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The Role of Ionizing Radiation in Cellular Signaling Pathways, Mutagenesis, and Carcinogenesis

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Abstract
One of the negative effects of ionizing radiation is the alteration of cellular signaling pathways which lead to carcinogenesis and tumorigenesis. In this review, we discussed the impacts of ionizing radiation on cells and cellular signaling pathways. In this regard, exposure to radiation can directly or indirectly alter cellular signaling pathways. Remarkably, irradiated cells release special mediators into cellular matrix, aberrating cell-cell and cell-environment interactions. Most notably, these mediators include nitric oxide (NO), reactive oxygen species (ROS), and cell growth factors which contribute to cellular interactions between irradiated cells and their neighbor cells, a phenomenon known as radiation-induced bystander effect. DNA molecule is the most important cellular compartment damaged by ionizing radiation. On the other hand, the ability of irradiated cells to repair the damaged DNA is very low. Therefore, DNA alternations are passed to the next generations, and ultimately lead to carcinogenesis. The study of ionizing radiations and their impacts on biological systems is of remarkable importance to divulge their impacts on cellular signaling pathways.
Keywords: Physics, Ionizing radiation, Cellular signaling pathways, Tumorigenesis, Carcinogenesis

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Ionizing Radiation and Cancer Development

Ionizing radiation is one of the most important factors contributing to carcinogenesis and tumor development. This is mainly promoted by inducing DNA mutations and altering cellular signaling pathways.[1] Ionizing radiation harbors enough energy to stimulate electron orbits surrounding biological molecules.[2,3] The ionizing beams are divided into two groups of particles and electromagnetic beams. Conspicuously, the most important particle beams are alpha, beta, electrons, and neutrons, as well as electromagnetic beams which include X and gamma rays.

Ionizing radiation has been used in a wide range of sciences including medicine. Since the discovery of X-ray by Roentgen in 1895, ionizing radiations have been utilized for diagnostic and therapeutic purposes in medicine with the advent of radiotherapy in 1898 and then throughout the twentieth century.[4,5] Today, these beams are commonly used in medical imaging devices such as CT scans, image enhancers, and also in radiation therapy devices such as cobalt devices and high-energy X-ray accelerators. They have also been employed in food industry to sterilize foods and kill bacteria and other microorganisms.[6-8]

Nowadays, most people are daily exposed to various sorts of radiations and this can enhance the prevalence of cancers if this phenomenon is not managed and controlled safely. In the carcinogenesis process caused by ionizing radiation, genetic and epigenetic alterations play important and central roles. Accordingly, both endogenous and exogenous agents can modify the impacts of radiation-induced genetic and epigenetic changes and carcinogenesis (Figure 1).

Direct and Indirect Impacts of Radiation

Despite extensive research in radiobiology, the identity of the most critical and

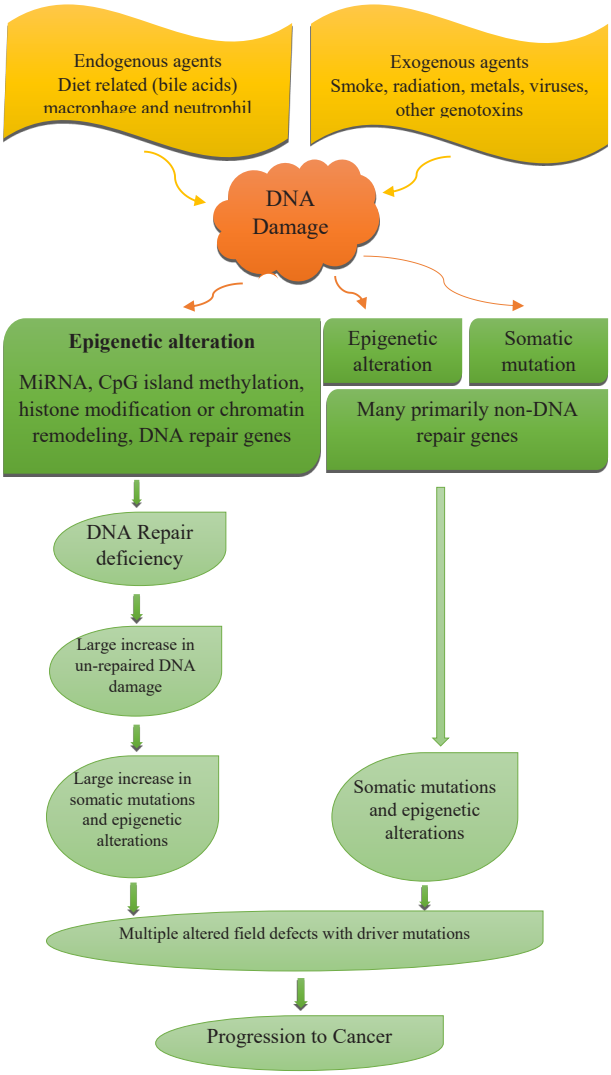

Figure 1. The Effect of Endogenous (Molecular Events) and Exogenous (Environmental Factors) on Different Genetic and Epigenetic Factors Participating in Cancer Development.

radiation sensitive cellular structures has been remained unknown. Damage to these structures is indispensable for promoting radiation-induced cellular death.[9] It has now been largely agreed that DNA represents the most critical target. However, the impacts of radiation on membrane lipids and proteins should not be disregarded.[11,12]

When radiation is absorbed into biological materials, it may directly collide with critical cellular targets and excite their atoms and electrons. The recent event itself can trigger a chain of reactions that lead to biological alternations. This phenomenon is called the direct action of radiation.[13, 14] Alternately, the beams may collide with atoms or other molecules (especially water) and produce free radicals that can penetrate the cell and damage the sensitive target molecules. This phenomenon is called indirect action of radiation.[15]

Free radicals are mediators not coupled with an electron orbit. An electron orbital not only spins around the nucleus but also around its own axis.[16] This electron circulation may be either clockwise or counterclockwise. In one atom with a pair of electrons, the electron spins are in parallel with one electron spinning clockwise and the other in the opposite direction. Regardless of whether the atom or molecule is electrically neutral or ionized, this chemical mode produces a lot of chemical stability.[17]

The Effects of Radiation on DNA

Ionizing radiation may release much of their energy near the DNA molecule and cause serious damages to either single or double strands of DNA.[18] If a cluster of these events occurs within a 2 nm diameter of helical DNA, it is likely that both DNA strands will be broken.[19] In the case of low-level beams, a linear and dose-dependent fracture response has been noted to double-stranded DNA.[20] The fracture of double-stranded DNA leading to DNA dissociation is warranted in particular when the fracture is larger than 5 nucleotides long. However, the double-stranded DNA damages occur in the ratio of 1: 50 in the favor of single-strand defects.[21]

Whether the DNA damage is double- or single-stranded, cells are able to repair both types of damages over a short period of several hours (Table 1). In the case of single-stranded DNA injuries, one of the 2 DNA strands serves as a transcription template which lowers the rate of error, rendering this type of repair error-free.[25] On the other hand, in the case of double-stranded DNA fractures, a number of nucleotides may be incompletely removed from each of the two DNA strands, so that only a part of the two-stranded defects caused by ionizing radiation is fully and correctly repaired. Accordingly, these unfixed alternations may ultimately lead to sustained cellular damages, DNA mutations, carcinogenesis, and tumor development.[22-24]

Radiation-Induced Bystander Effect

High dose radiations can expose excess energy to human body, thereby inflicting destructive effects on the living tissues.[26] Since the discovery of radiation, the biological effects of radiation has extensively been studied regarding the effects of different doses, dose rates, and types of radiations.[27,28] These data are largely derived from medical experiments and instruments such as radiation therapy, radiation accelerating devices such as cyclotron, radiation accidents from the nuclear power industries and nuclear weapons,[29, 30] and finally from experiments conducted on animals.[31]

A recently-suggested phenomenon participating in adaptive responses to radiation is the bystander effect in which radiated cells alter the biology of their surrounding environment. The radiation effects observed in neighboring cells include cell death, chromosomal defects, genetic and gene expression changes, cell cycle delay, genomic instability, and neoplastic transformation. The mechanisms underlying the impacts on neighboring

Table 1. DNA Lesions and Respective Repair Pathways

Type of DNA Lesions	Source	DNA Damage Repair Pathway
Base mismatches, incorrect insertion and deletion of nucleotides	Replication errors	MMR
DNA ICLs	Replication events and chemotherapeutic drugs like mitomycin C	NER, FA pathway
Bulky and helix-distorting DNA adducts	UV rays and chemical mutagens like cisplatin	NER, FA pathway
SSBs	Ionizing radiation and reactive oxygen species	Single-strand break repair
DSBs	Ionizing radiation, reactive oxygen species, and replication stress	DSBs are repaired either by NHEJ or by HRR in a cell cycle specific manner. Some overlap exists between HRR and NHEJ pathways. DSBs which are not processed by NHEJ can be processed by HRR during S and G2 phases.
Damaged bases and non-helix-distorting DNA lesions	Ionizing radiation and reactive oxygen species	BER. In case of impaired BER, the SSBs are converted to DSBs, which are repaired by HRR during S and G2 phases. This synthetic lethal relationship is exploited by the use of PARP inhibitors to kill HRR deficient tumors.

Abbreviations: MMR; mismatch repair, ICL; Interstrand cross-links, NER; Nucleotide excision repair, FA; Fanconi anaemia, DSBs; Double strand breaks, NHEJ; Non-homologous end joining, HRR; Homologous recombinational repair, SSBs; single strand breaks, PARP; poly ADP ribose polymerase.

cells are obscured. There is a vast amount of literature on this subject, however, no definitive conclusion could yet be reached.[32,33] Researchers believe that target cells communicate with their neighboring cells by releasing soluble materials or through cellular contacts, thereby causing them to eventually react to these effects.[34,35]

Some evidence suggests that these messenger molecules should be able to cross the gap between cells. Correspondingly, some of these mediators have been found as reactive oxygen species (ROS), nitric oxide (NO), cytokines, and growth factors which contribute to these cellular communications and act as the neighboring messengers. [36]

The Role of NO and ROS

The NO molecule is made by the conversion of L-arginine to L-citrulline in the presence of NADPH and oxygen. Sphingomyelinase, which is present in the cell membranes, stimulates the production of NO in the cells exposed to ionizing radiation.[37,38] On the other hand, the TP53 molecule inhibits NO production in irradiated cells. Nevertheless, in the cells containing mutated *TP53* gene, the NO molecule can effectively be produced. NO mainly acts through a dose-dependent manner. At high concentrations, NO and its derivatives (such as ONOO and N_2O_3) can promote cell death by inducing DNA damage.[39, 40] However, at low concentrations, NO prevents apoptosis [41] and stimulates cell growth.[42] ROS, superoxide, hydrogen peroxide, and hydroxyl are produced in the presence of oxygen in the cells exposed to radiation. These mediators can subsequently promote damages to cellular components such as DNA, lipids, and proteins.

Considering the roles of NO and ROS in cell damage, many studies have been conducted to determine their impacts in producing the bystander effect.[43, 44] Two approaches have been adopted to scrutinize the effects of these mediators in radiation-induced bystander effect. In the first approach, the concentration of NO or ROS is measured in the target and adjacent cells in order to determine whether or not the production of NO or ROS in surrounding cells is induced by irradiated cells. In the second approach, the NO and ROS inhibitors are employed to evaluate their effects in inducing the bystander effect.

Cytokines and Growth Factors

Cytokines and growth factors can regulate cell proliferation, differentiation, and death. These molecules play a leading role in preventing neoplastic transformation by provoking an integrated response to complex environmental stimuli.[45] Likewise, these mediators can contribute as secondary messengers to integrate cellular adaptive responses to ionizing radiation and develop the by stander effect. Studies have shown that transforming growth factor β 1 (TGFβ1) can promote similar effects against ionizing radiation in cultured cells, highlighting this growth factor as a potent bystander effect mediator (Figure 2).[46,47]

Other studies have also suggested that TGFα, tumor necrosis factor α (TNFα), TGFβ1, and interleukin 8 (IL-8) can promote the bystander effect.[48,49] In this regard, another study indicated that there was a relationship between the NO production and TGFβ1 level, proving an indirect role for NO in induction of bystander effect by triggering TGFβ1 in irradiated cells.[50]

TGFβ1 is a relatively stable molecule which can

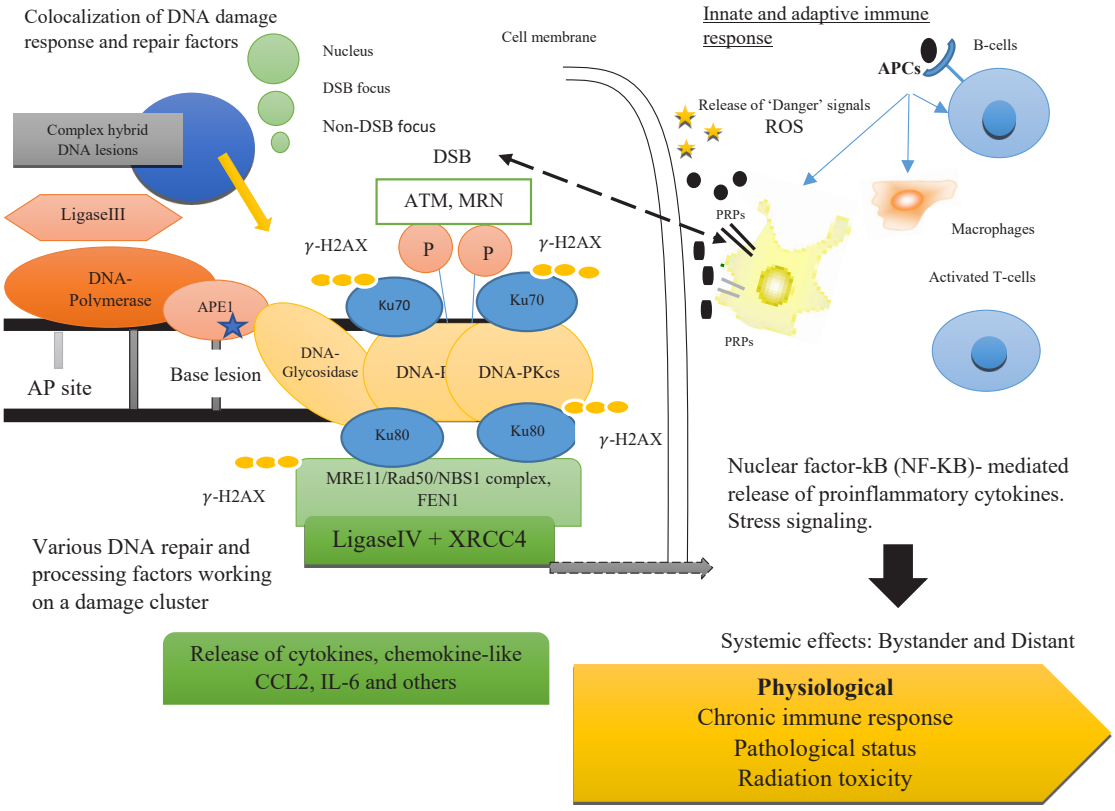

Figure 2. Extracellular Responses by Cytokines and Growth Factors Induce Cell Proliferation, Differentiation, and Death. These mechanisms play a key role in preventing neoplastic transformation by provoking an integrated response to external DNA damage. Abbreviations; AP site; apurinic/apyrimidinic site, XRCC4; X-Ray Repair Cross Complementing 4, MRE11; meiotic recombination 11, ATM; ataxia telangiectasia mutated, FEN1; Flap endonuclease 1, DNA-PKC; DNA-dependent protein kinase, DSB; double-strand break, ROS; reactive oxygen species, APC; antigen presenting cells.

easily penetrate into the intercellular matrix and in this way, reach neighboring cells and alter their biological functions partly by regulating cellular signaling and calcium-dependent pathways.

Radiation-Induced DNA Damage as a Bystander Effect

Formation of H2A histone family member X (γH2AX) foci, double-strand break (DSB) in DNA, chromosomal fractures, and cellular death in cells surrounding the irradiated cells indicate DNA molecule as a main target in bystander effect. Nonetheless, the γH2AX foci may also be formed by the influence of ROS over neighboring cells.[51] It has been shown that the number of γH2AX foci has been higher in the cells neighboring to radiation-exposed cells rather than normal cells.[52,53] This observation indicates the role of bystander effect in the DSB formation in neighboring cells. Increased concentration of DNA-dependent protein kinase (DNA-PKC) molecules involved in DSB regeneration is another evidence confirming the DSB formation in neighboring cells.[54] Accordingly, chromosomal fractures have also been reported as a bystander effect in the cells surrounding radiation-exposed cells. Regardless of these, whether bystander effects on DNA and chromosomes are directly induced by radiation or indirectly by some unknown mediators needs to be further investigated.[53]

Radiation, Microenvironment, and Carcinogenesis

Understanding the bystander effect is further expanded by acknowledging the fact that the ionizing radiation may directly act through collision with the cells or their microenvironment. Scientific findings have shown that ionizing radiation has multicellular and multifactorial effects on cells and the microenvironment.[55,56] Cellular microenvironment plays an essential role in the interactions of cells with each other and with other extrinsic factors. These interactions can regulate the cellular growth, proliferation, differentiation, and death by augmenting cell-environment interactions.

Extracellular matrix is a main microenvironment which affects irradiated cells. Radiation can trigger release of soluble materials such as proteases, cytokines, growth factors, and chemokines, which subsequently leads to tissue and extracellular matrix stress, thereby affecting cell-microenvironment interactions.[57,58]

Noticeably, adaptive responses to microenvironmental damage can restore the damage, maintain homeostasis, and eventually recover cell-microenvironment

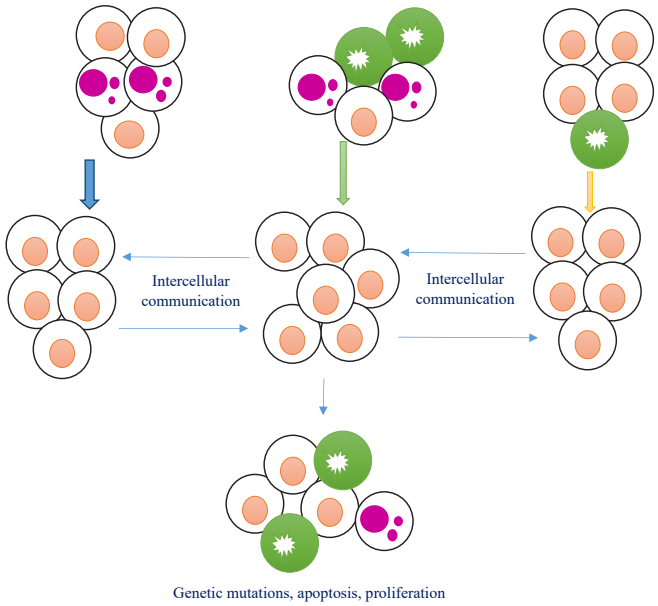

Figure 3. The Impact of Low and High Dose Radiations and Intracellular Communications in Cell Mutation.

interactions. Factors other than ionizing radiation such as ROS, TGFβ1, and cancerous cells' microenvironment can also affect the microenvironment and produce effects similar to that produced by radiation (Figure 3).[59-63]

Conclusively, it seems that microenvironmental impairment participates as a main route through which radiation may promote its effects on biological systems. Accordingly, the role of microenvironment alternations has been demonstrated in inducing bone marrow failure in the production of blood cells following acute radiation.[64] Furthermore, microenvironment of irradiated cells containing molecular messengers (such as ROS, NO, cytokines, growth factors-i.e. TGFβ1) has been reported to reproduce bystander effects in non-irradiated cells.

In particular, TGFβ1 molecule produced by stromal cells can impart an important role in regulating microenvironmental bystander effects.[65-69] The role of this molecule in three processes of maintaining tissue stability, responding to radiation, and developing bystander effect further confirms a link between the bystander effect and the microenvironmental response to radiation.

Conclusion

While high-dose radiation can promote direct damage to cellular components such as DNA, low-dose radiation can alter cellular communications by projecting the bystander effects. The study of radiation effects on genetic and epigenetic alternations in different cancers by suitable molecular techniques is highly recommended. Furthermore, identification of potential mediators exerting the bystander effects can boost our knowledge in radiation-induced adaptive responses.

Conflict of Interests

The author declares no conflict of interests.

Ethical Issues

Not applicable.

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