The Birth of Functionally Distinct T Cell Subsets

Leonard Chess

J Immunol 2006; 176:3859-3860; ;
http://www.jimmunol.org/content/176/7/3859

References
This article cites 17 articles, 9 of which you can access for free at:
http://www.jimmunol.org/content/176/7/3859.full#ref-list-1

Subscriptions
Information about subscribing to The Journal of Immunology is online at:
http://jimmunol.org/subscriptions

Permissions
Submit copyright permission requests at:
http://www.aai.org/ji/copyright.html

Email Alerts
Receive free email-alerts when new articles cite this article. Sign up at:
http://jimmunol.org/cgi/alerts/etoc
The Birth of Functionally Distinct T Cell Subsets

Leonard Chess 1

By the late 1960s and early 1970s, it was already clear that immune responses were effected by lymphoid cells and that an interesting subdivision of labor existed among populations of lymphocytes resident in distinct lymphoid organs. Thus, it was known that thymic-derived T cells migrated from the thymus to populate lymphoid organs and effect cell-mediated immune responses, whereas Ab production was mediated by bone marrow-derived B cells. Moreover, B cell Ab production was found to be dependent on help from thymic-derived T cells. Furthermore, in addition to this helper function of T cells, it was clear that T cells mediated other immune functions, including delayed-type hypersensitivity (DTH), 2 cytotoxic activity and regulatory suppressor functions. A question of paramount importance that surfaced was whether these various functions of T cells were conducted by a single T cell with various functions or, on the contrary, by distinct functional subsets. The seminal experiments of Cantor and Boyse, highlighted in this month's "Pillars of Immunology," provided unequivocal evidence that two major subsets of peripheral T cells exist and that they mediate distinct sets of functions (1). Using the genetically well-defined allo-antisera to the Ly-1 and Ly-2,3 differentiation Ags, they were able to isolate two mutually exclusive populations of T cells expressing either the Ly-1 or the Ly-2,3 surface molecules. The Ly-1 + T cells contained the functional subset responsible for B cell help and for inducing DTH reactions. In contrast, the Ly-2,3 + subset was devoid of helper cells but contained the cytotoxic cells important in mediating cell-mediated cytotoxicity directed to alloreactive cells (1, 2). Interestingly, the Ly-1 + subset did not mediate killing but amplified the killing mediated by the Ly-2,3 subset. Moreover, the suppressor functions were found to be largely contained in the Ly-2 subset (3). These findings were rapidly extended to the analysis of human T cells, initially with heteroantibodies and then with mAbs that defined the human T cell surface molecules, CD4 and CD8 (4, 5). These Abs defined functionally distinct human CD4 + and CD8 + T cell subsets, which functionally were analogous to the murine Ly-1 and Ly-2,3 subsets. Later, mAbs were also raised to the murine CD4 and CD8 molecules (6, 7). The murine CD4 + peripheral T cells were exclusively contained within the Ly-1 + population and mediated the helper function while the murine Ly-2 mAbs identified the population of cytotoxic and suppressor populations identical to the Ly-2,3 alloantibodies (6, 8). Thus, the major T cell subsets in both man and mice were virtually identical in that they comprised analogous functional populations. As will be discussed below, when the CD4 and CD8 molecules were cloned and sequenced in both species, the structural and expression patterns of the molecules were also highly homologous (9).

A fundamental question that arose from these studies was whether the two T cell subsets represented two separate lines of differentiation or whether they were sequential stages of a single differentiated pathway. In the latter case, one would give rise to the other. In elegant experiments in which Ly-1 or Ly-2,3 cells were parked in B mice deprived of all T cells, even after prolonged residence of Ly-1 cells in B hosts that have been deprived of Ly-2,3 + cells (B-Ly-1 mice), there was no appreciable generation of Ly-2,3 cells from Ly-1 cells, and the Ly-1 cells maintained their helper function and did not mediate alloreactive killing. Conversely there was no appreciable conversion to Ly-1 + cells in B-Ly-2,3 mice (10). Moreover, long-term in vitro culture of CD4 + or CD8 + T cell clones in vitro confirmed the phenotypic stability of both the function and the CD4 or CD8 surface expression. Together these studies demonstrated that the two subsets belong to distinct differentiation lineages and are not sequential stages of a single progression. Moreover, it is now recognized that the CD4 + and CD8 + subsets in fact arise from a common precursor, the double-positive CD4 + CD8 + thymocytes. It is this double-positive population in the thymus that gives rise to either the CD4 or CD8 lineage.

In addition to these functional distinctions, CD4 + and CD8 + T cell subsets also differed in a cognitive sense. Thus, CD4 + T cells were found to be MHC class II restricted, whereas CD8 + T cells were found to be MHC class I restricted (11, 12). Moreover, the expression of the CD4 and CD8 cell surface molecules correlates as well with the class of MHC molecules that restricts Ag recognition as with function. These correlations strongly suggested that the CD4 and CD8 molecules play a very important role in T cell responses by actually interacting with distinct conserved portions of the MHC class I and MHC class II molecules. In fact, when the CD4 and CD8 molecules were cloned in both man and mouse, the molecular sequences in both CD4 and CD8 molecules responsible for directly binding to MHC class II or MHC class I were defined (13, 14). The fact that the genetic programs that define the T cell subsets are intimately linked to the two predominant MHC pathways has biological significance not only in the thymus where the two subsets are selected on the basis of MHC but also in the periphery where the subsets mediate their distinctive functions. Thus, CD4 + T cells mediate B cell help and DTH responses by interacting with and inducing the MHC class II-expressing B cells, dendritic cells, and macrophages, whereas the CD8 + subsets can in principle interact with and kill all nucleated cells, which can express MHC class I molecules and thus

1 Address correspondence and reprint requests to Dr. Leonard Chess, Columbia University, College of Physicians and Surgeons, 630 West 168th Street, New York, NY 10032. E-mail address: LC19@columbia.edu

2 Abbreviation used in this paper: DTH, delayed-type hypersensitivity.
can present peptides derived from the universe of intracellular pathogens and tumors. Thus, the CD4 and CD8 molecules are not just markers of T cell subsets but in fact are functionally important molecules at the core of T cell recognition where they function in concert with the Ag-specific αβ TCR to recognize MHC/Ag-peptide complexes.

Finally, perhaps the most significant clinical ramification of the identification of T cell subsets to date was that it led to the identification of the CD4 molecule which turned out to also function as the cellular receptor for HIV (15, 16). In fact, Abs to CD4 (which were being made as the AIDS epidemic was in its infancy) permitted the initial clinical identification of AIDS as a disease. Moreover, the loss of the CD4+ subset of T cells during clinical evolution of HIV infection provided insight into the pathophysiology of this devastating immunodeficiency disease and will perhaps ultimately lead to the treatment of the disease (17, 18).

References


