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Genetic Differences in Immune Reactions to Radiation Exposure in Humans and Experimental Animals

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Examination of populations living in regions of fallout radiation revealed changes in the distribution of HLA genes not only in irradiated individuals, but also in their children and grandchildren. Combined irradiation of inbred mice in comparable doses showed that H-2 genes determine immune reactions in animals and their offspring to radiation. Our results indicate that the immune system in mammals is immunogenetically regulated by low-dose radiation.

Key Words: *radiation; immune system; major histocompatibility complex genes*

Delayed consequences of nuclear accidents lead to severe health disorders in people inhabiting irradiated areas [5]. These diseases are related to disturbances in the immune system, which is characterized by highest radiosensitivity. Immunopathological changes serve as a biological criterion for the severity of radiation injuries. This opens the way to immunocorrection and immunoprevention of radiation-induced disorders.

The severity and type of disturbances differ between people exposed to irradiation of the same type and dose. Moreover, randomized clinical trials showed that people inhabiting the same irradiated area have various diseases [6]. This is probably related to differences in the initial immune state and health in irradiated people. It cannot be excluded that endogenous constitutive factors determine the reaction of humans to adverse ecological factors, *i. e.*, radiation exposure.

High polymorphism in major histocompatibility complex genes (HLA in humans and H2 in mice) providing the intensity of the immune response to a variety of exo- and autoantigens is an endogenous factors determining different immune reactions to radiation. Allele variants of these genes (genes of the immune response) are associated with various human diseases and immune parameters [1].

Here we studied the effects of radiation factors at the Semipalatinsk test range on the immunogenetic structure in people inhabiting the area of fallout radiation (physically demonstrated) in the Altai region. Immune parameters in inbred mice exposed to radiation at the Kurchatov testing area were evaluated.

MATERIALS AND METHODS

Residents of the Uglovskii region (Altai) exposed to high-dose irradiation (n=288) and 100 residents of the Tyumen region beyond the zone of nuclear fallout were examined using the method of HLA serological typing [1]. Immunogenetic examination of people inhabiting the Tyumen region served as the control. We found no differences in the incidence of HLA antigens in residents of the Tyumen region and European people living in other West Siberian regions. We also examined children (n=115) and grandchildren (n=32) of main group people. The effective dose of irradiation was 50-100 cSv.

Proliferative activity of cells in small intestinal crypts, colony-forming properties of bone marrow cells, number of antibody-producing cells in the spleen, and expression of interleukin-1 (IL-1) and IL-6 genes in

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lymphocytes and epithelial cells of the small intestine were evaluated in BALB/c and C57Bl/6 mice and their first-generation offspring [4]. The dose of irradiation varied from 5 to 100 cSv.

RESULTS

The incidence of HLA gene alleles in residents of irradiated areas and their offspring markedly differed from that in a representative control population and Europeans [8].

The incidence of some HLA antigens considerably decreased in people exposed to radiation (Table 1). We found a decrease in the incidence of HLA-DR1 and HLA-DR4 antigens associated with autoimmune disorders (relative risks RR=-2.3 and -5.3, respectively).

These results indicate that considerable changes in the population 40 years after radiation exposure were related to elimination of certain genotypes. These changes in the population structure can be associated with high mortality rate in people carrying certain HLA gene alleles and their migration from irradiated regions. The incidence of individual HLA antigens or their combinations decreased in several generations of offspring. The phenomenon was not found in residents of the Tyumen region, which suggests that people carrying certain HLA antigens were excluded from reproduction due to radiation exposure. High incidence of other immunogenetic parameters in people inhabiting irradiated areas in the Altai region reflects not only compensatory changes, but also the resistance of people to radiation.

To test this hypothesis, we examined 3 generations of humans living in irradiated areas of the Altai region. The incidence of HLA gene alleles changed in 3 generations of offspring. The first-generation group included adult people living in settlements during nuclear tests at the Semipalatinsk range. The second- and third-generation groups consisted of their children and grandchildren, respectively. Table 2 represents HLA antigens and their combinations, whose incidence differed from the control for at least 1 generation (statistically significant).

Our results require detailed investigations combined with studies of the morbidity rate in 3 generations and comparison of the immunogenetic prognostic criteria with the incidence of HLA antigen-associated diseases. The incidence of various immunogenetic parameters was characterized by different deviations. These differences included an increase or decrease in the incidence of some parameters in the population (compared to the control). These deviations were probably associated with not only migration, selective mortality, and morbidity, but also the involvement of people carrying new HLA antigens and not exposed to radiation into the reproductive process.

The incidence of HLA-DR1 and HLA-DR4 antigens associated with autoimmune rheumatoid arthritis markedly decreased in 3 generations of people inhabiting irradiated areas. These changes were found in people living in the Uglovskii region during nuclear tests and their children. It remains unknown why the incidence of HLA-DR1 and HLA-DR4 antigens tended to normal in their grandchildren. It should be emphasized that independently on the dose of irradiation, the incidence of arthropathies and bone and muscle diseases increased more than by 2 times in men and women living in irradiated areas to August 1949 (older than 15 old) [5]. The incidence of HLA-DR5 antigen associated with hemopoietic disorders in Europeans (primarily, disturbances in the erythroid system) [3] increased in the following order: generation I<generation II<generation III.

In the first-generation offspring of people living in the Uglovskii region the incidence of HLA-A19, HLA-B16, and HLA-DR4 antigens decreased by 7, 5, and 2 times, respectively, compared to that in residents of the Tyumen region. HLA-B17 antigens were not found in these people. However, the first-generation

TABLE 1. Incidence of HLA Antigens in People Inhabiting the Area of Radiation Exposure (%)

HLA	Residents of the Uglovskii region	Regional control
Cw 3	7.45	31.22
Cw 4	9.94	55.27
Cw 6	0.00	4.01
DR1	13.04	25.14
DR4	4.75	21.70
DR5	24.22	35.48
C3w-Cw4	1.24	14.35
A1-Cw4	1.86	9.25
A2-Cw3	4.97	17.72
A2-Cw4	3.73	27.64
A3-Cw4	3.73	16.03
A9-Cw3	0.62	9.28
A9-Cw4	3.73	18.35
A10-B18	11.80	3.72
A11-Cw4	0.62	8.02
B0-Cw3	1.24	9.49
B0-Cw0	1.24	20.46
B5-Cw4	1.24	14.75
Cw4-DR5	1.86	15.21

Note. Significant differences compared to the control (p<0.05 and higher).

TABLE 2. Incidence of HLA Antigens in 3 Generations of People Inhabiting the Uglovskii Region and Exposed to Radiation (%)

HLA	Control	Generations		
		I	II	III
A1	23.00	32.22*	28.13	9.38
A3	34.00	18.89*	26.56	43.75
A9	18.00	28.89*	28.13*	15.63
A19	12.00	1.11*	1.56	15.63*
B15	15.00	8.89	4.69*	3.13
B41	2.00	6.67	9.38*	15.63*
Cw2	12.00	24.44*	9.38	18.75
Cw3	29.00	8.89*	10.94*	9.38*
Cw4	41.00	1.11*	0*	0*
Cw5	15.00	5.56*	1.56*	15.63
DR1	36.00	16.67*	7.81*	15.63*
DR4	20.00	8.89*	6.25*	15.63
DR5	20.00	32.22*	32.81*	43.75*
DR7	32.00	43.33*	54.69*	6.88

Note. *Significant differences compared to the control ($p<0.05$ and higher).

offspring was characterized by a higher incidence of HLA-B13, HLA-B14 (by 4 times), and HLA-B27 antigens associated with joint diseases (by 2 times) [7].

In the second-generation offspring of people living in the Uglovskii region the incidence of HLA-A19, HLA-A16, HLA-B17, and HLA-DR4 antigens decreased to a lesser degree than in the first-generation offspring. The incidence of HLA-B13, HLA-B14, and HLA-B27 antigens only slightly increased in these people. We revealed an increase in the incidence of HLA-DR3 antigen associated with autoimmune disorders. It should be emphasized that people living in various areas of the Altai region were not informed about fallout radiation to the beginning of the 1980s. Therefore, chronic psychoemotional stress and radiophobia typical of people inhabiting areas of radiation accidents did not affect demographic processes.

Our results suggest that radiation exposure markedly changes the incidence of major histocompatibility complex antigens not only in irradiated people, but also in their second- and third-generation offspring. Probably, human HLA genotype determines radioresistance and sensitivity of people to postirradiation immune diseases.

To test this hypothesis, we compared the effects of combined ionizing radiation on functional immune parameters in BALB/c and C57Bl/6 mice differing in gene alleles of H-2 histocompatibility complex.

In irradiated BALB/c mice the decrease in colony-forming activity of bone marrow cells was more pronounced than in C57Bl/6 mice. We studied functional activity of cells in the small intestine. Proliferative activity of cells in small intestinal crypts decreased in C57Bl/6 mice irradiated with 15 rad. However, in BALB/c mice this parameter decreased only after irradiation with 105 rad. In intact BALB/c mice IL-1 genes were not expressed in crypt cells. In C57Bl/6 mice IL-1 gene expression was inhibited after irradiation with 105 rad.

In the first-generation offspring of irradiated BALB/c mice functional activity of bone marrow cells slightly decreased, while the number of antibody-producing cells in the spleen increased (as differentiated from the offspring of irradiated C57Bl/6 and (BALB/c× C57Bl/6)F_1 mice). The intensity of IL-1 expression in lymphoid cells decreased in the offspring of both mouse strains and their hybrids. Proliferative activity of cells in small intestinal crypts markedly decreased in the offspring of C57Bl/6 mice irradiated with 15 rad (as distinct from the offspring of BALB/c mice and their first-generation hybrids).

Our results demonstrate interstrain differences in the reaction of animals with various H-2 complex gene alleles to radiation exposure. The highest radiosensitivity was typical of immune cells in BALB/c mice. However, in C57Bl/6 mice epithelial cells of the small intestine were most radiosensitive. It should be emphasized that the offspring of irradiated mice was characterized by not only functional changes in the immune and epithelial systems, but also interstrain differences in radiosensitivity.

Observations of uninformed people and experiments with linear mice indicate that allelic polymor-

phism in the major histocompatibility complex genes determines the reaction to radiation exposure. These genes probably regulate the main components of the immune system that determine the resistance, morbidity, aging, mortality, and reproductive activity of organisms.

Our results are of considerable theoretical importance. These data can used to develop immunogenetic prognostic criteria for radiosensitivity, which would decrease the risk of diseases in people professionally exposed to radiation.

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