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Low-dose or low-dose-rate ionizing radiation–induced bioeffects in animal models

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ABSTRACT

Animal experimental studies indicate that acute or chronic low-dose ionizing radiation (LDIR) (≤100 mSv) or low-dose-rate ionizing radiation (LDRIR) (<6 mSv/h) exposures may be harmful. It induces genetic and epigenetic changes and is associated with a range of physiological disturbances that includes altered immune system, abnormal brain development with resultant cognitive impairment, cataractogenesis, abnormal embryonic development, circulatory diseases, weight gain, premature menopause in female animals, tumorigenesis and shortened lifespan. Paternal or prenatal LDIR/LDRIR exposure is associated with reduced fertility and number of live fetuses, and transgenerational genomic aberrations. On the other hand, in some experimental studies, LDIR/LDRIR exposure has also been reported to bring about beneficial effects such as reduction in tumorigenesis, prolonged lifespan and enhanced fertility. The differences in reported effects of LDIR/LDRIR exposure are dependent on animal genetic background (susceptibility), age (prenatal or postnatal days), sex, nature of radiation exposure (i.e. acute, fractionated or chronic radiation exposure), type of radiation, combination of radiation with other toxic agents (such as smoking, pesticides or other chemical toxins) or animal experimental designs. In this review paper, we aimed to update radiation researchers and radiologists on the current progress achieved in understanding the LDIR/LDRIR-induced bionegative and biopositive effects reported in the various animal models. The roles played by a variety of molecules that are implicated in LDIR/LDRIR-induced health effects will be elaborated. The review will help in future investigations of LDIR/LDRIR-induced health effects by providing clues for designing improved animal research models in order to clarify the current controversial/contradictory findings from existing studies.

KEYWORDS: low-dose or low-dose-rate irradiation, bionegative and biopositive effect, animal model, molecular mechanism

INTRODUCTION

Low-dose ionizing radiation (LDIR), which is ubiquitous in our environment, is defined as a radiation dose of 100 mSv or less (≤100 mGy). Low-dose-rate ionizing radiation (LDRIR) is defined as the rate of radiation exposure at 6 mSv or less per hour (<6 mSv/h) [1–3]. With increased use of X-ray Computed Tomography (CT scan) for medical diagnosis and radiotherapy, diagnostic radiation examination is the largest man-made source of radiation exposure to the general population, contributing ~40% of the total annual worldwide exposure from all sources in advanced countries. Available data suggests that ~0·5% of cancer deaths in the USA over the last 30 years were attributable to diagnostic X-rays [4]. Increased construction of nuclear power plants worldwide (and consequently potential nuclear accidents), occupational radiation exposure, frequent-flyer risks, manned space exploration and possible radiological terrorism have made LDIR/LDRIR research much more imperative and urgent nowadays than ever before. This may explain why many new low-dose radiation research institutes have been established recently in varioust countries worldwide. While high-dose-radiation–induced human diseases are well known [5–8], the effects of LDIR or LDRIR on animal and human health is still under extensive scientific research. Available data indicates that

LDIR or LDRIR may induce cancer [9–12], cataract [13], cardiovascular diseases [14] and long-term psychological effects [15]. However, there exist many uncertainties in estimation of the health risks associated with exposure to LDIR or LDRIR based on existing published studies. These uncertainties significantly affect almost every facet of our lives, especially medical care, energy production, homeland security, defence, occupational health and safety, manufacturing, and industry, leading to unnecessary increased spending; they have also prevented society from exploiting nuclear energy for clean energy production. Recent conflicting research findings on LDIR- or LDRIR-induced health effects justify the need for a comprehensive review of these results.

In this review, by carefully reviewing published experimental data obtained from various animal species/strains, radiation sources/components, doses, animal ages, end-points, end-point biomarker changes and types of organs, and tissues or cells exposed to radiation, we aimed to update radiation researchers and radiologists on current progress made in the understanding of LDIR/LDRIR-induced bionegative (harmful effect on organism, with a focus on human diseases) and biopositive (beneficial effect on organism) effects in animal research models. The review will help in future investigations of LDIR/LDRIR-induced health effects by providing clues for designing improved animal research models in order to clarify the current controversial/contradictory findings from existing studies.

LDIR AND LDRIR-INDUCED BIONEGATIVE EFFECTS IN ANIMAL MODELS

EffectS of acute low-dose radiation exposure

Genetic and epigenetic changes after low-dose radiation exposures

Acute LDIR or LDRIR induces different genetic and epigenetic changes. In mice with pink-eyed unstable (p^{un}) mutation, prenatal exposure to very low doses of ionizing radiation (as low as 10 mGy) could induce reversion events in the mouse embryo, which was detected as black spots on the fur of the animals or microscopically as partially black hair in a background of colorless hair. A linear dose–response was observed between 10 mGy and 1000 mGy of X-ray irradiation [16]. In a separate study [17], γ-radiation at 10 mGy was reported to induce upregulation of transformation-related protein 53 (Trp53) in both radiosensitive (liver) and radioresistant (spleen) tissues. This protein plays a central role in both DNA damage and stress response by selecting downstream effectors for proliferation or apoptosis. There was no apparent lower threshold for induction of these effects [17]. At 100 mGy of γ-radiation, increased expression of *PARP-2*, *Gas2* and *PCNA* genes was reported in 8- to 10-week-old male B6C3F1/HSD mice. These genes are involved in the cellular DNA damage response where *PARP-2* detects DNA damage, *Gas2* acts as a growth-arrest-specific gene and *PCNA* is involved in DNA synthesis activities. Gamma-irradiation was also reported to upregulate the expression of the programmed cell death gene *Pdcd6* and to downregulate many of the glutamate receptor genes involved in synaptic signaling such as *Grik5*, *Grin1* and *Gria3*, motor protein and cytoskeletal element genes, as well as genes associated with vesicle trafficking. Changes in transcript levels of several genes involved in brain development were also observed, including downmodulation of developmental genes *Dbn* and *Rln*, neurotrophic factors like Fgf 9, Psap and Gfra2, and neural cell adhesion molecule (NCAM) [18]. While long-term monitoring was not performed post γ-rays irradiation in this study, initial upregulation of programmed cell death genes and downregulation of developmental, neurotrophic factors, neural cell adhesion molecules, synaptic signaling genes after low-dose irradiation at 100 mGy suggests that brain development, plasticity and functions may be affected at the later developmental stages of the animal life. Ultra-low radiation doses of 0.005–0.01 mGy were reported to induce chromosomal inversions in pKZ1 mouse prostatic tissue, whereas radiation doses of 1 and 10 mGy reduced inversions to below the sham-treated frequency. These studies suggested that the *pKZ* transgene is a sensitive passive gene expression reporter for low-dose radiation responses [19–21]. Low-dose proton radiation increased mutant frequencies in brain tissue but not in spleen tissue at 8 weeks after exposure. This indicates that brain tissue has higher sensitivity to low-dose proton radiation–induced negative effects [22]. Subjecting the bone marrow to internal ^{18}F-FDG radiation exposures at 33.43 mGy and higher doses, or to 25 mGy and above for external X-ray exposure, induced a significant elevation (dose response) in the micro-nucleated reticulocyte (MN-RET) frequency [23, 24]. Using a surface-based mass spectrometry approach, Lee *et al.* (2012) found statistically significant, low-dose-specific, changes to metabolic profiles 6 h post irradiation at 100 mGy [25]. Low-dose–low-LET X-ray irradiation induced delayed genomic instability in both CBA/H and C57BL/6J hemopoeitic stem cells [26].

Available data suggests that LDIR- or LDRIR-induced genetic and epigenetic changes may be affected not only by animal species, strains, genetic backgrounds (normal and genetically susceptible animals), developmental stages, and radiosensitive organs, but also by the nature of the irradiation source (i.e. proton, X-rays, γ-rays etc; Table 1). Further investigations are needed to demonstrate the long-term health effects arising from ionizing irradiation–induced genetic and epigenetic changes. The mechanisms behind these genetic and epigenetic changes remain unknown and may need further studies.

LDIR/LDRIR-induced carcinogenesis

The cancer risk associated with exposure to LDIR/LDRIR has traditionally been extrapolated from effects observed at high-dose/high-dose-rate radiation using a linear no-threshold model. Recent animal experimental data supports the association of cancer risk with LDIR (Table 2). Using a bitransgenic mouse model to measure the carcinogenic risk of exposure to multiple whole-body CT doses, a significant increase in the number of lung tumors per mouse was observed [27]. Irradiated females had significantly more excess tumors than irradiated males. Irradiated bitransgenic mice that did not express the *Ki-RAS* (*G12C*) oncogene had a low tumor incidence that was not affected by exposure to CT radiation. This study suggests that among individuals expressing cancer susceptibility genes, low-dose CT radiation may induce carcinogenesis. Genetic mechanisms may also influence susceptibility to LDIR-induced mammary cancer. After LDIR, the mammary glands of radiation-sensitive BALB/c but not resistant C57BL/6 inbred mice showed early transcriptional responses, including diminished immune response, increased cellular stress, altered

Table 1. Low-dose radiation–induced genetic and epigenetic changes in animal models

Animal strains	Radiation source	Age and dose	End-point from irradiation	End-point biomarker changes and types of cells monitored	References
Female mouse with pink-eyed unstable (p^{un}) mutation	X-rays	Prenatal exposure at 17.5 days from 10 mGy to 1 Gy	6-day-old offspring	Increased black spots (melansome streaks) on the fur at 10 mGy	[16]
Female mice	γ-rays	10-wk-old with doses from 10 mGy to 1 Gy (dose rate: 0.64 Gy/m)	1 h after irradiation	Increased induction of Trp53 at 10 mGy in spleen cells, suggesting no lower threshold for induction of Trp53	[18]
Male B6C3F1/HSD mice	γ-rays	8- to 10-wk-old with 100 mGy (dose rate: 0.18 Gy/m	30 min and 4 h after whole-body irradiation	Increased expression for Parp-2, Gas2, Pcna, Pdcd6, Grik5, Grin1 and Gria3; decreased expression for Bub3 in brain at 100 mGy	[19]
C57/Bl mice (male and female)	X-rays	Fractionated exposure at500 mGy applied as 50 mGy per day (2 mGy/s) for 10 days, or acute exposure 500 mGy (dose rate: 0.12 Gy/m)	2 h after irradiation	Global genome DNA methylation in the liver and muscle. There are sex- and tissue-specific differences in p16(INKa) promoter methylation upon LDR exposure. In male liver tissue, p16 (INKa) promoter methylation was more pronounced than in female tissue.	[65]
				Decrease in histone H4-Lys20 trimethylation in the thymus, which was accompanied by a significant decrease in global DNA methylation as well as the accumulation of DNA damage.	[68]
pKZ1 mouse	X-rays	1 μGy–2 Gyanimal age: not mentioned	3 days after irradiation	>100 mGy or <0.01 mGy: induction of chromosomal inversions in spleen cells; 0.1–100 mGy: decrease of chromosomal inversions	[19–21]
C57BL/6J plasmid-based *lacZ* transgenic mouse	Proton radiation	6–12-wk-old with100 mGy–4 Gy	1 day to 16 weeks after irradiation	Increased mutant frequencies in brain tissue from 2 days to 8 weeks at 100 mGy	[22]
Female B6.129S2-Trp53tm1Tyj/1x129×1/SvJ mouse	Positron emission tomography (PET) scans	7–9-wk-oldwith ^{18}F-FDG at 0–150 or γ-rays at 0–100 mGy	24 and 43 h after irradiation	Irradiation doses to the bone marrow corresponding to 33.43 mGy and above for internal ^{18}F-FDG exposure and to 25 mGy and above for external X-ray exposure induced significant increases in micronucleated reticulocyte formation in blood cells	[23, 24]
BALB/c and Spret/EiJ), and F1-backcross (F1Bx)	X-rays	100 mGy	6 h after irradiation	Significant low-dose-specific metabolic profiles	[25]
Male CBA/H and C57BL/6 mouse	X-rays	10–12-wk-old mice at 10 mGy–3.0 Gy	24 h after irradiation	Chromosomal instability, higher levels of TGF-β1 and TNF-α	[26]

Table 2. Low-dose radiation–induced carcinogenesis in animal models

Animal strains	Radiation source	Age and dose	End-point from irradiation	End-point biomarker changes and types of cells monitored	References
Bitransgenic CCSP-rtTA/Ki-ras mouse	Multiple whole-body CT doses	9-wk-old mice, fractionated whole-body exposures of 5, 15 or 25 mGy for 4 times + lung imaging exposures of 30 mGy at 3 and 6 months (with total lung doses of 80, 120 and 160 mGy).	9 months afterirradiation	Fractionated low-dose CT-radiation–induced carcinogenesis in individuals expressing cancer susceptibility gene. Irradiated females had significantly more excess tumors than irradiated males.	[27]
BALB/c and C57BL/6	X-rays	9-wk-old mice, fractionated whole-body exposures of 75 mGy (weekly for 4 weeks; dose rate: 0.196 Gy/m)	4 h and 1 month after last exposure	Low-dose radiation modified mammary gland cancer outcome, and mammary gland responses were strongly influenced by genotype,	[28]
Female BALB/c/An NBd mice	γ-rays	12-wk-old mice with a total dose of 2 Gy, fractionated exposure of 100 mGy/daily for 20 days (dose rate: 0.35 Gy/m)	Life-span monitoring carcinogenesis till natural death	For lung adenocarcinomas and mammary adenocarcinomas, carcinogenesis is dependent upon the per fractionated low-dose radiation exposure	[29]
BALB/c mice	γ-rays	>12-wk-old,0.1–5 Gy (dose rate: 0.35 Gy/m)	3 days afterirradiation	TGF-beta may serve as a mediator of tissue response to low-dose ionizing radiation, and orchestrate tissue response to oxidative stress	[30]
Female C57BL/6 and BALB/c mice	γ-rays	6-wk-old,4 weekly exposures to 75 mGy	4 or 10 h and 1 month after exposure	Low-dose radiation response, at least for a number of genes, is highly dependent on exposure context and genetic background.	[32]
Genotyped repair-deficient $ATM^{-/-}$, questionable repair-proficient $ATM^{+/-}$ and repair-proficient $ATM^{+/+}$ mice, SCID (CB17/Icr-Prkdcscid/Rj) mice	γ-radiation	6-wk-old,0.1 Gy or 0.1 Gy × 10, 0.1 Gy × 20, 0.1 Gy × 40	0.5 h or 72 h after irradiation at 0.1 Gy or 24 or 72 h after the last fractionated irradiations	Single or repeated irradiation with 0.1 Gy leads to the accumulation of persisting DNA damage foci in cortical neurons, and thus may adversely affect brain tissue and increase the risk of carcinogenesis	[33]
Female A/J mice treated with 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone (NNK)	whole-body CT	7-wk-old, irradiated 4 weekly doses of 0, 10, 30 or 50 mGy for total radiationdoses of 40 mGy	8 months after last CT scan	Exposure of sensitive populations to CT radiation increased the risk of tumorigenesis. Antioxidants could prevent the long-term carcinogenic effects of low-dose radiation exposure	[35]

transforming growth factor β1 (TGFβ)-signaling and inappropriate expression of developmental genes [28]. The low-dose fractionation irradiation protocol could significantly modify mammary gland cancer outcome. Tumor incidence rates appeared correlated to the delivered dose per fraction, which was in agreement with the previous study [29]. TGFβ activation was a non-targeted radiation outcome that mediated microenvironment composition and occurred in mouse mammary gland following LDIR. It persisted in the stroma for at least a week, where it mediated stromal extracellular matrix remodeling and cell fate decisions following DNA damage [30]. Evidence indicated that both TGFβ and p53 pathways might be involved in mammary tumor susceptibility to non-targeted radiation [31]. Single or repeated low-dose irradiation could result in accumulation of persisting DNA damage foci in cortical neurons, adversely affecting brain tissue and increasing the risk of carcinogenesis [32, 33]. Although such findings from animal experiments are not directly applicable to humans, these data can substantially add to our knowledge on the relationship between a wide range of ionizing radiation dose and cancer risk [34].

To mimic the effects of CT screening in heavy smokers and ex-smokers, Miller *et al.* (2013) assessed the effects of low-dose CT radiation in mice exposed to 4-(methyl-nitrosoamino)-1-(3-pyridyl)-1-butanone (NNK) and observed that irradiated mice exhibited significant increases in tumor multiplicity and size of tumour area compared with non-irradiated mice with no dose effect observed. In addition, female mice exhibited higher sensitivity to radiation exposure than their male counterparts. These data suggested that exposure of sensitive populations to CT radiation increases the risk of tumorigenesis [35]. The occurrence of LDIR/LIRIR-induced carcinogenesis in animal models appears to be dependent not only on animal genetic background (sensitive population), organ sensitivity, sex, but also on protocol for delivery of fractionation low-dose radiation, type of radiation employed (i.e. photon, proton or positron). More importantly, synergic interaction of LDIR/LIRIR with other toxic agents such as different chemicals from tobacco smoke was observed to significantly enhance the carcinogenesis rate, a finding that is likely to be relevant to carcinogenesis risk in human populations.

LDIR/LDRIR exposure and changes of brain neural plasticity

Radiation-induced alterations in the microenvironment can cause significant effects on brain neurogenesis in the mammalian brain. At different maturation stages, newly generated neurons in the dentate gyrus have distinct contributions to learning and memory, and events that decrease neurogenesis impair animal performance in learning and memory [36, 37] (Table 3). Subjecting pregnant mice to 100 mGy X-ray irradiation at Day 13 (E13) post coitus increased incidences of single-strand breaks (SSBs), but decreased mitochondrial biogenesis in hippocampal neuronal samples examined at postnatal Day 25 (P25) and at P180 [38]. It remains to be established whether prenatal irradiation-induced postnatal hippocampal pathophysiological changes will lead to schizophrenia or other neurological disorders [39]. Whole-body low-dose proton irradiation induced an acute decrease in cell division within the dentate gyrus of the hippocampus at doses as low as 100 mGy. The proliferation inhibitory effects from 100 mGy persist in the subgranular zone together with a decrease in hippocampal ICAM-1 immunoreactivity at 1 month post irradiation. At 3 months post irradiation, decrease in neurogenesis was still observable following 500 mGy irradiation [40]. Similar brain damage and impaired cognition were observed following exposure to 100 mGy of γ irradiation [41, 42].

The high degree of concordance between the affected pathways observed in the brain tissue of mice exposed to LDIR and those in the brain tissue of aging humans and Alzheimer's patients suggested that low-dose irradiation modulates the expression of gene pathways involved in cognitive function. This was supported by a recent study indicating that transgenic mice engineered to develop Alzheimer's disease–like neuropathology exhibit exacerbated short-term cognitive impairment when they are subjected to 100 mGy of silicon (250 MeV/n) radiation [43]. Observations of significantly smaller brains within birds living in areas contaminated by radioactive material from Chernobyl supports the hypothesis that LDIR/LDRIR has significant negative effects on normal brain development, resulting in impairment of cognitive ability [44]. Recent studies indicated that LDIR induced neuro-inflammation and significant reductions in the number and density of dendritic spines along hippocampal neurons of the dentate gyrus. These changes may contribute to impairment of cognition [45, 46]. Overall, existing experimental data suggest that different sources of low-dose radiation induce brain inflammation and dendro-architectonic changes, leading to the impairment of neurogenesis, neural plasticity changes and subsequent cognitive impairment. Further study will be required to establish the relationships between LDIR/LDRIR exposure, animal genetic background, age, changes in neural plasticity, and neurological and neuropsychological disorders.

LDIR exposure and cataractogenesis

The lens is a highly-ordered tissue with unique optical properties and is one of the most radiosensitive tissues in the body. Ocular ionizing radiation exposure results in characteristic, dose-related, progressive lens changes leading to cataract formation [47–49]. *In vitro* study on the isolated intact young rat lens indicated that radiation doses as low as 100 mGy induced cataract formation [50]. At very low doses of 2 mGy to 100 mGy, exposure to 600 MeV/amu ^{56}Fe or medium-energy (440 keV) neutrons, 250 MeV protons, 670 MeV/amu ^{20}Ne, 600 MeV/amu ^{93}Nb, 593MeV/amu ^{139}La ions and 50 Co γ-rays will induce micronucleus, meridional row disorganization and various stages of lens opacification in rodents [51–54]. (Table 4).

Prenatal LDIR induced malformations of embryos and fetuses

Prenatal LDIR exposure induces teratogenesis and mortality [55–61] (Table 5). In female CF1 and BALB/c strain mice, irradiation with X-rays (100 mGy) at 7 h post fertilization resulted in increased frequency of malformed fetuses and Dwarfism occurrence when examined 18 days later. Radiation induced a dose-dependent increase of pre-implantation loss in the BALB/c strain of mice and early post-implantation loss in the CF1 strain of mice. However, embryos of the BALB/c strain were refractory to the induction of teratogenic effects after such pre-implantation irradiation [59]. In the CF1 female Swiss mice, subjecting the half-day-old embryo (prior to the first cleavage) to a low-dose irradiation of 50 mGy increased embryonic death [62]. When entire oviducts and uteri were examined at 6 and 24 h after irradiation for signs of very early embryos, observations of delayed first

Table 3. Low-dose radiation–induced developmental changes in the animal brain

Animal strains	Radiation source	Age and dose	End-point from irradiation	End-point biomarker changes and types of cells monitored	References
Han:NMRI mice	X-rays	Gestational Day 13 with 100 mGy (dose rate: 0.59 Gy/m)	One day after, or postnatal Day 25 (P25) or P180	Increased single-strand breaks (SSBs) content and mitochondrial (mt) biogenesis	[38]
Male C57BL/6J mice	Proton	8–10–wk-old with 10 mGy	48 h–12 months	An acute decrease in cell division within the dentate gyrus of the hippocampus and a decrease in hippocampal ICAM-1 immunoreactivity at 1 month postirradiation	[40]
B6C3F1 male mice	γ-rays	8–10-wk-old with 100 mGy (dose rate: 0.64 Gy/m)	4 h	Induced expression of Troponin T1 (Tnnt 1) in pyramidal neurons of cerebral cortex and hippocampus, and in Purkinje cells of cerebellum	[41]
B6C3F1 male mice	γ-rays	8–10-wk-old with 100 mGy(dose rate: 0.64 Gy/m)	4 h	Activated nine neural signaling pathways in the mice showed a high degree of concordance in their transcriptional response with the aging human brain or the brain tissue from patients with Alzheimer's disease	[42]
APP/PSEN1 mice	Silicon radiation	Young mice with 0.1 Gy	3 months	Spatial learning ability was impaired	[43]
C57BL/6J	^{1}H	10-wk-old with 100 mGy ^{1}H	1 and 3 months	Novel object recognition was impaired, and newly born activated microglia were significantly elevated	[45]
Thy1-EGFP transgene mice	Proton	8-wk-old with 100 mGy (dose rate: 0.25 Gy/m)	1 month	Significant reduction of immature dendritic spines of granule cells	[46]

cleavage and increase in the number of abnormal embryos were made, suggesting that the newly fertilized egg was probably the most radiosensitive cell in the mouse [63]. Subjecting pregnant mice from two different strains (F/A and NMRI) to 10 mGy of whole-body pion- or X-ray irradiation at Day 8 of gestation resulted in a significant increase in the rate of abnormal fetuses compared with non-irradiated, but restrained fetuses [55]. When pregnant Swiss albino mice were exposed to low doses of X-rays (~9 mGy) on gestational Day 3.5 (pre-implantation period), Day 6.5 (early organogenesis period) or Day 11.5 (late organogenesis period), and the fetuses were examined on the 18th day of gestation, a significant increase in prenatal mortality was observed for those exposed at 3.5 days post coitus (d.p.c.). An increased incidence of retarded fetuses was also observed with exposure at 3.5 and 6.5 d.p.c. The major effect of exposure at 11.5 d.p.c. was a significant decrease in the fetal head size and brain weight [57]. When pregnant mice were exposed to 100 mGy of γ-radiation at 11.5 d.p.c., detectable levels of microcephaly and microphthalmia were evident [58]. These studies suggested that the late period of organogenesis in the mouse, especially between 10 and 12 d.p.c., was a particularly radiation-sensitive phase in the development of the skull, brain and eye. Experimental data in rodents suggested that prenatal radiation exposure to a very low dose (9 mGy) may induce prenatal mortality or malformations of embryos or fetuses. The exact degree of radiation-induced impairment is dependent on the animal developmental stages, radiation doses and animal strains. Further studies will still be needed to confirm the reproducibility of these animal experimental data and to find out whether similar doses could induce any abnormality in human embryos or fetuses.

Effects of chronic LDIR/LDRIR exposure

Animal models subjected to chronic LDIR/LDRIR exposure have been utilized to understand the effects of human exposure to various radiation sources, including nuclear fallout, diagnostics ionizing radiation exposure, and high background radiation exposure. Continuous LDRIR exposure of Holtzman rats for 11 generations induced a cumulative hereditary effect leading to reduced animal numbers per

Table 4. Low-dose radiation–induced cataractogenesis

Animal species and strains	Radiation source	Age and dose	End-point from irradiation	End-point biomarker changes and types of cells monitored	References
Wistar rat	γ-rays	Young rat with 0.1 Gy (dose rate: 1.25 Gy/m)	24 h	Cataractogenic degeneration	[50]
B6CF1 mouse	^{56}Fe	3–4-month-old with 50 and 100 mGy	16 months	Cytopathological changes, including micronucleation, interphase death, and meridional row disorganization, and a pronounced 'focal' loss of epithelial cytoarchitecture	[51]
Columbia-Sherman albino rats	Neutron	4-wk-old with 2, 10, 50 mGy	102 wk	Cataractogenesis	[52]
Columbia-Sherman albino rats	^{40}Ar Ions	4-wk-old with 10, 50 mGy	Every 2–3 wk, within a period of 3 days, up to a post-irradiation time of 67 wk	Cataractogenesis	[53]
B6CF1/An1 Mouse	Proton, ^{20}Ne, ^{56}Fe, ^{93}Nb, ^{193}La ions, ^{60}Co,	90–110 days with 100 mGy for Proton, ^{20}Ne, ^{56}Fe, ^{93}Nb, ^{193}La ions, ^{60}Co,	64 wk	Micronucleus frequency and meridional row disorganization	[54]

litter. LDRIR exposure from the 15th day of gestation through to the 23rd day of post-natal life resulted in dose-rate-dependent damage to the testes [64]. Chronic LDRIR exposure induced global genome DNA methylation in the mouse liver and muscle. These changes were sex- and tissue-specific in p16 (INKa) promoter methylation. In male liver tissue, p16 (INKa) promoter methylation was more pronounced than in female tissue [65]. In rat fetuses subjected to fractionated γ-irradiation at doses of 50 mGy during the 6th to 18th prenatal days, there was a deceleration of neuroblast migration into the primary cortex [66]. All cellular zones of the developing cortex showed increases in the absolute number of macroglial cells [67]. Decrease in histone H4-Lys20 trimethylation occurred in the thymus, which was accompanied by a significant decrease in global DNA methylation as well as the accumulation of DNA damage [68]. In natural populations of the bank vole that were chronically exposed to low doses of ionizing radiation over 22 animal generations within the 10 years following the Chernobyl accident, transgenerational accumulation of radiation damage occurred via genetic and/or epigenetic pathways [69]. Long-term monitoring of Chernobyl's radioactive impact on fauna showed increased occurrence of tumor and immunodeficiencies, decreased life expectancy, early aging, and changes in blood and the circulatory system. There were also higher mutation rates and transgenerational genomic instability in animal populations found within contaminated territories [70]. Chronic LDRIR decreased the tumor-specific immune response, enhanced tumorigenesis, and resulted in a variety of neoplasms and shortening of the mouse life span [71–74]. LDRIR of male germ cells cause genetic changes that could be transmitted to the offspring, leading to significant decreases in the mean litter size. The mean number of weaned pups per female bred to males exposed to LDRIR was also reduced compared with the non-irradiated controls [75]. Similarly, transgenerational LDIR exposure was observed to induce dose-rate-dependent, non-linear increase of unrepaired 8-hydroxyguanine (oxidized guanine) in muscle tissue of Japanese medaka fish with radiation-induced activation of DNA repair systems observed above a threshold radiation level [76] (Table 6). Current animal experimental data thus suggest that chronic LDIR/LDRIR exposures may induce genetic, epigenetic and transgenerational changes, reduce immune responses and promote carcinogenesis, in particular, leukemia. The radiation exposures may also affect brain development, decrease lifespan, and induce early aging, weight gain, premature menopause and diseases in circulatory system. These changes are low dose/low dose rate– and animal strain–dependent. While similar changes were not reported among Japanese A-Bomb survivors, this could be attributed to differences in the nature of the radiation involved, the radiation dose and dose rates applied, or simply to differences in response from human and rodents [28, 75].

LDIR/LDRIR–INDUCED BIOPOSITIVE EFFECTS IN ANIMALS

Both chronic and acute LDIR or LDRIR exposures have also been reported to elicit long-term biopositive effects (Table 7). Intergenerational supplementation with LDIR has been shown to be beneficial in enhancing reproductive outcome, as mice exposed to a constant low dose of 4.3 mGy/day of γ-irradiation for three generations had

Table 5. Prenatal low-dose radiation–induced malformations of embryos and fetuses in animal models

Animal strains	Radiation source	Age and dose	End-point from irradiation	End-point biomarker changes and types of cells monitored	References
CF1 female Swiss mice	X-rays	Gestational Day 0.5 with 43.85 mGy (dose rate: 0.15 Gy/m)	Gestational Day 18.5	The exposure caused 11% more deaths than the controls	[62]
CF1 female Swiss mice	X-rays	After fertilization but before any cleavage movements with 50 mGy (dose rate: 0.0455 Gy/m).	At 6 and 24 h after irradiation	The first cleavage was delayed, and there was an increase from 2.5% in the controls to 20% in the number of abnormals, among the irradiated.	[63]
F/A and NMRI mice	Pion- or X-irradiation	Gestational Day 8, 10 mGy	5 days after exposure	A significant increase in the rate of abnormal fetuses	[55]
Swiss albino mice	X-rays	Gestational Day 3.5, 6.5 and 11.5 at ~9 mGy (dose rate: 0.83 Gy/m).	Gestational Day 18	Significant increase in prenatal mortality, increased incidence of retarded fetuses and a significant decrease in the fetal head size and brain weight	[57]
	γ-rays	Gestational Day 11.5, exposed to 50 mGy to 500 mGy (dose rate: 0.83 Gy/m).	Gestational Day 18	Significant reduction in head size and brain weight, a linear dose response for these effects in the dose range of 50 mGy to 150 mGy.	[58]
BALB/c and CF1 mice	X-rays	7 h after fertilization exposed to100, 500 and 1000 mGy (dose rate: 0.8 Gy/m)	Gestational Day 18	frequency of malformed fetuses increased; dwarfism occurred in CF1 mice	[59]
ICR mice	X-rays	Gestational Day 9.5 with 20 mGy (dose rate: 0.667 mGy/m) 4 h after the priming irradiation	Gestational Day 18.5	Primary conditioning with low doses of radiation suppresses radiation-induced teratogenesis	[60]
C57BL/6J mice	X-rays	Gestational Day 11 with priming low dose from X-rays at 50 or 300 mGy (dose rate: 0.33 Gy/m) on gestation Day 11 followed by high dose of 3.5 Gy 1 day after	Gestational Day 18	The priming low dose of X-rays significantly reduced the occurrence of prenatal fetal death, malformation, and/or low body weight induced by the challenge high dose of radiation	[61]

increased litter size compared with the control groups [77]. A lightly irradiated Holtzman strain of rats were observed to be more fertile (increased ovulation in dams; increased litter number, viability and growth rates; and faster physical development) than the controls over several generations, with no evidence of mutations in the young that were exposed *in utero*. Irradiated colonies were maintained in good health throughout 21 generations [78]. Development of rat pups was accelerated after γ-irradiation on Day 21 of the post-natal development (28.8 mGy, dose rate of 1.2 mGy/h) [79]. In male Swiss mice, whole-body irradiation with 50 to 150 mGy of X-rays resulted in remarkable suppression of mounting behavior and psychological stress [80].

Chronic low-dose-rate γ irradiation of MRL-lpr/lpr mice carrying a deletion in the apoptosis-regulating *Fas* gene prolonged the life span and induced various immunological modifications, which included significant increase in $CD4^+$ $CD8^+$ T cells in the thymus and $CD8^+$ T cells in the spleen. Conversely, a significant decrease in $CD3^+$ $CD45R/B220^+$ cells and $CD45R/B220^+$ $CD40^+$ cells occurred in the spleen of these mice [81, 82]. Long-term low-dose-rate irradiation of

Table 6. Health effects of chronic low-dose/low-dose-rate radiation exposure in animal models

Animal strains	Radiation source	Exposure period	End-point from irradiation	End-point biomarker changes and types of cells monitored	References
Holtzman rat	γ-rays	20 mGy/23 h-day for 30 days, pre- and early post-natal exposure	11 successive generations	20 mGy given continuously for 11 generations had a cumulative hereditary effect resulting in a reduced number of individuals per litter	[64]
Mongrel rat fetuses	γ-rays	A total of 50 mGy, given at 6.25 mGy (dose rate: 0.43 mGy/h) daily for 8 days during the prenatal days from 6th to 18th,	Day 18 of pregnancy	Deceleration of neuroblast migration into the primary cortex, increases in the absolute number of macroglial cells in all cellular zones of the developing cortex	[66]
				Adverse effects on the processes of stem cellproliferation in the tissues of the developing cortex; also increased the intensity of cell destruction proportionally to the radiation dose	[67]
Male and female C57/Bl mice	X-rays	500 mGy applied as 50 mGy per day for 10 days (dose rate: 0.12 Gy/m)	2 h after thelast treatment on Day 10	Global genome DNA methylation in the mouse liver and muscle. In male liver tissue, p16(INKa) promoter methylation was more pronounced than in female tissue	[65]
Male and female C57/BL6 mice (45-day-old)	X-rays	Fractionated whole-body application of 500 mGy, 50 mGy daily for 10 days (dose rate: 0.12 Gy/m)	4 h after the last treatment on Day 10	A significant decrease in global DNA methylation as well as the accumulation of DNA damage in the thymus	[68]
Male Pzh:SFIS mice	X-rays	8-wk-old, 50 or 100 mGy/per day for 40 days (dose rate: 0.20 Gy/m), irradiated male mice mated with female mice without irradiation	Pregnant Day 17	Decreases in the number of live fetuses and induced dominant lethal mutations	[75]
Bank vole	^{137}Cs, ^{134}Cs, ^{106}Ru,^{144}Ce from Chernobyl accident	Over 22 animal generations in 10 year with <73 mGy	2 wks; 1, 2, 3 and 4 months; and 1 and 1.5 years	The radiation exposure of the parental generations led to an accumulated pool of germline mutations and/or of epigenetic changes, which resulted in elevated levels of chromosome aberrations and in increased embryonic losses in later generations.	[69]
Male and female B6C3F1	γ-rays	From 8-wk-old for 400 days with a dose rate of 1 or 20 mGy/per day	Life span	Induced neoplasms and shortening of the life span	[71, 72]
Female B6C3F1 mice	γ-rays	20 mGy/22 h/day for 400 days	400 days after irradiation	Decreased tumor-specific immune response and enhanced tumorigenesis	[73]

Table 7. Low-dose and low-dose-rate ionizing radiation induced a biopositive effect in the animals

Human population group	Radiation source	Dose exposed	End-point biomarkers	End-point biomarker changes and types of cells monitored	References
Mice (male and female)	γ-rays	4.3 mGy/22 h-day for 100 days	3 successive generations	Increased litter size	[77]
Rat	γ-rays	28.8 mGy, at dose rate of 1.2 mGy/h on Day 21 of the postnatal development	Body mass	Development of rat pups was accelerated (body mass made up 121% of control)	[79]
ICR Swiss mice (male)	X-rays	50 to 150 mGy(dose rate: 0.2 Gy/m)	Behaviour and psychological stress	Whole-body irradiation suppressed mounting behavioural and psychological stress	[80]
MRL-lpr/lpr mice carrying a deletion in the apoptosis-regulating *Fas* gene	γ-rays	0.35 or 1.2 mGy/h for 5 wks	Life span and immunological modifications	Chronic low-dose-rate γ irradiation prolonged the life span and induced immunological modifications, including a significant increase in $CD4^+$ $CD8^+$ T cells in the thymus and $CD8^+$ T cells in the spleen and also by a significant decrease in $CD3^+$ $CD45R/B220^+$ cells and $CD45R/B220^+$ $CD40^+$ cells in the spleen	[81, 82, 84]
C57BL/6, BALB/c, C3H/He, DBA/1, DBA/2 and CBA mice	γ-rays	γ radiation at 1.2 mGy/h for 1, 3, 5, 7, 9, 13 or 17 weeks	Immunological modifications	Increase in $CD4^+$ T cells and CD8 molecule expression, decrease in $CD40^+$ B cells. Increases of $CD4^+$ T cells, $CD40^+$ B cells and anti-SRBC antibody-producing cells by immunization were significantly enhanced by continuous low-dose-rate irradiation at 1.2 mGy/h. CD3- $CD4^+$ T cells, representative of abnormal immune cells,	[84]
C57BL/6 mice	γ-rays X-rays	γ radiation at 1.2 mGy/h for 450 days 35 days before high dose X irradiation	Thymic lymphoma	Low-dose-rate irradiation suppressed thymic lymphoma induction accompanied by immune activation	[83]
C57BL/6 mice	γ-rays X-rays	γ radiation at 1.2 mGy/h for 5 wks before high-dose X irradiation at 1.8 Gy × 4	Thymic lymphoma	A prolonged γ irradiation at 1 mGy/hr suppressed skin tumors induced by methylcholanthrene and delayed high-dose-radiation–induced thymic lymphomas in C57BL/6 mice.	[85]
db/db mice	γ-rays	0.94 mGy/h for 24 days	Type II diabetes	Continuous low-dose-rate γ irradiation ameliorated type II diabetes in db/db mice by maintaining insulin secretion	[86]

db/db mice (female)	γ-rays	0.94 mGy/h from 10 weeks of age throughout their lives	Life span, nephropathy and antioxidant activities	Continuous low-dose-rate radiation significantly increased life span in db/db mice, and increased the number of normal capillaries in glomeruli. Antioxidant activities of superoxide dismutase, catalase and glutathione were significantly increased in kidneys. It also ameliorated diabetic nephropathy and increased life span in db/db mice through the activation of renal antioxidants.	[87]
Trp53+/− female mice	CT scan or PET scan at 10–12 mGy	7–8- wk-old 10–12 mGy	Lifespan study of cancer development	Single CT scan significantly extends overall lifespan relative to controls	[92]
ApoE−/− (B6.129P2-Apoe ^{tm1Unc}/J) female mice	γ-rays	25, 50, 100 mGy (dose rate: 1 mGy/m) at 2 or 8 months of age. Mice were euthanized and tissues collected either 3 or 6 months (exposed at 2 months) or 2 or 4 months after exposure	Progression of atherosclerosis	Low doses given at low dose rate at either early or late stage of diseases were protective, slowing the progression of the diseases	[94]
Agouti viable yellow (A^{vy}) mice	X-rays	Gestational Day 4.5, 4–76 mGy	Upon weaning	Increased DNA methylation in male offspring, and epigenetic alterations resulting from LDIR play a role in radiation hormesis	[136]
Klotho mouse	γ-rays	0.35 or 0.7 mGy/h γ radiation from 40 days after birth	Life span	Low-dose-rate ionizing radiation prolonged the lifespan of mice	[88]
Kunming mice	X-ray	75 mGy (dose rate: 12.5 mGy/m) whole-body X-ray radiation 6 h before S180 sarcoma cell implantation	Antitumor effect and hormesis in an erythrocyte system	Increased the anti-tumor ability of the organism and improved the erythrocyte immune function and the O_2-carrying ability.	[96]

MRL-lpr/lpr mice suppressed induction of thymic lymphoma by whole-body X-irradiation with four doses of 1.8 Gy. This study suggested the presence of an adaptive response in tumor suppression involving LDIR-induced immune activation [83]. In wild-type mouse strains, chronic LDRIR alone induced a maximum of 30% increase in $CD4^+$ T cells and CD8 molecule expression, while $CD40^+$ B cells decreased significantly. Increases in $CD4^+$ T cells, $CD40^+$ B cells and anti-sheep red blood cells (SRBCs) antibody-producing cells by immunization were significantly enhanced by continuous LDRIR at 1.2 mGy/h. In these chronically low-dose-rate–irradiated mice, $CD3^-$ $CD4^+$ T cells, representative of abnormal immune cells, were absent, while a dose-dependent increase in these cells was observed in mice subjected to acute high-dose-rate irradiation suggesting that low dose rate irradiation induces biopositive effect [84].

In C57BL/6 mice, continuous irradiation at the low dose rate of 1.2 mGy/h was observed to suppress methylcholanthrene-induced skin tumors and delaythe appearance of thymic lymphomas induced by high-dose radiation [85]. It has also been reported that low-dose-rate continuous γ irradiation prolonged the life span of both db/db mice (an experimental model for Type II diabetes [86, 87]) and the accelerated aging Klotho mouse model [88]. Exposure to radon water or radon-rich mines has also been reported to alleviate a wide variety of diseases and pains in human with and without concurrent medical treatment [89–91]. A single 10 mGy CT scan or PET scan (7–22 mSv) of $Trp53^{+/-}$ female mice significantly extended the overall lifespan of these mice relative to the controls [92]. Primary conditioning with low doses of radiation was also reported to significantly suppress incidences of teratogenesis induced by a follow-on high dose of radiation [60, 61, 93]. In genetically susceptible $ApoE^{-/-}$ mice with normal *p53* function, γ-radiation exposures at doses as low as 25 mGy, given at either an early or late stage of the disease, protected against atherosclerosis in a manner distinctly non-linear with respect to dose [94]. However, in $ApoE^{-/-}$ mice with reduced *p53* function ($Trp53^{+/-}$), exposure at the late stage of the disease, produced generally detrimental effects. These observations suggested the *p53* functionality can dramatically alter the outcome of a LDIR exposure [95]. Whole-body low-dose X-ray irradiation of mice was reported to markedly increase anti-tumor response as well as improve the erythrocyte immune function and its ability to carry oxygen [96]. In summary, under certain circumstances, animal experimental data suggests that lLDIR/LDRIR exposure may not only promote fertility and prolong lifespan, but also induce immunological modification, give anti-tumor ability, slow the progression of atherosclerosis, and ameliorate diabetic nephropathy. While it has been suggested that safe supplementation with external low doses of ionizing radiation may produce biopositive effects in mammals [97], more data needs to be generated to validate existing claims of biopositive/hermetic effects of LDIR/LDRIR on humans.

THE MECHANISMS FOR LDIR- OR LDRIR-INDUCED BIONEGATIVE AND BIOPOSITIVE EFFECTS

The mechanisms for LDIR- or LDRIR-induced bionegative effects

The mechanisms for LDIR- or LDRIR-induced bionegative and biopositive effects vary according to animal species, strain, age, sex, organ and cell type exposed, cell metabolism, and cell cycle. The induction of carcinogenesis and cataractogenesis (mentioned previously) in various genetically susceptible mice suggests that the specific genes may be involved in LDIR- or LDRIR-induced carcinogenesis and cataractogenesis respectively. Low doses of radiation from medical diagnostic procedures (0.25–10 mGy) stimulate the expression of interleukin 2 (IL-2) receptors on the surface of peripheral blood lymphocytes taken from normal human donors, a process that could contribute to leukemogenesis [98, 99]. Diminished immune response, increased cellular stress, altered TGFβ1 signaling, inappropriate expression of developmental genes, and upregulation of ITGAX, RELB, SERPINA1, MMP12, FGF13, RSPO1 and FGG have been suggested to be involved in LDIR- or LDRIR–induced mammary gland carcinogenesis [30, 33, 34]. TGFβ1 also mediates tumor promotion of *Trp53* null mammary epithelium after LDIR exposure [31]. Induced expression of higher γ-H2AX foci in lymphocytes obtained from a patient at various sampling times post radiotherapy or CT examination suggested that *in vivo* induction and repair of DNA double-strand breaks (DSBs) may occur soon after irradiation [100]. The γ-H2AX assay may be a robust method for measuring DSB damage in peripheral blood lymphocytes (PBLs), which can be used to assess mutagen sensitivity and malignant tumor risk [101]. In the central nervous system, nerve growth factor (NGF) protein levels and the expression of brain-derived neurotrophic factor (BDNF) and neurotrophic tyrosine kinase receptor type 3 (trkC) (receptor serving to bind neurotrophin-3) mRNA are affected by prenatal irradiation at doses as low as 20 mGy, which may directly affect post-natal brain development [102]. *In vitro* and *in vivo* study of radiation response of neural precursor cells suggested that oxidative stress or reactive oxygen species (ROS) may be involved in LDIR- or LDRIR-induced inhibition of neurogenesis in the development of cognitive impairment [103]. This is supported by a recent study that acute low-dose irradiation (from 20 mGy) could elicit significant increases in ROS and reactive nitrogen species (RNS) over several days to weeks. These redox changes could activate NFκB signal transduction, leading to transcriptional activation of superoxide dismutase 2 (SOD2), which in turn plays a key role in the LDIR induction of oxidative stress response and the ultimate fate of the cell [104].

In the embryonic mouse brain, a statistically significant increase in DNA DSB formation and apoptosis in the embryonic neuronal stem cell compartment occurred after *in utero* exposure to 10–100 mGy of X-rays, with both end-points showing a linear response. Delayed DSB repair was reported following exposure to doses below 50 mGy as compared with exposure to a higher dose of 100 mGy [105, 106]. An *in vitro* study indicated that neural stem cells exposed to 10–150 mGy of Fe ions displayed a significant dose-dependent rise in ROS/ RNS levels at 12 and 24 h post irradiation [107]. Low-dose whole-body irradiation at 50 mGy or 75 mGy induced colony-stimulating factor (CSF) secretion from thymocytes and lung cells, respectively. The number of granulocyte colony-stimulating factor (G-CSF) receptors on bone marrow cells (BMCs) in mice was also increased significantly. These findings suggested the presence of synergic interaction of CSF and G-CSF, which may play a role in hematopoietic stimulation [108]. LDIR was also reported to induce increases in G-CSF and granulocyte-macrophage colony-stimulating factor (GM-CSF) mRNA

expression in splenocytes [109]. Irradiation of mice at 75 mGy was also reported to induce IL-12 and IL-18 secretion from macrophages, with paralleled activation of NF-κB as well as upregulated expression of CD14 and TLR4-MD2 on the macrophage surface and MyD88 in the cytoplasm [110]. Analysis of splenic lymphocytes from a mouse subjected to LDRIR, from 1 mGy to 20 mGy/20 h/daily, increased the incidences of chromosome aberrations with a positive dose-rate effect [111, 112]. With a total dose of 50 mGy (at 0.24 mGy/h), *Ccl11*, *Ccr5*, *Cd80*, *Inha*, and *Il9* genes were significantly modulated immediately after irradiation [113]. Irradiation with 100 mGy (0.2 mGy/h) demonstrated significant enhancement of expression of *Il27* and *Tcfcp2* genes, whereas *Inha* and *Socs5* genes were downregulated in $CD4^+$ T cells immediately after irradiation at doses of 10 mGy and 100 mGy respectively [114]. After 10 mGy at a dose rate of 1 mGy/h, *Ccr5*, *Cd40*, *Cebpb*, *Igsf6* and *Tnfsf4* genes were upregulated, whereas *Il4ra*, *Mapk8* and *Nfkb1* genes were downregulated immediately after irradiation. After 100 mGy, upregulation of *Ccr4*, *Cd40*, *Cebpb*, *Cxcr3*, *Socs5*, *Stat4*, *Tbx21*, *Tnfrsf4* and *Tnfsf4* genes were observed. These findings suggested that the pattern of gene expression in $CD4^+$ T cells was significantly modified after protracted low-dose proton irradiation, with the modifications highly dependent upon the total dose and dose rate of irradiation [115]. Very low dose rate γ-irradiation (100 mGy/year) was also reported to result in a significant decrease in levels of IgG1, IgG2b and IgG2a at 12, 18 and 24 months post irradiation respectively while the total number of B-cells within the spleen remained unchanged [116]. In addition, mouse lymphocytes subjected to LDIR were observed to have increased intracellular calcium ions and stimulated protein kinase C (PKC) activities [117]. As PKC is a common pathway for many signal transduction systems involved in apoptosis, such as radiation-induced ATM, P53, ceramide, and c-Abl activations [118], analysis of PKC activities in radiation-induced cellular responses may provide many clues for understanding the mechanism of radiation-induced biopositive and bionegative effects.

The mechanisms for LDIR- or LDRIR-induced biopositive effects

At low doses, ionizing radiation induces stress proteins and prostaglandins, which are involved in stabilizing the signal transduction, transcriptional and translational machineries [119]. It also induces SOD activities in immune organs of the irradiated rats [120], detoxification of ROS [121], and high-fidelity repair of DNA damage [122, 123], which may help explain how LDIR or LDRIR protect chromosomal damage from a subsequent high radiation dose [124], from spontaneous mutations occurrence [19, 125] and from spontaneous neoplastic decreases, and provide a novel explanation for how LDIR/LDRIR reduces the frequency of neoplastic transformation to a level below the spontaneous transformation rate [125–128]. Extension of tumor latency in cancer-prone mice [129, 130], activation of the immune response [119, 131, 132] and suppression of metastasis [133] and spontaneous cancers in humans [134, 135] were also observed after LDIR or LDRIR exposure. LDRIR was reported to significantly increase plasma calcium concentration in *Klotho* gene mutant mice, and concomitantly increase hepatic catalase activity and prolong the lifespan of mice [88]. Low-LET X-ray radiation (12 mGy/day; 84 mGy total) caused a significant offspring coat color shift towards pseudo-agouti and discordant methylation between experimental and control mice of the same coat color class during the first seven days of gestation in *Agouti viable yellow* (A^{vy}) mice. The exposure timing (Day 4.5 of gestation, or GD 4.5) coincides with post-fertilization epigenome-wide reprogramming, a window of vulnerability for exposure to epigenetic toxicants and environmental factors. LDIR increased the methylation at several loci, including imprinted genes of A^{vy} mice. Males were more affected at the A^{vy}allele, while sex did not play a factor for the other loci examined. The findings provided evidence that in the isogenic A^{vy} mouse model, epigenetic alterations resulting from LDIR played a role in radiation hormesis [136]. Furthermore, epigenetic alteration, ataxia telangiectasia-mutated (ATM), extracellular signal-related kinase (ERK), mitogen-activated protein kinase (MAPK), phospho-c-Jun NH_2-terminal kinase (JNK) and P53-related signal transduction pathways, clusterin gene expression may also be involved in LDIR- or LDRIR-induced beneficial effects [136–138]. In the mouse immune system, LDIR induced activation of lymphocytes through signals transmitted from antigen-presenting cells (APCs), including the upregulated surface molecules CD48, CD80, CD86 and increased IL-12, IL-1beta, t*umor necrosis factor* receptor alpha (TNFα), decreased cAMP/cGMP ratio, and downregulated the PLA2-PGE2 (phospholipase2-prostaglandin E2) pathway [132]. In the retina, the reported LDIR/LDRIR-induced upregulation of antioxidative gene peroxiredoxin-2 (Prdx2) could be applied as a novel therapeutic concept for retinitis pigmentosa and for other progressive neurodegenerative diseases regardless of the mechanism of degeneration involved [139]. *FOXO*, *SIRT1*, *JNK*, *ATM*, *ATR* and *p53* genes have been demonstrated to play essential roles in hormesis and radiation adaptive response in the whole organism of *Drosophila melanogaster* [140]. In the rat mesenchymal stem cell (MSC), the MAPK/ERK pathway may be involved in LDIR-induced MSC proliferations [141].

CONCLUSIONS

In our review of animal experimental studies involving the application of three different protocols for ionizing radiation exposures, i.e. (i) LDIR (<100 mSv) followed by high-dose-rate ionizing radiation exposure, (ii) LDIR with low dose rate (<6 mSv/h) ionizing radiation (LDRIR with low cumulative dose), and (iii) LDRIR with high accumulated radiation dose, we observed that all the radiation exposures induced either bionegative or biopositive effects on fertility, tumorigenesis, and lifespan depending on genetic background, age, sex, nature of radiation exposure (i.e. acute or chronic irradiation), type of ionizing radiation applied, experimental design and statistical methodology used. Radiation exposures also induce genetic and epigenetic changes, cataractogenesis and abnormal neurogenesis in the brain. At the molecular level, LDIR-induced ROS, inflammatory cytokines and chemokines, and downregulation of various neurotrophic factors resulted in the impairment of neurogenesis and cerebrovascular diseases, resulting in loss of cognitive functions.

Diminished immune response, increased cellular stress, altered TGFβ1 signaling, inappropriate expression of developmental genes,

and upregulation of ITGAX, RELB, SERPINA1, MMP12, FGF13, RSPO1 and FGG may be involved in LDIR- or LDRIR-induced mammary gland carcinogenesis. Upregulation of genes for cell surface receptors linked to signal transduction such as *Alk*, *Cd30* and *Il2ra*, which reduce DNA mismatch repair, may be involved in the occurrence of malignant lymphomas arising from LDIR/LDRIR exposure. On the other hand, epigenetic alteration, ATM, ERK, MAPK, JNK and P53-related signal transduction pathways, and clusterin gene expression may be involved in LDIR- or LDRIR-induced biopositive effects. While LDIR from LDRIR (LDRIR or LDRIR with accumulated LDIR) induced bionegative health effects, most of the previous studies used LDIR with high-dose-rate ionizing radiation or LDRIR with high accumulated dose radiation exposure (refer to Tables 1–7). Hence, additional studies evaluating the health effects posed by LDIR with LDRIR are urgently needed.

The development of sensitive biomarkers for detecting early pathophysiological changes induced by LDIR with LDRIR may provide some clues, not only for early diagnosis or detection of radiation exposure but also for the prevention of disease development. Evaluation of LDIR- and LDRIR-induced bionegative effects in radiosensitive animal populations may elucidate molecular mechanisms for LDIR- and LDRIR-induced human diseases. Further investigation and confirmation of LDIR- and LDRIR-induced biopositive effects may provide information for the development of cheap and effective therapeutic approaches for preventing or controlling chronic human diseases.

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CONFLICT OF INTEREST

The authors report no conflicts of interest.

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REFERENCES

1. United Nation Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). *Sources and effects of ionizing radiation. Report to General Assembly, with Scientific Annexes*. United Nations, New York, 2000.
2. National Council on Radiation Protection and Measurements. *Evaluation of the linear-non-threshold dose–response model for ionizing radiation. NCRP Report No.136*. Bethesda, 2001.
3. International Commission on Radiological Protection. *Recommendations of the International Commission on Radiological Protection. ICRP Publication 103*. Elsevier. 2007.
4. Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. *J Natl Cancer Inst* 1981;66:1191–308.
5. Wong FL, Yamada M, Sasaki H, et al. Noncancer disease incidence in the atomic bomb survivors: 1958–1986. *Radiat Res* 1993;135:418–30.
6. Rahu M. Health effects of the Chernobyl accident: fears, rumours and the truth. *Eur J Cancer* 2003;39:295–9.
7. Ron E. Cancer risks from medical radiation. *Health Phys* 2003; 85:47–59.
8. Little MP, Wakeford R, Kendall GM. Updated estimates of the proportion of childhood leukaemia incidence in Great Britain that may be caused by natural background ionising radiation. *J Radiol Prot* 2009;29:467–82.
9. Hatch M, Ron E, Bouville A, et al. The Chernobyl disaster: cancer following the accident at the Chernobyl nuclear power plant. *Epidemiol Rev* 2005;27:56–66.
10. Cardis E, Howe G, Ron E, et al. Cancer consequences of the Chernobyl accident: 20 years on. *J Radiol Prot* 2006;26: 127–40.
11. Busby CC. Very low dose fetal exposure to Chernobyl contamination resulted in increases in infant leukemia in Europe and raises questions about current radiation risk models. *Int J Environ Res Public Health* 2009;6:3105–14.
12. Shah DJ, Sachs RK, Wilson DJ. Radiation-induced cancer: a modern view. *Br J Radiol* 2012;85:e1166–73.
13. Ainsbury EA, Bouffler SD, Dörr W, et al. Radiation cataractogenesis: a review of recent studies. *Radiat Res* 2009;172:1–9.
14. Sumner D. Health effects resulting from the Chernobyl accident. *Med Confl Surviv* 2007;23:31–45.
15. Pastel RH. Radiophobia: long-term psychological consequences of Chernobyl. *Mil Med* 2002;167:134–6.
16. Schiestl RH, Khogali F, Carls N. Reversion of the mouse pink-eyed unstable mutation induced by low doses of X-rays. *Science* 1994;266:1573–6.
17. MacCallum DE, Hall PA, Wright EG. The Trp53 pathway is induced *in vivo* by low doses of gamma radiation. *Radiat Res* 2001;156:324–7.
18. Yin E, Nelson DO, Coleman MA, et al. Gene expression changes in mouse brain after exposure to low-dose ionizing radiation. *Int J Radiat Biol* 2003;79:759–75.
19. Hooker AM, Bhat M, Day TK, et al. The linear no-threshold model does not hold for low-dose ionizing radiation. *Radiat Res* 2004;162:447–52.
20. Sykes PJ, Day TK, Swinburne SJ, et al. *In vivo* mutagenic effect of very low dose radiation. *Dose Response* 2006;4:309–16.
21. Zeng G, Day TK, Hooker AM, et al. Non-linear chromosomal inversion response in prostate after low dose X-radiation exposure. *Mutat Res* 2006;602:65–73.
22. Chang PY, Bakke J, Orduna J, et al. Proton-induced genetic damage in lacZ transgenic mice. *Radiat Res* 2005;164:481–6.
23. Manning G, Taylor K, Finnon P, et al. Quantifying murine bone marrow and blood radiation dose response following (18)F-FDG PET with DNA damage biomarkers. *Mutat Res* 2004;770:29–36.
24. Taylor K, Lemon JA, Boreham DR. Radiation-induced DNA damage and the relative biological effectiveness of 18F-FDG in wild-type mice. *Mutagenesis* 2004;29:279–87.

25. Lee DY, Bowen BP, Nguyen DH, et al. Low-dose ionizing radiation-induced blood plasma metabolic response in a diverse genetic mouse population. *Radiat Res* 2012;178:551–5.
26. Irons SL, Serra V, Bowler D, et al. The effect of genetic background and dose on non-targeted effects of radiation. *Int J Radiat Biol* 2012;88:735–42.
27. Munley MT, Moore JE, Walb MC, et al. Cancer-prone mice expressing the *Ki-rasG12C* gene show increased lung carcinogenesis after CT screening exposures. *Radiat Res* 2011;176:842–8.
28. Snijders AM, Marchetti F, Bhatnagar S, et al. Genetic differences in transcript responses to low-dose ionizing radiation identify tissue functions associated with breast cancer susceptibility. *PLoS One* 2012;7:e45394.
29. Ullrich RK, Jernigan MC, Satterfield LC, et al. Radiation carcinogenesis: time–dose relationships. *Radiat Res* 1987;111:179–84.
30. Ehrhart EJ, Segarini P, Tsang ML, et al. Latent transforming growth factor beta1 activation *in situ*: quantitative and functional evidence after low-dose gamma-irradiation. *FASEB J* 1997;11: 991–1002.
31. Barcellos-Hoff MH, Mao JH. HZE radiation non-targeted effects on the microenvironment that mediate mammary carcinogenesis. *Front Oncol* 2016;6:57.
32. Soffritti M, Tibaldi E, Padovani M, et al. Life-span exposure to sinusoidal-50 Hz magnetic field and acute low-dose γ radiation induce carcinogenic effects in Sprague-Dawley rats. *Int J Radiat Biol* 2016;92:202–14.
33. Lorat Y, Schanz S, Rübe CE. Ultrastructural insights into the biological significance of persisting DNA damage foci after low doses of ionizing radiation. *Clin Cancer Res* 2016;22:5300–11.
34. Duport P, Jiang H, Shilnikova NS, et al. Database of radiogenic cancer in experimental animals exposed to low doses of ionizing radiation. *J Toxicol Environ Health B Crit Rev* 2012;15:186–209.
35. Miller MS, Moore JE, Walb MC, et al. Chemoprevention by N-acetylcysteine of low-dose CT-induced murine lung tumorigenesis. *Carcinogenesis* 2013;34:319–24.
36. Lemaire V, Koehl M, Le Moal M, et al. Prenatal stress produces learning deficits associated with an inhibition of neurogenesis in the hippocampus. *Proc Natl Acad Sci U S A* 2000;97:11032–7.
37. Shors TJ, Miesegaes G, Beylin A, et al. Neurogenesis in the adult is involved in the formation of trace memories. *Nature* 2001;410:372–6.
38. Korr H, Thorsten Rohde H, Benders J, et al. Neuron loss during early adulthood following prenatal low-dose X-irradiation in the mouse brain. *Int J Radiat Biol* 2001;77:567–80.
39. Lieberman JA. Is schizophrenia a neurodegenerative disorder? A clinical and neurobiological perspective. *Biol Psychiatry* 1999; 46:729–39.
40. Sweet TB, Panda N, Hein AM, et al. Central nervous system effects of whole-body proton irradiation. *Radiat Res* 2014;182: 18–34.
41. Lowe XR, Marchetti F, Lu X, et al. Molecular stress response in the CNS of mice after systemic exposure to interferon-alpha, ionizing radiation and ketamine. *Neurotoxicology* 2009;30:261–8.
42. Lowe X, Wyrobek A. Characterization of the early CNS stress biomarkers and profiles associated with neuropsychiatric diseases. *Curr Genomics* 2012;13:489–97.
43. Bellone JA, Hartman RE, Vlkolinský R. The effects of low doses of proton, iron or silicon radiation on spatial learning in a mouse model of Alzheimer's disease. *J Radiat Res* 2014; 55:i95–6.
44. Møller AP, Bonisoli-Alquati A, Rudolfsen G, et al. Chernobyl birds have smaller brains. *PLoS One* 2011;6:e16862.
45. Nelson G, Fike J, Limoli C, et al. Responses of the central nervous system to high linear energy transfer radiation: NSCOR project highlights. *J Radiat Res* 2014;55:i22–3.
46. Parihar VK, Pasha J, Tran KK, et al. Persistent changes in neuronal structure and synaptic plasticity caused by proton irradiation. *Brain Struct Funct* 2015;220:1161–71.
47. Tribondeau L, Recamier D. Alterations des yeux et du squelette facial d'un chat nouveau-ne par roentgenisation. *Compt Rend Soc de boil* 1905;58:1031.
48. Belley G. *Etude experimentalle de l'action de rayons x sur l'oeil en voie de developpement*. Bordeaux, 1907.
49. von Hippel E. Ueber experimentelle Erzeugung von angeborenem Star bei Kaninchen nebst Bemerkungen uber gleichzeitig Boebachten Mikrophthalmus und Lidcoloboma. *Arch f Ophth* 1907;65:326.
50. Ross WM, Creighton MO, Inch WR, et al. Radiation cataract formation diminished by vitamin E in rat lenses *in vitro*. *Exp Eye Res* 1983;36:645–53.
51. Worgul BV, Medvedovsky C, Powers-Risius P, et al. Accelerated heavy ions and the lens. IV. Biomicroscopic and cytopathological analyses of the lenses of mice irradiated with 600 MeV/amu 56Fe ions. *Radiat Res* 1989;120:280–93.
52. Worgul BV, Medvedovsky C, Huang Y, et al. Quantitative assessment of the cataractogenic potential of very low doses of neutrons. *Radiat Res* 1996;145:343–9.
53. Brenner DJ, Medvedovsky C, Huang Y, et al. Accelerated heavy particles and the lens. VI. RBE studies at low doses. *Radiat Res* 1991;128:73–81.
54. Tao F, Powers-Risius P, Alpen EL, et al. Radiation effects on late cytopathological parameters in the murine lens relative to particle fluence. *Adv Space Res* 1994;14:483–91.
55. Michel C, Fritz-Niggli H. Radiation damage in mouse embryos exposed to 1 rad x-rays or negative pions. *Rofo* 1977;127: 276–80.
56. Michel C. Radiation embryology. *Experientia* 1989;45:69–77.
57. Devi PU, Hande MP. Effect of low dose of 70 kVp X-rays on the intrauterine development of mice. *Experientia* 1990;46: 511–3.
58. Devi PU, Baskar R, Hande MP. Effect of exposure to low-dose gamma radiation during late organogenesis in the mouse fetus. *Radiat Res* 1994;138:133–8.
59. Jacquet P, de Saint-Georges L, Vankerkom J, et al. Embryonic death, dwarfism and fetal malformations after irradiation of embryos at the zygote stage: studies on two mouse strains. *Mutat Res* 1995;332:73–87.
60. Okazaki R, Ootsuyama A, Norimura T. Radioadaptive response for protection against radiation-induced teratogenesis. *Radiat Res* 2005;163:266–70.
61. Wang B, Ninomiya Y, Tanaka K, et al. Adaptive response of low linear energy transfer X-rays for protection against high

linear energy transfer accelerated heavy ion–induced teratogenesis. *Birth Defects Res B Dev Reprod Toxicol* 2012;95:379–85.
62. Rugh R, Grupp E. Response of the very early mouse embryo to low levels of ionizing radiations. *J Exp Zool* 1959;141:571–87.
63. Rugh R, Grupp E. Effect of low level x-irradiation on the fertilized egg of the mammal. *Exp Cell Res* 1961;25:302–10.
64. Brown SO. Effects of continuous low intensity radiation on successive generations of the albino rat. *Genetics* 1964;50:1101–13.
65. Kovalchuk O, Burke P, Besplug J, et al. Methylation changes in muscle and liver tissues of male and female mice exposed to acute and chronic low-dose X-ray-irradiation. *Mutat Res* 2004; 548:75–84.
66. Kornev MA, Kulikova EA, Kul'bakh OS. Cellular composition of cerebral cortex in rat fetuses exposed to low-dose fractionated radiation. *Morfologiia* 2004;125:78–81.
67. Kornev MA, Kulikova EA, Kul'bakh OS. The cellular composition of the cerebral cortex of rat fetuses after fractionated low-dose irradiation. *Neurosci Behav Physiol* 2005;35:635–8.
68. Pogribny I, Koturbash I, Tryndyak V, et al. Fractionated low-dose radiation exposure leads to accumulation of DNA damage and profound alterations in DNA and histone methylation in the murine thymus. *Mol Cancer Res* 2005;3:553–61.
69. Ryabokon NI, Goncharova RI. Transgenerational accumulation of radiation damage in small mammals chronically exposed to Chernobyl fallout. *Radiat Environ Biophys* 2006;45:167–77.
70. Yablokov AV. Chernobyl's radioactive impact on fauna. *Ann NY Acad Sci* 2009;1181:255–80.
71. Tanaka S, Tanaka IB 3rd, Sasagawa S, et al. No lengthening of life span in mice continuously exposed to gamma rays at very low dose rates. *Radiat Res* 2003;160:376–9.
72. Tanaka IB 3rd, Tanaka S, Ichinohe K, et al. Cause of death and neoplasia in mice continuously exposed to very low dose rates of gamma rays. *Radiat Res* 2007;167:417–37.
73. Takai D, Todate A, Yanai T, et al. Enhanced transplantability of a cell line from a murine ovary granulosa cell tumour in syngeneic B6C3F(1) mice continuously irradiated with low dose-rate gamma-rays. *Int J Radiat Biol* 2011;87:729–35.
74. Uehara Y, Ito Y, Taki K, et al. Gene expression profiles in mouse liver after long-term low-dose-rate irradiation with gamma rays. *Radiat Res* 2010;174:611–7.
75. Dobrzyńska MM, Czajka U. Male-mediated developmental toxicity in mice after 8 weeks' exposure to low doses of X-rays. *Int J Radiat Biol* 2005;81:793–9.
76. Grygoryev D, Moskalenko O, Hinton TG, et al. DNA damage caused by chronic transgenerational exposure to low dose gamma radiation in Medaka fish (*Oryzias latipes*). *Radiat Res* 2013; 180:235–46.
77. Muramatsu S, Sugahara T, Tsuchiya T, et al. Effects of chronic low-dose irradiation for three successive generations on the breeding behaviour of mice. *Int J Radiat Biol Relat Stud Phys Chem Med* 1964;8:523–31.
78. Luckey TD. *Radiation Hormesis*. Boca Raton: CRC Press, Inc., 1991.
79. Ruda VP, Kuzin AM. The occurrence of hormesis during gamma-irradiation of developing rat pups. *Radiobiologiia* 1991;31:345–7.
80. Miyachi Y, Yamada T. Low-dose X-ray-induced depression of sexual behavior in mice. *Behav Brain Res* 1994;65:113–5.
81. Ina Y, Sakai K. Prolongation of life span associated with immunological modification by chronic low-dose-rate irradiation in MRL-lpr/lpr mice. *Radiat Res* 2004;161:168–73.
82. Ina Y, Sakai K. Further study of prolongation of life span associated with immunological modification by chronic low-dose-rate irradiation in MRL-lpr/lpr mice: effects of whole-life irradiation. *Radiat Res* 2005;163:418–23.
83. Ina Y, Tanooka H, Yamada T, et al. Suppression of thymic lymphoma induction by life-long low-dose-rate irradiation accompanied by immune activation in C57BL/6 mice. *Radiat Res* 2005;163:153–8.
84. Ina Y, Sakai K. Activation of immunological network by chronic low-dose-rate irradiation in wild-type mouse strains: analysis of immune cell populations and surface molecules. *Int J Radiat Biol* 2005;81:721–9.
85. Sakai K, Nomura T, Ina Y. Enhancement of bio-protective functions by low dose/dose-rate radiation. *Dose Response* 2006; 4:327–32.
86. Tsuruga M, Taki K, Ishii G, et al. Amelioration of type II diabetes in db/db mice by continuous low-dose-rate gamma irradiation. *Radiat Res* 2007;167:592–9.
87. Nomura T, Li XH, Ogata H, et al. Suppressive effects of continuous low-dose-rate γ irradiation on diabetic nephropathy in type II diabetes mellitus model mice. *Radiat Res* 2011;176: 356–65.
88. Nomura T, Sakai K, Ogata H, et al. Prolongation of life span in the accelerated aging Klotho mouse model, by low-dose-rate continuous γ irradiation. *Radiat Res* 2013;179:717–24.
89. Deetjen P. Biological and therapeutical properties of radon. In: Katase A, Shimo, M (eds). *Radon and Thoron in the Human Environment*. Singapore: World Scientific, 1998, 515–22.
90. Salak K. Mining for miracles. *Nat Geo* 2003;205:118–22.
91. Becker K. Health effects of high radon environments in central Europe: another test for the LNT hypothesis. *Nonlinearity Biol Toxicol Med* 2005;1:3–35.
92. Taylor K, Lemon JA, Phan N, et al. Low-dose radiation from 18F-FDG PET does not increase cancer frequency or shorten latency but reduces kidney disease in cancer-prone *Trp53*+/– mice. *Mutagenesis* 2014;29:289–94.
93. Boreham DR, Dolling JA, Somers C, et al. The adaptive response and protection against heritable mutations and fetal malformation. *Dose Response* 2006;4:317–26.
94. Mitchel RE, Hasu M, Bugden M, et al. Low-dose radiation exposure and atherosclerosis in ApoE$^{-/-}$ mice. *Radiat Res* 2011; 175:665–76.
95. Mitchel RE, Hasu M, Bugden M, et al. Low-dose radiation exposure and protection against atherosclerosis in *ApoE*$^{-/-}$ mice: the influence of *p53* heterozygosity. *Radiat Res* 2013;179:190–9.
96. Yu HS, Liu ZM, Yu XY, et al. Low-dose radiation induces antitumor effects and erythrocyte system hormesis. *Asian Pac J Cancer Prev* 2013;14:4121–6.
97. Luckey TD. Nurture with ionizing radiation: a provocative hypothesis. *Nutr Cancer* 1999;34:1–11.

98. Tartakovsky B, Goldstein O, Krantghamer R, et al. Low doses of ionizing radiation induced systemic production of cytokines: possible contribution to leukemogenesis. *Int J Cancer* 1993; 551:269–74.
99. Xu Y, Greenstock CL, Trivedi A, et al. Occupational levels of radiation exposure induce surface expression of interleukin-2 receptors in stimulated human peripheral blood lymphocytes. *Radiat Environ Biophys* 1996;35:89–93.
100. Löbrich M, Rief N, Kühne M, et al. *In vivo* formation and repair of DNA doublestrand breaks after computed tomography examinations. *Proc Natl Acad Sci U S A* 2005;102:8984–9.
101. Xu E, Gong Y, Gu J, et al. Risk assessment of esophageal adenocarcinoma using γ-H2AX assay. *Cancer Epidemiol Biomarkers Prev* 2013;22:1797–804.
102. Dimberg Y, Vazquez M, Söderström S, et al. Effects of X-irradiation on nerve growth factor in the developing mouse brain. *Toxicol Lett* 1997;90:35–43.
103. Limoli CL, Giedzinski E, Rola R, et al. Radiation response of neural precursor cells: linking cellular sensitivity to cell cycle checkpoints, apoptosis and oxidative stress. *Radiat Res* 2004; 161:17–27.
104. Veeraraghavan J, Natarajan M, Herman TS, et al. Low-dose γ-radiation-induced oxidative stress response in mouse brain and gut: regulation by NFκB-MnSOD cross-signaling. *Mutat Res* 2011;718:44–55.
105. Saha S, Woodbine L, Haines J, et al. Increased apoptosis and DNA double-strand breaks in the embryonic mouse brain in response to very low-dose X-rays but not 50 Hz magnetic fields. *J R Soc Interface* 2014;11:20140783.
106. Barazzuol L, Jeggo PA. *In vivo* sensitivity of the embryonic and adult neural stem cell compartments to low-dose radiation. *J Radiat Res* 2016;57:i2–10.
107. Tseng BP, Giedzinski E, Izadi A, et al. Functional consequences of radiation-induced oxidative stress in cultured neural stem cells and the brain exposed to charged particle irradiation. *Antioxid Redox Signal* 2014;20:1410–22.
108. Zhang HL. Stimulation of low dose radiation on hematopoietic system. *Zhonghua Yi Xue Za Zhi* 1993;73:99–100.
109. Li W, Wang G, Cui J, et al. Low-dose radiation (LDR) induces hematopoietic hormesis: LDR-induced mobilization of hematopoietic progenitor cells into peripheral blood circulation. *Exp Hematol* 2004;32:1088–96.
110. Shan YX, Jin SZ, Liu XD, et al. Ionizing radiation stimulates secretion of pro-inflammatory cytokines: dose–response relationship, mechanisms and implications. *Radiat Environ Biophys* 2007;46:21–9.
111. Tanaka K, Kohda A, Satoh K. Dose-rate effects and dose and dose-rate effectiveness factor on frequencies of chromosome aberrations in splenic lymphocytes from mice continuously exposed to low-dose-rate gamma-radiation. *J Radiol Prot* 2013; 33:61–70.
112. Tanaka K, Satoh K, Kohda A. Dose and dose-rate response of lymphocyte chromosome aberrations in mice chronically irradiated within a low-dose-rate range after age adjustment. *Radiat Prot Dosimetry* 2014;159:38–45.
113. Rizvi A, Pecaut MJ, Gridley DS. Low-dose gamma-rays and simulated solar particle event protons modify splenocyte gene and cytokine expression patterns. *J Radiat Res* 2011;52:701–11.
114. Gridley DS, Rizvi A, Luo-Owen X, et al. Low dose, low dose rate photon radiation modifies leukocyte distribution and gene expression in $CD4^+$ T cells. *J Radiat Res* 2009;50:139–50.
115. Gridley DS, Pecaut MJ, Rizvi A, et al. Low-dose, low-dose-rate proton radiation modulates $CD4^+$ T cell gene expression. *Int J Radiat Biol* 2009;85:250–61.
116. Courtade M, Caratero A, Jozan S, et al. Influence of continuous, very low-dose gamma-irradiation on the mouse immune system. *Int J Radiat Biol* 2001;77:587–92.
117. Liu SZ, Su X, Han ZB, et al. Effect of low dose radiation on intracellular calcium and protein kinase C in lymphocytes. *Biomed Environ Sci* 1994;7:284–91.
118. Nakajima T. Positive and negative regulation of radiation-induced apoptosis by protein kinase C. *J Radiat Res* 2008; 49:1–8.
119. Makinodan T, James SJ. T cell potentiation by low dose ionizing radiation: possible mechanisms. *Health Phys* 1990; 59:29–34.
120. Yamaoka K, Edamatsu R, Mori A. Increased SOD activities and decreased lipid peroxide levels induced by low dose X irradiation in rat organs. *Free Radic Biol Med* 1991;11:299–306.
121. Feinendegen LE, Pollycove M, Sondhaus CA. Responses to low doses of ionizing radiation in biological systems. *Nonlinearity Biol Toxicol Med* 2004;2:143–71.
122. Joiner MC, Lambin P, Marples B. Adaptive response and induced resistance. *C R Acad Sci III* 1999;322:167–75.
123. Rothkamm K, Löbrich M. Evidence for a lack of DNA double-strand break repair in human cells exposed to very low x-ray doses. *Proc Natl Acad Sci U S A* 2003;100:5057–62.
124. Wolff S, Afzal V, Wiencke JK, et al. Human lymphocytes exposed to low doses of ionizing radiations become refractory to high doses of radiation as well as to chemical mutagens that induce double-strand breaks in DNA. *Int J Radiat Biol Relat Stud Phys Chem Med* 1988;53:39–47.
125. Scott BR. Stochastic thresholds: a novel explanation of nonlinear dose–response relationships for stochastic radiobiological effects. *Dose Response* 2006;3:547–67.
126. Azzam EI, de Toledo SM, Raaphorst GP, et al. Low-dose ionizing radiation decreases the frequency of neoplastic transformation to a level below the spontaneous rate in C3H 10T1/2 cells. *Radiat Res* 1996;146:369–73.
127. Redpath JL. Nonlinear response for neoplastic transformation following low doses of low let radiation. *Nonlinearity Biol Toxicol Med* 2005;3:113–24.
128. Redpath JL, Lu Q, Lao X, et al. Low doses of diagnostic energy X-rays protect against neoplastic transformation *in vitro*. *Int J Radiat Biol* 2003;79:235–40.
129. Mitchel RE. The bystander effect: recent developments and implications for understanding the dose response. *Nonlinearity Biol Toxicol Med* 2004;2:173–83.
130. Mitchel RE, Jackson JS, Morrison DP, et al. Low doses of radiation increase the latency of spontaneous lymphomas and

spinal osteosarcomas in cancer-prone, radiation-sensitive *Trp53* heterozygous mice. *Radiat Res* 2003;159:320–7.
131. Liu SZ, Liu WH, Sun JB. Radiation hormesis: its expression in the immune system. *Health Phys* 1987;52:579–83.
132. Liu SZ. On radiation hormesis expressed in the immune system. *Crit Rev Toxicol* 2003;33:431–41.
133. Jin SZ, Pan XN, Wu N, et al. Whole-body low dose irradiation promotes the efficacy of conventional radiotherapy for cancer and possible mechanisms. *Dose Response* 2007;5:349–58.
134. Rossi HH, Zaider M. Radiogenic lung cancer: the effects of low doses of low linear energy transfer (LET) radiation. *Radiat Environ Biophys* 1997;36:85–8.
135. Scott BR, Di Palma J. Sparsely ionizing diagnostic and natural background radiations are likely preventing cancer and other genomic-instability-associated diseases. *Dose Response* 2006;5:230–55.
136. Bernal AJ, Dolinoy DC, Huang D, et al. Adaptive radiation-induced epigenetic alterations mitigated by antioxidants. *FASEB J* 2013;27:665–71.
137. Klokov D, Criswell T, Leskov KS, et al. IR-inducible clusterin gene expression: a protein with potential roles in ionizing radiation-induced adaptive responses, genomic instability, and bystander effects. *Mutat Res* 2004;568:97–110.
138. Tang FR, Loke WK. Molecular mechanisms of low dose ionizing radiation induced hormesis, adaptive responses, radioresistance, bystander effects, and genomic instability. *Int J Radiat Biol* 2015;91:13–27.
139. Otani A, Kojima H, Guo C, et al. Low-dose-rate, low-dose irradiation delays neurodegeneration in a model of retinitis pigmentosa. *Am J Pathol* 2012;180:328–36.
140. Moskalev AA, Plyusnina EN, Shaposhnikov MV. Radiation hormesis and radioadaptive response in *Drosophila melanogaster* flies with different genetic backgrounds: the role of cellular stress-resistance mechanisms. *Biogerontology* 2011;12:253–63.
141. Liang X, So YH, Cui J, et al. The low-dose ionizing radiation stimulates cell proliferation via activation of the MAPK/ERK pathway in rat cultured mesenchymal stem cells. *J Radiat Res* 2011;52:380–6.