




Review

Low Dose Ionising Radiation-Induced Hormesis: Therapeutic Implications to Human Health

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Abstract: The concept of radiation-induced hormesis, whereby a low dose is beneficial and a high dose is detrimental, has been gaining attention in the fields of molecular biology, environmental toxicology and radiation biology. There is a growing body of literature that recognises the importance of hormetic dose response not only in the radiation field, but also with molecular agents. However, there is continuing debate on the magnitude and mechanism of radiation hormetic dose response, which could make further contributions, as a research tool, to science and perhaps eventually to public health due to potential therapeutic benefits for society. The biological phenomena of low dose ionising radiation (LDIR) includes bystander effects, adaptive response, hypersensitivity, radioresistance and genomic instability. In this review, the beneficial and the detrimental effects of LDIR-induced hormesis are explored, together with an overview of its underlying cellular and molecular mechanisms that may potentially provide an insight to the therapeutic implications to human health in the future.

Keywords: radiation-induced hormesis; bystander effects; adaptive response; hypersensitivity; radioresistance; genomic instability



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1. Introduction

Radiation hormesis is the phenomena whereby low doses of ionising radiation provoke a stimulatory or beneficial effect in otherwise unstressed cells, but increasingly larger doses are harmful [1]. Epidemiological studies have shown that radiation cumulative doses up to 100 mSv do not show any increases in the incidence of cancer in humans [2]. The range of low, medium and high doses are frequently used to qualify and specify radiation dose levels, and the ranges differ significantly depending on the context. The International Commission on Radiological Protection (ICRP 2007), the Health Risks from Exposure to Low Levels of Ionizing Radiation (BEIR) VII Report 2006, the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR 2006), and the National Council on Radiation Protection and Measurement (NCRP) have adopted 100 mSv or less as low dose [3–6]. Previously, the 2010 UNSCEAR Scientific Report defined low doses as those of ≤ 200 mGy, and low-dose-rate 0.1 mGy per minute (averaged over one hour or less) for external X- and γ -rays. [7]. Recently, the UNSCEAR 2015, Report to the General

Assembly with Scientific Annexes; and Multidisciplinary European Low Dose Initiative (MELODI), a European radiation protection research platform, have defined low doses as those between 10 and <100 mGy and moderate doses from 100 mGy to 1 Gy and >1 Gy as high doses [8–10]. However, radiation protection and radiotherapy treatment strategies differ. Radiotherapy is given with either curative or palliative intent. Curative treatment usually involves the use of much higher doses (deterministic) than those considered in radiation protection with the expectation of prolonged survival to beyond five years in treated patients. From a radiation therapy view, low doses are <0.5 Gy, medium doses are 0.5–5 Gy, high doses are 5–15 Gy, and very high doses are >15 Gy [11].

Ionising radiation (IR), via signals from irradiated cells, can elicit detrimental biological effects such as altering cell functionality, induce mutations in cells to become malignant, or directly induce cell death resulting from DNA damage [12–14]. One significant characteristic property of ionising radiations is that the energy released with ionisation may break up the molecular structure of the substance upon which it falls, thus liberating ions or electrons and other different types of radiation that could induce a succession of cellular damage. Hence, ionising radiation can cause direct or indirect forms of DNA damage. Indirect damage occurs through the generation of reactive oxygen species (ROS) and free radicals through water radiolysis that may damage nucleic acids, oxidise proteins and lipids [12,15,16]. Ionising radiation can also directly affect deoxyribonucleic acid (DNA) structure in the cells by inducing double-stranded breaks (DSBs) that pose a serious threat to genomic stability [16,17]. Radiation-induced DNA lesions can ultimately lead to cell death (such as apoptosis, necrosis, senescence), mitotic failure and mutations if these DNA lesions are not correctly repaired or unrepaired [18,19], the proportion of which depends on the absorbed dose [19,20]. Relative to lower doses of IR, DNA damage is more severe with greater potential for adverse biological effects at higher doses and higher dose rates, as the DNA repair mechanisms become less effective. Similarly, it has been shown that increasing the linear energy transfer (LET) of the particle increases the lethality of the irradiated cells due to the inability of damaged cells to repair clustered DNA damage [21]. However, the beneficial effects of a low irradiation dose (≤ 100 mGy) currently remain unclear and controversial despite reports that several cellular protective mechanisms are stimulated [22].

Annually, it has been estimated that human beings and other living organisms are typically exposed to radiation doses of some few mSv from natural background sources, extra-terrestrial as well as in soil and water [23,24]. Ionising radiations are forms of electromagnetic waves (γ , X-rays) or particles (neutrons, protons, β or α) that are typically used in medical interventions such as diagnostic radiology, nuclear medicine and radiation therapy [23], with other situations of utilisation and exposure arising in industry. With these increasing involvements of radiations, the low-dose ionising radiation (LDIR) effects on humans are of great concern to public health. The main question has been what is the lowest dose threshold that a human could be exposed to without detrimental effects being suffered, both post exposure and for future generations. Previously, the ICRP (1990) and the NCRP (1993) have recommended that the estimates of cancer risk for low-dose exposure be extrapolated from higher doses where the data are principally from the cancer incidence found in survivors of the atomic bombs in Japan [25,26]. There has been a long-standing controversy on determining the lowest dose threshold that could be considered safe for humans. The focus has been on how best to extrapolate cancer risks from high doses to low doses, and since there is much uncertainty concerning the lower dose points, epidemiologic data do not extend to the low doses for radiation protection. Hall and Giaccia (2019) [27] have succinctly described the controversy of the four different types of curves, as shown in Figure 1a–d. Figure 1a assumes that risks are greater at low doses than would be predicted from a linear extrapolation (low-dose hypersensitivity, a quasi-threshold dose) before repair kicks in. Figure 1b demonstrates the linear-no-threshold (LNT) hypothesis that has been much disputed due to the discovery of non-targeted effects that demonstrate a non-linear response at low dose. Figure 1c assumes that there is a threshold in dose, below which

there are no deleterious biologic effects, known as deterministic effects. Finally, Figure 1d shows the hormesis affect with a threshold dose that when exceeded, will have detrimental effects [27].

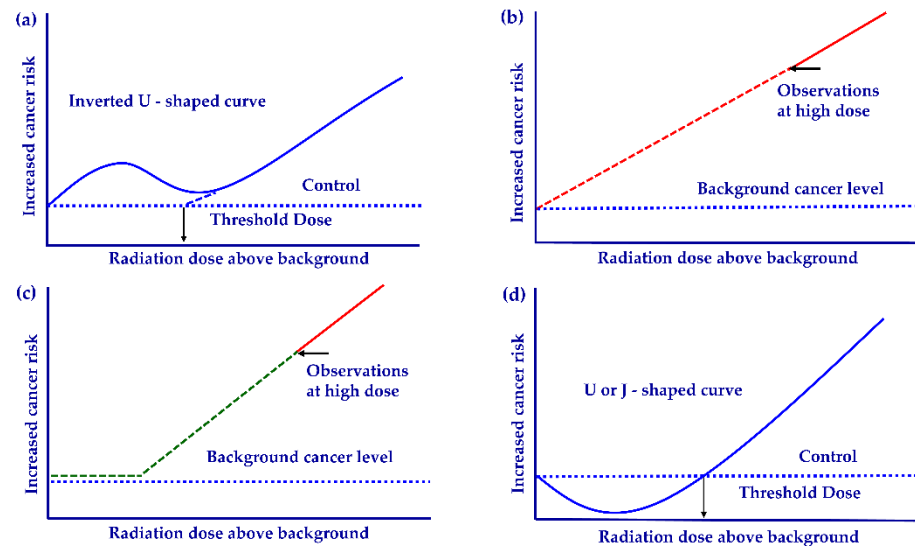


Figure 1. Controversy of extrapolating cancer risks from high doses to low doses characteristic of radiation protection principles (adapted from Hall and Giaccia 8th edition [27]). Legend: Line (a) assumes that risks are greater at low doses than would be predicted from a linear extrapolation; Line (b) illustrates the LNT hypothesis, adopted as the model for radiological protection by BEIR, UNSCEAR, ICRP, and NCRP; Line (c) assumes that there is a threshold in dose, below which there are no deleterious biologic effects; Line (d) illustrates the hypothesis that low levels of radiation are beneficial, activating repair mechanisms that protect against disease, known as hormesis.

Hormetic dose responses are biphasic and are generally represented by a non-linear relationship, either as an inverted U- or J-shaped dose–response curve, which is very much dependent on the endpoint measured [28]. Moreover, different types of radiation, tissue types, dose and dose rate also play important roles [29], albeit below the order of 100 mGy, to protect against genomic instability and cytogenetic damage [30,31]. Additionally, these inverted U- and J-shaped curves contain two thresholds. The inverted U-shaped curve displays the toxic traditional threshold or zero equivalent point, however, when the response crosses the control response, it becomes inhibitory. Conversely, the J-shaped curve (hormesis) demonstrates the lower dose threshold, whereby the stimulatory response decreases and in time reverts to being indistinguishable from the control and with increasing dose results in detrimental effects [28] as shown in Figure 1a,d.

In the 19th century, the biphasic dose–response phenomena were first observed in yeast experiments performed by Schulz, in which a low dose of numerous disinfectants stimulated yeast metabolism. Later, the dose–response theory of Schulz and Arndt was established and became more conceptualised based on their observation that low dose of veratrine was effective in the treatment of gastroenteritis by its biphasic characteristic. This induced the adaptive response of the host, resisting infection but not killing the bacterial itself, hence enhancing survival [32]. The concept has been paraphrased: “sufficiently diluted toxicants should have a beneficial effect on the organism” [33]. In general, many studies have claimed that all toxic compounds may have hormetic effects, where low doses are stimulatory and large doses are harmful.

However, the concept of LDIR-induced hormesis was not well received initially, and provoked considerable discussion since it contradicted the concept of the LNT model as shown in Figure 1b. The concept of LNT proposed that all radiation is harmful, with no threshold, indicating zero dose to be safest. This has been contradicted by the LDIR phenomena (described below). The ICRP has defined LNT as “a dose-response model which is

based on the assumption that, in the low dose range, radiation doses greater than zero will increase the risk of excess cancer and/or heritable disease in a simple proportionate manner" [3]. The dose limits for occupational and public exposures have been guided to be 20 mSv/year and 1 mSv/year, respectively, and national regulatory agencies generally adopt these control levels. The LNT theory has also been endorsed by the BEIR, UNSCEAR, ICRP, and the NCRP [3,4,6,7,26]. To date, LDIR hormesis is controversial and is a much-debated subject even though the therapeutic implications are potentially beneficial to society as depicted in Figure 2. Insufficient clinical findings have resulted in prevailing controversy and scepticism of the scientific evidence of hormetic effects. Hence, there is a need for supportive evidence of LDIR-induced hormesis to underpin claims of benefits in clinical indications. In this review of the literature, we discuss the asserted beneficial and detrimental effects of LDIR-induced hormesis, seeking to provide an insight into any potential therapeutic implications for human health. The LDIR-induced detrimental and hormetic effects are firstly briefly discussed, followed by a review of LDIR phenomena.

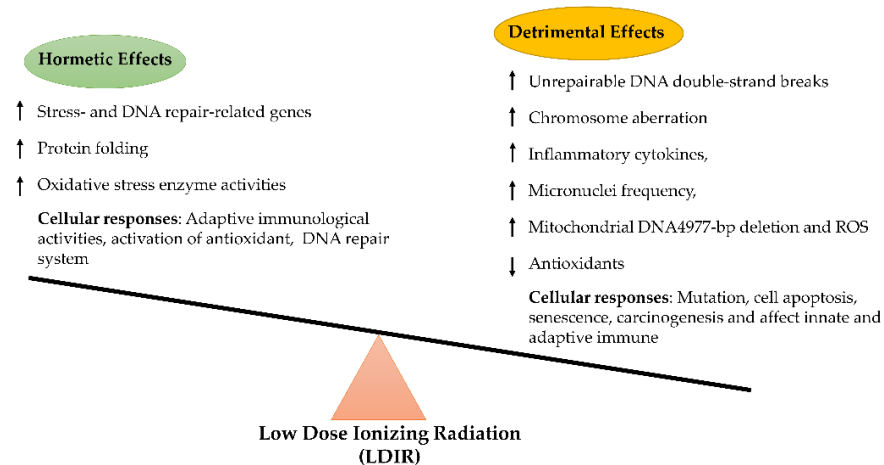


Figure 2. The molecular mechanisms and the cellular responses of low dose ionising radiation.

2. LDIR-Induced Detrimental Effects

In contrast to earlier findings on the bio-positive effects of LDIR, in recent decades, inconsistent and conflicting findings and contradictory data have by default lead to support for the LNT theory. High doses of ionising radiation are harmful to humans and all other living organisms, resulting in a high local yield of unrepaired base damage and unrepairable, complex double strand breaks (DSBs) that result in chromosome aberrations, mutations, cell apoptosis, senescence, and carcinogenesis [34,35]. The known risks of such radiation exposure have rightfully restricted the use of ionising radiation except when used under proper guidelines and regulations of authoritative organisations, controlled for example in medical applications, including X-ray imaging and radiotherapy treatments. Within this, the potential detrimental health effects of LDIR exposure in medical diagnostics and treatments are also treated as being of major concern; this is reflected in the overarching need to ensure that the benefits far outweigh the risks.

A pilot study in occupational exposure to LDIR among medical radiology staff has reported results of cytokinesis-block micronucleus assay and comet assay, showing a higher frequency of nuclear buds and tail length, respectively, among medical workers compared to the control group. At levels of 1.82 ± 3.60 mSv/year, the results indicated poor cytogenetic status and an increase in DNA damage following long-term exposure to LDIR [36]. In another study [37] concerning patients undergoing neuro-interventional radiological procedures, it was reported that this gave rise to an increased risk of DNA damage, as demonstrated by γ H2AX and p53^{Ser15} phosphorylation. The associated levels were found to be increased in peripheral lymphocytes following exposure to relatively low surface entrance doses (9 to 225 mGy), also with DNA damage being influenced by age, fraction

and a sub-population of lymphocytes (variable gene expression pattern) and repair kinetics among individuals. The study also made it clear that, balanced against the potential harmful radiation effects, patients greatly benefit from such procedures. At the same time, it was advocated that the use of ionising radiation in medical diagnosis purposes be carried out at the lowest possible radiation doses, not compromising diagnostic capability [37]. Indeed, many other studies have reported similar findings, not least concerning the occupational low dose exposures to ionising radiation, especially in healthcare workers. Reports have been concerned with long-term and adverse health effects, including increased levels of inflammatory cytokines, increased micronuclei frequency, reduced antioxidants and increased mitochondrial DNA4977-bp deletion [38–40]. These apart, several lines of evidence also suggest that there are negative biological effects of LDIR in cells and animal models. Low-dose ionising radiation has been demonstrated to affect innate and adaptive immune responses by attenuating mast cell migration through inhibition of monocyte chemoattractant protein-1 (MCP-1) expression by Nr4a2 [41]. Figure 2 shows the molecular mechanisms and the cellular responses of LDIR-induced detrimental effects.

3. LDIR-Induced Hormetic Effects

Cells in the human body are continuously exposed to free radicals and/or other ROS from normal essential metabolic processes that arise as a consequence of oxidative stress. Conversely, externally generated ROS are commonly due to exposure to radiation, cigarette smoking, industrial chemicals, air pollutants, and other substances that are known carcinogens at chronic and acute levels of exposure. It has been postulated that low dose radiation is essential to life, acknowledging that the natural production of free radical and formation of ROS is linked to a suggested triggering of DNA damage repair as a protective mechanism. This might well lead to a counteracting of deleterious effects that can prevail at more elevated radiation exposures, as well as other potential future damage [2,42]. Of associated note is that some naturally occurring radioprotectors are to be found within the diet [43,44]. The situation is rather more complex, not only involving enhanced exposures, as well expressed in the early 16th century by Paracelsus, a Swiss alchemist also arguably the first toxicologist, recording that “All things are poison and nothing is without poison; only the dose makes a thing not a poison”. The suggestion that adverse effects occur in exceeding certain doses is the more commonly understood of two underpinning potentialities, including in regard to the intake of essential molecules such as water and vitamins. In regard to radiation exposures, a cue to the less well discussed potentiality of harm from suppressed levels arises from the fact that all drugs work in a similar way. Drug overdose results in the depletion of the natural protecting enzymes or substances in the human body, that of paracetamol overdose resulting in depletion of glutathione, commonly needing the intravenous administration of glutathione. This has prompted radiobiology experiments that have not only been conducted at moderately enhanced radiation exposures but also at manifestly suppressed levels, as discussed in some detail below.

Several studies in yeast cells, protozoan, algae, bacteria, and rodent cell cultures have demonstrated the potential deleterious biological effects from suppressed levels of ionising radiation. The conditions for background radiation suppression are to be found in deep underground laboratories (e.g., the Laboratori Nazionali del Gran Sasso in L’Aquila, Italy) not least those established for high-energy particle physics experiments requiring improved signal-to-background ratios. In regard to the radiobiological investigations, observed effects have included lower cell numbers, increased generation time, greater sensitivity to mutational damage, increased apoptosis, up-regulated oxidative stress-related enzymes and an increased mutation rate [45–48]. Similarly, in a salt mine at some depth below the surface (with salt structures resulting in already known very low levels of 238 U, 232 Th and 40 K, manifesting at parts per billion (ppb) levels compared to the typical surface levels of parts per million (ppm) and more), Castillo and Smith reported the radiation deprivation effects of normal growth rate in bacteria cultures (*Shewanella oneidensis* and *Deinococcus*

radiodurans). For dose rates of 72.05 (control) and 0.91 (treatment) nGy/hr and exposure durations of up to 72 hr, an association has been made with an increase in intracellular ROS [49,50]. The stress- and DNA repair-related genes were found to be upregulated as a biological response, repairing DNA damage to maintain survival. Converse to these have been the experiments conducted at altitudes, providing for enhanced levels of cosmic radiation, indicating potential stimulatory effects to protozoa paramecia [45].

In another study, at a γ -irradiation dose of 50 cGy compared to 4 Gy, it was shown that LDIR effectively alleviates amyloid- β 1-42 (A β 42)-induced cell death via regulating AKT and p38 pathways in drosophila Alzheimer disease (AD) models, suggesting a potential hormetic effect in treating AD [51]. This concurred with the findings of Lowe et al. (2009) who analysed the transcriptome profiles of mouse brain tissue, previously whole-body irradiated with 10 cGy. They identified nine neural signalling pathways that are concordant in the irradiated mouse brain tissue, in the aging unirradiated human brain, and in Alzheimer's disease patients brain tissue. They indicated that 10 cGy exposure-induced molecular response involved the down-regulation of neural pathways associated with cognitive dysfunctions that were similarly down-regulated in normal human aging and Alzheimer's disease [52]. The underlying molecular mechanism of the hormetic effect is commonly associated with the increase in antioxidant activity, and accordingly, in the immune system. In Wistar rats, Sharma et al. (2019) have investigated LDIR exposures at a dose of 20 cGy (moderately low dose [4]), with the rats subsequently sacrificed 6 h and 24 h post-irradiation. Significant elevations of endogenous antioxidant activities such as catalase and glutathione-S-transferase were noted, accompanied by an increase in whole blood lymphocytes and eosinophils, indicative of an immune defence mechanism [53]. This sub-lethal radiation dose has been known to trigger a protective mechanism against stronger toxicity in subsequent stress events. In a recent study, thiocyanate (SCN⁻), a biomolecule that acts as a natural antioxidant in the immune system, was found to be increased in the saliva of 10 healthy orthodontic patients (age 12–17 years) subsequent to exposure to LDIR effective doses of 0.174–0.256 mSv, delivered during cone beam computed tomography (CBCT), inferring that LDIR may exert protective effects by activating the natural antioxidant system [54]. In addition, LDIR (0.1 Gy, γ -radiation) has also demonstrated a bio-positive effect in reducing the transformation of thyroid cancer cells by restoring the thyroid metabolising genes expression, PAX8 and suppressing thyroid cancer carcinogenesis by inhibiting STAT3-miR-330-5p pathways in both cells and a mouse model [55]. Moreover, other experimental studies have demonstrated that the hormetic effects of LDIR only occur in normal cells or tissues and not in malignant cells [56–58]. Furthermore, LDIR could also induce cell proliferation in normal cells via the Mitogen-Activated Protein Kinase (MAPK)/ERK signalling pathway, while p53 activation in cancer cells could induce cell cycle arrest or apoptosis, as shown in Figure 3.

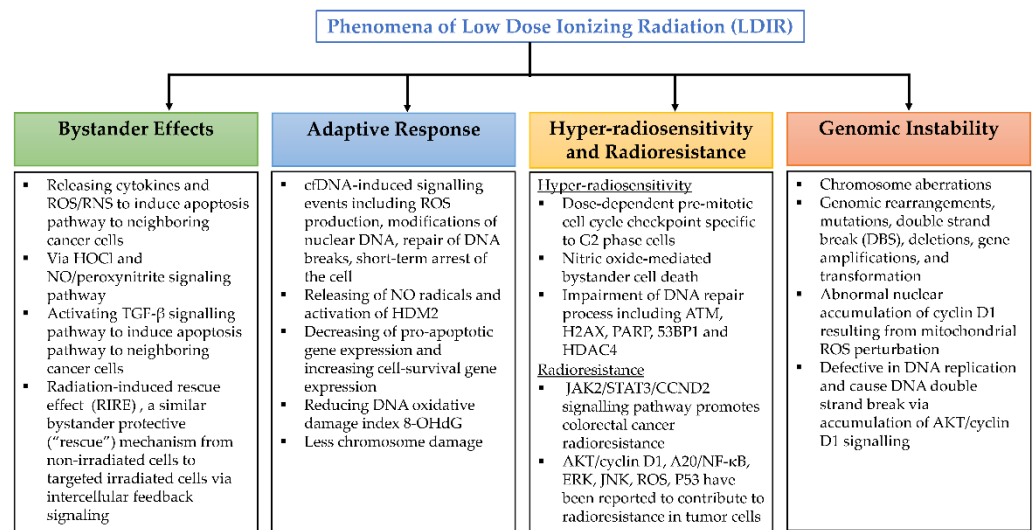


Figure 3. The underlying mechanisms for the phenomena of low dose ionising radiation.

Reviews of the beneficial effects of LDIR, also addressing the risk of carcinogenesis and the need for a re-assessment of the LNT model, have been published over the past 20 years and beyond, mainly by Luckey and Calabrese [32,33,59,60]. Not only have these reviews provoked controversy between evidence supporting an hormetic dose response versus the LNT risk model, but they have increasingly revived interest in exploring the evidence base for bio-positive effects of LDIR in epidemiological, animal model, and clinical studies [61–63]. These papers also discussed the underlying protective mechanisms of LDIR such as enhanced DNA repairs, increased protein folding and the upregulation of oxidative stress enzyme activities, resulting in induced cellular effects such as adaptive response, immunological activity and bystander effects. However, these reviews are not comprehensive nor exhaustive. There is a lack of description and discussion of studies involving bystander effects, adaptive response, hypersensitivity, radioresistance and genomic instability, matters now deliberated in this article.

4. The Phenomena of LDIR

Thus far, we introduced evidence for both the beneficial and detrimental effects induced by LDIR. The underlying biological responses of LDIR giving rise to several distinct phenomena have gained increasing attention and could provide better understanding of the potential impact of LDIR on human health, both detrimental and beneficial. The five phenomena [64–66] that have been reported to be associated with LDIR are: (1) bystander effects; (2) adaptive response; (3) hypersensitivity; (4) radioresistance; and (5) genomic instability, as displayed in Figure 3.

4.1. Bystander Effects

A large number of published studies have described the biological effects of LDIR, seen not only in irradiated cells but also in non-irradiated cells or non-targeted cells, arising as a consequence of radiation events which induce various signalling pathways [67–71]. This phenomenon is known as the bystander effect (BE), invoking biological effects through intercellular communications. Cell-to-cell interaction via gap junctions, protein mediators and signalling molecules released into a medium play a significant role in the BE, be it protective or detrimental, depending on the different cell types and their different responses [66,72]. Nitric oxide (NO), a signalling molecule, has been reported to play a role in the bystander response, inducing an increase in radioresistance in non-irradiated human wild-type p53 glioblastoma cells co-cultured with the medium of the cells irradiated with accelerated carbon-ion beams and/or X-ray irradiation [73,74]. Moreover, it has

also been shown that an NO-mediated bystander response stimulates cell proliferation and micronucleus (MN) formation in nonirradiated human salivary gland tumour cells irradiated with 290 MeV/u carbon ions, dependent on the LET used [75]. On the other hand, Portess et al. (2007) and colleagues, Abdelrazzak et al. (2011) have demonstrated a natural anticancer mechanism through the bystander effect, by showing the LDIR of both low and high LET stimulates anti-carcinogenic effects in irradiated non-transformed cell (fibroblasts, 208F rat cells) by releasing several signalling species such as cytokines and ROS/reactive nitrogen species (RNS) that eventually lead to apoptosis in the transformed 208Fsrc3 cancerous cells [76,77]. The transformed 208Fsrc3 cells were stably transfected with the src oncogene, resulting in excessive nicotinamide adenine dinucleotide phosphate (NADPH)-mediated superoxide anion generation in order to maintain its transformed state and proliferation. The data showed that the irradiation of non-transformed cells with low doses of 2 mGy γ -rays and 0.29 mGy α -particles was sufficient to stimulate transformed cell apoptosis through the activation of the transforming growth factor beta (TGF- β) signalling pathway. The activated TGF- β in turn stimulates the production of peroxidase and NO, resulting in a selective removal mechanism for the transformed cells; the membrane-bound NADPH oxidase is constitutively expressed and superoxide anion is produced as the targeting ROS/RNS-induced apoptosis signalling pathway [76,77]. Conversely, the release of peroxidase and NO by surrounding non-transformed cells are known to play a pivotal role in eliminating transformed cells through the classical intercellular induction of the apoptosis pathway, hypochlorous acid (HOCl) and NO/peroxynitrite signalling [78].

However, the BE has also been proposed as a risk-enhancing phenomenon, resulting in more harmful effects from irradiated cells to its neighbouring cells via cell-to-cell interactions [79,80]. It has been suggested that the irradiated cells may exert its bystander effect to distress the adjacent cells (extracellular) by activating a series of cellular signalling cascades such as interleukin-8, which correspond to an increased production of ROS [81], and the TGF β 1 (cytokine) pathway, activated by radiation, orchestrates multicellular response to damage triggering inflammatory and immune response [82]; and chemokines (CCL5 and CCL11) that influence the immune system [83] by recruiting leucocytes such as T cells, macrophages, eosinophils and basophils, a tumour promoter inflammatory mediator [84,85]. Studies have demonstrated that a high frequency of chromosomal aberrations and micronucleus formation were observed in the bystander effect induced by α -particles (^{241}Am) in human blood lymphocytes [86]. The degree of DNA damage induced by BE has been reported to be greater in high LET radiation compared to low LET such as X-rays and that it is cell type- and dose-dependent [86].

In 2011, Chen et al. demonstrated a new phenomenon known as “radiation-induced rescue effect” (RIRE), where the bystander cells rescued the irradiated cells through intercellular signal feedback, reducing the cytotoxicity and genotoxicity induced by ionising radiation. The study showed that α -particle-irradiated cancer (HeLa) cells were rescued by unirradiated bystander primary human lung fibroblast (NHLF) in two-cell co-culture systems after 24 h irradiation at doses of 20 or 40 cGy [87]. This finding has raised concerns over the efficiency of treatment of cancers using ionising radiation being compromised due to the rescue effect from unirradiated normal cells, as RIRE demonstrated a protective bystander effect [87–89]. Moreover, there are two types of RIRE, whereby Type 1 RIRE shows reduced detrimental effects on targeted cells upon receiving feedback signals from bystander cells [87,88], while Type 2 RIRE exacerbate the detrimental effects in targeted cells upon receiving feedback signals from bystander cells [88,90,91]. Both the protective or the detrimental phenomena of BE are dependent on several factors, such as the types and characteristic of the bystander cells and the species of bystander factors, types and qualities of radiation, the biological endpoint and the radiation dose [88,89].

4.2. Adaptive Response

Adaptive response (AR) is the existence of radioprotective mechanisms (stress response) that are upregulated in response to small doses of conditioning ionising radiation

exposure (<30 cGy); this could protect against a separate subsequent irradiation larger than the initial dose [92]. Joiner et al. (1996) have reported that there is indirect evidence that the low-dose hyper-radiosensitivity (HRS) and induced radioresistance (IRR) in response to single doses is a manifestation of the same underlying mechanism that determine AR in the two-dose case, irrespective of high or low LET as well as a variety of other stress-inducing agents [92]. It has been reported that the underlying AR mechanisms include the transcription of genes, the activation of diverse signalling and stress response pathways that trigger cell defences such as enhanced DNA repair systems, the induction of protein synthesis, enhanced detoxification of free radicals and antioxidant production, cell survival/death pathway (apoptosis), endoplasmic response to stress, cytoprotective processes including autophagy, cell cycle regulation, unfolding of proteins, and enhanced immune/inflammatory response and the suppression of genomic instability in animal and human cells (see references [93–96]). Generally, the AR is defined as a protective phenomenon induced by an LDIR of ≤ 10 cGy, as demonstrated in the use of ^{137}Cs or ^{60}Co γ rays delivered at ≤ 0.2 cGy/h [94]. Adaptive response is known to be highly variable and is influenced by radiation quality, dose and dose-rate, cell types, tissues, systems, organisms and individuals [97–99]. However, Bannister et al. (2016) demonstrated that both C57BL/6 and BALB/c mice bone marrow erythrocytes did not show any radio-adaptive response of induction of cytogenetic damage or suppression of erythrocyte proliferation/maturation index in the bone marrow of the mice when exposed to γ irradiation low priming single doses of 20 mGy or 100 mGy or multiples of 20 mGy that were administered at various times prior to 2 Gy radiation [100].

Olivieri and colleagues (1984) first observed AR in human lymphocyte cultures, where cells were pre-exposed to low-level chronic radiation with [^3H] thymidine before second exposure to a greater radiation level of 150 cGy of X-rays. As a result, the lymphocyte cells that were previously pre-exposed to low-level chronic radiation yielded less chromatid aberrations in the second challenge doses compared to those exposed separately [101]. With this encouraging finding, a considerable amount of literature over the last three decades has suggested similar phenomena in both in vitro and in vivo studies. A more recent study has highlighted that oxidised cell-free DNA (cfDNA) fragments, released from irradiated mesenchymal stem cells, play a pivotal role as a stress mediator to signal to the other living cells to invoke an adaptive response induced by an LDIR of 10 cGy [102]. These cfDNA fragments were released from apoptotic cells, that penetrated into the cytoplasm of other cells to induce radio-adaptive responses and bystander effect through a cascade of cfDNA-induced signalling events including ROS production, modifications of nuclear DNA, repair of DNA breaks and short-term cell-cycle arrest of the cell. This series of events eventually leads to the activation of DNA repair systems, antioxidant response, and the inhibition of apoptosis as part of the development of the protective response in which cells can rapidly adapt to future challenges. In addition, NO has also been shown to be responsible in the adaptive response post irradiation with a challenging irradiation of 6 Gy subsequent to a priming irradiation of 0.02 Gy through the activation of HDM2 and the depression of p53 accumulations in wild-type (wt) p53 [103,104]. Epidemiological studies from Guangdong, China (2018), have reported that adaptive responses, such as increasing DNA damage-repair capacity and antioxidant production could contribute to the lower cancer mortality rate in those low-dose high-background-radiation areas [105]. The blood samples of male resident (50–59 years old) analysis data also indicated a lower expression of pro-apoptotic gene mRNA, enhanced cell-survival gene expression and lesser DNA oxidative damage index 8-Oxo-2'-deoxyguanosine (8-OHdG) in high-background-radiation areas, as compared to the control population. In another recent epidemiology study from India (2016), individuals exposed to >5.0 mGy/year showed a significant decrease in chromosome damage, as indicated by cytokinesis-block micronucleus assay, when their blood samples were further challenged to 1.0 Gy and 2.0 Gy doses, as compared to individuals from normal-level natural radiation area [106]. Recently, in vivo animal studies have demonstrated that there are three dose thresholds for protective adaptive

responses to be initiated. The upper dose threshold is where low radiation doses increase to the point where they no longer elicit a protective response; however, the lower dose threshold below which the dose would no longer be able to initiate the cellular protective mechanisms (as it has not been irradiated) seen at the more elevated low doses [107]. Zeng et al. (2006) were the first to demonstrate a non-linear chromosomal inversions mutation in the prostate cells of mice following exposure to various ultra-low doses of 0.005–0.01 mGy X-ray doses. It was reported that a dose of 1 mGy produced a protective response and reduced spontaneous inversion, but a dose of 0.01 mGy did not, and actually increased spontaneous inversion frequency [108]. Recently, Hou et al. (2015) performed a gene profiling characterisation of AR in AGO1522 human fibroblasts exposed to 5 cGy (priming dose), followed by 2 Gy of X-rays, identifying gene transcripts or pathways associated with reduced micronuclei. mRNA and microRNA microarrays were used to detect altered genes and they also demonstrated that cell communication and intercellular signalling transduction played important roles after low-dose irradiation [109]. Taken together, studies of chronic LDIR exposure both in in vitro and in vivo have demonstrated LDIR as an important priming dose to induce radio-adaptive response in cells against subsequent exposure of higher radiation doses.

4.3. Low-Dose Hyper-Radiosensitivity and Increased Radioresistance

Joiner et al. (2001) have reported that most cell lines exhibit hyper-radiosensitivity (HRS) to very low radiation doses (<10 cGy), not being predicted by back-extrapolating the cell survival response from higher doses. Additionally, as the dose is increased above 30 cGy there is increased/(induced) radioresistance (IRR), up to doses beyond ~1 Gy [110]. This phenomenon of HRS precedes the occurrence of IRR to cell killing by radiation over the dose range from ~0.5 to 1 Gy, and generally HRS is observed in cell lines that are radioresistant to 2 Gy doses, albeit not all cell types [110]. It is therefore appropriate that we describe these two phenomena together.

Briefly, HRS refers to low-dose hyper-radiosensitive cells which die from a single LDIR that is between 0.1–0.3 Gy, due to the failure of the irradiated cell to trigger the repair mechanism [110–112], resulting in cell death. However, not all cells are hyper-susceptible to radiation, mainly depending on the different types of cells and also on the cell-cycle phase. Evidence of low-dose HRS in different cell types has been shown when human embryonic lung fibroblasts and lung cancer cells are exposed to the same range of low dose X-rays (20–100 mGy) [57]. When exposed to a low dose (50 mGy), a significant cell apoptosis rate was observed in the lung cancer cells compared to the normal human lung fibroblasts, demonstrating lung cancer cells to be extremely sensitive to LDIR [57]. This low-dose HRS characteristic may have important implications in cancer radiotherapy. Marples et al. (1997) [111] reported that low-dose HRS occurs in mammalian cells at doses as low as <0.3 Gy but radioresistance is found with higher doses, at 1 Gy and above [111–113]. The mechanisms involved were proposed to be associated with a three-component model, consisting of damage recognition, signal transduction, and damage repair [114]. The key control element that influences low-dose HRS in irradiated cells has been attributed to the dose-dependent pre-mitotic cell cycle checkpoint specific to G2 phase cells when exposed to an extreme low-dose radiation environment. In his review, Marples conceptualised a G2-centric concept of low-dose HRS that is exclusively associated with the survival response of cells in the G2 phase of the cycle but not in G1 or S phase cells [112]. The underlying mechanism of low-dose HRS has been partly attributed to the evasion of several cellular responses to the DNA repair process, including ATM, H2AX, PARP, 53BP1 and HDAC4 [114–116], and presumably affecting high-fidelity recombination repair. Moreover, Maeda et al. (2008) reported nuclei-only irradiation rather than the irradiation of the complete cell of V79 cells using synchrotron X-ray microbeam-induced HRS, suggesting that energy deposition in the cytoplasm might suppress HRS [117]. Maeda et al. (2013) also show that NO, a principal mediator of the induction of bystander cell death secreted by the irradiated cells, participate in mechanisms that suppress mutagenesis

by selectively killing those genetically unstable cells that have defects in their antioxidative activity [118]. Additionally, other factors such as the cellular environment, cell-to-cell contact, nutritional deprivation, and cell density have also been shown to play a significant role in the hyper-radiosensitivity of cells [65].

Conversely to the above, IRR refers to the phenomenon in which cells may become resistant to a higher radiation dose after exposure to a smaller dose of ionising radiation. A radioresistant response is seen as the radiation exposure dose is increased up to approximately 1 Gy, whilst most of the cells exhibit low-dose HRS when exposed to a single low radiation dose (below 0.1- to 0.3 Gy) [65,111]. In recent decades, efforts have sought to deal with the increased radioresistance of cancerous cells, which poses a major challenge to radiotherapy as DNA damage-repair and survival signalling mechanisms are activated, revealing the presence of a protective mechanism to alleviate radiation-induced cytotoxic effects [119]. Moreover, evidence has indicated that the radioresistant cells proliferate and survive with a more aggressive phenotype than their parental cells due to genetic mutation [120,121]. Experimental studies of colorectal cancer stem cells have indicated that the JAK2/STAT3/CCND2 signalling pathway is responsible for the radioresistance, while knocking down the long non-coding RNA TINCR was found to decrease radioresistance in colorectal cancer cells [121,122]. Note though that tumour stem cells exhibit the intrinsic characteristics of radioresistance, whereby the damaged DNA can be immediately repaired by the alteration of the DNA repair pathway involving DNA replication in the S phase. Thus, the genomic stability of the entire tumour population is sustainable and resistant against low radiation dose via an increase in the DNA repairing efficiency, with this in turn via the homologous recombination-mediated DNA repair process [123]. Other pathways, including the AKT/cyclin D1, A20/NF- κ B, ERK, JNK, ROS, and p53, have been reported to contribute to the radioresistance in tumour cells, therefore targeting these signalling pathways could act as an effective therapeutic strategy to overcome some of the poor clinical outcomes of radiotherapy [64,124,125].

4.4. Genomic Instability

Low dose ionising radiation that induces genomic instability has received considerable attention. Genomic instability is defined as an increase in the frequency of mutations and chromosome aberrations induced by radiation and is not only observed in irradiated cells but also the progeny of irradiated cells even in the subsequent multiple generations [126,127]. The impact of radiation on cytogenetics is potentially large, especially when considering not only chromosome aberrations but also mutagenesis and carcinogenesis as among the leading causes of human genetic disease. These chromosome aberrations may include genomic rearrangements, mutations, DBSs, deletions, gene amplifications, and transformation [128,129]. In severe events, the unrepaired cells may undergo cell death and mutation which results in cancer. More recent evidence of genomic instability induced by LDIR have clearly been seen in human peripheral blood lymphocytes [130]. High energy linear accelerator radiation at low doses from 0.1 to 0.5 Gy have shown a significant number of dicentric chromosomes, while increased micronuclei frequency has been observed for irradiations in the range of 0.1 to 2 Gy, and acentric chromosomes have been apparent at 2 Gy, indicating the damaging effects induced by LDIR [130]. Furthermore, mitochondria appear to be positively related to genomic instability, which may lead to vascular disease, neurodegeneration, ageing, and carcinogenesis. With 0.01 Gy/fraction and 0.05 Gy/fraction exposures in human fibroblasts, Shimura et al. (2016) recently demonstrated the genomic instability induced by chronic low-dose fractionated radiation (FR), this being strongly associated with the abnormal nuclear accumulation of cyclin D1 resulting from mitochondrial ROS perturbation [131]. Chronic low dose FR not only decreases cellular antioxidant activity in human cells, but also releases excessive ROS to cellular environments. Mitochondria are the target organelle for low dose radiation and mitochondrial ROS is identified as the causal factor that leads to serious subsequent oxidative damage. In this case, the accumulation of ROS from mitochondria has been linked to cycle perturbation

where protein phosphatase PP2A activity is inhibited, subsequently triggering a disruption in the normal negative feedback control of AKT/cyclin D1 signalling in cells [131]. Ultimately, the abnormal nuclear accumulation of cyclin D1 causes defects in DNA replication and results in DNA double-strand breaks and the genomic instability that is associated with growth retardation and cellular senescence [132].

5. Implication of Radiation Hormesis for Potential Therapeutic Study

5.1. Cancer

The hormetic effect of LDIR has been reported to promote growth and development, also to suppress the ageing process, enhancing immune functions, and delaying cancer progression [133,134]. The hormetic effect of LDIR on the immune system has a potential positive impact on human health and has attracted the attention of many scientists. Over the past two decades, radiation hormesis has been extensively studied by researchers, both in regard to animal and clinical studies. In the case studies by Kojima et al. (2017) [135], two prostate cancer patients who were treated with repeated low-doses of X-ray irradiation resulted in an immediate decrease in the level of prostate-specific antigen. High-dose radiation usually results in localised and sometimes systemic immune suppression [136]. However, LDIR induces a series of immune hormesis, modulates a variety of immune response processes and exerts its hormetic effect in normal stem cells [134,137,138]. Evidence has also indicated that LDIR treatment is effective in treating immune-related diseases by increasing the immune defence system in the body [139–141]. Several studies (at <75 mGy) have also demonstrated that the hormetic effect of X-rays can induce a significant increase in cell proliferation, including rat mesenchymal stem cells, bone marrow hematopoietic progenitor cells and neural stem cells [138,142,143]. Furthermore, Liang et al. (2016) have evidence on the hormetic effect of LDIR, in which 50 mGy of X-ray radiation induced cell proliferation in human embryonic lung fibroblasts but not in cancer cells via the ERK1/2 and AKT signalling pathway. This points to the potential significance of LDIR in protecting normal tissues from radiotherapy without diminishing the efficacy of tumour radiotherapy [57].

5.2. Inflammatory and Proliferative Diseases

There is a long history of research into radiation-induced inflammatory and proliferative diseases. While cancer is one of the well-known consequences of ionising radiation, evidence has also been accrued showing that ionising radiation can induce inflammatory and other proliferative diseases even after exposure to sub-lethal doses [144]. Conversely, an increasing number of reports in the literature have explored the contradictory findings of LDIR, exploring its potential therapeutic effects in treating various inflammatory and proliferative diseases, particularly for the treatment of inflammation-related disorders, including gas gangrene, sinus infections, arthritis, tendonitis, and serious inflammatory lung conditions [145–147]. The natural radiation sources that account by far for the background radiation found in soil, water and air includes radon. It has been discovered that radon (a naturally occurring gas, found for instance at elevated levels in abandoned mines and spas) and ultra-low doses of X-ray and γ -ray exposures and β/γ exposures from uranium-bearing rocks offer an effective low-dose radiation therapy strategy to treat chronic inflammatory and proliferative diseases [148]. The mechanism by which LDIR modulates the inflammatory processes involves its immunomodulatory properties. Endothelial cells are known to play a pivotal role in regulating proinflammatory responses by recruiting the immune cells from peripheral blood to the inflammation side [149]. Schröder et al. (2019) indicated that a single low dose of X-ray radiation exposure (0.01–0.05 Gy) can result in non-linear dose-dependent effects in stimulating pro-inflammatory cytokines from endothelial cells including IL-8; G-CSF and PDGF-BB [150]. Several other in vitro studies have also revealed the anti-inflammatory effects of LDIR, including the reduction in leukocyte adhesion to endothelial cells, activation of the antioxidative system, decreased expression of inducible nitric oxide synthase (iNOS), and enhanced phagocytosis

by macrophages in cells. In vivo studies have found that doses from 0.1 to 0.2 Gy have significantly increased CD8+ T cell production, reduced lung metastases from implanted syngeneic L1 sarcoma cells and increased NK cell numbers [151,152].

5.3. Diabetes

Diabetes mellitus is a condition known to be associated with major risk factors for cardiovascular diseases, the incidences of which continue to increase globally. Recent studies have shown that excessive oxidative stress caused by an increased production of ROS, particularly superoxide anion and its derivatives, may account for its pathogenesis, including several complications observed in the early stages of diabetes. Reactive oxygen species play important pathological roles in cardiovascular diseases due to their abilities to alter the function of specific cellular proteins and enzymes, which eventually leads to alteration in the expression of pro-inflammatory molecules and endothelial dysfunction. As described earlier, one of the mechanisms by which LDIR exerts its protective effects is strongly associated with increased antioxidant activities. Consequently, LDIR has been used as an experimental tool in studying the development of diabetes and in the prevention or amelioration of diabetic cardiovascular complications. Animal studies have demonstrated that the anti-diabetic effect of low-dose-rate gamma radiation can ameliorate type II diabetes, at least in part through the increased insulin secretion and pancreatic superoxide dismutase activity [153]. In addition, it has been found that the repetitive exposure of diabetic mice (type I and type II) to whole-body low dose rate X-ray radiation at 0.025 or 0.050 Gy produced remarkable results in alleviating diabetes-induced renal oxidative stress damage and inflammation. This is reported to arise through the increased expression of AKT and renal nuclear factor Erythroid 2-related factor-2 (Nrf-2), a key regulator of cytoprotective responses to oxidative stress [154,155]. Animal data have indicated that the bio-positive effect of LDIR in diabetes is not only obtained in terms of enhanced insulin sensitivity but also leads to significantly reduced complications, especially in diabetic nephropathy and dyslipidaemia and cardiomyopathy through Akt/Nrf2-mediated antioxidant signalling pathways [154–156]. Clearly, it would not be ethical nor practical to irradiate humans solely for this purpose, especially because of the risk of carcinogenesis (which may be underestimated in small animal experiments), but the development of surrogate drugs might confer therapeutic benefits. Moreover, mice immune systems may not adequately reflect human immune systems. Nevertheless, the results of Yamaoka et al. (2004) [157] support the concept of LDIR protection against diabetes and its complications through the induction of antioxidants. However, it also needs to be mentioned that lifestyle changes and carefully designed targeted drugs are known to achieve effective results.

6. Discussion

A summary of both the hormetic and detrimental effects of LDIR and its underlying cellular and molecular mechanisms have been discussed. Low-dose radiation exposures can be used as an experimental tool to induce bio-responses such as the bystander effect, adaptive response, HRS, radioresistance, and genomic instability. Notably, the distinct biological effects of LDIR can be seen to be different in normal and cancerous cells. It has been shown that LDIR exerts its hormetic effect through its increased DNA repair efficiency, the antioxidant capacity, and the stimulated immune responses—albeit confined to in vitro studies; however, in vivo evidence is currently insufficient. In view of present-day radiotherapy that utilises photon, neutron, proton, and C-ions, it should be noted that radiation hormesis is also dependent on the LET of the radiation modality [75,86,88,89,92,97,98]. While it is clear that very a low dose of both low and high-LET radiation can result in the perturbation of intra and inter-cellular signalling and potentially produce protective effects, such as apoptosis in transformed pre-cancerous cells [77], the pattern of energy deposition is very different. For low-LET radiation down to approximately 1 mGy, essentially all cells will be traversed, on average receiving a similar dose and therefore damage (with some variability due to the stochastic nature of the interactions). However, for high-LET particles,

such as α -particles, the same average dose to the cell population would result in the vast majority of the cells not being traversed, but the small fraction of cells that are traversed will receive a significant amount of damage along the path of the traversing particle, due to the high average dose of that particular cell. Interestingly, data suggest that the fraction of cells traversed is important in determining whether signalling within the cell population as a whole is perturbed [77]. Thus, further studies are required to rigorously determine the circumstances of how the low dose radiotherapy of both low and high LET may be used to maximise its bio-positive effects while preventing the cellular and molecular signalling pathways that could potentially contribute to the bio-negative effects of LDIR treatment. Hormesis has mostly been supported using *in vitro cell* culture and lower invertebrate models. Therefore, a survey of animal models (including vertebrate and invertebrates) and occupational radiation workers exposed to low-dose IR, demonstrating life-span changes, cancer, and other metabolic disease risks would be important to develop a consensus on IR-induced hormesis and would benefit this field by addressing the prevailing controversies. However, epidemiological studies on radiation workers will be particularly challenging due to the need to deal with multiple confounding factors and the large numbers needed. Furthermore, this aspect of radiobiology is controversial and requires further discussion and debate in order to determine how future research should be conducted. In addition to animal studies, future epidemiological investigations with large sample sizes are also required to provide further evidence of potential clinical application for treating human diseases. In particular, the development of sensitive biomarkers may be crucial for the detection of early pathophysiological changes induced by LDIR.

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Abbreviations

8-OHdG	8-hydroxydeoxyguanosine
A β 42	amyloid- β 1-42
AD	Alzheimer disease
AR	adaptive response
BE	bystander effect
BEIR	biologic effects of ionising radiation
CBCT	cone beam computed tomography
CCL5	chemokine C–C motif ligand 5 (also known as RANTES)
CCL11	chemokine C–C motif 11 (also known as eosinophil chemotactic protein)
cfDNA	cell-free DNA
DNA	deoxyribonucleic acid
DSB	double-strand break
ERK	extracellular-signal-regulated kinase pathway
FR	fractionated radiation
Gy	gray

HOCl	hypochlorous acid
HPRT	Hypoxanthine–guanosine phosphoribosyl transferase
HRS	low-dose hyper-radiosensitivity
ICRP	International Commission on Radiological Protection
iNOS	inducible nitric oxide synthase
IR	ionising radiation
IRR	induced radioresistance
LDIR	low dose ionising radiation
LET	linear energy transfer
LNT	linear-no-threshold
MAPK	mitogen-activated protein kinase
MCP-1	monocyte chemoattractant protein-1
MELODI	Multidisciplinary European Low Dose Initiative
MN	micronucleus
mSv	millisievert
NADPH	nicotinamide adenine dinucleotide phosphate
NCRP	National Council on Radiation Protection and Measurement
NHLF	human lung fibroblast
NO	nitric oxide
Nrf-2	nuclear factor erythroid 2-related factor-2
ppm	parts per million
ppb	parts per billion
RIRE	radiation-induced rescue effect
RNS	reactive nitrogen species
ROS	reactive oxygen species
SCN [−]	thiocyanate
TGF-β	transforming growth factor beta
UNSCEAR	The United Nations Scientific Committee on the Effects of Atomic Radiation
Wt	wild type

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