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New understanding of the low-dose radiation-induced hormesis☆

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ABSTRACT

Dr. Liu Shuzheng as a well-known educator and radiobiologist has started to work on the physiological benefits of low-dose radiation since 1970s. His research on the distinct effects of low-dose radiation from those of high-dose radiation has nationally and internationally impacted radiobiology, medicine and oncology. Therefore, here we briefly review the research from his research team from early years to last two decades. Two important facts related to LDR biological effects are the hormesis and adaptive response, both have been the main focuses of Dr. Liu Shuzheng early research. In the last couple of decades Dr. Liu Shuzheng have further investigated how to apply these important mechanisms into clinical translational research, such as the potential to application of LDR-hormesis to enhance tumor's chemo- or radio-therapy and LDR-induced adaptive response to protect normal tissue from chemo- or radio-therapy related side toxic effects. Therefore, Dr. Liu has provided important guidance and role model for his trainees in the continue of their research career in radiation biology, medicine and oncology.

Introduction

First of all, we want to congrats the launch of the new journal, *Radiation Medicine Protection*, in the year of 2020. I emphases the year of 2020 because it is the 30th anniversary of my PhD graduation (1990) along with my first scientific publication in English.[1] Apparently both are important for me, however, I would say, these achievements are attributed to my PhD mentor, Dr. Shuzheng Liu due to his well training of us. At this special moment, therefore, I would like to invite, with a great pleasure, Dr. Shunzi Jin who was also trained by Dr. Shuzheng Liu, and Dr. Hongyu Jiang who is one of my trainees, to co-author the special, brief review on the elegant works, done by Dr. Shuzheng Liu with his many PhD graduates, for the origin, development and expansion of the concepts "hormesis" and "adaptive response" induced by low-dose radiation (LDR) and its impacts on the academic and regulatory aspects in radiation research, medical application and protection.

Since Dr. Shuzheng Liu was in 1991–2000, and Dr. Shunzi Jin is the current Director of the Key Laboratory of Radiobiology at the School of Public Heath, Jilin University (see Box for Biography of Dr. Liu Box 1), here Drs. Jin and Jiang with myself, on behalf of Dr. Liu's trainees, review Dr. Liu's academic thoughts and spirits that have significantly impacted his trainees who have inherited his academic ideas and talents to engage the radiobiological research for keeping his dream and ideas moving forward forever.

General review of his research interests

Dr. Liu Shuzheng as an educator and radiologist in China is nationally and internationally well-known, and his academic achievements are well-recognized world-wide. Dr. Liu studied the effects of radiation at high doses on nonspecific immune functions and the endocrine regulation in the 1960s. After investigated systemic effects of radiation at high doses, Dr. Liu begun to study LDR effects in 1965 in accordance with the need for peaceful use of nuclear science and technology as well the development of nuclear energy. Beginning in the mid-1970s, a series of epidemiological investigations were conducted based the population survey of Guangdong residents in high level of natural radiation (HNR) area, with the finding of increased DNA repair ability and T-cell reactive ability of HNR residents who received exposure levels of three times compared to the control. Then a series of animal experiments were designed to further examine and confirm the findings of HNR area resident, in laboratory levels for possible mechanisms underlying these findings and potential implication of LDR-induced stimulation, "hormesis".

Dr. Liu's findings[1–13] can be mainly summarized in the following aspects: (1) Cytogenetic adaptive response induced by LDR, as shown by pre-LDR (D1) able to increase the tolerance of chromosomes and DNA to high-dose radiation (D2)-induced damage; the molecular mechanism responsible for the adaptive response, cell signal transduction and protective protein expression; (2) LDR stimulates immune function probably via LDR-induced cascade activation of T-cell signal transduction, increase in the expression of immune cell-promoting genes, anti-tumor cytotoxic effect, antibody formation ability, and the central link for the activation of T-cell-to-cell reactions; (3) LDR reduces the function of the hypothalamus-pituitary-adrenal cortex (HPA) axis, characterized by reduced gene expression of hypothalamus POMC and reduced plasma ACTH and corticosteroid contents, all which can partially relieve the tension of the HPA axis on the immune system, resulting in the

☆ Dr. Liu Shuzheng early research interests and scientific contributions.

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BOX 1
Biography of Dr. Shuzheng Liu

Dr. Liu Shuzheng was born November 19, 1925 in Changsha, Hunan Province. In high school, he started to love the natural sciences and medicine. In the summer of 1945, he graduated with honors from Yali Middle School in Shaoling, Hunan Province, and was admitted to the Xiangya Medical College in the same year. After graduated in 1951 Dr. Liu was assigned to the Department of Internal Medicine at Tianjin First Military Medical University. In April 1960, he was assigned to establish the Radiation Medicine by the requirement of university medical graduate education and training, and to restructure to form the first Department of Radiobiology in China and he served as the director of this department. Over the more than 50 years since the establishment of this department, the University has changed its name several times, from Jilin Medical University, Bethune University of Medical Science to currently Jilin University, however, Dr. Liu Shuzheng has continually worked in the same department and dedicated himself to the radiobiological field to educate and train many master and PhD graduates and direct the scientific research. During this period, he has even served as President of the Bethune University of Medical Science for eight years (1983–1991). He also successfully developed the Radiobiological Department into the first Key Laboratory for Radiobiology in 1990, with the support of the National Health and Health Commission (formerly the Ministry of Health). For this State Key Laboratory, he has served as the first and second Director of administration and Chairman of the Academic Committee from 1991 to 2000.

stimulation of immune function; (4) LDR increases the body's anti-carcinogenesis ability and inhibits tumor growth and metastasis. Therefore, these LDR-induced distinct responses from high doses of radiation have built the fundament for exploring its potential enhancing the tumor suppression effect of local radiotherapy and reducing systemic chemo- and radiotherapy related side toxicity.

Representative contributions of Dr. Liu's research to the fields of radiobiology, radiation medicine and oncology

LDR adaptive response, and its potential implication

The first example of the excellent works that have been conducted by the team led by Dr. Liu as a pioneer in China and even world-wide is the genetic (or genomic) adaptive response induced by LDR. The survival adaptive response was recognized in bacteria exposed to very low doses of mutagen N-methyl-N′-nitro-nitrosoguanidine in 1970s,[14] attributed to adaptive DNA repair pathway[15]; however, whether ionizing radiation could also induce genetic adaptive response was unclear at that moment although Dr. Luckey had proposed the physiological benefits from LDR.[16] Therefore, Dr. Liu research team investigated the stimulating effect of LDR on DNA synthesis and DNA damage repair capacity in 1980s. In 1983, Dr. Wolf with his colleagues reported LDR-induced protective and repair mechanisms, reflected by a phenomenon, called "cytogenetic adaptive response".[17] They specifically showed that when human lymphocytes were cultured with [3H]-thymidine as a source of LDR and then exposed to 1.5 Gy X-rays, the yield of chromatid aberrations was significantly less in [^{3}H]-thymidine/X-rays group than those in X-rays alone group,[17] which was found associated with LDR-stimulated DNA repair activity in these lymphocytes.[18]

Meanwhile, Dr. Liu's team also reported, for the first time, the stimulation by 50 mGy LDR of unscheduled DNA synthesis (UDS) of spleen cells.[19] Then in 1990, these in vitro studies were consequently confirmed under in vivo condition, respectively, in mouse spleenocytes[20] and rabbit lymphocytes and mouse bone marrow and testicular cells.[21–23] These studies from Dr. Liu's group have systemically revealed that when the inductive LDR (D1) of X-rays at 10 mGy with a dose rate of 10 mGy/min was given for the in vitro studies and at 2, 10, 50, 75 and 100 mGy with a dose rate of 50 mGy/min given for the in vivo studies while the challenging dose (D2) was 1.5 Gy X-rays for the in vitro experiments and 0.65 or 0.75 Gy for the in vivo experiments at a dose rate of 0.44 Gy/min, (1) 10 mGy could induce the adaptive response in human as well as rabbit lymphocytes irradiated not only in G1, S and G2 phases, but also in the G0 state; (2) although D1-induced adaptive response could only last three cell cycles, this adaptive response could be revived when the inductive D1 was repeated after the third cell cycle; (3) the adaptive response could be induced by LDR not only in somatic cells, both in vitro (lymphocytes) and in vivo (bone marrow cells), but also in germ cells (spermatocytes); (4) the magnitude of the adaptive response induced by whole-body irradiation was found to be dose-dependent and dose-rate dependent, which was also different in different organs with different radiosensitivities.

Mechanistically (Fig. 1), the induction of cytogenetic adaptive response by pre-exposure of human lymphocytes to LDR, shown by a decrease of chromatid aberrations caused by subsequent D2, might include two possible mechanisms, i.e., (a) activation of enzymatic processes by D1 to facilitate the repair of chromosomal damage; (b) induction of protective proteins by D1 to reduce the number of chromosomal aberrations[22]; This conclusion was derived from the facts: (1) the cytogenetic adaptive response could be enhanced by hyperthermia (41°C and 43°C) and suppressed by hypothermia (4°C); (2) hyperthermia (41°C) alone could also induce the cytogenetic adaptive response; (3) the cytogenetic adaptive response could be inhibited by cycloheximide–an inhibitor of protein synthesis; (4) supernatant from cultured lymphocytes treated with D1 failed to show the protective effect. These results implied that the cytogenetic adaptive response is not only related to the activation of repair enzymes, but also to the induction of protective proteins.[24] Although the genomic adaptive response has been extensively investigated, more and more studies with more findings in terms of its diversity in different conditions and potential mechanisms remain undergoing by subsequent studies including those from Dr. Liu's team.[25–31]

Now the adaptive response could be seen in a wide-range of conditions and measurements, these earlier research from Dr. Liu team has formed the solid base for the development of several new concepts in the fields: (1) Increased anti-oxidative proteins,[32] signaling pathways[33–35]

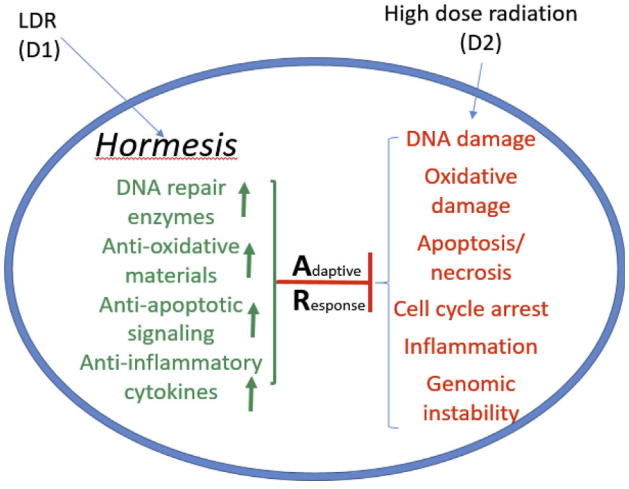

Fig. 1. LDR induces adaptive response (AR) by up-regulating DNA damage repair enzyme, anti-oxidative components, anti-apoptotic signaling, and anti-inflammatory cytokines. All these mechanisms make DNA, chromosome and cellular organelles resistant to subsequently high dose of radiation induced damage, shown by reduced D2-induced DNA damage, oxidative damage, apoptosis, necrosis, cell cycle arrest and inflammation in D1/D2 group compared to cells or tissue with D2 alone.

and DNA repair components,[36] by LDR mediates the adaptive response; (2) LDR-induced adaptive response has been explored for its potential to the prevention of various diseases[37–39]; (3) LDR epigenetic modulation may involve the LDR adaptive responses[40–42]; (4) LDR-induced adaptive response may be a strategy to preventing anticancer drug side effects.[43–45] Although these potential application of LDR-induced adaptive response into clinics for improving chronic diseases or preventing anticancer therapeutic side toxicity remain controversy, the adaptive response induced by LDR has been extensively accepted and will be properly applied in the future.

LDR-induced immune stimulation and its anti-tumor effect

The second example of the excellent works done by Dr. Liu's team is the discovery of LDR able to stimulate immune function, which was called "hormesis", based on the epidemiological study on the immune status of the residents of the HNR, a fact that among the population of 15–25 year old in the HNR there were a few stimulating indexes, including the significant increase in reactivity of T lymphocytes to phytohemagglutinin (PHA), an increase in the percentage of B lymphocytes and a tendency toward enhancement of UDS in peripheral blood lymphocytes.[46] The human data was consistent with the laboratory evidence that plague-forming cell (PFC) reaction of the spleen in mice was increased in response to single dose of 75 mGy X-rays or chronic accumulated 65 mGy at a dose rate of 5.4 mGy/6 h.[19] In the same study, the number of cells in the thymus of mice exposed to 25 or 50 mGy of X-rays was also increased. There is not only increase in immune cells, but also increases in DNA repair system UDS in the spleen cells of mice either exposed to single dose of 50 mGy or to chronic accumulated 130 mGy compared to control. Consequently, a study from Dr. Liu group reported for the first time that LDR could stimulate immunologic functions through facilitation of the signal transduction process.[25] Due to these excellent works, Dr. Liu has been invited to systemically summarize the concept, advance, and potentially application of LDR hormesis.[47]

One of the potential application is the potential for preventing the tumor growth, invasion and metastasis via LDR-stimulated immune function.[47] First, Dr. Liu team demonstrated that if the total body irradiation of 75 mGy was given mice before inoculating Lewis lung cancer cells, the volume of transplanted tumors was significantly smaller than that of the tumor-bearing mice without pre-exposure to 75 mGy. In addition, the 40-day mortality rate was significantly decreased, the average life expectancy was significantly increased, and tumor cell metastasis was significantly decreased in pre-LDR treated mice.[48] In another study with X-ray to induce thymus lymphoma in C57BL/6 J mice, whole body exposure of mice to 25–100 mGy 6 h before each 1.75 Gy exposure could significantly reduce the carcinogenic effects of multi-exposures to 1.75 Gy, most likely via stimulating immune function,[49] which was confirmed by a later study.[50] These studies suggest LDR-stimulated immune function is able to prevent large-dose radiation-induced cancer, and also to inhibit the growth and invasion of implanted tumor cells. Second, LDR is also able to enhance tumor's radio- or chemo-therapy efficacy. For instance, 12 or 24 h before local 10 Gy therapeutic radiation, S180 tumor-bearing mice were given 50, 75 or 100 mGy. The tumor growth percentage was significantly reduced by pre-exposure to LDR.[51] Similarly, pre-exposure to 75 mGy at 6 h before cyclophosphamide (CTX) chemotherapy was given to Lewis lung cancer bearing mice also significantly enhanced the CTX-treatment efficacy.[52] As shown in Fig. 2, therefore, the enhanced radio- or chemo-therapeutic efficacy might be not only related to the stimulation of immune function to inhibit residual tumor cells after radio- or chemo-therapy and also adapt normal tissue to therapeutic dose-induced side toxicity.[53,54]

In the last decade, the role of LDR in tumor gene-radiation therapy was further explored in the lab. To explore whether conditional cancer radiotherapy protocols could be promoted by reducing therapeutic dose without reducing its treatment efficacy, we have established tumor-bearing mouse models with melanoma (B16) and Lewis lung carcinoma. Then conventional local radiotherapy was given with whole-body LDR in the presence or absence of gene therapy by intratumor injection of a recombinant plasmid Egr-mIL-18-B7.1 (E18B). For this protocol tumor local exposure to 2Gy (radiotherapy dose) was given 24 h after intratumor injection of 10 μg of the plasmid E18B followed by whole-body exposure to LDR (75 mGy) every other day for 2 sessions in 1 week. After several trials with different combinations, a protocol of 2-week treatment with 2 x (E18B + 2 Gy + 75 mGy x 2)/week was able to promote treatment efficacy at a reduced radiation dose compared to protocol of [2Gy every other day x 3]/week for 2 weeks and increased average survival rate, reduced mean tumor weight, reduced pulmonary metastasis and suppressed intratumor capillary growth. Mechanistically the enhanced therapeutic efficacy of LDR/gene-therapy with radiotherapy was related to the anti-tumor immune function of the body stimulated by LDR.[11,12] These experimental data show that the hermetic effect of LDR is not only theoretical, but also has the prospect of clinical application, which might be the clue for the late study using 50 mGy as LDR to protect the tumor-bearing mice from the adverse effect of conventional radiotherapy without reducing therapeutic efficacy.[54]

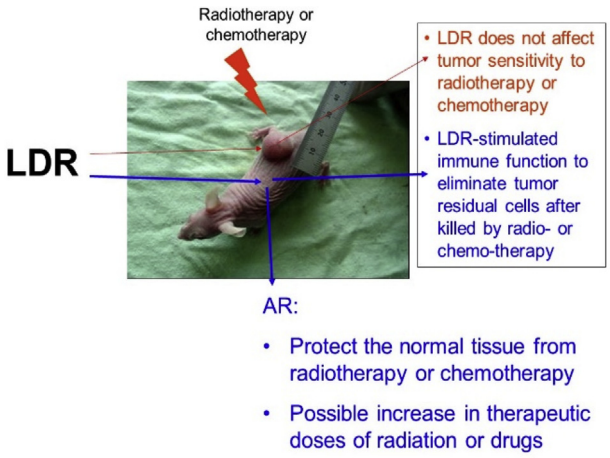

Fig. 2. Possible benefits of LDR on cancer radio- or chemo-therapy. AR: adaptive response.

Comprehensive remarks for the contribution of his conceptual revolution to current status of radiobiological research

Apparently Dr. Liu Shuzheng has demonstrated with a large amount of experimental data that LDR can cause biological effects distinct from those cause caused by high-dose radiation, which in most cases is quite the opposite. On this basis, he proposes the "J-curve" and "inverted J-curve" of the dose-effect relationship. He confirmed the existence of this dose-effect relationship at different levels of overall immune function, cytological basis, molecular expression and gene transcription, and pointed out the importance of dose rate and dose fraction in revealing this dose-effect relationship. Low dose rate (12.5 mGy/min or lower) is required for low dose radiation to effectively induce the adaptive response. He has proposed that the radiation dose range should be divided into three orders of magnitude for dose range of 25 mGy to 10 Gy: LDR of lower than 100 mGy at low dose rate radiation usually causes adaptive response, 0.1–1 Gy radiation is a transition zone and 1–10 Gy radiation causes a damaging or inhibiting effect. The specific form of dose-effect curve varies depending on the biological parameters observed, but its nonlinear characteristics are consistent.

Since the above conclusion is based on the effect of systemic radiation on the immune system, which is a major component of the body's anti-tumor defense mechanism, this finding is undoubtedly a challenge to the linear non-threshold (LNT) hypothesis for radiation-induced cancer risk. However, Dr. Liu Shuzheng has not only proposed, but also

approved its existence and potential mechanisms at multi-levels from molecular signaling and cellular regulation and systemic neuroendocrine regulation among organs. These results have enriched the current international theory of LDR hormesis and adaptive response, provided a theoretical basis for radiobiology for epidemiological investigation data that did not see an increase in the incidence of cancer or even decrease in the residents of the natural radiation high background area and even in the nuclear industry, and promoted the clinical application of LDR, which was greatly reproduced by the international academic community.

Along with other researchers in the biological research fields, the elegant and solid publication from Dr. Liu's team on the induction of LDR hormesis and adaptive response indeed have recieved more and more attention from the radiobiologist, radiologists and radio-oncologist as well as policy makers and regulatory agents, with extensively debating and discussing the LNT policy for the radiation protection, particularly regarding the issue whether LNT theory is proper and supported by scientific evidence for guiding the LDR protection.[55–57]

In summary, at the moment of new journal, *Radiation Medicine and Protection* is launched, reviewing Dr. Liu Shuzheng's earlier scientific research ideas and studying on his scientific spirits are really a great pleasure and also encourage us to further investigate LDR-induced biological effects, especially LDR-induced hormesis, adaptive response, bystander effect, longevity, genomic instability, and epigenetic modulation, to better and systemically understanding the biological effect of LDR and to provide a proper and scientific evidence-supported guidance for radiation protection, and may also apply these unique features to clinics for patients. We will more confidently and persistently follow Dr. Liu steps and/or paths he has made for us moving forward.

Conflict of Interest

None.

Acknowledgements

We apologize to all the colleagues from Dr. Liu's team whose work could not be cited because of the scope and space limitation. We thank Dr. Su Xu from at the National Institute for Radiological Protection, Chinese Center for Disease Control and Prevention, Beijing, China for his reading with critical and constructive inputs during the drafting and finalizing process of the review.

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