Low-Dose Radiation Prevents Chemotherapy-Induced Cardiotoxicity

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Abstract

Purpose of Review In this review, we will address the cardioprotective effect of low-dose radiation (LDR) on chemotherapeutic agents.

Recent Findings Cancer has become the most important cause of death in the world, and the morbidity and mortality are gradually increased. The application of anti-tumor drugs is an important therapeutic tool for cancer therapy at present, while its potential cardiotoxicity cannot be ignored. How to prevent and reduce the occurrence of cardiotoxicities needs further exploration.

Summary LDR induces an adaptive or hormetic response in cells and tissues, showing a tolerance to subsequently high dose of radiation- or chemical-induced damage in vitro and in vivo. LDR may exert its cardioprotective effects through different mechanisms, such as stimulating the proliferation of normal cells during anti-tumor therapy, enhancing anti-tumor immunity, stimulating antioxidative functions in normal tissues, activating DNA damage repair system, and improving metabolic function in normal tissues. Therefore, there may be a potential to apply LDR as an adjunct to myocardial protection for anti-tumor therapy.

Keywords Low-dose radiation · Adaptive response · Hormesis · Cardiotoxicity · Cancer drug

Introduction

Distinct from high-dose radiation that causes cytotoxic effects in vitro and in vivo, LDR has been proven able to stimulate immune function, increase expression and function of antioxidant molecules, and activate DNA repair systems, all of which are enhancements as a consequence of its hormetic effects [1–3, 4•]. The hormetic effects of LDR also are reflected by the effects of stimulating proliferation in normal cells, increasing lifespan,

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and enhancing fertility. When the cells or tissues pre-irradiated by LDR with the induction of hormesis receive subsequently high-dose radiation (HDR), the cells with LDR and HDR show less damage than the cells with HDR alone, i.e., LDR adaptive responses. Increasing evidence shows that LDR protects normal tissues around the tumors from impairment caused by subsequent HDR treatment by increasing normal tissue antioxidant activity and DNA repair capacity [1, 5]. However, these hormetic effects and adaptive responses are not observed in some malignant cell types, or at least the optimal dose frames for LDR to induce the hormetic effect may be different between tumor cells [2, 6]. There are many investigators with different experimental models, including cultured cells and experimental animals [3, 7–9], studying the role of LDR. A study reported that pre-chemotherapeutic LDR was able to alleviate anticancer drug, cyclophosphamide-induced damaging effects on the liver [10].

In 2016, it was reported that human exposure to LDR (CT scans of the brain) might relieve symptoms of both Alzheimer's disease (AD) and Parkinson's disease (PD), for which the mechanism may be related to X-ray stimulation of the patient's adaptive systems against neurodegenerative diseases [11]. Some studies also have shown that LDR has

positive effects on the proliferation of cell types such as fibroblasts, osteoblasts, hippocampal neurons, mesenchymal stem cells, and mouse bone marrow hematopoietic progenitor cells [12, 13, 14•]. Otsuka et al. [12] demonstrated that animals primed with pre-exposure to γ-rays at 0.5 Gy developed increased resistance to DNA damage caused by subsequent exposure to 1.6 Gy radiation, compared with mice irradiated with the high-dose radiation alone, indicative of a radioadaptive response. Our previous study also suggested that 75 mGy LDR-stimulated growth of normal cells but not leukemia or solid tumor cells in vitro and LDR also did not stimulate growth of solid tumor cells in vivo [5]. However, there were few studies that have explored whether LDR could provide protective effect against Dox-induced cardiotoxicity in vivo.

The Cardiotoxicity of the Chemotherapy

Chemotherapy has shown great progress over the past two decades, leading to the gradual increase in the survival of cancer patients [15]. However, along with this benefit, the cardiotoxic effects have also become an increasing problem, even years after completion of therapy [16, 17•]. The development of cardiotoxic effects not only has a negative impact on the patient's cardiac prognosis but also considerably restricts the therapeutic opportunities. The clinical manifestations of cardiotoxicity cover a broad spectrum of disorders, ranging from mild transient arrhythmias to potentially lethal conditions such as myocardial ischemia or infarction and cardiomyopathy. There are two main types of anticancer drugs more frequently correlated with cardiotoxic effects: (1) chemotherapeutic agents: including anthracycline, taxanes, alkylating agents, and antimetabolites; and (2) molecular-targeted drugs: such as trastuzumab and vascular endothelial growth factor (VEGF) inhibitors.

The Cardiotoxicity of Chemotherapeutic Agents

The Cardiotoxicity of Anthracycline

Anthracycline (ANT)-chemotherapeutic agents have been employed in the treatment of a wide variety of solid tumors and hematologic malignancies, including leukemia, lymphoma, breast cancer, lung cancer, multiple myeloma, and sarcoma. However, its clinical utility is markedly hampered by the high incidence of a dose-dependent cardiotoxicity [18]. The most feared is the chronic forms of cardiotoxicity, characterized by irreversible cardiac damage and congestive heart failure [19]. Four types of ANT cardiotoxicity can be recognized [20–23]: (1) "Acute" cardiotoxicity occurs during ANT administration or immediately afterwards; (2) "Subchronic"

cardiotoxicity is extremely uncommon; (3) "Early chronic" ANT cardiotoxicity develops later in the treatment course, or weeks to months after the completion of chemotherapy; (4) "Delayed" cardiotoxicity is also called "late-onset chronic". Whereas acute cardiotoxicity does not constitute a major clinical problem and it usually resolves shortly after the end of an infusion, the types of chronic toxicity are serious, clinically significant, and substantially affecting the overall morbidity and mortality, which is required for a long-term therapy. Given the difficulty or even impossibility of effective treatment, the prevention of ANT cardiotoxicity is highly urgent and of crucial importance.

The Cardiotoxicity of Alkylating Agents

Cisplatin is used to treat osteosarcoma and ovarian, head and neck, esophageal, bladder, and lung cancers [24]. It can cause atrial fibrillation, supraventricular tachycardia, left bundle branch block, myocardial ischemia, myocardial infarction, and so on [25]. It is usually related to vascular toxicities, hypertension, and cerebral ischemia.

Cyclophosphamide is used to treat lymphoma, leukemia, multiple myeloma, lung cancer, and breast cancer. Cyclophosphamide's cardiotoxicity is associated with a high dose of cyclophosphamide (> 150 mg/kg and 1.5 g/m^2/day) and the incidence of heart failure is 7–28% [18]. The common expressions are tachyarrhythmias, low voltage of QRS, nonspecific T or ST segment abnormalities, and AV conduction disturbances [25, 26].

Ifosfamide is an analogue of cyclophosphamide which is used to treat soft tissue sarcoma and non-small-cell lung cancer and is associated with arrhythmias, ST segment changes, and heart failure [27].

The Cardiotoxicity of Antimetabolite Agent

The synthetic pyrimidine metabolite 5-FU is used to treat breast, gastrointestinal, head and neck, and ovarian cancers. Angina-like pain is common during 5-FU treatment which is difficult to discriminate from myocardial ischemia or infarction, particularly with the administration method use of continuous infusion. However, myocardial ischemia, heart failure, arrhythmias (including atrial fibrillation, VT, and VF), and cardiogenic shock have rarely been reported [28]. The incidence of myocardial ischemia associated with 5-FU ranged from 1 to 68% [18].

Capecitabine is an oral prodrug of 5-FU used to treat metastatic breast and colorectal cancers. The incidence and risk factors of capecitabine-associated cardiotoxicity are not well defined. The slight change of ST segment and cardiac markers have been noted.

The Cardiotoxicity of Molecular-Targeted Agent

The Cardiotoxicity of Trastuzumab

Trastuzumab, an HER2-targeted agent, is used in the treatment of metastatic breast neoplasm. It interferes with cellular repair, leading to increased apoptosis that can cause reversible and transient cardiomyopathy and even left ventricular systolic dysfunction or heart failure [29], particularly when used concomitantly with ANT/cyclophosphamide.

The Cardiotoxicity of VEGF Inhibitors

VEGF inhibitors, which include tyrosine kinase inhibitors (TKIs) sorafenib and sunitinib, as well as monoclonal antibodies bevacizumab and ramucirumab, not only contributes to the development of cancer via the formation of new blood vessels in tumors but also has an important role in the normal physiologic function of endothelial and renal cell survival, vasodilation, and cardiac contractile function. Therefore, its inhibition has significant cardiovascular side effects. Specifically, VEGF inhibition induces conditions such as hypertension, thromboembolism, ischemia, cardiac contractile dysfunction, and heart failure. A retrospective analysis of clinical trials demonstrated elevated blood pressure within 4 weeks of initiating therapy with sunitinib [30].

The Possible Mechanism of Cardiotoxicity Induced by Chemotherapy

Chemotherapeutic cardiotoxicity can be characterized as either type 1 or type 2 cardiotoxicity based on the effect of the agent on cardiomyocytes [31]. Type I cardiotoxicity is caused by cardiomyocyte death, either through necrosis or apoptosis, and the result is irreversible. Type II cardiotoxicity is caused by cardiomyocyte dysfunction rather than cell death and therefore may be reversible. Chemotherapy-induced cardiotoxicity includes a combination of mechanisms which influence several intracellular signaling cascades, critical to both cancer progression and normal function of the heart. In view of the extensive research and general application of ANT, this paper will introduce the mechanism of myocardial injury of chemotherapeutic drugs with doxorubicin (DOX), as well as ANT as the representative.

The Possible Mechanism of Cardiotoxicity Induced by ANT

The long-term cardiotoxicity caused by ANT includes cardiomyocyte death and therefore represents a type I toxicity. The generally accepted mechanisms for ANT-induced cardiomyopathy include oxidative stress, inflammation, dysregulation of calcium handling

and cellular contractility, mitochondrial degeneration, and necrosis or apoptosis [17•, 32, 33, 34•]. However, oxidative stress is the major contributor in triggering and progressing ANT-induced myocardial biochemical and pathological changes, leading to the final structural remodeling and dysfunction [32, 35]. A considerable body of evidence points that mitochondria are the key targets for ANT-induced cardiotoxicity, and therefore, it could be also crucial for effective cardioprotection [36].

Oxidative Stress

Reactive oxygen species (ROS), such as the hydroxyl radical (•OH), whose reactivity is so high that it reacts very close to its site of formation [37], and other species, such as superoxide ($O_2^{\cdot-}$) and hydrogen peroxide (H_2O_2). ROS were considered one of the key players in tissue injury, when an imbalance occurs in favor of the ROS generation rather than increasing antioxidant capacity, oxidative stress ensues [38]. Oxidative stress is related to the development of many pathological conditions including cardiovascular disease, diabetes, rheumatoid arthritis, cancer, and neurodegenerative disorders [39]. One hypothesis was that ANT-induced cardiotoxicity is primarily mediated by the generation of ROS in cardiomyocytes and increased oxidative stress in the cardiomyocyte mitochondria [40, 41]. Oxidative stress is also a trigger for cardiomyocyte death by apoptosis or necrosis [42, 43].

ANTs are well known for their ability to produce ROS through multiple pathways [21, 35, 44]. First, one-electron reduction of ring C of the ANT tetracycle leads to the formation of a semiquinone free radical. Suitable flavoproteins catalyze the formation of reduced semiquinone radicals by accepting electrons from NADH or NADPH and passing them to ANT in a sequence of redox cycling reactions. This process was accompanied by the formation of $O_2^{\cdot-}$, and the further formation of •OH could be catalyzed by SOD, and very slow unless catalyzed by transition metals—especially iron [45]. Thomas et al. [46] have shown that ANTs may increase the amount of free redox-active iron by generating $O_2^{\cdot-}$, which mediates an iron release from ferritin. The •OH reacts with every oxidizable compound in its vicinity and thus can induce damage to all types of macromolecules, including lipids, nucleic acids, and proteins [45]. The second basic mechanism by which iron may promote the oxidative stress induced by ANTs is the formation of ANT-Fe complexes [44]. No matter in the presence of a reducing system or not the ANT-Fe3$^+$ oxidized and reduced to •ANT-Fe2$^+$ resulting in •OH. Furthermore, apart from the ROS, cardiac exposure to ANTs may be also connected with the deregulation of the nitric oxide (NO) network [47]. Involvement of iron in the ANT-induced oxidative stress and cardiotoxicity has been supported by rich experimental evidence as reviewed in detail elsewhere [35]. In both vivo/vitro studies, the unfavorable effects of iron on ANT-induced cardiotoxicity could be eliminated by the iron chelator deferoxamine (DFO) [48, 49].

Mitochondrial Damage

Mitochondria are abundant and dynamic organelles that not only produce ATP for cellular function but also participate in a number of intracellular processes such as cell division, the initiation of mitochondrial signaling pathways, modulation of cytosolic metabolic pathways, and modulation of cytosolic Ca^{2+} signals and concentration, and ultimately, determination of cell life or death. In addition, mitochondria is a continuous source of O_2^- and their ROS products [50–52] particularly during cell injury. ANT causes significant cardiotoxicity characterized by marked increases in oxidative stress and mitochondrial dysfunction.

The target organelle of ANT-induced toxicity in cardiomyocytes is mitochondria. ANTs are well known for their ability to inhibit mitochondrial function through multiple pathways. First, ANT accumulated in mitochondria and the mitochondrial concentration of ANT was several folds greater than the simultaneous clinical relevant serum concentration [53], which leads to increased oxidative stress. It has been shown that the ANT redox cycling takes place in the mitochondrial electron transport chain (METC) [54], more specifically at complex-I, which, alongside complex-III, is more of a substantial ROS generator in the heart [55]. High mitochondrial ROS production after Adriamycin (ADR or DOX) administration results in molecular oxidative damage that affects membrane-bound proteins and enzymes, lipids, the mitochondrial genome, as well as significant other biomolecules [56]. Second, DOX-induced accumulation of ROS in mitochondria results in dissipation of the $\Delta\Psi m$, direct activation of the MPTP, cytochrome C release followed by caspase-3 activation and DNA fragmentation [57]. Mitochondrial fragmentation during apoptosis was connected with the collapse of the $\Delta\Psi m$ that was considered an irreversible point in the death cascade [58]. Third, DOX treatment of cardiomyocytes causes caspase-9 and caspase-3 activation [59–61], opening of the mitochondrial permeability transition pore, and subsequent release of cytochrome C into the cytosol [57, 62]. Furthermore, DOX binds directly to the mitochondrial phospholipid and cardiolipin, disrupting the association of inner mitochondrial membrane proteins with cardiolipin [63–65], which could enhance cytochrome C release in response to oxidative stress.

Apoptosis and Other Mechanisms

Apoptosis is a tightly regulated physiologic process of programmed cell death occurs in both normal and pathologic tissues. Numerous in vitro or in vivo studies have indicated that cardiomyocyte death through apoptosis or necrosis is a primary contributor to the progression of ANT-induced cardiomyopathy. The two main pathways that stimulate apoptosis are the intrinsic and the extrinsic pathways [34•]. The intrinsic apoptotic pathway is always initiated by the p53 tumor suppressor gene, a sensor of cellular stress, which can directly regulate a host of Bcl-2 family proteins such as Bcl-2 anti-apoptotic and Bax pro-apoptotic proteins in DOX-induced cardiomyocyte apoptosis [66, 67]. A study proposed that these proteins can regulate the collapse of mitochondrial membrane potential, cytochrome C release, activation of caspase-9, and subsequent activation of caspase-3, which is the key executioner of apoptosis [68, 69]. Previous reports indicate that the mitogen-activated protein kinase (MAPK) family is responsible for the expression of p53 and Bcl-2 family-mediated apoptosis [70–72]. MAPK consists of three major signaling cascades: the extracellular signal-related kinases (ERK1/2), the c-Jun N-terminal kinases (JNK), and the p38 MAPK. Numerous studies suggest that MAPK activation is involved in cardiomyocyte apoptosis induced by DOX [66, 73]. In addition to the activation of the intrinsic mitochondrial apoptotic pathway, activation of extrinsic apoptotic pathway also contributes to ANT-induced cardiomyocyte apoptosis [34•]. ANTs activate the extrinsic apoptotic pathway by several mechanisms which include (1) activation of nuclear factor-activated T cell-4 (NFAT4) by increased mitochondrial ROS production and activation of the calcium/calcineurin signaling pathway, leading to upregulation of Fas/FasL [74]; (2) activation of transcription factor NF-κB by ROS leading to increased Fas/FasL and p53 [75–77]; (3) downregulated expression of FLIP, a FLICE/caspase-8 inhibitory protein, by ROS thereby sensitizing Fas-mediated apoptosis [78]; and (4) downregulation of ARC, an endogenous inhibitor of the extrinsic pathway through interaction with Fas, FADD, and caspase-8 to prevent the formation of DISC [79, 80].

In cardiomyocytes, Ca^{2+} cycling is essential for effective myocyte contraction and relaxation [81], and the precise control of intracellular Ca^{2+} homeostasis relies on a series of specialized regulatory proteins, including transcription factors, ion channels, and Ca^{2+}-binding proteins. DOX-mediated alternation of Ca^{2+} homeostasis is another possible mechanism of cardiotoxicity [82]. The main causes of calcium overload in cardiomyocytes caused by DOX were (1) increased permeability of myocardial membrane and influx of Ca^{2+} [83, 84]; (2) inhibited the expression of Ca^{2+} ATPase-related genes, causing the decrease uptake of Ca^{2+} in the sarcoplasmic reticulum and disturbance of the formation of ATP, eventually lead to energy metabolism disorder [85, 86]. (3) activated the Ca^{2+} channel in sarcoplasmic reticulum to increase the release of Ca^{2+} [86].

Autophagy, regarded generally as a protective mechanism that maintains cell viability by recycling unwanted and damaged cellular constituents, is nevertheless subject to dysregulation having detrimental effects for the cell. Autophagic cell death has been described and has been proposed to contribute to DOX-induced cardiotoxicity. Additionally, mitophagy, autophagic removal of damaged mitochondria, is affected by

DOX in a manner contributing to toxicity [87•]. There is strong evidence based on in vitro and in vivo studies in rat, mouse, and rabbit models that DOX inhibits mTOR, an inhibition that is expected to contribute to cardiomyocyte injury [88–92], possibly by causing an exacerbated autophagy-initiation response. Another pathway by which DOX can promote autophagy initiation may be through the p53-mediated suppression of the transcription factor GATA-4 and the resulting downregulation of the pro-survival protein Bcl-2. Bcl-2 binds to Beclin-1 and thus prevents it from interacting with VPS34, and from initiating autophagy [87•]. DOX can also promote Bcl-2 phosphorylation which inhibits the Bcl-2/Beclin-1 interaction again facilitating autophagy initiation [87•]. Overall, DOX affects a number of signaling pathways converging to a robust initiation of autophagy and stimulation of autophagosome formation.

The Possible Mechanism of Cardiotoxicity Induced by Other Chemotherapeutic Drugs

Inhibition of HER2 (also known as ErbB2) by trastuzumab modifies mitochondrial integrity via the Bcl-X protein family, depleting ATP, and leading to contractile dysfunction [93, 94]. HER2 conjugates with HER4/neureguline-1 complex forming heterodimers that promote the activation of several signaling pathways, such as sarcoma-focal adhesion kinase complex (Src–FAK), which increases intercellular contact and mechanical junction [95], or phosphatidylinositol 3-kinase and MAPK, which stimulate the proliferation, survival, and contractile function of cardiac myocytes [96]. Experimental studies have shown that HER2, HER4, and neuregulin-1 play an essential role in heart development, considering the fact that the development of mouse embryos is impossible if one of them is absent.

There are two classes of anti-angiogenesis therapies for the use of cancer therapeutics: (1) antibodies specific for VEGF and (2) small molecular tyrosine kinase inhibitors (TKI) against the VEGF receptor. Mechanisms that contribute to these pathophysiological states include inhibition of NO and prostacyclin, increased production of endothelin-1, and oxidative stress and cell apoptosis [16].

Although the cardiotoxicity mechanisms of 5-FU are not fully understood, small coronary artery thrombosis, arteritis of small-sized vessels, and vasospasm have been suggested as possible mechanisms [27].

The Possible Mechanism by which LDR Affords Cardioprotective Effect on Cancer Chemotherapy

It has been generally accepted that both natural and man-made sources of ionizing radiation contribute to human exposure and consequently pose a possible risk to human health. Therefore, studying the effects of LDR is of great interest. There is increasing evidence indicating that radiation below certain doses could stimulate repair mechanisms to reverse the initial damage and protect the organism from subsequent radiation or other exposures that might otherwise cause cancer, such as the evidence that the epidemiological data from Japanese atomic bomb survivors and occupationally exposed workers [97–104]. Based on these findings, further studies were conducted to explore the protective role of LDR in anti-tumor therapy and the underlying mechanisms.

LDR Stimulates the Proliferation of Normal Cells during Anti-Cancer Therapy

In previous studies, LDR-induced proliferative effects were documented extensively in different normal cell types such as thymocytes, splenocytes, lymphocytes, lung fibroblasts, and diploid cells [105–110]. Some studies showed that LDR can activate the Raf, AKT signaling pathway which remodels the chromatin structure and regulates cell cycle, resulting in induced expression of genes related to cell survival [107]. LDR can also activate several members of the MAPK/ERK signaling pathways because inhibition of MEK function significantly abolished LDR-induced ERK1/2 activation and LDR-stimulated cell proliferation [2].

LDR Enhances Anti-Tumor Immunity in Anti-Tumor Therapy

Radiotherapy with HDR induces time-restricted immune suppression by directly destroying the immune cells [111]. However, in contrast with HDR, LDR offers an effective treatment for cancer through the stimulation of innate and adaptive immune response. In innate immune, LDR played an anti-tumor effect through (1) enhancing the expansion and cytotoxicity of NK cells by activating the P38 MAPK pathway [112] and (2) enhancing the cytotoxic function of macrophages against tumor cells and programs macrophage differentiation to an iNOS+/M1 phenotype that overcomes the barrier of cancer immunotherapy through efficiently recruiting tumor-specific T cells in malignant solid tumors [113, 114]. The adaptive immune plays an anti- tumor effect through (1) augmenting the proliferative response of T cells to antigenic, allogeneic, and mitogenic stimulation enhance the adaptive immune response directly, with a concomitant increase cytotoxic effects on tumor cells [115–117]; (2) enhancing the expression of surface markers both on antigen-presenting cells (APCs) and on T cells which lead to a reduction of self-tolerance induced by cancer cells [118, 119]; (3) affecting the T regulatory cells, which was used by cancer cell to comprise an important immune-evasion strategy [120–122]; and (4) increasing antibody secretion and enhancing the antibody-dependent cellular cytotoxicity response in tumor-bearing mice [123].

LDR Stimulates Antioxidative Functions in Normal Tissues

It is well known that radiotherapy may promote ROS formation, which can kill tumor cells via necrosis or apoptosis, but the exceeding ROS can also lead to DNA fragmentation, lipid peroxidation, and other negative effects of normal cell structural molecules [1]. LDR has been reported to increase the level of various kinds of antioxidants in vitro and in vivo. It is reported that LDR can regulate the expression of most antioxidants through increasing the activity of nuclear factor erythroid-2-related factor 2 (Nrf2), a major transcription factor of the antioxidative system [124].

LDR Activates DNA Damage Repair and Metabolic Modification in Normal Tissues

To ensure genome stability in irradiated cells, mammalian cells harbor cellular defense systems against radiation-induced single-strand breaks (DSBs). It is clear that DNA damage response (DDR) is one of the mechanisms involved in LDR-induced adaptive immune [6, 125, 126]. However, how and which DNA repair pathway coordinates in the DDR in response to LDR still need more in-depth research. The DDR associated with DSB repair pathways includes homologous recombination (HR) and non-homologous end joining (NHEJ) and a signal transduction process related with ataxia telangiectasia-mutated kinase. The DSB repair pathway is always controlled by the cell cycle phase. LDR may activate one pathway of single-strand break repair to stimulate the expression of DNA repair enzymes either in cycling or in resting normal cells, which leads to genetic stability and, eventually, radioresistance [1].

It has been reported that the aerobic glycolysis and oxidative phosphorylation included in metabolic pathways of glucose were related with radiosensitivity and radioresistance of cells [127]. The increase of aerobic glycolysis leads to the resistance of cell to radiation. Research showed that LDR could induce a metabolic shift from oxidative phosphorylation to aerobic glycolysis leading to the increase of radiation resistance in both cell and animal models [128].

The Protective Role of LDR on Chemotherapy-Induced Cardiotoxicity

It is known that LDR triggers repair mechanisms via adaptive response mechanism that can be recast in more qualitative terms as physical or metabolic processes. Physical mechanisms include molecular repair of cellular structures such as DNA; removal of the damaged cells by apoptosis, necrosis, and phagocytosis; cell differentiation and senescence; and response of the immune system to facilitate removal of damaged cells [11]. Experimental and clinical data have reported that LDR can mitigate damage through antioxidative defenses; mitigate EAE through upregulation of regulatory T cells and suppression of proinflammatory cytokines such as IFN-γ, IL-6, and IL-17; and also can impede tumor growth, diminish metastasis, as well as alleviate the suppression of immunity due to tumor burden [11, 129]. Abdel-Rafei et al. [12] demonstrated that exposure to fractionated 0.5 Gy (twice 0.25 Gy at 2-day interval) γ irradiation prior to biochemical insult can ameliorate lipid peroxidation and produce an anti-apoptotic effect in the hippocampus, whilst also increasing levels of glutathione, SOD, and catalase activity in this region. Studies also demonstrated that LDR can accelerate skin wound healing and ameliorate renal injury in diabetic rats [130]. Interestingly, in studies of medical professionals and hospital staff, blood antioxidant levels were significantly higher in participants exposed to LDR ranging from 0.1 to 3.8 mGy per month compared with unexposed controls [12].

The effects of LDR could contribute to antioxidative potential, reduce cancer incidence, and modulate a variety of immune responses [130]. Several experimental findings were reviewed recently and showed that LDR induces anti-inflammatory properties and may thereby protect against inflammatory disease [131]. We have additionally demonstrated that diabetic mice exposed to repetitive LDR at 25 mGy showed significant prevention of diabetes-induced renal and cardiac damage in type 1 and type 2 diabetes in animal studies. Exposure of normal or tumor-bearing mice to 25–75 mGy LDR significantly prevented the tumor growth and metastasis [132]. The fact that LDR has the potential to prevent chemotherapy-induced cardiotoxicity has garnered significant interest. Based on the evidence that LDR increases antioxidant activity and DNA repairing capacity, many studies were conducted to explore the role of cardioprotective and the possible underlying mechanisms of LDR in chemotherapy with Dox. Our study [133••] demonstrated that LDR-stimulated cardiac antioxidative capacity in reducing oxidative stress derived from mitochondria-dependent ROS/RNS generation which suggests that LDR could induce adaptation of the heart to DOX-induced toxicity. In addition, the cardiac protection by LDR may attribute to attenuate DOX-induced cell death via suppressing mitochondrial-dependent oxidative stress and apoptosis signaling.

Conclusions

All together, the above evidence offers a rationale chemotherapy protocol that LDR exposure before chemotherapy could properly prevent chemotherapy-induced cardiotoxicity. The mechanism of cardioprotection is not yet clear and needs further study. We can further study whether its cardioprotective effect in chemotherapy is related to inflammation, immune mechanism, autophagy, or others. Therefore, LDR may be a novel approach to prevent chemotherapy-induced cardiotoxicity and enhance the effectiveness of cancer therapeutics via stimulating multiple functions in the heart without impact on tumors.

Compliance with Ethical Standards

Conflict of Interest Jing Xu, Dandan Liu, Shengxiang Xiao, Xinxin Meng, Di Zhao, Xin Jiang, Xue Jiang, Lu Cai and Hongyu Jiang declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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133.•• Jiang X, Hong Y, Zhao D, et al. Low dose radiation prevents doxorubicin-induced cardiotoxicity. Oncotarget. 2018;9(1):332–45. **Suggest that LDR could induce adaptation of the heart to DOX-induced toxicity. Cardiac protection by LDR may attribute to attenuate DOX-induced cell death via suppressing mitochondrial-dependent oxidative stress and apoptosis signaling.**