REVIEW

Effects of ionizing radiation on nucleic acids and transcription factors

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Nucleic acids and transcription factors represent biopolymers of vital importance in all living organisms. Their main aim is coding, transcription and translation of genetic information and responsible for complex regulation of these fundamental physiological processes. However ionizing radiation is ubiquitous and played crucial role in evolution probably, long-term exposition to low doses possess broad spectrum of negative effects on health. Interaction of ionizing radiation with nucleic acids and transcription factors result in damage and non-physiological activation of these polymers. Effects of ionizing radiation on nucleic acids, different kinds of DNA damage and reparation mechanisms are broadly discussed in this work together with effects on important proteins – transcription factors.

Keywords: cancer; DNA damage; phosphorylation; mutation; signaling pathway

1. Introduction

Ionizing radiation (IR) is ubiquitous natural phenomenon. It represents effective therapeutic modality for treatment of several kinds of tumors. Nevertheless is also well known carcinogen. IR attracted big attention due to its negative effects on organisms but also played important role during life creation and evolution [1]. Although IR effect on important molecules can be destructive due to their various chemical modifications, some were probably beneficial for next development of organism during evolution [2]. Organisms are exposed to natural sources of IR (extraterrestrial and terrestrial sources) and also to artificial sources (radiotherapy eg.) [3]. As was mentioned previously, IR causes several negative effects on living organisms like direct interaction with DNA or reactive oxygen species (ROS) generation which damages biomacromolecules (DNA, proteins, lipids) [4, 5]. Introduction of mutations within genetic information represent one of the most serious effects and can result in malignant transformations. The aim of this work is to describe main types of IR and biological effects of DNA and transcription factors damaged by IR.

2. Ionizing radiation

Individual types of IR possess different biological effectiveness. In order to it unit of equivalent dose was defined – 1 Sievert (Sv). Equivalent dose represents absorbed dose multiplied with factor connected with biological effectiveness of IR. More precisely, this factor expresses how many times is precise IR effective than photons of X or gamma radiation (röentgen radiation of energy 200 keV is reference). The value of factor depends on kind and energy of radiation [6]. Sensitivity of tissues and organs to IR exposition is different. Radiation weighting factor (wT) was introduced to quantify the sensitivity of organs and probability of stochastic effects on them. The sum of wT for whole organism is 1 (Tab. 1).

Type of tissue	w_T	Sum of w_T
Red bone marrow, colon, lungs, stomach, breast tissue, other tissues*	0,12	0,72
gonads	0,08	0,08
bladder, esophagus, liver, thyroid glands	0,04	0,16
Bone surface, brain, salivary glands, skin	0,01	0,04
Total	-	1,0

* Adrenal gland, gall bladder, heart, kidney, lymphoid tissue, muscle, oral mucosa, pancreas, prostate (♂), small intestine, spleen, thymus, uterus (♀) [7]

2.1. Alpha radiation

Alpha radiation consists of fast and heavy alpha particles (the nucleus of helium – helions). They carry two elemental charges, strongly ionize environment but lose energy very fast. The strong decrease of ability to ionize environment is the consequence of particles slow down and their change to neutral atoms during capturing electrons from vicinity. Due to it the reach of alpha particles is relatively low. Alpha radiation is absorbed by air layer of 10 cm. The most dangerous is internal contamination or more precisely the presence of alpha radiation source within organism [8].

2.2. Beta radiation

Beta radiation consists of fast electrons or positrons. In comparison with alpha radiation beta particles are many times lighter, they are several time faster in case of same energy and the ability of ionization is not so high. Hence beta radiation radius in environment is higher. In gaseous environment, the radius is several meters. Deceleration and Cherenkov radiation contribute to absorption of beta radiation. If the beta particle penetrates the electron shell and reaches the nucleus, electric field of nucleus accelerate the particles, whereas particle emits deceleration radiation. Cherenkov radiation can be observed during beta particle pass through transparent environment (water, glass) as a blue to violet radiation [9].

2.3. Gama radiation

Gama radiation is electromagnetic radiation (flow of photons) and originates mostly from nucleus. It is generated together with alpha and beta particles during radionuclides conversion. It possesses line spectrum (radionuclide emits photons with precise energies which are characteristic nuclide conversion). Gama radiation is not influenced by electric or magnetic field [10].

2.4. Neutron radiation

Nowadays neutron radiation attracts a lot of attention. It is generated during radionuclides conversion nevertheless the only important source of this kind of radiation are nuclear reactors. Neutron radiation is a flow of fast neutrons and possesses high penetration ability due to neutral charge of neutrons. Neutrons can´t lose the energy via direct ionization because their electromagnetic capture in matter is not possible [11].

3. Transcription factors and nucleic acids

Nucleic acids (NAs) is vital biomolecules of all known living forms. They comprise DNA and RNA and with proteins are the most important biopolymers. The function of NAs is coding, transcription and expression of genetic information. NAs was isolated for first time by J. F. Miescher in 1869 from white blood cells [12], nevertheless its helix structure was described

84 years later by J. Watson and F. Crick [13].

Transcription factors (TFs) are proteins with ability to activate, block or lead RNA polymerase to specific DNA sequence [14]. Opposite to NAs, TFs regulate the rate of transcription to mRNA. As in case of NAs, TFs are presented in all living forms, however their amount is increasing with genome size. Clinical importance is related to the possibility of TFs structure mutation, which can cause alteration of their function and inability to regulate transcription. Many TFs possess tumor suppressor function and their mutations can have fatal consequences as was described in case of p53, NF-κB, AP-1, STAT and other steroid receptors [15].

From abovementioned information is evident that any unrepaired damage of this biomolecules by chemical or physical way can lead to development of pathological states.

4. Effects of ionizing radiation on transcription factors and nucleic acids

Direct and indirect effect of IR on cells can be distinguished. Direct damage is considered to be caused by direct interaction of biomacromolecule and IR particle or secondary electron in case of röentgen or gamma radiation. Direct effect causes serious damage mostly to NAs, since it disrupts hydrogen bonds between complementary bases [16]. Indirect effect is connected with water radiolysis and ROS generation [17].

4.1. IR and nucleic acids

It is well known that IR is able to cause broad spectrum of NAs damage (nucleotide damage, single-strand and double-strand breaks) (Fig. 1) [18].

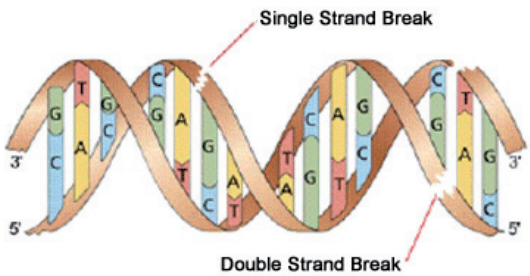

Figure 1: Single-strand break (SSB) and double-strand break (DSB) scheme. Adopted from http://teachnuclear.ca/all-things-nuclear/radiation/biological-effects-of-radiation/effects-of-ionizing-radiation-on-dna/.

Previously published studies suggest that IR is able to induce broad range of products within NAs like 8-hydroxydeoxyguanosin, however reparative mechanisms effectively cut altered nucleotides, which play minor role in radiation caused mutagenesis [19, 20]. It was also showed that SSB are not biologically relevant too. The vast majority of SSB are repaired by ligases [21].

On the contrary DSB caused by IR or chemical compounds are considered as the most serious NAs damage, which very often induces mutations and causes carcinogenesis due to inability to be repaired correctly [22]. DSB lead to chromosomal aberrations, damages genes and causes their malfunctions and cell death [23]. MRN (MRE11/Rad50/NBS1) complex and kinase ATM (Ataxia Telangiectasia Mutated) is activated as a response to DSB induced by IR [24]. ATM phosphorylates the DSB which results in activation and phosphorylation surrounding substrates like H2AX (H2A form of histone) on chromatin [25]. Phosphorylation of H2AX leads to its switch to H2AX which interacts with MDC1 (mediator of DNA-damage checkpoint 1) and amplify the signals important for other proteins involved in reparative mechanisms (RAP80, 53BP1, KAP-1 or BRCA1). These proteins are binded to breaks by ubiquitin ligase RNF 8 [26]. Mentioned signal cascade leads to CHK2, p53 and cdc25 phosphorylation and stop of cell cycle in G1/S or G2/M phase, which provides enough time for DNA repair (Fig. 2) [26].

It is surprising that IR is able to influence NAs which are not directly exposed to it. This radiation-induced bystander effect (RIBE) was described in 1992 by Nagasawa et al. [27]. The mechanism of this effect is not nowadays fully understood, however three of them were suggested:

a) Cells exposed to IR secret transport molecules like TGF-β1 or interleukin-8 which signaling cascades induce further NAs damage [28].

b) propagation of RIBE via GJIC (gap-junctional intercellular communication) [29].

c) RIBE can be activated by oxidative

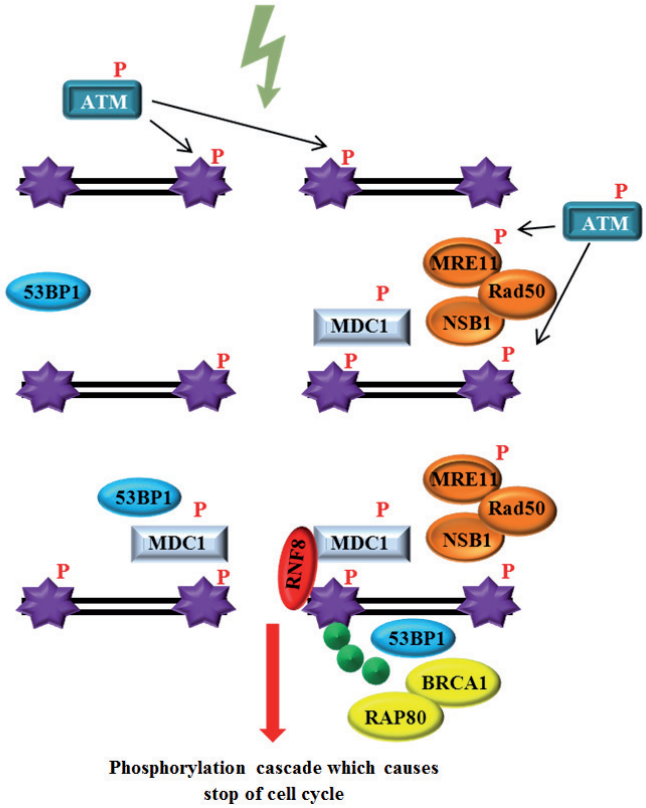

Figure 2: Scheme of protein signaling cascade which cause stop of cell cycle due to induction of DSB by IR (red P shows the phosphate group of phosphorylated proteins, violet star depicts H2AX and green points ubiquitins).

metabolism (generation of free radicals which causes NAs damage)

Except these mechanisms of RIBE propagation and creation several others were suggested and illustrate multifactoriality of this biological process. Fast and proper reparative mechanism is necessary for successful genome protection against IR. Two main mechanisms are responsible for protection against negative effects of DSB – homologous recombination (HR) and nonhomologous end joining (NHEJ) (Fig. 3) [30, 31]. In case of NHEJ free ends of broken chromosome are connected by ligase IV without the need of undamaged sister chromatid. This process is very fast bur prone to errors. On the contrary HR is slow precise process where sister chromatid is required. HR takes place mostly during S phase since both chromatids are in suitable conformation for homologous interaction [32]. Both mentioned reparative processes are highly conserved in eukaryotic organisms, however their importance differ through taxons. In general HR is dominant in case of yeasts and NHEJ in case of mammal cells.

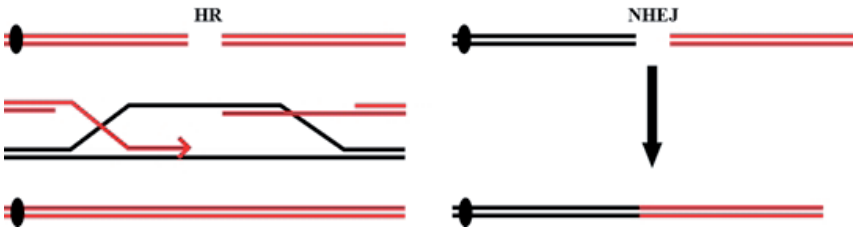

Figure 3: Schemes of reparative processes of DSB.

4.2. Ionizing radiation and transcription factors

Creation of ROS is one of the consequences of cell irradiation with IR. The effects of IR on proteins (TFs are proteins) are in details described in Radiation chemistry of organic compounds [33]. Interaction of ROS with proteins result in amino acid residue oxidation which can cause creation of protein-protein cross-links, oxidation of protein backbone (peptide bond cleaving) leading to protein fragmentation or total radiolysis [34]. Cysteine, histidine and methionine residues are extremely prone to oxidation [35]. Majority of TFs contain mentioned amino acids at zinc-finger motifs which enables their stabilization with metal ions and localization of DNA promoter region (Fig. 4).

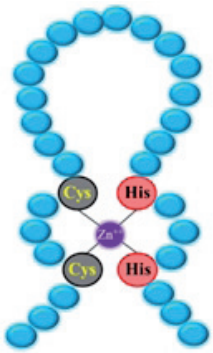

Figure 4: Scheme of zinc-finger structure.

Enzymes disulfide reductases and methionine sulfoxide reductases are able to eliminate amino acids oxidation by conversion of oxidized forms to original [36]. Due to it biological significance of amino acids oxidation is lowered, however oxidized TFs accumulation which can't be degraded by proteases can result in several serious pathological states. The lack of TFs can lead to deficit of specific products of translation and can result in inflammation or cancer.

In comparison with direct interaction of ROS with TFs indirect transactivation effect is not elucidated at all [37]. IR exposition induces lesions in cell membrane and result in activation of several transduction mechanisms (MAPK, metabolic pathway of ceramide, casein kinase eg.). Cell membrane damage by IR is subsequently transduced to cell nucleus via activation of TFs or more precisely IR-activated transcription factors (IR-TF) [38]. IR-TF comprises p53, Nf-κB, Sp1 or Oct-1 [38-40]. However it the number of IR-TF in different cells can be several times higher.

4.2.1. Tumor supresor p53

Tumor supresor protein p53 plays important role in preservation of gene integrity during cell stress and as TFs manages cell cycle and apoptosis [41]. As was described above, signal for p53 activation comes from damaged DNA. Experimental data shows that Ser153 phosphorylation and subsequent p53 accumulation is able to stop cell cycle and cause apoptosis during IR exposition [42, 43]. ATM kinase plays important role in Ser153 phosphorylation [44]. After phosphorylation induced by IR exposition p53 activates genes GADD45, p21waf1/cip1,

14-3-3σ eg. in order to stop cell cycle. Cell cycle is blocked in G1-S or G2-M phase [45]. P53 dependent genes involved in IR-induce apoptosis are not well described and probably differ according to cell type. Genes Bax, BID, PUMA and NOXA were discovered as first pro-apoptic genes activated by p53 [46, 47]. Nevertheless activation of these genes was described in case of relatively high expositions and the mechanism in case of clinically relevant expositions is poorly understand.

4.2.2. Nf-κB

Nf-κB (nuclear factor kappa B) is transcription factor presented often in latent form with inhibition protein IκB. Several signaling pathways leading to IκB degradation and Nf-κB release were described. The aim of Nf-κB is cell nucleus where it regulate broad range of genes involved in apoptosis, proliferation, adhesion, migration or immune response [48]. IR doses which are able to activate Nf-κB strongly depend on cell type. For example in case of human lymphoblastoid cells caused exposition 0.5 Gy full activation of Nf-κB [49]. But in case of human fibroblasts exposition to 20 Gy failed in pathway activation [50]. Cells which over-expressed this TF are more or less chemoresistant and radioresistant [51]. The mechanism of Nf-κB activation as a response to IR is not still fully understood. It is not known if DSB can induce TFs activation alone or if other effectors like ROS are involved. If we take into account that different molecular mechanisms are involved in Nf-κB activation in different IR doses it is needed to evaluate Nf-κB role in response to IR exposition in complex systems like 3D cell lines or in vivo models. Baldwin suggests that elucidation of this mechanism can significantly influence effectiveness of radiotherapeutic procedures [52].

4.2.3. Sp1

Sp1 is one of IR-dependent TF ubiquitous in mammalian cells which possesses high affinity to GC-rich sequences (GC boxes). Sp1 plays important role in cell cycle regulations, chromatin remodelation and methylations [53]. Importance of Sp1 is evident - Sp1-null mouse die in 10th day due to extensive placental defects [54]. Activation of Sp1 was observed in case of high doses (>4 Gy), however post-transcriptional modification of Sp1 was altered after exposition to 2 cGy [55, 56]. Meighan-Mantha et al. showed that in case of spinocellular carcinoma cells exposition to 15 Gy caused 15-times higher affinity of Sp1 to its premotor RCE (retinoblastoma control region) [67]. However identification of activated genes is needed to reveal the role of Sp1 in IR-dependent signaling pathways.

4.2.4. Oct-1

Transcription factor Oct-1 (or NF-Y) is in general activated by cell stress, which was several-time showed using cytostatic compounds (camptothecin, etoposide, cisplatin) [68,69]. Higher activity of Oct-1 was also observed in case of tumor cell lines after exposition to IR with dose higher than 5 Gy (prostatic cell line PC3 and human breast adenocarcinoma cell line MDA-MB-231) [70]. In comparison with application of cytostatics, activation of TF was significantly shorter. As in case of other IR-dependent TFs it was not elucidated how Oct-1 is activated and how affects gene expression. Bertanga and Jahroudi showed that IR is able to induce secretion of VWF (von Willenbrand factor) which mediates activation of Oct-1 and his interaction with CCAAT motif of promoter, which is essential for several genes transcription [71].

5. Conclusion

Prevalence of cancer is steadily increasing and detail understanding of IR interaction with important biomacromolecules like nucleic acids and transcription factors can help to improve radiotherapeutic and radiodiagnostic procedures. Radioresistance which is often presented with chemoresistance complicates the therapy and significantly decreases survival rate of some malignancy like non-small lung carcinoma. Modern nanotechnology and development of nuclease-resistant nucleic acids (phosphorothioate, peptide nucleic acid or morpholino) are able to regulate proteins responsible for these resistances (antisense therapy) and improve therapy effectiveness.

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Conflicts of Interest

The authors declare they have no potential conflicts of interests concerning drugs, products, services or another research outputs in this study. The Editorial Board declares that the manuscript met the ICMJE „uniform requirements" for biomedical papers.

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