SOMATIC GENE MUTATIONS IN PATIENTS WITH BENIGN TUMORS LIVING IN RADIATION CONTAMINATED REGIONS

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Radiation-induced somatic cell mutations are likely to be the principal cause of cancer risk elevation after radiation exposure. Therefore, estimation of frequency of cells with gene mutations has been suggested to be a useful method for cancer risk assessment in irradiated individuals [1,2]. One of the methods for estimation of somatic mutagenesis level is determination of mutant cell frequency at T-cell receptor (TCR) locus. Although mutations at this locus are not directly related to carcinogenesis, they are likely to reflect probability of cancer-associated mutations. To confirm this suggestion we evaluated the TCR-mutant cell frequency in group at high risk in respect to oncological diseases. The aim of this study was to research level of somatic mutagenesis in women with benign tumors of reproductive system living in radiation contaminated regions in comparison with control healthy individuals.

Materials and Methods

139 persons were investigated and divided in two groups. The first group consisted of 97 patients with myoma who had been living in Novozibkovskiy region of Bryansk oblast during 18 years since the moment of the Chernobyl accident. The residents were 0-30 years old at the moment of the Chernobyl accident. Mean $^{137}$Cs density in this region was 799kBq/m$^2$. The second (control) group included 42 age-matched unexposed healthy individuals.

Flow cytometry was used to evaluate the frequency of peripheral blood lymphocytes bearing mutations at the TCR locus as it as described earlier in details [3]. Number of variant (or TCR-mutated) lymphocytes is determined by means of enumeration of the CD4+(positive) cells lacking the CD3 antigen on their surface. Studies performed by the inventors of the assay, S. Kyoizumi and associates from RERF (Hiroshima, Japan), have demonstrated that the absence of the CD3 on the CD4+ cells was mainly due to alterations of the TCR underlain by the mutations of the genes encoding the TCR polypeptides. Following these findings, the test has been termed the “TCR assay” [4]. Such mutations occur in mature lymphocytes after the passage through the thymus, as cells with defective TCR are eliminated in the gland by apoptosis and cannot enter the bloodstream.
Results and Discussion

The mean frequency of the TCR variant cells was significantly higher in patients with myoma (n=97) than in controls (n=42): $(5,3\pm0,5)\times10^{-4}$ vs $(4,0\pm0,2)\times10^{-4}$ on average ($p<0.05$, Mann-Whitney test). 18 patients (18,6%) had the TCR–mutant cell frequencies exceeding the 95% confidence interval in control group ($>7,0\times10^{-4}$). The frequencies of mutant cells in other patients corresponded to those in control group.

Data on the frequency of the TCR variant cells in the inhabitants of radiation-contaminated regions and age-matched control donors are presented in Table 1.

Table 1. Frequency of the TCR mutant cells in unexposed control donors and residents of Bryansk oblast contaminated with radionuclides as a result of the Chernobyl disaster

<table>
<thead>
<tr>
<th>Study groups</th>
<th>Number of persons</th>
<th>Age at the moment of analysis, yr</th>
<th>TCR mutant cell frequency, $\times10^{-4}$</th>
<th>Range</th>
<th>Mean</th>
<th>Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residents with myoma 18 years after the Chernobyl accident</td>
<td>97</td>
<td>20-65</td>
<td>1,1 -52,9</td>
<td></td>
<td>44</td>
<td>5,3±0,5a</td>
</tr>
<tr>
<td>Unexposed control donors</td>
<td>42</td>
<td>40-50</td>
<td>1,0-10,0</td>
<td></td>
<td>45</td>
<td>4,0±0,2</td>
</tr>
</tbody>
</table>

a$p<0.05$ as compared to unexposed controls by t-test

Number of mutations is known to increase with radiation dose at any genetic locus tested. Therefore, elevated TCR-mutant cells frequencies in an individual may imply higher probability of the occurrence of cells harboring gene mutations at loci that eventually may cover critical oncogenes and tumor suppressors. It was plausible to suggest that individuals with elevated TCR-mutant cells scores might belong to a high-risk group potentially prone to the development of neoplasm. As an argument demonstrating such reasoning, one may mention results of a study performed in Scandinavia [5]. During a long-term epidemiological investigation, cancers were found to occur more often in a cohort of individuals with elevated level of chromosomal aberrations. Similar investigations of cancer incidence in the individuals with elevated rates of gene mutations have not been published so far. At the same time, data on high and early onset of cancer in patients with inherited genome instability syndromes (ATM, Bloom’s syndrome, etc.) who also have elevated frequency of spontaneous gene mutations are well known [6,7]. The rationale of the hypothesis was indirectly demonstrated in our work: resident of Bryansk oblast
with benign tumors of reproductive system had statistically significant higher levels of variant cells than individuals from the control groups.

Conclusion

The significant elevation of the TCR-mutant frequency was observed in the certain proportion of persons with benign tumors of reproductive system who belonged to high risk cancer group. Our results confirm that the TCR-method may be used for individual assessment of long-term health consequences after the irradiation. Individuals with elevated TCR-mutant cell scores might belong to high-risk group potentially prone to the development of neoplasm and need more thorough medical observation than the rest of population.

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References