



Review Article

The Role of DNA Damage Induced by Low/High Dose Ionizing Radiation in Cell Carcinogenesis

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Abstract

Cell damage caused by ionizing radiation is very complex, and has generalities and specificities regarding different ionizing radiation types, characters and radiating methods. These specificities have a complicated molecular mechanism and result in various radiobiological responses; however, the details remain unclear. Ionizing radiation can impair biological macromolecules in cells, such as DNA, RNA, signal proteins. Moreover, different radiation doses, as well as linear energy transfer (LET), cause various effects. Cells show a certain adaptive response to low-dose ionizing radiation (LDIR) when they receive a secondary larger dose of radiation. By contrast, high-dose or LET ionizing radiation can lead a much more serious attack on macromolecules, especially to the molecules involved in gene mutations, DNA single strand breaks (SSBs), DNA double strand breaks (DSBs) and DNA damage repair responses. Under extreme conditions, such as space radiation during a space mission, a large amount of abnormally repaired DNA may vastly affect the cell signal transduction pathway, initiate apoptosis, uncontrolled cell proliferation, and even carcinogenesis. In this mini-review, the molecular mechanism of carcinogenesis induced by high-dose and LET ionizing radiation in cell lifespan is elucidated.

Introduction

With the wide application of nuclear energy in industry, energy and military fields, ionizing radiation influences human beings more and more. Especially after the nuclear power plant leakage due to the earthquake in Fukushima, Japan, radiation threat to life has become a hot topic again.¹ The molecular mechanism of ionizing radiation damage has long been the focus of radiobiology, cell biology, cancer, biophysics and radiation protection. The atoms in ionization and excitation status, or molecules produced by ionizing radiation are unstable and thereafter rapidly transform into

free radicals and neutral molecules that result in complex chemical changes. The structure of biomolecules in cells maintain the normal function of cells, and thus the effect of ionizing radiation on cells shows a similar pattern. Ionizing radiation exists everywhere all the time; however, the exact molecular mechanism between ionizing radiation and cells remains unclear. In this mini-review, the cellular effects of different ionizing radiation doses and linear energy transfer (LET, meaning the energy deposition at a given distance through the path of penetrating rays) are discussed. In conclusion, low dose ionizing radiation (LDIR) can induce an adaptive response of cells. High dose ionizing radiation (HDIR) generally causes DNA and RNA damage, cell signal transduction changes and carcinogenesis. High LET radiation exhibits a higher potential for inducing cell damage and eventually results in carcinogenesis. We expect that further exploration will help reveal the interactive mechanism between ionizing radiation and cells, and provide suggestions for better protection from radiation. A summary of the ionizing radiation works are in [Table 1](#).

Keywords: Cancer; Mechanism; DNA damage; Linear energy transfer; Ionizing radiation.

Abbreviations: LDIR, low dose ionizing radiation; HDIR, high dose ionizing radiation; LET, linear energy transfer; SSB, single-strand break; DSB, double-strand break; ROS, reactive oxygen species.

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LDIR-induced cells elicit an adaptive response

LDIR can enhance the resistance of cells to HDIR, and thus reduce

Table 1. Comparison of LDIR with HDIR in terms of their biological response and clinical applications

Radiobiological effect	Radiation type	LDIR (with low LET)	HDIR (with high LET)
Dose range		≤0.2 Gy	>0.2 Gy
Biological effects (including clinical application)		Adaptive response	Carcinogenesis
		Harmful effect	Radiotherapy
Lesions	Signal transduction abnormalities	weak	strong
	ROS inducing	weak	strong
	DNA damage (SSB, DSB)	weak	strong
	miRNA damage	weak	strong
Outcome		No more harmful impact	Bi-lateral outcomes

LDIR, low dose ionizing radiation; HDIR, high dose ionizing radiation; LET, linear energy transfer; SSB, single strand break; DSB, double strand break; ROS, reactive oxygen species

the secondary multiple effects on chromosome distortion and DNA damage. This process is called the “adaptive response”.^{2,3} Its molecular mechanism involves signal transduction, the role of reactive oxygen species (ROS) and the excitatory effect of DNA repair.

LDIR-induced signal transduction abnormalities

Intracellular signal transduction is a complex process affected by various factors. Normal cell growth, proliferation and differentiation, and physiological functions are modulated by strict signal conditioning. LDIR is a special extracellular stimulation factor and can induce the phosphorylation and ethylation of intracellular and extracellular signal transduction proteins. Thus, LDIR can affect gene transcription and expression, and can result in cell structure and functional changes that involve cell growth, proliferation and differentiation.⁴⁻⁷ Though the mechanism of ionizing radiation on the cell signal transduction pathway that leads to abnormal cell proliferation regulation is not fully understood, it was recently found that intracellular signal transduction molecules, such as Protein kinase C (PKC), protein kinase A (PKA), receptor tyrosine kinase (RTK), exhibited better function after exposure.

PKC is the main component of the cell signal transduction pathway, which plays an important role in the adaptive response of LDIR.⁸⁻¹⁰ PKC can not only catalyze the phosphorylation of Ca²⁺ channels on plasma membrane, promote the influx of Ca²⁺ channels, increase the concentration of Ca²⁺ in cytoplasm, but can also catalyze the phosphorylation of Ca²⁺ ATP enzyme in sarcoplasmic reticulum. This can make calcium ions enter the sarcoplasmic reticulum and decrease the concentration of Ca²⁺ in the cytoplasm to regulate various physiological activities that are dependent on Ca²⁺ and to maintain a dynamic balance. In the signal transduction pathway of the PKC system, the receptor binds to the first messenger molecule to activate the GQ protein on the membrane. Thereafter, the GQ protein decomposes phosphatidylinositol 4, 5-diphosphatase (PIP2) into diacylglycerol (DAG) and a second messenger called inositol 1, 4, 5-triphosphatase (IP3) to activate phosphatase Cβ (PLC). DAG coactivates PKC, with PS and Ca²⁺, and thus causes a series of target protein phosphorylations that include serine residues or threonine residues.¹¹⁻¹³ Previous studies showed that DAG, PKC and other signals exposed to LDIR were significantly activated, and thus changed the downstream signal transduction pathway and induced apoptosis. Other studies have found that PKC may be involved in the signal transduction process of radiation-induced apoptosis/survival of tumor cells, as well as the different initiation pathways that may be related to the subtypes

of PKC.^{14,15}

The PKA signal pathway is usually composed of hormone receptor G protein and cAMP kinase A, and influences the gene transcription process. It has been reported that ionizing radiation can activate the cAMP response elements to activate downstream PKA, and thus change gene transcription in the nucleus.¹⁶ Cho *et al.*¹⁷ used lung cancer cells to inhibit gamma-ray-induced DNA damage repair by promoting the degradation of X-ray repair cross complementing 1 (XRCC1) ubiquitin proteasome that is dependent on the exchange protein activated by cAMP (Epac). Other studies have shown that PKA, in cooperation with other substances, inhibits tumor growth after radiation exposure *in vitro* and *in vivo*.^{18,19} In conclusion, the function of the PKA signaling pathway in radiation-exposed cells is complex, which may be due to the complexity of cell damage caused by ionizing radiation.

Receptor tyrosine kinase is a large family of receptors on the surface of cells. They are usually composed of epidermis growth factor (EGF) receptor, platelet derived growth factor (PDGF) receptor, vascular endothelial growth factor (VEGF) receptor and so on. Once the signal molecule binds to the extracellular domain of the receptor, the two monomer receptor molecules form two dimers on the cell membrane, and the tail of the two receptor intracellular domains contact each other and facilitate tyrosine phosphorylation in the tail. The resulting signal complexes initiate a variety of different signal transduction pathways and expand information to activate a series of intracellular biochemical reactions or integrate different information to introduce synthetic reactions, such as cell proliferation. In recent years, some reports have mentioned the positive effect of ionizing radiation on RTK. For example, Tamaishi *et al.*²⁰ irradiated mutated 549 cells with 0.1 Gy gamma rays to induce the P2Y6 receptor to activate extracellular signal-regulated kinase. The whole process depends on the activation of EGFR. However, in the wild type 549 cell line, ionizing radiation can lead to overexpression of VEGF in cells alone.^{21,22} This is very interesting, but further demonstrates the easy interaction between radiation exposure and mutant genes. Dadrach *et al.*²³ treated mechanical cells and endothelial cells with a certain dose of irradiation and fibroblasts to produce PDGF, autocrine and paracrine signals, and finally directly or indirectly promoted cell proliferation.

LDIR-induced ROS in cells

ROS, hydrogen peroxide (H₂O₂), hydroxyl radical (-OH), *etc.*,^{24,25} can be produced by ionizing radiation. These substances can not

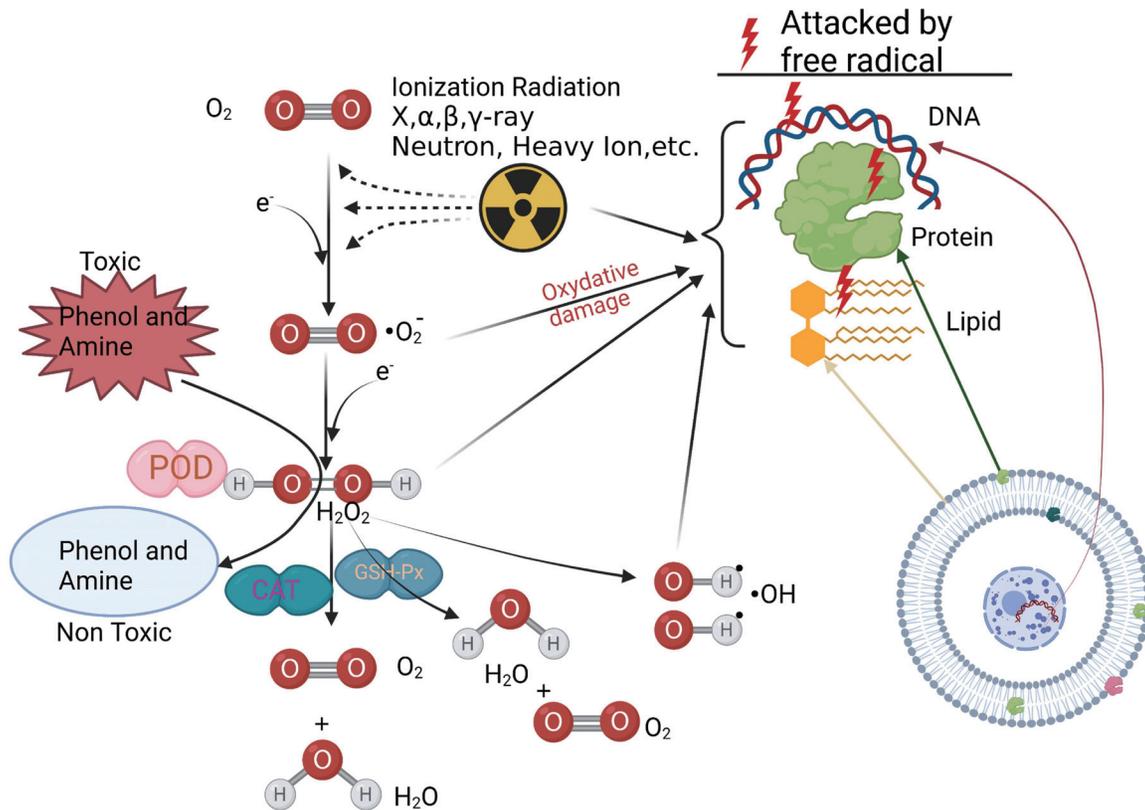


Fig. 1. The process of active oxygen metabolism in cells by irradiation. Reactive oxygen species (ROS), hydrogen peroxide (H_2O_2), hydroxyl radical ($\cdot OH$) can be produced by ionizing radiation. These substances can not only attack the cell membrane and organelles, but can also destroy proteins, membrane phospholipids and nucleic acids, resulting in cell death or apoptosis.

only attack cell membrane and organelles, but can also destroy protein, membrane phospholipid and nucleic acid, resulting in cell death or apoptosis. ROS is related to ionizing radiation damage,²⁶ which promotes radiation damage to a certain extent. Fang *et al.*²⁷ proved that the accumulation of ROS in cells may lead to radiosensitization. However, during the long-term evolution, cells formed a mature antioxidant enzyme system to reduce oxidative damage. There are many enzymes in the cells that can destroy ROS, which are mainly composed of superoxide dismutase (SOD), catalase (CAT), ascorbate peroxidase (APX) and glutathione peroxidase (GPX).^{28,29} The activity of copper and zinc SOD in *Chironomus larvae* irradiated with low dose gamma rays also presented three to four times higher than that of the control. However, the activities of GR and GPX showed a downward trend. Eken *et al.*³⁰ found that the monthly absorbed dose of 0.10–3.8 mGy radiation can significantly enhance the activities of copper and zinc SOD and GPX, while the CAT and MDA level were significantly lower than those in the control group. LDIR can cause changes in the activities of several different enzymes and may be due to the difference of cell type, irradiation time and spatial construct of enzymes.³¹ All these complexities are elucidated in Figure 1.

DNA repair under LDIR

The adaptive response induced by LDIR is mainly associated with DNA damage repair hormone modulated by ataxia telangiectasia mutated (ATM) phosphorylation. ATM is an important gene that

can detect and initiate DNA damage repair in normal cells. ATM protein kinase can activate the DNA repair cascade signal after cells are exposed to radiation.³² It has been reported that ATM plays an important role in activating apoptosis and downstream elements of DNA repair, such as p53 and Chk1. Bardelle *et al.*³³ found that ATM will be activated in irradiated cells, resulting in the phosphorylation of many downstream target proteins and the regulation of various damage response pathways, include the change of cell cycle checkpoint (Fig. 2).^{34,35} More experiments provide evidence that the p53 gene response induced by ionizing radiation damage is modulated by ATM.^{36,37} Activated ATM can phosphorylate serine kinase, stabilize p53 and significantly increase p53 concentration. Thus, p21CIP gene expression can both activate or inhibit downstream signal transduction.³⁸ During this process, ATP release is tightly related to this process. For example, van Gisbergen *et al.*³⁹ found the increase of intracellular ATP in human lung cancer 549 cells that were irradiated by gamma rays with a total dose of 2.0Gy. Beishline *et al.*⁴⁰ compared the expression of mitochondrial genes in GM 13740 (Leigh syndrome) and GM 15036 (normal subjects) irradiated with X-ray (dose range from 0 to 4 Gy) for 24 h, and found that the gene expression level was associated with the radiation dose and time. The above process may occur under different irradiation conditions, which is necessary to explore how common the radiation effect is and to possibly clarify its mechanism. In addition, there are other genes related to ionizing radiation, such as H2AXCDKN1A, P53, pChk2, Cdc25C, etc., which can be differentially affected by ionizing radiation in terms of their expression level and subsequent responses (Fig. 2).^{41–43}

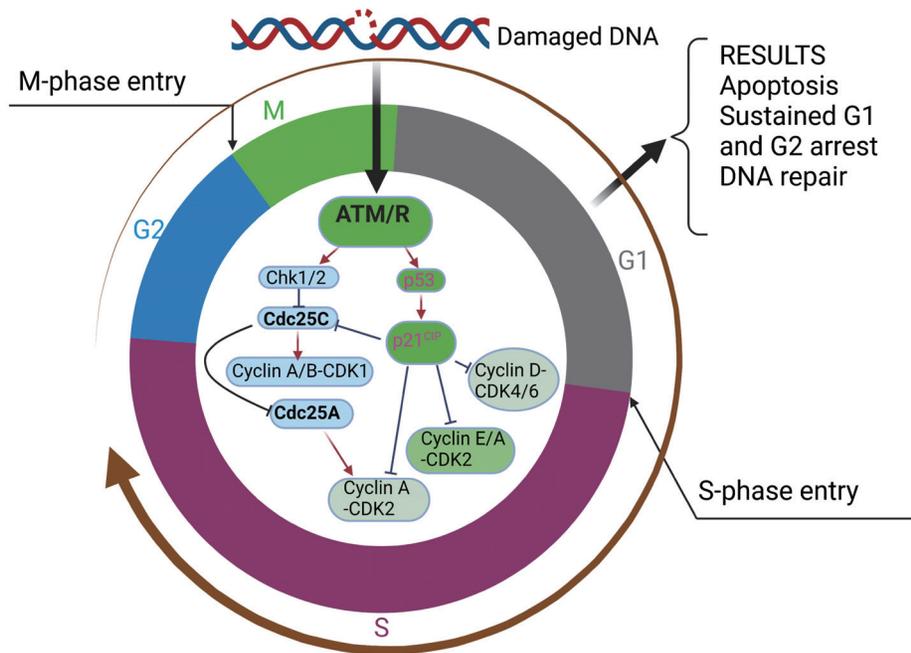


Fig. 2. The pathway of checkpoint controls by ATM in the cell cycle. The adaptive response induced by LDIR is mainly associated with DNA damage repair hormone which is modulated by ataxia telangiectasia mutated (ATM) phosphorylation. ATM can detect and initiate DNA damage repair in normal cells. ATM protein kinase can activate the DNA repair cascade signal after cells are exposed to radiation.

HDIR-induced DNA strand break

DNA damage caused by ionizing radiation mainly includes changes of nuclear acids, glycosylation, DNA single-strand breaks (SSBs), DNA double-strand breaks (DSBs) and DNA cross-linkages.⁴⁴⁻⁴⁷ HDIR can initially cause damage and glycosylation of the DNA. The change of DNA stability will result in the destruction of the internal structure. DNA strand breaks are the main lesions of HDIR whereby the SSBs damage gradually replaces the DSBs damage as the LET increases and exceeds the adaptive threshold.⁴⁸ The dynamic repair of human liver cancer SMMC-7721 and normal liver L02 cells was observed at and after 24 h exposed to radiation. The results showed that the effect of high LET on the DNA DSBs of SMMC-7721 and L02 cells was much greater than that of SSBs. In the same laboratory, they used γ -rays produced by ⁶⁰Co to irradiate SMMC-7721 and used the early chromosomal condensation technique induced by Calyculin-A to study chromosome damage. The results showed that there was a linear relationship between chromatid breaks and radiation dose in the G₂ phase. There was also a strong correlation between the fragmentation of the chromatid and cell viability.⁴⁹ In addition, different radiation particles have different radiation damage effects.

Possible molecular mechanisms of DNA repair

DNA is the control center of all life activities in the cell, but DNA is not static. It is well known that many factors, including ionizing radiation, can change the DNA structure and influence its functions. DNA damage may be fatal, or affect the growth, proliferation and differentiation of normal cells. Cells evolve the capacity of protective repair in order to reduce the risk of pernicious gene mutation. These protective repairs mainly rely on cell cycle regu-

lation. When the DNA structure changes, some molecules can be identified and repaired to prevent DNA damage. Here, the damage checkpoint is activated to recognize these changes, and appropriate signal pathways begin to protect the integrity of the genome. This series of processes is called DNA damage repair.^{50,51} There are many types of DNA damage repair processes related to ionizing radiation, including excision repair, recombinant repair and SOS reactions. Several genes can initiate DNA repair. For example, ATM, located on human chromosome 11q22-23, is an important gene to identify and repair DNA damage. It is involved in many complex cell cycle checkpoints like G₁ to S, S and G₂ to M. ATM mediates intermolecular interaction activations and parasitic corresponding cytokines through signal transduction pathways and then regulates the cell cycle (Fig. 2). Given successfully repaired DNA damage, cells will survive and complete normal proliferation and differentiation. As for severe DNA damage, which is difficult to fix, the cells can activate the checkpoint and initiate the apoptosis pathway. Simple DNA damage caused by LDIR can generally be repaired and have function recovered. However, HDIR is a kind of higher denaturation, which can lead to DNA DSBs,^{52,53} which is a very severe lesion that is difficult to be repaired and eventually develops into cancer. Yang *et al.*⁴⁸ observed the dynamic repair process of normal human hepatocytes 48 hours after gamma-ray irradiation and found that DSBs and SSBs increased with an increasing irradiation dose, and that the amount of DSBs was much greater than that of SSBs. After 24 hours of culture, both DSBs and SSBs were repaired to a certain extent. About 50% of the stained haplotypes and up to 15% of the allochromatic DNA breaks were repaired. However, the isochromatid breaks were difficult to repair, although this population was relatively small.

Ionizing radiation can induce homologous recombination of alleles, which is unusual in mammalian cells. Radiation-induced DSBs tend to lead to non-homologous end joining (NHEJ) repairment, which is an important factor in the formation of chromo-

somal abnormalities and gene mutations, and can further induce mutations and malignant transformations.⁵⁴

Base excision repair (BER) is a principle approach to repair DNA damage.^{55,56} A great deal of evidence shows that DNA damage caused by ionizing radiation or intrinsic ROS can be repaired by base excision.⁵⁷ Miné-hattab *et al.*⁵⁸ found that the key enzyme in the process of BER is DNA glycosylase, which can remove damaged bases by breaking the N-sugar bond between the base and the deoxyribose residue. The initiation mechanism varies with repair time, but its processes mainly include site recognition, anuria or pyrimidine (AP) processing incision, DNA synthesis and DNA junction. Chromatin recombinant repair is an important dynamic repair process.^{59,60} d'Ari R⁶¹ irradiated U87MG and A549 cells in which Amir-vectors, Amir-XRCC2, Amir-XRCC4 were stably expressed with different doses. It was found that inhibition of the NHEJ protein XRCC4 and homologous recombinant protein XRCC2 could improve the sensitivity of tumor cells to LDIR *in vitro* and *in vivo*. It has thus been suggested that recombinant repair plays an important role in cells. For example, in emergency conditions, DNA DSBs can cause a cell SOS response, genomic instability and cell death.⁶² Some studies have shown that the SOS response of cells is different. For example, *Escherichia coli*⁶³ and *Bacillus subtilis* (*Bacillus subtilis*) over-killed by ionizing radiation showed differences in SOS response, with the SOS reaction more obvious with an increase of radiation dose. In addition, the cell cycle checkpoint was emptied and suppressed by cyclin, in which case the ionizing radiation damaged DNA was repaired.⁶⁴⁻⁶⁶

Ionizing radiation induces carcinogenesis

Oncogenes and tumor suppressors are pairs of converse-function genes related to cell life activity in normal eukaryotic cells. Cancerous cells are highly associated with these pairs of genes. The activation of proto-oncogene is caused by point mutations or chromosome shifts, while the inactivation of tumor suppressor genes is caused by mutation, deletion and insertion.^{67,68} In general, the change of single proto-oncogene or tumor suppression genes cannot possibly induce cell carcinogenesis, however, the accumulated mutations of multiple cell proliferation-related genes can unavoidably induce such disastrous results. Unfortunately, this can ultimately lead to a disorder of the cell proliferation control system and finally to cancer.⁶⁹ The carcinogenic mechanism by ionizing radiation exposure remains unclear to date due to the various influencing factors. Briefly, the genetic changes caused by ionizing radiation mainly arise from large DNA segment deletions, and hence prevent gene changes and effectively reduce carcinogenesis.⁴³ HDIR is often considered to be the cause of cell carcinogenesis. For example, ionizing radiation leads to structural changes of some signal transduction proteins, the formation of spontaneous dimerization and further phosphorylation, resulting in the continuous activation of downstream signals and the proliferation of malignant cells. Radiation can lead to the deletion of the extracellular domain of normal EGFR. In the absence of the corresponding ligand,^{70,71} it can be transformed into an ErbB tumor protein dimer through self-binding, which can induce abnormal cell proliferation. In addition, the lack of cell checkpoint gene p53 can lead to the disappearance of the DNA damage checkpoint,⁷²⁻⁷⁴ which will result in cell carcinogenesis. Normally, the concentration of Cyclin p53 in cells is very low because it is very unstable and can degrade rapidly.⁷⁵ While under stress, the expression of p53 gene increases, similar to HDIR conditions. When the p53 G1 checkpoint is abnormally modulated, the damaged DNA can replicate and continue to mu-

tate and recombine. This process can subsequently transmit to the progeny cells and eventually lead to deformed cells. In addition, p53 induces p21 CIP protein to inhibit the mitosis of the cell cycle B-CDK1 complex, resulting in G2 phase arrest.⁷⁶⁻⁷⁸ However, in fact, LDIR also plays a role in inducing^{79,80} the continuous activation and inhibition of some special cycle genes related to cell proliferation. Bong *et al.*⁸¹ irradiated AKR/J mice with IDIR and HDIR to explore the difference in gene expression. Their microarray results showed that the expression of tumor related genes CDS1, Itga 4, Myc and Itgb 1 gene were up-regulated. This implied that the radiation exposure impacted the gene expression level effectively,

Ionizing radiation effects on microRNA

Hundreds of microRNAs are highly conserved non-coding RNA, which can change protein expression and regulate a variety of cell processes, including the control of development time, cell proliferation, apoptosis,⁸² and tumor and cell stress response. In the case of DNA injury, miRNAs can activate apoptosis⁸³ and block the cell cycle.⁸⁴ Thus, this process can directly and indirectly activate the tumor suppression target gene p53. With the deepening knowledge of radiology research and the maturity of advanced radiotherapy technology, it has been found that radiation dose also has an effect on RNA.⁸⁵ In daily life, the expression of miRNA can be ignored under LDIR because it generally does not have acute or chronic side effects. However, the significant expression level change of miRNA under HDIR needs to be emphasized.⁸⁶ A study showed that 1.25 Gy X-ray irradiation in radiotherapy significantly upregulates the expression of miRNA.⁸⁷

Perspective

We must realize that radiation always surrounds us all the time and everywhere. LDIR has an adaptive response, which can be further applied to radiation protection. Meanwhile, the HDIR and high LET ionizing radiation have bi-direction radiobiological effects, which can potentially induce carcinogenesis and can be used for radiotherapy for most solid tumors with limited metastasis. Elucidating the detailed mechanisms regarding how radiation particles interact with the body at the microscopic and macroscopic level is the main task in the present and future works, especially for those studies that examine what and how radiation particles induce cancers and are affected by radiotherapy.

Conclusion

Cell damage caused by ionizing radiation has made remarkable progress both at macro and micro level. However, radiobiological effects are highly different for various types of radiation. Even when the same kind of cells are exposed to different ionizing radiation, the mechanism of action may be very different. Studies have shown that radiation can cause cancer, but can also treat cancer. Research in this field has opened up a new way to solve the problem of cancer. Elucidating the molecular mechanism of cell damage caused by ionizing radiation will make this field a game-changing development. Different radiation types induce different effective damages. For example, light and X-ray are the most common types of ionizing radiation, and a very low dose can have

a limited effect on the human body. HDIR may initially lead to DNA base changes and glycosylation damage, which can affect the stability of DNA and result in damage to the internal structure of DNA. DNA strand breaks are the main lesion type of HDIR. As LET increases and exceeds the adaptive threshold, SSBs will gradually replace DSBs, which is a very serious lesion due to the high risk of carcinogenesis.

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Conflict of interest

The authors have no conflicts of interest to declare.

Author contributions

Study design (YJS), interpretation of data and writing (JCY, WQ, YXH and YJS), critical revision and funding (YJS). All authors have made a significant contribution to this study and have approved the final manuscript.

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