How to Cite:
Mohammed, Z. M., & Lafta, F. M. (2022). The effect of exposure to low-dose ionizing radiation on DNA methylation and relation to genomic stability: Review article. *International Journal of Health Sciences*, *6*(S8), 4167–4173.
https://doi.org/10.53730/ijhs.v6nS8.13126

The effect of exposure to low-dose ionizing radiation on DNA methylation and relation to genomic stability: Review article

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***Abstract*---**Ionizing radiation is one of the toxic and carcinogenic factors that potentially have direct and indirect long-term effects that are depending on the amount of doses and periods of exposure to radiation. These risks can appear in the form of changes in gene expression due to the influence of epigenetic mechanisms, especially DNA methylation. Exposure of DNA methylation to ionizing radiation for long periods of time can lead to genetic instability, which can be passed down through generations. In this review will. The aim of this study is to shine new light on these debates through an examination of.

***Keywords*---**ionizing radiation, DNA methylation, genomic stability.

Introduction

Ionizing radiation (IR) now occupies wide range of industrial and medical applications in different areas of life despite the wide knowledge of its potential genetic cytotoxicity and its ability to induce genomic instability by targeting epigenetic marks, especially in DNA methylation [1]. Where the biological effects of IR can be sub-categorized into direct and indirect influences the direct impact of IR on living cells may lead to disruption of the atomic structures of the cells' mitochondria causing chemical and biological change that ultimately leads to the early aging and death of the cell (Figure 1).

While the indirect effect of IR exposure have the potential to influence genetic structures, particularly DNA [2]. The phenomenon caused by the indirect effect of radiation (oxidizing changes of the living cell exposed to IR) may continue to appear for a period of time that may take several days or months due to reactive

Manuscript submitted: 9 May 2022, Manuscript revised: 18 July 2022, Accepted for publication: 27 August 2022

oxygen species generation (ROS) and reactive nitrogen species (RNS). This also happened in the progenitor of the radioactive cells through the mechanisms of communication between cells these also suffer from disorders of the biological mechanism of the living cells, such changes are ultimately. supported by the occurrence of genetic mutations and neoplastic transformation if exposed to IR again (Figure 2) [2].

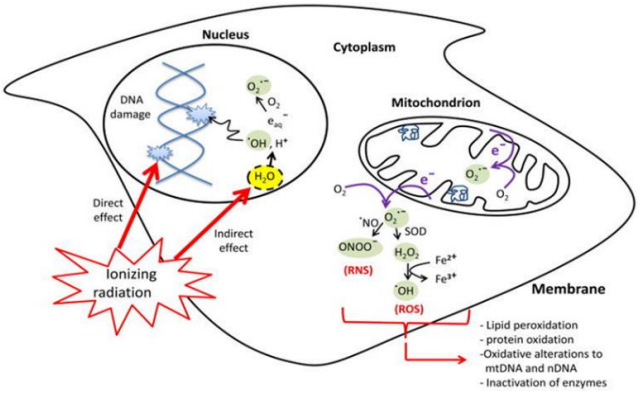

Figure 1 :Potential biological effects resulting from ionizing radiation and the role that radiation plays in cell degradation and nuclear damage [2]

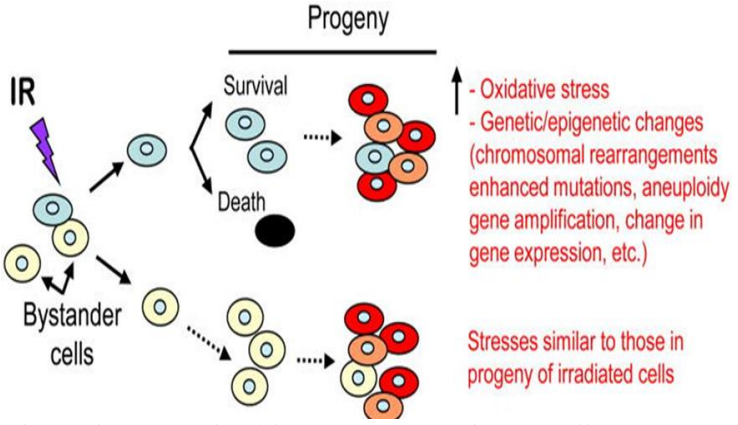

Figure 2 :The induction of oxidative stress in living cells as a result of their exposure to ionizing radiation[2]

Focusing on the negative effects of occupational exposure to ionizing radiation, it was found that these effects are not isolated from cells exposed to ionizing radiation and that this may lead to genome instability in the germ line, and is also associated with transgenerational genetic instability [3]. Although the impact of IRs on genetic material is well-established by several studies, however, what is not yet clearly uncovered is their impact on the epigenome. There is very little scientific understanding of the role of IR in inducing epigenetic changes and the mechanisms associated with it were poorly known ignored for a long period of time. Of important such IR-induced epigenetic aberrations could be the primary precancerous events that occur several years earlier in the period before the emergence and development of the tumor. Therefore, it was necessary to shed

light on these epigenetic mechanisms and their crucial role, especially when exposed to one type of radiation [4]. This means that radiation has the potential to have long-term, multi-generational effects through its effect on epigenetic modifications, especially DNA methylation [5]. Because DNA methylation is the first epigenetic mechanism to influence IR, as exposure of the DNA methylation to IR could lead to cellular genetic reprogramming that may ultimately lead to genomic instability, Therefore, DNA methylation acts as the guardian of the genome to ensure its stability by preventing translocation-mediated gene disruption. Prominent nuclear abnormalities occur in cells that lack the stabilizing effect of DNA methylation because they have spontaneous defects in DNA methyltransferases (DNMTs, enzymes that methylate cytosines in CpG) or experimentally disrupted DNMTs [6].

IR has been shown to be effective in inducing DNA methylation changes specifically within repetitive elements (Koturbash, Miousse *et al.* 2016). A comprehensive study of the effect of radiation on the global DNA methylation conducted at the Seoul National University also showed the extent of the levels of global DNA methylation affected by radiation, as the results stipulated a decrease in the levels of global DNA methylation when exposed to IR for a period of 1.5 years, in addition to a low expression *DNMT1*. These impressive results supported the assumption that exposure to IR may affect DNA methylation in human blood [7]. IR beam urges the breaking of the DNA strand in the non-radiation part while working to suppress the global methylation in the radioactive part with an addition to a decrease in the levels of de novo DNA methyltransferases *DNMT3a* and 3b.This could accompany by an increase in the levels of maintenance of DNA methyltransferase *DNMT1* in the non-radioactive tissue as well as an increase in levels of methyl binding proteins known to be involved in silencing genes, particularly MeCP2 and MBD2, in the non-radioactive part [8].

Despite the wide knowledge of the association of cancers with radiation, there is still great controversy regarding the risks resulting from the exposure to Low-dose Ionizing Radiation LDIR [9]. Studies have concluded that exposure to ionizing radiation, even at low doses lead to increased risk of developing leukemia or other tumors in various tissues of the body. Accordingly IR is generally now classified as carcinogen for the human [10]. The issue of chronic environmental exposure to LDIR (exposure to a large part of an organism' life of or even over several generations) represents a major concern for its severe consequences for the exposed individual's offspring because these consequences interfere with the epigenetic mechanisms that can cause transcription and proteomes changes. On this basis, epigenetic modifications represent channels for the environmental impact on the genome [11].

However, the risk posed by exposure to HDIR largely made the biological effects of LDIR insignificant or unnoticeable by conventional assessment techniques, despite the evidence that suggests the role of LDIR in promoting oxidative stress that may cause genetic modifications by epigenetic mechanisms (DNA methylation, histone modulation, coded RNA regulation). While it is well-established that epigenetic alterations could lead to the formation of permanent transformed cell phenotype without altering the primary DNA nucleotide sequence [12].

The role of DNA methylation in maintaining genomic integrity (Chromosomal stability)

The formation of the organism is related to cell divisions and how the genetic material is distributed in an equal percentage between cells. This process requires a control center that secures the proper and equal transmission of genes between the divided cells. This center is called centromeres "they are special sites on chromosomes where kinetochores form on repetitive DNA sequences to enable accurate chromosome segregation". These sites are subject to highly regulated physiological control by the epigenetic and in particular the DNA methylation that is abundantly localized in the centromere that may be associated with protecting it from the malignant formation of tumors [13]. Some preliminary studies yielded results showing the potential role of DNA metabolism in regulating genome stability. This was evident in DNMT-deficient cells that showed detectable chromosomal abnormalities and a significant increase in the number of new chromosome transmission [14, 15]. The protection of the genetic content and the stability of the genome by DNA methylation are thought to be through the participation of methyltransferases in identifying the basic mismatches resulting from replication and symmetric recombination and repairing them mainly through the DNA mismatch repair system (MMR) [16]. In addition to the fact that DNA methylation in the heterochromatin repetitive contributes to reducing unwanted transmission and proliferation, ensuring appropriate functions for telomeres and telomerase centers, as well as maintaining genetic integrity [17]. Despite their substantial regulation in telomere regions, the DNA methylation seems to presence in CpG rich regions at the distal two kilobases of the sub telomeres (the regions at the ends of the chromosome, immediately adjacent to the terminal telomere replication). These regions are believed to undergo preservation and representation during early fetal development by de novo DNA methyltransferase *DNMT3B* [18] It is genetally thought that loss of DNA methylation is associated with increase genomic instability.

Understanding the side effects of dose of IR especially in relation to genomic instability, by generating genetic changes across generations in epigenetic mechanisms, of great interest. Indeed, different patterns of global DNA methylation alterations caused by exposure to low doses of chronic radiation were noted. This was confirmed by the results of previous studies that claimed that chronic exposure to IR increased the instability of the genome more than acute exposure [19]. The emergence of deviations in the epigenetic landscape, especially in *LINE1*in the daughter cell of radiation exposed parental cells, has led to a broad consensus that radiation causes long-term and non-target effects [20]. DNA methylation changes, in particular the loos of methylation that is termed hypomethylation, ultimately can cause genomic instability as a result of oxidative stress from IR [21]. Although there is ample evidence linking DNA methylation to genetic instability, understanding of the true underlying causes is remain unclear [22]. Thus, radiation-induced genomic instability (RIGI) can be defined as stereotypical changes in the daughter cells that appear late in the time after the parental cells are irradiated. Such mechanism that leads to the formation of cancers that cannot be explained by changes in the DNA sequence only due to the role that epigenetic inheritance plays in many cellular processes that may leads to

the formation of genetic deviations including the inactivation and silencing of key regulatory genes such as those of tumor suppressing role [23].

Therefore, the occurrence of genetic instability can be through two mechanisms, either by genetic mechanisms represented by genetic aberrations caused by changes in the DNA sequence such as (mutation, deletion, insertion, inversion, translocation, and chromosomal aneuploidy) while the second type of mechanisms is epigenetic aberrations [24]. Epigenetics alternations are an alternative pathway to the mutations where genetic and epigenetic changes can be two side of the same coin. Cells of the body that exposed to low doses of IR for a long period of time may not show any symptoms and this makes the cells of the body appear to be normal or similar to that. However, in the case that the symptoms of low doses accumulate to become visible in the ancestors of cells (non-irradiated cells) this is due to the exchange of molecular signals and complex tissue interactions involving adjacent or distant cells. This shortens the rationale behind the occurrence of genomic instability in the offspring of non-radioactive cells as a result of the predecessors of their cells being exposed to LDIR for long periods of time in addition to the remaining state that was not repaired by metabolic processes such as DNA damage due to direct exposure to radiation [25]. This was also confirmed by the results of a study of genomic instability across generations occupationally exposed to LDIR. The results showed the occurrence of genomic instability in parents, while these low doses lead to genetic disruption in the lifespan of children caused by a change in the individual characteristics of genomic instability (as a result of a response to primary DNA damage) [26].

Conclusions

In sum, radiation has become one of the risk factors that cause genetic instability, in other words, radiation can partially or completely damage cells, or cause different pressures on cells in the future that may develop into cancerous diseases in subsequent generations. In light of this, four types of relationships can be found that link DNA methylation and radioactive response, especially low-dose radiation responses, as follows:

- First, the methylated gene is associated with radiation sensitivity and the DNA methylation status of many key genes is thought to affect their expression levels. This has been observed through hyper-methylation of the *P73* gene associated with a decrease or absence of protein expression P73 for cervical cancer.
- Second, DNA methylation regulates cell response to LDIR, such as regulating genomic instability and carcinogenesis. This process coincides with a decrease in de novo DNA methyltransferases (DNMT) i.e. DNMT3a and 3b associated with a decrease in DNMT1 maintenance in adjacent tissues and methyl binding protein CpG 2 (MeCP2) which is involved in silencing transcription. This means that DNA methylation plays a key role in the development of side effects from exposure to LDIR.
- Thirdly, exposure to LDIR that regulates DNA methylation is demonstrated by changes in the radioactive induced DNA methylation as a result of changes in the methyl transferase enzyme, such as de novo methyl transferase *DNMT3a* and *DNMT3b*.

- Fourthly, and most importantly, some drugs are involved in suppressing methylation of DNA and promoting radiation therapy, such as zebularine, where it works to remove methylation and promote radiation therapy by delaying tumor development. In addition to the ability of IR to induce genomic instability, its effectiveness in causing mutations has been revealed through its direct impact on biological molecules. Mutations resulting from DNA damage affect cells as a result of increased oxidative stress due to exposure to IR that affects epigenetic modifications through reducing the activity of methyltransferases, which in turn leads to reduction of global DNA hypomethylation, leaving cumulative effects inherited by the cells exposed to radioactive elements.

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