; CDK1, cyclin-dependent kinase 1; WEE1, mitosis inhibitor protein kinase; BRAF, B-Raf; EGFR, epidermal growth factor receptor; PARP, poly (ADP-ribose) polymerase; ATR, ataxia telangiectasia and Rad3-related protein.

Redox Status

Su et al. [86] (2018) postulated that the enhanced antioxidant capacity, DNA repair capacity, and inhibition of apoptosis might play an essential role in AR in populations living in high-background radiation population. The cell microenvironment is highly imbalanced in its redox status, compromising DNA repair and apoptosis, and thus may have a higher probability of activating the phenomena of RIAR.

Gene Expression Changes and RIAR

Radiation doses administered as single fraction or multi-fractions significantly affect the expression of several genes and contribute to RIAR. Multi-fractionation of 5 × 2 Gy of ^{60}Co γ-rays results in an upregulation of IFN and TGF-β genes responsible for RIAR in in vitro cell cultures [87]. Hyper-fractionated radiation (1.8 Gy/4 weeks) resulted in upregulation of STAT1 and IFN-inducible genes compared to hypo-fractionation (3–20 Gy/week). Thus, hyper-fractionation revealed the presence of RIAR in primary human normal endothelial and prostate cancer cells [88]. Differential expression of genes and micro-RNA has been observed in murine Lewis lung cancer cells exposed *in vitro* to single dose of 10 Gy of X-rays or fractionated dose of 5 × 2 Gy of X-rays [89]. High levels of p53 and BAX and low levels of Bcl-2 were observed in tumor cells exposed to PD of

75 mGy of X-rays, and CD of 4 Gy of X-rays resulted in an absence of RIAR, whereas the same doses revealed the presence of RIAR in normal cells in vitro and in vivo [46]. The studies showed a differential gene expression after the dose was delivered as a single or multi-fraction, which indicates that the expression of genes also plays an essential role in the existence of the RIAR.

The findings from recent studies helped us understand the various mechanisms involved in the RIAR; regardless, they appear highly complex as they depend on the model (in vitro and in vivo) used, the endpoint, the dose, or the dose rate for radiation, and the interval between exposure and the observed biological effects. The reduced radiation effect studies induced by PD have focused on cell survival mechanisms [90].

Implications of RIAR on Cancer Radiotherapy

As cancer is a significant public health problem and the leading cause of death, to combat and reduce the disease burden, multifaceted research efforts are being made to enhance the therapeutic index [91]. The treatment choices are isolated or combined based on the tumor size, volume, and microenvironment. Among the existing modalities, the use of IR, such as X- and γ-rays, mediates various forms of cancer cell death (apoptosis, necrosis, autophagy, mitotic catastrophe, and senescence) and remains a primary option for the management of many tumors [92]. Although IR-based therapy is curative in a number of cancer types, failure to respond during therapy, and recurrence and relapse remain the challenges [93]. AR to PDs of IR or chemical exposures at the cellular level and a tissue or organism results in detrimental effects due to multiple PD and CD exposures at various levels of organization [85]. The RIAR in tumor cells is considered one of the reasons for developing resistance in a patient followed by failure to respond to therapy; it is mediated by factors that interfere with and modulate intrinsic stress response pathways during cancer development along with those induced by the therapy [10]. The mechanistic study has shown the commonality of molecules and pathways involved in maintaining normal cell homeostasis and in the induction of the AR phenomenon [8]. A better understanding of the AR phenomenon upon radiation induction may improve the fractionated radiotherapy strategy. If so, the desired therapeutic outcome with an improvement in the quality of therapy, prolonged life expectancy, and reduced probability of other secondary malignancies can be achieved [8].

Reputable reviews are available on the mechanism, such as molecules involved and pathways mediating the stress response during disease development and therapy. The involvement of free radicals, upregulation repair mechanism (NHEJ andHR), reduced fixation of damage, increased synthesis of new proteins/genes, activation of the antioxidant system (upregulation of manganese superoxide mutase, glutathione peroxidase/reductase, catalase, SOD, glucose-6 phosphate-dehydrogenase, oxysterol, prostaglandine, glutathione, etc.) in RIAR [19]. DNA damage response is considered a primary and intrinsic factor among many factors (tumor microenvironment, sensors molecules of membrane signaling, patient immune system, gut microbiota, nutritional status, and mental health status) associated with radiation resistance in cancer cells [73]. Out of IR-induced lesions, DSBs are the most harmful form of DNA damage, resulting in cell death and possible chromosomal rearrangements that are mediated by multiple signaling molecules and divergent pathways. Proteins (γH2AX, 53BP1, Nbs1, BRCA1/2, and Ku) act as DNA damage sensors, recruiting the transducer proteins (Nbs1/hMre11/hRad50 complex) to convey signals to enzymes and then respond to the breaks. Primary pathways evolved to process DSB repair are the HR pathway, NHEJ, and alternative end joining; inherent DNA damage repair efficiency of cancer cells may cause cellular resistance and weaken the therapeutic outcome [73]. Alteration, interaction, translocation, and regulation of those molecules and dysregulated (rewired signaling) signaling pathways can impact the repair process, making cancer cells more resistant or sensitive to RT [94].

As the study has shown, the involvement of molecules and pathways implicated in the induction of RIAR are similar to that involved in maintaining normal cell homeostasis; it remains a challenge to overcome this phenomenon by mitigating it with a single molecule/pathway [93]. Regardless, existing literature demonstrated that therapeutic gain could be achieved by mitigating the levels of prominent signaling molecules and the pathways that maintain tumor cell viability and thus represent key target resistance mechanisms. Figure 1 provides an overview of molecules, pathways, and functions associated with the existence of RIAR and the likely inhibitors of RIAR in cancer cells. The majority of these pathways involved in RIAR pathways are reported to be targeted using various inhibitors. DNA repair is one of the main pathways associated with increased radioresistance; olaparib and berzosertib were used to target DNA repair-associated PARP and ATR [95, 96]. The HR-associated RAD51 and BRCA2 are reported to be targeted using

CYT-0851 and BRCA2 siRNA, whereas the NHEJ repair can be inhibited by targeting DNA-PKcs using LY294002 [97, 98]. MTOR is responsible for the upstream regulation of cell survival pathways, which is reported to be targeted using temsirolimus, whereas BRAF is responsible for the downstream regulation of the MAPK pathway and is reported to be targeted using vemurafenib [99, 100]. The metabolic reprogramming associated with CDK4, CDK6, and EGFR is responsible for ROS and is reportedly targeted by abemaciclib and cetuximab [101, 102]. Inhibiting genomic stability via targeting ATM by fenofibrate and enhancing cell death by inhibiting CHK1 by WEE1 and kinases-PI3K by alpelisib can decrease radioresistance [103, 104].

Despite the development and understanding of the role of high-dose RIAR in radio-residence development, many questions still require further investigation. While DDR and repair signaling pathways activate upon exposure to high-dose exposure (during RT) have been intensively investigated, the similar effects after low-dose radiation exposure are yet to be explored extensively. The tumor cells show little or no response during the initial course of RT, but upon multi-fraction radiation regime, the therapeutic gain is achieved; however, in the conventional multi-fractionated regime, radiation delivery at high dose (2 Gy/fraction) induces cellular adaptations and may probably end up in radioresistance [105]. In line with Olivieri et al. [3] classical definition of RIAR, the PD is reported as a very low dose in the order of mGy. In the modern era of cancer RT (IGRT/IMRT), patients receive low doses while undergoing radiation-based imaging [106]. Based on the literature and our understanding (a low dose is required to induce AR), we are curious to know that such a low dose received at imaging times can induce RIAR. If so, do DNA damage signaling kinases function differently when subjected to high, low, and very low-dose IR exposure? Therefore, the authors believe such an understanding might increase the cancer therapy index by radiation.

Conclusion

Scrutiny of the literature suggests that the RIAR observed in vitro, in animal models, and epidemiological studies manifests as an AD after acute and chronic low-dose exposure. This phenomenon has been reported predominantly in human PBL, normal (human skin fibroblasts, mouse spleen cells, and CHO) and transformed cell lines (mouse mammary carcinoma cell and human leukemic cells), and animal models (*Drosophila melanogaster* and Mouse models) following exposures to isotopes of tritium, X- and γ-rays, RF waves, and high LET particulate radiations. The response was heterogeneous among the cell types and doses, dose rate, time gap between the primary and CD, assay methodology, level of induced DNA damage, and DNA repair efficiency. Moreover, this phenomenon is also demonstrated under clinical scenarios, i.e., during multi-fractionated RT, and proposed as a mechanism for developing resistance. Inhibitors mitigating the radiation-mediated AR have shown the promise of therapeutic gain by understanding the pathways and molecules mediating such a response after a high radiation dose. However, the sample type and assay methods to relate the response to overcome resistance remain non-conclusive. Moreover, in the modern era of cancer RT (IGRT/IMRT), patients receive low doses while undergoing radiation-based imaging. Such a low dose received at times of imaging can induce RIAR. If so, do DNA damage signaling kinases function differently when subjected to high, low, and very low-dose IR exposure? Based on the emerging scientific literature, the authors believe, that such an understanding of RIAR might contribute to an increase in the cancer therapy index by radiation.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Aishwarya Thathamangalam Ananthanarayanan: review of literature and preparation of the draft. Venkateswarlu Raavi, Satish Srinivas Kondaveeti, and Ilangovan Ramachandran: draft design, revision, and editing. Venkatachalam Perumal: conceptualization and approval of the final version of the manuscript.

Data Availability Statement

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

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