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Research article

ROLE OF CELLULAR IMMUNITY IN MALIGNANT TUMORS DEVELOPMENT IN INDIVIDUALS CHRONICALLY EXPOSED TO IONISING RADIATION

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Some long-term effects of radiation could be related to changes in the immune system resulting from radiation exposure. Immunity disorders caused by radiation can influence carcinogenesis.

Cellular immunity factors were investigated in peripheral blood of workers chronically exposed to occupational combined radiation (external gamma-rays and internal alpha-particles), with malignant neoplasms diagnosed after blood samples were taken or without them, and in the control group.

The aim of this study was to examine effects of radiation on the cellular immunity status in individuals chronically exposed to ionizing radiation who had malignant neoplasms developed after blood sampling.

The relative and absolute number of lymphocyte subpopulations (total T-cells, T-helpers, T-cytotoxic, total B-cells, NK-cells, NKT-cells and activated T-cells) was detected by flow cytofluorometry.

The absolute number of T-cells was significantly reduced in workers chronically exposed to occupational combined irradiation, with or without malignancies, compared to the control, which may contribute to tumor progression at an early stage of its onset. At the same time, workers without malignancies had a significant increase in the relative number of T-cytotoxic lymphocytes, which may be a factor preventing tumor development. A significant increase in the relative number of natural killer cells (NK cells) was detected in individuals with malignant neoplasms chronically exposed to occupational combined irradiation, compared with the control, which may indicate enhanced antitumor defense that developed in response to exposure to tumor antigens. In addition, a significant decrease in the absolute and relative number of T- and B-lymphocytes was found in the group of workers with malignant neoplasm, compared with the control. A significant increase in the relative number of T-helpers was found in both groups of workers. Since the role of T-helpers in the antitumor response is ambiguous, additional research on types of T-helpers is planned to clarify the results of the present study.

Keywords: *occupational exposure, ionizing radiation, malignant neoplasms, innate immunity, adaptive immunity, antitumor immunity, T- and B-lymphocytes, T-helpers.*

People who have been exposed to ionizing radiation are known to have elevated risks of malignant neoplasms (MNs) [1–4]. Ionizing radiation can produce mutagenic effects and promote cancerous cell transformation by damaging their genetic apparatus and inducing epigenetic changes in organs and tissues [5]. A close relationship has been established between the state of the immune system and MNs progression [6–8]. The immune system is responsible for genetic stability of the body internal environment. It removes both alien and own mutated molecules and cells thereby providing body resistance to MN progression.

Ionizing radiation can modulate carcinogenesis by inducing changes in the immune system. At present, the opinions about the interaction between ionizing radiation and the immune system under exposure to it are largely controversial. High-dose radiation has been shown to induce immunosuppression. At the same time, various cellular components of

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the immune system give rather ambiguous quantitative and functional responses under exposure to low and medium doses [7].

Some radiation-induced late effects are considered to be caused by changes in the immune system induced by the radiation exposure [9]. Thus, liquidators examined in the preclinical MN period were compared with liquidators without MN or any pre-tumor states. In the former group, some changes were observed in the T-cell sub-population (lower CD3+ and CD4+-T-lymphocytes percentage, lower CD4+/CD8+ immune regulation index, elevated relative and absolute levels of cytotoxic CD8+-T-lymphocytes) and there was also an increase in relative and absolute levels of NK-cells and elevated levels of total IgE [10]. Also individuals with pre-cancer diseases tended to have activated absorbing and lysosomal functions of the phagocytic section in the immunity, a moderate decrease in levels of CD4+ (T-helpers), CD8+ (T-killers) and CD5+ lymphocytes[1].

Findings of the studies focusing on the role of the immune system in MN progression and on radiation-induced carcinogenesis are plentiful in research literature. Despite that, the state of the immune system in people with MNs who were earlier exposed to ionizing radiation, especially chronically, has not been studied enough yet.

The aim of this study was to examine effects of ionizing radiation on the cellular immunity status in chronically exposed individuals with MNs developed after blood sampling.

Materials and methods. Three groups were examined to estimate the cellular immunity status. The first group included nuclear workers chronically exposed to combined (external gamma-ray and internal alpha-particle) radiation without MNs in pre- and post-morbid medical histories (workers without MNs). The second group comprised nuclear workers chronically exposed to combined radiation and diagnosed with MNs one year after blood sampling or later (workers with MNs). The third (control) group comprised individuals never exposed to ionizing radiation in occupational activities and without a MN reported in either pre- or post-morbid medical histories. The following exclusion criteria were applicable for these three groups: radiotherapy; living in areas contaminated with radionuclides; diseases of the circulatory system (DCSs); acute or exacerbated chronic diseases at the moment of examination within this study,

Basic description of the analyzed groups is provided in Table 1.

Table 1

Description of the analyzed groups

Parameter		Workers without MNs; *M*; *SD* [*CI* 95 %] (*Median*; min–max)	Workers with MNs; *M*; *SD* [*CI* 95 %] (*Median*; min–max)	Control; *M*; *SD* [*CI* 95 %] (*Median*; min–max)
The number of people		72	22	72
Sex	Women (%)	37 (51.4)	4 (18.2)	38 (52,8)
	Men (%)	35 (48.6)	18 (81.8)	34 (47,2)
Age, years		72.1; 10.9 [69.6–74.7] (73.0; 49.0–89.0)	78.2; 3.2* [76.8–79.6] (79.0; 71.0–84.0)	70.7; 9.2 [68.6–72.9] (72.0; 51.0–87.0)
Total dose of external gamma-ray exposure absorbed in the BM, Gy		0.750; 0.699 [0.585–0.914] (0.630; 0.018–2.293)	1.573; 0.600 [1.307–1.839] (1.533; 0.491–3.065)	–
Total dose of internal alpha-particle exposure absorbed in the BM, Gy		0.072; 0.092 [0.050–0.094] (0.051; 0.000–0.521)	0.090; 0.074 [0.057–0.123] (0.075; 0.003–0.298)	–

N o t e: BM is for bone marrow.

[1] Akleyev A.V., Silkina L.A., Veremeyeva G.A. Radiation-induced immunity changes and their potential role in the development of late radiation effects in humans. *Radiatsiya i risk (Byulleten' Natsional'nogo radiatsionno-epidemiologicheskogo registra)*, 1997, no. 10, pp. 136–145 (in Russian).

The lymphocyte subpopulation structure was identified with flow cytometry [11]. Blood samples were taken between 7 and 9 a.m. on empty stomach from the basilic or cephalic vein into 2-ml vacutainers for venous blood with lithium-heparin. After sampling, the samples were mixed gently by not less than 8 stirs.

Relative and absolute counts of lymphocyte subpopulations (total T-cells, T-helpers, T-cytotoxic lymphocytes, total B-cells, NK-cells, NKT-cells and activated T-cells) were established by using the panel of monoclonal antibodies with the two-color combination of fluorochromes (Beckman Coulter, USA) in accordance with the user instruction provided by the manufacturer. Obtained samples were analyzed on Fc 500 flow cytometer (Beckman Coulter, USA).

The resulting data were statistically analyzed in Statistica 10 software package (StatSoft. Inc., USA). Validity of the zero hypothesis was estimated by using the non-parametric Mann – Whitney test. Correlations were estimated by using the Spearman non-parametric rank correlation coefficient[2].

Results and discussion. Comparative analysis of cellular immunity indicators revealed that workers without malignancies chronically exposed to combined radiation had significantly lower absolute T-lymphocyte levels and significantly elevated relative levels of T-helpers and T-cytotoxic lymphocytes compared to the control (Table 2).

No significant differences were found in the cellular immunity indicators between nuclear workers with MNs diagnosed after blood sampling and without MNs; only a descending trend in relative levels of T- and B-lymphocytes was observed (Table 3).

Relative levels of natural killers and T-helpers were significantly higher in radiation-exposed workers with MNs than in the control group. In addition to that, we observed a significant decrease in absolute and relative levels of T- and B-lymphocytes in workers with malignancies compared to the control group (Table 4).

Therefore, our findings indicate that workers with MNs developed after blood sampling, who were chronically exposed to combined radiation, had a significantly lower absolute T-lymphocyte level compared to the control. This is consistent with the results obtained by other researchers [12–14]. T-cells are components of the adaptive immunity system and can adopt either a regulatory or effector phenotype producing both pro- and anti-inflammatory effects [15]. Tumor-specific T-cells (TSTs) are actively investigated for different tumor types [16]. At an early stage in tumor development, immunogenic antigens are produced in sufficient quantities and naïve T-cells are primed in drainage lymph nodes. Then they are activated and migrate into a developing tumor where they perform a protective effector immune response by eliminating immunogenic cancer cells. Hence, an observed decrease in T-lymphocyte levels in workers with malignancies developed after blood sampling might promote tumor progression at its early stage.

Workers chronically exposed to combined radiation, both with and without MNs, had elevated relative T-helper levels compared to the control, which is in line with literature data [17]. CD4+ T-helpers 1 (Th-1), which determine anti-tumor response by secreting large quantities of pro-inflammatory cytokines, such as IL-2, TNF-α and IFN-γ, promote not only priming and activation of cytotoxic T-lymphocytes but also anti-tumor activity of macrophages and natural killers (NK) and enhanced presentation of anti-tumor antigens in general [18]. However, T-helper activation as per Th2-type has a negative effect since Th2-cytokines (IL-4 in particular) can activate both myeloid cells and macrophages as per an alternative type, which does not promote tumor rejection [19]. Some studies report a direct cytotoxic effect of CD4+-T-lymphocytes on a tumor [20]. As can be seen from the foregoing data, T-helpers play a rather controversial role in anti-tumor responses; therefore, this study needs to be supplemented by investigating T-helper types to clarify its findings.

[2] Zar J.H. Biostatistical analysis. New Jersey, Prentice Hall Publ., 1999, 663 p.

Table 2

Lymphocyte subpopulations in the examined groups

Indicator	Workers without MNs; ($n = 72$) *M*; *SD* [*CI* 95 %] (*Median*; min–max)	Control; ($n = 72$) *M*; *SD* [*CI* 95 %] (*Median*; min–max)	*p*-value*
NK-cells, × 10^6/l (CD3-CD16+CD56+) Reference range: 123–369	293.7; 207.1 [245.0–342.4] (232.2; 35.0 –1054.0)	299; 237.3 [243.3–354.8] (227.2; 37–1448)	0.9300
NK-cells, % (CD3-CD16+CD56+) Reference range: 9–21	13.2; 8.1 [11.3–15.1] (10.0; 1.7–38.3)	14; 25.9 [7.9–20.1] (9.3; 2.1–224.7)	0.2806
T–NK-cells, × 10^6/l (CD3+CD16+CD56+) Reference range: 7–165	100.1; 132.4 [69.0–131.2] (64.5; 6.0–780.0)	77.3; 103.7 [52.9–101.6] (50.5; 7–838)	0.5745
T–NK-cells, % (CD3+CD16+CD56+) Reference range: 1–6	4.4; 5.5 [3.1–5.6] (2.8; 0.2–32.5)	2.7; 1.9 [2.3–3.1] (2.2; 0.5–8.8)	0.1542
B-lymphocytes, × 10^6/l (CD3-CD19+) Reference range: 111–376	191.1; 98.3 [168.0–214.2] (170.0; 29.0–472.5)	292.9; 536 [167–418.9] (211; 12–4610)	0.0751
B-lymphocytes, % (CD3-CD19+) Reference range: 7–17	8.5; 3.7 [7.6–9.4] (8.4; 1.0– 18.1)	9.8; 5.2 [8.6–11] (8.9; 0.6–36.3)	0.1555
T-lymphocytes, × 10^6/l (CD3+CD19-) Reference range: 946–2079	1658.8; 694.3 [1495.6–1822.0] (1504.0; 756.0–4250.0)	1988.4; 1045.4 [1742.7–2234.1] (1846; 836–9398)	0.0028*
T-lymphocytes, % (CD3+CD19-) Reference range: 61–85	74.7; 11.2 [72.1–77.4] (76.5; 42.9–95.2)	76; 8.6 [74–78.1] (75.8; 47.9–91.7)	0.5664
T–h (helpers), × 10^6/l (CD3+CD4+) Reference range: 576–1336	931.0; 358.8 [846.7–1015.3] (895.5; 407.0–2278.7)	903.2; 402.3 [808.7–997.7] (877; 260–3378)	0.6821
T–h (helpers), % (CD3+CD4+) Reference range: 35–55	42.4; 8.8 [40.3–44.5] (44.0; 24.8–60.2)	35.3; 8.7 [33.3–37.4] (34.2; 14.8–57.5)	0.0000*
T–c (cytotoxic), × 10^6/l (CD3+CD8+) Reference range: 372–974	626.4; 376.9 [537.8–714.9] (558.5; 188.0–2597.0)	638.8; 467 [529.1–748.6] (560.5; 167–3874)	0.8542
T–c (cytotoxic), % (CD3+CD8+) Reference range: 19–35	27.6; 9.5 [25.4–29.9] (27.0; 8.2–49.8)	23.3; 6.5 [21.7–24.8] (23.9; 8.7–41.7)	0.0046*

N o t e: * means estimated as per the Mann – Whitney test.

Table 3

Lymphocyte subpopulations in the examined groups

Indicator	Workers with MNs; (*n* = 22) *M*; *SD* [*CI* 95 %] (*Median*; min–max)	Workers without MNs; (*n* = 72) *M*; *SD* [*CI* 95 %] (*Median*; min–max)	*p*-value*
NK-cells, × 10^6/l (CD3-CD16+CD56+) Reference range: 123–369	359.6; 228.5 [258.3–460.9] (294.0; 57.0–1006.0)	293.7; 207.1 [245.0–342.4] (232.2; 35.0–1054.0)	0.1467
NK-cells, % (CD3-CD16+CD56+) Reference range: 9–21	16.4; 9.4 [12.3–20.6] (16.3; 3.7–34.9)	13.2; 8.1 [11.3–15.1] (10.0; 1.7–38.3)	0.1556
T–NK-cells, × 10^6/l (CD3+CD16+CD56+) Reference range: 7–165	105.2; 119.8 [52.1–158.4] (50.5; 4.0–411.0)	100.1; 132.4 [69.0–131.2] (64.5; 6.0–780.0)	0.8095
T–NK-cells, % (CD3+CD16+CD56+) Reference range: 1–6	4.7; 5.0 [2.5–7.0] (2.8; 0.2–14.8)	4.4; 5.5 [3.1–5.6] (2.8; 0.2–32.5)	0.8372
B-lymphocytes, × 10^6/l (CD3-CD19+) Reference range: 111–376	162.1; 100.8 [117.4–206.8] (139.5; 51.0–451.0)	191.1; 98.3 [168.0–214.2] (170.0; 29.0–472.5)	0.1312
B-lymphocytes, % (CD3-CD19+) Reference range: 7–17	7.6; 6.1 [4.9–10.3] (5.7; 2.0–31.5)	8.5; 3.7 [7.6–9.4] (8.4; 1.0–18.1)	0.0548
T-lymphocytes, × 10^6/l (CD3+CD19-) Reference range: 946–2079	1565.2; 618.2 [1291.1–1839.3] (1370.5; 788.0–3501.0)	1658.8; 694.3 [1495.6–1822.0] (1504.0; 756.0–4250.0)	0.6552
T-lymphocytes, % (CD3+CD19-) Reference range: 61–85	69.5; 11.8 [64.2–74.7] (69.8; 49.5–88.5)	74.7; 11.2 [72.1–77.4] (76.5; 42.9–95.2)	0.0699
T–h (helpers), × 10^6/l (CD3+CD4+) Reference range: 576–1336	888.1; 320.2 [746.1–1030.1] (847.5; 450.0–1814.0)	931.0; 358.8 [846.7–1015.3] (895.5; 407.0–2278.7)	0.6360
T–h (helpers), % (CD3+CD4+) Reference range: 35–55	40.1; 8.5 [36.3–43.8] (37.9; 26.4–54.3)	42.4; 8.8 [40.3–44.5] (44.0; 24.8–60.2)	0.3172
T–c (cytotoxic), × 10^6/l (CD3+CD8+) Reference range: 372–974	598.5; 286.1 [471.6–725.3] (573.5; 166.0–1114.0)	626.4; 376.9 [537.8–714.9] (558.5; 188.0–2597.0)	0.8583
T–c (cytotoxic), % (CD3+CD8+) Reference range: 19–35	26.8; 10.9 [22.0–31.7] (28.4; 8.1–45.1)	27.6; 9.5 [25.4–29.9] (27.0; 8.2–49.8)	0.9005

N o t e: * means estimated as per the Mann – Whitney test.

Table 4

Lymphocyte subpopulation in radiation-exposed workers with MNs diagnosed after blood sampling and in individuals non-exposed to radiation and free of MNs (control)

Indicator	Workers with MNs, (n = 22) *M*; *SD* [*CI* 95 %] (*Median*; min–max)	Control, (n = 72) *M*; *SD* [*CI* 95 %] (*Median*; min–max)	*p*-value*
NK-cells, × 10^6/l (CD3-CD16+CD56+) Reference range: 123–369	359.6; 228.5 [258.3–460.9] (294.0; 57.0–1006.0)	299; 237.3 [243.3–354.8] (227.2; 37–1448)	0.1129
NK-cells, % (CD3-CD16+CD56+) Reference range: 9–21	16.4; 9.4 [12.3–20.6] (16.3; 3.7–34.9)	14; 25.9 [7.9–20.1] (9.3; 2.1–224.7)	0.0241*
T–NK-cells, × 10^6/l (CD3+CD16+CD56+) Reference range: 7–165	105.2; 119.8 [52.1–158.4] (50.5; 4.0–411.0)	77.3; 103.7 [52.9–101.6] (50.5; 7–838)	0.8582
T–NK-cells, % (CD3+CD16+CD56+) Reference range: 1–6	4.7; 5.0 [2.5–7.0] (2.8; 0.2–14.8)	2.7; 1.9 [2.3–3.1] (2.2; 0.5–8.8)	0.6423
B-lymphocytes, × 10^6/l (CD3-CD19+) Reference range: 111–376	162.1; 100.8 [117.4–206.8] (139.5; 51.0–451.0)	292.9; 536 [167–418.9] (211; 12–4610)	0.0265*
B- lymphocytes, % (CD3-CD19+) Reference range: 7–17	7.6; 6.1 [4.9–10.3] (5.7; 2.0–31.5)	9.8; 5.2 [8.6–11] (8.9; 0.6–36.3)	0.0061*
T- lymphocytes, × 10^6/l (CD3+CD19-) Reference range: 946–2079	1565.2; 618.2 [1291.1–1839.3] (1370.5; 788.0–3501.0)	1988.4; 1045.4 [1742.7–2234.1] (1846; 836–9398)	0.0075*
T- lymphocytes, % (CD3+CD19-) Reference range: 61–85	69.5; 11.8 [64.2–74.7] (69.8; 49.5–88.5)	76; 8.6 [74–78.1] (75.8; 47.9–91.7)	0.0199*
T–h (helpers), × 10^6/l (CD3+CD4+) Reference range: 576–1336	888.1; 320.2 [746.1–1030.1] (847.5; 450.0–1814.0)	903.2; 402.3 [808.7–997.7] (877; 260–3378)	0.6045
T–h (helpers), % (CD3+CD4+) Reference range: 35–55	40.1; 8.5 [36.3–43.8] (37.9; 26.4–54.3)	35.3; 8.7 [33.3–37.4] (34.2; 14.8–57.5)	0.0290*
T–c (cytotoxic), × 10^6/l (CD3+CD8+) Reference range: 372–974	598.5; 286.1 [471.6–725.3] (573.5; 166.0–1114.0)	638.8; 467 [529.1–748.6] (560.5; 167–3874)	0.9644
T–c (cytotoxic), % (CD3+CD8+) Reference range: 19–35	26.8; 10.9 [22.0–31.7] (28.4; 8.1–45.1)	23.3; 6.5 [21.7–24.8] (23.9; 8.7–41.7)	0.1181

N o t e: * means estimated as per the Mann – Whitney test.

Workers chronically exposed to combined radiation and free of MNs in pre- and postmorbid medical histories had elevated relative T-cytotoxic lymphocyte levels compared to the control. This is also consistent with findings reported in other studies[3] [10, 21]. Cytotoxic CD8+ T-cells are basic anti-tumor ones. During priming and activation by antigen-representing cells, CD8+ T-cells are differentiated into cytotoxic T-lymphocytes. They perform an effective attack of a tumor, which usually ends in direct destruction of tumor cells by exocytosis of perforin- and granzyme-containing granules [22]. Occurrence of infiltrating CD8+ T-cells and Th-1 cytokines in a tumor correlates with a favorable prognosis for many tumors [23]. Elevated levels of cytotoxic T-lymphocytes in exposed workers without malignancies in their case history can, therefore, be considered a factor preventing tumor progression.

A role that belongs to B-lymphocytes in tumor progression is less clear than that of T-cells. Literature data indicate that B-lymphocytes promote carcinogenesis [24]. Different pathways were described to explain this tumor-promoting role of B-lymphocytes, from immunosuppression through secretion of IL-10 [25] and TGFβ [26] to direct stimulation of proliferation of tumor cells by IL-35 produced by B-cells in pancreatic neoplasia [27]. Also, B-cells stimulate angiogenesis and chronic inflammation by depositing immunoglobulins in a tumor [28]. A decrease in relative B-cell levels in workers chronically exposed to combined radiation with later developed MNs can be considered a favorable sign since these cells promote carcinogenesis.

Comparative analysis of cellular immunity indicators between workers chronically exposed to combined radiation with MNs and the control individuals revealed a higher relative level of natural killers, which might be a sign of intensified anti-tumor protection as a response to effects produced by tumor antigens.

Therefore, our findings indicate that radiation exposure modifies various components of the cellular immunity. Effects of the ionizing radiation on lymphocyte subpopulations are controversial since changes in their counts and rates have both stimulating and inhibiting impacts on MNs. However, given the fact that T-lymphocytes are considered the main anti-tumor effector by most researchers and that their level goes down due to the exposure to ionizing radiation, we can conclude that ionising radiation has a negative impact on the cellular immunity of nuclear workers due to chronic occupational exposure to ionizing radiation.

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