Radiation-Induced Normal Tissue Damage: Oxidative Stress and Epigenetic Mechanisms

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Radiotherapy (RT) is currently one of the leading treatments for various cancers; however, it may cause damage to healthy tissue, with both short-term and long-term side effects. Severe radiation-induced normal tissue damage (RINTD) frequently has a significant influence on the progress of RT and the survival and prognosis of patients. The redox system has been shown to play an important role in the early and late effects of RINTD. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are the main sources of RINTD. The free radicals produced by irradiation can upregulate several enzymes including nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase), lipoxygenases (LOXs), nitric oxide synthase (NOS), and cyclooxygenases (COXs). These enzymes are expressed in distinct ways in various cells, tissues, and organs and participate in the RINTD process through different regulatory mechanisms. In recent years, several studies have demonstrated that epigenetic modulators play an important role in the RINTD process. Epigenetic modifications primarily contain noncoding RNA regulation, histone modifications, and DNA methylation. In this article, we will review the role of oxidative stress and epigenetic mechanisms in radiation damage, and explore possible prophylactic and therapeutic strategies for RINTD.

1. Introduction

Cancer is one of the most challenging diseases in modern times. In 2015, China reported about 4.2 million new cancer cases and 2.8 million cancer-related deaths [1]. Radiotherapy (RT) is currently one of the leading therapeutic approaches for several cancers; however, it carries the potential to cause injury to normal tissue, with both short-term and long-term side effects. In recent years, studies have shown that the oxidation/reduction (redox) system was associated with several types of damage after radiation exposure [2]. In addition, the redox system is related to epigenetic regulation and can regulate the expression of microRNAs (miRNAs) and other molecules, thus playing a role in sustained oxidative damage after radiation [3].

Cells and tissues are composed of about 80% or more water, and most of the radiation damage occurs due to the radioactivation of water, which induces the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) [4]. ROS and RNS are the main sources of radiation-induced normal tissue damage (RINTD). The generation of ROS induces molecular changes and causes oxidative damage to proteins, lipids, and DNA. It can also activate signal transduction pathways and early-response transcription factors [5]. The redox system plays an important role in acute radiation damage and is responsible for some radiation-induced early and late effects including inflammation, out-of-field effects, fibrosis, bystander effects, and others [6–9].

In recent years, several studies have demonstrated that epigenetic modulators play an important role in normal tissue damage, after redox-induced ionizing radiation. Epigenetic modifications are made up of the heritable changes in the expression of the gene that do not influence the sequence of the DNA. In mammals, epigenetic modifications primarily
contain noncoding RNA regulation, histone modifications (methylation, phosphorylation, and acetylation), and DNA methylation. Epigenetic changes can be reversible and can easily respond to natural bioactive dietary compounds [10]. Afanas’ev et al. has reported that free radicals such as NO and ROS can regulate and control the epigenetic processes [11]. In addition, the regulation of some miRNAs may decrease or increase the oxidative damage [11].

In regard to the damage caused by RT, treatment strategies are still lacking. Here, we review the role of oxidative stress and epigenetic mechanisms in radiation damage to explore possible therapeutic strategies for RINTD.

2. Oxidative Stress

Oxidative stress is involved in the development of many diseases including RINTD. The redox system plays an important role in the early and late effects of RINTD [12]. When cells are exposed to radiation, they immediately form free radicals with a half-life of nanoseconds. The redox system begins producing free radicals a few hours after exposure, with the potential to last for years [13, 14]. The free radicals produced by ionizing radiation can upregulate several enzymes, including nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase), lipoxigenases (LOXs), nitric oxide synthase (NOS), and cyclooxygenases (COXs). Their effects on mitochondrial function are distinct. These enzymes are expressed in specific ways in various cells, tissues, and organs (Figure 1).

2.1. NADPH Oxidases. NADPH oxidase (NOX) is thought to be a membrane-bound oxidoreductase. It can transfer electrons from NADPH to the oxygen molecules. In addition, some subtypes of these enzymes have been found in cells [12]. NADPH oxidase enzymes such as DUOX1, DUOX2, and NOX1-5 are the most crucial subtypes. They participate in the process of respiratory chain rupture after radiation [15]. These enzymes have the ability to transfer electrons across the plasma membrane and produce superoxide and other downstream ROS. However, the tissue distribution and activation mechanisms of the individual members of the NOX family are undoubtedly different [16]. In addition, many inflammatory cytokines and chemokines such as TGF-β, TNF-α, IL-1, and IFN-γ are involved in the NOX system activation [17]. NADPH oxidase enzymes play a key role in acute and chronic oxidative stress in bystander and directly irradiated cells [18]. Also, it has been shown that the expression of NOX2 and NOX4 can be upregulated in nontargeted tissues [19].

NOX1 is the first homolog of NOX2 described (then called gp91^phox^) [20, 21]. NOX1 can be expressed in a variety of cells including endothelial cells in the uterus, prostate, and placenta, as well as osteoclasts. It can also be expressed in some malignant tumors including colon cancer and melanoma [22–24]. Choi et al. reported that the NOX1-specific inhibitor can limit radiation-induced collagen deposition and fibroblastic changes in the endothelial cells, thereby alleviating pulmonary fibrosis induced by radiation [25]. In addition, the production of ROS was significantly decreased after inhibition of NOX1.

NOX2 is considered the prototype of the NADPH oxidase. A report by Kim et al. confirmed that NOX2 was involved in radiation-induced salivary gland damage. After 56 days of exposure to 18 Gy radiation, the expression of the NOX2 gene in the salivary glands of rats was significantly increased. In addition, the apoptotic genes such as caspase-9 and MAPKs, including p-38 and JNK, participate in NOX2 signaling cascades [26].
conducted by Narayanan et al. demonstrated that irradiation of human lung fibroblasts generated \( \text{O}_2^- \) and \( \text{H}_2\text{O}_2 \) with alpha particles. The plasma membrane-bound NOX2 is responsible for the production of \( \text{O}_2^- \) and \( \text{H}_2\text{O}_2 \) [27]. Datta et al. confirmed that long-range mitochondrial dysfunction and the increased NADPH oxidase, including NOX1 and NOX2 activity, are the main factors for radiation-induced continuous oxidative stress in the intestinal epithelial cells [28].

NOX3 was first described in the year 2000 based on its similarity to the sequences of other NOX subtypes [29], although the function of the protein was first studied in 2004 [30, 31]. At present, the study of NOX3 in radiation damage is limited. Shin et al. confirmed that the expression of NOX3 was upregulated after the irradiation of the oral mucosa of rats. The increased expression of NOX3 is thought to be related to the necrotic inflammatory exudate and oral mucosa ulcers [32].

NOX4 was initially thought to be an NADPH oxidase homolog, highly expressed in the kidney [33, 34]. Pazhiansamy et al. found that systemic irradiation in mice can selectively induce sustained oxidative stress in hematopoietic stem cells (HSCs), at least in part, by the upregulation of NOX4. The increased production of ROS by NOX in HSCs can mediate radiation-induced hematopoietic genomic instability [35]. The experimental results of Wang et al. showed that systemic irradiation selectively induces chronic oxidative stress in HSCs, at least in part by the upregulation of NOX4 expression, thereby giving rise to the induction of HSC senescence and residual bone marrow damage [36]. In addition, the TGF-\( \beta \)-NOX4 pathway may be responsible for the continuous production of ROS/NO and the subsequent genomic instability after bone marrow irradiation [37].

NOX5, found in the lymphoid and testis, contains an N-terminal extension with three EF hands, and it can produce superoxide dismutase and conduct \( \text{H}^+ \) ions when intracellular free Ca\(^{2+} \) increases [38–40]. NOX5 may participate in Ca\(^{2+} \)-activated, redox-dependent processes of spermatozoa and lymphocytes including cytokine secretion, cell proliferation, and sperm-oocyte fusion [41]. Weyemi et al. showed that the two members of NADPH oxidase, NOX4 and NOX5, participated in the process of radiation-induced DNA damage in human primary fibroblasts.

Currently, there is a small amount of evidence supporting the role of DUOX1/DUOX2 in chronic oxidative stress. Both DUOX1 and DUOX2 are highly expressed in the thyroid gland [42, 43]. Furthermore, DUOX1 can be found in the prostate and airway epithelia [44–47]. DUOX2 has been described in the salivary gland, airway epithelia, prostate, rectal mucosa, duodenum, cecum, and colon [44–49]. Ameziane-El-Hassani et al. demonstrated that radiation-induced DUOX1-dependent \( \text{H}_2\text{O}_2 \) production by NADPH oxidase was delayed in a dose-dependent manner for several days. In addition, p38 MAPK, which was activated after irradiation, can increase DUOX1 through the expression of IL-13, giving rise to sustained DNA damage and growth stagnation [50]. Wu and Doroshow showed that IL-4/IL-13 can induce the expression of DUOX2/DUOX2A and the production of ROS in human colon and pancreatic cancer cells, which in turn may be related to the occurrence of inflammatory gastrointestinal malignancies [51]. There are some studies that have shown the upregulation of DUOX1 and DUOX2 in the lung and heart. Some radioprotectors and antioxidants such as melatonin, metformin, and selenium have been shown to reduce the expression of these genes following exposure to ionizing radiation, relieving the heart damage and lung damage caused by radiation [52–56]. However, the relationship between DUOX2 expression and radiation-induced carcinogenesis has not been established and demands further verification.

2.2. COX-2. Cyclooxygenase-2 (COX-2), an isoform of cyclooxygenase, is responsible for the time-dependent and localized production of prostaglandins (PGs) at inflammatory sites [57], including tissues exposed to ionizing radiation. COX-2 plays a crucial role in the inflammatory response that converts arachidonic acid released by membrane phospholipids into PGs. In addition, ROS production is a standard secondary byproduct of arachidonic acid metabolism in the synthesis of PGE2 [58]. Several studies have shown that increased COX-2 expression is related to radiation toxicity after the irradiation of organs, such as the lungs, heart, kidneys, intestines, colon, and the brain [59, 60]. Other studies have reported that COX-2 is involved in the pathogenesis of vascular damage, atherosclerosis, and fibrosis induced by ionizing radiation [61]. Cheki et al. demonstrated that celecoxib, an inhibitor of COX-2, can decrease dermal inflammation, MCP-1 mRNA expression, and radiation-induced skin reactions [62]. In addition, several studies have investigated the role of nonsteroidal anti-inflammatory drugs (NSAIDS) as an inhibitor of COX on radiation damage in the lung and joints [63–65]. Clinically approved inhibitors are represented by NSAIDs like aspirin or ibuprofen and by selective COX-2 inhibitors such as celecoxib [60].

2.3. LOXs. LOXs are enzymes that dioxygenate unsaturated fatty acids, which can initiate lipoperoxidation of the membrane, synthesize signaling molecules, or induce cell structural and metabolic changes [66]. Currently, the role of LOX in radiation damage has been reported. Matyshovskaya et al. demonstrated that activated LOX is involved in the production of ROS after exposure and plays an important role in the process of radiation-induced DNA fragmentation in lymphocytes [67]. Another experimental study showed that LOX was activated immediately after exposure to thymocytes. High LOX activity was observed in cells within an hour after irradiation. In addition, radiation-induced generation of lipid peroxides may be a factor in LOX activation [68]. In another study, Halle et al. showed that chronic adventitial inflammation, vasa vasorum expansion, and 5-LOX upregulation are involved in radiation-induced arterial damage in cancer survivors. In previously irradiated arterial segments, the expression of 5-LOX was increased in exogenous macrophages surrounding vascular dilatation [69].

2.4. Nitric Oxide. Under conditions of stress, including inflammation, inducible nitric oxide synthase (iNOS) was thought to be the primary source of nitric oxide (NO) and
played an important role in carcinogenesis and the oxidative stress process. NO is generated by macrophages under the stimulation of inflammation through the iNOS enzyme, and it can interact with the mitochondria-derived superoxide to further produce peroxynitrite [70]. iNOS enzymes play a key role in the radiation damage via posttranslational regulation of the BER pathway of DNA repair. The main effect of NO is nitroacetylation of 8-oxoguanine glycosylase (Ogg1). Ogg1 inhibition by NO can result in increased accumulation of oxidative DNA lesions [71, 72]. Malaviya et al. noted that iNOS is involved in radiation-induced lung damage. In addition, there are complex interactions between oxidative and nitrosative stress, as well as inflammatory pathways that mediate lung damage after radiation [73]. In another study, the inhibitors of iNOS such as aminoguanidine and N-nitro-L-arginine methyl ester have been shown to reduce radiation-induced lung damage [74, 75]. In a study by Ohta et al., increased levels of NO were directly related to the radiation dose, and NO levels increased in the first few hours after receiving the radiation [76].

The role of NO in the radiation-induced bystander effect has been explored. The peculiarity of NO as a redox signaling molecule is partly due to its hydrophobic properties and relative stability [77]. The hydrophobicity of NO allows it to diffuse through the cytoplasm and plasma membrane, allowing this kind of signaling molecule to readily diffuse from irradiated cells to bystander cells without the involvement of gap junction intercellular communication. NO generated in the irradiated tissues can mediate cellular regulation through posttranslational modification of many regulatory proteins [78]. Ghosh et al. have shown that activated iNOS in irradiated cells are crucial to the bystander response. In addition, lipopolysaccharide-induced iNOS activity and the production of NO after irradiation increased bystander cell DNA damage [79, 80]. Han et al. showed that within 30 min of low-dose alpha-particle irradiation, NO played an important role in the process of DNA double-strand breaks in bystander cells [81].

2.5. Oxidative Stress and Inflammation. Inflammatory responses are thought to play an important role in redox activation. Normal cells that are directly exposed to irradiation or ROS will give rise to nuclear and mitochondrial DNA damages, which can lead to cell death via processes such as mitotic catastrophe, apoptosis, and necrosis [82]. Necrosis can trigger the release of inflammatory cytokines such as IL-1, IL-4, IL-13, and other inflammatory mediators, while apoptosis may cause the release of anti-inflammatory cytokines including TGF-β and IL-10 [83, 84]. ROS are the main cause of RINTD. The continuous formation of ROS after irradiation can be the source of radiosensitivity of the T lymphocytes and other cells [85]. Moreover, ROS can activate the NF-κB signaling pathway along with proinflammatory cytokines. NF-κB plays a key role in chronic inflammatory diseases after RT [86]. Inflammatory cytokines and growth factors can give rise to a variety of signaling cascades, such as NADPH oxidase, COX-2, and iNOS [87]. It has also been reported that COX-2 is an important gene which can mediate the subsequent inflammatory responses [88]. Mitochondria is thought to be an energy and free radical reservoir. In normal conditions, antioxidant defense systems neutralize superoxide and form free radicals and protect cells from oxidative damage resulting from mitochondrial activity [89]. However, mitochondrial dysfunction and apoptosis can be induced by ROS, pro-IL-1β, iNOS, and inflammatory responses. Also, studies have shown that the ROS-derived NOX system participated in mitochondrial dysfunction and in the subsequent production of ROS in this organelle [90]. Next, the damaged mitochondria will release ROS and activate the nucleotide-binding domain and the leucine-rich-repeat-containing family pyrin 3 (NLRP3) inflammasome pathway [91]. The activation of the NLRP3 inflammasome is the platform of caspase-1 activation. Finally, it will lead to the secretion of proinflammatory cytokines IL-18 and IL-1β [92]. Recent experiments and studies have shown that the upregulation of the NLRP3 inflammasome has a big impact on radiation damage [93–96]. Chronic inflammatory processes can exist for ages after irradiation, and the immune system does not suppress them. This is related to chronic oxidative damage giving rise to the genomic instability and impaired normal tissue function [97].

2.6. Oxidative Stress and Cellular Senescence. Cellular senescence can be induced by ionizing radiation. Radiation-induced senescence is mainly one of the mechanisms in radiation-induced pathological changes. Radiation-induced cellular senescence is thought to be caused by p53 activation, which is associated with a radiation-induced double-strand DNA break [98]. However, the exact mechanism of inducing cellular senescence is still unclear, but the involvement of ROS has been widely reported [99, 100]. The study of Kobashigawa et al. suggested that the delayed increase of intracellular oxidative stress levels plays a key role in the process of radiation-induced cellular senescence by p53 accumulation [101]. Sakai et al. showed that NOX4 can mediate the production of ROS in radiation-induced senescent cells and lead to normal tissue damage after irradiation through recruitment of inflammatory cells and intensification of tissue inflammation [102].

3. Epigenetic Mechanisms

3.1. Epigenetics and Cancer. Cancer is commonly thought to be caused by genetic alterations including deletions, insertions, mutations, recombination, copy number gains, single-nucleotide polymorphisms, and genomic instability [103, 104]. The latest evidence suggests that cancer may occur without changes in the nucleotide sequence, by means of alleged epigenetic alterations. Combinational crosstalk between epigenetic alterations and genetics has been known to play a role in the development, progression, and recurrence of cancer [105]. Mousse et al. reported that epigenetic alterations are among the driving forces of irradiation-induced carcinogenesis, by observing long interspersed nucleotide element 1 DNA methylation changes in the mouse hematopoietic system after irradiation [106].

Epigenetic dysregulation including increased activity of histone deacetyltransferases (HDACs), DNA methyltransferases...
(DNMTs), and changes in the noncoding RNA expression, can give rise to changes in gene transcription and expression, which regulate cell cycle, cell differentiation and proliferation, and apoptosis [107, 108]. Yi et al. showed that the combined action of DNMT and HDAC inhibitors could stagnate the cell cycle at the G2/M phase and suppress the growth of endometrial cancer by upregulating E-cadherin and downregulating Bcl-2 [107]. Choi et al. noted that DNMTs including DNMT3A, DNMT3B, and DNMT1 are overexpressed in the hepatocellular carcinoma compared with noncancerous liver samples [109]. One such study has demonstrated that HDAC5 can promote glioma cell proliferation by upregulating the expression of Notch 1 at both the mRNA and the protein level [110]. In addition, HDAC5 can also promote human HCC cell proliferation by upregulating the expression of Six1 [111]. Epigenetic regulation, as a molecular target for cancer prevention and therapy, has aroused wide interest. For example, some studies showed that (-)-epigallocatechin-3-gallate, a main component of green tea, could possibly bind with the DNMTs, reducing the methylation activity of cancer cells through epigenetic mechanisms, and thus leading to cancer prevention or treatment [112, 113]. At present, there is increasing evidence that targeting epigenetic modifications is an effective cancer prevention strategy.

### 3.2. Epigenetics and RINTD

In recent years, the relationship between epigenetic mechanisms and radiation damage has been studied extensively [114–116]. Currently, epigenetic mechanisms such as DNA methylation and miRNA and histone modifications are reported to be associated with radiation damage. These mechanisms are summarized in Table 1.

#### 3.2.1. DNA Methylation

DNA methylation is a crucial means of epigenetic modification, which primarily occurs in the CPG islands of the gene promoter regions. Multiple DNMT functions are required to establish and maintain DNA methylation patterns [117]. Therapeutic radiation can give rise to biological responses to confront the subsequent DNA damage and genomic stress, to avoid cell death. Antwih et al. showed that the DNA methylation response to radiation is parallel to the classical biological responses to radiation. The differential methylation level of DNA repair, cell cycle, and apoptosis pathways varied with different radiation doses.

#### 3.2.2. Regulation of miRNAs

miRNAs play critical roles in various biological processes, especially in regulating gene expression at the post-transcriptional level. Radiation can modulate the expression of miRNAs, and these changes can affect the expression of target genes and proteins, thus contributing to cancer prevention and therapy.
Fractionated low-dose radiation exposure has been reported to cause the accumulation of DNA damage and profound alterations in DNA methylation in the murine thymus. This could be the source of the risk of radiation-induced leukemia and thymic lymphoma [119].

Acharya et al. showed that neuroepigenetic mechanisms played an important role in affecting the functional and structural changes in the brain and in cognition after irradiation. In irradiated mice with cognitive impairment, 5-hydroxymethylcytosine and 5-methylcytosine were detected in the region of the hippocampus consistent with increased levels of Ten Eleven Translocation- (TET-) 1, TET3, and DNMT3a. DNMT3a and TET enzymes including TET1 and TET3 are related to addiction behavior and memory formation. In addition, they found an obvious improvement in the epigenetic effects of irradiation by inhibiting methylation using 5-iodotubercidin [116]. Koturbash et al. demonstrated the role of epigenetic effects in maintaining the long-term, persistent bystander effect in the spleen, in vivo. After localized cranial irradiation for 24 h and 7 months, the levels of methyltransferases DNMT3a, DNMT3b, and DNMT1 and methyl-binding protein MeCP2 in the spleen tissue were significantly decreased [120].

The above results indicate that radiation can cause changes in DNA methylation to modify and regulate the expression of related genes and proteins, thus causing the corresponding tissue and organ damage. Future research is essential to confirm the role of DNA methylation in radiation-induced normal tissue damage. In addition, DNA methylation can be used as a target to prevent and treat radiation damage in the future.

### 3.2.2. Histone Modifications

Histone modification is rarely studied in radiation-induced normal tissue damage. Most reports have focused on the regulatory role of histone modification in radiation approaches for killing tumor cells [121–123]. Histone modifications include methylation, phosphorylation, and acetylation. Herberg et al. showed that mismatch repair-deficiency leads to genome-wide changes in histone H3 methylation profiles prior to tumorigenesis. Analogous changes constitute a lasting epigenetic feature of radiation-induced DNA damage [124]. Zhang et al. showed that solar-simulated ultraviolet radiation can influence both histone acetyltransferase and HDAC activities causing decreased histone acetylation. This could be the main cause for radiation-induced skin DNA damage [125]. Further research is needed to verify the role of histone modifications in radiation damage.

### 3.2.3. Regulation of miRNAs

miRNAs combined with mRNAs can lead to posttranscriptional degradation or repression [126]. It is well known that the role of miRNAs in ROS production and oxidative stress is to increase the superoxide level by suppressing antioxidant enzymes. A good example is the upregulation of miR-21 in both targeted and bystander cells. MiR-21, which is triggered by TGF-β, can inhibit SOD2 gene expression, giving rise to a decrease in the activity of SOD2 and damage to irradiated and bystander cells by superoxide [3, 127]. In addition, the SOD activity and glutathione level were inhibited which have been revealed in nontargeted lung tissues [128]. Many studies have shown a link between miRNA regulation and RINTD. miRNAs can play an important role in the early evaluation of radiation-induced hematopoietic damage, as functional dosimeters of radiation [129, 130]. Li et al. also demonstrated that miR-30c plays a key role in radiation-induced hematopoietic and osteoblast cell damage, possibly by regulating the expression of the gene REDD1 [131].

Another study by Li et al. reported that the isomer of vitamin E, delta-tocotrienol, can inhibit radiation-induced miR-30 and protect human and mice CD34+ cells from radiation damage by inhibiting IL-1β-induced NF-κB/miR-30 signaling [132].

Radiation-induced lung damage includes chronic fibrosis and acute pneumonia [133]. miRNAs have been reported in many diseases including those with lung involvement [134]. Gao et al. showed that miR-19a-3p, miR-144-5p, and miR-144-3p are upregulated in rats 2 weeks after thorax irradiation [135]. Recently, Xie et al. also studied the response of lung mRNA expression to radiation-induced lung damage in rats [136]. MiRNAs may serve as biomarkers for early stages of radiation-induced lung damage.

Radiation-induced spleen damage has also been reported in recent years. Ghosh et al. reported that whole-body radiation exposure resulted in higher expression of miRNAs in the spleen tissue on day 4 and on day 250. In addition, the vitamin E analog gamma-tocotrienol can modulate radiation-induced miRNA expression in the mouse spleen, preventing radiation damage to the spleen [137]. Collectively, miRNAs can serve as promising candidates for radiation biodosimetry. In addition, the prevention and treatment of RINTD through miRNA regulation may have a promising future.

### 4. Conclusions

In summary, oxidative stress responses and epigenetic mechanisms play important roles in RINTD. The redox system and various oxidases upregulated by free radicals and generated by irradiation, including NADPH oxidase, LOXs, NOS, and COXs, participated in RINTD through different regulatory mechanisms. ROS and NOS produced by inflammatory cells and mitochondria are involved in oxidative damage to bystander cells and targeted tissues. In addition, a variety of inflammatory factors including the NLRP3 inflammasome play an important role in radiation-induced oxidative stress damage. Epigenetic mechanisms such as DNA methylation, regulation of miRNAs, and histone modifications have been extensively studied in recent years in relation to RINTD. New progress has been made in the field of radiation damage treatment through the regulation of epigenetic mechanisms. With a further understanding of oxidative stress and epigenetic regulatory mechanisms, we hope to better explore the preventive and therapeutic strategies in RINTD in the future.

### Conflicts of Interest

The authors report no conflicts of interest in this work.


Authors’ Contributions

Jinlong Wei and Bin Wang contributed equally to this work.

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References

[1] W. Chen, R. Zheng, P. D. Baade et al., “Cancer statistics in China, 2015,” CA: A Cancer Journal for Clinicians, vol. 66, no. 2, pp. 115–132, 2016.

[2] D. R. Spitz, E. I. Azzam, J. J. Li, and D. Gius, “Metabolic oxidation/reduction reactions and cellular responses to ionizing radiation: a unifying concept in stress response biology,” Cancer Metastasis Reviews, vol. 23, no. 3–4, pp. 311–322, 2004.

[3] Y. Jiang, X. Chen, W. Tian, X. Yin, J. Wang, and H. Yang, “The role of TGF-beta1-miR-21-ROS pathway in bystander responses induced by irradiated non-small-cell lung cancer cells,” British Journal of Cancer, vol. 111, no. 4, pp. 772–780, 2014.

[4] E. Vorotnikova, R. A. Rosenthal, J. J. Li, and D. Gius, “Novel synthetic SOD/catalase mimetics can mitigate capillary endothelial cell apoptosis caused by ionizing radiation,” Radiation Research, vol. 173, no. 6, pp. 748–759, 2010.

[5] P. Dent, A. Yacoub, P. B. Fisher, M. P. Hagan, and S. Grant, “MAPK pathways in radiation responses,” Oncogene, vol. 22, no. 37, pp. 5885–5896, 2003.

[6] M. Najafi, A. Shirazi, E. Motevaseli et al., “The melatonin immunomodulatory actions in radiotherapy,” Biophysical Reviews, vol. 9, no. 2, pp. 139–148, 2017.

[7] R. Yahyapour, D. Shabeeb, M. Cheki et al., “Radiation protection and mitigation by natural antioxidants and flavonoids: implications for radiotherapy and radiation disasters,” Current Molecular Pharmacology, vol. 11, no. 4, pp. 285–304, 2018.

[8] R. Yahyapour, E. Motevaseli, A. Rezaeyan et al., “Mechanisms of radiation bystander and non-targeted effects: implications to radiation carcinogenesis and radiotherapy,” Current Radiopharmaceuticals, vol. 11, no. 1, pp. 34–45, 2018.

[9] R. Yahyapour, A. Salajegheh, A. Safari et al., “Radiation-induced non-targeted effect and carcinogenesis; implications in clinical radiotherapy,” Journal of Biomedical Physics & Engineering, vol. 8, no. 4, pp. 435–446, 2018.

[10] S. M. Meeran, A. Ahmed, and T. O. Tollefsbol, “Epigenetic targets of bioactive dietary components for cancer prevention and therapy,” Clinical Epigenetics, vol. 1, no. 3-4, pp. 101–116, 2010.

[11] I. Afanas’ev, “Mechanisms of superoxide signaling in epigenetic processes: relation to aging and cancer,” Aging and Disease, vol. 6, no. 3, pp. 216–227, 2015.

[12] R. Yahyapour, E. Motevaseli, A. Rezaeyan et al., “Reduction-oxidation (redox) system in radiation-induced normal tissue injury: molecular mechanisms and implications in radiation therapeutics,” Clinical and Translational Oncology, vol. 20, no. 8, pp. 975–988, 2018.

[13] F. Sieber, S. A. Muir, E. P. Cohen et al., “High-dose selenium for the mitigation of radiation injury: a pilot study in a rat model,” Radiation Research, vol. 171, no. 3, pp. 368–373, 2009.

[14] W. Zhao and M. E. Robbins, “Inflammation and chronic oxidative stress in radiation-induced late normal tissue injury: therapeutic implications,” Current Medicinal Chemistry, vol. 16, no. 2, pp. 130–143, 2009.

[15] G. R. Drummond, S. Selemidis, K. K. Griendling, and C. G. Sobey, “Combating oxidative stress in vascular disease: NADPH oxidases as therapeutic targets,” Nature Reviews Drug Discovery, vol. 10, no. 6, pp. 453–471, 2011.

[16] K. Bedard and K. H. Krause, “The NOX family of ROS-generating NADPH oxidases: physiology and pathophysiology,” Physiological Reviews, vol. 87, no. 1, pp. 245–313, 2007.

[17] A. Panday, M. K. Sahoo, D. Osorio, and S. Batra, “NADPH oxidases: an overview from structure to innate immunity-associated pathologies,” Cellular & Molecular Immunology, vol. 12, no. 1, pp. 5–23, 2015.

[18] K. Mortezaee, N. H. Goradel, and A. Momi et al., “NADPH oxidase as a target for modulation of radiation response: implications to carcinogenesis and radiotherapy,” Current Molecular Pharmacology, vol. 12, no. 1, pp. 50–60, 2019.

[19] M. Najafi, A. Shirazi, E. Motevaseli et al., “Melatonin modulation of NOX2 and NOX4 following irradiation in the lung,” Current Clinical Pharmacology, vol. 14, 2019.

[20] B. Bánfi, A. Maturana, S. Jaconi et al., “A mammalian H+ channel generated through alternative splicing of the NADPH oxidase homolog NOH-1,” Science, vol. 287, no. 5450, pp. 138–142, 2000.

[21] Y. A. Suh, R. S. Arnold, B. Lassegue et al., “Cell transformation by the superoxide-generating oxidase Mox1,” Nature, vol. 401, no. 6748, pp. 79–82, 1999.

[22] Z. Sun and F. Liu, “Association of Nox1 and vinculin with colon cancer progression,” Cancer Investigation, vol. 31, no. 4, pp. 273–278, 2013.

[23] F. Liu, A. M. Gomez Garcia, and F. L. Meyskens Jr., “NADPH oxidase 1 overexpression enhances invasion via matrix metalloproteinase-2 and epithelial-mesenchymal transition in melanoma cells,” The Journal of Investigative Dermatology, vol. 132, no. 8, pp. 2033–2041, 2012.

[24] X. J. Fu, Y. B. Peng, Y. P. Hu, Y. Z. Shi, M. Yao, and X. Zhang, “NADPH oxidase 1 and its derived reactive oxygen species mediated tissue injury and repair,” Oxidative Medicine and Cellular Longevity, vol. 2014, Article ID 282854, 10 pages, 2014.

[25] S. H. Choi, M. Kim, H. J. Lee, E. H. Kim, C. H. Kim, and Y. J. Lee, “Effects of NOX1 on fibroblastic changes of endothelial cells in radiation-induced pulmonary fibrosis,” Molecular Medicine Reports, vol. 13, no. 5, pp. 4135–4142, 2016.

[26] J. H. Kim, M. K. Kim, M. H. Jung et al., “Protective effects of alpha lipoic acid on radiation-induced salivary gland injury in rats,” Oncotarget, vol. 7, no. 20, pp. 29143–29153, 2016.
[27] P. K. Narayanan, E. H. Goodwin, and B. E. Lehnert, "a particles initiate biological production of superoxide anions and hydrogen peroxide in human cells," Cancer Research, vol. 57, no. 18, pp. 3963–3971, 1997.

[28] K. Datta, S. Suman, B. V. S. Kallakury, and A. J. Fornace, "Exposure to heavy ion radiation induces persistent oxidative stress in mouse intestine," PLoS One, vol. 7, no. 8, article e42224, 2012.

[29] H. Kikuchi, M. Hikage, H. Miyashita, and M. Fukumoto, "NADPH oxidase subunit, gp91(phox) homologue, preferentially expressed in human colon epithelial cells," Gene, vol. 254, no. 1-2, pp. 237–243, 2000.

[30] B. Bänfi, B. Malgrange, J. Knisz, K. Steger, M. Dubois-Dauphin, and K. H. Krause, "NOX3, a superoxide-generating NADPH oxidase of the inner ear," The Journal of Biological Chemistry, vol. 279, no. 44, pp. 46065–46072, 2004.

[31] H. Kikuchi, M. Hikage, H. Miyashita, and M. Fukumoto, "Human thyroid cDNAs encoding new members of the NADPH oxidase family," The Journal of Biological Chemistry, vol. 279, no. 44, pp. 46065–46072, 2004.

[32] K. Datta, S. Suman, B. V. S. Kallakury, and A. J. Fornace, "Regulated hydrogen peroxide production by Duox in human airway epithelial cells," American Journal of Respiratory Cell and Molecular Biology, vol. 32, no. 5, pp. 462–469, 2005.

[33] G. Cheng, Z. Cao, X. Xu, E. van Meir, and J. D. Lambeth, "NADPH oxidase subunit, gp91(phox) homologue, preferentially expressed in human colon epithelial cells," Gene, vol. 254, no. 1-2, pp. 131–140, 2001.

[34] N. Salles, I. Szanto, F. Herrmann et al., "Expression of mRNA for ROS-generating NADPH oxidases in the aging stomach," Experimental Gerontology, vol. 40, no. 4, pp. 353–357, 2005.

[35] B. Bänfi, G. Molnár, A. Maturana et al., "A Ca²⁺-activated NADPH oxidase in testis, spleen, and lymph nodes," The Journal of Biological Chemistry, vol. 276, no. 40, pp. 37594–37601, 2001.

[36] X. De Deken, D. Wang, M. C. Many et al., "Cloning of two human thyroid cDNAs encoding new members of the NADPH oxidase family," The Journal of Biological Chemistry, vol. 275, no. 30, pp. 23227–23233, 2000.

[37] C. Dupuy, R. Ohayon, A. Valenti, M. S. Noël-Hudson, D. Deme, and A. Virion, "Purification of a novel flavoprotein involved in the thyroid NADPH oxidase. Cloning of the porcine and human cdnas," The Journal of Biological Chemistry, vol. 274, no. 52, pp. 37265–37269, 1999.

[38] R. Fortea, M. Salathe, F. Miot, R. Forteza, and G. E. Conner, "Regulated hydrogen peroxide production by Duox in human airway epithelial cells," American Journal of Respiratory Cell and Molecular Biology, vol. 32, no. 5, pp. 462–469, 2005.

[39] C. Schwarzer, T. E. Machen, B. Illek, and H. Fischer, "NADPH oxidase-dependent acid production in airway epithelial cells," The Journal of Biological Chemistry, vol. 279, no. 35, pp. 36454–36461, 2004.

[40] M. Geiszt, J. Witta, J. Baff, K. Lekstrom, and T. L. Leto, "Dual oxidases represent novel hydrogen peroxide sources supporting mucosal surface host defense," The FASEB Journal, vol. 17, no. 11, pp. 1502–1504, 2003.

[41] Y. Wang, X. de Deken, M. Milenkovic et al., "Identification of a novel partner of duox: EFP1, a thioredoxin-related protein," The Journal of Biological Chemistry, vol. 280, no. 4, pp. 3096–3103, 2005.

[42] C. Dupuy, M. Pomerance, R. Ohayon et al., "Thyroid oxidase (THIOX2) gene expression in the rat thyroid cell line FRTL-5," Biochemical and Biophysical Research Communications, vol. 277, no. 2, pp. 287–292, 2000.

[43] R. A. El Hassan, N. Benfares, B. Caillou et al., "Dual oxidase2 is expressed all along the digestive tract," American Journal of Physiology-Gastrointestinal and Liver Physiology, vol. 288, no. 5, pp. G933–G942, 2005.

[44] R. A. El Hassan, N. Benfares, B. Caillou et al., "Dual oxidase2 is expressed all along the digestive tract," American Journal of Physiology-Gastrointestinal and Liver Physiology, vol. 288, no. 5, pp. G933–G942, 2005.
D. Citrin, A. P. Cotrim, F. Hyodo, B. J. Baum, M. C. Krishna, M. Laube, T. Kniess, and J. Pietzsch, A. Rezaeyan, G. H. Haddadi, M. Hosseinzadeh, M. Moradi, M. Cheki, R. Yahyapour, B. Farhood et al., D. Wang and R. N. Dubois, T. A. Zykova, F. Zhu, X. Zhai et al., P. Rao and E. E. Knaus, M. Maccarrone, M. Halle, T. Christersdottir, and M. Back, J. Y. Fu, J. L. Masferrer, K. Seibert, A. Raz, and P. Needleman, O. E. Grichenko, A. C. Pushin, V. V. Shaposhnikova, M. K. H. Levitman, and N. Korystov Iv, D. Song, Y. Wei, Q. Chen, and D. Xing, “Cyclooxygenase 2-mediated apoptotic and inflammatory responses in photodynamic therapy treated breast adenocarcinoma cells and xenografts,” Journal of Photochemistry and Photobiology B, vol. 134, pp. 27–36, 2014.

D. Wang and R. N. Dubois, “The role of COX-2 in intestinal inflammation and colorectal cancer,” Oncogene, vol. 29, no. 6, pp. 781–788, 2010.

M. Laube, T. Kniess, and J. Pietzsch, ”Development of antioxidant COX-2 inhibitors as radioprotective agents for radiation therapy—a hypothesis-driven review,” Antioxidants, vol. 5, no. 2, p. 14, 2016.

A. Rezaeyan, G. H. Haddadi, M. Hosseinzadeh, M. Moradi, and M. Najafi, “Radioprotective effects of hesperidin on oxidative damages and histopathological changes induced by X-irradiation in rats heart tissue,” Journal of Medical Physics, vol. 41, no. 3, pp. 182–191, 2016.

M. Cheki, R. Yahyapour, B. Farhood et al., “COX-2 in radiotherapy: a potential target for radioprotection and radiosensitization,” Current Molecular Pharmacology, vol. 11, no. 3, pp. 173–183, 2018.

T. A. Zykova, F. Zhu, X. Zhai et al., “Resveratrol directly targets COX-2 to inhibit carcinogenesis,” Molecular Carcinogenesis, vol. 47, no. 10, pp. 797–805, 2008.

P. Rao and E. E. Knaus, “Evolution of nonsteroidal anti-inflammatory drugs (NSAIDs): cyclooxygenase (COX) inhibition and beyond,” Journal of Pharmacy & Pharmaceutical Sciences, vol. 11, no. 2, pp. 81s–110s, 2008.

D. Citrin, A. P. Cotrim, F. Hyodo, B. J. Baum, M. C. Krishna, and J. B. Mitchell, “Radioprotectors and mitigators of radiation-induced normal tissue injury,” The Oncologist, vol. 15, no. 4, pp. 360–371, 2010.

M. Maccarrone, “Lipoxygenases, apoptosis, and the role of antioxidants,” in Photoprotection, Photoinhibition, Gene Regulation, and Environment, B. Demmig-Adams, W. W. Adams, and A. K. Mattow, Eds., vol. 21 of Advances in Photosynthesis and Respiration, pp. 321–332, Springer, Dordrecht, 2006.

O. P. Matyshevskaia, V. N. Pastukh, and V. A. Solodushko, “Inhibition of lipoxygenase activity reduces radiation-induced DNA fragmentation in lymphocytes,” Radiation and Environmental Biophysics, vol. 39, no. 2–3, pp. 282–286, 1999.

O. E. Grichenko, A. C. Pushin, V. V. Shaposhnikova, M. K. H. Levitman, and N. Korystov Iv, “Analysis of 15-lipoxygenase activity in irradiated thymocytes,” Izvestia Akademii Nauk. Seria Biologicheskaya, vol. 5, pp. 517–521, 2004.

M. Halle, T. Christersdottir, and M. Back, “Chronic adventitial inflammation, vasa vasorum expansion, and 5-lipoxygenase up-regulation in irradiated arteries from cancer survivors,” The FASEB Journal, vol. 30, no. 11, pp. 3845–3852, 2016.

F. Aktan, “iNOS-mediated nitric oxide production and its regulation,” Life Sciences, vol. 79, no. 6, pp. 639–653, 2004.

M. Najafi, E. Motetavaseli, A. Shirazi et al., “Mechanisms of inflammatory responses to radiation and normal tissues toxicity: clinical implications,” International Journal of Radiation Biology, vol. 94, no. 4, pp. 335–356, 2018.

M. Jaiswal, N. LaRusso, R. A. Shapiro, T. R. Billiar, and G. J. Gores, “Nitric oxide-mediated inhibition of DNA repair potentiates oxidative DNA damage in cholangiocytes,” Gastroenterology, vol. 120, no. 1, pp. 190–199, 2001.

R. Malaviya, A. J. Gow, M. Francis, E. V. Abramova, J. D. Laskin, and D. L. Laskin, “Radiation-induced lung injury and inflammation in mice: role of inducible nitric oxide synthase and surfactant protein D,” Toxicological Sciences, vol. 144, no. 1, pp. 27–38, 2015.

Y. Nozaki, Y. Hasegawa, A. Takeuchi et al., “Nitric oxide as an inflammatory mediator of radiation pneumonitis in rats,” The American Journal of Physiology, vol. 272, 4 Part 1, pp. L651–L658, 1997.

C. Tsuji, S. Shioya, Y. Hirota et al., “Increased production of nitrotyrosine in lung tissue of rats with radiation-induced acute lung injury,” American Journal of Physiology-Lung Cellular and Molecular Physiology, vol. 278, no. 4, pp. L719–L725, 2000.

S. Ohta, S. Matsuda, M. Gunji, and A. Kamogawa, “The role of nitric oxide in radiation damage,” Biological & Pharmaceutical Bulletin, vol. 30, no. 6, pp. 1102–1107, 2007.

J. S. Beckman and W. H. Kopperol, “Nitric oxide, superoxide, and peroxynitrite: the good, the bad, and ugly,” American Journal of Physiology-Cell Physiology, vol. 271, no. 5, pp. C1424–C1437, 1996.

V. A. Yakovlev, “Role of nitric oxide in the radiation-induced bystander effect,” Radiox Biology, vol. 6, pp. 396–400, 2015.

S. Ghosh, D. K. Maurya, and M. Krishna, “Role of iNOS in bystander signaling between macrophages and lymphoma cells,” International Journal of Radiation Oncology, Biology, Physics, vol. 72, no. 5, pp. 1567–1574, 2008.

V. A. Yakovlev, “Nitric oxide-dependent downregulation of BRCA1 expression promotes genetic instability,” Cancer Research, vol. 73, no. 2, pp. 706–715, 2013.

W. Han, L. Wu, S. Chen et al., “Constitutive nitric oxide acting as a possible intercellular signaling molecule in the initiation of radiation-induced DNA double strand breaks in non-irradiated bystander cells,” Oncogene, vol. 26, no. 16, pp. 2330–2339, 2007.

J. Pugin, “How tissue injury alarms the immune system and causes a systemic inflammatory response syndrome,” Annals of Intensive Care, vol. 2, no. 1, p. 27, 2012.

B. Frey, M. Rücker, L. Deich et al., “Immumomodulation by ionizing radiation-impact for design of radioimmunotherapies and for treatment of inflammatory diseases,” Immunological Reviews, vol. 280, no. 1, pp. 231–248, 2017.

Y. Shen, X. Jiang, L. Meng, C. Xia, L. Zhang, and Y. Xin, “Transplantation of bone marrow mesenchymal stem cells prevents radiation-induced artery injury by suppressing oxidative stress and inflammation,” Oxidative Medicine and Cellular Longevity, vol. 2018, Article ID 5942916, 13 pages, 2018.

Y. Ogawa, T. Kobayashi, A. Nozaki et al., “Radiation-induced reactive oxygen species formation prior to oxidative DNA damage in human peripheral T cells,” International Journal of Molecular Medicine, vol. 11, no. 2, pp. 149–152, 2003.

K. Mortezaee, M. Najafi, B. Farhood, A. Ahmadi, D. Shabeb, and A. E. Musa, “NF-κB targeting for overcoming tumor
resistance and normal tissue toxicity,” Journal of Cellular Physiology, vol. 234, no. 10, pp. 17187–17204, 2019.

[87] V. Bours, G. Bonizzi, M. Bentires-Alj et al., “NF-κB activation in response to toxic and therapeutic agents: role in inflammation and cancer treatment,” Toxicology, vol. 153, no. 1-3, pp. 27–38, 2000.

[88] S. M. Meeran, S. Akhtar, and S. K. Katiyar, “Inhibition of UVB-induced skin tumor development by drinking green tea polyphenols is mediated through DNA repair and subsequent inhibition of inflammation,” The Journal of Investigative Dermatology, vol. 129, no. 5, pp. 1258–1270, 2009.

[89] M. A. Packer and M. P. Murphy, “Peroxynitrite formed by simultaneous nitric oxide and superoxide generation causes cyclosporin-A-sensitive mitochondrial calcium efflux and depolarisation,” European Journal of Biochemistry, vol. 234, no. 1, pp. 231–239, 1995.

[90] R. A. Kowluru and M. Mishra, “Oxidative stress, mitochondrial damage and diabetic retinopathy,” Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, vol. 1852, no. 11, pp. 2474–2483, 2015.

[91] F. Ortiz, D. Acuña-Castroviejo, C. Doerrier et al., “Melatonin blunts the mitochondrial/NLRP3 connection and protects against radiation-induced oral mucositis,” Journal of Pineal Research, vol. 58, no. 1, pp. 34–49, 2015.

[92] J. C. Leemans, S. L. Cassel, and F. S. Sutterwala, “Sensing damage by the NLRP3 inflammasome,” Immunological Reviews, vol. 243, no. 1, pp. 152–162, 2011.

[93] R. Han, D. Wu, S. Deng, T. Liu, T. Zhang, and Y. Xu, “NLRP3 inflammasome induces pyroptosis in lung tissues of radiation-induced lung injury in mice,” Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi, vol. 33, no. 9, pp. 1206–1211, 2017.

[94] D. Shin, G. Lee, S. H. Sohn et al., “Regulatory T cells contribute to the inhibition of radiation-induced acute lung inflammation via bee venom phospholipase A2 in mice,” Toxins, vol. 8, no. 5, p. 131, 2016.

[95] S. H. Sohn, J. M. Lee, S. Park et al., “The inflammasome accelerates radiation-induced lung inflammation and fibrosis in mice,” Environmental Toxicology and Pharmacology, vol. 39, no. 2, pp. 917–926, 2015.

[96] Y. G. Liu, J. K. Chen, Z. T. Zhang et al., “NLRP3 inflammasome activation mediates radiation-induced pyroptosis in bone marrow-derived macrophages,” Cell Death & Disease, vol. 8, no. 2, article e2579, 2017.

[97] R. Yahyapour, P. Amini, S. Rezapoor et al., “Targeting of inflammation for radiation protection and mitigation,” Current Molecular Pharmacology, vol. 11, no. 3, pp. 203–210, 2018.

[98] K. Suzuki, I. Mori, Y. Nakayama, M. Miyakoda, S. Kodama, and M. Watanabe, “Radiation-induced senescence-like growth arrest requires TP53 function but not telomere shortening,” Radiation Research, vol. 155, no. 1, pp. 248–253, 2001.

[99] N. J. Linford, S. E. Schriner, and P. S. Rabinovitch, “Oxidative damage and aging: spotlight on mitochondria,” Cancer Research, vol. 66, no. 5, pp. 2497–2499, 2006.

[100] S. E. Schriner, N. J. Linford, G. M. Martin et al., “Extension of murine life span by overexpression of catalase targeted to mitochondria,” Science, vol. 308, no. 5730, pp. 1909–1911, 2005.

[101] S. Kobashigawa, G. Kashino, H. Mori, and M. Watanabe, “Relief of delayed oxidative stress by ascorbic acid can sup- press radiation-induced cellular senescence in mammalian fibroblast cells,” Mechanisms of Ageing and Development, vol. 146–148, pp. 65–71, 2015.

[102] Y. Sakai, T. Yamamori, Y. Yoshikawa et al., “NADPH oxidase 4 mediates ROS production in radiation-induced senescent cells and promotes migration of inflammatory cells,” Free Radical Research, vol. 52, no. 1, pp. 92–102, 2018.

[103] J. S. You and P. A. Jones, “Cancer genetics and epigenetics: two sides of the same coin?,” Cancer Cell, vol. 22, no. 1, pp. 9–20, 2012.

[104] M. Verma, D. Seminara, F. J. Arena, C. John, K. Iwamoto, and V. Hartmuller, “Genetic and epigenetic biomarkers in cancer: improving diagnosis, risk assessment, and disease stratification,” Molecular Diagnosis & Therapy, vol. 10, no. 1, pp. 1–15, 2006.

[105] M. Verma, “Cancer control and prevention: nutrition and epigenetics,” Current Opinion in Clinical Nutrition and Metabolic Care, vol. 16, no. 4, pp. 376–384, 2013.

[106] I. R. Miousse, J. Chang, L. Shao et al., “Inter-strain differences in LINE-1 DNA methylation in the mouse hematopoietic system in response to ionizing radiation,” International Journal of Molecular Sciences, vol. 18, no. 7, p. 1430, 2017.

[107] T. Z. Yi, J. Li, X. Han et al., “DNMT inhibitors and HDAC inhibitors regulate E-cadherin and Bel-2 expression in endometrial carcinoma in vitro and in vivo,” Chemotherapy, vol. 58, no. 1, pp. 19–29, 2012.

[108] N. Reichert, M. A. Choikrallah, and P. Matthias, “Multiple roles of class I HDACs in proliferation, differentiation, and development,” Cellular and Molecular Life Sciences, vol. 69, no. 13, pp. 2173–2187, 2012.

[109] M. S. Choi, Y. H. Shim, J. Y. Hwa et al., “Expression of DNA methyltransferases in multistep hepatocarcinogenesis,” Human Pathology, vol. 34, no. 1, pp. 11–17, 2003.

[110] Q. Liu, J.-M. Zheng, J.-K. Chen et al., “Histone deacetylase 5 promotes the proliferation of glioma cells by upregulation of Notch 1,” Molecular Medicine Reports, vol. 10, no. 4, pp. 2045–2050, 2014.

[111] G. W. Feng, L. D. Dong, W. J. Shao et al., “HDAC5 promotes cell proliferation in human hepatocellular carcinoma by up-regulating S6X1 expression,” European Review for Medical and Pharmacological Sciences, vol. 18, no. 6, pp. 811–816, 2014.

[112] M. Z. Fang, Y. Wang, N. Ai et al., “Tea polyphenol (--)epigallocatechin-3-gallate inhibits DNA methyltransferase and reactivates methylation-silenced genes in cancer cell lines,” Cancer Research, vol. 63, no. 22, pp. 7563–7570, 2003.

[113] A. S. Tsao, D. Liu, J. Martin et al., “Phase II randomized, placebo-controlled trial of green tea extract in patients with high-risk oral premalignant lesions,” Cancer Prevention Research, vol. 2, no. 11, pp. 931–941, 2009.

[114] C. Weigel, P. Schmezer, C. Plass, and O. Popanda, “Epigenetics in radiation-induced fibrosis,” Oncogene, vol. 34, no. 17, pp. 2145–2155, 2015.

[115] C. Weigel, M. R. Veldwijk, C. C. Oakes et al., “Epigenetic regulation of diacylglycerol kinase alpha promotes radiation-induced fibrosis,” Nature Communications, vol. 7, no. 1, article 10893, 2016.

[116] M. M. Acharya, A. A. D. Baddour, T. Kawashita et al., “Epigenetic determinants of space radiation-induced cognitive dys- function,” Scientific Reports, vol. 7, no. 1, article 42885, 2017.
I. Pogribny, I. Koturbash, V. Tryndyak et al., M. Herberg, S. Siebert, M. Quaas et al., H. Denis, M. N. Ndlovu, and F. Fuks, “Role of epigenetic effectors in maintenance of the long-term persistent bystander effect in spleen in vivo,” Carcinogenesis, vol. 28, no. 8, pp. 1831–1838, 2007.

I. Pogribny, I. Koturbash, V. Tryndyak et al., “Fractionated low-dose radiation exposure leads to accumulation of DNA damage and profound alterations in DNA and histone methylation in the murine thymus,” Molecular Cancer Research, vol. 3, no. 10, pp. 553–561, 2005.

I. Koturbash, A. Boyko, R. Rodriguez-Juarez et al., “Role of epigenetic effectors in maintenance of the long-term persistent bystander effect in spleen in vivo,” Carcinogenesis, vol. 28, no. 8, pp. 1831–1838, 2007.

B. Maroschik, A. Gürtl, A. Krämer et al., “Radiation-induced alterations of histone post-translational modification levels in lymphoblastoid cell lines,” Radiation Oncology, vol. 9, no. 1, p. 15, 2014.

S. Matsuda, K. Furuya, M. Ikura, T. Matsuda, and T. Ikura, “Absolute quantification of acetylation and phosphorylation of the histone variant H2AX upon ionizing radiation reveals distinct cellular responses in two cancer cell lines,” Radiation and Environmental Biophysics, vol. 54, no. 4, pp. 403–411, 2015.

M. Herberg, S. Siebert, M. Quaas et al., “Loss of Msh2 and a single-radiation hit induce common, genome-wide, and persistent epigenetic changes in the intestine,” Clinical Epigenetics, vol. 11, no. 1, p. 65, 2019.

X. Zhang, T. Kluz, L. Gesumaria, M. S. Matsui, M. Costa, and H. Sun, “Solar simulated ultraviolet radiation induces global histone hypoacetylation in human keratinocytes,” PLoS One, vol. 11, no. 2, article e0150175, 2016.

D. P. Bartel, “MicroRNAs: target recognition and regulatory functions,” Cell, vol. 136, no. 2, pp. 215–233, 2009.

B. Farhood, N. H. Gorodel, K. Mortezaee et al., “Intercellular communications-redox interactions in radiation toxicity; potential targets for radiation mitigation,” Journal of Cell Communication and Signaling, vol. 13, no. 1, pp. 3–16, 2019.

M. Najafi, R. Fardid, M. A. Takhshid, M. A. Mosleh-Shirazi, A. H. Rezaeyan, and A. Salajegheh, “Radiation-induced oxidative stress at out-of-field lung tissues after pelvis irradiation in rats,” Cell Journal, vol. 18, no. 3, pp. 340–345, 2016.

S. S. Acharya, W. Fendler, J. Watson et al., “Serum microRNAs are early indicators of survival after radiation-induced hematopoietic injury,” Science Translational Medicine, vol. 7, no. 287, article 287ra69, 2015.

M. Port, F. Herodin, M. Valente et al., “MicroRNA expression for early prediction of late occurring hematologic acute radiation syndrome in baboons,” PLoS One, vol. 11, no. 11, article e0165307, 2016.