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Persistent epigenetic modulation by radiation exposure/insults in mammalian cells

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Abstract. Effects of radiation in biological systems are quite interesting. Interaction of radiation to epigenetic mechanisms has been also demonstrated earlier. The aim of this review is to sketch a current scenario on radiation exposure/insults on the epigenetic mechanisms in mammalian cells. Evidence from the databases, mainly from *Pubmed* and *Science Direct* were considered. Findings suggest that radiation has a dose and time-dependent effect in our body. Cells and tissues from different sources have differential responses towards radiation insults. Although radiation has impacts on epigenetic modulation, but it has beneficial combinatorial effects with a number of epigenetic modalities. Radiation has both bad and good impacts on epigenetic mechanisms.

Keywords: Radiation; Epigenetics; Combined therapy; Cancer.

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Introduction

Radiotherapy is one of effective modalities in cancer treatment. Ionizing radiation (IR) exposure is essential to improve radiotherapy in this case. IR exposure and insults may occur from various origins, including environment, diagnostic center (e.g., computed tomography), work place and so on (Miousse et al., 2017). However, radiation exposure induces a multitude of biological effects, including cancer and degenerative diseases (Boerma et al., 2016; Kutanzi et al., 2016). Radiation insults can have deterministic effects, short-term and long-term injury in normal (non-tumor) tissues (Hall and Giaccia, 2011). Radiation therapy induces DNA base damage, single strand breaks (SSBs), and double-strand breaks (DSBs).

The latter one is un-repairable (Qiu et al., 2009).

Epigenetics, the recent field of molecular biology has been arisen over past 25 years. Epigenetics is the study of heritable changes in gene expression that are not associated with alterations in the primary DNA sequence. The epigenetic mechanisms of regulation include methylation of DNA, post-translational histone modifications, nucleosome positioning (chromatin remodelling) along DNA, and non-coding RNAs (non-coding RNA modulation) are vital for normal development and maintenance of cellular homeostasis (Espada and Esteller, 2007; Jones, 2012). Epigenetic mechanisms are also essential for normal development and function of the immune system (Strickland and Richardson, 2008). This review focuses radiation exposure/insults on epigenetic mechanisms in mammalian cells.

Radiological effects on epigenetic modulation

Radiation induces histone hyperacetylation, and can cause an increase in histone H3 acetylation within the promoter regions of COX2, interleukin 8 (IL-8) and MnSOD (Pollack et al., 2009). IR can also cause histone H3 hyperacetylation at the transcriptional repressed mating pheromone a-factor 2 (MFA2) promoter (Yu and Waters, 2005). Cells whose chromatin are naturally compacted, are more hypersensitive to radiation-induced killing, primarily by single-hit mechanism (Biade et al., 2001). When DNA damage occurs, chromatin structure is altered by: (i) covalent histone modifications, (ii) incorporation of histone variants into nucleosomes, and (iii) ATP-dependent chromatin remodelling (Vaquero et al., 2003, Shogren-Knaak et al., 2006). Radiation induces diubiquitylation of γ-H2AX presents a model for chromatin reorganization and the sequential binding of adaptor proteins in response to DSB (Mailand et al., 2007).

Generally, DNA methylation plays pivotal roles in normal development, proliferation, and proper maintenance of genome stability in a given organism. 20 Gy of X-rays in rat spleen tissue showed a significant loss of global DNA methylation and down-regulation of DNA methyltransferases and MeCP2. Irradiation significantly altered expression of microRNA 194 (miR-194), a miRNA putatively targeting both DNA methyltransferase-3a and MeCP2 (Koturbash et al., 2007). After whole body irradiation of 50 cGy as well as 5 cGy of X-rays per day (0.2 cGy/s) for 10 days, protein 16 inhibitor kinase (p16INKa) promoter methylation was seen in C57/Bl rat liver (Kovalchuk et al., 2004).

DNA and/or histone methylation, the loss of global DNA methylation, and DNA hypermethylation at the promoter regions of tumor-suppressor genes has also reported in various cancers (Pfeifer and Rauch, 2009). In some studies, IR-induced hypermethylation of *p16INK4a* (Belinsky et al., 2004), DNA and histone methylation and loss of global DNA methylation in the bone marrow, thymus and spleen (Koturbash et al., 2005; Pogrlbny et al., 2005; Miousse et al., 2014), DNA methylation stem primarily from RE (Prior et al., 2016), and histone H3 lysine 9 (H3K9me3) and histone H4 lysine 20 (H4K20me3) trimethylation at low and high-dose IR (Pogrlbny et al., 2005; Koturbash et al., 2007) have been reported. However, DNA methylation and histone methylation may exist at low-dose and high-dose radiation area, respectively (Ma et al., 2010).

Low-dose IR-induced adaptive response range was shown decades ago from 0.01 to 0.2 Gy. This type of IR can cause bystander effect, possibly *via*- (a) gap-junction intercellular communication; (b) interactions between ligands and their specific receptors; (c) interaction between the secreted factors and their specific receptors; and (d) directly through plasma membranes. According to Joiner

et al. (1996) hyper-radiosensitivity is seen between 0.02 to 80 Gy in different mammalian cells, where ells irradiated by low-dose radiation (LDR) (about 0.02 ~ 0.50 Gy) are more sensitive to radiation than with higher dose ranges (0.50 ~ 1.00 Gy). However, chromosomal aberrations and spontaneous DNA damage in the progeny of cells irradiated with 50 or 100 cGy (Maxwell et al., 2008), this may be due to a persistent increase of reactive oxygen species (ROS) (Dahle and Kvam, 2003) and subsequent mitochondrial dysfunction-linked elevated ROS levels, reduced Mn-Superoxide Dismutase (Mn-SOD) activity and TGF-β inhibition capacity of IR (Kim et al., 2006; Maxwell et al., 2008), cell cycle arrest and modulation of some important proteins (Sak et al., 2017).

Phosphoinositide 3-kinase (PI3K)/chromosomal gene that encodes protein kinase B (AKT) pathway is closely associated with three major radiation resistance mechanisms: (i) tumor intrinsic radiosensitivity, (ii) tumor cell proliferation ability, and (iii) the hypoxia microenvironment (Zhan and Han, 2004). After IR treatment, effective inhibition the activity of PI3K and its downstream component mammalian target of rapamycin (mTOR) will help to maintain the DNA damage status and increase the numbers of γH2AX foci, together with the enhanced G2 phase cell cycle delay (Fokas et al., 2012). However, inducing the function of transforming growth factor beta (TGF-β) receptor or constitutively activating SMAD family may reduce DNA fragmentation, caspase-3 cleavage and γH2AX foci formation in irradiated cells (An et al., 2013).

It is evident that poly (ADP-ribose) polymerase-1 (PARP-1) activity is essential in the upstream regulation of IR-induced nucler factor kappa B (NF-κB) activation and sensitizes cancer cells (Veuger et al., 2009). However, mitogen-activated protein kinase (MAPK) pathway activates the downstream of death receptors and procaspases, and DNA damage signals, such as the JNK, p38 MAPK and NF-κB pathways (Dent et al., 2003). IR, through the MAPK signaling pathway, can induce the initiation of extra-cellular growth factor receptor (EGFR)-extra-cellular receptor kinase (ERK) signaling and upregulate the expression of DNA repair genes XRCC1 and ERCC1 in an ERK1/2-dependent fashion.

Although, the exact mechanism of IR-induced changes in DNA and histone methylation remain largely unknown, but it has been through that, IR can affect mRNA and protein levels of DNA methyltransferases, as well as their enzymatic activity such as the levels of *de novo* DNA methyltransferases *Dnmt1*, *Dnmt3a* and *Dnmt3b* (Pogrlbny et al., 2005; Koturbash et al., 2016). IR is evident to cause a loss in histone H4 lysine 20 trimethylation (H4K20me3) in a study (Pogrlbny et al., 2005). In another study, nuclear DNA methyltransferase activity was found to decrease up to 3 days after exposure to10 Gy of γ-rays in cell lines (Kalinic et al., 1989). Moreover, It can disturb methyltransferases and affect the availability of methyl donors (Koturbash et al., 2016; Ghosh et al., 2013).

Cancer, interacts extensively with underlying genetic mutations is now understood to be a disease of widespread epigenetic dysregulation. Although, a number of epigenetic drugs have been approved by the Food and Drug Administration (FDA), but there are lots of limitations that are obstacles to the success. The application of epigenetic sensitization to radiotherapy may be one of the best modalities in case of solid tumor management (Abdelfatah et al., 2016). In a phase-I trial, Ree et al. (2010) found a positive outcome in GI cancer, where radiosensitization was supposed to result hyperacetylation of histone using histone deacetyltransferases (HDAC).

Ultraviolet (UV) irradiation and carcinogens have been reported to induce epigenetic alterations in animals.

In a study, the genome-wide DNA methylation profiles of skin cancers were induced by ultraviolet B (UV_B) irradiation in SKH-1 mice, where 6003 genes in the UV_B insult group exhibited a greater than 2-fold change in CpGmethylation. The top canonical pathways identified by IPA after the treatment were related to cancer development, cAMP-mediated signaling, G protein coupled receptor signaling and phosphatase and tensin homolog deleted on chromosome ten (PTEN) signaling associated with UV_B treatment. In addition, the mapped interleukin (IL)-6-related inflammatory pathways displayed alterations in the methylation profiles of inflammation-related genes linked to UV_B treatment (Yang et al., 2014).

An open chromatin pattern related to radiation-inducibility of diacylglycerol kinase alpha (DGKA) is associated with the onset of radiation-induced fibrosis. In a recent study, BET-bromodomain inhibition suppressed induction of DGKA in bleomycin-treated fibroblasts, reduced H3K27ac at the DGKA enhancer and repressed collagen marker gene expression (Valinciute et al., 2017). Alterations in fibroblast morphology and reduction of collagen deposition were also observed in this study.

However, alterations in the DNA sequence cannot explain these biological effects of, unless it is thought that epigenetics factors may be involved. Detection of some specific microRNAs (or miRNAs) can be potential biomarkers to understand this situation. A study performed with human blood exposed to 0.5 Gy, 1 Gy, 2.5 Gy, and 5Gy suggests that up to 1 Gy radiation exposure up-regulation occurs to hsa-miR-107, hsa-miR-126-3p, hsa-miR-144-3p, hsa-miR-17-5p, hsa-miR-20b-5p, hsa-miR-5194, and hsa-miR-185-5p; while down-regulation occurs of hsa-miR-3180 and hsa-miR-4730. Radiation exposure at 5 Gy caused down-regulation of hsa-miR-142-3p, hsa-miR-142-5p, hsa-miR-223-3p, and hsa-miR-451a. Generally, hsa-miR-20b-5p, hsa-miR-17-5p, and hsa-miR-185-5p may be involved in modulating genes underlying cell cycle control and the development of some cancers, including thyroid and prostate cancer. Thus, the miRNA-gene interactions associated with 1 to 5 Gy of radiation dosage treatment may be the key molecular signatures underlying the damages caused by radiation exposure. Moreover, hsa-miR-20b-5p and hsa-miR-17-5p share many target genes, thus, they can modulate gene expression through a cooperative manner (Lee et al., 2014). The expression of tumor-suppressor miR-34a was upregulated whereas miR-7 was downregulated in irradiated hematopoietic tissues after 2.5 Gy of X-rays (Ilnytskyy et al., 2008). miR-521 significantly sensitizes prostate cancer cells to radiation treatment using a miR-521 mimic which can overexpress miR-521 (Josson et al., 2008). Moreover, *ban* encoding a 21 nt miRNA was evident to activate by IR to repress *hid* to limit, IR-induced apoptosis in *Drosophila* (Jaklevic et al., 2008). At 20 Gy of X-rays in rats induced a bystander effect in lead-shielded, distant spleen tissue. Additionally, miR-194 was significantly upregulated in the animal's spleen after 7 months exposure to IR (Koturbash et al., 2007). However, the effect of radiation on microRNA expression may vary according to cell type, radiation dose, and post-irradiation time point (Ma et al., 2010). It is evident that, miRNA can effectively activate the expression of DNA damage response genes and cell cycle related genes in the nucleus, and play a critical role in the modulation of radiation insults and radiosensitivity in tumor cells (Zhao et al., 2013). Impacts of IR insults on miRNAs have been given in Table 1.

Table 1. Expression of miRNA after IR insults in different organs/cells in mammals.

Organ or cell type	Up-regulation	Down-regulation	References
Brain	let-7a; let-7b; let-7c; let-7d; let-7e; let-7f; let-7g; let-7i; miR-15a; miR-16; miR-17-3p; miR-17-5p; miR-19a; miR-19b; miR-21; miR-22; miR-142-3p; miR-142-5p; miR-143; miR-155; miR-191; miR-379; miR-601	miR-107; miR-181a; miR-521	Karube et al., 2005; Wang et al., 2007; Kumar et al., 2009; Rhodes et al., 2012
Thyroid	let-7c; let-7d; let-7g; miR-17-3p; miR-17-5p; miR-27b; miR-34a; miR-34b; miR-188-5p; miR-365	let-7f; let-7g; miR-10a; miR-106a; miR-152	Grelier et al., 2009; Lin et al., 2010
Thorax	miR-15a; miR-16; miR-17-5p; miR-19a; miR-19b; miR-20b; miR-22; miR-24; miR-27a; miR-27b; miR-30a-5p; miR-99a; miR-106a; miR-148a; miR-221; miR-365; miR-126; let-7a; miR-495; miR-451; miR-128b	let-7a; let-7b; let-7c; let-7d; let-7e; let-7f; let-7i; miR-26b; miR-125a; miR-155; miR 130a, miR-106b, miR-19b, miR-22, iR-15b, miR-17-5p; miR-21	Martello et al., 2010; Guo et al., 2012; Piovan et al., 2012
Breast		miR-302a; miR-302b; miR-302c; miR-302d; miR-302e	Dent et al., 2003
Prostate	miR-191; miR-379; miR-29b 7; miR-191; miR-22; miR-200c; miR-141; miR-24 ; miR-30a-5p; miR-9-1	miR-100; miR-107; miR-133b; miR-143; miR-145; miR-196a; miR-521; miR-106b; miR-199a	Engels et al., 2006; Burk et al., 2008; Mott et al., 2010
Rectum	miR-1183; miR-483-5p; miR-622; miR-125a-3p; miR-1224-5p; miR-188-5p; miR-1471; miR-671-5p; miR-1909; miR-630; miR-765; miR125b; miR137	miR-1274b; miR-720	Bussing et al., 2008; Deng et al., 2008
Blood	let-7f; miR-106a; miR-106b; miR-126; miR-1280; miR-142-5p; miR-145; miR-148a; miR-148b; miR-16; miR-17-3p; miR-17-5p; miR-188-5p; miR-1913; miR-19a; miR-19b; miR-19b; miR-20a; miR-20b; miR-21; miR-221; miR-222; miR-24; miR-27a; miR-27b; miR-29a; miR-29c; miR-34a; miR-34b; miR-589; miR-601; miR-663; miR-BHRF1-1; miR-Plus-F1147; miR-Plus-G1246-3p	let-7e; miR-100; miR-10a; miR-143; miR-152; miR-17; miR-181a; miR-193b; miR-196a; miR-19b; miR-200b; miR-21; miR-29a; miR-33a; miR-335; miR-340; miR-483-3p; miR-99a; miR-Plus-E1098	Johnson et al., 2005; Dickey et al., 2011; Koturbash et al., 2011; Surova et al., 2012
Human normal fibroblasts	let-7d; let-7e; let-7f; let-7g; let-7i; miR-15a; miR-17-3p; miR-17-5p; miR-19b; miR-21; miR-26b; miR-142-3p; miR-142-5p; miR-143; miR-145; miR-155; miR-663	let-7a; let-7b; let-7d; miR-24; miR-155; miR-222	Simone et al., 2009
Human 3-D airway model tissues		let-7a; let-7b; let-7c; let-7d; let-7e; let-7f; let-7g; let-7i	Tarasov et al., 2007
Endothelial cell	let-7g; miR-16; miR-20a; miR-21; miR-29c	miR-125a	Kraemer et al., 2011

In another study, a differential genomic DNA response to radiotherapy was observed in TK6 and WTK1 cells through the modulation of maintenance and de novo methyltransferases in irradiated cells. Though, DNMT3A and DNMT3B were induced in both cells after radiation treatment, but, DNMT1 mRNA levels were increased in TK6 cells, while repressed in WTK1 cells. TET1, involved in the conversion of 5-methylcytosine (5-mC) to 5-hydroxymethylcytosine (5-hmC), was induced in both cells (Chaudhry and Omaruddin, 2012). It seems, the radiation exposure has a differential response in mammalian cells.

It has been assumed that, a fine balance of DNA methylation is needed to ensure proper radiation responsiveness. Hypoacetylated and methylated genes are thought to be more sensitive to IR other than the genes within the highly ordered structure of heterochromatin and hyperacetylation (Bar-Sela et al., 2007). Generally, chemoresistant tumors fail to respond to radiotherapy. Although, the mechanisms of cross resistance are not fully understood, but believed to be epigenetic in nature. In a study, MCF-7 cells and their doxorubicin-resistant variant MCF-7/DOX cells were found to show a differential response towards IR, probably due to their dissimilar epigenetic status as in MCF-7/DOX cells, there were significant global DNA hypomethylation in comparison to the MCF-7 cells (Luzhna and Kovalchuk, 2010).

Loss of *jmjd-5* results in hypersensitivity to IR (Gy 80-120) and in meiotic defects, which is associated with aberrant retention of RAD-51 (a commonly used marker of DSBs) at sites of double strand breaks (Amendola et al., 2017).

Radiation therapy, in combination with DNA methyltransferase (DNMT) inhibitors is straightforward since the use of latter class drugs offers greatly improved the targeting of DNA-protein complex (Bar-Sela et al., 2007; Gravina et al., 2010). For an example, NSCLC cell lines when treated with abexinostat (a novel pan HDACi) and irradiation (0-6 Gy) *in vitro* in normoxia and hypoxia, enhanced radiosensitivity in a time-dependent manner, where abexinostat treated cells were found to increase radio-induced caspase dependent apoptosis and persistent DNA double-strand breaks associated with decreased DNA damage signalling and repair (Rivera et al., 2017).

Conclusion

Radiation insults from various sources are common phenomena. Irradiated cells may elevate the risk for genetic instability, mutation, and cancer. Radiation-induced bystander effect can develop cancer, even at low radiation doses. Therefore, adequate precautions should be taken during environmental, medical and other sources' radiation exposure.

Conflict of interest

The author declares that there are no conflicts of interest.

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