Naive CD4 T Cells Highly Expressing the Inflammatory Chemokine Receptor CXCR3 Increase with Age and Radiation Exposure in Atomic Bomb Survivors

Authors: Yoshida, Kengo, Misumi, Munechika, Yamaoka, Mika, Kyoizumi, Seishi, Ohishi, Waka, et al.

Source: Radiation Research, 201(1) : 71-76

Published By: Radiation Research Society

URL: https://doi.org/10.1667/RADE-23-00065.1

RADIATION RESEARCH **201**, 71–76 (2024)
0033-7587/24 $15.00

DOI: 10.1667/RADE-23-00065.1

Naive CD4 T Cells Highly Expressing the Inflammatory Chemokine Receptor CXCR3 Increase with Age and Radiation Exposure in Atomic Bomb Survivors

Kengo Yoshida,[a,1] Munechika Misumi,[b] Mika Yamaoka,[a] Seishi Kyoizumi,[a] Waka Ohishi,[c] Hiromi Sugiyama,[d] Tomonori Hayashi,[a] Yoichiro Kusunoki[a]

Departments of [a] Molecular Biosciences, [b] Statistics, [c] Clinical Studies, [d] Epidemiology, Radiation Effects Research Foundation, Hiroshima

Yoshida K, Misumi M, Yamaoka M, Kyoizumi S, Ohishi W, Sugiyama H, Hayashi T, Kusunoki Y. Naive CD4 T Cells Highly Expressing the Inflammatory Chemokine Receptor CXCR3 Increase with Age and Radiation Exposure in Atomic Bomb Survivors. Radiat Res. 201, 71–76 (2024).

The numbers of naive T cells that react to novel pathogens not yet encountered by an immune system, decrease during aging, mainly due to age-associated involution of the thymus. CD45RA$^+$ naive CD4 T cells consist of heterogeneous populations, including highly CXCR3-expressing cells that appear during the homeostatic proliferation of naive T cells and exhibit enhanced type-1 inflammatory phenotypes. Based on previous evidence of radiation-associated reductions in thymic function and peripheral blood naive CD4 T cells, we hypothesized that the homeostatic proliferation of naive CD4 T cells compensates for deficits in peripheral T-cell populations after radiation injury, which may increase the proportion of CXCR3^{high} cells in naive CD4 T cells and enhance inflammation. The statistical models employed in this study revealed positive associations between the number of CXCR3^{high} naive CD4 T cells and age as well as radiation dose among 580 Hiroshima atomic bomb survivors. In addition, the CXCR3^{high} cells in these survivors increased not only with the levels of homeostatic cytokines, IL6 and IL7, but also with those of inflammatory indicators, CXCL10 and CRP. These results suggest that thymic T-cell production deficiency due to radiation and aging results in enhanced homeostatic proliferation that drives the appearance of CXCR3^{high} naive CD4 T cells poised for an inflammatory response. Molecular mechanisms and clinical relevance of increasing CXCR3^{high} cells in naive CD4 T populations should be further investigated in the context of inflammatory disease development long after radiation exposure.

INTRODUCTION

Naive T cells are important for immune responses against newly arising pathogens or cancer cells, but their numbers decrease with age. The hallmarks of the T-cell immune system in older adults are, first, decreases in the number and repertoire diversity of naive T cells, mainly due to involution of the thymus where T cells develop, and second, naive memory T-cell imbalances leading to the accumulation of pro-inflammatory and senescent T cells with enhanced production of inflammatory cytokines (*1*). Similar changes in the human immune system have been observed in association with radiation exposure, for example in the immune system of atomic bomb survivors, such as involuted thymic tissues, reduced numbers of circulating naive T cells, shortened T-cell telomere lengths, elevated CXCR3 (C-X-C chemokine receptor type 3)$^+$ type 1 helper CD4 T (T_H1) cells, and enhanced plasma levels of inflammatory cytokines (*2–6*). This suggests that exposure to ionizing radiation may accelerate immunological aging in humans, especially processes related to T-cell immunity.

Naive T cells, heterogeneous populations that differ in their phenotypes and functions, dynamically change in number with aging (*7*). As a subset of such heterogeneous populations, CD45RA$^+$ naive phenotype T cells expressing CXCR3 (which typically recruits T cells to sites of inflammation) at a high level, have been found to favorably respond to activating signals and to exhibit enhanced effector phenotypes (*8–10*). In contrast to the age-related reduction of the overall naive T-cell population, the proportion of CXCR3$^+$ cells among naive CD4 T cells tends to increase with age, ranging from several percent in younger age groups to 10–20% in older adults (*8*, *11*). Although we previously found increased T_H1 cells (CD4 T cells highly expressing CXCR3) with radiation dose in atomic bomb survivors, the effect of radiation on the proportion of CXCR3$^+$ naive T cells remains unexplored.

Enhanced homeostatic proliferation of peripheral T cells is known to induce an increase in CXCR3^{high} naive-phenotype T cells (*8*, *12*). Given that radiation induces massive cell death in naive T cells and T-cell precursors, homeostatic T-cell proliferation accompanied by CXCR3 expression in some naive T cells may occur in a compensatory manner to restore the T-cell immune system. Therefore, in this study, we tested the hypothesis that a naive CD4 T-cell population reduction induced by radiation and aging is accompanied by an increase in the proportion of CXCR3^{high} naive-phenotype T cells, which

[1] Corresponding author: Kengo Yoshida, Ph.D., Department of Molecular Biosciences, Radiation Effects Research Foundation, 5-2 Hijiyama Park, Minami-ku, Hiroshima 732-0815, Japan; email: kyoshi@rerf.or.jp.

TABLE 1
Distribution of Age, Radiation Dose, and other Variables in the Subjects

	N	Median	5 Percentile	95 Percentile
Age, year	580 (256 males, 324 females)	70.0	55.0	87.1
Dose, Gy	580	0.364	0.000	2.038
BMI	550	22.7	17.8	28.4
$CD4^+CD45RA^+$ $CXCR3^{high}$, %[a]	580	5.1	1.5	14.5
$CD4^+CD45RA^-$ $CXCR3^{high}$, %[b]	580	33.1	12.8	52.4
Monocyte, %[c]	580	7.3	4.7	10.5
CXCL10, pg/mL	412	616.2	179.8	2392.4
IL6, pg/mL	412	5.2	1.6	82.2
IL7, pg/mL	412	3.0	0.9	53.3
CRP, mg/dL	550	0.07	0	0.94

[a] Percentages of $CXCR3^{high}$ cells in $CD4^+$ $CD45RA^+$ naive cells.
[b] Percentages of $CXCR3^{high}$ cells in $CD4^+$ $CD45RA^-$ memory cells.
[c] Percentages of monocytes in white blood cells.

potentially contributes to enhanced inflammatory responses in atomic bomb survivors.

METHODS

Study Population and Data Sources

A total of 810 study participants were randomly selected from Hiroshima participants of the Adult Health Study (*13*) conducted at the Radiation Effects Research Foundation (RERF). The selected study population included atomic bomb survivors who were potentially exposed to a high radiation dose (for example, 1 Gy or more in bone marrow dose; N = 193) as well as those whose estimated radiation doses were below 0.005 Gy (N = 186), based on the Dosimetry System 2002 revision 1 (*14*). The data analysis in this study drew from several data sources: 1. percentages of $CXCR3^{high}$ cells in circulating $CD45RA^+$ naive and $CD45RA^-$ memory CD4 T cells measured by flow cytometry using a FACScan flow cytometer (BD Biosciences, San Jose, CA), PerCP-labeled CD4 monoclonal antibody (mAb; from Becton Dickinson, Franklin Lakes, NJ), PE-labeled CD45RA mAb (Beckman Coulter, Brea, CA), and FITC-labeled CXCR3 mAb (R&D Systems, Minneapolis, MN) for the assessment of $CXCR3^{high}$ and $CXCR3^{low}$ naive CD4 T cells in peripheral blood lymphocytes (PBL) [N = 810, from years 1998–2003 (*15*)]; 2. percentages of monocytes in white blood cells measured with a Beckman Coulter MAXM hematology analyzer (N = 810, from 1998–2003); 3. serum CRP levels measured using a latex agglutination immunoassay (Nissui Pharmaceutical Co. Ltd., Tokyo; N = 764, from 1999–2008); and 4. CXCL10, IL6, and IL7 levels simultaneously quantified from 25 μL of plasma with a Bio-Plex Pro Human Cytokine assay kit (Bio-Rad, Hercules, CA) according to the manufacturer's instructions (N = 519, from 2000–2002). We excluded participants who had been diagnosed with cancer based on the Hiroshima Tumor Registry to avoid potential influences of cancer development or treatment on peripheral blood phenotypes. Those exposed to atomic bomb radiation in utero and those who had an extreme monocyte percentage value (>30%) were also excluded from the analysis. However, missing covariate values varied across analyses, as shown in Table 1. Informed consent was obtained from all study participants for the analysis of the measurement data. The study was approved by the RERF Institutional Review Board (RP P1-22) and conducted according to the principles expressed in the Declaration of Helsinki.

TABLE 2
Regression Coefficients for Age, Sex, and Radiation to $CD4^+$ $CD45RA^+$ $CXCR3^{high}$ Cell Percentages

	Coefficient	95% CI	P value
Age (10 years)	0.070	[0.011, 0.128]	0.021
Sex (female)	0.079	[–0.037, 0.128]	0.18
Radiation dose (1 Gy)	0.093	[0.009, 0.177]	0.030

Statistical Analysis

We assessed associations between percentages of $CXCR3^{high}$ cells in circulating $CD45RA^+$ naive and $CD45RA^-$ memory CD4 T cells and participant age at examination, radiation dose to the bone marrow, and inflammatory indicators (monocytes, CXCL10, IL6, IL7 and CRP). A multiple linear regression was conducted on each percentage of $CXCR3^{high}$ cells in $CD45RA^+$ naive and $CD45RA^-$ memory CD4 T cells. In addition, associations of $CD45RA^+$ CD4 cells among PBLs with age and radiation were also investigated with a multiple linear regression. Log-transformation was conducted to make the model fit for the cell percentage and to take the asymmetric distribution of the response variables into account. Measurements with a highly skewed distribution were log-transformed (adding the minimum value of the measurements among those greater than zero when there were zeros in the measurements) if necessary, and an outlier of the logarithm of CRP detected by Smirnov-Grubbs test was removed from the analysis. All tests were two-sided, and analyses were conducted using R (version 4.2.1; R Core Team 2022).

RESULTS

Table 1 shows the basic characteristics of participants statistically analyzed in this study (N = 580). We examined the effects of participant age at the time of measurement, sex, and atomic-bomb radiation exposure on the percentages of $CXCR3^{high}$ cells among $CD4^+$ $CD45RA^+$ naive and total $CD4^+$ T cells. Typical flow cytometry patterns are shown in Supplementary Fig. S1[2] (https://doi.org/10.1667/RADE-23-00065.1.S1). We found that the percentage of $CXCR3^{high}$ cells in naive CD4 T cells significantly increased with both aging and radiation doses (Table 2). Although there were large variations across participants (Fig. 1), the overall $CD4^+$ $CD45RA^+$ $CXCR3^{high}$ cell percentage was 1.073 times (= exp[0.07]) greater by 10 years of age, and 1.1 times (= exp[0.093]) greater by 1 Gy of radiation. While percentages of $CD45RA^+$ $CXCR3^{high}$ cells among CD4 T cells were not associated with age or radiation dose, $CD45RA^+$ CD4 T cells, that is, a whole naive CD4 T-cell population among lymphocytes, decreased with both age and radiation dose [both $P < 0.05$, Supplementary Table S1 (https://doi.org/10.1667/RADE-23-00065.1.S1) and Supplementary Fig. S2], in line with our previous observations (*2*, *15*). Furthermore, there was a strong inverse association between the number of whole naive CD4 T cells and $CXCR3^{high}$ cell percentages among naive CD4 T cells ($P < 10^{-7}$, coefficient: –0.017). Thus, a decrease of the entire naive CD4 T-cell population with age and radiation dose was accompanied by an increase in the proportion of $CXCR3^{high}$ cells.

[2] Editor's note. The online version of this article (DOI: https://doi.org/10.1667/RADE-23-00065.1) contains supplementary information that is available to all authorized users.

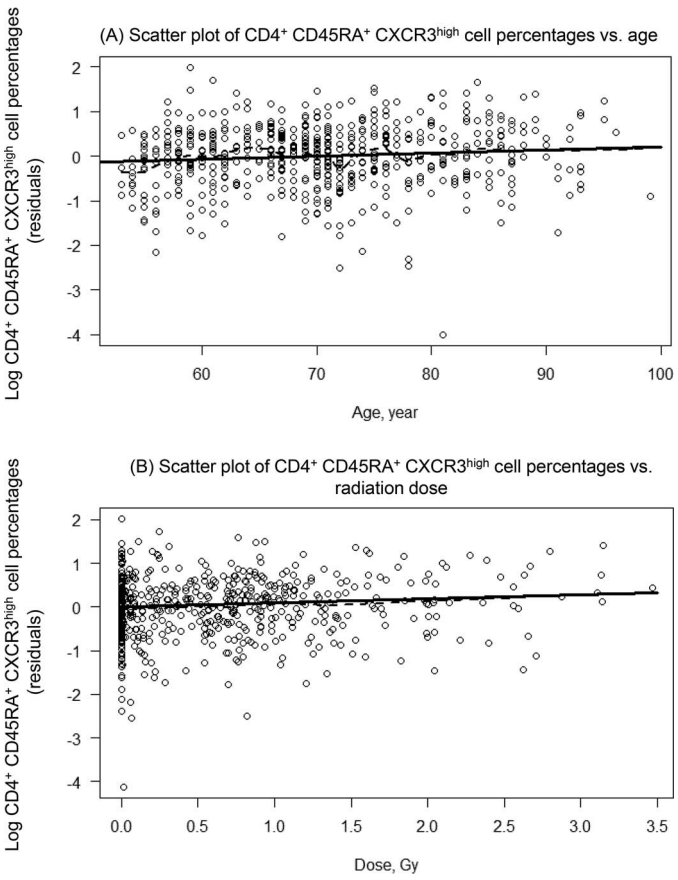

FIG. 1. Age and radiation dose relationships with CXCR3^{high} cell percentages among naive CD4 T cells. The covariate-adjusted relationship between cell percentage and age (panel A) or radiation dose (panel B) is shown. Residuals were calculated from adjusted linear regression models that did not include age or radiation dose. The solid lines are estimated regression lines and the dotted lines are nonparametric smoothing curves based on the super smoother.

Homeostatic proliferation of naive T cells in response to IL7 is known to involve the frequent appearance of CXCR3^{high} naive T cells (*12*), which can be enhanced by IL6 signaling (*16*). We therefore examined the relationships between CXCR3^{high} cell percentages among naive CD4 T cells and plasma IL7 and IL6 levels measured at the same or a closer date to the date of naive T cell measurement. The relationships between CXCR3^{high} cell percentages among naive CD4 T cells and several inflammatory indicators were also examined, given that CXCR3^{high} naive T cells exhibit enhanced effector phenotypes that potentially lead to type-1 inflammation (*8*, *11*). We found no significant effects of radiation on the levels of monocytes, CXCL10, IL6, IL7, or CRP (data not shown), probably because of the limited number of participants. By contrast, the percentage of CXCR3^{high} cells significantly increased with the levels of homeostatic cytokine IL7 and inflammatory indicators CXCL10, IL6, and CRP (Table 3 and Fig. 2).

In similar analyses of memory T-cell populations, percentages of CXCR3^{high} cells among CD4$^+$ CD45RA-negative memory T cells decreased with aging but did not change with radiation dose [Supplementary Table S2 and Supplementary Fig. S3; (https://doi.org/10.1667/RADE-23-00065.1.S1)]. Percentages of CD45RA$^-$ CXCR3^{high} cells among CD4 T cells were not associated with age or radiation dose (data not shown). We also found no association between CXCR3^{high} memory cell percentages and any inflammatory indicators similarly examined (Supplementary Table S3).

TABLE 3
Associations of CD4$^+$ CD45RA$^+$ CXCR3^{high} Cells with Inflammatory indicators[a]

	Coefficient	95% CI	P value
Monocyte, %	0.027	[0.005, 0.058]	0.10
CXCL 10, pg/mL	0.215	[0.017, 0.413]	0.034
IL6, pg/mL	0.165	[0.043, 0.287]	0.008
IL7, pg/mL	0.056	[0.003, 0.109]	0.037
CRP, mg/dL	0.058	[0.017, 0.099]	0.006

[a] Age, sex, and radiation dose were adjusted in each regression analysis using a single inflammatory indicator.

DISCUSSION

The statistical models employed in this study reveal that the proportion of CXCR3^{high} naive CD4 T cells increases (Table 2) while the entire naive CD4 T cells decrease with aging and radiation dose in atomic bomb survivors (Supplementary Table S1; https://doi.org/10.1667/RADE-23-00065.1.S1), suggesting that radiation exposure still accelerated immunological aging decades later, and that this process involves changes in not only numbers but also phenotypes of naive CD4 T cells. The fact that proportions of CXCR3^{high} cells were positively associated with plasma IL6 and IL7 levels indicates that radiation exposure may augment CXCR3-expressing cell appearance due to enhanced homeostatic proliferation. This notion is supported by previous studies reporting that CXCR3^{high} naive T cells were induced by homeostatic proliferation in response to cytokines, typically IL7 (*12*) and that IL7-dependent homeostatic proliferation of CD4 T cells was enhanced by IL6 signaling (*16*).

We cannot exclude the possibility that the CD4$^+$ CD45RA$^+$ CXCR3^{high} cells evaluated in this study include T effector memory CD45RA (T_{EMRA}) cells. However, unlike CD8 subpopulations, CD4 T_{EMRA} cell numbers are generally low in peripheral blood and are not affected by radiation exposure, particularly in this atomic bomb survivor population (*15*). In addition, it has been demonstrated that CD4$^+$ CD45RA$^+$ CXCR3^{high} T cells are entirely naive phenotypes expressing both CD28 and CD62L (*11*) and that they have intermediate levels of T-cell receptor rearrangement excision circles (TREC) between CD4$^+$ CD45RA$^+$ CXCR3-negative T cell and CD4$^+$ CD45RA$^-$ memory T-cell populations (*8*); these observations indicate that CD4$^+$ CD45RA$^+$ CXCR3^{high} T cells are not derived from the memory pool.

Previous studies in atomic bomb survivors consistently suggested a link between T-cell aging, in particular the reduced number of naive CD4 T cells, and enhanced inflammatory responses reflected by the elevation of several inflammatory

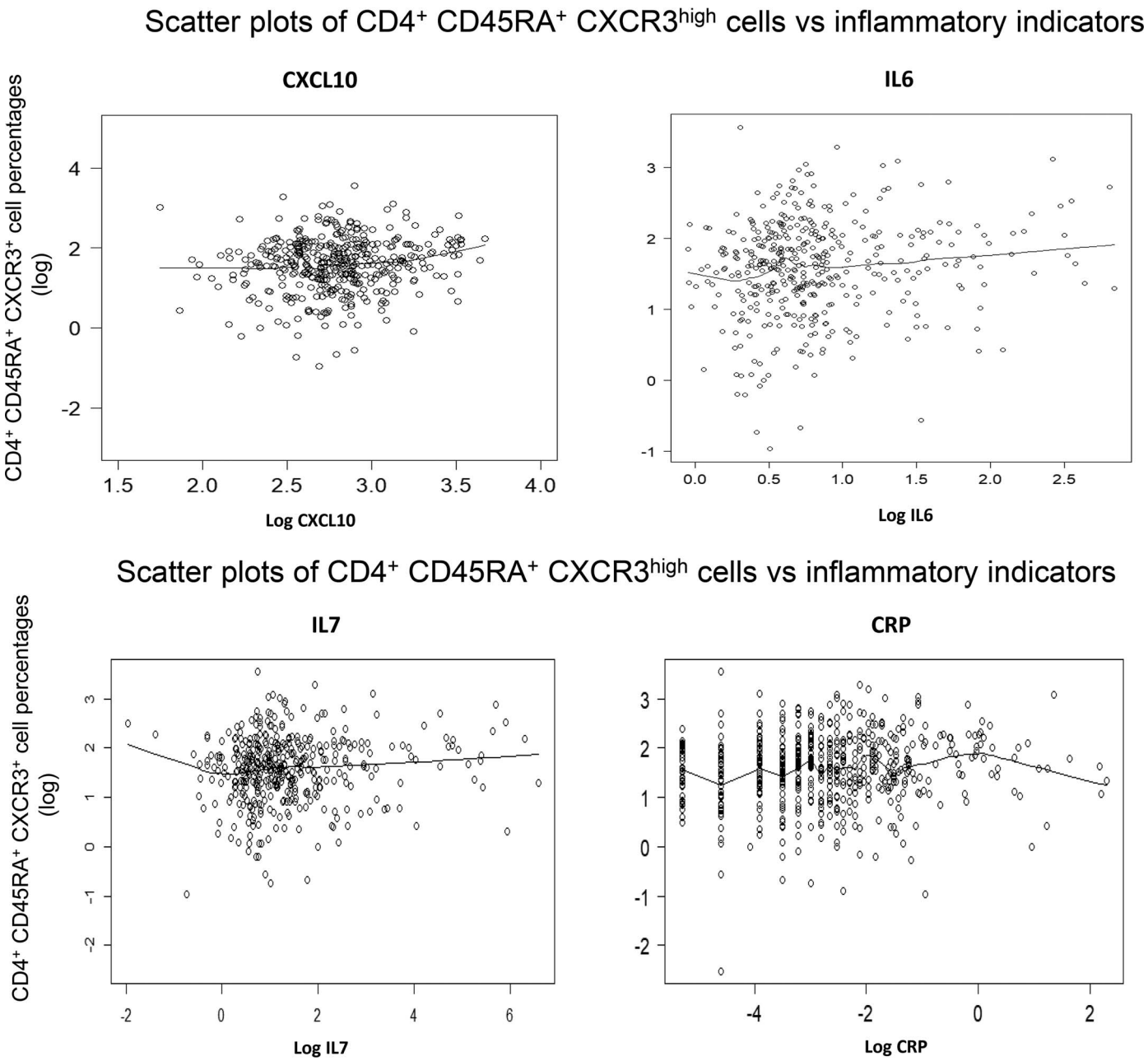

FIG. 2. Relationships between inflammatory indicators and percentages of CXCR3^{high} cells among naive CD4 T cells. The covariate-adjusted relationship between cell percentage and CXCL10, IL6, IL7, or CRP is shown. The lines are smoothed curves by the super smoother.

cytokines and other indicators (*2*, *17*). In the current study, CXCR3^{high} naive cell proportions were inversely associated with the number of entire naive CD4 T cells, but positively associated with inflammatory indicator levels [CXCL10 (a ligand for CXCR3), IL6, CRP, and IL7] as shown in Table 3. By contrast, there was no association between proportions of CXCR3^{high} memory CD4 T cells and the plasma levels of such inflammatory indicators (Supplementary Table S3; https://doi.org/10.1667/RADE-23-00065.1.S1). Taken together, the results of this study suggest that radiation exposure and aging may preferentially expand the naive CD4 T-cell subpopulation poised for type-1 inflammation. Nevertheless, it is important to investigate the precise biological mechanisms responsible for this stronger radiation effect on CXCR3^{high} naive CD4 T cells than on CXCR3^{high} memory cells and to determine why the associations with inflammatory indicators were observed only in the naive CXCR3^{high} cell population.

Age-associated epigenome and metabolite changes in T cells are explained with alterations in the phenotypes and differentiation potentials of naive T cells in aged populations (*18*). More specifically, T-cell mitochondrial dysfunction presumably caused by telomere shortening and DNA damage response signaling (*19*) leads to the acquisition of T_H1 pro-inflammatory phenotypes with elevated production of inflammatory cytokines (*20*) through molecular mechanisms involving metabolic

alterations, reactive oxygen species (ROS) production, and inflammasome activation in T cells (*1*). Radiation dose-associated telomere shortening and ROS level increments have been observed in the peripheral blood T cells of atomic bomb survivors (*5*, *21*). With a deeper understanding of the presumed mitochondrial dysfunction and epigenetic/metabolic reprogramming in T cells of atomic bomb survivors, CXCR3 surface expression enhanced in naive T cells can be viewed as one of the steps that CD4 T cells take to manifest the T_H1 inflammatory response (*3*).

Our analysis did not yield a large effect size for the radiation dose association (i.e., 10% increase in the $CXCR3^{high}$ naive cell proportion with 1 Gy of radiation), which is comparable to the increase with 10 years in this study population. However, our findings of elevated $CXCR3^{high}$ naive CD4 T-cell proportions imply long-lasting proinflammatory conditions potentially related to cancer or noncancer disease risks long after radiation exposure. Epidemiological studies of atomic bomb survivors have observed relationships between radiation dose and the mortality or morbidity of not only cancer, but also various noncancer diseases (*22*). It is presumed that radiation-associated enhancement of inflammatory responses (at a low level but persistent) is involved in the perturbation of tumor immunosurveillance and/or progression of noncancer diseases, including atherosclerotic cardiovascular diseases, in atomic bomb survivors. To date, reduced naive CD4 T cells have been found to be associated with a history of myocardial infarction (*23*). In addition, both IL6 and CRP levels, negatively correlated with CD4 T-cell proportions, were found to be higher in survivors with a history of myocardial infarction (*17*). T-cell migration to atherosclerotic plaques via the CXCR3-CXCL10 axis and T_H1-mediated inflammation represent important pathogenic mechanisms of atherosclerosis (*24*). To investigate the causal relationships between radiation exposure and T-cell aging and cancer or noncancer disease development after radiation exposure, longitudinally accumulated data and biosamples related to T-cell immunity, inflammation, and the pathology and incidence of such diseases in atomic bomb survivors should be fully utilized.

SUPPLEMENTARY MATERIAL

FIG. S1. Flow cytometry patterns of $CXCR3^{high}$ naive and memory CD4 cells in the peripheral blood from an atomic bomb survivor. A typical scatter plot in the flow cytometry is shown.

FIG. S2. Age and radiation dose relationships with naive CD4 T cell percentages among lymphocytes. The covariate-adjusted relationship between cell percentage and age or radiation dose is shown. Residuals were calculated from adjusted linear regression models that did not include age or radiation dose. The solid lines are estimated regression lines and the dotted lines are nonparametric smoothing curves based on the super smoother.

FIG. S3. Age and radiation dose relationships with $CXCR3^{high}$ cell percentages among memory CD4 T cells. The covariate-adjusted relationship between cell percentage and age or radiation dose is shown. Residuals were calculated from adjusted linear regression models that did not include age or radiation dose. The solid lines are estimated regression lines and the dotted lines are nonparametric smoothing curves based on the super smoother.

ACKNOWLEDGMENTS

This work was supported by the Radiation Effects Research Foundation (RERF; Hiroshima and Nagasaki, Japan) Research Protocol P1-22. The RERF is a public interest foundation funded by the Japanese Ministry of Health, Labor, and Welfare (MHLW) and the U.S. Department of Energy (DOE). The authors' views do not necessarily reflect those of the two governments.

Received: April 1, 2023; accepted: November 3, 2023; published online: November 21, 2023

REFERENCES

1. Mittelbrunn M, Kroemer G. Hallmarks of T cell aging. Nat Immunol. 2021; 22(6):687-98.
2. Kusunoki Y, Yamaoka M, Kubo Y, Hayashi T, Kasagi F, Douple EB, et al. T-cell immunosenescence and inflammatory response in atomic bomb survivors. Radiat Res. 2010; 174(6):870-6.
3. Yoshida K, Ohishi W, Nakashima E, Fujiwara S, Akahoshi M, Kasagi F, et al. Lymphocyte subset characterization associated with persistent hepatitis C virus infection and subsequent progression of liver fibrosis. Hum Immunol. 2011; 72(10):821-6.
4. Hayashi T, Morishita Y, Khattree R, Misumi M, Sasaki K, Hayashi I, et al. Evaluation of systemic markers of inflammation in atomic-bomb survivors with special reference to radiation and age effects. FASEB J. 2012; 26(11):4765-73.
5. Yoshida K, Misumi M, Kubo Y, Yamaoka M, Kyoizumi S, Ohishi W, et al. Long-Term Effects of Radiation Exposure and Metabolic Status on Telomere Length of Peripheral Blood T Cells in Atomic Bomb Survivors. Radiat Res. 2016; 186(4):367-76.
6. Ito R, Hale LP, Geyer SM, Li J, Sornborger A, Kajimura J, et al. Late Effects of Exposure to Ionizing Radiation and Age on Human Thymus Morphology and Function. Radiat Res. 2017; 187(5): 589-98.
7. Davenport MP, Smith NL, Rudd BD. Building a T cell compartment: how immune cell development shapes function. Nat Rev Immunol. 2020; 20(8):499-506.
8. Song K, Rabin RL, Hill BJ, De Rosa SC, Perfetto SP, Zhang HH, et al. Characterization of subsets of CD4+ memory T cells reveals early branched pathways of T cell differentiation in humans. Proc Natl Acad Sci U S A. 2005; 102(22):7916-21.
9. Orlando V, La Manna MP, Goletti D, Palmieri F, Lo Presti E, Joosten SA, et al. Human CD4 T-Cells With a Naive Phenotype Produce Multiple Cytokines During Mycobacterium Tuberculosis Infection and Correlate With Active Disease. Front Immunol. 2018; 9:1119.
10. De Simone G, Mazza EMC, Cassotta A, Davydov AN, Kuka M, Zanon V, et al. CXCR3 Identifies Human Naive CD8(+) T Cells with Enhanced Effector Differentiation Potential. J Immunol. 2019; 203(12):3179-89.
11. Gomez I, Hainz U, Jenewein B, Schwaiger S, Wolf AM, Grubeck-Loebenstein B. Changes in the expression of CD31 and CXCR3 in CD4+ naive T cells in elderly persons. Mech Ageing Dev. 2003; 124(4):395-402.
12. Kato A, Takaori-Kondo A, Minato N, Hamazaki Y. CXCR3(high) CD8(+) T cells with naive phenotype and high capacity for IFN-gamma production are generated during homeostatic T-cell proliferation. Eur J Immunol. 2018; 48(10):1663-78.

13. Kodama K, Mabuchi K, Shigematsu I. A long-term cohort study of the atomic-bomb survivors. J Epidemiol. 1996; 6(3 Suppl):S95-105.

14. Cullings HM, Grant EJ, Egbert SD, Watanabe T, Oda T, Nakamura F, et al. DS02R1: Improvements to Atomic Bomb Survivors' Input Data and Implementation of Dosimetry System 2002 (DS02) and Resulting Changes in Estimated Doses. Health Phys. 2017; 112(1):56-97.

15. Yamaoka M, Kusunoki Y, Kasagi F, Hayashi T, Nakachi K, Kyoizumi S. Decreases in percentages of naive CD4 and CD8 T cells and increases in percentages of memory CD8 T-cell subsets in the peripheral blood lymphocyte populations of A-bomb survivors. Radiat Res. 2004; 161(3):290-8.

16. Sawa S, Kamimura D, Jin GH, Morikawa H, Kamon H, Nishihara M, et al. Autoimmune arthritis associated with mutated interleukin (IL)-6 receptor gp130 is driven by STAT3/IL-7-dependent homeostatic proliferation of CD4+ T cells. J Exp Med. 2006; 203(6):1459-70.

17. Hayashi T, Kusunoki Y, Hakoda M, Morishita Y, Kubo Y, Maki M, et al. Radiation dose-dependent increases in inflammatory response markers in A-bomb survivors. Int J Radiat Biol. 2003; 79(2): 129-36.

18. Zhang H, Weyand CM, Goronzy JJ. Hallmarks of the aging T-cell system. FEBS J. 2021; 288(24):7123-42.

19. Schank M, Zhao J, Wang L, Li Z, Cao D, Nguyen LN, et al. Telomeric injury by KML001 in human T cells induces mitochondrial dysfunction through the p53-PGC-1alpha pathway. Cell Death Dis. 2020; 11(12):1030.

20. Desdin-Mico G, Soto-Heredero G, Aranda JF, Oller J, Carrasco E, Gabande-Rodriguez E, et al. T cells with dysfunctional mitochondria induce multimorbidity and premature senescence. Science. 2020; 368(6497):1371-76.

21. Hayashi T, Furukawa K, Morishita Y, Hayashi I, Kato N, Yoshida K, et al. Intracellular reactive oxygen species level in blood cells of atomic bomb survivors is increased due to aging and radiation exposure. Free Radic Biol Med. 2021; 171:126-34.

22. Yamada M, Wong FL, Fujiwara S, Akahoshi M, Suzuki G. Noncancer disease incidence in atomic bomb survivors, 1958-1998. Radiat Res. 2004; 161(6):622-32.

23. Kusunoki Y, Yamaoka M, Kasagi F, Hayashi T, Koyama K, Kodama K, et al. T cells of atomic bomb survivors respond poorly to stimulation by Staphylococcus aureus toxins in vitro: does this stem from their peripheral lymphocyte populations having a diminished naive CD4 T-cell content? Radiat Res. 2002; 158(6):715-24.

24. Saigusa R, Winkels H, Ley K. T cell subsets and functions in atherosclerosis. Nat Rev Cardiol. 2020; 17(7):387-401.