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"Inverse Associations between Obesity Indicators and Thymic T-cell Production Levels in Aging Atomic-bomb Survivors"

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Study Findings

T-cell receptor excision circles, or TRECs, are circular molecules of DNA excised from chromosomes when T cells are produced in the thymus. They indicate new production of T cells, and their numbers, which decrease with aging, represent an immunological marker of thymic capacity to produce naïve T cells. In this study, low TREC numbers were found to be associated with diseases related to high body mass index (BMI) and obesity, such as diabetes and fatty liver. These results suggest the possibility that reduction of immunological competence associated with aging may be further accelerated by obesity.

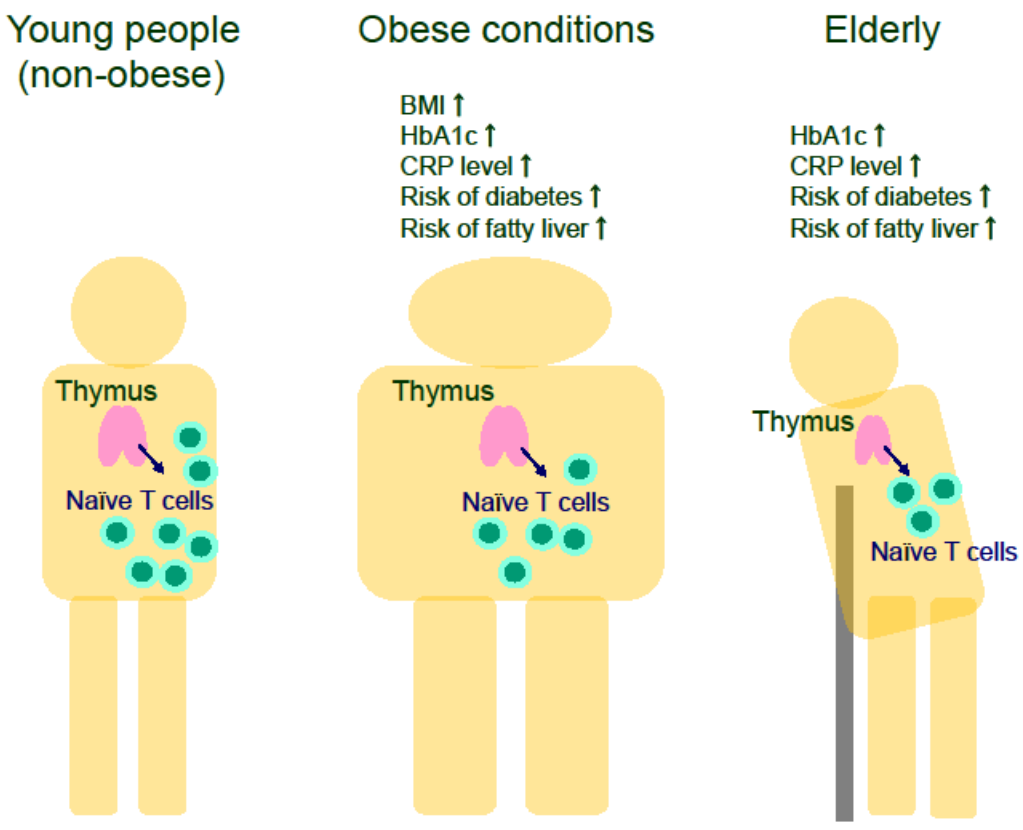

Figure. Relationship of naïve T-cell production levels to aging and obesity

Explanation

The production of T cells, which are blood cells with immunological functions, starts in the bone marrow and then continues in the thymus. In previous immunological studies at the Radiation Effects Research Foundation (RERF), the number of naïve T cells in peripheral blood was found to decrease after radiation exposure, leading to a hypothesis describing the mechanism behind this decline as the effect of radiation exposure on the ability of the thymus to produce naïve T cells.

Based on animal model studies conducted in recent years, obesity has been linked to the functional decline of the T-cell immune system associated with aging. However, findings based on studies of human populations were extremely limited.

We therefore conducted a study of RERF's Adult Health Study (AHS) participants, whose health has been followed for many years, in order to determine the effects of age, radiation dose, and obesity on indicators of thymic capacity to produce naïve T cells (TREC number).[Note]

> Note) TRECs, excised from chromosomes when T cells are produced in the thymus, are by-products of this process and characteristic of newly produced naïve T cells. Because they are not replicated by subsequent cell divisions in blood, TREC number can be used as an indicator of thymic capacity to produce naïve T cells.

1. Objectives

The objectives of the study were to examine the relationship between radiation exposure and TREC number, an indicator of thymus capacity to produce naïve T cells, and to determine the association of TREC number to obesity indicators and diseases associated with obesity, after adjusting for the effects of age, sex, radiation exposure, alcohol consumption, and smoking.

2. Methods

Among 1,073 A-bomb survivors who participated in the AHS from 2003 to 2009, we measured TREC number per 10,000 CD4 T cells (helper T cells, which control immune response) and per 10,000 CD8 T cells (killer T cells, which detect and destroy infected or transformed cells) in peripheral blood, utilizing polymerase chain reaction. We used information obtained from the AHS on BMI as an indicator of obesity, total cholesterol level, HbA1c level (which represents blood glucose levels over the previous 2–3 months), and CRP level (an indicator of inflammation), as well as diseases related to obesity (type 2 diabetes, fatty liver, and hypertension), alcohol consumption, and smoking. We conducted linear regression statistical analysis, with adjustment made for age, sex, radiation dose, amount of alcohol consumed, and number of cigarettes smoked.

3. Results

(1) Relationship between TREC number and age

Subject ages ranged from 58 to 109 years. Even in this elderly population, TREC number in CD4 and CD8 T cells decreased with age ($p < 0.001$ in terms of significance).

(2) Relationship between TREC number and radiation dose

Radiation exposure had no effect on TREC number in either CD4 or CD8 T cells. We also conducted a preliminary analysis by selecting, from among the 1,073 subjects, a high-dose group (radiation dose of at least 1 Gy) and a control group (radiation dose of less than 5 mGy), matched by such factors as age and sex, and then comparing the two groups. No difference in TREC number was observed in relation to radiation dose.

(3) Association between TREC number and obesity indicators

TREC number in CD4 and CD8 T cells significantly decreased with an increase of HbA1c and CRP levels ($p < 0.05$). TREC number also tended to be inversely associated with BMI. Further, TREC number was small in cases of diabetes and fatty liver ($p < 0.05$).

In this study, no association between TREC number and radiation exposure was observed, but TREC number was found to decrease with an increase in the levels of obesity indicators in a human

population. This result provides evidence to suggest that obesity may accelerate immunological aging in humans. Because obesity is known to increase the risk of several age-related diseases, attenuated immune competence due to the reduction in naïve T-cell production may be one of the developmental mechanisms of diseases associated with obesity.

The Radiation Effects Research Foundation has studied A-bomb survivors and their offspring in Hiroshima and Nagasaki for more than 60 years. RERF's research achievements are considered the principal scientific basis for radiation risk assessment by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) and for recommendations regarding radiation protection standards by the International Commission on Radiological Protection (ICRP). RERF expresses its profound gratitude to the A-bomb survivors and survivors' offspring for their cooperation in our studies.

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