Dose-Response:
An International Journal
January-March 2019:1-16

DOI: 10.1177/1559325819833488
journals.sagepub.com/home/dos
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Research Progress on the Biological Effects of Low-Dose Radiation in China

Kaihua Ji[1], Yan Wang[1], Liqing Du[1], Chang Xu[1], Yang Liu[1], Ningning He[1], Jinhan Wang[1], and Qiang Liu[1]

Abstract

Human are exposed to ionizing radiation from natural and artificial sources, which consequently poses a possible risk to human health. However, accumulating evidence indicates that the biological effects of low-dose radiation (LDR) are different from those of high-dose radiation (HDR). Low-dose radiation–induced hormesis has been extensively observed in different biological systems, including immunological and hematopoietic systems. Adaptive responses in response to LDR that can induce cellular resistance to genotoxic effects from subsequent exposure to HDR have also been described and researched. Bystander effects, another type of biological effect induced by LDR, have been shown to widely occur in many cell types. Furthermore, the influence of LDR-induced biological effects on certain diseases, such as cancer and diabetes, has also attracted the interest of researchers. Many studies have suggested that LDR has the potential antitumor and antidiabetic complications effects. In addition, the researches on whether LDR could induce stochastic effects were also debated. Studies on the biological effects of LDR in China started in 1970s and considerable progress has been made since. In the present article, we provide an overview of the research progress on the biological effects of LDR in China.

Keywords

low-dose radiation, biological effects, research progress, China

Introduction

Currently, ionizing radiation from natural and artificial sources is ubiquitous in our daily life.[1-3] Abnormal exposure to ionizing radiation, such as that experienced by individuals involved in nuclear mishaps, astronauts, and some medical professionals, can cause side effects.[4] In addition, radiation therapy, one of the most important therapeutic strategies for treating malignancies, can also injure the normal cells and tissues surrounding the tumors.[5]

Moderate and high doses of radiation induce DNA strand breaks and impair immune function, which may result in apoptosis and transformation into cancer cells.[6,7] Extensive epidemiological studies on atomic bomb survivors suggested that the incidence of solid cancers is significantly related to radiation exposure. Currently, the linear no-threshold (LNT) hypothesis, which assumes risk increases linearly with increasing radiation dose, is applied to assess the radiation-associated risk in many countries.[8] However, the LNT hypothesis emphasizes the DNA damage caused by ionizing radiation and ignores the defensive and adaptive reactions in the body often activated by low-dose radiation (LDR).[9] Therefore, many reports suggest that using the LNT hypothesis to assess the risk from LDR is unwise. While the effects of LDR are still controversial, many reports have shown that LDR, unlike high-dose radiation (HDR), can be beneficial to living organisms.[3,10,11]

Low-dose radiation is defined as a dose of radiation below which it is not possible to detect adverse health effects and has been set previously as less than 200 mGy for low linear energy transfer (LET) radiation or 50 mGy for high LET radiation by the UN Scientific Committee on Atomic Radiation.[12,13]

[1] Tianjin Key Laboratory of Radiation Medicine and Molecular Nuclear Medicine, Department of Radiobiology, Institute of Radiation Medicine of Chinese Academy of Medical Science & Pecking Union Medical College, Tianjin, PR China

Received 27 August 2018; received revised 19 December 2018; accepted 29 December 2018

Corresponding Author:
Qiang Liu, Tianjin Key Laboratory of Radiation Medicine and Molecular Nuclear Medicine, Department of Radiobiology, Institute of Radiation Medicine of Chinese Academy of Medical Science, Tianjin 300192, PR China.
Email: liuqiang@irm-cams.ac.cn

Recently, LDR was considered to be less than 100 mGy of low LET radiation (Nuclear Regulatory Commission, 2006) in the seventh report in a series of publications from the US National Academy concerning radiation health effects called the biological effects of ionizing radiation VII. Studies on the biological effects of LDR began in the 1970s. In 1982, Luckey was the first to conclude that LDR benefited animal growth, development, health, and longevity and termed these effects "radiation hormesis" in his monograph *Hormesis with Ionizing Radiation*.[10] In 1984, Olivieri et al documented that the cultured human lymphocytes can acquire the resistance to chromosomal aberrations induced by subsequently HDR when preexposed to LDR and termed these effects an adaptive response (AR).[14] More recently, the "bystander effect" of LDR was defined as exposure of a cell population to LDR causing in significant cytotoxic and genotoxic effects in nonirradiated cells in the population.[15] Over the past several decades, the biological effects of LDR, such as the hormesis, AR, and bystander effect, have been the focus of many investigators.

In China, early studies on LDR aimed to identify indicators of damage and evidence that could be used for diagnosing "chronic radiation injury." However, in a population health survey with high-background levels of natural radiation in Yangjiang, Guangdong Province, in the late 1970s, Liu observed an increase in the reactivity of T lymphocytes in the peripheral blood of a population exposed to a dose of radiation equivalent to more than 3 times the population in the control area.[16] Later, it was found the DNA damage repair capacity of these T lymphocytes was increased and there was significantly more unscheduled DNA synthesis than in the control group.[16] These 2 population-based observations prompted Chinese researchers to consider that LDR may have different biological effects than HDR. Subsequently, Luckey's monograph *Hormesis with Ionizing Radiation* and Olivieri's paper about the AR induced by LDR that was published in *Science* were introduced in China and Chinese researchers developed a new understanding and shifted research on the biological effects of LDR. Initially, Chinese researchers mainly focused on the hormesis, AR, and bystander effects of LDR. Since then, research on the mechanisms of the biological effects of LDR has developed with the further development and application of new technologies in molecular and cellular biology. In addition, the biological effects of LDR on germ cells, tumor cells, and cancers have attracted the attention of Chinese researchers. In this review, we summarize the research advances made on the biological effects of LDR in China.

Low-Dose Radiation Hormesis

Hormesis is a dose–response phenomenon that occurs in a wide spectrum of organisms in response to different environmental agents.[3] Radiation hormesis is characterized by LDR stimulation and HDR inhibition of certain biological parameters.[3] Over the past several decades, increasing evidence has indicated that LDR-induced hormesis was extensively observed in different biological systems, including immunological and hematopoietic systems.[3,7,17] Here, we review the developments on LDR hormesis in China.

Low-Dose Radiation Hormesis of the Immune System

The immune system is one of the most important defenses against environmental insults and is strongly affected by ionizing radiation.[18] In China, LDR hormesis was firstly observed in Chinese people exposed to high-background radiation at a low-dose rate of 1.96 mSv/y in Yangjiang, Guangdong Province.[16] In this population, the reactivity and DNA repair ability of T cells were significantly higher than in people in surrounding low-background radiation areas. Therefore, some Chinese researchers began to concentrate on LDR hormesis of the immune system (Figure 1).

First, the dose–response relationship of ionizing radiation with immunological parameters following exposure, particularly LDR, was analyzed. Liu observed that the lymphocytes and related functions displayed a J- or inverted J-shaped dose–response curve, which is not consistent with LNT, in a model where Kunming mice were exposed to X-rays whole-body irradiation (WBI); specifically, 25, 50, 75, 100, 200, 500, 1000, 2000, 4000, and 6000 mGy and a sham-irradiated control were used.[19] Notably, this dose–response curve is still applicable when evaluating natural killer (NK) cell activity and antibody-dependent cell-mediated cytotoxicity activity at different doses, but more doses on the higher end are needed in order to reveal the suppressive effect.[19,20]

Second, LDR enhancement of the immune response has been demonstrated, especially for the adaptive immunity. Liu et al reported a significant reduction in the rate of thymocyte apoptosis to below control levels when doses within 0.2 Gy were given as WBI to male Kunming mice and in vitro irradiation of EL4 cells.[21,22] In their study, the messenger RNA (mRNA) and protein expression levels of prosurvival molecules, such as Bcl-2 and Bcl-xl, and the ratio of prosurvival and proapoptotic molecules, such as Bcl-2/Bax and Bcl-xl/Bad, were significantly increased. Correspondingly, the mRNA and protein expression levels of proapoptotic molecules, such as p53, Bax, Bad, FasL, and Gadd45, were significantly decreased. Some studies have reported that LDR may also stimulate thymocytes through promoting thymocyte proliferation and cell-cycle progression.[23,24] When Kunming mice were exposed to LDR through WBI (75 mGy), the total number of thymocytes, proportion of cells in S phase and thymocytes proliferation in response to ConA stimulation were increased. Liu et al demonstrated that LDR may also shift cytokine secretion and T-helper differentiation. When Kunming mice were exposed to whole-body LDR (75 mGy), the mRNA and protein levels of interleukin 10 (IL-10) were both suppressed while IL-12 expression was simultaneously stimulated, which may contribute to a shift in the immune response in favor of Th1 differentiation.[25,26] They suggested that the effect of LDR on T-lymphocyte surface molecule expression and interactions with antigen-presenting cells may be the main reason for this alternation in cytokine secretion and Th-cell differentiation. In

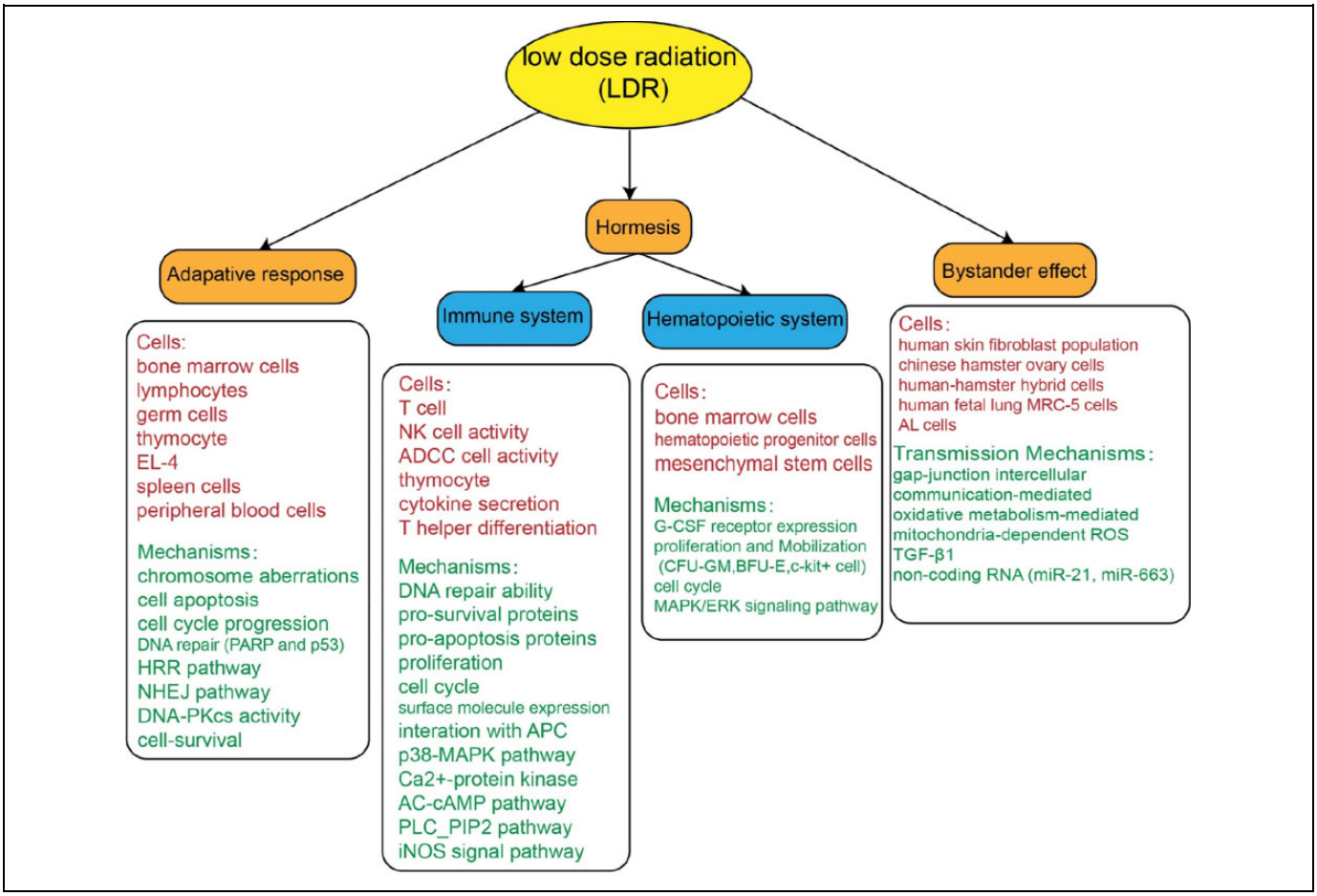

Figure 1. Research on hormesis, adaptive responses, and bystander effects from low-dose radiation (LDR) by Chinese scholars.

addition, the biological effects of LDR on NK cells, which are an important part of innate immunity, have also been investigated. Yang et al found NK cells expansion and cytotoxicity were significantly augmented by LDR. Interferon-γ and tumor necrosis factor α (TNF-α) levels in the supernatants of the cultured NK cells were markedly increased after LDR exposure. These findings also indicate LDR induces the expansion and activation of NK cells possibly through the p38-MAPK pathway.[7]

Third, the molecular mechanisms underlying the biological effects of LDR on the immune system have also been extensively studied by the Chinese researchers. Liu et al demonstrated the phospholipase C-phosphatidylinositol biphosphate signaling pathway (PLC-IP2) and the G-protein–adenylate cyclase-cyclic adenosine monophosphate (AC-cAMP) signaling pathway may be involved in the activation of thymocytes in response to WBI with LDR.[27] When Kunming mice were exposed to whole-body LDR, Ca^{2+} mobilization, protein kinase C activation, and PLC-IP2 signaling pathway in T lymphocytes were increased, unlike when exposed to HDR. Furthermore, G-protein–AC-cAMP pathways signaling molecules were downregulated in response to LDR. They also suggested that alternations in these signaling pathways may achieve functional activation by activating transcription factors associated with cytokine secretion, cell proliferations, and cell-cycle progression. Besides, cell signal transmission in different immune cells may be one of the molecular mechanisms of the effect of LDR. For example, Yang et al suggested the p38-MAPK pathway is involved in the activation and expansion of NK cells in response to LDR.[7] The results of the above Chinese studies demonstrate that LDR enhances the immune response by augmenting the proliferation-reactive response and suppressing the apoptosis-reactive response of immune cells, altering immune cell populations, and cytokine release, through complex signal transduction pathways.

Low-Dose Radiation Hormesis of the Hematopoietic Systems

In China, studies on LDR-induced hormesis first focused on the immune system. However, recently, many reports have been published indicating LDR may induce hormesis of the hematopoietic system. Depression of hematopoietic function often takes place in patients undergoing radiotherapy and/or chemotherapy, due to the high sensitivity of the hematopoietic system to these therapies.[28-31] Activation of the immune system by LDR prompted us to consider whether LDR can activate the hematopoietic system. Therefore, many researchers began

focusing on the LDR hormesis of the hematological system. Here, we review the research by Chinese researchers on the biological effects and the mechanisms of LDR on the hematopoietic system (Figure 1).

In 1993, Zhang detected the granulocyte colony-stimulating factor receptor expression on the surface of bone marrow cells (BMCs) was increased when Kunming mice were exposed to LDR, which resulted in a stimulating effect by LDR on hematopoietic cells proliferation.[32] Low-dose radiation hormesis of the hematopoietic system was also observed in in vitro blood samples.[33] Wang and Cai observed the obvious proliferative effects on hematopoietic progenitor cells that play an important role in the maintenance and development of the hematopoietic system, when Kunming mice were exposed to whole-body LDR through X-rays.[34] Li et al reported bone marrow HPC proliferation (colony-forming unit granulocyte-macrophage and burst-forming unit erythroid formation) and mobilization were significantly stimulated when male Kunming mice were exposed to LDR (especially 75 mGy).[31] Based on LDR hormesis of the hematopoietic systems, especially HPCs, Zhang et al investigated the effects of LDR-induced hormesis effect on hematopoietic reconstitution.[17] When exposed to LDR (60 and 80 mGy) in vitro, BMCs underwent significant proliferation. In irradiated recipient BALB/C mice receiving these preexposed BMCs, there are consistently more white blood cells, bone marrow mononuclear cells, and CFUs in the recipient spleens than in the control. These results suggest LDR-induced hormesis may facilitate hematopoietic reconstitution in recipient mice. In addition, mesenchymal stem cells (MSCs), an important component of the hematopoietic system, have captured increased attention from researchers.[35,36] Liang et al showed proliferation of rat MSCs in vitro significantly increases following exposure to LDR at 50 and 75 mGy, where 75 mGy is the most stimulating. There is also a significant increase in the proportion of MSCs in S-phase cells in response to LDR. The result also suggests that activation of the MAPK/ERK signaling pathway may have contributed to the MSCs proliferation.[37] The results gathered by Chinese researchers suggest that LDR hormesis on the hematopoietic system occurs through promotion of proliferation of HPCs and MSCs.

Low-Dose Radiation–Induced ARs

Adaptive responses are potential adaptations of the living body to the external environment and are a widespread phenomenon in the living nature.[38] Recently, many efforts have been made to prove LDR can induce ARs.[12,39] An LDR-induced AR is a phenomenon in which pre-exposure of cells to LDR (inductive dose, D1) renders cells more resistant to damage from subsequent HDR (challenge dose, D2) or other toxic agents.[14] In this section, we focus on the efforts and achievements made by Chinese researchers on AR and LDR-associated mechanisms of induction, especially for immune and hematopoietic systems (Figure 1).

As early as 1990, Liu et al found that WBI of C57BL/6 mice with LDR in the range of 2 to 100 mGy induces an AR in BMCs in the form of a reduction in chromosomal aberrations following subsequent exposure to HDR (650 mGy).[40] Cai et al showed cross-induction of ARs occurs between ionizing radiation and chemical agents, including mitomycin C and H_2O_2, both in vitro in human lymphocytes and in vivo mouse BMCs and germ cells.[41] Gong et al observed that when male Kunming mice were irradiated with LDR (D1, 75 mGy) 3 to 12 hours before exposure to HDR (D2, 1.5 Gy), the ARs of cell apoptosis and cell-cycle progression could be induced in thymocytes cultured for 4 and 20 hours after WBI with D2, which suggests there is a time-dependent effect for LDR-induced ARs in the form of mouse thymocyte apoptosis and cell-cycle progression.[42]

Several hypotheses have been considered for the mechanisms underlying LDR-induced AR. Many studies have suggested that LDR may minimize damage caused by subsequent HDR by enhancing DNA repair ability, antioxidant activity, production of protective proteins, and cell survival.[43-45] Ionizing radiation-induced DNA double-strand breaks (DSBs) are a severe threat to cell survival. Many previous studies have demonstrated LDR-induced ARs may be mainly related to enhancement of DNA repair.[46-48] Cheng et al found AR was induced in the form of cell apoptosis and cell-cycle progression in EL-4 cells preexposed to LDR (D1, 75 mGy) before being exposed to HDR (D2, 1.0, 1.5, and 2.0 Gy). The authors also demonstrated that poly-(ADP ribose) polymerase and p53, which might be crucial mediators of DNA repair, might play important roles in LDR-induced AR.[38] Yu et al found that the protective role of LDR in reducing HDR-induced cell killing might depend on promotion of nonhomologous end joining through stimulation of DNA-protein kinase cytalytic subunit activity.[49] Yu et al demonstrated LDR can induce an apoptosis-based AR in mouse spleen cells. When Kunming mice were irradiated with LDR (D1, 25, 50, 75, and 100 mGy) 6 hours before exposure to HDR (D2, 1.5 Gy), expression of caspase-3 and the apoptosis-related protein Bcl-2 increased, and proapoptotic protein Bax expression decreased, leading to a decrease in spleen cell apoptosis compared to the D2 group.[50] All of the above studies documented that pre-exposure of cells to LDR in vivo and in vitro enhances DNA repair activity and reduces activity related to DNA damage-associated apoptosis.

However, a few studies have addressed the issue of LDR-induced cell proliferation and cell survival ARs to subsequent HDR-induced cytotoxicity. Wang and Cai suggested LDR could induce a cell survival AR to subsequent HDR in BMCs. When Kunming mice were irradiated with 0.5 Gy X-rays as an inductive dose (D1) before exposure to HDR (D2, 6 Gy), an AR to the D2-induced cytotoxic effect, termed the cell survival AR, was observed in both peripheral blood cells and BMCs.[34] In summary, Chinese researchers have done a great deal of work in the field of LDR-induced ARs. However, further studies are required to delineate both the phenomenological features and mechanisms underlying LDR-induced ARs.

Bystander Effects of LDR

Radiation-induced bystander effects (RIBEs) were originally termed to describe the nontargeted effects exhibited by nonirradiated cells upon receiving signals from irradiated cells through diffusion of soluble molecules into the medium or cellular gap junctional intercellular communication.[51,52] The RIBE was firstly discovered by Nagasawa and Little in an in vitro study, which revealed an induced frequency of sister chromatid exchanges of 20% to 40% of Chinese hamster ovary (CHO) cells when only 0.1% to 1% of the nuclei of the cells were exposed to a low dose of α particles.[15] Compared to the bystander effects induced by HDR, the RIBE is very weak.[53,54] However, the RIBE of LDR over the past 2 decades has received increasing attention.[54-58] In this section, therefore, the progress made on LDR-associated RIBEs by Chinese researchers is reviewed and also illustrated in Figure 1.

During initial studies on RIBEs of LDR, scientists mostly focused on providing the evidence for the existence of the RIBEs by measuring DNA damages in bystander cells after exposure to LDR. Through in situ γ-H2AX immunofluorescence, Hu et al discovered the existence of the RIBE by finding more DSBs in bystander cells in a full confluent human skin fibroblasts than in cells subjects to a low dose of α particles.[59] Following this, detection of the DNA damage sensor p53-binding protein 1 (53BP1) foci, which colocalized with γ-H2AX, was also be used as a method to measure DNA damage to show the existence of RIBEs in response to LDR. Han et al found a significant increase in 53BP1 foci formation in proliferating bystander CHO cells when they were cocultured with cells irradiated with α particles.[60]

Based on advancements of experimental techniques, various research groups began to study the earliest time point for the induction of RIBE by LDR. He et al found increased γ-H2AX foci formation in irradiated cells and nonirradiated cells could be visualized 2 minutes after radiation that peaked after 30 minutes.[61] In addition to DSBs, Chen et al observed that conditioned medium harvested at 10 minutes postirradiation from 10 mGy irradiated human–hamster hybrid cells could induce reactive oxygen species (ROS) production, CD59-gene loci mutations, and delayed cell death in the bystander cells.[62]

The possible mechanisms underlying RIBEs may include the transmission of soluble factors generated by irradiated cells to nonirradiated cells, the gap junctional intercellular communication, and the ROS-based transmission. For instance, Hu et al found when AG1522 normal human diploid skin fibroblasts cells were pretreated with either lindane (a gap junctional communication inhibitor) or dimethyl sulphoxide (DMSO; a free radical scavenger), the fraction of DSBs-positive cells was reduced in nonirradiated cell population, suggesting gap junctional intercellular communication and ROS might play important roles in the induction of RIBEs.[61] Regarding the possible role of ROS generated from irradiated cells in the induction of RIBEs, Chen et al provided further finding that mitochondria-dependent generation of ROS seems required.[62,63] Chen et al showed that RIBE in the nonirradiated A_L human–hamster hybrid cells was induced with the conditioned medium collected from donor cells irradiated by LDR only in the cells contain normal mitochondrial function and not in the cells with the deletion of mitochondrial DNA. This may be due to the fact that ROS production was increased only in irradiated cells with normal mitochondrial DNA but not in the cells without mitochondrial DNA. These results demonstrate that mitochondria-dependent ROS might be very important in RIBEs.[62]

The transmitted soluble factors generated by irradiated cells to nonirradiated cells may include NO, O_2^- and TGF-β1. The study by Han et al showed that DSBs formation using 53BP1 immunofluorescence staining and proliferation using flow cytometry were increased in bystander CHO cells cocultured with LDR-irradiated CHO cells. These RIBEs were reduced when c-PTIO (a scavenger of NO), DMSO (a scavenger of ROS), or anti-TGF-β1 was added to the cultures collected from LDR-irradiated cells.[60] These results are consistent with studies performed in different systems.[64,65]

In addition, recent studies implied that small noncoding RNAs, particularly microRNAs, are possible mediators of RIBEs. Xu et al found miR-21 was significantly upregulated in both directly irradiated and bystander human fetal lung Medical Research Council cell line 5 (MRC-5) fibroblasts cells and RIBE-like response can be induced in nonirradiated MRC-5 cells by transfecting miR-21. These data indicate miR-21 is involved in RIBEs.[66] Hu et al also suggested miR-663 participates in regulation of biological effects in both directly irradiated and bystander nonirradiated human cervical cancer cells (HeLa) via targeting of TGF-β1.[67]

Biological Effects of LDR on Germ Cells

For the past 3 decades, the biological effects of LDR, such as hormesis, ARs, and bystander effects, in somatic cells have attracted the interest of many investigators. The LDR can stimulate cell proliferation and prevent HDR-induced inhibition of cell proliferation in lymphocytes, splenocytes, and hematopoietic cells under both in vitro and in vivo conditions.[34,68,69] However, in terms of apoptotic cell death, there is controversy on the effects of LDR. Some researchers have found decreased apoptosis of HDR-exposed cells after pretreatment with LDR,[21,70] whereas others have observed increased apoptosis.[71,72] These discrepancies may be due to differences in doses and rates of LDR and cells types.[70-73]

The testes are among the most radiosensitive organs. Low-dose radiation mostly leads to apoptotic death of male germ cells, while HDR mainly induces necrotic death.[12,74] Over the past 20 years, the biological effects of LDR on germ cells, especially apoptosis, have been the focus of intense research.[12] In this section, we summarize the work of Chinese researchers studying LDR-induced biological effects on germ cells (Figure 2).

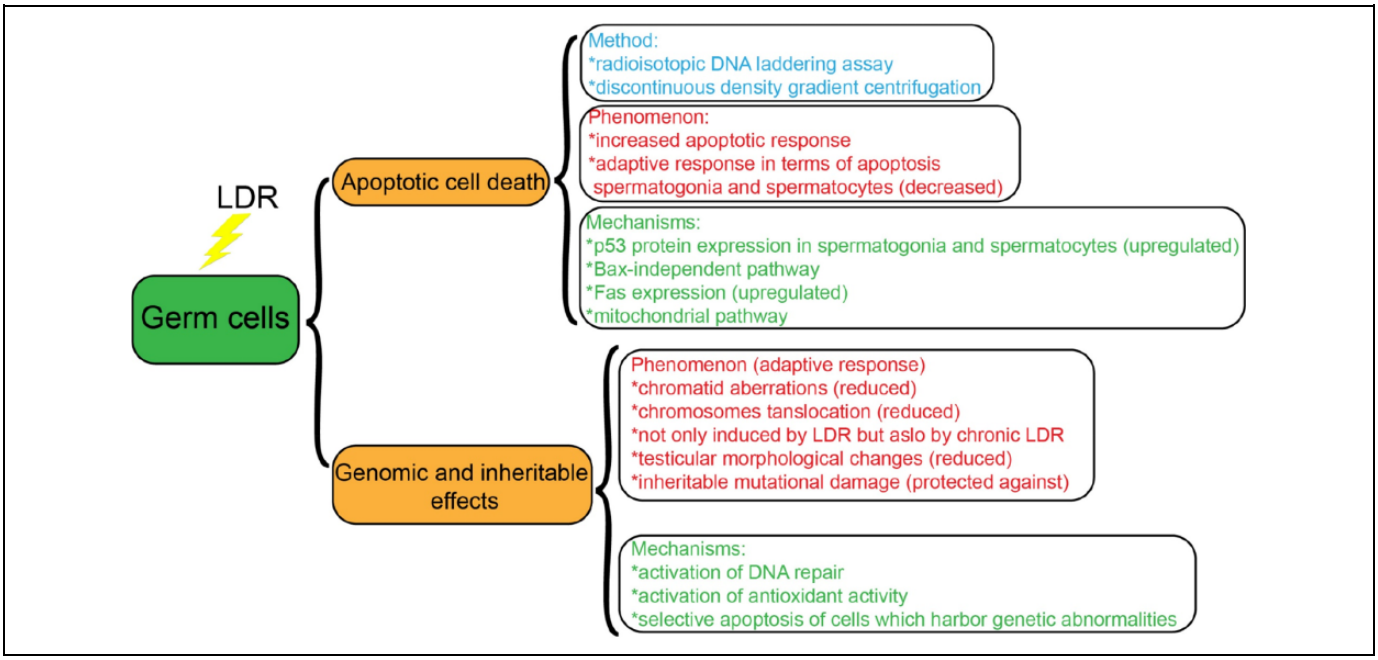

Figure 2. Research on the biological effects of low-dose radiation (LDR) on germ cells by Chinese scholars.

Low-Dose Radiation–Induced Apoptotic Germ Cell Death

As mentioned above, apoptotic cell death is a major manifestation of the biological effects of LDR on germ cells. Therefore, methods for detecting apoptotic germ cell death are needed. Currently, there are several well-established assays for apoptosis, including morphologic methods, quantitative DNA fragmentation assays, and flow cytometry measurement assays, used for male germ cells. The DNA-laddering assay, which is a well-established quantitative assay for apoptotic cell death, was optimized by Chinese researchers Cai et al to be a radioisotopic DNA-laddering assay and has been used to study apoptotic cell death of testicular cells. The radioisotopic DNA-laddering assay is more sensitive at detecting apoptotic cells within testicular tissue samples.[75] Subsequently, the invention of flow cytometry permitted investigators to quantify the percentage of germ cells undergoing apoptosis. However, due to inherent differences in DNA content in male germ cells at different stages, apoptotic testicular cells cannot be identified by flow cytometry without first isolating and separating the different types of germ cells. Liu et al first used discontinuous density gradient centrifugation to separate the different types of germ cells. This method, which minimizes the distribution alternation of different cells types, promotes flow cytometry for detection of apoptotic cells in mouse testes exposed to LDR.[76]

Benefiting from the development of apoptotic cell death detection methods, some studies have focused on the apoptotic response of male germ cells induced by LDR in China. In 2006, Liu et al characterized the effect of LDR on apoptosis at doses of X-rays ranging from 25 to 200 mGy on germ cells of Kunming mice after irradiation, where the maximal effect was observed at 75 mGy, using multiple apoptotic cell death detection methods. It was found that germ cells exhibit increased apoptosis in response to LDR compared to somatic cells, which exhibit decreased apoptosis in response to the same doses of LDR.[76] However, the differential responses to LDR of somatic and germ cells cannot be explained based on current studies. Recently, many studies have been performed on the LDR-associated ARs in somatic cells. When LDR induction of ARs in male germ cells was investigated based on apoptosis, Liu et al found the number of apoptotic spermatogonia and spermatocytes significantly decreased when the Kunming mice were preexposed to 75 mGy 6 hours before being irradiated with HDR (1, 2, or 3 Gy). Low-dose radiation did not induce the same AR in spermatids and spermatozoa.[76]

As summarized above, there is an apoptotic cell death response due to LDR in germ cells. Therefore, the mechanisms of apoptotic cell death due to LDR in germ cells have attracted wide interest from Chinese researchers. The molecule p53 has been reported to play a critical role in radiation-induced apoptotic cell death in testes.[77,78] Liu et al observed a significant upregulation in p53 protein expression in spermatogonia and spermatocytes of Kunming mice exposed to LDR in the form of X-rays at 25 to 75 mGy but not 200 mGy. This result suggests that LDR-induced apoptotic cell death in the testes is likely p53 dependent within a low-dose range of LDR.[76] Bcl-2, as an antiapoptotic molecule, and Bax, as a proapoptotic molecule, have been reported to have important roles in regulation of apoptotic germ cell death.[79,80] However, Liu et al found that no statistical correlation between apoptotic cell death and Bcl-2 and Bax protein expression in germ cells exposed to 25 to 200 mGy LDR.[76] This finding demonstrates induction of testicular apoptosis by LDR via a Bax-independent pathway. In addition, Liu et al examined alterations in Fas expression in the testes of

Kunming mice exposed to 25 to 200 mGy. Significant increases in Fas expression were detected, and a positive correlation between Fas expression and apoptosis was observed.[12] It is well known the mitochondrial pathway is another apoptosis pathway found in both somatic and germ cells. Fang et al found that when male Kunming mice were exposed to whole-body LDR, the total NO synthase, ROS levels, and expression of apoptotic factors, such as cytochrome C, caspase-9, and caspase-3, were increased and ATPase activity and mitochondrial membrane potential in testicular cells were decreased, suggesting LDR can induce testicular cell apoptosis through a mitochondrial signaling pathway.[81] All of the above studies suggest that LDR-induced apoptosis of testicular cells may be directly correlated with the p53, Fas, and mitochondrial signaling pathways. Many reports have suggested apoptosis plays an important role in eliminating overproduced, genetically abnormal, or accidentally damaged germ cells.[80,82,83] Along these lines, apoptosis induced by LDR may serve as a checkpoint to control and eliminate abnormal cells caused by LDR.

Low-Dose Radiation–Induced Genomic and Inheritable Effects in Germ Cells

Apoptosis of germ cells can be induced by LDR. However, when preexposed to LDR, apoptosis of germ cells is reduced in response to subsequent HDR. Genetic material can be passed on to offspring by germ cells. Therefore, the reduction in apoptosis by LDR-induced AR in male germ cells should be investigated in terms of its genomic and inheritable effects.

In 1990, Cai and Liu demonstrated LDR can attenuate chromosomal damage caused by HDR. They found the rates of chromatid aberrations were reduced in spermatocytes from male Kunming mice exposed to whole-body LDR of 10 to 150 mGy that were subsequently exposed to HDR of 0.75 to 1.5 Gy compared to the spermatocytes of males exposed to HDR alone.[84] The researchers also observed translocation of chromosomes was significantly reduced in spermatogonia from male Kunming mice exposed to whole-body LDR of 10 to 150 mGy that were subsequently exposed to HDR of 1.5 Gy compared to the spermatogonia from males exposed to HDR alone. In addition, the researchers, who found HDR induction of chromosomal aberrations was markedly reduced when Kunming mice were exposed to prechronic LDR compared to HDR only, suggested that ARs from LDR damage to chromosomes in male germ cells were induced not only by acute LDR but also by chronic LDR.[85] Subsequently, Cai et al found the incidence of dominant lethal mutations was markedly decreased in adapted males compared to nonadapted males when they were mated to nonirradiated females; here, the fertilizing sperm was irradiated during the premeiotic stages of development, suggesting preexposure of male germ cells to LDR can protect against inheritable mutations in germ cell DNA. In addition to attenuation of chromosomal damage, Zhang et al observed testicular morphological changes were reduced in B6C3F1 hybrid strain male mice preexposed to LDR and then exposed to HDR compared to mice exposed to HDR only.[86]

Furthermore, the mechanisms by which LDR causes an AR that can reduce chromosomal and DNA damage were investigated. Many studies have suggested activation of DNA repair and antioxidant activity may be the major mechanisms responsible for LDR-induced ARs in germ cells. Zhang et al found a significant increase in superoxide dismutase activity in testes pre-irradiated with LDR and then exposed to HDR and a significant decrease in peroxidized lipid substrates compared to testes exposed to HDR alone.[87] In addition to triggering antioxidant protective mechanisms, Cai and Wang suggested that LDR may induce selective apoptosis of cells that harbor genetic abnormalities.[85,88]

Biological Effects of LDR on Tumor Cells

Low-dose radiation–induced biological effects, such as hormesis, adaptive effects, and bystander effects, have been extensively documented by many investigators in different experimental models, including cultured cells and experimental animals. However, it is unclear whether such LDR-induced biological effects can also occur in tumor cells. Over the past 2 decades, Chinese researchers have done a lot of work investigating the biological effects of LDR on tumor cells using cultured tumor cells in vitro and tumor-bearing animal models. Here, we review the progress of Chinese researchers in this field (Figure 3).

Jiang et al demonstrated that LDR does not induce tumor cells proliferation in vitro or in vivo. In their study, they found a stimulating effect on 4 normal human cell lines (MRC-5, HL7702, 293T, and 6550), but not on all of the human tumor cells lines (K56, HL-60, NCI-H446, U251, BEL7402, HCT-8, and HeLa) and the tumor-bearing mice (NCI-H446 and U251) when they were exposed to LDR (25-200 mGy X-rays for cells and 75 mGy for tumor-bearing mice).[89] In addition, Jiang et al demonstrated LDR does not induce an AR in tumor cells either in vitro or in vivo.[90] Yu et al also found that there was a stimulating effect on the normal cell line AG01522, but not the cancer cell line Lewis cells when they were exposed to LDR in vitro and in vivo. And, lack of an LDR-induced AR in tumor cells was also observed in tumor-bearing mice. Furthermore, they found a higher apoptotic effect and lower expression of the antiapoptotic gene *Bcl-2* in tumor cells of tumor-bearing mice exposed to D1 + D2 than those exposed to D2 alone.[91]

Liang et al proved LDR can induce cell proliferation in the human embryonic lung fibroblast cells 2BS, but not in the lung cancer cells NCI-H446 in response to 20 to 75 mGy X-rays. Using specific inhibitor, they also suggest LDR stimulates cell proliferation via the activation of both the MAPK/ERK and P13K/Akt signaling pathways in 2BS cells, but not in NCI-H446 cells.[92] Yang et al demonstrated LDR can induce distinct biological effects on HBE135-E6E7 normal lung epithelial cells and A549 cancerous human lung cells through ataxia-telangiectasia mutated (ATM) signaling. They found the activation of ATM/Akt/GSK-3β signaling pathway, nuclear accumulation of nuclear factor erythroid 2-related factor 2, and

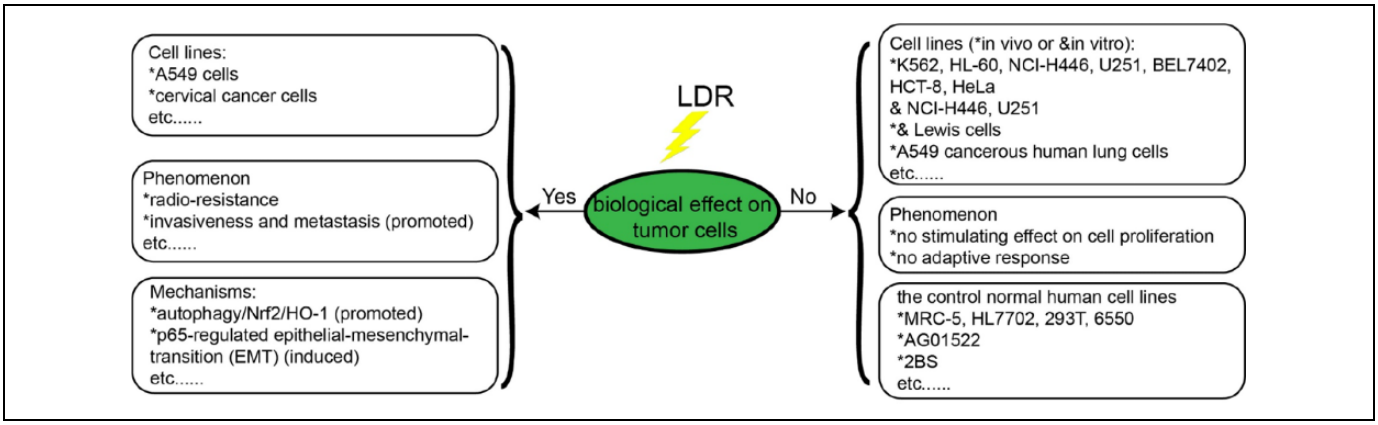

Figure 3. Research on the different biological effects of low-dose radiation (LDR) on tumor cells by Chinese scholars.

the expression of antioxidant were induced by LDR in normal lung epithelial cells (HBE135-E6E7), which can mitigate cellular damage from excessive HDR-induced ROS productions. However, all of these effects were not observed in A549 cells and the failure to activate these pathways may explain the distinction between normal and cancer cells in response to LDR.[93]

However, some studies have reported an opposite phenotype, where LDR can induce radioresistance in cancer cells. For example, Chen et al showed exposure to 50 mGy α particles can induce radioresistance following exposure to 750 mGy α-particles radiation in human lung adenocarcinoma A549 cells. They also suggested that ROS elevation in response to LDR may promote autophagy/Nrf2/HO-1 and confer radioresistance in A549 cells.[94] Yan et al found LDR can induce p65-regulated epithelial–mesenchymal transition in cervical cancer cell lines Siha and C33A, thus promoting invasiveness and metastasis of cervical cancer cells.[95] Some researchers speculate these discrepancies may be due to differences in cancer cell lines, LET, and experimental time points.[93]

In recent years, laboratory and clinical studies have shown the occurrence and development of malignant tumors is closely related with immune dysfunction or suppression. Therefore, effectively improving the immune functioning of patients with cancer is considered an important means of anticancer treatment. It has been demonstrated that LDR can induce hormesis and ARs in the immune system. In addition, many researchers have suggested LDR can induce distinct biological effects on normal and cancerous cells. Therefore, the hypothesis that LDR may have antitumor effects in vivo has been proposed. Over the past 30 years, Chinese scientists have conducted extensive research on this hypothesis (Figure 4).

In 1995, Yin et al reported the tumor incidence in Kunming mice and C57BL/6J mice irradiated with 50 mGy before tumor inoculation (78.31%) was significantly lower than in nonirradiated direct inoculation tumor mice (91.7%) on day 12 after tumor inoculation. In the LDR-irradiated group, tumor growth was slower and tumor mass was smaller than in the group not exposed to LDR.[96] Fu et al found when C57BL/6J mice were irradiated with 50 to 150 mGy X-rays and then inoculated with Lewis lung cancer cells, the mean number of lung tumor nodules was significantly lower than in the LDR nonirradiated tumor-inoculated mice 14 days after LDR irradiation. Furthermore, IL-2 secretion and NK cell activity in the LDR group were significantly higher than in the nonirradiated tumor inoculation group.[97] Yu et al demonstrated that LDR (75 mGy) markedly increases antitumor abilities in tumor-bearing Kunming strain mice and improves erythrocyte immune function and the ability to carry O_2.[98] Wang et al demonstrated low-dose splenic radiation can inhibit liver tumor development in Sprague-Dawley (SD) male rats through functional changes in $CD4^+CD25^+$ T regulatory cells.[99]

Li et al observed that, in C57BL/6J mice subcutaneously transplanted with S180 tumor cells were preexposed to 75 mGy whole-body LDR and then irradiated with 10 Gy, the tumor growth rate was significantly lower than in tumor-bearing mice only exposed to 10 Gy irradiation. Natural killer and lymphokine-activated killer cell activity in the spleen in the group preexposed to LDR and then irradiated with 10 Gy were significantly higher than in the group only exposed to 10 Gy.[100] Fu et al found that preexposure to 75 mGy before mitomycin C systemic chemotherapy significantly improved the effect of the chemotherapy in an experimental model utilizing C57BL/6J mice inoculated with Lewis lung cancer cells. At the same time, evaluation of immune indicators revealed a decrease in the number of spleen cells, NK cell and cytotoxic T-lymphocyte activity, phagocytosis by macrophages, and the responses of splenocytes to ConA due to chemotherapy in the tumor-bearing mice. However, all of the abovementioned immune indicators surpassed the chemotherapy-alone group when tumor-bearing mice were preexposed to LDR before chemotherapy.[101] Yu et al showed LDR can enhance the antitumor effect of the chemotherapy agent cyclophosphamide (CTX) in S180 sarcoma-bearing mice. In their study, Kunming mice implanted with S180 sarcoma cells were exposed to 75 mGy whole-body γ rays and then 300 mg/kg CTX was administered by intraperitoneal injection after the LDR. Tumor growth was discovered to be significantly reduced and tumor cell apoptosis significantly increased in the group exposed to CTX in addition to LDR. Increased cell-cycle arrest was

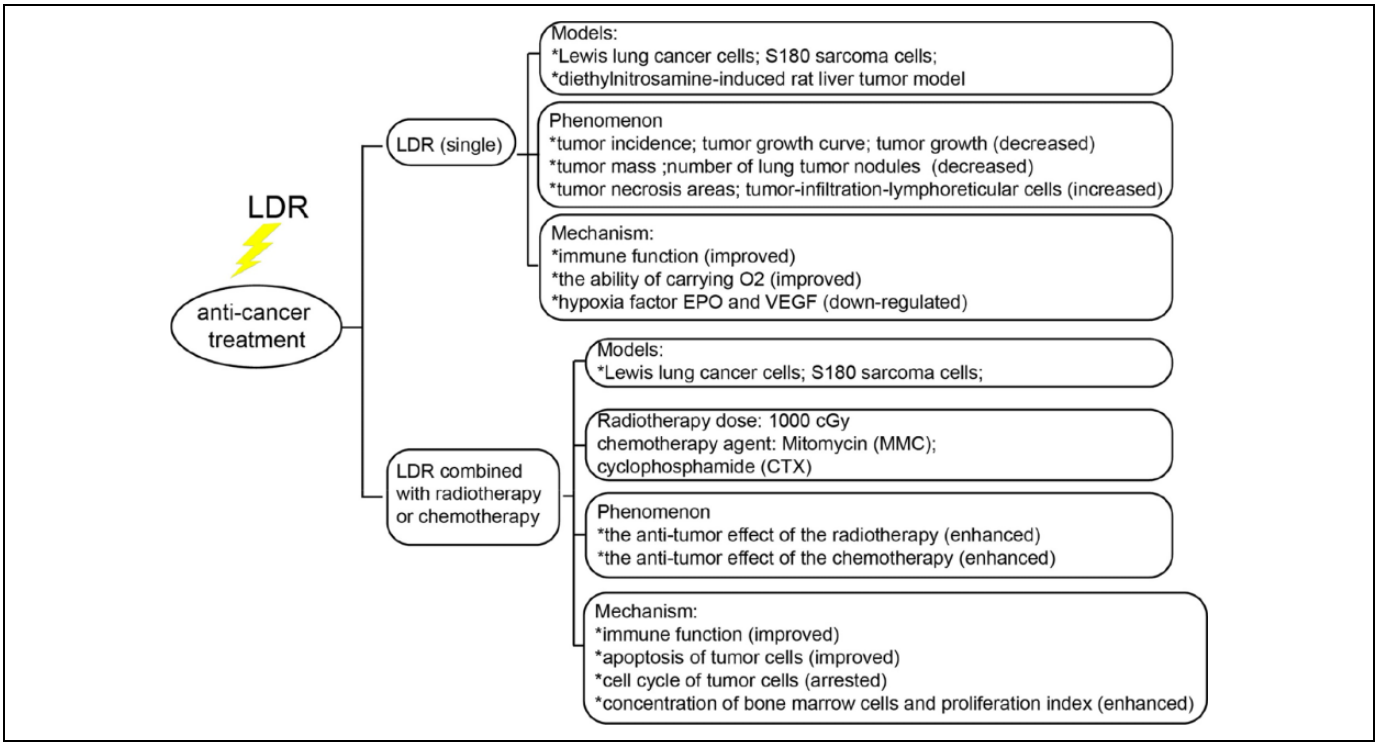

Figure 4. Research on the models, phenomena, and mechanisms of low-dose radiation (LDR)-induced anticancer treatment by Chinese scholars.

observed in mice exposed to LDR followed by CTX than in mice exposed only to LDR or CTX. In addition, BMCs concentrations and proliferation in CTX + LDR mice were higher than in the untreated mice. Therefore, LDR was suggested to significantly protect the hematopoietic functions of the bone marrow, which may be of practical significance for adjuvant chemotherapy.[102]

All the above studies showed LDR may have antitumor effects in vivo that are perhaps related to enhancements in immune function or others LDR-induced functions. These findings imply LDR has potential for protecting normal tissues from radiotherapy while enhancing or not diminishing the efficacy of tumor therapy.

Biological Effects of LDR on Diabetes

Diabetes mellitus, including types 1 and 2, which is characterized by destruction of insulin-producing cells of the pancreas (called β cells), has dramatically increased worldwide.[103] Oxidative stress is now known to be involved in almost of all pathological states of pancreatic β cells in diabetes.[104] In addition, secondary oxidative stress caused by diabetic hyperglycemia, hyperlipidemia, and inflammation plays a critical role in almost all diabetic complications.[105] This raises an important issue: whether LDR can prevent the development of diabetes and its various complications. Researchers in China have conducted extensive studies on this issue, especially on the prevention of diabetic complications, including on diabetic nephropathy (DN), and diabetes-induced testicular damage, cardiomyopathy, and skin ulcers. Therefore, we collected the available from these studies and described it below (Figure 5).

Diabetic nephropathy is a major microvascular complication in patients with diabetes. Renal oxidative damage induced by systemic inflammation caused by hyperglycemia and hyperlipidemia plays an important role in the initiation of DN.[106-108] Zhang et al showed multiple exposures to LDR can attenuate diabetes-induced renal dysfunction and this effect is associated with the suppression of systemic and renal inflammation. In their study, when diabetic male C57BL/6J mice were exposed to whole-body 25 mGy X-rays, diabetes-induced renal dysfunction and pathological changes were markedly attenuated. In addition, multiple exposures to LDR increased TNF-α, intercellular adhesion molecule 1 (ICAM-1), IL-18, monocyte chemoattractant protein 1 (MCP-1), and plasminogen activator inhibitor 1 (PAI-I) levels in the serum and kidneys.[109] Xing et al suggested LDR can prevent DN by stimulating Akt phosphorylation and upregulating Nrf2 expression and function.[110] Zhang et al also proved a single 75 mGy and accumulated 75 mGy can stimulate SOD1 expression and activity; this may be one of the mechanisms preventing DN.[111] Shao et al demonstrated exposure to LDR (50 or 75 mGy) can significantly prevent type 2 diabetes-induced kidney injury characterized by renal dysfunction and pathological changes. They also suggested the protective mechanisms of LDR can be mainly attributed to the attenuation of dyslipidemia the subsequent

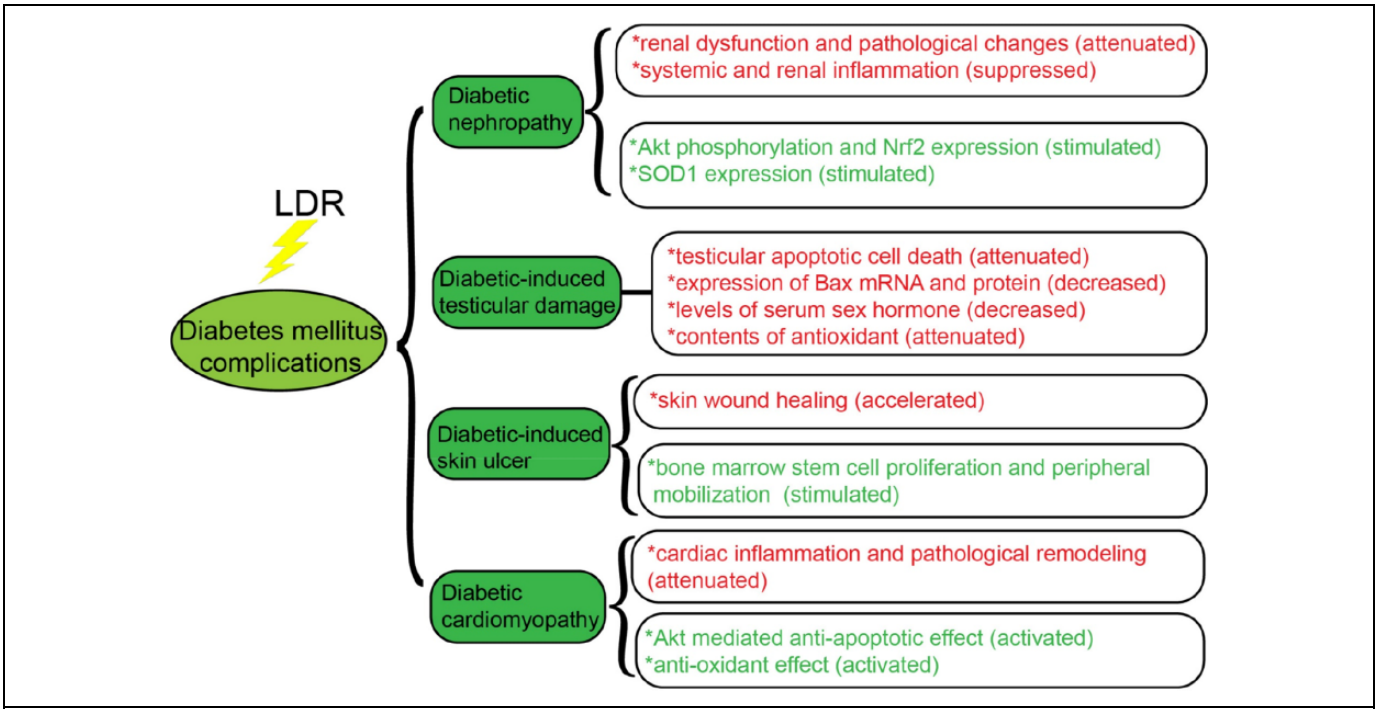

Figure 5. Research on the biological effects of low-dose radiation (LDR) on diabetes mellitus complications by Chinese scholars.

lipotoxicity-induced insulin resistance, inflammation, and oxidative stress.[112]

In recent years, many studies have demonstrated diabetes has a significant impact on the fertility of men, including through erectile dysfunction and reduced sperm motility and semen volume. In 2000, Cai et al reported a significant increase in apoptotic cell death in the testes of diabetic male SD rats.[113] Low-dose radiation (less than 100 mGy) was found to induce genomic damage and cell death in the testes.[12,76,84,114] Therefore, it was hypothesized exposure to LDR can attenuate diabetes-induced testicular damage. Zhao et al found repeated exposure to LDR significantly attenuates testicular apoptotic cell death, decreases expressions of Bax mRNA and protein, decreases levels of serum sex hormones (testosterone, luteinizing hormone, and follicle-stimulating hormone), and attenuates antioxidant levels (lipid peroxides) and oxidative damage both in the serum and testes in a type 1 diabetic experimental male Wistar rat model, where diabetes is induced with a single injection of streptozotocin (STZ). Their results suggest diabetes-induced testicular cell death may be mediated by increased oxidative stress and LDR protection from the cell death is most likely mediated through preservation of antioxidants.[115]

In addition, some studies have studied impaired wound healing as a complication associated with diabetes.[116,117] The lack of cellular and molecular signals required for normal wound repair processes, including angiogenesis, epithelialization, and remodeling, is likely the main factor contributing to impaired wound healing in patients with diabetes.[118,119] In 2010, Guo et al investigated the biological effects of repeated LDR exposure (75 mGy X-rays) on skin wound healing in a male Wistar rat model of diabetes. Their results suggest repeated exposure of diabetic rats to LDR can significantly accelerate skin wound healing compared to nonirradiated diabetic rats. They also demonstrated the LDR-induced improvement in wound healing was associated with increases in bone marrow and circulating $CD31^{+}/CD34^{+}$ stem cells, vessel regeneration, and cell proliferation in the wound tissue and the expression of matrix metalloproteinases 2 and 9. They concluded LDR-induced acceleration of wound healing in diabetic rats is associated with stimulation of bone marrow stem cell proliferation and peripheral mobilization.[120]

Diabetic cardiomyopathy, characterized by cardiac remodeling, including profibrotic changes and cardiac hypertrophy associated with cardiac dysfunction, is another severe complication of diabetes.[121,122] Diabetes-induced inflammation, oxidative stress, and apoptosis are thought to be the main features of diabetic cardiomyopathy.[123,124] In 2009, Zhang et al investigated the preventive effects of repeated LDR exposure on diabetes-induced cardiac inflammation and damage in a C57BL/6J mice model of diabetes. In their study, they observed diabetes caused significant increases in cardiac inflammation, as indicated by increases in IL-18, TNF-α, ICAM-1, PAI-1, and MCP-1 mRNA and protein levels. Compared to nonirradiated diabetic mice, repeated exposure to LDR significantly reduced diabetes-enhanced cardiac expression of IL-18, TNF-α, MCP-1, and PAI-1. There was also a lesser extent of cardiac histopathological abnormalities, oxidative damage, and fibrosis in diabetic mice exposed repeatedly to LDR than in those that were not. Their results suggest LDR can attenuate diabetes-induced cardiac inflammation and pathological remodeling.[125] However, some studies found significant inflammation was normally observed in short-term rather than long-term

diabetes.[126,127] Therefore, the same group investigated whether LDR can prevent late-stage diabetic cardiomyopathy and whether this protection is due to induction of antiapoptotic and antioxidant pathways. In the study, they found LDR can prevent cardiomyopathy in C57BL/6J mice with STZ-induced diabetes treated with whole-body LDR. In addition, they observed this protection induced by LDR associated with p53 inactivation, Nrf2 function, and Akt activation enhancement.[128] The above studies by Chinese scholars indicate LDR may be an effective treatment for diabetes-induced complications.

Stochastic Effects of LDR

At present, a consensus has been reached that HDR could have injurious effects; however, whether the effects of LDR are beneficial or injurious still remains controversial.[129] The beneficial effects include hormesis and adaptive effects, which were reviewed above. The possible injurious effects include bystander effect, stochastic effect, and so on. The stochastic effect means the potential possibility of carcinogenesis resulting from radiation-induced DNA mutations and damage. Nowadays, it remains unclear whether multi-exposure to LDR has any risk of increasing tumorigenesis. Scientists in China have done many works on the stochastic effects of LDR. Here, we summarized the works in this field.

In 2000, Tao et al estimated the cancer risk associated with the LDR exposure of average annual effective dose of 6.4 mSv in the high-background radiation areas in Yangjiang, China.[130] They observed 1 698 316 person-years by following up 125 079 patients, and accumulated 10 415 deaths, among which 1003 were caused by cancer during period 1979 to 1995. In their study, they did not find any increased cancer risk associated with the high levels of natural radiation in high-background radiation areas. And, on the contrary, they found that the mortality of all cancers in high-background radiation areas was generally lower than that in the control area, but not statistically significant. In 2009, Yu et al investigated the effects of multi-exposure to LDR on tumorigenesis using a C57BL/6J mouse model. Their results suggested that 0.1 Gy, even after multiple exposures (0.1 Gy $\times$ 10), does not increase tumorigenesis.[131]

However, there were also many researches indicating that LDR could induce stochastic effect. Hwang et al assessed the cancer risk in a population who received prolong LDR for about 10 years as a result of occupying building containing ^{60}Co-contaminated steel in Taiwan. Their results indicated that protracted LDR could higher cancer risks in the general public, especially for leukemia.[132] In the study of Wang et al, the relative risk of developing different types of cancers among medical X-ray workers in China was determined.[133] They found the significant relationship between the risk of malignant and occupational radiation factor. Their results also suggested that the risk of lung cancer in medical diagnostic X-ray workers was significantly higher than that in control group. In 2010, Feng et al measured the radiation dose from computed tomography (CT) scans in anthropomorphic phantom using a 64-slice multiple detector CT and estimated the associated cancer risk.[134] They concluded that the effective doses from these common pediatric CT examinations ranged from 0.7 to 3.5 mSv, and the cancer risks were found to be up to 0.16% with some organs of higher radiosensitivity, including the breast, thyroid gland, colon, and lungs. And these above researches indicated that it is still controversial whether LDR induces stochastic effect. This may be due to the insufficient sample size. Compared with HDR, the risk of LDR is likely to be lower, and progressively larger epidemiological studies are required to quantify the risk.

Conclusions

In this review, we summarized research progress by Chinese scholars on LDR-induced biological effects, including hormesis, ARs, bystander effects, and stochastic effect, as well as on germ cells, tumor cells, and diabetes. Low-dose radiation–induced hormesis has been extensively observed in different biological systems, especially immune and hematopoietic systems. The research progress made by Chinese scholars on enhancement of immunity and hematopoiesis by LDR was reviewed with an emphasis on associated cellular and molecular mechanisms. The LDR-induced AR is described as the induction of cellular resistance to genotoxic effects caused by subsequent exposure to HDR. Here, the research progress by Chinese scientists on LDR-induced AR is reviewed.

In addition, the data available from Chinese scientists on LDR-induced bystander effects, which refer to the induction of damage in cells not directly hit by radiation, were collected and evaluated. Although fundamental scientific evidence on the biological effects of LDR exposure is already available, further studies are required to illustrate both the phenomenological features and mechanisms underlying the biological effects of LDR, which can be studied through genomics and proteomics research. Animal models are also necessary methods of research.

Furthermore, the biological effects of LDR on germ cells, tumor cells, and diabetes have also been studied by Chinese researchers. Although there are fewer studies on the biological effects of LDR on germ cells than somatic cells, it is clear that the biological effects of LDR on germ cells cannot be simply extrapolated from those observed in somatic cells. Apoptotic cell death and genomic and inheritable effects induced by LDR in germ cells have been investigated by Chinese scientists. Further investigations on associated mechanisms are urgently needed to provide further insight into the biological effects of LDR on germ cells. Considerable evidence gathered over nearly half a century suggests that LDR may be used as a treatment for cancer and diabetic complications. And, the controversy of the stochastic effects and cancer risk induced by LDR were also discussed. The resolution of the controversy may depend on the future epidemiological investigation with large sample size.

We hope these beneficial applications of LDR will be achieved soon and become commonplace in treating cancer

and diabetic complications. Although the beneficial biological effects of LDR on different biological systems were reviewed in this article, the potential risks of LDR need to be considered in future applications.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the National Natural Science Foundation of China (31670859), CAMS Innovation Fund for Medical Science (2017-I2M-1-016), China Postdoctoral Science Foundation (2018M630106), Natural Science Foundation of Tianjin (18JCYBJC26800, 18JCQNJC12300), and the Fundamental Research Funds for the Central Universities (10023201601602).

ORCID iD

Kaihua Ji https://orcid.org/0000-0002-0155-9506

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