IRF8 dependent classical dendritic cells are essential for intestinal T cell homeostasis

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Effect of past radiation exposure on the circulating dendritic cell populations in A-bomb survivors

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Previous A-bomb survivor studies suggested that radiation exposure might induce long-lasting immunological changes, such as enhancement of aging-related T-cell phenotypes, in the survivors. However, radiation effects on dendritic cells (DC) that may be a key factor behind the immunological changes remain unknown. In this study, we investigated numerical and functional alterations associated with radiation and aging in the circulating DC populations among A-bomb survivors.
Method and materials: Peripheral blood samples were collected with informed consent from 229 participants in the Adult Health Study at Radiation Effects Research Foundation. The two major DC populations, conventional DC (cDC) and plasmacytoid DC (pDC), were numerically analyzed and sorted by flow cytometry. The sorted cDC and pDC were stimulated with TLR3 and TLR7 ligands, respectively; and then, alterations in cytokine production levels and gene expression profiles of the DC populations were determined, using a bead-based multiplex assay and a PCR array, respectively.
Results and discussion: In female survivors, both the number and functions of cDC decreased with age but not radiation dose, whereas the number of pDC decreased but function of pDC increased with age and radiation exposure dose. However, no significant numerical and functional changes associated with age or radiation dose were observed in male survivors. Our results suggest that aging-associated alterations in the DC populations, especially those in pDC, might be accelerated by past radiation exposure in a gender-dependent manner.

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The role of dendritic cells (DCs) in intestinal immune homeostasis remains incompletely defined. Here we show that mice lacking IRF8 dependent DCs have reduced numbers of T cells in the small intestine (SI), but not large intestine (LI), including an almost complete absence of SI $CD8ab^+$ and $CD4^+CD8aa^+$ T cells; the latter requiring b8 integrin expression by migratory IRF8 dependent $CD103^+CD11b^-$ DCs. SI homing receptor induction was impaired during T cell priming in mesenteric lymph nodes (MLN), which correlated with a reduction in aldehyde dehydrogenase activity by SI derived MLN DCs, and inefficient T cell localization to the SI. Finally, mice with a DC deletion in IRF8 lacked intestinal T helper 1 (Th1) cells, and failed to support Th1 cell differentiation in MLN and mount Th1 responses to *Trichuris muris* infection. Collectively these results highlight multiple non-redundant roles for IRF8 dependent DCs in the maintenance of intestinal T cell homeostasis.

