II. 研究成果の刊行に関する一覧表

＜平成18年度＞

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
Kusunoki Y, Hayashi T and Nakachi K	T-cell homeostasis and inflammatory response among A-bomb survivors	Tanaka S, Fujikawa F, Oghiso Y	Low-Dose Radiation Exposures and BioDefense System	The Institute for Environmental Sciences	Aomori	2006	13-17

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III. 研究成果の刊行物・別刷

T-Cell Homeostasis and Inflammatory Response among A-Bomb Survivors

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ABSTRACT

More than 50 years after damage to their immune systems by A-bomb radiation, we still find significant alterations in T-cell immunity among survivors. To test the hypothesis that immune reconstitution of T-cell homeostasis following radiation damage might have been incomplete and/or deteriorated, we evaluated the ability of individual subjects to maintain naïve and memory T-cell pools. It was suggested that there might be a dose-dependent decrease in the number of T-cell receptor rearrangement excision circles in the CD4 T-cell fraction of the survivors. Although maintenance of memory T-cell pools of A-bomb survivors appeared to be close to normal in terms of size, T-cell repertoire deviation possibly associated with clonal expansion of T-cell populations was also suggested. It seems likely that A-bomb radiation exposure perturbed the mechanisms responsible for T-cell homeostasis, by impairing the ability to maintain naïve T-cell pools with a supply of new T cells from the thymus and also by inducing clonal expansion of a small fraction of T cells, which may lead to a long-term reduction in the diversity of T-cell repertoire in memory T-cell populations. In addition, we found that the plasma levels of the inflammatory cytokines IL-6, TNF-α, and IFN-γ appeared to increase with A-bomb radiation dose. It was concluded that perturbation of T-cell homeostasis associated with reduced immune function might have lead to long-lasting inflammation among A-bomb survivors.

INTRODUCTION

The immune systems of A-bomb survivors were dose-dependently damaged 60 years ago, mainly due to radiation-induced cell death. Although the systems of the survivors regenerated as the hematopoietic system recovered from the radiation damage, we can still observe significant immunological alterations among A-bomb survivors, including impairments in both T-cell proliferation ability to respond to mitogens *(1, 2)* and alloantigens *(3)* and the frequency of T cells bearing the IL-2 production capability *(4, 5)*, and a decrease in CD4 T-cell population *(6)*. Based on these observations, we hypothesized that immune reconstitution to restore T-cell immunological homeostasis following radiation damage might have been incomplete and/or deteriorated. Two distinct mechanisms are possibly involved in ensuring immune reconsitution after T-cell depletion by radiation *(7)*: The first mechanism depends upon renewed proliferation of surviving mature T cells that can repopulate the memory T-cell pool, whereas the second relies upon the differentiation of hematopoietic stem cells into the new T cells that comprise the naïve T-cell pool. In the present study, we first evaluated the sizes of naïve and memory T-cell populations among A-bomb survivors. We also examined the number of T-cell receptor rearrangement excision circles (TRECs), which are markers of recently produced T cells in the thymus, to investigate whether the impairment in the ability to maintain normal-sized CD4 T-cell pools among A-bomb survivors could have resulted from an insufficient supply of new CD4 T cells from the thymus.

A major question remains: Are the immunological changes detected in A-bomb survivors associated with disease development? The key to addressing this question is persistent inflammation that may be involved in the perturbation of T-cell homeostasis. It is noteworthy that advancing age accompanied by alterations in the immune system — particularly age-dependent decreases of T-cell count and function — can lead to persistent infections and chronic inflammation *(8)*. In the present study, we therefore examined inflammatory cytokine levels among A-bomb survivors.

MATERIALS AND METHODS

Study population

Blood samples were obtained from individuals of an A-bomb survivor cohort in which 1,280 survivors, distributed almost equally by age, gender, and radiation dose, had been selected from Hiroshima participants in the Adult Health Study (AHS) at the Radiation Effects Research Foundation (RERF) in 1992 *(2)*. Blood samples were obtained with the informed consent of the survivors. We obtained approval from the Human Investigation Committee at RERF before the work was started.

Flow cytometry

Analytical flow cytometry was conducted using a FACScan machine (BD Biosciences, San Jose, CA, USA). CD45RO and CD62L expressions were analyzed using a combination of FITC-labeled anti-CD45RO antibody (CALTAG Laboratories, Burlingame CA, USA), PE-labeled anti-CD62L and PerCP-labeled anti-CD4 or PerCP-labeled anti-CD8 antibodies (BD-PharMingen, San Diego, CA, USA). $CD45RO^{-}/CD62L^{+}$ naive,

$CD45RO^+$ and $CD45RO^-/CD62L^-$ memory cell fractions in CD4 and CD8 T-cell populations were determined using the Cell Quest software (BD Biosciences). Note that we used only CD8-bright expression to identify CD8 T cells in order to exclude NK cells which are dully CD8 positive.

Measurement of TREC numbers

TRECs in 1 x 10^5 cells from each CD4 or CD8 T-cell fraction were enumerated by the real-time PCR method previously reported by Yasunaga, et al *(9)* with some modifications. To measure cell equivalents in the real-time PCR, *RAG-1* sequence in each sample was similarly quantified. All experiments were performed and analyzed using ABI PRISM 7900 Sequence Detection Systems (Applied Biosystems, Foster City, CA). The number of TRECs in each sample was calculated using the following formula:

Number of TREC copies per 10,000 cells

= 10,000 / 2 (cycles required for the significant amplification of TREC) - (cycles required for the significant amplification of *RAG-1*) - 1

Measurement of cytokine levels in the plasma

Plasma samples were obtained from heparinized blood and stored at –80 °C until use. Levels of TNF-α, IFN-γ, IL-6 and IL-10 in the plasma were measured in duplicate using a highly sensitive enzyme-linked immunosorbent assay kit (Quantikine HS, R&D systems, Minneapolis, MN).

RESULTS

Naïve and memory T-cell populations among A-bomb survivors

In the present study, we used double labeling with CD45RO and CD62L to ensure reliable identification of naïve and memory cell subsets in both CD4 and CD8 T-cell populations among 533 Hiroshima A-bomb survivors (Table 1). In the CD4 T-cell population, the percentage of naïve cells significantly decreased with age ($P < 0.01$) or increased radiation dose ($P < 0.05$), and a decrease in the percentage of naïve CD8 T cells was also statistically significant with age ($P < 0.01$) or dose ($P < 0.05$). And for CD8, but not CD4, T-cell population, the percentages of memory T cells in PBL were found to significantly increase with age for A-bomb survivors ($P < 0.01$). Furthermore, the percentages of memory T cells were found to significantly increase with increasing radiation dose in the CD8 T-cell population ($P < 0.05$), but not in the CD4 T-cell population. These results indicate that previous A-bomb exposure has induced long-lasting deficits in both naïve CD4 and CD8 T-cell populations along with an increased proportion of memory CD8 T-cell population.

Table 1. Alterations in the size of peripheral T-cell pools among 553 A-bomb survivors

T-cell subsets	Factors (unit)	
	Age (10 years)	Radiation (Gy)
CD4 total	Decrease (5.0%)*	Decrease (2.0%)
Naïve	Decrease (7.5%)	Decrease (4.5%)
Memory	Not significant	Not significant
CD8 total	Not significant	Not significant
Naïve	Decrease (42.3%)	Decrease (7.7%)
Memory	Increase (7.3%)	Increase (5.6%)

*Associations of percentage of each lymphocyte subpopulation with age at the time of examination, gender, and the radiation dose were analyzed based on a multiple-linear-regression model.

TREC analyses among A-bomb survivors

The number of TREC copies in CD4 T-cell fractions from 445 survivors and that in CD8 T-cell fractions from 426 survivors were examined: The number of TREC copies significantly ($P < 0.01$) decreased with age in both the CD4 and CD8 T-cell fractions. Multiple regression analysis was conducted for the number of TREC copies in the CD4 or CD8 T-cell fraction among survivors who were less than 20 at the time of the bombing (ATB), since the individual TREC number in this group appeared to be close to the normal distribution (especially in the CD4 T-cell fraction). As shown in Fig.1, there appeared to be a dose-dependent decrease in the number of TRECs in the CD4 T-cell fraction of the survivors ($P < 0.1$), and the number of TRECs in the CD8 T-cell fraction of the survivors also appeared to decrease somewhat with increased radiation dose, but this dose trend was not statistically significant ($P > 0.1$). There was a strong correlation ($r = 0.7$) between the numbers of TREC copies in the CD4 and CD8 T-cell fractions for the same survivors who were age ATB <20.

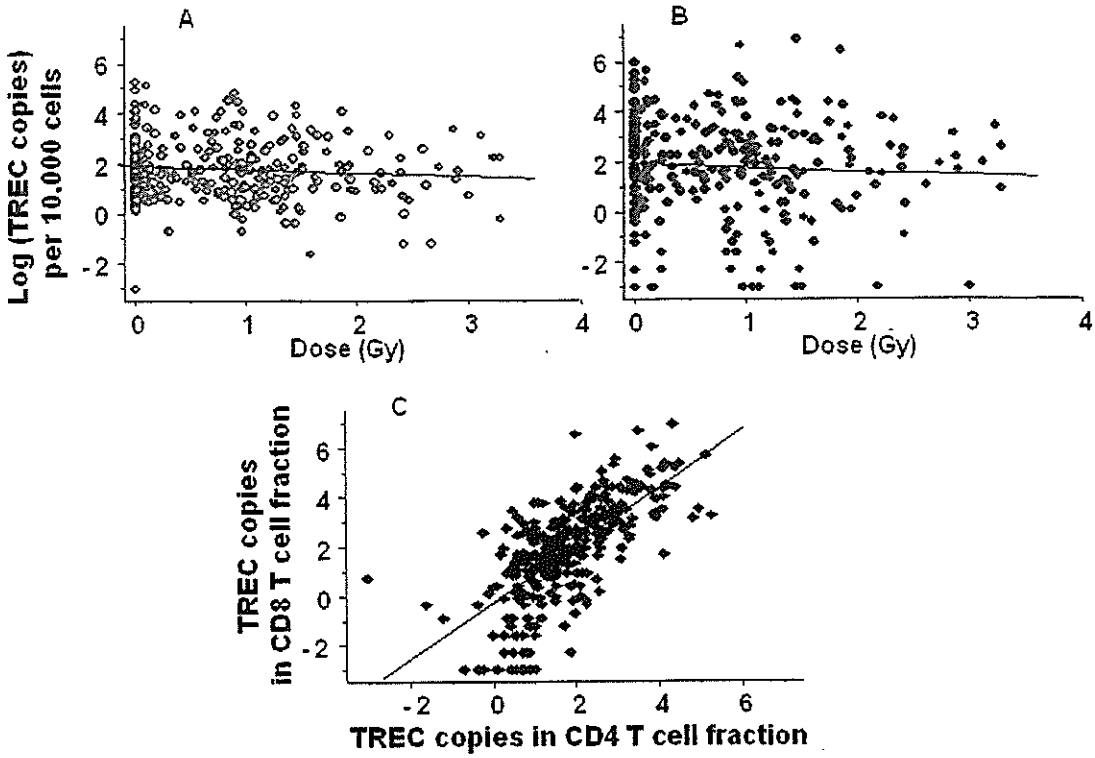

Figure 1. The number of T-cell receptor rearrangement excision circles (TRECs) in CD4 T-cell fractions from 313 individuals (panel A) and that in CD8 T-cell fractions from 300 individuals (panel B) among survivors who were age less than 20 at the time of the bombing (ATB). For the CD4 ($P < 0.1$) but not CD8 ($P > 0.1$) T-cell fractions, the radiation dose trend was suggestive. Pannel C: There was a strong correlation (r = 0.7) between the number of TREC copies in the CD4 and CD8 T-cell fractions from the same survivors who were age ATB <20.

Inflammatory cytokine levels among A-bomb survivors

The plasma levels of the inflammatory cytokines IL-6, IFN-γ, and TNF-α, and the anti-inflammatory cytokine IL-10 were examined among 442 A-bomb survivors (Table 2). In contrast to the age-dependent decreases in the proportion of naïve T-cell populations and the number of TRECs, plasma levels of IL-6, TNF-α, and IL-10 significantly increased with age among A-bomb survivors ($P < 0.01$). We also observed statistically significant dose-dependent increases in plasma levels of IL-6 ($P < 0.01$), TNF-α ($P < 0.01$), IFN-γ ($P < 0.01$), and IL-10 ($P < 0.05$).

Table 2. Alterations in the plasma cytokine levels among 442A-bomb survivors

Cytokines	Factors (unit)	
	Age (10 years)	Radiation (Gy)
IL-6	Increase (24%)*	Increase (13%)
IL-10	Increase (8%)	Increase (6%)
IFN-γ	Not significant	Increase (12%)
TNF-α	Increase (15%)	Increase (7%)

*Associations of each cytokine level with age at the time of examination, gender, and the radiation dose were analyzed based on a multiple-linear-regression model.

DISCUSSION

T-cell homeostasis is regulated and maintained by the balance between renewal and survival vs. death among naïve and memory T cells *(10)*. Naïve T-cell pools of A-bomb survivors are not appropriately maintained, probably because of lower proportions of naïve CD4 and CD8 T cells compared with those of unexposed controls of the same age. This may indicate that the naïve T cell pools insufficiently recovered after radiation-induced damage of the T cell system and did not reach normal size level. In this study, we also observed a dose-dependent decrease in the number of TRECs in CD4 T-cell fractions among A-bomb survivors. The results show a possibility that A-bomb radiation exposure induced long-term impairment in thymic CD4 T-cell production. To strengthen this hypothesis, we plan to investigate a larger study population.

In contrast to the naïve T-cell pools, the sizes of memory T cell pools of A-bomb survivors appeared to be almost normal (CD4), or somewhat larger (CD8) than those of controls. However, the extent of T-cell receptor

repertoire deviation in memory CD4 T cells appeared to significantly increase with increased radiation dose *(11)*. Further evidence for the perturbation of memory T-cell populations of A-bomb survivors was provided by studies unique to the Radiation Effects Research Foundation, which involved identification and characterization of clonally expanded T-cell populations using chromosome aberrations as genetic markers *(12)*. It is therefore likely that A-bomb radiation exposure perturbed the mechanisms responsible for T-cell homeostasis by impairing the ability to maintain naïve T-cell pools with a supply of new T cells from the thymus, and by inducing clonal expansion of a small fraction of T cells that may have lead to a long-term reduction in the diversity of T-cell repertoire in memory T-cell populations.

In this study, we found that the plasma levels of the inflammatory cytokines IL-6, TNF-α, and IFN-γ appeared to increase with increased A-bomb radiation dose. We also found that the plasma level of IL-6 was elevated significantly in survivors who had a lower percentage of peripheral blood CD4 T cells *(13)*, and that the prevalence of myocardial infarction was significantly higher in individuals who had reduced CD4 T-cell percentages *(14)* or elevated IL-6 levels *(13)*. These results suggest that pre-clinical inflammatory status linked to T-cell impairments may at least partly be involved in the development of the diseases, such as cardiovascular disease, which have been observed frequently in A-bomb survivor populations *(15, 16)*. In conclusion, we hypothesize that A-bomb radiation perturbed T-cell homeostasis and induced long-lasting inflammation, and that such immunological alterations might have lead in some way to disease development among A-bomb survivors. Clearly, prospective studies that will follow up the survivors who were examined for immunological and inflammatory endpoints will be required to directly test these hypotheses.

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ORIGINAL ARTICLE

Reg IV is a serum biomarker for gastric cancer patients and predicts response to 5-fluorouracil-based chemotherapy

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Regenerating gene family, member 4 (Reg IV), a secreted protein, is overexpressed in several cancers, including gastric cancer (GC). In the present study, we measured Reg IV levels in sera from patients with GC by enzyme-linked immunosorbent assay. We also examined the effect of forced Reg IV expression on the apoptotic susceptibility to 5-fluorouracil (5-FU). Forced expression of Reg IV inhibited 5-FU-induced apoptosis. Induction of Bcl-2 and dihydropyrimidine dehydrogenase was involved in inhibition of apoptosis. Among 36 GC patients treated with a combination chemotherapy of low-dose 5-FU and cisplatin, all 14 Reg IV-positive patients showed no change or disease progression. The serum Reg IV concentration was similar between healthy individuals (mean ± s.e., 0.52 ± 0.05 ng/ml) and patients with chronic-active gastritis (0.36 ± 0.09 ng/ml). However, the serum Reg IV concentration in presurgical GC patients was significantly elevated (1.96 ± 0.17 ng/ml), even at stage I. The diagnostic sensitivity of serum Reg IV (36.1%) was superior to that of serum carcinoembryonic antigen (11.5%) or carbohydrate antigen 19-9 (13.1%). These results indicate that expression of Reg IV is a marker for prediction of resistance to 5-FU-based chemotherapy in patients with GC. Serum Reg IV represents a novel biomarker for GC.
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Keywords: Reg IV; apoptosis; 5-fluorouracil; serum tumor marker; SAGE; gastric cancer

Introduction

Gastric cancer (GC) is one of the most common human cancers. Early detection remains the most promising approach to improve long-term survival of patients with GC. Assessment of tumor markers in serum may be useful for detection of GC. There are two available tumor markers for GC, carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9). However, CEA and CA19-9 are not suitable for early screening because preoperative positivity for these markers depends on the tumor stage at the time of detection (Kochi *et al.*, 2000). Therefore, there is an urgent need for new biomarkers for GC. Genes encoding transmembrane/secretory proteins expressed specifically in cancers may be ideal diagnostic biomarkers (Buckhaults *et al.*, 2001). Moreover, if the gene product functions in the neoplastic process, the gene is not just a biomarker but may also be a therapeutic target (Yasui *et al.*, 2004).

Despite improvements in cancer diagnosis and therapy, many patients are still diagnosed at the late stages of the disease, and the disease often recurs even after curative surgery. 5-fluorouracil (5-FU) is one of the most widely used chemotherapeutic agents for breast cancer, colorectal cancer (CRC), and GC (Longley *et al.*, 2003). Unfortunately, some patients showed a poor response, possibly owing to inefficiency of the chemotherapy. For effective treatment, identification of the patients who will respond well to a specific chemotherapy may be important. Therefore, it is also important to look for biomarker to predict patients' response to 5-FU in GC.

We previously performed serial analysis of gene expression (SAGE) of four primary GCs (Oue *et al.*, 2004) and identified several GC-specific genes (Aung *et al.*, 2006). Of these genes, Regenerating gene family (REG), member 4 (*REG4*, which encodes Reg IV) is a candidate gene for cancer-specific expression, at least in patients with GC. Reg IV, a member of the REG gene family, was originally identified by high-throughput sequencing of a complementary DNA (cDNA) library derived from inflammatory bowel disease patient (Hartupee *et al.*, 2001). Quantitative reverse transcription–polymerase chain reaction (PCR) analysis revealed that approximately 50% of GCs overexpress the *REG4* gene (Oue *et al.*, 2004). Although various normal tissues express *REG4* (Hartupee *et al.*, 2001), the levels of expression are much lower in normal tissues than in

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