TRANSCRIPTIONAL ACTIVITY OF DNA-METHYLTRANSFERASE GENES IN THE CHRONICALLY EXPOSED RESIDENTS OF THE URAL REGION

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In addition to damaging the genetic apparatus of the cell, ionizing radiation can cause epigenetic alterations. DNA methylation that plays a vital part in regulation of cellular processes is a common epigenetic modification. DNA methylation ensured by DNA methyltransferases occurs in the CpG-rich sequences. The study was aimed to assess mRNA expression of genes encoding DNA methyltransferases (*DNMT1*, *DNMT3A*, *DNMT3B*) in the chronically exposed individuals who live along the River Techa over a long-term period. A total of 112 people were examined more than 65 years after the beginning of chronic exposure. The average accumulated dose to red bone marrow (RBM) was 782.0 ± 82.3 mGy, and the average accumulated dose to thymus and peripheral lymphoid organs was 93.2 ± 13.6 mGy. The subjects' age at the time of examination was 67.9 ± 0.8 years (54–83 years). The relative mRNA levels for the studied genes were assessed by real-time polymerase chain reaction (real-time PCR). mRNA expression of *DNMT1* correlated positively with the dose to RBM ($p = 0.04$), thymus and peripheral lymphoid organs ($p = 0.02$), as well as with the dose rate in these organs ($p = 0.05$, $p = 0.04$, respectively) during the period of the highest levels of radiation exposure. In individuals exposed in the high dose range (over 1000 mGy) there was a significant increase in the expression of *DNMT1* mRNA compared to the comparison group ($p = 0.02$). The findings may indicate the *DNMT1* gene involvement in epigenetic alterations that occur in the chronically exposed people in the long term.

Keywords: gene expression, chronic radiation exposure, DNA methylation, Techa River, low doses

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ТРАНСКРИПЦИОННАЯ АКТИВНОСТЬ ГЕНОВ ДНК-МЕТИЛТРАНСФЕРАЗ У ЖИТЕЛЕЙ УРАЛЬСКОГО РЕГИОНА, ПОДВЕРГШИХСЯ ХРОНИЧЕСКОМУ РАДИАЦИОННОМУ ВОЗДЕЙСТВИЮ

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Помимо повреждения генетического аппарата клетки, ионизирующее излучение способно приводить к эпигенетическим изменениям. Распространенной эпигенетической модификацией является метилирование ДНК, играющее важную роль в регуляции клеточных процессов. Метилирование ДНК происходит в последовательностях, богатых CpG-динуклеотидами, и осуществляется при помощи ферментов ДНК-метилтрансфераз. Целью работы было изучить экспрессию мРНК генов ДНК-метилтрансфераз (*DNMT1*, *DNMT3A*, *DNMT3B*) в отдаленные сроки у лиц, подвергшихся хроническому радиационному облучению на р. Теча. Обследование 112 человек было проведено спустя более чем 65 лет после начала хронического облучения. Средняя накопленная доза облучения красного костного мозга составляла 782,0 ± 82,3 мГр, а средняя накопленная доза облучения тимуса и периферических лимфоидных органов — 93,2 ± 13,6 мГр. Возраст людей на время проведения обследования составил 67,9 ± 0,8 лет (54–83 года). Оценку относительного содержания мРНК исследуемых генов проводили с использованием метода полимеразной цепной реакции в реальном времени. Установлена прямая корреляция между экспрессией мРНК гена *DNMT1* и дозой облучения красного костного мозга ($p = 0,04$), тимуса и периферических лимфоидных органов ($p = 0,02$), а также мощностью дозы облучения этих органов ($p = 0,05$, $p = 0,04$ соответственно) в период максимального радиационного воздействия. У облученных лиц в диапазоне больших доз (более 1000 мГр) наблюдается значимое увеличение экспрессии мРНК гена *DNMT1* относительно группы сравнения ($p = 0,02$). Полученные результаты могут свидетельствовать о вовлеченности гена *DNMT1* в изменение эпигенетического статуса у людей, подвергшихся хроническому радиационному воздействию в отдаленные сроки.

Ключевые слова: экспрессия генов, хроническое облучение, метилирование ДНК, река Теча, малые дозы

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Genome-wide DNA methylation profile is a dynamic feature capable of changing during ontogenetic development or under the influence of environmental factors. Methylation that involves enzymes DNA methyltransferases (DNMT1, DNMT3A, DNMT3B, DNMT3L) occurs in the CpG-rich sequences [1]. Methyltransferases DNMT3A and DNMT3B display de novo methylation activity. Methyltransferase DNMT1 ensures restoration and maintenance of the previously established methyl labels. Methylation levels of each DNA segment result from two opposing processes, methylation and demethylation, which generally depend on the activity of DNA methyltransferases and DNA demethylating enzymes [2].

The ionizing radiation-induced alterations in expression of DNA methyltransferases were studied in cells cultured in vitro: in some cases these alterations correlated with DNA methylation levels [3]. The experiments with mice and human thymocytes that involved the use of the combined radiation regime (exposure to an initial low dose administered prior to a subsequent higher radiation dose) revealed the decrease in expression of *DNMT2*, *DNMT3B*, *DNMT3L* in murine thymocytes and *DNMT2*, *DNMT3A* in the exposed *in vitro* human thymocytes [4]. The increased expression of DNA methyltransferases was observed in surgeons who had been practicing interventions for more than three years [5]. Protein p53 that binds directly to DNA is one of methyltransferase expression regulators in response to the ionizing radiation exposure. Direct binding of the protein is reduced upon exposure, which results in the increased transcritional activity of *DNMT1* [6].

It is shown that radiosensitivity of cells (including stem cells) is affected by the genome-wide DNA methylation levels and methyltransferase activity. This is due to the fact that methyltransferase activity and methylation of certain DNA sites can potentially alter secretion of such factors, as TNFα, NO, and TGFβ [7]. Furthermore, the ionizing radiation-induced methylation and methyltransferase gene expression alterations contribute to induction of genome instability [8].

Thus, the study was aimed to assess mRNA expression of genes encoding DNA methyltransferases (*DNMT1*, *DNMT3A*, *DNMT3B*) in the chronically exposed individuals (mostly exposed to low-dose radiation) over a long-term period.

METHODS

The object of the study were peripheral blood samples collected from 112 residents of the villages located along the Techa River, who were cronically exposed after the discharge of liquid radioactive waste from PA Mayak. Internal exposure occurred due to radionuclides that entered the body through consuming river water and locally manufactured food products, and external gamma exposure resulted from radionuclide contamination of bottom sediments and floodplain soils.

Massive discharge of radioactive waste started in 1950. The short-lived radionuclides were the main source of exposure during the first few years. Then, as a result of protective actions and the decay of short-lived radionuclides, external and internal dose rate in soft tissues significantly decreased: after 1960 it did not exceed 10^{-5} Gy/year in all people living along the river banks. The features of red bone marrow (RBM) exposure were slightly different, since the main contribution to the radiation dose was made by the long-lived osteotropic radionuclide ^{90}Sr, which provided chronic exposure with the monotonically decreasing dose rate that became less than 10^{-5} Gy/year by 1985 in all the exposed people [9].

Inclusion criteria: permanent residence in one of 41 villages located along the Techa River between January 1, 1950 and December 31, 1960; availability of reconstructed absorbed doses to RBM, thymus and peripheral lymphoid organs, calculated using the Techa River Dosimetry System-2016 (TRDS-2016) [10]. Exclusion criteria: autoimmune disorders; acute or chronic (exacerbation) inflammatory diseases; taking antibiotics, glucocorticoids or cytostatic drugs during a period of six months prior to blood sample collection.

The study participants were divided into the following groups based on the absorbed dose to RBM: the comparison group (67 individuals), where the doses to RBM did not exceed 70 mGy throughout the subjects' life, and the group of chronically exposed people (45 individuals), whose doses exceeded 70 mGy.

The average accumulated dose to RBM in the cronically exposed individuals was 782.0 ± 82.3 mGy (dose range: 77.8–3179.7 mGy), and the average dose rate in RBM during the period of the highest levels of radiation exposure (years 1950–1951) was 145.7 ± 16.3 mGy/year (dose rate range: 0.1–542.6 mGy/year). The average accumulated dose to thymus and peripheral lymphoid organs was 93.2 ± 13.6 mGy (dose range: 2.8–644.8 mGy), while the average dose rate during the period of the highest levels of radiation exposure was 42.8 ± 6.8 mGy (dose range: 0.1–320.9 mGy/year). The average accumulated dose to RBM in the comparison group was 20.7 ± 2.7 mGy (dose range: 1.3–63.2 mGy), and the average accumulated dose to thymus and peripheral lymphoid organs was 8.8±1.6 mGy (dose range: 0.2–33.5 mGy).

The average age of chronically exposed individuals was 72.2 ± 0.7 years (63–83 years), and the average age of people in the comparison group was 63.7 ± 1.0 years (54–79 years). The vast majority of samples were obtained from females in both groups. Thus, in the group of chronically exposed people women accounted for 70.1% (47 individuals), and in the comparison group they accounted for 68.9% (31 individuals).

To assess the relative mRNA levels of methyltransferases, 3 mL of blood were collected from the cubital vein in sterile vacuum Tempus Blood RNA Tubes (Thermo Scientific; USA). RNA was isolated by the column-based extraction method using the GeneJET Stabilized and Fresh Whole Blood RNA Kit (Thermo Scientific; USA). Qualitative and quantitative characteristics of the isolated total RNA samples were

Table 1. Olygonucleotide sequences of primers and probes

Gene	Olygonucleotide sequences
DNMT1	Forward: 5'-CCTTCACGTTCAACATCAAGC-3' Reverse: 5'-GCTCTGGGTACAGGTCCTCATC-3' Probe: FAM-BHQ1 - 5'-CCAGTCCCGTGAAACGCCCA-3'
DNMT3A	Forward: 5'- GGCTCCAGATGTTCTTCGCTA-3' Reverse: 5'- GGATGGGCTTCCTCTTCTCA-3' Probe: FAM-BHQ1 - 5'-CACGACCAGGAATTTGACCCTCCA-3'
DNMT3B	Forward: 5'- GAATCAAGGAAATACGAGAACAAGAC-3' Reverse: 5'- CTTCATCCCCTCGGTCTTTG-3' Probe: FAM-BHQ1 - 5'-CGACTCAGCCACCTCTGACTACTGCC-3'

Table 2. Relative mRNA levels (Me) of DNA methyltransferase genes (RU) in peripheral blood cells of chronically exposed people over a long-term period

Group	*n*	*DNMT1*	*DNMT3A*	*DNMT3B*
Comparison group	45	1.18 (0.78–1.67)	0.71 (0.58–0.82)	0.78 (0.18–1.37)
Chronically exposed individuals	67	1.43 (0.99–1.67)	0.71 (0.55–0.83)	0.46 (0.20–1.18)

Note: in parentheses are 25th–75th percentile; *n* — sample size.

assessed with the NanoDrop 2000C Spectrophotometer (Thermo Scientific; USA). Sample purity was determined based on absorption values at wavelengths of 260 nm and 280 nm (A260/280). The reverse transcription reaction was performed as a separate step using the MMLV RT Kit (Evrogen; Russia). The relative mRNA levels were defined by real-time polymerase chain reaction (real-time PCR) using the Real-Time CFX96 Touch system (Bio-Rad Laboratories; USA). Olygonucleotide sequences of primers and probes were synthesized by LLC DNA-Synthesis (Russia) (Table 1).

Real-time PCR was carried out as follows: initial denaturation at 95 °C for 5 min, cycles of denaturation at 95 °C for 20 s, primer annealing and elongation at 65 °C for 60 s (50 cycles). Each sample was tested three times.

The $2^{-\Delta\Delta Ct}$ method was used to calculate relative gene expression [11]. *ACTB* housekeeping gene was used as an endogenous control. Calculations were performed with the software installed in the Real-Time CFX96 Touch system (BioRad; USA).

Statistical processing of the results was carried out with the SPSS Statistics 17.0 (IBM; USA) and Graph Pad Prism 8.4.3 (GraphPad Software Inc.; USA) software packages. Distributions of indicator values were tested for normality using the Kolmogorov–Smirnov test. Mean values (M), standard error of the mean (± SE), and the range of values (min–max) were used to characterize samples with normal distribution. The indicators with non-normal distribution were presented as median (Me), 25th–75th percentile (Q_1–Q_3). Samples were compared using the Mann–Whitney U test, since the majority of values had non-normal distribution. Correlation analysis for assessment of the effects of dose characteristics on the relative mRNA levels of methyltransferases was performed by calculating Spearman's rank correlation coefficients (*R*). The differences were considered significant at $p < 0.05$ in all tests. When $0.05 < p < 0.1$, the difference was considered as a trend towards significant difference.

RESULTS

When comparing two samples, no significant differences in the relative mRNA levels of the *DNMT1*, *DNMT3A*, and *DNMT3B* methyltransferase genes were observed (Table 2).

Correlation analysis of the combined sample revealed a weak correlation of the relative mRNA levels of *DNMT1* with the accumilated dose to RBM ($R = 0.19$; $p = 0.04$), thymus and peripheral lymphoid organs ($R = 0.19$; $p = 0.05$), and the dose rate in RBM ($R = 0.21$; $p = 0.02$), thymus and peripheral lymphoid organs ($R = 0.20$; $p = 0.04$) during the period of the highest levels of radiation exposure (Table 2).

The relationship between the relative mRNA levels of *DNMT1* and the dose characteristics was assessed by regression analysis of the combined sample. The analysis confirmed the correlation between the changes in expression on the *DNMT1* gene mRNA and the dose rate in RBM ($R = 0.20$; $p = 0.03$), thymus and peripheral lymphoid organs ($R = 0.19$; $p = 0.04$) during the period of the highest levels of radiation exposure. No correlations were found between the relative *DNMT3A* and *DNMT3B* mRNA levels and the dose parameters (Table 3).

In individuals with the accumulated dose to RBM exceeding 1000 mGy (1044.8–3179.7 mGy) the significant increase in the expression of the *DNMT1* gene mRNA (the average value: 1659.0 ± 155.7; $p = 0.02$) compared to the comparison group was observed (Fig. A).

Furthermore, it was found that relative mRNA levels of *DNMT1* were significantly higher ($p = 0.04$) in individuals with accumulated doses to thymus and peripheral lymphoid organs of 103.9–644.8 mGy (average value: 200.9 ± 30.3 mGy) compared to individuals with accumulated doses not exceeding 10.0 mGy (average value: 2.5 mGy) (Fig. B).

DISCUSSION

DNMT1 is one of the main DNA methyltransferases in mammalian cells. It is a highly dynamic enzyme with multiple regulatory functions that is capable of controlling DNA methylation. In particular, DNMT1 expression is necessary for maintaining the pattern of DNA methylation during mitosis. Furthermore, DNMT1 plays a direct role in the recovery of epigenetic information during the DNA repair [8].

DNMT1 gene upregulation is often associated with global DNA hypomethylation [12]. It is worth noting that such an effect of genome-wide hypomethylation was observed in employees of nuclear facilities exposed to the combination of high- and low-LET radiation. The researchers [13] noted that

Table 3. Spearman's rank correlation (*R*) between the relative mRNA levels of DNA methyltransferase genes and the values of dose and dose rate during the period of the highest levels of radiation exposure

Gene	Dose to RBM, mGy	Dose rate in RBM during the period of the highest levels of radiation exposure, mGy/year	Dose to thymus and peripheral lymphoid organs, mGy/year	Dose rate in thymus and peripheral lymphoid organs during the period of the highest levels of radiation exposure, mGy/year
	R (*p*)			
DNMT1	0.19 (0.04)	0.21 (0.02)	0.19 (0.05)	0.20 (0.04)
DNMT3A	–0.03 (0.74)	–0.07 (0.45)	–0.04 (0.65)	–0.04 (0.65)
DNMT3B	–0.13 (0.17)	–0.17 (0.08)	–0.14 (0.16)	–0.15 (0.11)

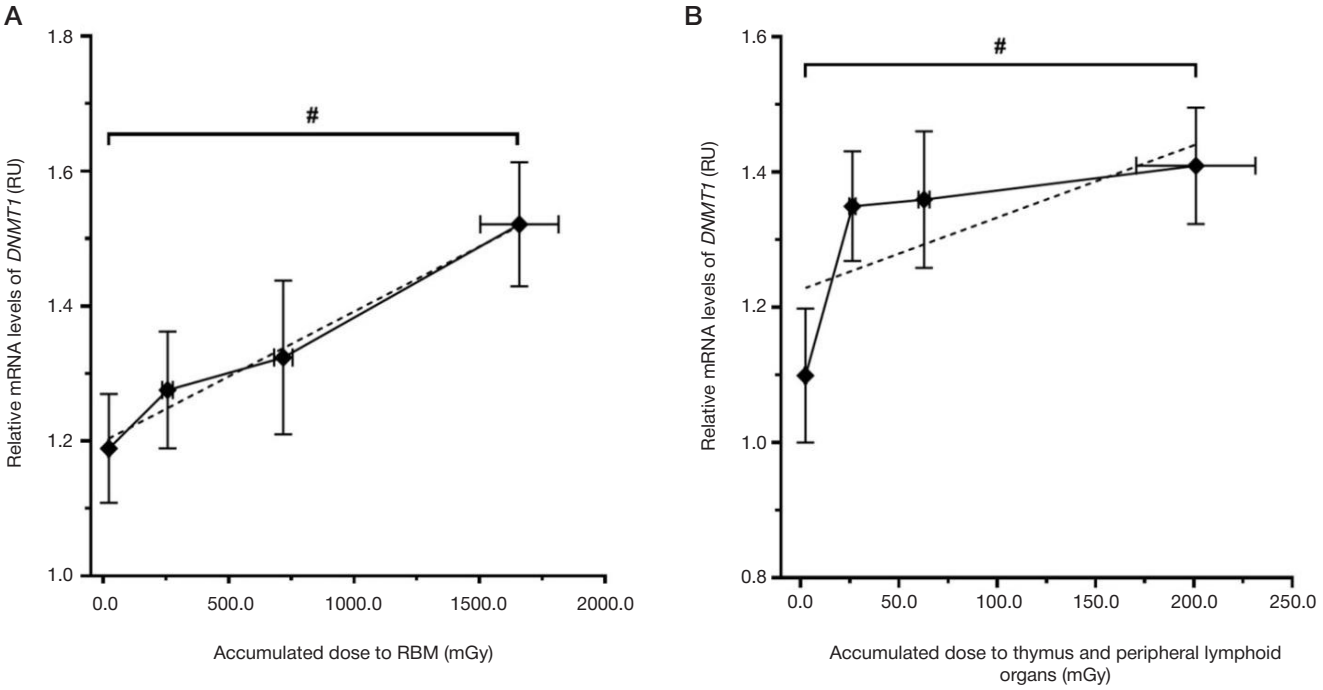

Fig. Relative mRNA levels of *DNMT1* (RU) in exposed individuals as a function of dose to RBM (**A**), thymus and peripheral lymphoid organs (**B**): the *dotted line* indicates linear approximation (trend line); # indicates significant differences in *DNMT1* gene expression between the comparison group and the group of chronically exposed people; vertical error bar corresponds to the error of the mean of the relative mRNA levels of *DNMT1*; horizontal error bar corresponds to the error of the mean of the accumulated dose to RBM (**A**), thymus and peripheral lymphoid organs (**B**)

workers whose total cumulative dose exceeded 103.14 mSv, had significantly higher global methylation levels compared to workers with lower doses (below 103.14 mSv), which indicated a differential response of epigenome to the effects of exposure to low and high doses.

The other study reported by the same authors showed reduced total levels of 5-methylcytosine in leukocytes of employees exposed to gamma ray and X-ray radiation [14].

DNA methyltransferase expression alterations are often associated with the locus-specific changes in methylation of genes responsible for maintaining cell homeostasis. The paper [15] reports CpG island hypermethylation in promoters of some genes (particularly, *p16/INKA* and *GSTP1*) in normal leukocytes of individuals who were exposed to radiation long time ago. Further examination of the PA Mayak employees with available reconstructed absorbed doses from external exposure to gamma ray radiation or combined exposure to external gamma- and internal alpha-radiation performed using the extended range of the studied loci revealed the combination of genes *p16/INKA*, *p53*, *GSTP1*, *SOD3*, *ATM*, *ESR1*, hypermethylation of which was associated with radiation exposure [16].

Our previously published studies revealed a positive correlation between the promoter methylation levels of the *ATM* gene and the dose to RBM, thymus and peripheral lymphoid organs in exposed individuals [17]. Moreover, *ATM* gene expression was significantly reduced in the group of chronically exposed people with the doses to RBM exceeding 1000 mGy [18].

It is possible that alterations in expression of human gene *DNMT1* in the long term after the beginning of chronic exposure in case the doses to RBM exceed 1000 mGy could be involved in induction of epigenetic alterations. To answer the question whether DNMT1 is involved in epigenetic mechanisms, it is necessary to study the impact of the gene transcriptional activity on the promoter methylation levels of genes involved in regulation of repair, cell proliferation and death in exposed individuals.

CONCLUSIONS

The significantly increased expression of the human *DNMT1* mRNA in the long term after the beginning of the low-dose radiation exposure with the dose range exceeding 1 Gy has been revealed. Positive correlations of the *DNMT1* mRNA expression with the dose to red bone marrow, thymus and peripheral lymphoid organs, and the dose rate in these organs during the period of the highest levels of radiation exposure (years 1950–1951) are observed in the chronically exposed individuals.

References

1. Arand J, Spieler D, Karius T, Branco MR, Meilinger D, Meissner A, et al. In vivo control of CpG and non-CpG DNA methylation by DNA methyltransferases. PLOS Genetics. 2012; (8): 1002750. DOI:10.1371/journal.pgen.1002750.
2. Jeltsch A, Jurkowska RZ. New concepts in DNA methylation. Trends in Biochemical Sciences. 2014; 39 (7): 310–18. DOI: 10.1016/j.tibs.2014.05.002.
3. Chaudhry MA, Omaruddin RA. Differential DNA methylation alterations in radiation-sensitive and -resistant cells. DNA and Cell Biology. 2012; 31 (6): 908–16. DOI: 10.1089/dna.2011.1509.
4. López-Nieva P, González-Vasconcellos I, González-Sánchez L, Cobos-Fernández MA, Cobos-Fernández S, Pérez RS, et al. Differential molecular response in mice and human thymocytes exposed to a combined-dose radiation regime. Sci Rep. 2022; (12): 3144. DOI: 10.1038/s41598-022-07166-8.
5. Chen B, Dai Q, Zhang Q , Yan P, Wang A, Qu L, et al. The relationship among occupational irradiation, DNA methylation status, and oxidative damage in interventional physicians.

Medicine (Baltimore). 2022; 98 (39): e17373. DOI: 10.1097/MD.0000000000017373.
6. Peterson EJ, Bogler O, Taylor SM. p53-mediated repression of DNA methyltransferase 1 expression by specific DNA binding. Cancer Res. 2003; 63 (20): 6579–82.
7. Armstrong CA, Jones GD, Anderson R, Iyer P, Narayanan D, Sandhu J, et al. DNMTs are required for delayed genome instability caused by radiation. Epigenetics. 2012; 7 (8): P. 892–902. DOI: 10.4161/epi.21094.
8. Rugo RE, Mutamba JT, Mohan KN, Yee T, Greenberger JS, Engelward BP. Methyltransferases mediate cell memory of a genotoxic insult. Oncogene. 2011; 30 (6): 751–6. DOI: 10.1038/onc.2010.480.
9. Degteva MO, Napier BA, Tolstykh EI, Shishkina EA, Bougrov NG, Krestinina LYu, et al. Individual dose distribution in cohort of people exposed as a result of radioactive contamination of the Techa River. Medical Radiology and Radiation Safety. 2019; 64 (3): 46–53. DOI: 10.12737/article_5cf2364cb49523. 98590475.
10. Degteva MO, Napier BA, Tolstykh EI, Shishkina EA, Shagina NB, Volchkova AYu, et al. Enhancements in the Techa River Dosimetry System: TRDS-2016D code for reconstruction of deterministic estimates of dose from environmental exposures. Health Physics. 2019; 117 (4): 378–87. DOI: 10.1097/HP.0000000000001067.
11. Livak KJ, Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C(T)). Methods. 2001; 25 (4): 402–8. DOI: 10.1006/meth.2001.1262.
12. Svedruzic ZM. Dnmt1 structure and function. Prog Mol Biol Transl Sci. 2011; 101: 221–54. DOI: 10.1016/B978-0-12-387685-0.00006-8.
13. Lee Y, Kim YJ, Choi YJ, Lee JW, Lee S, Cho YH, et al. Radiation-induced changes in DNA methylation and their relationship to chromosome aberrations in nuclear power plant workers. Int J Radiat Biol. 2015; 91 (2): 142–9. DOI: 10.3109/09553002.2015.969847.
14. Cho YH, Jang Y, Woo HD, Kim YJ, Kim SY, Christensen S, et al. LINE-1 hypomethylation is associated with radiation-induced genomic instability in industrial radiographers. Environ Mol Mutagen. 2018; 60 (2):174–84. DOI: 10.1002/em.22237.
15. Kuzmina NS, Lapteva NSh, Rubanovich AB. Hypermethylation of gene promoters in peripheral blood leukocytes in humans long term after radiation exposure. Environ Res. 2016; 146: 10–17. DOI: 10.1016/j.envres.2015.12.008.
16. Kuzmina NS, Lapteva NSh, Rusinova GG, Azizova TV, Vyazovskaya NS, Rubanovich AV. Dose dependence of hypermethylation of gene promoters in blood leukocytes in humans exposed to both gamma-radiation and alpha-particles. Genetika. 2018; 54: S22–26. DOI: 10.1134/S0016675818130118.
17. Blinova EA, Nikiforov VS, Kotikova AI, Yanishevskaya MA, Akleyev AV. Methylation status of apoptose genes and intensity of apoptotic death of peripheral blood lymphocytes in persons chronically exposed to radiation. Molecular Biology. 2022; 56 (5): 1–11.
18. Nikiforov VS, Blinova EA, Akleyev AV. The transcriptional activity of cell cycle and apoptosis genes in chronically exposed people with an increased frequency of TCR mutant lymphocytes. Radiation and Risk (Bulletin of the National Radiation and Epidemiological Registry). 2020; 29 (2): 89–100. DOI: 10.21870/0131-3878-2020-29-2-89-100.

Литература

1. Arand J, Spieler D, Karius T, Branco MR, Meilinger D, Meissner A, et al. In vivo control of CpG and non-CpG DNA methylation by DNA methyltransferases. PLOS Genetics. 2012; (8): 1002750. DOI:10.1371/journal.pgen.1002750.
2. Jeltsch A, Jurkowska RZ. New concepts in DNA methylation. Trends in Biochemical Sciences. 2014; 39 (7): 310–18. DOI: 10.1016/j.tibs.2014.05.002.
3. Chaudhry MA, Omaruddin RA. Differential DNA methylation alterations in radiation-sensitive and -resistant cells. DNA and Cell Biology. 2012; 31 (6): 908–16. DOI: 10.1089/dna.2011.1509.
4. López-Nieva P, González-Vasconcellos I, González-Sánchez L, Cobos-Fernández MA, Cobos-Fernández S, Pérez RS, et al. Differential molecular response in mice and human thymocytes exposed to a combined-dose radiation regime. Sci Rep. 2022; (12): 3144. DOI: 10.1038/s41598-022-07166-8.
5. Chen B, Dai Q, Zhang Q , Yan P, Wang A, Qu L, et al. The relationship among occupational irradiation, DNA methylation status, and oxidative damage in interventional physicians. Medicine (Baltimore). 2022; 98 (39): e17373. DOI: 10.1097/MD.0000000000017373.
6. Peterson EJ, Bogler O, Taylor SM. p53-mediated repression of DNA methyltransferase 1 expression by specific DNA binding. Cancer Res. 2003; 63 (20): 6579–82.
7. Armstrong CA, Jones GD, Anderson R, Iyer P, Narayanan D, Sandhu J, et al. DNMTs are required for delayed genome instability caused by radiation. Epigenetics. 2012; 7 (8): P. 892–902. DOI: 10.4161/epi.21094.
8. Rugo RE, Mutamba JT, Mohan KN, Yee T, Greenberger JS, Engelward BP. Methyltransferases mediate cell memory of a genotoxic insult. Oncogene. 2011; 30 (6): 751–6. DOI: 10.1038/onc.2010.480.
9. Дегтева М. О., Напье Б. А., Толстых Е. И., Шишкина Е. А., Бугров Н. Г., Крестинина Л. Ю. и др. Распределение индивидуальных доз в когорте людей, облученных в результате радиоактивного загрязнения реки Течи. Медицинская радиология и радиационная безопасность. 2019; 64 (3): 46–53. DOI: 10.12737/article_5cf2364cb49523. 98590475.
10. Degteva MO, Napier BA, Tolstykh EI, Shishkina EA, Shagina NB, Volchkova AYu, et al. Enhancements in the Techa River Dosimetry System: TRDS-2016D code for reconstruction of deterministic estimates of dose from environmental exposures. Health Physics. 2019; 117 (4): 378–87. DOI: 10.1097/HP.0000000000001067.
11. Livak KJ, Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C(T)). Methods. 2001; 25 (4): 402–8. DOI: 10.1006/meth.2001.1262.
12. Svedruzic ZM. Dnmt1 structure and function. Prog Mol Biol Transl Sci. 2011; 101: 221–54. DOI: 10.1016/B978-0-12-387685-0.00006-8.
13. Lee Y, Kim YJ, Choi YJ, Lee JW, Lee S, Cho YH, et al. Radiation-induced changes in DNA methylation and their relationship to chromosome aberrations in nuclear power plant workers. Int J Radiat Biol. 2015; 91 (2): 142–9. DOI: 10.3109/09553002.2015.969847.
14. Cho YH, Jang Y, Woo HD, Kim YJ, Kim SY, Christensen S, et al. LINE-1 hypomethylation is associated with radiation-induced genomic instability in industrial radiographers. Environ Mol Mutagen. 2018; 60 (2):174–84. DOI: 10.1002/em.22237.
15. Kuzmina NS, Lapteva NSh, Rubanovich AB. Hypermethylation of gene promoters in peripheral blood leukocytes in humans long term after radiation exposure. Environ Res. 2016; 146: 10–17. DOI: 10.1016/j.envres.2015.12.008.
16. Кузьмина Н. С., Лаптева Н. Ш., Русинова Г. Г., Азизова Т. В., Вязовская Н. С., Рубанович А. В. Дозовая зависимость гиперметилирования промоторов генов в лейкоцитах крови лиц, подвергшихся сочетанному воздействию гамма- и альфаизлучений. Генетика. 2018; 54: S22–26. DOI: 10.1134/S0016675818130118.
17. Блинова Е. А., Никифоров В. С., Котикова А. И., Янишевская М. А., Аклеев А. В. Статус метилирования генов апоптоза и интенсивность апоптотической гибели лимфоцитов периферической крови у лиц, подвергшихся хроническому радиационному облучению. Молекулярная биология. 2022; 56 (5): 1–11.
18. Никифоров В. С., Блинова Е. А., Аклеев А. В. Транскрипционная активность генов клеточного цикла и апоптоза у хронически облученных лиц, имеющих повышенную частоту TCR-мутантных лимфоцитов. Радиация и риск (Бюллетень национального радиационно-эпидемиологического регистра). 2020; 29 (2): 89–100. DOI: 10.21870/0131-3878-2020-29-2-89-100.