Chapter

Radiation and DNA Methylation Mechanisms

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Abstract

There are two types of radiation, namely ionising and non-ionising radiation, the former of which interacts with atoms or molecules while the latter does not. Technological advances, evolving with the development of mankind, have led to gradually increasing exposure to radiation. Radiation-related influences affect the cells that make up organisms in different ways, which means that they result in various effects in the affected organism. DNA methylation altered by radiation is one of the cellular systems affected in this context. DNA methylation is a major epigenetic mechanism that is particularly associated with cellular radiosensitivity, and it may also be associated with increased resistance to radiotherapy or chemotherapy. There is increasing scientific evidence that support this notion across a variety of study types from those that involve plants to those conducted with human subjects. Recent results with an increasing trend are available in this field. Our aim in this chapter is to describe the radiation environment and increasing exposure among humans as well as other living species, and to shed light on the effects of radiation on epigenetic mechanisms based on relevant scientific studies.

Keywords: ionising radiation, non-ionising radiation, epigenetic, DNA damage, methylation

1. Introduction

There are two types of radiation, namely ionising and non-ionising radiation, the former of which interacts with atoms or molecules while the latter does not. Radiation exposure is known to be gradually increasing among humans, and such exposure affects organisms in different ways. DNA methylation, a major epigenetic mechanism, is one of the cellular systems affected by radiation and of particular importance, it is involved in cancer in that it may alter sensitivity or resistance to radiotherapy at cellular level [1, 2]. In physics, radiation is defined as the emission or transmission of energy in the form of waves or particles through space or through a material medium. This is generally divided into two main types. The first type includes radiowaves, microwaves, visible light, ultraviolet and infrared. Radiation such as X-rays and gamma-radiation shows wave characteristics, while the other type of radiation refers to particles such as alpha, beta and neutron particles in electromagnetic spectrum (**Figure 1**) [3, 4]. In addition to these, there is also wave-like radiation in sound radiation and in the magnetic field of the earth. Ionising radiation is the type that has the power to displace electrons in the orbits of the atoms they encounter. Examples of this type of radiation include medical imaging devices

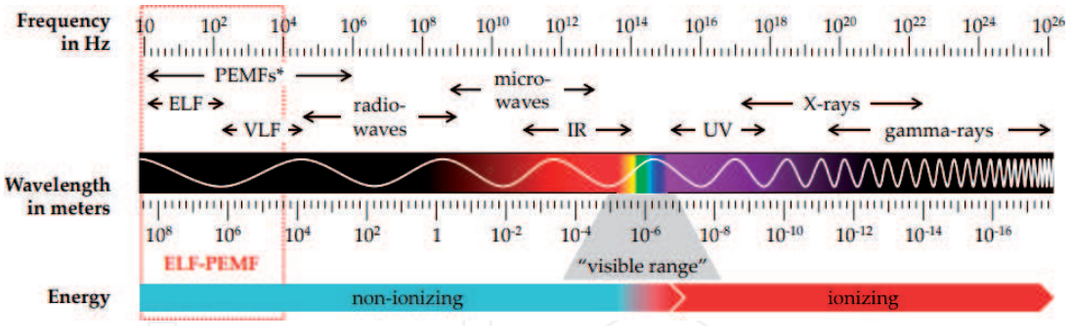

Figure 1.
Electromagnetic spectrum [6].

such as X-rays, tomography and PET (positron emission tomography) and certain medical applications including radiotherapy devices as well as the security X-rays, alpha, beta and gamma rays utilised in imaging systems used in airports and shopping malls, etc. [5]. Other types of radiation we often encounter and use include radio-TV waves, microwaves, visible light, ultraviolet and infrared radiation. All these radiation types have a variety of effects on individual species and living cells, depending on the dose and duration of exposure.

2. Effects of radiation on the cell

The effects of radiation on the cell are dose-dependent, and the radiation dose is expressed in Grey (Gy) units. Gy is briefly defined as the energy absorbed by a substance. However, spatial distribution of the irradiated volume is not taken into consideration in this definition. On the other hand, linear energy transfer (LET) is more important in radiobiology. LET is the amount of energy transferred by an ionising particle to the material traversed per unit distance, and homogeneous distribution can be achieved with low-LET, while heterogeneous distribution may occur with high LET (particulate energy). As a result of the energy transfer, different damages occur in the cell. DNA is the main target of radiation in the cell. Under normal circumstances, DNA breaks can be repaired within minutes or hours, and such breaks do not result in cell death. However, cell death may occur after double-strand breaks. The effect of radiation on DNA can be classified in two categories, i.e., direct and indirect effects [7, 8].

2.1 Direct effect

When ionising radiation strikes an atom or molecule and breaks electrons from the atom to form ionisation, direct interaction occurs. Alpha, beta and high-dose gamma rays, both with low and high unit-distance energy transfer (LET), ionise a given molecule at the point of radiation impact of radiation. This results in formation of two adjacent reactive parts in DNA structure. There may be no resultant damage if these two fragments are immediately reassembled to form the same original molecule. However, in a large macromolecule such as DNA, bond fractures may occur with this direct effect. Ionising radiation directly acting on DNA may result in open purine rings, or phosphodiester bonds may be broken, or breaks may occur in single- or double-strand DNA. On the other hand, ionising radiation is utilised in medicine, especially in nuclear medicine and radiation oncology clinics, for the treatment of cancer patients by destroying cancer cells [9, 10].

2.2 Indirect effect

Radiation can interact with molecules in the body without directly affecting DNA, such effects include ionising molecules and forming free radicals. The effect of these reactive free radicals on DNA is defined as an indirect effect. A free radical is a highly reactive atom or molecule containing one or more unpaired electrons. The unpaired single electron imparts characteristic chemical properties to the free radical, which translate into toxic effects in living cells. For example, ionised radiation can be delivered through free radicals by acting on water molecules that are present abundantly in the human body [11, 12].

The disintegration of water with radiation (radiolysis) occurs as follows: (1) H_2O + IR (ionising radiation) → e^- + H_2O^+, (2) e^- + H_2O → H_2O^-, (3) H_2O^- → OH^- + H^+, (4) H_2O^- → H^+ + OH^-. This reaction results in formation of four free radical products, i.e., H •, OH •, H^+ and OH^- (**Figure 2**) [13, 14]. Ionising particles react with DNA and cross-linking results in breakage of chemical bonds as well as structural breakdown. In the presence of oxygen, radiation produces highly destructive reactions within the cell. As a result of the indirect interaction of these toxic chemical structures with DNA, the cell may repair itself and continue to live, may fail to repair itself and die (apoptosis), or the repair may fail and lead to a mutation in the cell. With the indirect effect of ionising radiation, DNA damage can be almost two-fold higher than that caused by direct effect.

The severity of this damage depends on the radiation dose. DNA base damage is the most important type of DNA damage. Thymidine is the most radiosensitive base in this regard, followed by cytosine, adenine and guanine [15]. A 100 Rad (1 Gy) dose of low-LET radiation can produce 60–70 double-strand breaks and 1000 single-strand breaks per cell. Simple single- or double-strand breaks are responsible for cell death. Damage in DNA strands is a serious cellular phenomenon [16, 17]. However, the cell is equipped with chromosomal repair mechanisms. These repair

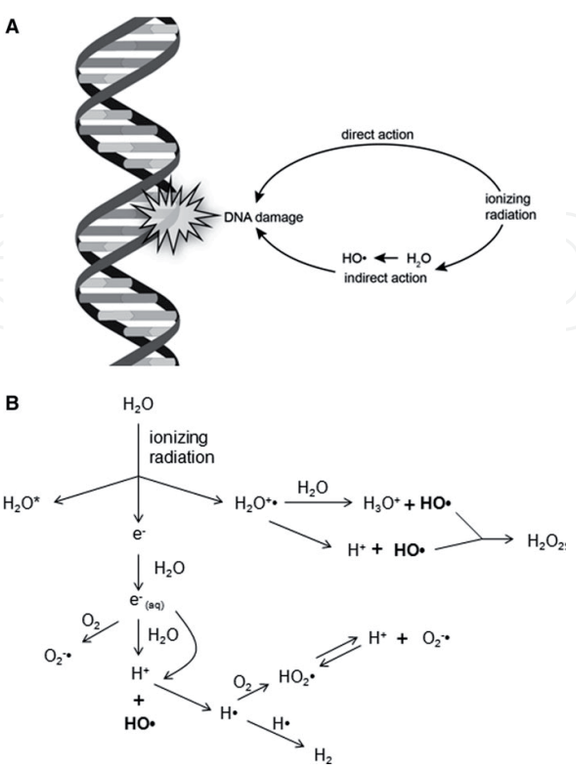

Figure 2.
(A) DNA damage by ionising of water and (B) ionise to water by ionising radiation.

mechanisms, like any other biological mechanism, are not 100% effective. DNA repairing enzymes are more effective in single-strand breaks than in double-strand breaks. If both strands of DNA are mutually damaged, they cannot repair the problem, and the damage results in cell death. Chromosomal abnormalities caused by ionising radiation generally manifest as chromosome breaks and chromatid breakage. Chromosome breaks usually occur as a result of radiation exposure in a cell during the first stage (G or early S phase) of interphase during the cell cycle [18, 19]. Chromatid breaks occur as a result of radiation exposure in the last stage of interphase (late S or G2 phase). If the chromosomal repair mechanisms fail to repair the chromosomal damage before the cell enters mitosis or meiosis, the pairing is bound to fail. This results in cell death or genetically problematic generations. Generally, cells exposed to radiation during mitosis have less time for repair; therefore, a greater number of genetic mutations and abnormal cell functions are triggered in the mitosis phase. Cells that exhibit less frequent mitotic activity (e.g., cells in the lens, nerve cells, muscle cells, skeletal cells), on the contrary, show less radiosensitivity. In radiation oncology, treatment is administered as fractions of low radiation doses (5 days, 2 Gy/day). Radiation in fractions causes both single- and double-strand breaks. Single-strand breaks are repaired between fractions within 0.3–3 h on average. Additionally, the repair capacity is higher in normal tissue compared to that in tumour tissue [20, 21]. Thus, normal tissues are protected during radiation therapy. There are several reasons for radiation to be delivered in fractions. These are called the five Rs: (1) radiosensitivity: Tissues within the organism exhibit different levels of radiosensitivity. (2) Repair: Cells have DNA repair mechanisms. In particular, single-strand breaks can be repaired rapidly by highly complex biological mechanisms. (3) Repopulation: Cells have the opportunity to replicate in between the fractions. During fractions, hypoxic cells may regain oxygen and become more susceptible to radiation. Radiation can be applied without interruption during radionuclide treatment. Both single- and double-strand breaks may occur. Within this continuity, single-strand breaks can be repaired. Radionuclide treatments may also be administered in fractions. For example; the radioactive iodine treatment, Lu-177 octreotide, and prostate-specific membrane antigen treatments are given at intervals of 6–8 weeks with intervals of 3–6 months. However, there is no scientific basis for such fractionation [22–24]. Effect of Radiation on the Cell Membrane: The main function of cell membranes is to control intracellular and extracellular substance exchange. Radiation affects the double-layer lipid structure of the cell membrane, and ionisation of membrane proteins inactivates all transport mechanisms by inactivating associated molecules. Oxidation of unsaturated molecules in their compounds with oxygen forms free radicals in double bonds and carbonyl groups, and this mechanism interacts with other organic molecules by intracellular chain reactions to convert those molecules into free radicals. There are various defence mechanisms in the body to slow down and stop this chain reaction. The Effect of Radiation Outside the Cell: There are no cells that are completely resistant to radiation. Each cell has a different level of sensitivity to radiation. While radiosensitivity is higher in frequently dividing and slightly differentiating cells (ovarian and testicular germinal cells, haematopoietic system cells, epithelial cells of the gastrointestinal system), non-dividing and highly differentiating cells (liver, kidney, muscle, nerve cells) are less sensitive to radiation [25, 26].

Effects of radiation on different types of cells: (1) change in blood parameters: Generally, a decrease in blood components may occur after a gamma dose of 500 mGy (500 rad). (2) Symptoms in the blood-producing system: Doses around 200 mGy (2 Gy) cause damage in the bone marrow, while doses above 4–6 Gy may result in complete destruction. Bone marrow may sometimes repair itself and survive at these doses; however, bone marrow repair is impossible at 7 Gy and

above. (3) Symptoms in the digestive system: Doses of and above 10 Gy in whole body irradiation cause intestinal exfoliation. (4) Symptoms in the central nervous system: Doses of and above 20 Gy and in whole body irradiation cause loss of consciousness within a few hours or days. Extracellular effects of radiation are classified as deterministic effects and stochastic effects [27–30]. Deterministic Effects: Exposure to high-dose ionising radiation may result in sudden death, particularly owing to the rapid effect on bone marrow and the digestive tract. Individuals may survive acute exposure to radiation doses of up to 5 Gy. However, exposure to radiation of 50 Gy or more results in death even if medical treatment is applied. If ionising radiation exposure affects a particular region, and not the whole body, the effect of radiation exposure varies depending on the radiosensitivity of the exposed body part as well as the type and intensity of the radiation exposure. Possible consequences include skin burns and infertility with radiation exposure of the gonadal region in men (3.5–6 Gy) and in women (2.5–6 Gy), and cataract may develop due to radiation exposure of the eye (5 Gy). The deterministic effect may occur in external radiotherapy and radionuclide treatments. Stochastic Effects: These effects can be observed in a delayed manner (somatic) in non-acute (severe) radiation exposure. In particular, the effects of doses between 0.01 Sv (1 rem) and 1 Sv (100 rem) are the subject matter of extensive research. Detailed reviews have been published by the United Nations Scientific Committee on the Effects of Atomic Radiation and the United States National Academy of Sciences, The Committee on the Biological Effects of Ionising Radiation. Delayed effects of radiation can occur either by exposure to extremely high doses of irradiation at one time, or through continuous exposure to high doses of irradiation. No threshold dose can be determined for the occurrence of harmful effects. When the relation is linear and more radiation is received, the greater the likelihood of developing radiation-related harm (nonlinear model). There is no concrete data to show that low-dose radiation exposure is the cause of cancer in humans. The effects of low-dose exposure are estimated based on animal experiments and studies in subjects exposed to high-dose radiation. Possible side effects of exposure to low-dose radiation may include cancer and genetic changes [31–34].

2.3 Factors affecting the effectiveness of radiation

The health effects of exposure to ionising radiation depend on several factors. These factors are as follows: type of radiation: any type of ionising radiation may cause detrimental effects on healthy tissue. However, different radiation types at the same dose exhibit different effects. This depends on the quality factor (Q) of the radiation in question. X-rays, β-rays and positrons (Q = 1) cause the same damage in tissues, while certain heavy particles such as alpha particles, neutrons and protons cause greater damage in biological tissues than X-rays. The quality factor for alpha particles is Q = 20 [35]. Dose received: high doses cause greater health problems. Dose rate: Low-dose and time intervals of radiation exposure make biological systems resistant. While DNA and chromosomes are exposed to multiple damage in a short period of time, the repair process in response to damage takes a longer time. Single-strand breaks in DNA can usually be repaired in less than 1 h. However, double-strand breaks are more difficult to repair. Exposed body part: Although parts of extremities, such as hands and feet, are exposed to higher radiation doses, less damage occurs in these parts compared to that in other organs and tissues, such as blood. The affected individual's age: the body becomes less susceptible to the effects of radiation as cell division decreases with age. Biological differences: The tolerance against radiation varies across individuals. The studies in this area are not sufficient to determine these differences. Heat: due to the suppression of DNA

repair at low temperatures, most cells are more sensitive to radiation at high temperatures. Chemical agents: Certain natural or artificial chemical agents may affect radiosensitivity, resulting in higher damage with radiation exposure. If dissolved oxygen in the tissues can increase the stability and toxicity of free radicals [36, 37].

One of the important biological effects of ionising radiation is that it can alter the epigenome, thereby leading to changes that may be transferred from one generation to the next. Such effects of radiation may occur at the somatic or reproductive cell level. These effects are often in the form of reduced global methylation of cellular DNA. Ionising radiation can damage intracellular molecules, mainly complex molecules such as proteins, lipids and RNA, leading to double-strand breaks in DNA. Therefore, such damage may cause cell cycle arrest and when this exceeds a certain level, it may even lead the cell to apoptosis or may sometimes cause abnormal cell growth. Several types of cancer cells can be completely eliminated by radiotherapy with ionising radiation; however, some others, such as stem cells, and certain types of cancer cells with survivin protein expression may exhibit resistance. Non-coding RNAs, different histone forms and chemical changes in histones as well as DNA methylations, particularly those involving cytosine and to a smaller extent, adenine, are known to be epigenetic markers. In vertebrates, especially cytosine methylation is known to affect the chromatin structure and gene expression. Epigenetic modifications such as histone modification and non-coding RNAs may be transferred through generations via cross-transitions. Several studies have shown that epigenetic changes in the first generation exposed to environmental pollutants, such as methylone, may be passed on through approximately four generations. Although there is currently no data concerning the intergenerational transmission of genome-wide methylation changes caused by ionising radiation in vertebrates, the intergenerational transmission of methylated DNAs associated with low-dose ionising radiation has been demonstrated in invertebrates [38–40].

3. Herbal effects

Flavonoids, which often have low molecular weight, are a group of secondary metabolites that may show a broad spectrum of effects in reproductive and signalling pathways such as UV-protection, protection against phytopathogens and providing signalling pathways as well as playing certain roles in different physiological pathways. The synthesis of these molecules, usually synthesised by plants, occurs via the phenylpropanoid pathway, which forms the basis of biosynthetic pathways. These molecules are synthesised by the shikimic acid pathway, leading to the formation of p-Coumaroyl-CoA through the phenylpropanoid pathway, following the formation of aromatic amino acids containing phenylalanine. This synthesis metabolism is carried out by three enzymes, namely phenylalanine ammonia lyase (PAL), cinnamate 4-hydroxylase (C4H), and 4 coumarate-CoA (4CL). Coumaroyl-CoA is also converted to naringenin from different flavonoid molecules by interacting with chalcone synthase (CHS) and chalcone isomerase (CHI). Ultraviolet-B (UV-B) radiation, a type of non-ionising radiation, generally shows a positive effect on flavonoid biosynthesis in plants. Ultraviolet-B rays usually enhance flavonoid synthesis. Ultraviolet-B rays are the only type that lead to an increase in the synthesis of flavonoids. However, apart from ultraviolet-B, ROS of solar or non-solar sources in a wider band range affect haemostasis [41, 42]. Current stress conditions may neutralise several enzymatic antioxidants, while flavonoids can act as a secondary defence system. Due to the increasing knowledge about the effects of epigenetic mechanisms on gene expression in recent years, effective mechanisms have emerged also in this field. In particular, intracellular regulation of the increase or

decrease in gene expression by methylated cytosines has been shown to be also valid in plants. A number of abiotic stress factors have been found to be effective on DNA methylation dynamics. An association has been shown between cytosine methylation and ultraviolet-B rays for demethylation of the DBR2 gene and the biosynthesis of artemisinin [42, 43].

3.1 SPACE radiation

In recent years, the National Aeronautics and Space Administration (NASA) and other countries' space agencies have begun to pursue policies to develop manned-space missions and technologies between meteors or to the Moon and Mars, or on asteroids close to the Earth, in other words, they have had to initiate such policies in order to replace the diminishing resources of the Earth. As expected, the biggest problem with these tasks is the several dangerous situations astronauts may face in deep space environment, some of which may be predicted while others tend to be unpredictable. Among these dangerous situations, the major ones include protons, radiation with high-energy (H) or high-atomic number (HZE; high-atomic number (Z) and energy) and galactic cosmic radiation (GCR). HZEs, owing to their electrical charge being +2, cause damage in the cells or tissues they encounter through ionisation. This type of radiation, which the astronauts would be exposed to during deep space missions such as travelling to Mars, has been shown to cause serious cognitive disorders [44–46]. Other radiation-related effects in space missions include increased oxidative stress in the brain, neuroinflammation and other functional and structural changes, including disruption of neuronal structures and synaptic integrity [47]. There is rather a small number of studies on the mechanisms by which space radiation may cause these effects; however, molecular mechanisms likely to produce these dramatic changes in central nervous system (CNS) functions have been relatively elucidated. Biological functions of the brain are multi-layered and multi-functional, and epigenetic mechanisms—particularly DNA methylation and histone modifications—are highly important for proper functioning, which is critical for cognition. Recent developments, especially those in the field of neuroepigenetics, have shown that permanent changes in DNA methylation can significantly affect learning skills and memory. In particular, reduced activity of the DNA methyltransferase (DNMT) enzyme by 5-azadeoxycytidine (5-aza) or Zebularine, a cytidine analogue nucleoside, has been observed as well as loss or reduction of normal memory stability, reward learning or spatial learning abilities in rats that were administered RG108, a direct DNMT inhibitor [48–50]. Studies in animals exposed to a methyl-group donor diet for the manipulation of DNA methylation have shown expression changes in glutamate receptor-associated genes, and new object recognition and fearlessness [51]. Considering the effects of DNMT inhibitor agents on major methylation enzymes in the absence of toxicity and chemical stability, it has been shown that the learning and memory of certain DNA methylation enzymes can be genetically altered through DNA methylation mechanisms [51–53]. Some studies have demonstrated that memory organisation and behaviours such as dependence may be altered by decreasing the activity of certain DNMTs that add or remove methyl-group via viruses and through the changes in the expression of 10–11 translocation methylcytosine dioxygenase (TET) enzymes. Of the several epigenetic modifications, the most investigated one is the 5-methylcytosine (5mC) modification of the cytosine in DNMT. Such modifications are mostly concentrated in the promoter regions that affect the transcription of genes [48, 54, 55]. However, scientific research shows that 5mC is dynamic and may also be concentrated along the entire DNA strand or on a particular chromosome, such as the X chromosome.

DNA methylation of the DNMT enzyme group (especially DNMT1) in dividing cells is quite important for cell differentiation. In terminally differentiated neurons that make up an adult's brain, DNMT enzymes (DNMT3a and 3b in particular) are especially important since the de novo methyltransferase activity adds methyl groups to the predetermined cytosines in the DNA making up the genome. Especially when the amount of DNMT3a expression is high in mitotic neurons, it is important for the adult brain. In addition, 5mC can be oxidised by ambient oxygen or modified by TET enzymes. Of the TET enzyme group, TET3 is the most common enzyme in CNS and is known to be closely associated with learning and memory function. Likewise, the potential importance of TET1 is related to DNA methylation motifs, which may vary according to neuronal activity. Although there is less data on TET2, it is thought to be involved in developmental processes [56–59]. 5-hydroxymethylcytosine (5hmC), a highly stable, modified and oxidised form of 5mC, is found at higher levels in the brain than other organs of the body [58]. In addition, 5hmC can be actively deaminated by DNA repair mechanisms when necessary, and, despite its stability, it can be reversed to unlabelled cytosines.

3.2 Low-dose ionising radiation and oxidative stress

Ionising radiation may exhibit ionising effects directly or indirectly on the atoms of the substances it encounters. The positively charged particles are direct ionisers since they contain enough energy to disrupt the atomic structure of the substances they encounter. These charged particles are relatively large-mass and highly effective over short distances. However, since massless and wave-like radiation such as gamma travels at the light of speed and ionising radiation travels rapidly as is the case with electrons, they leave their energy in the atoms they encounter, thereby producing charged particles. As a result of this rapid action, should they encounter biological organisms, they can directly damage biomolecules such as DNA, RNA and proteins in living cells, or form highly reactive oxygen species (ROS). It has also been reported that radiation such as Laser Direct Infrared (LDIR) has considerable effects on biological substances [32, 60, 61]. Ionising radiation can also stimulate ROS production by causing nitric oxide synthase (NO) formation in the presence of biological substances such as amino acids. This NO molecule can interact with the superoxide radical (O_2-) to produce peroxynitrite (ONOO-). Peroxynitrite is a powerful oxidant radical that can interact with biomolecules such as DNA bases, proteins and lipids. Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is another important molecular source that causes intracellular ROS production. NADPH oxidase is a complex enzyme with multiple subunits located in the membrane of activated and non-phagocytic cells [62–64]. NADPH oxidase produces superoxide anions by transporting electrons from the cell membrane to extracellular molecular oxygen through cytoplasmic NADPH. Activation of NOX4 and NOX5, members of the NADPH oxidase family, by LDIR accelerator has been associated with potential DNA damage. The effect of stimuli such as LDIR on mitochondria occurs almost through the same pathway. Mitochondria are organelles that contain a group of enzymes. A series of reactions occurring in mitochondria may also lead to formation of free radical by-products due to the escape of electrons from the mitochondria. These escaping electrons contribute to the formation of superoxide at the basal level [65, 66]. High-energy radiation affects the electron flow by increasing the electron release from mitochondria, resulting in excessive superoxide production. Furthermore, ionising radiation disrupts the function of mitochondria by inhibiting the electron transport chain (ETC) enzymes from mitochondrial proteins, including aconitase. Such LDIR-mediated mitochondrial effects increase intracellular

oxidative stress levels and lead to high ROS signalling. These programmed cellular changes occur in daughter cells that are formed after cell divisions following the first exposure. Genomic instability and increased changes in non-Mendelian mechanisms after LDIR-induced changes suggest that LDIR acts through epigenetic-based mechanisms. Although studies have shown cellular alterations such as RNA expression of radiation-induced DNA methylation, histone modification and nonsense transformation of gene sequences often in cancer models, the molecular and mechanical information gained across these studies are highly applicable to several biological cellular systems. Recent studies have demonstrated that LDIR exposure can change the intracellular DNA methylation profile. Using animal models, LDIR exposure has been shown to have different dose-, gender- and tissue-specific effects on reduced global methylation [67–69]. LDIR-type radiation has been shown to cause locus-specific DNA hypomethylation in the TRAPC1, FOXC1 and LINE1 (Long Interspersed Nuclear Element-1) genes in breast cancer cells. As a result of such hypomethylation, a decrease was observed in expression levels of DNA methyltransferase enzymes such as DNMT1, DNMT3A and DNMT3B as well as methylated CpG binding proteins such as MeCP2. Similarly, LDIR has been associated with the hypomethylation and activation of LINE-1, leading to increased levels of LINE-1 expression and increased genomic irregularities as a result of enhanced LINE-1 mobilisation. The effects of LDIR on reduced global DNA methylation appear to be more favourable in control groups compared to those who work in nuclear industry, thereby inherently exposed to irradiation. In relevant studies, the amount of LINE-1 methylation was higher in irradiated workers compared to controls. In these workers, reduced global methylation is observed to be significantly greater in cellular chromosomal anomalies. Thus, LDIR-mediated reduced global methylation models indicate a connection between radiation exposure and increased genomic irregularity. Although exposure to LDIR energy causes reduction in global methylation, promoter hypermethylations have been shown to be more stable compared to global hypomethylation [70–72].

4. Conclusion

After the discovery of radiation at the end of the nineteenth century, radioactivity came into use in many disciplines and in everyday life and started to be used for human benefit in some areas. It is used for the destruction of cancer cells, especially in the field of medicine, and has been increasingly used in industry, agriculture and scientific studies in recent years. The ionised radiation has effects on DNA and cells. The type of radiation varies depending on the total energy trapped in the tissues, the energy of the radiation and the tissue properties. Ionising radiation can cause different types of damage to organic tissues depending on the dose taken. Radionuclide treatments, which have been developing and diversifying rapidly in recent years, have revealed the fact that we know well the effects of radiation on tissues and cells. In addition, while the researches of the effects of this kind of radiation, especially on epigenetic mechanisms, will be important for human health. For this reason, it is important for belief that such studies are increasing gradually. This chapter summarises the recent studies, which provide compelling evidence that ionising radiation provides a mechanistic link between LDIR and epigenetic gene regulation via ROS or other mechanisms, such as low-LET. Epigenetic changes are mediated by oxidative stress. Numerous studies have demonstrated that ROS scavengers such as n-acetylcysteine and tempol prevent epigenetic DNA methylation changes induced by oxidative stress through direct or indirect mechanisms.

Conflict of interest

There is no conflict of interest.

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