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RESEARCH ARTICLE

New Conceptual Interpretations of Mechanisms for the Repair of Double-Strand DNA Breaks and Their Mathematical Modeling

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ABSTRACT:
The genetic apparatus of the cell is exposed to a serious risk of damage under the constant influence of endogenous and exogenous factors. One of the most complex damage for repair is double-strand DNA breaks and DNA-protein cross-links, leading to various types of mutations and chromosomal rearrangements that can induce genome instability, carcinogenesis, or the start of the cell apoptosis process. Nevertheless, numerous data from studies of DNA repair pathways do not provide the final pattern of the repair of double-strand DNA breaks and DNA-protein cross-links, as well as any mathematical model for calculating the survival of cells irradiated by photon radiation at various stages of the cell cycle. According to our assumptions, during the repair of double-strand breaks, damaged DNA segments are cut out from both sides at the boundaries of the entire damaged loop domain (replicon). The degradation of the damaged strand has an analogy with the mechanism of apoptosis, because during chromatin degradation, as during apoptosis, DNA is destructurized to the level of nucleosomes, followed by their "use" by the cell. As for the repair of DNA-protein cross-links, they are one of the stages of the multi-stage hierarchy of the repair pathways of double-strand DNA breaks. Apparently, in some cases, the repair of double-strand DNA breaks requires the creation of additional protein structures by the cell, which spatially fix the damaged DNA segment of the cell during repair. The creation of these structures requires additional time and additional protein synthesis. After repair, this additional protein is completely detached from the sites that define the boundaries of those cell structures that participated in the repair process.
A mathematical model has been proposed for estimating the probability of the repair of double-strand DNA breaks depending on the stage of the cell cycle and on the value of the absorbed dose, as well as the probability of survival of the irradiated cells for different durations of the repair interval.
The article shows the possibility of calculating the probability that the cell at the time of irradiation is at such a stage of the cell cycle, at which repair is either impossible, or the time required for the repair of one double-strand break is not sufficient. The study calculates the probability of cell survival at different stages of the cell cycle, when it is possible to repair one double-strand break, no more than two double-strand breaks, and, in general, *n* units of double-strand breaks.

KEYWORDS: Double-Strand DNA Breaks, DNA-Protein Cross-Links, Repair Mechanisms, Mathematical Probabilistic Modeling.

INTRODUCTION:
Currently, the integrated development of radiobiology, along with technical processes and technological developments, is one of the main tools for improving clinical results in radiation therapy.

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This approach requires a new conceptual framework for explaining cellular behavior under the influence of ionizing radiation and sets new directions for scientific research against oncological diseases [1, 2]. The use of radiation therapy in medical practice was discussed in a number of studies [3-10]. In order to evaluate existing therapies and suggest novel therapies, mathematical models are widely used [11, 12]. At the same time, in this field of science there are still some problematic issues, which have been either poorly studied or

debatable, and need more detailed discussion. That is why new conceptual interpretations of the results of some well-known radiobiological studies, which are interesting, but, in our opinion, may have other than traditional interpretations, are relevant. The purpose of this article was to represent new conceptual interpretations of mechanisms for the repair of double-strand DNA breaks and DNA-protein cross-links, and to propose a mathematical model for estimating the probability of DNA DB repair depending on the stage of the cell cycle during irradiation and the value of the absorbed dose. To achieve this purpose, we used methods of mathematical probabilistic modeling. Let us discuss the interpretation of the following three aspects.

ON THE REPAIR OF DOUBLE-STRAND DNA BREAKS IN IRRADIATED CELLS:

DNA double breaks (DBs) arising during the normal replication process or under the influence of exogenous DNA damaging agents, such as ionizing radiation, pose a serious danger to genome stability. In the course of evolution, eukaryotic cells developed molecular mechanisms for the effective repair of this type of damage [13]. However, various types of DB repair errors can lead to different types of mutations and chromosomal rearrangements that can induce genome instability, carcinogenesis, or the start of the apoptosis process — programmed cell death [14-19]. Unreported DNA breaks, in turn, also increase the probability of chromosomal aberrations [20, 21].

It is known that global genomic nucleotide excision repair (NER) is one of the main ways to protect cells from various structurally and chemically different DNA damage. In cells of higher eukaryotes, it is a multistage process, during which damage causing the noticeable disruption of the DNA regular structure is recognized and removed. The NER system of eukaryotes removes fragments consisting of 24-32 nucleotides from the damaged DNA chain, with the subsequent restoration of the intact double helix using reparative synthesis and ligation. At the beginning of the process, the damaged DNA chain is cleaved from the 5'-end (in 15-25 nucleotides from the damage site) with the formation of a free 3'-hydroxyl group, necessary for the initiation of reparative synthesis and the appearance of a mobile single-strand fragment containing the damage. Then, DNA is cleaved from the 3'-end (in 3-9 nucleotides from the damage), completing the excision of the damaged area [22, 23].

According to some other studies [24, 25], in prokaryotes, NER is performed by the Uvr protein system, with the help of which cuts are made in DNA on both sides of the damage: extending 7 nucleotides from the 5'-end and 3-4 nucleotides from the 3'-end. Making cuts requires ATP costs. Further, the UvrD helicase unwinds DNA between the notches, due to which the damaged chain is released. The synthesis of the new chain instead of the damaged one is carried out by DNA polymerase I, although it can be replaced by DNA polymerase II and III. In 99% of cases with excision repair mediated by the Uvr system, a DNA fragment of about 12 base pairs (bp) is replaced. In 1% of cases, more extended sections of about 1500 bp, and in exceptional cases – of more than 9000 bp, are replaced. During NER in eukaryotes, a 25-30 bp long fragment is removed. The mechanisms that regulate the length of the fragment being replaced (short or long) are unknown.

Speaking about mechanisms for the repair of double-strand DNA breaks, one can identify two main biochemical ways of repairing nuclear genomic DNA DBs [13]. The first is DB repair, based on homologous recombination between sister chromatids or chromatids of homologous chromosomes (Homologous recombination, HR or homology directed repair, HDR) [21, 26]. The second is DB repair by non-homologous joining of DNA chain ends (Non-homologous end joining, NHEJ) [27, 28].

According to the generally accepted interpretation of the first DB repair pathway, it is considered that proteins of the repair system help a broken strand find such a chromatid region of the intact chromosome that is homologous to this strand. But it remains completely unclear how a loosely moving strand finds a homologous region in a very strictly definite time (about 60 minutes) [29].

Moreover, it is known that the cell contents are in a continuous, complex circular-oscillatory motion with a constant movement of organelles in the cytoplasmic streams. It is believed that one of the sources of this movement is the active contractile activity of mitochondria and nuclei, contributing to the pulsating movement of fluid through the cavities of these organelles and the creation of directional flows in the surrounding cytoplasm [30]. These data also testify against the traditional interpretation of homology directed DNA DB repair.

Our hypothetical approach to the issue under discussion boils down to the following. We assume that all or almost all functionally important DNA segments are bounded on both sides by certain sites.

It is well known that the eukaryotic genome is divided into a number of relatively independent functional domains: replication units (replicons) and transcription units (transcriptons). DNA in nucleoids is organized into topologically closed domains (loops), the size of which

is 10-200 kb. These loops can be directly observed in electron-microscopic pictures of spread metaphase chromosomes and interphase nuclei from which histones have been removed. In these pictures, one can see some protein structures (in the case of metaphase chromosomes, the latter retain the shape of chromosomes) with attached DNA loops, the contour length of which is from 20 to 90 kb. Estimates of the average size of DNA loops are somewhat different, but in all cases the values obtained (20–200 kb) are comparable with the length of replicons and transcriptons.

According to our assumptions, the following basic processes occur during double-strand DNA breaks.

First, DNA segments within the boundaries of the damaged loop domain (replicon) on both sides are cut out from the damaged DNA strand at the corresponding sites. In this case, speaking of the removed DNA strands, the term "DNA degradation" is often used. In the future, the damaged strand segment is destroyed. Probably, the degradation of the damaged strand has an analogy with the mechanism of apoptosis, because during chromatin degradation, as during apoptosis, DNA is destructurized to the level of nucleosomes, followed by their use by the cell. The restoration of the damaged strand is similar to homologous recombination.

The accuracy of the proposed DB repair model can be proven by the fact that the amount of DNA lost during DB repair (DNA degradation) is approximately equal to the amount of DNA contained in the replicon [31].

ON THE REPAIR OF DNA-PROTEIN CROSS-LINKS:

DNA-protein cross-links are one of the most harmful and insufficiently studied forms of DNA damage. They can effectively block gene transcription and DNA replication, i.e. represent a steric blockade of transcription and replication. Cross-links are also dangerous because they hamper the availability of DNA repair factors and chromatin remodeling [32]. If this damage is not properly corrected, it can lead to mutations, genome instability, and cell death. DNA-protein cross-links can be induced by endogenous cross-linking agents, such as formaldehyde or acetaldehyde, as well as ionizing radiation, environmental carcinogens, anticancer chemotherapeutic drugs, and abortive effects of certain enzymes [33].

It is known that the peculiarity of DNA organization in the nucleus of eukaryotes lies in its association with histones and non-histone proteins as part of chromatin, and in the period of replication and transcription – with nuclear matrix proteins. The adverse factors affecting the cell cause the formation of covalent cross-links between DNA and protein [34-37].

Generally, DNA-protein cross-links are formed when the nucleotide residue in DNA forms a covalent bond with the protein.

In vitro model experiments show that during irradiation of chromatin solutions DNA cross-links are formed with both histones and non-histone proteins. During γ-irradiation of cells there are cross-links with nuclear matrix proteins; with these proteins the largest number of cross-links are usually formed [36]. Protein cross-links form predominantly transcriptionally active DNA sequences.

When cells are incubated in a nutrient medium at 37°C after γ-irradiation for 1 hour, DNA is gradually released from the DNA-protein complex. The repair of cross-links is slower than the DNA DB repair, and a small portion of them are still registered 2 hours after γ-irradiation of CHO cells at a dose of 50 Gy [38-41].

The formation and repair rate of DNA-protein cross-link damage also depends on the quality of radiation. For example, when human melanoma HMV-1 cells are irradiated with accelerated nitrogen ions, DNA-protein cross-links are detected 6 hours after irradiation, while after X-ray irradiation during this period they are completely eliminated [34, 42].

Thus, the complexity of the repair of DNA-protein cross-links is indicated by the fact that the cell needs a longer time for this process than for DNA DB repair.

The recovery of cross-links seems to be associated with complex mechanisms that encompass a large number of protein factors. Although the general pathway(s) of the recovery of DNA-protein cross-links has not yet been fully disclosed, some possible interpretations of the description of this mechanism have recently arisen [43].

Hypothetically, it can be assumed that DNA DB repair is always associated with the subsequent repair of DNA-protein cross-links. Only with successful DNA repair, DNA-protein cross-links are repaired successfully. Based on this, we believe that those processes that are traditionally called DNA-protein cross-link repair are in fact one of the stages of the multi-stage hierarchy of DNA DB repair pathways, which is confirmed by Grabarz et al (2012) and Cheng et al (2011) [44, 45]. Apparently, in some cases, the implementation of DNA DB repair requires the creation by the cell of some sort of "supports", or rather, additional protein structures that keep the cell DNA from breakdown during repair. These proteins traditionally were taken for cross-links. The

creation of these structures requires additional time and additional protein synthesis. After repair, this additional protein is completely detached from the sites that define the boundaries of those cell structures that participated in the repair process, after which the protein is used by the cell for other purposes.

ON THE DEPENDENCE OF THE PROBABILITY OF THE REPAIR OF DOUBLE-STRAND DNA BREAKS ON THE STAGE OF THE CELL CYCLE:

Radiation damage in an asynchronous population can occur at any stage of the cell cycle. Therefore, the duration of DB repair (repair interval) is a random variable having a uniform distribution.

It should be emphasized that the duration of the repair interval can take on different values, but it has a minimum value equal to the minimum duration of the repair of one DB under the conditions of normoxia lasting about an hour [34, 46].

Mathematical modeling of the survival of cells affected by photon radiation is complicated by the fact that their radiosensitivity largely depends on the stage of the cell cycle at which the irradiation took place. In addition, DB repair can occur not at all stages of the cell cycle. For example, for the stage of mitosis, in particular, the highest radiosensitivity of cells is observed and, presumably, there is no repair.

When an asynchronous cell population is irradiated, the probability of irradiating any cell in a certain interval of the cell cycle is directly proportional to the duration of this interval, and in the case of equal intervals, the probabilities of irradiation will be the same.

The probability of cell survival after irradiation depends on the dose of radiation and the ability of the cell to repair radiation damage, including, first of all, double-strand DNA breaks. In turn, the maximum number of DBs that can be repaired by the cell is determined by the duration of the repair interval (i.e. it depends on the stage of the cycle at which repair is performed). Therefore, the probability of cell survival is a sum of the products of the following probabilities: the probability of occurrence of a certain number of DBs in the cell due to irradiation and the probability of repair of all the resulting DBs in the cell in a certain part of the cell cycle (which depends on the maximum number of DBs that can be repaired by the cell in this cycle). In this case, the summation involves all the previously mentioned parts of the cell cycle.

Let us calculate these probabilities.

Various stages of the cell cycle differ in the duration of the repair interval, and hence, in the maximum number of DBs that can be repaired by the cell.

There is a time interval corresponding to such a stage of the cell cycle at which the irradiated cell does not repair the DB, and cell survival is possible only if there is not a single double-strand break. Let T_0 be the duration of this period of time; T – the duration of the cell cycle; and T_i – the duration of the repair interval during cell irradiation at some stage of the cycle.

As mentioned, depending on the duration of the repair interval, the cell has the ability to repair a different amount of DBs.

Let T_r be the repair time of one DB, and N – the maximum number of DBs, which can be repaired by the cell. The number N is the integer part of the expression, calculated by the formula:

$$N = \frac{T - T_0}{T_r}. \quad (1)$$

As a rule, the N value is not an integer.

Let τ denote the value calculated by the formula:

$$\tau = T - T_0 - NT_r. \quad (2)$$

Since the duration of the time interval τ is less than T_r, during this interval the repair of not a single DB will be complete, although this interval is related to the cycle stage at which repair is possible. Consequently, this interval is essentially similar to the time interval designated above as T_0. Based on this, one can calculate the probability (k_0) that the cell at the time of irradiation is at such a stage of the cell cycle, at which repair is either impossible, or the time required for the repair of one DB is not sufficient.

This probability is calculated by the following formula:

$$k_0 = \frac{T_0 + \tau}{T}. \quad (3)$$

If the cell is irradiated in a time interval with a duration of T_r, starting from the moment of recovery of the cell's ability to repair, the cell can repair the maximum number of DBs, and this number is equal to N. If the irradiation occurs in the later parts of the cycle, the maximum number of DBs repaired by the cell is less than N. If the cell is irradiated in a time interval starting from the beginning of the recovery of the ability to repair and having a duration of T_r, the maximum possible number of DBs repaired by the cell is equal to N. In each subsequent interval with a duration of T_r, the maximum number of DBs that can be repaired by the cell is reduced by one.

Let k_1, k_2, k_3,... k_N be the probabilities that the cell was irradiated at such a stage of the cycle at which the maximum possible number of repairs was 1, 2, 3, ... N, respectively. It is clear that

$$k_1 = \frac{T_r}{T}, \quad k_2 = \frac{T_r}{T}, \quad k_3 = \frac{T_r}{T} \ldots \; k_N = \frac{T_r}{T}. \quad (4)$$

Let us calculate the probabilities of forming DBs with certain values of the absorbed dose.

As a simplifying assumption, suppose that the duration of the repair of each DB is the same.

Let S be the survival rate (survival probability) of the irradiated cell; D – the radiation dose (the absorbed dose); n_0 – the average number of DBs, which are additionally formed in the cell when the dose is increased by 1 Gy; n_u – the number of structural and functional units (SFUs) of chromatin in the cell.

In this case, the value $\varphi \cdot n_u$ can be called the effective fraction of the chromatin SFU, where φ is the degree of chromatin condensation during irradiation.

We will use the traditional for radiobiology assumption that the formation of DNA DBs is described by the Poisson distribution. Moreover, the Poisson distribution parameter, often referred to as λ, is equal to $n_0 D$.

A complex issue in modeling the processes of DNA radiation damage is the question of what is the number of SFUs in each of the chromosomes. There is no exact answer to this question in the literature known to us. Therefore, it is necessary to accept the simplifying assumption that the number of SFU is the same in each chromosome.

It is obvious that the condition for cell survival after irradiation is the repair of all the DBs in each of the SFUs of each of the cell chromosomes until the cell enters the phase of the cell cycle in which repair stops.

Calculate the survival of the irradiated cells as they move through the stages of the cell cycle. We will start from the moment the cell enters the stage at which repair does not occur. In this case, the cell survives only if no SFU is damaged in any chromosome.

Let P_0 be the probability of this event.

Considering that radiation damage in each SFU occurs independently of each other, we can write down:

$$P_0 = k_0 \left(\exp(-n_0 D)\right)^{\varphi \cdot n_u}. \quad (5)$$

Calculate the probabilities of cell survival for various durations of the repair interval. Let the duration of the repair interval be sufficient for the repair of one (and no more) DB. At the same time, the cell survives if no more than one DB has been formed in each SFU of the cell (i.e. either no DB has been formed or one DB has been formed). The above corresponds to the condition:

$$T_r \le T_i < 2T_r. \quad (6)$$

Denote the probability of such an event as P_1.

It is obvious that the above probability is equal to the sum of the probabilities that in each SFU one or no DB is formed. Then

$$P_1 = k_1 \cdot \left(\exp(-n_0 D)(1 + n_0 D)\right)^{\varphi \cdot n_u}. \quad (7)$$

If irradiation occurs at such a stage of the cycle, at which the following condition is fulfilled,

$$2T_r \le T_i < 3T_r, \quad (8)$$

then the cell survives, if, during irradiation, no more than two DBs have been formed in each SFU. Denote the probability of such an event as P_2. Then

$$P_2 = k_1 \cdot \left(\exp(-n_0 D)\left(1 + n_0 D + \frac{n_0 D^2}{2}\right)\right)^{\varphi \cdot n_u}. \quad (9)$$

In general, if the cell is at the cycle stage that no more than n DBs can be repaired in each SFU of the cell, the probability of cell survival is calculated by the formula

$$P_n = \exp(-n_0 D) \cdot \left(1 + \sum_{i=1}^{n} \left(\frac{1}{i}(n_0 D)\right)^i\right)^{\varphi \cdot n_u}. \quad (10)$$

Combining the obtained results of cell survival calculations at various stages of the cell cycle, the total (integral) value of survival S can be expressed as:

$$S = \sum_{j=0}^{N} P_j. \quad (11)$$

CONCLUSIONS:

The article presents new conceptual interpretations of mechanisms for the repair of double-strand DNA breaks and DNA-protein cross-links, as well as a mathematical model for estimating the probability of DNA DB repair depending on the stage of the cell cycle during irradiation and the value of the absorbed dose.

1. When repairing double-strand DNA breaks, DNA segments are cut off within the boundaries of the damaged loop domain (replicon) on both sides of the DNA strand damage area at the corresponding sites. In the future, the damaged strand segment is destroyed. Probably, the degradation of the damaged strand has an analogy with the mechanism of apoptosis, because during chromatin degradation, as during apoptosis, DNA is destructurized to the level of nucleosomes, followed by their use by the cell. The restoration of the damaged strand is similar to homologous recombination.
2. The repair of DNA-protein cross-links is one of the stages of the multi-stage hierarchy of DNA DB repair pathways. Apparently, in some cases, the repair of double-strand DNA breaks requires the creation of additional protein structures by the cell, which

spatially fix the damaged DNA segment of the cell during repair. The creation of these structures requires additional time and additional protein synthesis. After repair, this additional protein is completely detached from the sites that define the boundaries of those cell structures that participated in the repair process.

3. An approach has been proposed for estimating the probability of DNA DB repair depending on the stage of the cell cycle and on the value of the absorbed dose, as well as the probability of survival of the irradiated cells for different durations of the repair interval.

The study shows the possibility of calculating the probability that the cell at the time of irradiation is at such a stage of the cell cycle, at which repair is either impossible, or the time required for the repair of one double-strand break is not sufficient.

The article calculates the probability of cell survival at different stages of the cell cycle, when it is possible to repair one double-strand break, no more than two double-strand breaks, and, in general, *n* units of double-strand breaks.

CONFLICT OF INTEREST:

The authors declare no conflict of interest.

REFERENCES:

1. Garson O, Plazas MC, Salazar EJ. Evolution of physico-mathematical models in radiobiology and their application in ionizing radiation therapies. Tecciencia. 2014; 9(17):15-22. http://dx.doi.org/10.18180/tecciencia.2014.17.2
2. Knigavko VG, Bondarenko MA, Zaytseva OV. The generalized mutation theory of oncogenesis. Journal of Clinical and Diagnostic Research. 2018; Nov, 12(11):XE01-XE04.
3. Sudhakar GK, Pai V, Pai A. An overview on current strategies in breast cancer therapy. Research J. Pharmacology and Pharmacodynamics. 2013; 5(6):353-355.
4. Saleh NA, Abdul Wahid TA. Nanotechnology with X-rays plays an essential role in improving radiation therapy for malignant breast cells. Research J. Pharm. and Tech. 2017; 10(12):4129-4132.
5. Mathew J., Doss K JJ, Gohil D, Gohil D. A Study to Evaluate the Effectiveness of Apitherapy on Oral Mucositis among Cancer Patient undergoing Radiation Therapy in Selected Hospital Rajkot. Int. J. Nur. Edu. and Research. 2017; 5(1):55-58.
6. Abulmajeed AA, Neda FS, Alabidi HH. Assessments and Dosimatric Evaluation of Matching Fields Technique in the Treatment Cranio-Spinal Cancers. Research J. Pharm. and Tech. 2019; 12(1):83-86.
7. Nandi H. A study to assess the effect of health teaching on coping mechanism among patients undergoing radiation therapy admitted in selected hospitals of Pune city. Int. J. Adv. Nur. Management. 2015; April-June, 3(2):81-82.
8. Sampoornam. W. Emotional Support Improves Quality of Life in Women Undergoing Radiation Therapy for Breast Cancer - A Wait List Control Arm. Asian J. Nur. Edu. and Research. 2015; July-Sept., 5(3):316-318.
9. Saha D, Maity T, Jana M, Mandal S. Cancer Treatment Strategy-An Overview. Asian J. Pharm. Tech. 2011; April-June, 1(2):28-33.
10. Brundha MP, Pathmashri VP, Sundari S. Quantitative Changes of Red Blood cells in Cancer Patients under Palliative Radiotherapy-A Retrospective Study. Research J. Pharm. and Tech. 2019; 12(2):687-692.
11. Jyothi KTN, Subrahmanyam PSR, Sravanthi AC. Application of Differential Equations in Medical Science. Research J. Science and Tech. 2017; 9(3):425-426.
12. Sravanthi AC, Venkata Lakshmi K, Jyothi KTN. Mathematical modeling in Epidemiology. Research J. Science and Tech. 2017; 9(3):353-354.
13. Litvinov SV. The main pathways of repairing genomic DNA double breaks and the interaction between them. Cytology and Genetics. 2014; 48(3):64-77.
14. Kovaleva OA. Cytogenetic anomalies and causes for their occurrence in somatic cells. Cytology and genetics. 2008; 42(1):48-59.
15. Acilan C, Potter D, Saunders W. DNA repair pathways involved in anaphase bridge formation. Genes. Chrom. Cancer. 2007; 46(6):522-531.
16. Mills K, Ferguson D, Alt F. The role of DNA breaks in genomic instability and tumorigenesis. Immun. Rev. 2003; 194:77-95.
17. Schwartz M, Zlotorynski E, Goldberg M. et al. Homologous recombination and nonhomologous end-joining repair pathways regulate fragile site stability. Genes Dev. 2005; 19:2715-2726.
18. Bondarenko M, Knigavko V, Zaytseva O. Approach to evaluate the risk of cancer for different number of tumor suppressor genes in the individual. East European Journal of Physics. 2018; 5(2):23-26. http://doi:10.26565/2312-4334-2018-2-03
19. Knigavko VG, Bondarenko MA, Batyuk LV, Ponomarenko NS. Role of phosphorus and sulfur atoms in radiation damage of nucleic acids and proteins. Nuclear Physics and Atomic Energy. 2016; 17(1):76-79. https://doi.org/10.15407/jnpae2016.01.076
20. Bennardo N, Gunn A, Cheng A. et al. Limiting the persistence of a chromosome break diminishes its mutagenic potential. PLoS Genet. 2009;5(10): e1000683.
21. Gandhi M, Evdokimova V, Cuenco K. et al. Homologous chromosomes make contact at the sites of double-strand breaks in genes in somatic G0/G1-phase human cells. Proc. Nat. Acad. Sci. USA. 2012; 109(24):9454-9459.
22. Petruseva IO, Evdokimov AN, Lavrik OI. Molecular Mechanism of Global Genome Nucleotide Excision Repair. Acta Naturae. 2014; 6(1):24-36.
23. Gillet LC, Scharer OD. Molecular mechanisms of mammalian global genome nucleotide excision repair. Chem. Rev. 2006; 106(2):253-276.
24. Krebs JE, Goldstein ES, Kilpatrick ST. Lewin's Genes. Moscow: Laboratoriya znaniy. 2017. ISBN 978-5-906828-24-8.
25. Carroll SB, Wessler SR, Griffiths AJF, Lewontin RC. Introduction to genetic analysis. New York: W.H. Freeman and CO. 2008. ISBN 0-7167-6887-9.
26. Hiom K. Coping with DNA double strand breaks. DNA Rep. 2010; 9(12):1256-1263.
27. Ciccia A, Elledge S. The DNA damage response: making it safe to play with knives. Mol. Cell. 2010; 40:179-204.
28. Kruman I. (Ed.). DNA Repair. Rijeka: InTech. 2011.
29. Synzynys BI, Saenko AS, Pelevina II. DNA replication in irradiated cells. Results of Science and Technology. VINITI. Series: Radiation biology. 1990; 9:114-213.
30. Berezovsky VA. Oxygen tension in animal and human tissues. Kyiv: Naukova Dumka. 1975.
31. Grodzinsky DM. Radiobiology [Textbook]. Kyiv: Lybid'. 2001.
32. Baker DJ, Wuenschell G, Xia L, Termini J, Bates SE, Riggs AD, O'Connor TR. Nucleotide excision repair eliminates unique DNA-protein cross-links from mammalian cells. The Journal of Biological Chemistry. 2007; 282:22592–22604.
33. Yudkina AV, Dvornikova AP, Zharkov DO. Variable termination sites of DNA polymerases encountering a DNA–protein cross-link. 2018; June 1. https://doi.org/10.1371/journal.pone.0198480
34. Moskaleva EYu, Ilyushina NA. DNA damages caused by ionizing radiation and their repair. Results of Science and Technology.

VINITI. Series: Radiation biology. 1990; 9:5-113.
35. Peng Y, Sun L, Jia Z, Li L, Alexov E. Predicting protein-DNA binding free energy change upon missense mutations using modified MM/PBSA approach: SAMPDI webserver. Bioinformatics. 2018; Mar 1; 34(5):779-786. https://doi.org/10.1093/bioinformatics/btx698
36. Chiu SM, Friedman LR, Sokany NM. et al. DNA-protein cross links in nuclear matrix. Radiat. Res. 1986; 107:24-38.
37. Nikonov AYu, Zaytseva OV, Serhiienko MO, Krychka NV, Breslavets NN. Dynamics of the content of free amino acids in blood of patients during the long-term use of orthopedic dental metal prostheses. National Journal of Physiology, Pharmacy and Pharmacology. 2018; 8(2):1-6.
38. Vasireddy RS, Karagiannis TC, El-Osta A. γ-radiation induced γH2AX formation occurs preferentially in actively transcribed euchromatic loci. Cell. Mol. Life Sci. 2010; 67:291-294.
39. Cowell IG, Sunter NJ, Singh PB, Austin CA, Durkacz BW, Tilby MJ. γH2AX foci form preferentially in euchromatin after ionizing radiation. PLoS One. 2007; 2:e1057.
40. Goodarzi AA, Noon AT, Deckbar D, Ziv Y, Shiloh Y, Lobrich M, Jeggo PA. ATM signaling facilitates repair of DNA double-strand breaks associated with heterochromatin. Mol. Cell. 2008; 31:167-177.
41. Falk M, Lukasova E, Kozubek S. Chromatin structure influences the sensitivity of DNA to γ-radiation. Biochim. Biophis. Acta. 2008; 1783:2398-2414.
42. Eguchi-Kasai K, Murakami M, Itsukaichi H, Fukutsu K, Yatagai F, Kanai T, Ohara H, Sato K. Repair of DNA double-strand breaks and cell killing by charged particles. Adv. Space Res. 1998; 22(4):543-9.
43. Klages-Mundt NL, Li L. Formation and Repair of DNA-Protein Crosslink Damage. Sci China Life Sci. 2017; Oct; 60(10):1065-1076.
44. Grabarz A, Barascu A, Guirouilh-Barbat J. et al. Initiation of DNA double strand break repair: signaling and single-stranded resection dictate the choice between homologous recombination, non-homologous end-joining and alternative end-joining. Amer. J. Cancer Res. 2012; 2(3):249-268.
45. Cheng Q, Barboule N, Frit P. et al. *Ku* counteracts mobilization of PARP1 and MRN in chromatin damaged with DNA double-strand brakes. Nucl. Acids Res. 2011; 39(22):9605-9619.
46. Bondarenko M, Ponomarenko N, Zaytseva O, Knigavko V. Evaluation of the cell cycle duration of tumour cells under the changes of their oxygenation degree. European Science Review. 2017; 7-8:3-5.