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"Linkage between Dendritic and T-cell Commitments in Human Circulating Hematopoietic Progenitors"

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Study Findings

Dendritic cells (DCs) play an indispensable role in the differentiation and functional expression of T cells. These two types of cells differentiate from hematopoietic stem cells (HSCs), and the current study finds that the frequencies of T-cell and DC precursors are significantly linked with each other in stem cells existing in blood, whereas they are not linked to the precursor frequency (PF) of natural killer (NK) cells.

Explanation

1. Objectives

DCs are a type of leukocyte with dendrites. They initiate an adaptive immune response by conveying antigen information about viruses and bacteria that have invaded the body to T cells, which serve as a 'control tower' for the adaptive immune response. DCs also prevent the generation of self-antigen-responsive T cells in the thymus as a negative selection. Because self-antigen-responsive T cells recognize substances that make up their host body as antigens, these cells are detrimental. DCs are thus essential for the differentiation and functional expression of T cells. Based on this understanding, we hypothesized that there may be a correlation between the potency of HSCs to differentiate into DCs and their potency to differentiate into T cells, suggesting a linkage between DC and T-cell commitments. (HSCs are the least differentiated cells that can give rise to all blood cell types, are long lived, and have the ability to self-replicate.) Verifying this hypothesis was considered to provide important findings for ongoing studies of A-bomb survivors involving T-cell progenitors and DCs. DCs can be classified as conventional DCs (cDCs, which inform T cells of antigens to initiate direct attack) or plasmacytoid DCs (pDCs, which produce type-I interferon and induce anti-viral infection immunity). In the present study, we analyzed DC progenitors of both types.

2. Methods

It is possible to separate hematopoietic progenitor cells (HPCs, cells with the potency to differentiate into T cells and DCs) in human peripheral blood using a cell sorter, and then to differentiate HPCs into T cells and NK cells using the culture method reported in Kyoizumi *et al.*: *J Immunol* 2013; 190:6164–72. NK cells are a type of cytotoxic lymphocyte that is important for the innate immune system. Since the present study confirmed that this culture method could induce differentiation of HPCs into DCs, we used it as an experimental system to simultaneously assay T cells, NK cells, and DC progenitors. Blood samples were collected, based on informed consent, from 20 RERF in-house volunteer donors aged 26–65 years, and we measured the PFs of T cells and NK cells, as well as cDCs and pDCs, based on the culture method, to examine correlations among the PFs of these cells. Furthermore, we examined the potencies of single precursor cells to differentiate into T cells and NK cells, as well as cDCs and pDCs, based on precursor cell clonal culture.

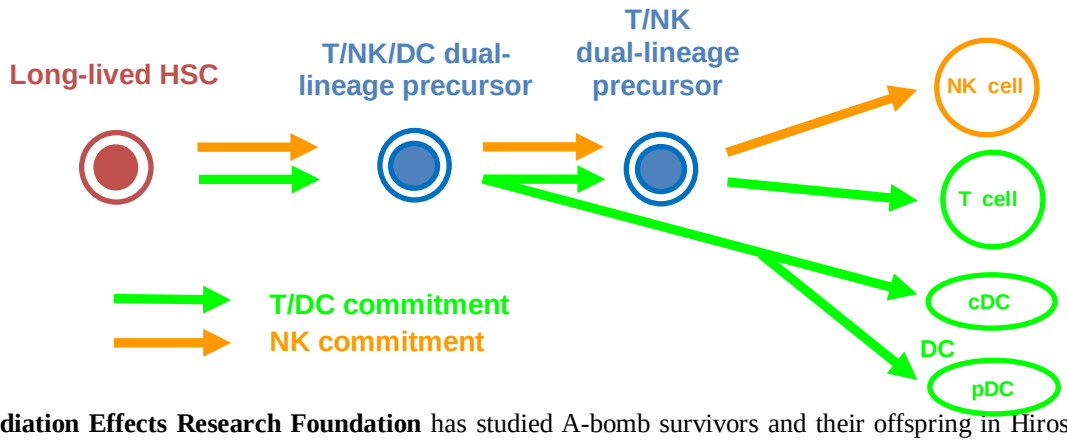
3. Results

(1) The PFs of cDCs and pDCs in HPCs were found to correlate significantly with T-cell PFs, but not with NK-cell PFs.
(2) The precursors producing T cells and NK cells were classified into clones producing T/NK dual-, T single-, and NK single-lineage precursors. The clones of T/NK dual- and T single-lineage precursors produced cDCs or pDCs at high frequencies. The clones of NK single-lineage precursors, however, produced very few cDCs or pDCs.

4. Consideration and Conclusion

These findings show that T-cell and DC commitments are linked with each other, as indicated with the green lines below. On the other hand, this research suggests that NK-cell commitment is induced independently from DC commitment. In addition, the linkage between T-cell and DC precursors might be intrinsically imprinted in long-lived HSCs existing in bone marrow that are self-replicating, since the T-cell and DC progenitors in the human body have short life spans.

Note: Progenitors are specific cells, generated from stem cells, that are able to differentiate into more specific types of 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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