Commentary

on

Delayed Immune Aging in Diet-Restricted B6CBAT6 F1 Mice Is Associated With Preservation of Naive T Cells

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This issue of the Journal of Gerontology: Biological Sciences contains a research article entitled “Delayed Immune Aging in Diet-Restricted B6CBAT6 F1 Mice Is Associated With Preservation of Naive T Cells” by Jichun Chen, Clinton Astle, and David Harrison (pp. B000–B000). The authors’ major findings are that dietary restriction (DR) initiated at weaning and maintained throughout the life span slows certain age-related changes in the T-cell compartment—perhaps the most remarkable of which are the effects of DR on the rates of decline in numbers of CD4+CD8+ double-positive (DP) cells in the thymus and naive CD4+ and CD8+ T cells in the peripheral blood. Based upon these observations, the authors hypothesize that the developmental window bounded by these cell phenotypes is better maintained in aging DR mice, thus providing stronger host responses to neo-antigens in late life.

Although the use of DR as a clinical approach to immunosenescence is somewhat problematic, studies like that of Chen and colleagues in this issue may help to uncover age-sensitive switches in T-cell homeostasis as well as the causal relationships among such events. The possibility that DR slows the age-associated decay rate of thymic precursors, thereby helping to maintain naive T cells in the periphery during aging, is intriguing and provides a target for future mechanistic studies; however, at this point, it is not clear that these two DR-mediated corrections are interrelated or rather are merely coincidental. Uncertainty arises from three of the authors’ findings: first, there were no significant DR effects on the number of DP thymocytes at any age (Table 3); second, the numbers of immediate precursors for naive T cells (i.e., single-positive thymocytes) were only modestly altered by DR during aging (Table 3); and, third, correlations of DP thymocyte and naive T-cell numbers were not significant in late middle-aged mice (16 months; Table 4), even though thymic output is dramatically reduced well before this age in ad libitum (AL)–fed mice (1). If indeed these events prove to be independent, then other possibilities might be considered: for example, DR-mediated effects on the intermitotic life span or on the extrathymic regeneration of naive T cells. In this latter regard, the naive T-cell pool appears to have some capacity for self-renewal without overt changes in membrane phenotype (2).

An extremely important issue for T-cell biologists engaged in aging research is whether the well-documented, age-related change in the representations of naive and memory T cells is causally related to a deterioration of protective immunity and, further, whether the pace of this change can have a significant impact on the life span of the host. Past studies cited by the authors, combined with their own work, show convincing effects of DR on all three indices (i.e., shifts in T-cell subset frequencies, protective immunity, and life span) as well as on thymic involution; however, given that correlative studies are often not performed, the work by Chen and colleagues is a welcome addition to the literature. Relevant to this issue are recent studies by the Miller group (3), who found that in longitudinal analyses of genetically heterogeneous mice the proportion of memory CD4+ cells in the peripheral blood at 18 months of age was a strong predictor of life span. Although longitudinal studies relating the proportions of thymocyte subpopulations and life span in DR and AL mice are not feasible, the use of follow-up approaches to examine whether the frequencies of peripheral blood T-cell subsets in individual mice can predict earlier death might provide important insights into DR-mediated effects.

As a final comment, age-related changes in the mature T-cell compartment may go beyond the shift from a predominance of naive cells in early life to a prevalence of memory cells in late life. There is a newer, growing body of literature indicating that aging may affect the function of naive, memory, or both T-cell subsets at the levels of early signal transduction, clonal expansion, or cytokine expression (reviewed in refs. 4,5), although the exact extent and form of these subset-specific changes have yet to be established firmly. Nevertheless, age-related alterations in the immune response to novel or recall antigens may be influenced by changes in both the representation and the function of indi-
individual T-cell subsets. Given that DR is a tried-and-true method for manipulating life span, particularly in rodents, then the extension of the work reported by Chen and colleagues to the analysis of T-cell subset-specific functions may prove an area of fruitful research.

In conclusion, the comprehensive analyses of the effects of DR on age-related changes in the T-cell compartment reported by Chen and colleagues provides not only a strong first step in dissecting the mechanisms of DR-mediated effects on immune function in aging mice, but also yields information pertinent to age-related changes in the T-cell compartment in general. If, as the authors argue, poor retention of the precursor DP thymocyte pool is the major cause of the dwindling naive T-cell number, which then leads to diminishing immune function, then DP thymocytes may be an attractive target for development of therapeutic agents to counteract immunosenescence.

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REFERENCES


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