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"Circulating hematopoietic stem and progenitor cells in aging atomic bomb survivors"

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Study Findings

Counts of hematopoietic stem and progenitor cells (HSPCs) in the blood of atomic bomb (A-bomb) survivors decreased with age, but no significant association with radiation dose was found.

Explanation

1. Study purpose

Hematopoietic stem cells (HSCs) are known to be highly radiosensitive. Deterioration in hematopoietic function and decrease in peripheral erythrocytes and leukocytes have been reported as some of the acute effects of radiation observed in A-bomb survivors. However, as a result of the regenerative capacity of HSCs, hematopoiesis among A-bomb survivors was reported to have recovered to a considerable extent about 10 weeks after A-bomb radiation exposure. Nonetheless, gene abnormalities such as mutations persist in the HSCs of A-bomb survivors even now, 70 years after radiation exposure. To determine whether or not effects of radiation persist in the HSC function of A-bomb survivors, this study examined the counts of circulating hematopoietic stem and progenitor cells per unit volume of blood, as well as their proportions vis-à-vis all HPSCs in blood, reviewing whether dose-dependent effects of radiation were observed.

2. Study methods

Peripheral blood was collected from 231 Hiroshima survivors (aged 66–91 years) who had participated in the Adult Health Study (AHS) during the period 2011–2013 and, using a cell sorter, separated CD34-positive/lineage marker-negative ($CD34^{+}Lin^{-}$) cells thought to contain HSPCs. The counts of the following types of colony-forming units in this cell population were evaluated using cell culture: cobblestone area-forming cells*; long-term culture-initiating cells*; erythroid burst-forming units*; granulocyte and macrophage colony-forming units*; and T-cell

and natural killer cell progenitors.* Cobblestone area-forming cells and long-term culture-initiating cells reflect the self-renewal and the multilineage differentiation functions of HSCs, respectively. Other colony-forming units reflect lineage-committed hematopoietic progenitor cells.

Cobblestone area-forming cells: Because these cells form an undifferentiated, cobblestone-like colony in the absence of hematopoietic factors and under the presence of stromal cells, they are thought to originate from self-renewable HSCs.

Long-term culture-initiating cells: Because these cells can produce erythroid burst-forming units and granulocyte and macrophage colony-forming units over a prolonged period, they are thought to originate from HSCs with capacity for multi-lineage differentiation.

Erythroid burst-forming units: Hematopoietic progenitors that can produce erythrocytes

Granulocyte and macrophage colony-forming units: Hematopoietic progenitors that can produce granulocytes and macrophages

T-cell and natural killer cell progenitors: Hematopoietic progenitors that can produce T lymphocytes or NK lymphocytes

3. Study results

(1) Association with age

We found that the counts of $CD34^{+}Lin^{-}$ cells, which are thought to include all HPSCs in blood, significantly decreased with age per unit volume of blood ($P = 0.0022$). Furthermore, the counts of respective colony-forming units significantly decreased with age ($P = 0.0001–0.0047$). As for the proportions of respective colony-forming units in the $CD34^{+}Lin^{-}$ cell population, only T-cell progenitors decreased with age ($P = 0.010$), suggesting an aging-related decline in the stem-cell function (capacity) of T-cell differentiation induction, even among subjects aged around 70 and older.

(2) Association with radiation dose

With regard to the $CD34^{+}Lin^{-}$ cell population and colony-forming units, no significant effects of radiation exposure were observed in either the absolute cell numbers per unit volume of blood or in their proportions vis-à-vis all HPSCs in blood.

Study Significance

Our findings showed that aging in HSC function continued, even among subjects aged around 70 and older. Specifically with regard to T cells, it is believed that decline in thymic function induces a decrease in mature peripheral naïve T cells.* This study, however, revealed that decline in the stem-cell function of T-cell differentiation induction due to stem cell aging was one reason for the aforementioned decrease. This study also suggests that the numbers and

function of HSPCs overall in living A-bomb survivors have recovered to normal levels even as the survivors aged over the decades since A-bomb radiation exposure (compared to the levels in unexposed individuals of the same ages).

Mature naïve T cells: Different from T-cell progenitors shown in the fifth line of (1) "Association with age" under the section titled "3. Study results," these cells are mature lymphocytes that arise by differentiation from T-cell progenitors in the thymic environment and differentiate into memory T cells in response to antigen stimulation in the periphery. This study suggested the possibility that aging of HSCs decreased production of T-cell progenitors, resulting in a decrease in thymic production of mature naïve T cells.

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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