Review

Medical Radiation Exposure and Human Carcinogenesis-Genetic and Epigenetic Mechanisms

Yildiz Dincer[1,#] and Zeynep Sezgin[1,2]

Ionizing radiation (IR) is a potential carcinogen. Evidence for the carcinogenic effect of IR radiation has been shown after long-term animal investigations and observations on survivors of the atom bombs in Hiroshima and Nagasaki. However, IR has been widely used in a controlled manner in the medical imaging for diagnosis and monitoring of various diseases and also in cancer therapy. The collective radiation dose from medical imagings has increased six times in the last two decades, and grow continuously day to day. A large number of evidence has revealed the increased cancer risk in the people who had frequently exposed to x-rays, especially in childhood. It has also been shown that secondary malignancy may develop within the five years in cancer survivors who have received radiotherapy, because of IR-mediated damage to healthy cells. In this article, we review the current knowledge about the role of medical x-ray exposure in cancer development in humans, and recently recognized epigenetic mechanisms in IR-induced carcinogenesis.

CARCINOGENESIS

Cell proliferation is tightly regulated under physiological conditions. Cancer is a disease that arises from uncontrolled growth of a transformed cell. Control of cellular growth is lost in cancer. Cancer development is a multi-stage process characterized by the cumulative effects of cellular processes such as increased replication rate, suppressed apoptosis, enhanced angiogenesis and metastasis. Various alterations occur in the expression of the genes associated with many critical cellular processes during the carcinogenesis. Primary target genes in carcinogenesis are proto-oncogenes, tumor suppressor genes, DNA repair genes, apoptosis-related genes and the genes regulating cell cycle. Alterations in these genes involve 1) gene mutations, DNA deletions or DNA rearrangements which result in the conversion of proto-oncogenes to oncogenes and/or loss of the function of tumor suppressor genes; 2) epigenetic changes that effect expression of the target genes[1-3]. Only a small fraction of cancers are associated with inheritance, the majority of the various forms of cancer are caused by environmental factors which are able to cause genetic and epigenetic changes. The role of environmental factors in carcinogenesis has been revealed by epidemiological data and experimental animal studies. Cumulated genetic alterations because of carcinogenic exposures during the lifetime may result in malignancy if apoptosis is inhibited and the immune system can not eliminate the transformed cells. The environmental factors leading cancer development are classified as physical, chemical and biological carcinogens. The major physical agents causing cancer are IR and UV.

CELLULAR EFFECTS OF IONIZING RADIATION

IR is a kind of radiation which has sufficient energy to break chemical bonds and displace electrons from atoms and molecules. IR consists of electromagnetic radiation, such as x-rays or gamma rays (γ-rays), or of subatomic particles, such as protons, neutrons, and α-particles. When organisms exposed to IR, radiation energy is transferred to the cellular atoms and molecules, and biomolecules are ionized or excited. By this way IR can cause breaks in chemical bonds, production of free radicals, crosslinking between biomolecules, and finally damage in all cellular macromolecules. Radiobiological studies have suggested the DNA as the main target for biologic effects of IR that can be categorized in three groups: genetic effects, epigenetic effects and bystander effects. In addition, IR effects on expression of small non-coding RNAs has been introduced.

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1. Department of Medical Biochemistry, Istanbul University Cerrahpasa Medical Faculty, Istanbul, Turkey; 2. Department of Medical Biochemistry, Yeni Yuzyıl University Medical Faculty, Istanbul, Turkey

Genetic Effects of IR

The damaging effects of IR on DNA occur through direct or indirect manner, and initiate a series of molecular signaling events that may result in permanent physiological changes or cell death. Radiation-induced DNA lesions can cause cell death, mutation, chromosome aberration, cell transformation and carcinogenesis.

Direct action IR has a potential to directly interact with DNA molecules. It initiates the chain of events that lead to biological changes, and causes a broad spectrum of DNA lesions. Transfer of radiation energy in DNA results in formation of strand breaks. Formed strand breaks either triggers apoptosis or stimulates DNA repair. Strand breaks temporarily formed during the repair process increases the cell death. The most important biological effects of IR in humans arises through double-strand breaks (DSB). Single-strand breaks (SSB) are usually repaired properly. However, DSB can be repaired by an error prone mechanism. DNA strands may rejoin itself incorrectly and this triggers cell death. Alternatively, strands may rejoin as a symmetrical translocation which may lead to oncogene expression during cell division.

Indirect Action Indirect effect of IR arises via oxidative stress. When cells exposed to radiation, most of the energy is absorbed primarily by intracellular water. Excited water molecule undergoes cleavage and then reactive oxygen species (ROS) are produced rapidly.

$H_2O^{\bullet} + H_2O \rightarrow H_3O^{+} + OH^{\bullet}$

$H_2O^{*} \rightarrow H^{\bullet} + OH^{\bullet}$

ROS have unpaired electrons in separate orbitals in theirs outer shell and exhibit a high reactivity. They cause structural and functional defects in nucleic acids, proteins and lipids by interacting with these molecules. Hydroxyl radicals ($OH^{\bullet}$) are the most reactive radical species and they interact with pyrimidines, purines and chromatin proteins. $OH^{\bullet}$ attacks to DNA results in formation of strand breaks, base modifications and genomic instability. These lesions are largely repaired by DNA repair systems. However, damages that have missed by repair activity and become permanent may effect the structure of genome. Intracellular accumulation of ROS leads tumor development by increasing the mutational rate[4]. 8-hydroxydeoxyguanosine (8-OHdG) is the most abundant and most mutagenic lesion formed as the result of interaction of ROS with DNA. 8-OHdG is able to pair with cytosine instead of adenine during the replication and causes GC-TA mutation. Depending on the altered DNA sequences gene amplification, proto-oncogene activation and tumor suppressor gene repression may develop[5]. Increased 8-OHdG adducts have been reported at all stages of carcinogenesis, and in many tumor types. However, oxidized bases has been thought to have a minor role in IR-induced mutagenesis. Oxidized bases can be repaired through the base excision repair pathway. Investigations on radiation damages have shown that SSB are also not very important since they can be repaired via DNA ligation with high fidelity. It has been determined that DSB is responsible for IR-induced carcinogenesis. Repair of DSB is more complex than repair of SSB. In mammalian cells, DSB are repaired by non-homologous end joining (NHEJ) which is an error-prone pathway. In this process, the two ends of DSB rejoins without the requirement of sequence homology between the two ends, but a few nucleotides may be lost or may be added during this process. Misrepaired DSB cause to deterioration of genomic structure[6].

The predominant molecular-structural alterations associated with IR are deletions, chromosomal rearrangements or recombinational processes. Ras and p53 are the most investigated target genes in carcinogenesis. Many investigators have reported IR-associated ras and p53 mutations[5,7]. The data obtained from subjects investigated in late period of radiation accidents have shown that the mutations in areas of codons 246-250 exon 7 of p53 gene and codon 12 of N-ras gene are more frequent in survivors of radiation accidents than those in control group[7]. It has been thought for a long time that the initiating event in radiation carcinogenesis would be more likely to involve inactivation of a tumor suppressor gene by loss of heterozygocity rather than the activation of a proto-oncogene[1,8-9]. One specific example supporting this idea is the *RB* tumor suppressor gene. It has been suggested that hypersensitivity of retinoblastoma patients to the development of secondary cancers, primarily osteosarcomas in the irradiated area following radiotherapy, is probably derived from radiation-induced loose of heterozygocity of the *RB* gene[9].

ROS-mediated oxidative damage in mitochondrial DNA (mtDNA) also plays an important role in the carcinogenesis. In general, mtDNA is more susceptible to oxidative damage than nuclear DNA. Because mtDNA is not protected by histones and its