Table 3 Continued

Species	*Live*	*Killed*	*Recombinant*	*DNA*
Porcine	Pseudorabies	Pseudorabies		
	Enterovirus	Influenza		
	Parvovirus	Circovirus		
	Rotavirus	Rotavirus		
	Transmissible gastroenteritis	Transmissible gastroenteritis		
	Reproductive and respiratory syndrome	Reproductive and respiratory Syndrome		
	Hog cholera	Hog cholera		

Several of the described vaccines are being administered as combination vaccines.

See also: AIDS: Vaccine Development; Antigen Presentation; Antigenic Variation; Antigenicity and Immunogenicity of Viral Proteins; Cytokines and Chemokines; Diagnostic Techniques: Serological and Molecular approaches; DNA Vaccines; Immune Response to viruses: Cell-Mediated Immunity; Neutralization of Infectivity; Vaccine Production in Plants; Vaccine Strategies.

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Immune Response to Viruses: Cell-Mediated Immunity

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Glossary

Antigen presentation The process by which proteins are degraded into peptides that are loaded onto MHC molecules and these complexes are targeted to the cell surface.

Central-memory T cell A population of memory T cells which primarily reside in secondary lymphoid organs; characterized by the expression of CD62L and CCR7.

Chemokines Chemotactic cytokines which stimulate the migration of cells.

Cytokines Secreted proteins that regulate cellular actions by signaling via specific receptors.

Cytotoxic T lymphocyte (CTL) T cells which can kill virus-infected cells upon activation.

Effector T cell Cells capable of immediate functional activity resulting in pathogen removal.

Effector-memory T cell A population of memory T cells poised for immediate effector

function that primarily resides outside the lymphoid organs.

Immune homeostasis Maintenance of lymphocyte populations at steady-state levels.

Immunodominance The hierarchy of T-cell responses to the array of individual epitopes which are presented during any given viral infection.

Immunological memory The ability of the host to mount rapid recall responses upon re-exposure to the inducing antigen.

Immunopathology Tissue damage that results from the actions of the host's immune response.

Major histocompatibility complex (MHC) A cluster of genes involved in immune recognition and regulation; MHC class I molecules couple with β2 microglobulin to present peptides to CD8 T cells; MHC class II molecules present peptides to CD4 T cells.

T-cell exhaustion The progressive loss of antiviral T-cell functions which can culminate in the complete deletion of specific T-cell populations during chronic viral infections.

T-cell receptor (TCR) Heterodimeric receptor expressed by T cells that binds specific peptide–MHC complexes.

T helper 1 (Th1) cell Effector CD4 T-cell subset characterized by the production of IFN-γ; associated with immune responses to intracellular bacteria and viruses.

T helper 2 (Th2) cell Effector CD4 T-cell subset characterized by the secretion of IL-4, IL-5, and IL-13; important for helminth infections; linked to allergies and asthma.

General Overview

Cell-mediated immune responses play a critical role in combating viral infections. They are comprised of T-cell responses, which fundamentally differ from antibody (humoral) responses in the way they bring about infection control. The cardinal trait of cell-mediated responses is that the physical presence of reactive T cells is required for immunity, whereas humoral responses are conferred by the presence of soluble antibodies. T cells, together with B cells, form the adaptive immune response to viral infections. The hallmarks of adaptive immunity include antigen specificity and memory. These features allow T cells to elaborate responses which specifically target the numerous viruses which may infect the host. The ability to establish long-lived immunological memory provides a unique mechanism to better protect the host during subsequent viral exposures.

Due to their importance in controlling pathogens, cell-mediated immune responses are widely studied. Significantly, much of our understanding of cell-mediated immunity, including the fundamental concepts of major histocompatibility complex (MHC) restriction, tolerance, T-cell diversity, and immunological memory, has been determined by analyzing immune responses to viruses. Cell-mediated immune responses are dynamic, diverse, and display a broad range of phenotypic and functional properties.

T-Cell Recognition

T cells differ from antibodies (humoral responses) in the way they recognize viral antigens. Antibodies are capable of binding to intact viral proteins, including structural components of viral particles and also viral proteins present at the surface of infected cells. By being able to bind to conformationally complex structures, antiviral antibodies have the unique ability to neutralize the infectivity of viral particles present in the circulation or at mucosal surfaces, a function that cannot be performed by T cells. T cells cannot recognize intact viral proteins and therefore play no role in directly neutralizing whole viral particles. Instead, T cells recognize short peptide fragments presented at the cell surface in a noncovalent association with MHC molecules (see **Figure 1**). Thus, T-cell recognition is referred to as being MHC-restricted, since an individual T cell will only bind strongly to one particular MHC molecule, and is also peptide specific, as a T cell will predominately only recognize one specific short antigenic peptide.

T-Cell Receptors

CD4 and CD8 T cells express a unique surface receptor, the T-cell receptor (TCR) that determines the MHC restriction and peptide specificity of an individual T cell. In the vast majority of T cells, this is a heterodimeric receptor comprised of the TCR α- and β-chains. A smaller population of T cells (~5% of circulating T cells in humans) express an alternative form of the TCR, formed by the noncovalent association of TCR γ- and δ-chains; however, the roles of γδ T cells in controlling viral infections are not well defined. Each T cell expresses only one unique version of the TCR whose precise sequence and structure represents the end result of a series of gene rearrangements. This recombinatorial process, which occurs during T-cell ontogeny in the thymus, generates a massive repertoire of T cells with tremendous diversity between their individual TCR sequences. Estimates of the size of the T-cell repertoire suggest that 2.5×10^7 different TCRs are detectable in human blood. This large ensemble of

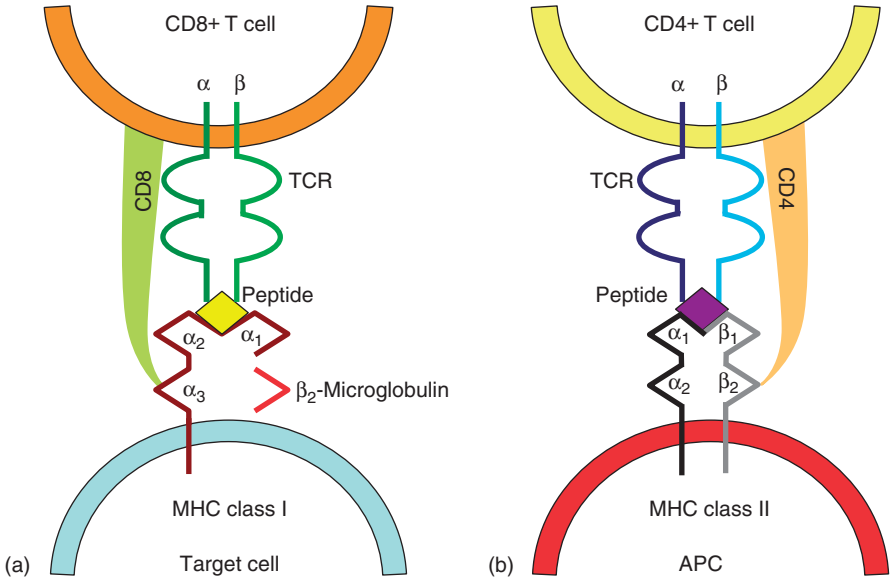

Figure 1 Similarities and differences between CD4 and CD8 T-cell recognition. Both CD4 and CD8 T cells express unique T-cell receptors at the cell surface which determine their antigen specificity and MHC restriction. (a) CD8 T cells recognize MHC class I molecules together with a non-covalently associated antigenic peptide, typically of 8–10 amino acids in length. MHC class I complexes are widely expressed and usually present endogenously synthesized antigens, including peptides derived from the degradation of viral proteins. (b) CD4 T cells recognize peptide antigens presented by MHC class II molecules. These antigenic peptides are typically 13–17 amino acids in length. These peptides are usually derived from extracellular antigens which have been endocytosed into professional antigen-presenting cells where they are proteolytically processed and re-presented at the cell surface bound to MHC class II molecules. MHC class II complexes have a much more limited tissue distribution than MHC class I molecules and are primarily expressed by macrophages, dendritic cells, and B cells.

individual T-cell clones is collectively capable of recognizing and responding to the vast array of antigens, including virally encoded antigens, which may be encountered during the lifespan of the host.

Antigen Processing and Presentation

CD8 T cells recognize MHC class I complexes (Figure 1). MHC class I molecules are expressed on virtually all cell types and usually present peptides derived from endogenously synthesized proteins. Antigen processing occurs continuously as newly synthesized proteins become degraded into peptide fragments by proteasomes. These fragments, typically of 8–10 amino acids in length, enter the endoplasmic reticulum and, if they have sufficient binding affinity, associate with MHC class I heavy chains together with the nonpolymorphic protein β2-microglobulin. These assembled MHC peptide complexes are then transported to the cell surface. This process allows MHC class I molecules to sample peptide fragments derived from proteins which are produced within the cell, including normal cellular proteins as well as virally encoded proteins, and present them for inspection by CD8 T cells. This ongoing immunological surveillance allows CD8 T cells to detect, respond to, and remove host cells which express 'non-self' viral proteins.

Although the endogenous pathway of antigen presentation provides a valuable mechanism for revealing the presence of virally infected cells to CD8 T cells, an alternative 'cross-presentation' pathway also operates. During cross-presentation, viral particles (or other antigens) are endocytosed by professional antigen-presenting cells and then undergo proteolytic degradation. The resulting peptide fragments can then bind to MHC class I molecules, and traffic to the cell surface. This enables antigen-presenting cells, such as dendritic cells, to display virally derived peptides to CD8 T cells even if the antigen-presenting cell itself is not capable of supporting virus replication.

CD4 T cells differ from CD8 T cells as they recognize peptides presented by MHC class II rather than MHC class I complexes (Figure 1). Unlike MHC class I complexes, which are ubiquitously expressed, MHC class II molecules are only presented by certain cell types such as dendritic cells, macrophages, and B cells. This limits CD4 T-cell recognition to professional antigen-presenting cells, since it is these specialized cells that have the capacity to display peptide–MHC class II complexes to CD4 T cells. Due to structural differences in the peptide-binding groove of MHC class I and MHC class II complexes, the viral peptides that are presented to CD4 T cells are typically longer (~13–17 amino acids in length) compared to those displayed by MHC class I molecules. In addition, whereas MHC class I complexes primarily present endogenously synthesized antigens, MHC class II molecules usually present antigens derived from

extracellular sources. These exogenous antigens can include viral particles and also remnants of virally infected cells. Following uptake by professional antigen-presenting cells, these antigens are degraded into peptide fragments within acidified endosomes. Alternatively, if the antigen-presenting cell is actively infected with the virus, then intracellular vesicles containing viral proteins can serve as a source of peptides for associating with MHC class II complexes. Once at the cell surface these presented antigens can be detected by, and activate, CD4 T cells which express TCRs that are capable of specifically recognizing the peptide–MHC class II combination.

Immunodominance

Individual viruses encode multiple potential T-cell epitopes; therefore T-cell responses elicited during viral infections are not monoclonal or monospecific. Instead, oligoclonal subsets of cells are induced and, although each individual T cell is responsive to only one particular peptide–MHC combination, the overall pool of cells is sufficiently diverse to ensure that numerous epitopes can be detected. The kinetics, magnitudes, phenotypic and functional traits, as well as the stability of T responses to each individual virally encoded epitope can differ. Consequently, an ordered hierarchy can emerge as certain epitopes elicit more abundant, or immunodominant responses, whereas others are less prevalent and give rise to subdominant responses (Figure 2).

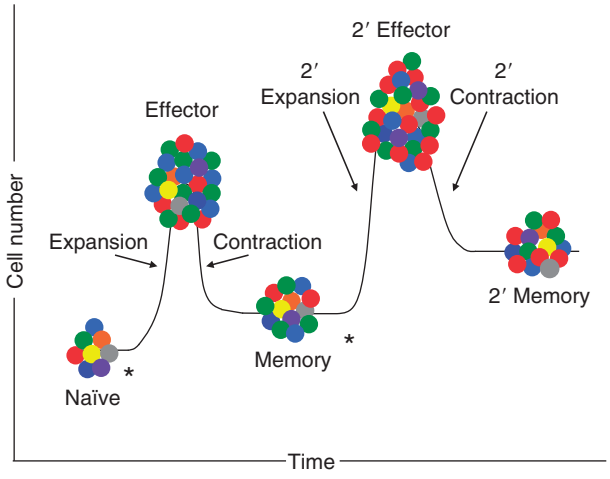

Figure 2 Changes in T-cell immunodominance can occur during primary and secondary immune responses following acute viral infections. Viruses elicit T-cell responses to a range of individual viral epitopes. These responses are not necessarily equal and in the example depicted the T cells specific for the 'green' epitope are immunodominant following the primary infection. This pattern of immunodominance is maintained during the memory phase but secondary exposure to the virus results in an anamnestic recall response during which the 'red' epitope-specific T cells predominate. Asterisk indicates when exposure to the virus occurred.

Our understanding of the precise determinants of immunodominance is incomplete; however, the hierarchy of T-cell responses is likely to be shaped by many factors. The magnitude of responses to individual viral epitopes is influenced by properties of the host's T cells including precursor frequencies and the avidity of the T cells for the presented viral antigen, as well as viral related factors including the ability of viral peptides to bind MHC complexes, the abundance of presented antigen, the kinetics of viral protein synthesis, and the types of cells which present the viral antigens. Changes in the patterns of immunodominance have been reported most notably during the course of persistent viral infections, as well as following secondary exposures to viruses which have been previously controlled (Figure 2). In the case of lymphocytic choriomeningitis virus (LCMV) infection of C57BL/6 mice, the NP396 epitope is co-dominant following well-controlled acute infections, and CD8 T cells specific for this epitope respond most vigorously during secondary exposures to LCMV. By contrast, during persistent LCMV infections, responses to this usually dominant epitope can become completely undetectable. During Epstein–Barr virus (EBV) infections shifting patterns of immunodominance are observed as responses to immediate early and early viral proteins are initially detected, but as viral latency becomes established responses to lytic cycle proteins decline and responses to latent viral proteins predominate. These observations demonstrate that not all antiviral T cells respond equally and suggest that certain specificities of T cells may be more effective at combating particular viral infections.

Induction of Cell-Mediated Immunity during Viral Infections

As a virus infection becomes established in the host, a series of molecular and cellular signals are initiated which activate cell-mediated immune responses. These signals include the production of interferons, other cytokines, and inflammatory mediators, in addition to the mobilization of local dendritic cells. Dendritic cells are thought to provide a critical cellular link for priming naive CD4 and CD8 T cells (Figure 3). It has been proposed that these cells are especially prone to infection by viruses which facilitate their role as cellular sensors for signaling the occurrence of an infection. Even if dendritic cells are not permissive to active infection with particular viruses, they can also present antigens through cross-priming to CD8 T cells, as well as to CD4 T cells via the classical exogenous antigen processing pathway.

The primary activation events which induce cell-mediated immunity predominately occur in secondary lymphoid organs including regional lymph nodes and the

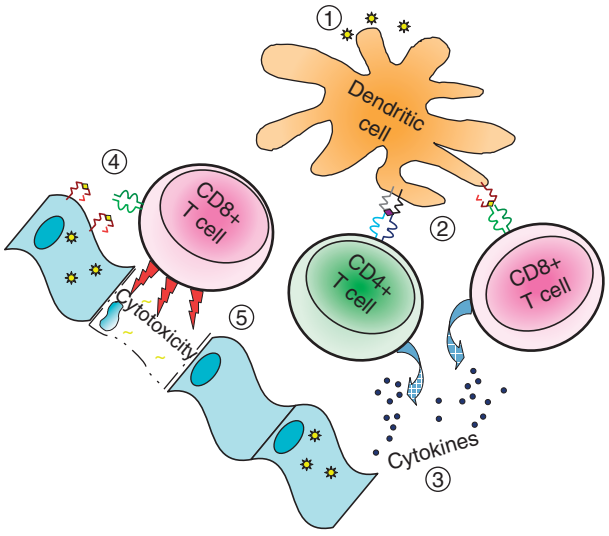

Figure 3 The induction and function of cell-mediated immune responses. (1) The presentation of viral antigens by professional antigen-presenting cells is a critical step in initiating cell-mediated immune responses. (2) Recognition of cognate peptide–MHC complexes by CD4 and CD8 T cells stimulates their proliferation and differentiation into effector cells. (3) Antigen-activated effector CD4 and CD8 T cells can express cytokines such as IL-2, TNF-α, and IFN-γ. These cytokines have important roles in coordinating the antiviral immune response and can also have direct antiviral effects. (4) Once activated antiviral T cells disperse into tissues where can they respond locally, at the sites of viral infection. (5) If viral peptide–MHC complexes are recognized, then effector CD8 T cells can elaborate cytotoxic effector functions which kill the infected cells. CD4 T cells can also become cytotoxic during certain infections; however, their impact is less promiscuous as they recognize the MHC class II complexes which are only expressed by professional antigen-presenting cells.

spleen. During the early stages of viral infections dendritic cells residing at the initial sites of infection take up viral antigens, become activated, and migrate to regional lymph nodes. Within the lymph nodes these dendritic cells encounter naïve T cells which are circulating through these organs as part of their normal immunosurveillance protocol. Engagement of TCRs on the naive T cells with viral–peptide MHC complexes presented by the dendritic cells results in sequestration of the T cells and launches the antiviral T-cell response (**Figure 2**). The ensuing proliferation and differentiation of virus-specific T cells also occur in conjunction with inflammatory mediators such as interferons and other danger signals. Many parameters, including the duration and strength of antigenic stimulation, co-stimulatory interactions, the presence of cytokines, and the provision of CD4 T cells help guide the developing response. These early events play a critical role in driving the generation of both the effector T cells as well as the subsequent establishment of the memory T cell pool.

CD8 T Cells

One of the most impressive aspects of CD8 T-cell responses is the massive proliferation of these cells which occurs during the initial phase of many viral infections (**Figures 2** and **4**). Experimental studies of acute LCMV infection of mice have demonstrated that antiviral CD8 T cells can increase over 10 000-fold during the first week of infection; over 50%, and perhaps even more, of the host's CD8 T cells are LCMV-specific at the peak of the response! Marked expansions of virus-specific CD8 T cells are a common feature of many virus infections including influenza, vaccinia virus, EBV, yellow fever virus, and early following human immunodeficiency virus (HIV) infection. During this expansion phase the patterns of gene expression change promoting the synthesis of cytokines and cytotoxic effector molecules as well as alterations in surface molecules including cytokine receptors and adhesion molecules. This results in an expanded pool of virus-specific effector cells with functional attributes necessary to control the infection. The ensemble of virus-specific effector cells which emerge during the acute phase of the infection is remarkably heterogeneous and comprises of subsets which differ in their epitope specificity, clonal abundance, effector potential, expression of adhesion molecules and cytokine receptors, and ultimate fate. Although the initial activation of T-cell responses occurs in secondary lymphoid organs, the effector cells become dispersed throughout the host. In this way the T cells are available locally, at the sites of infection, where they operate to eliminate the host of virally infected cells.

CD8 T cells are potent antiviral effector cells due to their ability to produce both inflammatory mediators as well as cytotoxic effector molecules (**Figure 3**). CD8 T cells are commonly referred to as cytotoxic T lymphocytes (CTLs), which emphasizes their ability to kill virally infected target cells. These killing functions are triggered as the effector T cell become activated following engagement with a virally infected target cell displaying an appropriate peptide–MHC complex. The subsequent release of perforin and granzyme molecules by the T cells ensures the swift destruction of the infected cell. Ideally, this targeted removal of the infected cell occurs before progeny virus is released. Alternative Fas and TNF-dependent cytotoxic mechanisms have been reported but their *in vivo* significance in killing virus infected cells is not well defined. In addition to their direct killing functions, CD8 T cells also produce a range of cytokines and chemokines. In the laboratory the production of these effector molecules is often used to detect the presence of antiviral T cells. Most importantly, within the infected host the production of these soluble mediators, such as IFN-γ and TNF-α, can also help clear viral infections without causing death

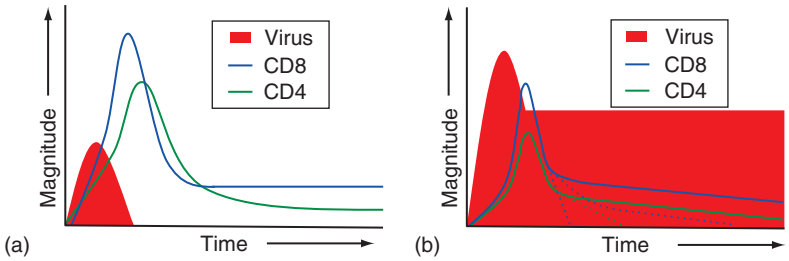

Figure 4 Successful and unsuccessful T-cell responses during acute and chronic viral infections. (a) During acute viral infections massive T-cell responses can be induced which play a principal role in clearing the infection. Following the resolution of the infection, the responding T-cell pool is downregulated but a long-lived pool of memory T cells becomes established which helps protect against subsequent viral exposures. (b) During chronic viral infections T-cell responses are elicited but a variety of phenotypic and functional defects manifest as these responses succumb to exhaustion. A gradation of exhausted phenotypes is often observed, ranging from an inability to produce effector cytokines to the complete deletion of virus-specific T cells.

of infected cells. This cytokine-mediated purging of infected cells has been most convincingly shown during viral hepatitis.

CD4 T Cells

CD4 T cells are traditionally known as helper T cells because of their ability to provide help to B cells and CD8 T cells, resulting in antibody production, class switching, cytotoxic T cell activity, and memory development. In addition to assisting cells of the adaptive immune system, CD4 T cells produce an array of cytokines and chemokines that stimulate cells of the innate immune system, such as macrophages and neutrophils, to traffic to the sites of infection and elaborate their effector activities. It has also been demonstrated that CD4 T cells are directly capable of antiviral functions, through the production of IFN-γ and, in some circumstances, by inducing lysis of virally infected cells (**Figure 3**). Thus, CD4 T cells are critical constituents of the cell-mediated immune response to viral infections; however, it should be emphasized that innate immunity as well as humoral immune responses, which are helped by CD4 T cells, are key components of the host overall antiviral response.

Like CD8 T cells, naive CD4 T cells circulate through secondary lymphoid organs in a relatively quiescent state. Following recognition of antigen in the context of MHC class II, a cascade of signaling events is initiated within the CD4 T cell which results in activation, proliferation, and differentiation into an effector CD4 T cell (**Figure 3**). Classically effector CD4 T cells have been divided into two polarized subsets based on their cytokine production profile. T helper 1 (Th1) cells primarily produce IFN-γ and are critical for the immune responses to various viral infections, as well as infections with intracellular bacteria. This subclass of effector cells is typically associated with antiviral cell-mediated immunity. Conversely, T helper 2 (Th2) cells predominantly secrete the cytokines IL-4, IL-5, and IL-13, assist with the eradication of helminth infections, and have historically been linked with the production of antibodies and humoral immune responses.

In recent years, the definition of CD4 T-cell subsets has expanded beyond Th1 and Th2 cells, with the importance of unique populations of regulatory CD4 T cells and also IL-17 producing 'Th17' cells becoming evident. Regulatory cells are pivotal for preventing autoimmunity by suppressing the activation of autoreactive T cells. Regulatory T cells are typically characterized by the expression of the transcription factor Foxp3 and by the production of the suppressive cytokines IL-10 and TGF-β. Relatively little is known regarding the significance of these CD4 T-cell populations during viral infections; however it has been proposed that regulatory T cells are both beneficial to the host, by limiting immunopathology, and detrimental, by dampening effector functions.

T-Cell Memory

Ideally, the primary immune response overwhelms the infection and results in the complete eradication of the virus from the host. If the infection is successfully resolved then the expanded pool of effector T cells does not remain constitutively activated. Instead, a downregulation phase ensues during which typically the majority (<90%) of the virus-specific T cells present at the peak of the immune response die by apoptosis. The remaining 5–10% of T cells survive the contraction phase and constitute a long-lived pool of memory T cells (**Figures 2** and **4**). In this way, a beneficial memory of past infections is established as, by comparison with naïve hosts, an increased number of virus-specific T cells are maintained which are tuned to rapidly respond if they re-encounter infected cells. The population of memory T cells which emerges following the resolution of the infection and restoration of homeostasis is not uniform, as phenotypic and functional

diversity is apparent even within subsets of memory T cells which recognize the same viral epitope. This is well illustrated by the classification of memory T cells into broad categories termed effector- and central-memory T cells. These subsets have been defined based upon their anatomical location, functional quality, proliferative potential, and expression of surface molecules.

Since T cells neither recognize nor neutralize the infectivity of viral particles they do not confer sterilizing immunity and cannot prevent secondary infections. Nevertheless, as the host cells become infected, preexisting memory T cells which developed following prior viral exposures can mount robust recall responses. These anamnestic responses are characteristically more rapidly induced, greater in magnitude, and possibly more functionally competent than primary T-cell responses. Such pronounced secondary responses help protect the host by contributing to the swift control of the infection thereby reducing the morbidity and mortality. Memory T-cell responses are not the only components of secondary immune responses as these cells act in conjunction with antiviral antibodies to protect the host during viral reexposures.

Analysis of both clinical specimens and experimental animal models has demonstrated that acute viral infections can induce very long-lived memory T-cell responses (**Figure 4**). Studies using experimental mice have demonstrated that memory CD8 T cells reactive against various infections such as LCMV, vaccinia virus, and influenza are maintained at remarkably stable levels for over 2 years following infection. By contrast, CD4 T-cell responses are not as consistent and have been reported to gradually decay over time. Although natural exposures to viruses lead to the formation of immunological memory, these advantageous responses are also induced following vaccinations. Vaccines are successful in protecting the host against subsequent infections because of their ability to promote long-lived memory responses. In humans the longevity of T-cell responses has been investigated in detail following smallpox vaccination. Smallpox-specific T-cell responses are detectable in individuals who received a single dose of the vaccine 75 years previously! Notably, the findings suggested that the responses do decline slowly with predicted half-lives of 8–15 years.

Persistent Viral Infections

Although T-cell responses can be highly effective at controlling acute infections and contribute to protective secondary responses, persistent viral infections do arise and are often associated with the development of phenotypically and functionally inferior responses (**Figure 4**). These types of infections include many viral pathogens which are of significant public health importance such as HIV and hepatitis C virus (HCV). A common feature of these infections is that T-cell responses are initially induced but qualitative and quantitative defects become apparent as the generation of robust sets of effector cells, as well as the progression of memory T-cell development are subverted. By comparision with successful T-cell responses elaborated during acute viral infections, a spectrum of phenotypic and functional defects have been detected during persistent infections. The production of cytokines including IL-2, TNF-α, and IFN-γ, as well as cytotoxic effector molecules such as perforin may be diminished or abolished, and decreased proliferative potential has also been observed. The severe loss of effector activity as well as the physical deletion of antiviral T cells which can occur during persistent infections has been termed exhaustion (**Figure 4**).

The parameters which contribute to T-cell exhaustion are not fully understood. Comparative analysis of T-cell responses to viral infections which result in different levels of antigenic exposure, such as influenza, cytomegalovirus, EBV, HCV, and HIV, indicate that antiviral T cells may adopt different preferred phenotypic and functional set points. Experimental studies suggest that many factors including, but not limited to, viral targeting and destruction of dendritic cells, the production of immunosuppressive cytokines such as IL-10, the depletion of CD4 T cell subsets, and the induction of weak neutralizing antibody responses can all contribute inferior cell-mediated immune responses. Changing viral loads may also impact the functional quality of the T-cell response. During acute HCV infection antiviral CD8 T cells transiently lose the ability to produce IFN-γ, but recover from this 'stunned' state as the viral loads are brought under control. Importantly, this suggests that under certain conditions the exhaustion of virus-specific T cells may be prevented or even reversed. Several reports have now demonstrated that during persistent LCMV, HIV, and HCV infections, antiviral T cells can express the inhibitory receptor PD-1. Antibody-based therapeutic treatments to block this receptor have been shown to promote proliferation of previously exhausted T cells and restore their functional activities. This is a promising experimental observation; however, the jury is still out on whether this approach will be a beneficial treatment for persistent infections of humans.

Immunopathology

Since viruses are obligate intracellular pathogens they must infect permissive host cells in order to replicate. Infected cells die as a direct result of the virus' lytic replication cycle or are killed as a consequence of the

actions of the antiviral immune response. Although immune-mediated destruction of virally infected cells is necessary to contain the infection, it can also result in immunopathology, which represents collateral damage to the host caused by the actions of the immune response. A classical example of immunopathology occurs following intracranial infection of adult mice with LCMV. Mice infected by this route succumb to a characteristic lethal disease and expire approximately 1 week following infection. Death can be prevented by immunosuppression of the mice, which has shown that the disease is a consequence of a vigorous CD8 T-cell response rather than due to the infection *per se*. HBV-associated viral hepatitis is another instance where anti-viral CD8 T-cell responses, which are attempting to clear the infection, cause liver damage in the infected individual.

Most viral infections are associated with the development of an IFN-γ-producing Th1-CD4 T cell response. In various animal models, the absence of CD4 T cell help during viral infection results in impaired clearance of the infectious agent. However, not all CD4 T-cell responses are beneficial as the induction of inappropriate types of CD4 T-cell responses can be deleterious to the host, due to immunopathology. In the 1960s, a group of young children were administered a formalin-inactivated vaccine for respiratory syncytial (RS) virus and following exposure to live RS virus, these children exhibited enhanced infection rates and immunopathology linked to increased frequencies of eosinophils and neutrophils within the airways. Animal studies have indicated that the vaccine was associated with a Th2-biased virus-specific immune response (increased levels of IL-4 and IL-13, as well as eosinophil recruitment to the lungs) that upon live infection displayed many of the signatures of immunopathology which manifested in these vaccinated children. Supporting experiments suggest that immunization to promote the Th1 responses or ablation of Th2 responses prevents the development of these pathological effects following live viral infection.

Immune Evasion

Arguably, one of best indications of the importance of cell-mediated immunity in controlling viral infections is the observation that many viruses have evolved strategies to evade the actions of the host immune response. There is, however, no one universal evasion mechanism; instead, viruses have adopted various preferred approaches to escape antiviral T-cell responses. A common strategy is to change the amino acid sequence of T-cell epitopes or nearby flanking residues that impede the recognition or processing of the antigenic peptide. Many viruses rely on error-prone polymerases in order to replicate, which favor the incorporation of mutations in progeny viral genomes. The resulting variant viruses will have a selective advantage if the amino acid substitution abolishes the ability of the epitope to associate with MHC molecules, negatively impacts recognition of the epitope by T cells, or prevents antigen processing.

In addition to mutating epitope sequences, many viruses encode specific molecules which function to interfere with the antiviral immune response. Both MHC class I and class II antigen-presenting pathways are targeted by several viral proteins. These immune evasion molecules block antigen presentation in various ways, ranging from preventing the transport of antigenic peptides into the endoplasmic reticulum to inhibiting the egress of peptide-loaded MHC complexes. The end result of these inhibitory strategies is to impair immunological surveillance. Although there is much anecdotal evidence that interference with antigen processing diminishes cell-mediated immune responses, experimental studies using murine cytomegalovirus (MCMV) question this notion. Infection of mice with mutants which lack several viral genes known to block antigen processing did not effect the ability of the host to elaborate an anti-MCMV CD8 T-cell response.

See also: Antigen Presentation; Antigenic Variation; Antigenicity and Immunogenicity of Viral Proteins; Cytokines and Chemokines; Immune Response to viruses: Antibody-Mediated Immunity; Immunopathology; Innate Immunity: Defeating; Innate Immunity: Introduction; Persistent and Latent Viral Infection; Vaccine Strategies; Viral Pathogenesis.

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