Immunity
Review

CD8$^+$ T Cells: Foot Soldiers of the Immune System

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DOI 10.1016/j.immuni.2011.07.010

Resting naive CD8$^+$ T cells have an astounding capacity to react to pathogens by massive expansion and differentiation into cytotoxic effector cells that migrate to all corners of the body to clear the infection. The initial interaction with antigen-presenting cells in the central lymphoid organs drives an orchestrated program of differentiation aimed at producing sufficient numbers of effectors to get the job done without resulting in clonal exhaustion. Interactions with antigen-presenting cells and other immune cells continue at the site of infection to regulate further on-site expansion and differentiation, all with the goal of protecting the host with minimal bystander tissue damage. Here we review recent advances in CD8$^+$ T cell recognition of antigen in lymphoid as well as in nonlymphoid tissues in the periphery, and how CD8$^+$ T cell expansion and differentiation are controlled in these contexts.

Introduction to Cytotoxic T Cells

Much of the early work that would eventually lead to the recognition of antigen-specific cell-mediated lysis of target cells relied on allogeneic, MHC-disparate tissue and tumor transplantation models and allogeneic mixed lymphocyte cultures. In many of these systems, a subset of thymus-derived T lymphocytes with clonally distributed receptors was shown to be responsible for in vitro cell-mediated lysis of target cells (Cantor and Boyse, 1975; Cerottini et al., 1970; Golstein et al., 1972). However, it was work in a syngeneic system with lymphocytic choriomeningitis virus (LCMV)-infected mice that revealed the dual specificity of specific T lymphocytes for viral antigen plus self-MHC that explained the involvement of MHC class I molecules with CD8$^+$ T cell recognition of antigen and introduced the notion of "altered self" (Zinkernagel and Doherty, 1974). Just how readily viruses and other infections stimulate potent cytotoxic T lymphocyte (CTL) responses is illustrated by human cases of acute infectious mononucleosis or "kissing disease" caused by exposure to the Epstein-Barr gamma herpes virus (EBV). The disease is characterized by swollen lymph nodes and a remarkable rise in the number of peripheral blood monocytes. In fact the bulk of the monocytosis turns out to be a lymphocytosis consisting mostly of activated CD8$^+$ CTL with specificity for EBV peptides (Callan et al., 1996). The response to EBV provides a remarkable example of the magnitude of the proliferative burst of clones of antigen-specific CD8$^+$ lymphocytes in response to an infectious agent. Similarly, it had been realized for many years that infection of mice with LCMV led to an inversion of the CD4:CD8 ratio because of a dramatic increase in CD8$^+$ T cell numbers but it was not until tetramer staining or the adoptive transfer of small numbers of TCR transgenic CD8$^+$ T cells was employed that it was realized that the bulk of the CD8$^+$ expansion was due to antigen-driven proliferation (Butz and Bevan, 1998; Murali-Krishna et al., 1998). During many infections, all T lymphocytes regardless of specificity may undergo cytokine-driven phenotypic changes—so-called bystander activation—but only those T cells that recognize pathogen-encoded antigen go through multiple rounds of replication to generate enormous numbers of CTL effector progeny that are the foot soldiers of the adaptive immune response.

Recruiting: Initial CD8$^+$ T Cell Activation

During an infection, naive CD8$^+$ T cells are primed by antigen-presenting cells (APCs) in secondary lymphoid organs such as lymph nodes (LN) and spleen. How are the CD8$^+$ T cells activated by the APCs? Seeing is believing. The application of multi-photon-based intravital microscopy (IVM) has greatly advanced our knowledge about immune response initiation. Previous work had shown that in the absence of antigen, naive T cells in the LNs engage in what appears to be a random walk in the T cell area, which is actually their wandering on the fibroblastic reticular network (Bajénoff et al., 2006). Subsequent to injection of peptide-loaded dendritic cells (DCs), T cells scan the HEV-associated DC forming antigen-specific contacts with the DCs, leading to T cell activation (Bousso and Robey, 2003; Mempel et al., 2004; Miller et al., 2003). However, because injected peptide-pulsed DCs supply the antigenic stimulus in these experiments, where and when APC and naive T cells interact during an infection remained undefined. More recent research has revisited this issue of CD8$^+$ T cell recruitment in infectious settings (Chtanova et al., 2009; Hickman et al., 2008; John et al., 2009). Two groups using virus or parasite infection models have shown that naive CD8$^+$ T cells first contact the antigen-bearing DCs in the subcapsular sinus region or the interfollicular region of the draining LN (Hickman et al., 2008; John et al., 2009). This peripheral location in the LN is in sharp contrast to the central HEV region after peptide-pulsed DC immunization. In naive mice, CD8$^+$ T cells mainly reside in the T cell zones while the DCs form an extensive network throughout the T cell zone, B cell follicle, and some areas of the subcapsular sinus (Lindquist et al., 2004). Shortly after infection, at the same time that the infectious agents can be detected in the LNs, the CD8$^+$ T cells and DCs are quickly enriched in the peripheral regions of the nodes (Hickman et al., 2008; John et al., 2009). Particulate antigen and pathogens arrive via the lymphatics at the subcapsular sinus of the draining LN. The first and major cell population infected by pathogen is CD169$^+$ macrophages lining the subcapsular sinus. However, instead of these antigen-rich macrophages, naive CD8$^+$ T cells favor the DC population to deliver the first kiss to start their differentiation to effector cells. During vaccinia virus (VV) or vesicular stomatitis virus (VSV) infection, naive CD8$^+$