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Activation of CD8 T Lymphocytes during Viral Infections

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Abstract

CD8 T lymphocytes are a major cell population of the adaptive immune system. A fundamental characteristic of the CD8 T lymphocyte pool is that it is composed of millions of clones; each with a unique T cell receptor capable of recognizing a limited number of peptides displayed at the cell surface bound to the grooves of major histocompatibility complex class I (MHC I) molecules. Naïve CD8 T lymphocytes are normally resting and circulate between the blood and secondary lymphoid organs in search of their cognate peptide–MHC complexes. During viral infections, bone marrow–derived professional antigen-presenting cells (pAPCs) in secondary lymphoid organs display viral peptides on their MHC I molecules. Specific CD8 T lymphocytes that recognize these peptide–MHC adducts become activated (primed), proliferate extensively, and develop into effectors capable of killing infected cells, identified by the presence at their surface of the pertinent viral peptide–MHC complexes. This article describes how the process of priming naïve CD8 T lymphocytes occurs.

Introduction

During viral infections, cells of the adaptive immune system become activated when they recognize antigens through their antigen-specific receptors. The B cell receptor (BCR) is a membrane immunoglobulin that binds to the antigen directly. For T cells, however, the process is more complex because the T cell receptor (TCR) only recognizes antigens as small peptides bound to major histocompatibility complex (MHC) molecules at the surface of antigen-presenting cells. While the basic principles of antigen recognition by CD4 and CD8 T cells are similar, there are also major differences. This article focuses on the activation of CD8 T cells.

CD8 T Lymphocytes Are an Important Arm of the Antiviral Immune Response

Effector CD8 T lymphocytes kill virus-infected cells and produce antiviral cytokines such as interferon gamma. In this way, CD8 T lymphocytes contribute to resisting primary and secondary viral infections. For example, CD8 T lymphocytes have been shown to be essential for the efficient control of several viral infections of mice and humans including influenza virus, poxviruses, coronavirus, and herpes viruses (Lau et al., 1994; Karupiah et al., 1996; Welsh et al., 2004; Fang and Sigal, 2005; Xu et al., 2007; Doom and Hill, 2008; Channappanavar et al., 2014; Terrazzini and Kern, 2014). Once an infection is cleared, most effector CD8 T cells die but many of them remain in the circulation and tissues as resting memory cells. These memory cells can help control secondary infections more rapidly (Welsh et al., 2004).

The activation of CD8 T lymphocytes requires an antigen-specific signal through the TCR (Yanagi, 1991; Matis, 1990), which recognizes viral peptides (Townsend et al., 1985, 1986a,b; Townsend and Bodmer, 1989) bound to a groove on MHC class I (MHC I) molecules (Bjorkman et al., 1987a,b). The interaction of the TCR with peptide–MHC I is enhanced by the binding of the CD8 coreceptor on the T cell to a region of the MHC I molecule away from the peptide-binding groove (Gao et al., 2002). In addition, optimal CD8 T lymphocyte priming may require other signals such as costimulation (signal 2) (Duttagupta et al., 2009; Welten et al., 2013). Direct signals to CD8 T cells by proinflammatory soluble cytokines such as type I interferons and interleukin-12, known as signal 3, are also important for efficient CD8 T cell responses to viruses but their effect seems to be during their early proliferation rather than priming (Haring et al., 2006; Curtsinger and Mescher, 2010; Kim and Harty, 2014).

The T Cell Receptor of CD8 T Lymphocytes Binds Peptides Loaded into MHC I Molecules

MHC I molecules are heterodimers composed of a polymorphic alpha (α) chain with three extracellular domains, one transmembrane domain, one cytosolic domain, and a monomorphic beta-2 microglobulin chain with a single extracellular domain whose role is to stabilize the α chain. The membrane-proximal $\alpha 3$ domain of the α chain interacts with the CD8 coreceptor, while the membrane-distal $\alpha 1$ and $\alpha 2$ domains form a polymorphic groove that binds a diverse array of peptides, 8–10 amino acid long (Bjorkman et al., 1987a,b), with a sequence motif that is characteristic for each α chain allele and determined by its polymorphic amino acids (Rammensee, 1995; Rammensee et al., 1993a,b; Grey et al., 1995). The TCRs of CD8 T lymphocytes bind very loosely to most peptide–MHC I–peptide combinations but with much higher affinity to a small subset. This specificity is acquired during the development of the CD8 T lymphocyte in the thymus. In this process, the variable (V), diversity (D), and joining (J) segments of the TCR β and the V and J segments of the TCR α genes recombine randomly to generate unique complementarity-determining regions that bind with higher

strength to particular peptide–MHC I adducts. This gives rise to millions of CD8 T lymphocyte clones, each with a distinctive peptide–MHC I specificity, that circulate between the blood and secondary lymphoid tissues in search of their cognate peptide–MHC I combinations (Gras et al., 2012; Godfrey et al., 2008). Importantly, most CD8 T lymphocytes that randomly recognize self peptides are eliminated or rendered tolerant during T cell development. On the other hand, those that recognize nonself peptides, such as those derived from the degradation of viral proteins, become part of the activatable CD8 T lymphocyte pool (Klein et al., 2014; Parello and Huseby, 2015; Morris and Allen, 2012).

Direct Presentation of Self and Viral Peptides by MHC I Molecules

During normal cellular housekeeping, the proteasome and other peptidases in the cytosol progressively degrade mature proteins and defective ribosomal products to their constitutive amino acids. The intermediate peptides generated in this process are very short-lived, if free in the cytosol. However, some of them are rapidly shuttled into the lumen of the endoplasmic reticulum (ER) by the transporter associated with antigen presentation. In the ER, the peptides can be further trimmed by ER aminopeptidase 1 and those with the appropriate motif bind to MHC I molecules that protect them from further degradation. After acquiring their peptide cargo, the MHC I molecules transit to the plasma membrane, where they display the peptides at the cell surface for CD8 T lymphocyte recognition. In this process, known as 'direct presentation' (DP), MHC I molecules present to CD8 T lymphocytes a sampling of the cellular proteome, which, in virus-infected cells, includes viral proteins (York and Rock, 1996; Cresswell et al., 2005; Rock and Shen, 2005; Rock et al., 2010) (**Figure 1a**). Of note, DP is the only mechanism of MHC I antigen presentation available to most cells. Hence, for most cells, only direct viral infection triggers recognition and killing by antiviral CD8 T lymphocyte effectors (Rock et al., 2010). Therefore, the quasiuniversal expression of MHC I allows effector CD8 T lymphocytes to kill almost every type of infected cells.

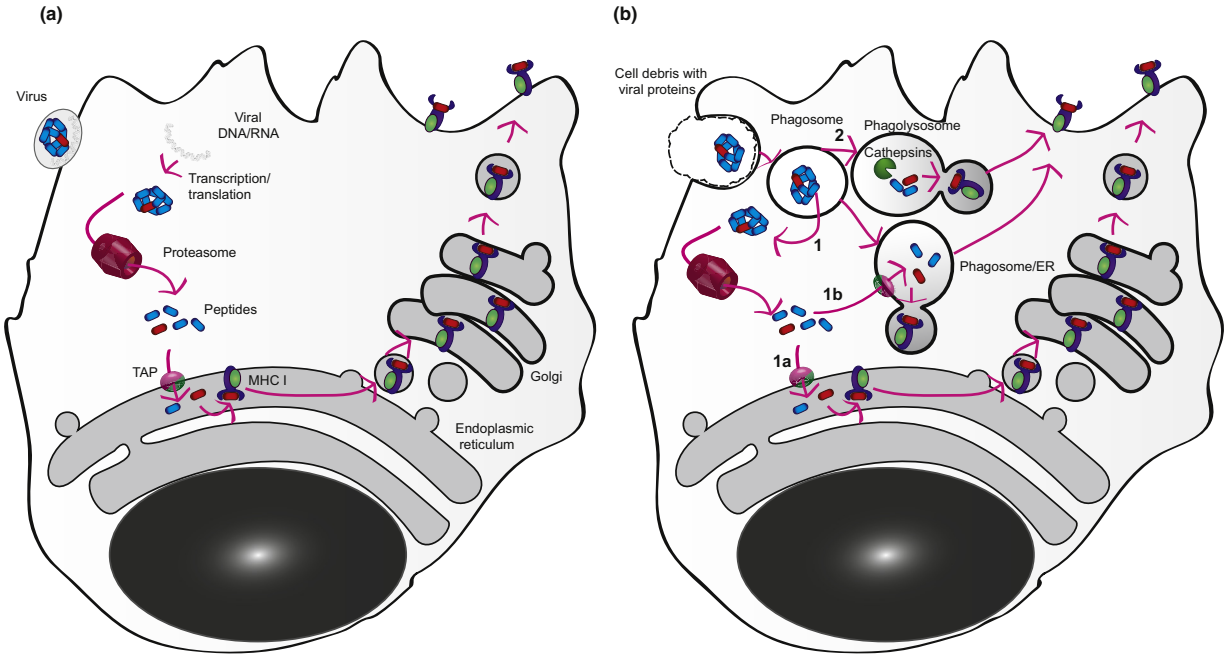

Figure 1 Pathways of MHC I antigen presentation in viral infections. (a) *Direct presentation (DP)*: The virus infected the cell and the RNA or DNA (here in the cytosol but it can also be in the nucleus) is transcribed (if necessary) into RNA and translated into viral protein. When this protein is degraded by the proteasome and some of the resulting peptides are transported by transporter associated with antigen presentation (TAP) into the endoplasmic reticulum. Peptides with the appropriate motif bind to newly synthesized MHC I molecules and transported through the Golgi to the cell surface for presentation to CD8 T cells. This pathway is active in all cells and for all viruses. It has been shown the dominant pathway for the priming of CD8 T cell responses to vaccinia virus (VACV). (b) *Cross-presentation (CP)*: Viral proteins are phagocytosed (here in cell debris such as apoptotic cells, but could also be in other forms such as viral particles). In the cytosolic pathway (1), the protein is transferred to the cytosol and then follows a pathway similar to DP (1a). Alternatively, TAP acquired from ER membranes can transport peptides back to the phagosome, where it is loaded to MHC I and transported to the cell surface ((1b), never demonstrated for viral infections). In the vacuolar pathway (2), the phagosome fuses with lysosomes. Lysosomal peptidases, mainly cathepsins, degrade the antigen and some of the resulting peptides are loaded into recycling MHC I molecules for transport to the cell surface. CP is active only in bone marrow–derived professional antigen-presenting cells and, in particular, in CD8α dendritic cells. Cytosolic CP is known to be important for the priming of CD8 T cells against herpes simplex 1 virus and to be operative for poliovirus, VACV, influenza A virus (IAV), and lymphocytic choriomeningitis virus. Vacuolar CP has been shown to play a role in CD8 responses to some peptides of IAV.

Efficient CD8 T Lymphocyte Responses to Viruses Generally Require Bone Marrow–Derived Antigen-Presenting Cells

Although effector $CD8^+$ T cells can recognize and kill every cell displaying their cognate peptide–MHC I combination, the initial activation (priming) of CD8 T lymphocytes generally requires antigen presentation by bone marrow–derived cells (BMDCs) (Lenz et al., 2000; Sigal et al., 1999; Sigal and Rock, 2000). The importance of BMDCs in the priming of antiviral CD8 T lymphocyte responses was initially shown in the mouse for vaccinia virus (VACV), poliovirus (PV), influenza A virus (IAV), and most antigenic peptides of lymphocytic choriomeningitis virus (LCMV). Yet, for one peptide from LCMV, BMDC dependency could not be demonstrated (Sigal et al., 1999; Sigal and Rock, 2000; Lenz et al., 2000). This may indicate that there might be exceptions to the need of professional antigen-presenting cells (pAPCs) for CD8 T lymphocyte activation.

The BMDC responsible for the priming of CD8 T cells are called pAPCs. The ability of pAPCs to initiate CD8 T lymphocyte responses relies in their expression of high levels of MHC, costimulatory ligands and cytokines, and the capacity to migrate to the areas of secondary lymphoid organs where CD8 T lymphocyte responses are primed. Traditionally, dendritic cells (DCs), monocytes/macrophages, and B lymphocytes have been considered pAPCs. However, it has been shown that when recovered from secondary lymphoid tissues of mice infected with herpes simplex 1 (HSV-1), VACV, and IAV, the only pAPC that can prime CD8 T lymphocytes *ex vivo* are those DCs that express the CD8α molecule (Allan et al., 2003; Smith et al., 2003; Belz et al., 2004). Moreover, mice deficient in the transcription factor Batf3, which lack CD8α DCs, do not generate CD8 T lymphocyte responses to HSV-1 or MCMV (Nopora et al., 2012). Thus, there is current consensus that CD8α DCs are key pAPCs during viral infections. However, it remains to be formally demonstrated that these are the only pAPCs that prime CD8 T lymphocytes *in vivo*.

Some pAPCs Can Present Exogenous Antigens on Their Own MHC I Molecules

In addition to DP, some pAPCs have the capacity to phagocytose dead or dying cells, processing some of their proteins, and presenting their peptides on their own MHC I molecules. This process is known as cross-presentation (CP) and allows pAPCs to cross-present viral antigens inside virus-infected cells (Shen and Rock, 2006; Gutierrez-Martinez et al., 2015; Cresswell et al., 2005).

Two major pathways of CP have been defined. In the cytosolic pathway, the exogenous proteins in vacuoles, such as endosomes and phagosomes, gain access to the cytosol, are processed by the proteasome, and are transferred to the ER or back to phagosomes to be loaded onto newly synthesized MHC I molecules. Alternatively, in the vacuolar pathway, access to the cytosol is not necessary and the peptides are generated in endosomes and phagolysosomes by proteases in the vacuoles (Shen and Rock, 2006) (**Figure 1b**).

Direct- and Cross-Presentation in Antiviral CD8 T Lymphocyte Responses

The initial demonstration that cytosolic CP can be sufficient to prime an antiviral CD8 T lymphocyte response *in vivo* was done with PV in a situation where DP was not possible (Sigal et al., 1999). However, the physiological role of CP in the normal priming of antiviral CD8 T lymphocytes remained hotly debated with some arguing that CP is essential and others considering it irrelevant (Melief, 2003; Heath et al., 2004; Wilson et al., 2006; Zinkernagel, 2002; Amigorena, 2003; Lizee et al., 2003). In the middle ground, it appears that CP is important for some viral infections or viral antigens and not for others. For example, CP by CD8α DCs is necessary for an efficient CD8 T cell response to HSV-1 (Nopora et al., 2012; Wilson et al., 2006). Also, vacuolar CP is partly responsible for the CD8 T cell response to IAV (Shen et al., 2004). On the other hand, DP is sufficient for efficient priming of CD8 T cell responses to WT VACV, even though at least some of its antigens can be cross-presented (Larsson et al., 2001; Ramirez and Sigal, 2002; Serna et al., 2003; Xu et al., 2010). Conversely, it has been reported that CP dominates the CD8 lymphocyte response to the replication-deficient strain of VACV-modified vaccinia Ankara (Gasteiger et al., 2007). However, this finding has been challenged (Wong et al., 2013).

Costimulatory Molecules and Their Role in Antiviral CD8 T Cell Priming

In addition to TCR ligation, optimal CD8 T lymphocyte responses require costimulation, which is also known as 'signal 2.' Most costimulatory molecules expressed by T cells belong to either the CD28 or the tumor necrosis factor receptor (TNFR) families. The CD28 family includes CD28, which binds CD80 and CD86 on pAPCs and ICOS which binds B7h on most cells. The TNFR family includes CD27, OX40, and 4-1BB, which respectively bind CD70, OX40-L, and 4-1BBL (Duttagupta et al., 2009; Welten et al., 2013). For the priming of CD8 T cells, the most important costimulatory molecule is CD28, while the others play roles at other stages of the response such as expansion or maintenance (Duttagupta et al., 2009). In contrast to the CD8 T cell responses to inert antigens, where absence of CD28 costimulation results in anergy, the CD8 T lymphocyte responses to virus in the absence of CD28 still occur, but their timing and strength may vary according to the specific pathogen. For example, absence of CD80 and CD86 results in reduced responses to vesicular stomatitis virus, murine gammaherpesvirus 68, and IAV, but the response to LCMV is normal (Duttagupta et al., 2009). Of note, during VACV infection, the strength of the CD8 T lymphocyte response in CD28-deficient mice is normal, but the kinetics is delayed by one or two days. Yet, because VACV is only mildly pathogenic to mice, this delay is inconsequential to the health of the mice. On the other hand, when CD28-deficient mice are infected with the related ectromelia virus, a poxvirus that is very pathogenic to mice, this delay in the CD28 response results in the death of the majority of CD28-deficient mice (Fang and Sigal, 2006).

Differences with Other T Cells

In contrast to CD8 T cells, CD4 T cells recognize antigens bound to MHC II molecules. For CD4 T cells, the major pAPCs are also DCs, but B cells that acquire antigen through the BCR also play a very important role. The process of antigen presentation on MHC II is quite different because the peptide is loaded in vesicular compartments and not in the ER. This requires a special mechanism to prevent the binding of peptides to MHC II in the ER (Blum et al., 2013). In general, it is thought that CD4 T cells recognize viral antigens acquired by the pAPCs from the outside. Yet, endogenous viral proteins can also be presented on MHC II (Eisenlohr, 2013).

NKT cells are another type of T cells that recognize antigen as exogenous and endogenous glycolipids bound to the nonclassical MHC I molecule CD1d. The mechanisms of antigen loading on CD1d and the role of NKT cells in antiviral immunity are less well understood.

Summary

Naïve CD8 T cells become activated when they recognize peptide antigen bound to MHC I at the surface of bone marrow–derived pAPCs. In contrast to other cells, pAPCs produce cytokines and express costimulatory molecules that are important for optimal CD8 T cell activation. For several viral infections, it has been shown that the key pAPCs are CD8α^+ DCs. As most other cells, pAPCs can directly present antigen synthesized within the cell. Yet, pAPCs, and in particular CD8α^+ DCs, can also acquire viral antigens from other infected cells and cross-present them with their own MHC I. While DP is more efficient, it is thought that CP is important for CD8 T cell responses to viruses that do not infect pAPCs or those that produce immune evasion molecules that target DP. Once activated by pAPCs, effector CD8 T cells can recognize any infected cell expressing MHC I loaded with its cognate peptide. This results in the killing of the infected cell and/or the production of antiviral cytokines both being important to control or clear viral infections. After the infection subsides, some antiviral CD8 T cells remain as memory cells, with their numbers being proportional to the strength of the initial response. These memory CD8 T cells can help control secondary infections, and their induction is a main goal of vaccination. Thus, understanding the process of CD8 T cell activation can help develop better vaccines.

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See also: **Cytokines and Their Receptors:** Interferon γ: An Overview of Its Functions in Health and Disease. **Development of T Cells and Innate Lymphoid Cells:** Control of Early T Cell Development by Notch and T Cell Receptor Signals. **Immunity to Viral Infections:** CD8 T Cell Memory to Pathogens; Dendritic Cells in Viral Infection; Vaccination against Viruses. **MHC Structure and Function:** Immune Epitope Database and Analysis Resource; Ligand Selection and Trafficking for MHC I; Molecular Immunoevasion Strategies Targeting Antigen Processing and Presentation; Origin and Processing of MHC-I Ligands; Repertoire of Classical MHC Class I and Class II Molecules; Structure of Classical Class I MHC Molecules. **Signal Transduction:** Immunological Synapses. **Structure and Function of Diversifying Receptors:** Organization and Rearrangement of TCR Loci; Structure and Function of TCR$\alpha\beta$ Receptors. **T Cell Activation:** Conventional Dendritic Cells: Identification, Subsets, Development, and Functions; Cytotoxic Lymphocytes; Recirculating and Resident Memory CD8$^+$ T Cells; Transition of T Cells from Effector to Memory Phase.

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