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IMMUNOLOGY:

Ex Uno Plura

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Abstract

T cells that respond quickly to infection and later to reinfection arise from a single precursor cell type.

The response of a specific subset of immune cells (T cells) to infection is characterized by the capacity to become functionally specialized in response to the particular pathogen and, consequently, to shift T cell population dynamics. Two reports in this issue, by Bannard *et al.* on page 505 (1) and Texeiro *et al.* on page 502 (2), shed new light on how the distinct subsets of T cells that mediate acute versus long-term protection to infection can arise from a single precursor.

Our long-term health and survival depend on the ability of a subset of T cells (CD8⁺) to quickly generate a potent population of effector T cells that can limit an ongoing infection, as well as memory T cells that provide long-term immunity should the same pathogens be reencountered. Accordingly, two main subsets of CD8⁺ T cells, distinguishable by their location, function, and longevity, are generated in response to vaccination or acute infection. Effector cells are short-lived and numerous, comprising 90 to 95% of CD8⁺ T cells at peak response, and can deploy a variety of cytokine and cell contact-dependent cytotoxic mechanisms to eradicate infected cells and thereby control acute infection. Memory T cells serve as a long-term “insurance policy” by providing a swift and effective response to reinfection by the same pathogen. There is further heterogeneity within this memory cell population. Cytotoxic effector memory T cells act as sentinels in the blood and peripheral tissues where reinfection is most likely to occur, and central memory T cells in the secondary lymphoid organs undergo a second round of clonal expansion upon reencounter of their inducing antigen (3).

Given the phenotypic and functional heterogeneity among the CD8⁺ T cell responders, a central goal has been to determine the ontogeny and lineage relationships among their apparently disparate constituent subsets. Of the several models that have been proposed, two posit that the effector and memory T cells measured after infection or immunization descend from either distinct or common precursors. A single naïve CD8⁺ T cell (mature but not yet stimulated by a foreign antigen) can give rise to each of the effector and memory subsets measurable after acute infection, indicating that naïve cells are pluripotent and that specific fates are determined either coincident with or after the first round of cell division (4). In addition, the first round of CD8⁺ T cell division is asymmetric with respect to the portioning of key molecules, producing one daughter cell that serves as a precursor to the effector cell subset whereas the other daughter cell is destined to become the memory cell precursor (5) (see the figure). This model predicts that primary effector T cells are incapable of secondary expansion, a hallmark function of the memory subset. The second model proposes that memory cells arise directly from effector T cells, with their specific subspecialty and location (effector versus central memory T cells) determined by additional events, and perhaps being subject to interconversion (6,7). Under this

model, effector cells would either possess replicative function or differentiate directly into memory cells. A key difference between these models, therefore, lies in whether bona fide effector cells retain the ability to undergo a secondary proliferative response.

Bannard *et al.* approached the question of lineage relationship by devising an elegant experimental system through which CD8⁺ T cells differentiating into the effector lineage in response to viral infection can be conditionally and irreversibly marked to allow their secondary proliferative response to be measured after rechallenge. This was achieved by creating transgenic mice in which treating the animals with the compound tamoxifen induced the expression of a fluorescent reporter protein, but only in cells that expressed Granzyme B, a cytolytic granule protein that mediates cytotoxicity in CD8⁺ T cells (8,9). Thus, Bannard *et al.* could follow the repertoire of endogenous, antigen-specific T cells responding to infection in an animal and avoid the artifacts in clonal expansion and differentiation that can occur in approaches that use the adoptive transfer of transgenic T cells (10–12). By administering tamoxifen at various times after viral infection, Bannard *et al.* found that CD8⁺ T cells that have differentiated into the effector lineage can nonetheless display a secondary replicative potential upon rechallenge that is comparable with that of all virus-specific CD8⁺ T cells. This finding would not have been predicted by the asymmetric division model, and shows that cells that have acquired effector cell function during primary infection can indeed display the secondary replicative capacity of memory cells, a result that is consistent with a linear differentiation model.

The ability of memory CD8⁺ T cells to mount a secondary proliferative response appears to be “programmed” by inductive signals transmitted to clonal precursors during their initial priming and executed by their clonal progeny upon restimulation by the same antigen. These include signals provided by a subset of helper T cells (CD4⁺) and the cytokine interleukin-2 (13–17). Teixeira *et al.* show that the T cell receptor, a heterodimeric protein that serves as the antigen-specific sensor for T cells, also helps to generate the intracellular signals necessary for a primed T cell to differentiate into a memory cell. The authors found that antigen-specific CD8⁺ T cells expressing a T cell receptor bearing a single point mutation in the transmembrane domain portion of the β chain undergo a primary response to antigen that is indistinguishable from that of cells bearing a wild-type version of the same receptor. Despite this normal primary response, the cells with the mutated T cell receptor are nonetheless unable to mount a secondary proliferative response to antigenic rechallenge, thus failing a key test of the ability to function as memory cells. This finding supports the idea that secondary clonal expansion is a discrete functional capacity that is conferred, among other signals, by T cell receptor stimuli that are qualitatively distinct from those that lead to differentiation into an effector cell. Given that the relevant signals were received by the clonal precursors for both effector and memory cells, this “action at a distance” suggests that unique signaling events within a clonal precursor cell are integrated into a distinct program of gene expression that regulates the fate of its daughter cells. Consistent with this idea, Teixeira *et al.* found that cells expressing the T cell receptor with the mutation displayed differences in recruiting an intracellular signaling protein (protein kinase C- θ) to the “immune synapse” formed between a T cell and an antigen-presenting cell (APC) and in translocation of the transcription factor nuclear factor κ B to the nucleus. Though it is unknown how the pattern of gene expression in CD8⁺ T cells expressing the mutated T cell receptor might differ from that of their wild-type counterparts after primary and secondary stimulation with antigen, this information should add to the list of molecules expressed in CD8⁺ T cells that help establish and maintain the memory state. In this way the operationally defined state of immune memory can be put on a more rigorous and defined molecular foundation that will facilitate the next generation of experimental studies.

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Figure 1. From one, many

The development of the distinct types of memory $CD8^+$ T cells from a single clonal precursor might occur according to the asymmetric cell division model, in which a stimulated naïve T cell produces two daughter cells with distinct fates—one giving rise to effector T cells and the other to memory T cells. Only the latter can undergo secondary expansion in response to antigen. In the linear T cell differentiation model, memory T cells that descend from effector T cells retain the capacity for secondary clonal expansion.