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# Host defenses to viruses

Viruses as obligate intracellular parasites require their host to replicate them and to facilitate their spread to others. In humans, viral infections are rarely lethal, even if they are highly cytolytic to individual cells. Mortality commonly occurs when viruses jump species (such as Ebola or human immunodeficiency virus (HIV)), when the virus undergoes a major antigenic change (i.e., influenza viruses), or when host immunity is compromised. HIV represents one of the most dramatic human examples of an exotic virus that kills its host. However, HIV kills slowly, providing ample time to spread to new hosts and an effective strategy for persistence in the species. Death or dire consequences following virus infection in mammals with inadequate immunity are well illustrated by observations that fetuses or neonates, especially if deprived of passive immunity, succumb to many agents well tolerated by normal adults. The increasing wealth of immunological tools, such as transgenic animal models and major histocompatibility complex (MHC) tetramers, have provided sensitive methods for defining the relevance of immune mechanisms for antiviral defense. In most situations, defense against viruses involves multiple immune components, and the impact of a single mechanism varies greatly according to the method by which individual viruses enter, replicate, and spread within the host. In this chapter, we highlight the principal means by which the host achieves immunity following infection by viruses. Table 27.1 presents an overview.

## Viral entry and infection

Access to target tissues presents numerous obstacles for entry and infection by most human viruses. Most effective of these are the mechanical barriers provided by the skin and mucosal surfaces, as well as the chemically hostile environment of the gut (Fig. 27.1). A number of common human viral pathogens enter through the gastrointestinal tract, including rotavirus, enteric adenoviruses, and hepatitis A virus (HAV). These are usually spread via person-to-person contact or contaminated food and water. Respiratory infections caused by influenza viruses, rhinoviruses, coronaviruses, measles virus, varicella-zoster virus (VZV), and respiratory syncytial virus (RSV) are often spread by aerosol transmission, as well as person-to-person contact. Many of the herpes viruses target the skin or the mucosae, such as herpes simplex virus (HSV) and VZV. HSV in particular can infect oral and genital mucosa, the eye, and the skin through small cuts and abrasions. Other herpes viruses, such as Epstein–Barr virus (EBV) and cytomegalovirus (CMV), target the mucosa. CMV can also spread vertically from mother to baby or rarely via blood transfusions. Human papillomavirus (HPV) targets skin and mucosa and causes warts and may transform cells, inducing cancers such as cervical cancer. Viruses such as West Nile virus, Dengue virus and Semliki forest virus may also enter through the skin via insect vectors. HIV and hepatitis B virus (HBV) are commonly spread via sexual contact. HIV, HBV, and hepatitis C virus (HCV) can also infect humans via direct entry into the bloodstream via transfusions or contaminated needles.

Most human viruses replicate only in certain target tissues, this being mainly the consequence of viral receptor distribution. Many viruses use two receptors, such as the use of the CD4 co-receptor and the chemokine receptor CCR5 by HIV. After attachment to a cellular receptor, viruses may fuse with the cell membrane or be endocytosed and then gain entry into the cytoplasm or nucleus by fusing with the vesicular membrane (enveloped viruses such as HSV and HIV), or translocate across the cell membrane or induce lysis of the endocytic vesicle once in the cytoplasm (nonenveloped viruses such as Norwalk virus and poliovirus).[1] Viruses then utilize host cell machinery and specialized virally encoded proteins to replicate rapidly within the cell. Once they have multiplied within the cell, many viruses induce cytolysis in order to facilitate release of new infectious virions (the poxviruses, poliovirus, and herpes viruses, for example). Other viruses are released from infected cells by budding through the cell membrane in the absence of cell death (e.g., HIV and influenza virus). Having entered the body, however, viruses encounter numerous innate defenses and activate the components of adaptive immunity. The latter usually assures that clinical disease, if not infection, will not become evident. Successful exploitation of these defenses through the use of vaccines remains a central challenge for many human viruses, particularly those that cause chronic infections such as HIV and HCV.[2]

## Innate immunity to viruses

Viral infection induces an extensive array of defense mechanisms in the host. Innate defenses come into play to block or inhibit initial infection, to protect cells from infection, or to eliminate virus-infected cells; these occur well before the effectors of adaptive immunity become active (Chapter 3). The innate immune defenses are initiated via pathogen recognition receptors (PRRs), which recognize pathogen-associated molecular patterns (PAMPs). These include transmembrane receptors of the Toll-like receptor (TLR) family, two families of intracellular receptors including the NOD-like receptors (NLRs) and the RIG-I-like helicases (RLHs), as well as the sensor molecule absent in melanoma 2 (AIM2) (Table 27.2). These cellular sensors promote the expression of interleukin-1 (IL-1) and IL-18, type I (α/β) interferons (IFN-I) and a variety of IFN-stimulated genes and inflammatory cytokines. TLRs are cell surface or endosomal

**Table 27.1** Viral infections and immunity

| Viral event | Obstacles | Time course |
|---|---|---|
| Transmission | Mechanical and chemical barriers | 0 |
| Infection and replication | Innate immunity | 0 → |
| Infection stopped or spreads | Viral antigens transported to lymphoid tissues | Within 24 hours |
| Infection controlled | Specific antibodies and cell-mediated immunity | 4–10 days |
| Sterile immunity | Immune memory | 14 days to years |
| Viral persistence if infection not controlled | Immune disruption or evasion | Weeks to years |

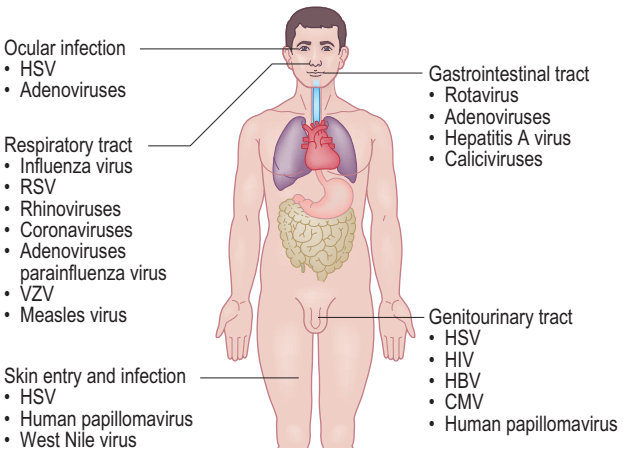


**Fig. 27.1 Common routes of entry and infection for human viral pathogens.** CMV, cytomegalovirus; HBV, hepatitis B virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; RSV, respiratory syncytial virus; VZV, varicella-zoster virus.

membrane-bound proteins expressed by numerous cells including dendritic cells (DC), macrophages, lymphocytes, and parenchymal cells. Expression of TLRs is largely inducible in most cell types, though some (TLR7/8/9) are constitutively expressed at high levels by specialized plasmacytoid DC for rapid IFN production. Different TLR molecules recognize specific viral products such as single- and double-stranded RNA (TLR 3 and TLR7/8, respectively) or double-stranded DNA (TLR9). Much of our understanding of the roles of TLRs to antiviral defense have been discovered in mice, yet our understanding of the similarities and differences in the functions of human TLRs is rapidly improving.[3]

The more recently discovered RLHs, retinoic acid-inducible gene I (RIG-I) and melanoma differentiation-associated gene (MDA-5), mediate cytoplasmic recognition of viral nucleic acids.[4] These activate mitochondrial antiviral signaling proteins (MAVS) to stimulate IFN-I production and activate the inflammasome, a molecular complex that facilitates the activation of caspases and induces the production of proinflammatory IL-1β and IL-18.[5] NLRs are a second class of cytosolic sensors of PAMPS that activate the inflammasone.[6] These include the NLRP (or NALP), NOD, and IPAF/NAIP receptors. Three major inflammasomes have been shown to be involved in antiviral immunity: the NLRP3 inflammasome, the RIG-I inflammasome, and the AIM2 inflammasome. Other cytoplasmic sensors of viruses, such as the more recently discovered cytosolic dsDNA sensor DAI (**D**NA-dependent **a**ctivator of **I**FN), may also play important roles in sensing viral pathogens.

**Table 27.2** Sensors of viral infection

| | |
|---|---|
| **Toll-like receptors (TLRs)** | |
| TLR3 | dsRNA, MCMV, VSV, LCMV, HSV, EBV |
| TLR7 and TLR8 | ssRNA, Influenza virus, HIV, VSV |
| TLR9 | dsDNA, HSV, MCMV |
| TLR2 | MV hemagglutinin protein, HSV, HCMV |
| TLR4 | MMTV envelope protein, RSV |
| **RIG-I-like helicases (RLHs)** | |
| RIG-I | Influenza virus, VSV, HCV, JEV, MV, RSV, Sendai virus, EBV |
| MDA-5 | Poly(I:C), MV, Sendai virus, VSV, MCMV, Picornaviruses |
| **NOD-like receptors (NLRs)** | |
| NLRP3 | Influenza virus, Sendai virus, Adenovirus, Vaccinia virus |
| NOD2 | Influenza virus, VSV, RSV |
| AIM2 | Vaccinia virus, MCMV |
| DAI | Cytosolic dsDNA, HSV |

AIM2, absent in melanoma 2; DAI, DNA-dependent activator of IFN; dsRNA, double-strand RNA; EBV, Epstein-Barr virus; HCMV, human cytomegalovirus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus 1/2; JEV, Japanese encephalitis virus; LCMV, lymphocytic choriomeningitis virus; MCMV, murine cytomegalovirus; MDA-5, melanoma differentiation-associated gene; MMTV, mouse mammary tumor virus; MV, measles virus; NLR, NOD-like receptor; RLH, RIG-I-like helicase; RSV, respiratory syncytial virus; ssRNA, single-strand RNA; TLR, Toll-like receptor; VSV, vesicular stomatis virus.

## KEY CONCEPTS

### Major antiviral innate defense mechanisms

**Acting to block infection:**
- Natural antibodies
- Complement components
- Some cytokines and chemokines

**Acting to protect cells from infection:**
- Interferon-α/β
- Interferon-γ
- IL-1, IL-18

**Acting to destroy or inhibit virus-infected cells:**
- Natural killer cells
- NKT cells
- Macrophages
- Neutrophils
- γδ T cells
- Nitric oxide

**Involved in regulating antiviral inflammatory response:**
- Interleukins-1, 6, 10, 12, 18, 23, 33
- Transforming growth factor-β
- Chemokines (CCL2, 3, 4, 5)

The innate defense system consists of multiple cellular components and many specialized proteins. The longest known and best studied antiviral proteins are the α/β IFNs, which act by binding to the type I IFN receptor and result in the transcription of more than 100 IFN-stimulated genes. One consequence of this "antiviral state" is the inhibition of cell protein synthesis and the prevention of viral replication.[7] Type I IFNs also activate natural killer (NK) cells and induce other cytokines such as IFN-γ and IL-12 that promote NK responses (Chapter 17). NK cells produce pro-inflammatory cytokines, they can kill infected cells and interact with DC, and are an important component of innate defense against viruses. NK cells are regulated by an array of activating and inhibitory receptors whose expression and function are just beginning to be understood. Uninfected cells are usually protected from NK cell cytolysis as they deliver negative signals such as high expression of MHC molecules. In contrast, virus-infected cells are killed either because they deliver positive signals or because they lack adequate MHC-negative signals. The NK defense system appears important against some herpes viruses, which downregulate MHC expression in the cells they infect. NK cells are also important in resistance to mouse and human cytomegalovirus, and possibly to HIV, influenza virus, and Ebola viruses.[8] A distinct NK cell population, NKT cells, may provide some antigen-specific innate immune protection against certain viruses.[9] Many other leukocytes are involved in innate defense, including macrophages, DC, neutrophils, and perhaps T cells expressing γδ T-cell receptors for antigen. Furthermore, tissue cells including fibroblasts, epithelial and endothelial cells express PRRs and can respond to viral infection via the production of innate cytokines, including IFN-I and IL-1.

Several classes of innate host proteins function in antiviral defense. These include natural antibody, which may play a role in defense against some virus infections, as well as the pentraxins and complement proteins.[10] Some viruses may be directly inactivated by complement activation or be destroyed by phagocytic cells that bind and ingest complement-bound virions. Several pro-inflammatory cytokines and chemokines induced by virus infection also play key roles in defense. Foremost among these is IL-1 and other members of the IL-1 family, including IL-18 and IL-33.[11] These cytokines influence both innate and adaptive immune cells and play critical roles in antiviral defense. Other anti-viral cytokines are produced early following infection, such as TNF-α, IFN-γ, IL-12, IL-6, and chemokines such as MIP-1α. In particular, IL-12 is a potent inducer of IFN-γ from NK cells. Inflammatory chemokines may also play an important role in innate antiviral defense by orchestrating macrophage, neutrophil, DC, and NK responses at the site of infection (Chapter 10). Not only are these components of innate immunity involved in mediating initial protection against viruses; several components (such as the PRRs, the cytokines IFN-I, IL-I, and IL-12, and phagocytes including macrophages, monocytes, and DC) serve to shape the nature and effectiveness of the subsequent adaptive response to viral pathogens.

## Adaptive immunity to viruses

Innate immunity generally serves to slow, rather than stop, viral infection, allowing time for the adaptive immune response to begin. The two major divisions of adaptive immunity, antibody and T-cell-mediated, are mainly directed at different targets. Antibodies usually function by binding to free viral particles, and in so doing block infection of the host cell. In contrast, T cells act principally by recognizing and destroying virus-infected cells, or by orchestrating an inflammatory response that includes several antiviral components. As all viruses replicate within cells and many can spread directly between cells without re-entering the extracellular environment, resolution of infection is reliant more on T-cell function than on antibody. Antiviral antibody, however, does assume considerably more importance as an additional immunoprotective barrier against reinfection. It is the presence of antibody at portals of entry—most often mucosal surfaces—that is of particular relevance to influenza, HSV, and HIV infections.[12] Accordingly, vaccinologists try to design vaccines that optimally induce mucosal antibody.

Initiation of adaptive immunity is closely dependent upon early innate mechanisms that activate antigen-presenting cells (APC), principally subsets of DC. APC and lymphocytes are drawn into lymphoid tissues by chemokine and cytokine signals and retained there for a few days in order to facilitate effective interactions between these cells. The architecture of the secondary lymphoid tissues supports the coordinated interactions between cells of the adaptive immune system through a network of supportive stromal cells and local chemokine gradients.[13] The induction events occur in lymph nodes draining the infection site, or in the spleen if virus enters the bloodstream. The passage of viral antigens to lymph nodes usually occurs in DCs.[14] Some viruses are able to compromise the function of APC, such as HSV and measles virus, which can inhibit DC maturation.

B-cell activation occurs following antigen encounter in the B-cell follicles, and possibly the T-cell zones, in the spleen or lymph nodes.[15] Some activated B cells become short-lived plasma cells while others move to the edges of the B-cell follicles and interact with antigen-specific helper CD4 T cells via presentation of antigenic peptides on B-cell MHC class II molecules. These activated B cells initiate germinal center (GC) reactions, which ensure somatic hypermutation and affinity maturation for the selection of high-affinity, antibody-producing long-lived plasma cells, as well as memory B cells (Chapter 7). Recent advances have greatly improved our understanding of the signals that control the generation of these important B-cell subsets, particularly at the molecular level.[16] We now know that upregulation of the transcription factors Blimp-1, XBP-1, and IRF-4 dictates plasma cell formation, whereas Pax-5 expression delineates B cells destined for GC reactions and the memory B-cell lineage.

Antibody binding to epitopes expressed by native proteins at the surface of free virions usually blocks viral attachment or penetration of target cells. Sometimes the consequence is viral lysis (with complement proteins also involved), opsonization, or sensitization for destruction by Fc receptor-bearing cells that mediate antibody-dependent cellular cytotoxicity (ADCC). Occasionally, however, Fc receptor binding of antibody-bound virus may facilitate infection and result in more severe tissue damage. This occurs in dengue fever and may happen in some instances in HIV infection.

As indicated previously, antibody may function most effectively to prevent reinfection, especially at mucosal surfaces. The antibody involved in humans is predominantly secretory immunoglobulin A (IgA), but serum-derived IgG may also be protective, particularly in sites such as the vaginal mucosa. Both antibody isotypes act mainly to block infection of epithelial cells, although in some instances the antibody may transport antigen from within the body across epithelial cells to the outside. Mucosal antibody persists for a much shorter period than does serum antibody, which explains in part why immunity to mucosal pathogens is usually of much shorter duration than is immunity to systemic virus infections.

## KEY CONCEPTS

**Antiviral T- and B-cell immunity**

| Effector systems | Recognized molecules | Control mechanisms |
|---|---|---|
| Antibody | Surface proteins or virions | Neutralization of virus, opsonization, or destruction of infected cells by ADCC |
| Antibody + complement | Surface proteins expressed on infected cells | Infected cell destruction by ADCC or complement-mediated lysis |
| Mucosal antibody (IgA) | Surface proteins or virions | Viral neutralization, opsonization, and transcytosis |
| CD4 T cells | Viral peptides (10–20 mers) presented on MHC class II – surface, internal or nonstructural proteins presented by APC | Antiviral cytokine and chemokine production; help for CD8 T-cell and B-cell responses; killing infected cells; regulatory functions to reduce immunopathology |
| CD8 T cells | Viral peptides (8–10 mers) presented on MHC class I – surface, internal or nonstructural proteins presented on infected cells or by cross-presentation | Killing infected cells or purging virus without cell death; antiviral cytokine and chemokine production |

ADCC, antibody-dependent cellular cytotoxicity; APC, antigen-presenting cell; IgA, immunoglobulin A; MHC, major histocompatibility complex.

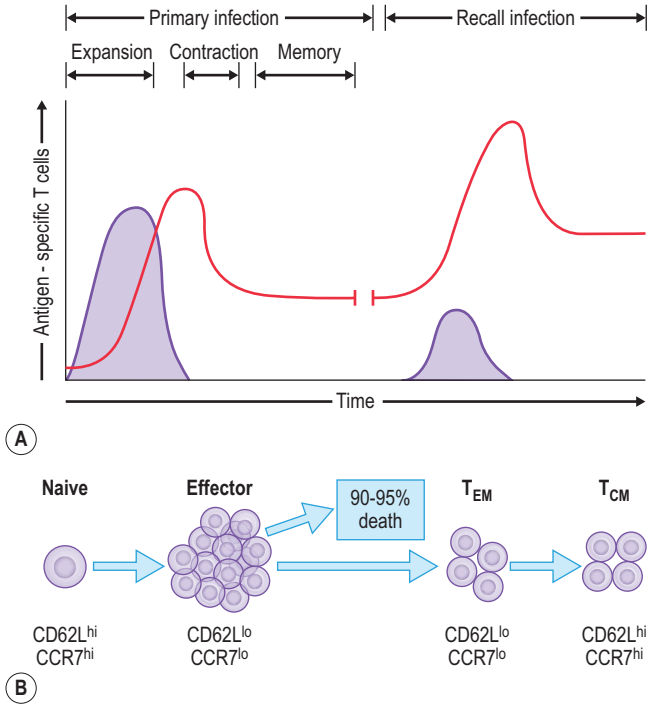


**Fig. 27.2 Expansion/contraction/memory phases of adaptive immunity and memory cell subsets.** (A) Dynamics of primary and secondary (recall) T-cell responses to viral infection. Both primary and recall T-cell responses undergo expansion and contraction phases, followed by stable immune memory. Recall responses induce a larger effector pool and reduced contraction further boosting the memory pool. (B) Effector and memory T-cell differentiation. Antigen stimulation expands effector cells, most of which die during the contraction phase. $T_{EM}$ cells that are formed gradually convert to $T_{CM}$ cells over time, with corresponding changes in surface marker expression.

Like B-cell responses, T-cell responses to viral infections also begin within the lymphoid tissues. Specific CD8 cytotoxic T lymphocyte (CTL) precursors recognize antigen in the context of MHC class I–peptide antigen complexes on professional APC, such as DC. The CD8 T cells become activated, proliferate, and differentiate into effectors. Expansion of these naïve antigen-specific precursors is considerable, often exceeding 10,000-fold, and results in an effector population that can account for 40% or more of a host's total CD8 T-cell population (Fig. 27.2). Various factors, including antigen and APC, co-stimulatory molecules (such as CD28 and 4-1BB), and inflammatory cytokines (such as IFN-I and IL-12) are required to program the development of functional effector lymphocytes.[17] The CTL effectors enter the efferent lymph and bloodstream and access almost all body locations, including both primary and subsequent sites of infection. However, effectors do not stay activated for long once the virus is cleared, and approximately 95% die by a process termed activation-induced cell death. Following this contraction phase, the remaining cells differentiate into memory cells, which remain as a more or less stable population in the host for many years. They represent an expanded pool of CTL precursors that can be activated upon secondary encounter with antigen, and provide enhanced protection upon reinfection with the same virus (see next section). Though much of our knowledge of T-cell responses to viruses have been obtained using mice, recent work has demonstrated that most of the fundamental principles (described below) are the same or similar in humans.[18]

T-cell immunity against a particular virus commonly involves both CD4 and CD8 T-cell subsets. Both CD4 and CD8 T cells recognize peptides derived from viral antigens bound to surface MHC proteins (class II and class I, respectively). Complexes of viral peptides bound to MHC class II proteins are generated by APC from scavenged and processed virus-infected cells or viral particles. Antigen–MHC class I complexes are expressed on the surface of infected cells, and antigen can also be transferred to APC from infected cells by a process known as cross-presentation.[19] Recent experiments in mice have also demonstrated a role for transfer of antigen between DC[20] as they migrate from infected tissues to the lymphoid tissues. Curiously, although many peptides derived from viral proteins have an appropriate motif that permits MHC binding, the majority of CD8 T cells, and possibly CD4 T cells, are often specific for a few immunodominant epitopes. Use of MHC class I and class II tetramers to directly visualize antigen-specific CD8 and CD4 T-cell responses, respectively, has demonstrated the significant size of T-cell responses to viruses and that the majority of the activated T cells seen at the peak of the response are virus-specific.

CTL function by recognizing virus-infected cells and killing them (Chapter 17). This often involves perforins and cytotoxic granules containing granzymes. Effector CTL can also induce death in target cells following engagement of Fas ligand on the CTL with Fas on target cells. Both pathways lead to apoptosis of the target cell, involving the degradation of nucleic acids, including those of the virus. Alternatively, CD8 T cells also mediate defense through the release of various cytokines following antigen recognition. Some of the cytokines and chemokines most highly produced by CTL include IFN-γ, TNF-α, lymphotoxin-α,

and RANTES (Chapters 9 and 10). These cytokines can have multiple antiviral effects on infected cells and the cells around them, including purging of virus from infected cells without killing the cell. This is particularly important for viruses like HSV, which infects non-rejuvenating cells such as nerve cells.

CD4 T cells are also involved in antiviral defense. They are important for controlling infections such as HSV, influenza virus, HIV, and many others. CD4 T cells participate in antiviral immunity in several ways. First, the subset acts as helper cells for the induction of both antiviral antibodies and CD8 T-cell responses to most virus antigens.[21] CD4 T cells also function as antiviral effector cells, and generate stable memory cell populations similar to those of CD8 T cells. The differentiation of CD4 T cells into effectors occurs in a manner very similar to that with CD8 T cells. At present less is known about the size and specificity of CD4 T-cell responses, but effector CD4 T-cell populations appear to consist of a broader epitope specificity than CD8 T cells responding to a given virus. CD4 T cells are activated by recognizing viral peptides associated with class II MHC molecules, which are present on more specialized cells such as APC. Thus, CD4 T cells rarely recognize viral epitopes present on cells as a consequence of viral gene expression within that cell, dictating their function as helper cells for B cells and CD8 T cells, and as producers of cytokines for help and viral clearance.

In some instances CD4 T cells can perform cytotoxic functions, though not as effectively as CD8 CTL. More commonly, however, effector CD4 T cells act by synthesizing and releasing numerous cytokines following their reaction with antigen (Chapter 9). Subsets of CD4 T effectors produce different groups of cytokines. The type most often involved in antiviral defense are designated T-helper 1 (Th1) cells, and primarily produce IFN-γ, LTα, TNF-α, and IL-2 to help orchestrate the inflammatory response and act directly or indirectly in antiviral defense. Conversely, Th2 effectors produce an array of cytokines that may downregulate the protective function of Th1 cells, such as IL-4, IL-5, and two anti-inflammatory cytokines, IL-10 and transforming growth factor-β (TGF-β). Th2 T cells play a protective function against some parasite infections (Chapter 29), though in some virus infections an exuberant Th2 response may be associated with immunopathology or impaired immunity. Indeed, blocking the Th2 cytokine IL-10 was recently shown to assist in the clearance of chronic viral infection. Th17 cells that produce IL-17, and also IL-22, are generated under certain inflammatory conditions, though it is unclear whether these cells play a vital role during viral infections.[22] Lastly, CD4 T cells can differentiate into T follicular helper (Tfh) cells following interactions with antigen-specific B cells, which are important for germinal center formation and antibody responses to viruses.[23]

## Immunological memory

Immunological memory is a cardinal feature of adaptive immunity. The goal of vaccinology is to induce long-lived immunological memory to protect against reinfection. Following infection with certain viruses, memory can be exceptionally long-lived, potentially for the life of the host (e.g., yellow fever and smallpox viruses).[18,24] Memory is defined by the persistence of specific lymphocytes and antibody-producing plasma cells, rather than that of antigen to induce continuous lymphocyte activation. Humoral memory to viruses involves long-lived plasma cells in the bone marrow that provide a continuous low-level source of serum antibody. This maintenance of humoral immunity also involves a population of homeostatically maintained memory B cells, which may be required to maintain stable numbers of long-lived plasma cells over time. The pool of memory T cells is regulated by low-level homeostatic division controlled by the cytokines IL-7 and -15. For memory CD8 T cells, IL-7 is primarily important for survival while IL-15 is crucial for low-level proliferation to maintain the size of the memory T-cell pool.[25]

### KEY CONCEPTS

**Principles of antiviral immunity**

- Many human viral infections are successfully controlled by the immune system
- Certain emerging viruses may overwhelm the immune system and cause severe morbidity and mortality
- Other viruses have developed mechanisms to overwhelm or evade the immune system and persist
- Individuals with defects in innate or adaptive immunity demonstrate more severe viral infections
- T-cell immunity is more important for control than antibody with many viral infections
- Antibody is important to minimize reinfection, particularly at mucosal sites
- Immune memory is often sufficient to prevent secondary disease, though not in all viral infections
- Tissue-specific immune memory may be important to rapidly protect against reinfection at peripheral sites (such as the skin and mucosae)

Immunological memory is defined by a pool of antigen-specific cells whose increased frequency enables rapid control of viral reinfection (Fig. 27.2). A population of IL-7Rα-expressing effector cells are the precursors of this memory pool.[26] This population of cells, which constitutes about 5–10% of the effector pool, preferentially survives the contraction phase, and gradually differentiates into a stable memory population. Upon reinfection, these memory cells can be rapidly activated, and by virtue of their increased frequency mediate more rapid clearance of the viral pathogen. Moreover, repeated stimulation of memory cells via multiple infections with the same virus, or prime-boost vaccine regimes, further increases the size of the antigen-specific memory T-cell pool.[27] Re-stimulation also affects the activation status and tissue distribution of memory T cells, which may enhance protection from viral infection in mucosal, and other, tissues.

Experiments in humans and mice have demonstrated that memory T cells are heterogeneous.[27] Memory T cells have been divided into effector memory ($T_{EM}$) and central memory ($T_{CM}$) subsets, defined by expression of two surface molecules involved in T-cell migration: CD62L and CCR7. The $CD62L^{lo}CCR7^{lo}$ $T_{EM}$ subset is found primarily in non-lymphoid tissues and spleen, whereas the $CD62L^{hi}CCR7^{hi}$ $T_{CM}$ subset is largely present in the lymph nodes and spleen. The current model predicts that effector T cells form the $T_{EM}$ subset and these cells gradually convert to a $T_{CM}$ phenotype over time. Though the conditions that control the rate of this conversion are unknown, it is likely that the amount of antigen and inflammatory signals received during the effector phase greatly influences this. It has also been shown that CD4 T-cell help is required for the generation of long-lived memory CD8 T cells, via interactions with DC.[21]

Studies suggest that $T_{CM}$ are capable of mounting stronger proliferative responses following reinfection. However, the tissue-specific homing of $T_{EM}$ cells permits them to reside in sites of potential viral infection, such as the skin and mucosae. Indeed, the hallmark of a recently described subset of memory CD8 T cells involves long-term residence within tissues at sites of previous viral infection.[28–30] This includes the skin, intestine, and brain.

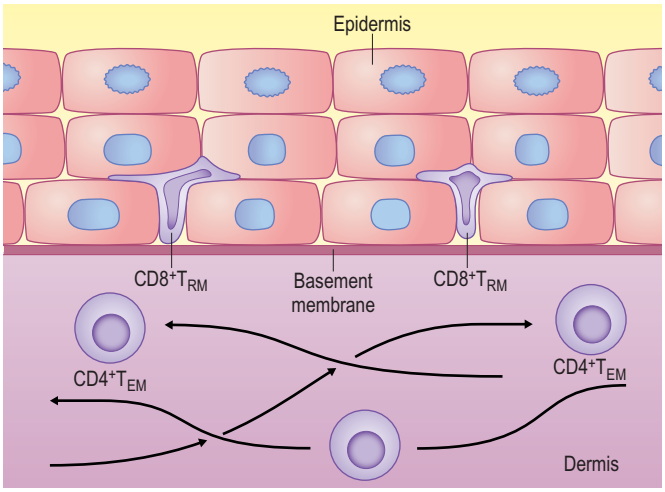


**Fig. 27.3 Unique subsets of memory CD8 and CD4 T cells reside within peripheral tissues, at sites of previous viral infection, and provide rapid protection against reinfection.** Resident memory CD8 T cells ($T_{RM}$) remain localized in the epidermis in skin after HSV infection. CD4 $T_{EM}$ continue to migrate through the dermal layers of skin, with access to the blood and the lymphoid tissues.

These resident memory T cells ($T_{RM}$) are sequestered from the circulation and provide rapid protection against viruses such as HSV in skin, where they localize with a unique dendritic morphology and undergo slow surveillance of the tissue (Fig. 27.3).[44] This is in contrast to CD4 $T_{EM}$, which continue to migrate through the nonlymphoid tissues rather than being sequestered in the peripheral tissues, and also differs from the CD8 and CD4 $T_{CM}$, which migrate largely through the lymphoid organs (spleen and lymph nodes). These differences may define the physiological *raison d'être* for these memory T-cell subsets. However, memory in certain peripheral tissues, such as the lungs, may be less effective or wane over time.[31] This may explain in part why vaccines against respiratory viruses have a poor record.

## Immune evasion and immunity to chronic viral infections

Many, if not all, viruses employ immune blunting or delay tactics to circumvent aspects of the immune system, allowing them time to replicate further or escape detection (Table 27.3).[32] One such mechanism may involve killing or infecting APC. Viruses may also delay or prevent apoptosis induced by CTL within infected cells. Other viral evasion measures aimed at the CD8 T-cell-mediated antiviral defense system serve to inhibit antigen processing, thereby minimizing effector CTL induction. Many viruses also downregulate MHC molecules on the surface of infected cells to escape CTL killing. In addition, viruses may produce various mimics or modulators/inhibitors of cytokines, chemokines, or other components of the immune system or their receptors. Viruses also resort to antigenic hypervariability to escape antibody or T-cell recognition. This can occur during transmission from host to host (e.g., influenza virus), or within hosts during chronic infection through the generation of viral escape mutants. The latter is particularly important for HIV and HCV infections.

The success of many viral pathogens rests in their ability to subvert the host immune response. The most successful human viruses can escape the immune system and persist for the life of the host.[33] Two well-studied examples of this are CMV and EBV. T-cell responses to these viruses are prominent and readily

**Table 27.3** Mechanisms and examples of viral immune evasion

| Mechanism | Example |
|---|---|
| Interference with viral antigen processing and presentation | HSV (ICP47), EBV (EBNA-1), HIV (Nef, Tat), HPV (E5), CMV (UL6) |
| Evasion of NK cell function | HIV (Nef), EBV (EBNA-1), CMV (UL40, UL18) |
| Inhibition of cell apoptosis | Adenovirus (RID complex and E1B), HIV (Nef), EBV (BHRF-1) |
| Destruction of T cells | HIV |
| Interference with antiviral cytokines and chemokines | EBV (IL-10 homologue), CMV (US28 chemokine receptor homologue), vaccinia virus (IL-18-binding protein), HIV (Tat chemokine activity) |
| Inhibition of complement action | HSV, pox viruses |
| Inhibition of DC maturation | HSV, vaccinia virus |
| Frequent antigenic variation | Influenza virus, HIV |
| Infection of immune privileged site | Measles virus, VZV and HSV (neurons) |
| Immune exhaustion | HIV, HCV, HBV |

CMV, cytomegalovirus; DC, dendritic cell; EBV, Epstein–Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HPV, human papillomavirus; HSV, herpes simplex virus; IL-18, interleukin-18; NK, natural killer; RID, receptor internalization and degradation; VZV, varicella-zoster virus.

detectable in people, yet the immune system is unable to clear either pathogen completely. However, these viruses generally remain undetectable in immunocompetant individuals. Other viral infections, such as those caused by the herpes viruses HSV and VZV, are marked by periods of latency, where no virus can be detected. Yet periods of viral reactivation, often triggered by stress, can lead to episodes of disease. These are controlled by the immune response, which plays a central role in controlling herpes virus latency.[34]

Many of the most medically important human viruses are associated with persistent viremia. These include chronic infections such as HIV, HCV, HBV, and human T-lymphotropic virus (HTLV), among others. Such viral infections are marked by high levels of persisting antigen and can result in skewed T-cell immunodominance hierarchies, altered tissue localization of immune cells, and severely impaired T-cell function.[33] This altered T-cell function is hierarchical and results in functional T-cell defects ranging from reduced cytokine production and altered proliferative capacity (exhaustion) to death (deletion) of the responding T cells (Fig. 27.4). Recent work has shown that viral antigen levels are responsible for this immune dysfunction.[35] This is in stark

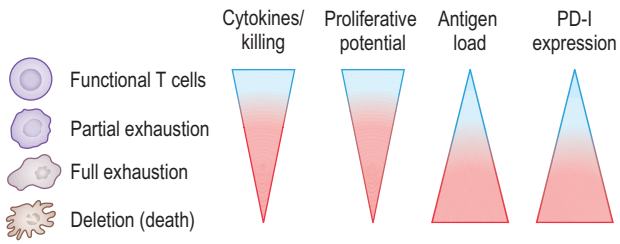


**Fig. 27.4 Hierarchical model of T-cell exhaustion during persistent viral infection.** T-cell function (cytokine production, killing, and proliferative potential) is negatively influenced by increasing levels of antigen. Low levels of persistent antigen may lead to partial loss of function and intermediate levels of programmed death (PD)-1 expression. High, sustained levels of antigen over time can lead to full loss of function, high levels of PD-1, and eventually cell death (deletion).

contrast to normal memory T-cell development, which occurs in the absence of persisting antigen (see previous section). Recent studies have demonstrated that signaling through the cell-surface receptor programmed death (PD)-1 on effector CTL causes exhaustion during chronic infections.[36] This pathway may be essential for preventing excessive immunopathology by effector T cells, yet appears to contribute directly to failed immunity to HIV infection, and other chronic human viral infections. These studies implicate this pathway as a potential therapeutic target.

## Outcomes of virus infection: immunity or immunopathology

Typically, individual humans respond to a virus infection in different ways. When the common cold or even pandemic influenza infection occurs, only a small percentage of exposed persons may develop overt clinical disease. In the pre-vaccine days, poliomyelitis was a much-feared consequence of poliovirus infection, but only a very small percentage of infected persons developed the paralyzing complications. Similarly, only an unfortunate few develop life-threatening meningoencephalitis following infection with the insect–transmitted West Nile fever virus. It is particularly characteristic of chronic viral infections that clinical expression is highly variable. With hepatitis C, for example, 70-80% of patients develop some form of chronic liver disease and fail to clear infection. However, up to 30% do control the infection, clear virus, and can be immune to reinfection. The latter group of individuals make a type of immune response that includes protective antibodies along with an appropriate pattern of T-cell responsiveness.[37]

We do not fully understand the reasons for the varying outcome of virus infections in different persons and almost certainly multiple factors are involved. Many of these factors impact the response pattern made by the innate immune system that in turn affects the magnitude and type of adaptive immune response that occurs. Some of the circumstances that do influence the outcome of infection include genetic susceptibility of the host, the age of the host when infected, the dose and route of infection, the variable induction in the host of anti-inflammatory cells and proteins, and the presence of concurrent infections and past exposure to cross-reactive antigens.[37]

## Immunopathology and autoimmunity

Immune responses against virus-infected cells often result in tissue damage, especially if cell killing is involved or there is extensive recruitment and activation of inflammatory cell types such as macrophages and sometimes neutrophils. If the response is brief and is quickly repaired, it is usually judged as an immunoprotective event. A prolonged tissue-damaging effect resulting from an immune reaction against viruses is considered immunopathology. Such situations most commonly involve persistent viruses, which are themselves often mildly cyto-destructive in the absence of an immune reaction. Chronic tissue damage initiated by viruses may also result in development of an autoreactive and an occasionally oncogenic response. For example, some autoimmune diseases (AID) may be initiated or exacerbated by virus infections, but no named virus has been regularly incriminated as a cause of human AID.[38] Circumstantial evidence exists for a virus link in multiple sclerosis (MS), insulin-dependent diabetes, and possibly systemic lupus erythematosus (SLE). In MS, many viruses have been isolated from patients, although no specific one has been tied to the disease etiology. The current hypothesis is that viral infections set up an inflammatory environment that may exacerbate or tip the balance towards disease in genetically susceptible individuals.[38]

Immunopathological reactions involving viruses have several mechanisms, but T cells are usually involved as orchestrators of the inflammatory events (Table 27.4). The clearest example of immunopathology involving a virus is lymphocytic choriomeningitis virus (LCMV) in the mouse. This model has dominated ideas and has set several paradigms in viral immunology in general. The first virus-induced immunopathological lesion recognized was glomerulonephritis and arteritis, noted in mice persistently infected with LCMV. The lesions were assumed to represent inflammatory reactions to tissue-entrapped immune complexes that activate complement. Similar immune complex-mediated lesions occur in other infections, which include lung lesions found in severe influenza and respiratory syncytial virus, as well as viral hepatitis and arthritis.[39] However, only rarely have viral antigens been shown to contribute to the antigen component of the complex. An example where the inclusion of viral antigen in immune complexes has been demonstrated is chronic hepatitis B virus infection of humans. Autoimmune disease such as SLE also results from immune complex-mediated tissue damage. However, evidence linking viruses to the etiology or pathogenesis of SLE is scarce, since the immune complexes in SLE do not appear at any stage to include viral antigens.

Thanks largely to the LCMV model, it is clear that CD8 T-cell recognition of viral antigens can result in tissue damage. In LCMV damage occurs in the leptomeninges of immunocompetent mice infected intracerebrally. Hepatitis can also occur in mice infected intravenously. Neither lesion becomes evident if the CD8 T-cell response is suppressed. CD8 T-cell-mediated immunopathology is a causative mechanism of chronic hepatitis associated with hepatitis C and B infection as well as with some lesions that occur

**Table 27.4** Lesions resulting from immunopathology

| | |
|---|---|
| Primarily involving CD8 T cells acting as cytotoxic T lymphocytes or sources of pro-inflammatory cytokines: | Murine lymphocytic choriomeningitis virus;<br>Hepatitis B virus-induced chronic hepatitis;<br>Coxsackie B virus-induced diabetes;<br>Coxsackie B virus-induced myocarditis;<br>Demyelination caused by some strains of mouse coronavirus and Theiler's virus |
| Primarily involving CD4 T cells that produce Th1 cytokines: | Demyelination caused by some strains of mouse coronavirus and Theiler's virus;<br>Herpes simplex virus-induced stromal keratitis |
| Involvement of CD4 T cells that produce Th2 cytokines: | Respiratory syncytial virus-induced pulmonary lesions |
| Involvement of antibody: | Glomerulonephritis in chronic hepatitis B;<br>Dengue hemorrhagic fever |

during HIV infection.[40] The immunopathological mechanisms involved in hepatitis B infection have been carefully analyzed in a mouse model in which the whole HBV was expressed as a transgene. In this model, CD8 T cells orchestrated the immunopathology, but the process was complex. Initially, CTL-mediated killing events occurred, but since hepatocytes die by apoptosis it was not clear how this related to subsequent inflammatory events. However, the CD8 T cells also released numerous cytokines and chemokines that recruited inflammatory cells, primarily macrophages. Interestingly, liver-infiltrating CTL have been shown to be inhibited by PD-1–PD-L1 interactions, which may greatly reduce the severity of local immunopathology. Additional viral immunopathology models where lesions result primarily from CD8 T-cell involvement include myocarditis and insulin-dependent diabetes associated with coxsackie B virus infection. In both instances, CD8 T cells mainly orchestrate events, but tissue damage may result from the bystander effects of cytokines and other molecules such as lipid mediators, metalloproteinases, and components of the oxygen burst. Although coxsackie virus can be a cause of diabetes in the mouse, attempts to relate viral infection directly to the etiology of human diabetes have so far failed.[38]

## CLINICAL RELEVANCE

**Hypothesized role of viruses in autoimmunity**

- Molecular mimicry: similar epitopes shared by virus and host
- Bystander activation: chronic release of cytokines and host antigens activates local autoreactive lymphocytes
- Viral persistence: chronic viral antigen presentation on host cells leads to prolonged immunopathology

Immunopathological reactions against viruses can also involve subsets of CD4 T cells. Most commonly Th1 cells are responsible for such reactions, but Th17 and occasionally Th4 subsets may also play the main role. One well-studied example involves persistent infection with Theiler's virus in mice.[41] This infection causes a demyelinating syndrome that resembles the AID experimental allergic encephalomyelitis. In both situations, CD4 T cells that produce Th1 cytokines appear to serve as the pathologic mediators. Furthermore, in both models an increase in the involvement of myelin-derived autoantigens occurs as the disease progresses. Once again, such observations indicate the possible role of a virus in an autoimmune disease. With the Theiler's virus model the virus persists in the nervous system and chronically stimulates CD4 T cells to secrete an array of cytokines. The demyelinating events appear to result from cytokine action on oligodendrocytes. Myelin components such as myelin basic protein, proteolipid protein, and myelin oligodendroglial glycoprotein may be released and participate as additional antigens in immunoinflammatory events. This scenario is referred to as epitope spreading.

Another model of virus-induced immunopathology that mainly involves the Th1 subset of CD4 T cells is stromal keratitis caused by herpes simplex virus infection (Fig. 27.5).[42] The pathogenesis of this immunopathological lesion is unusual in that it occurs and progresses when viral antigens can no longer be demonstrated. The chronic immunoinflammatory lesions are mainly orchestrated by CD4 T cells, but multiple early events occur that induce the subsequent pathology. Viral replication, the production of certain cytokines and chemokines (IL-1, IL-6, IL-12, and CXCL8), recruitment of inflammatory cells (such as neutrophils), and neovascularization of the avascular cornea all precede immunopathology.[42] Recently, it has become evident that Th17 T cells participate in stromal keratitis lesions. The role of Th17 T cells as orchestrators of inflammatory reactions has been a major research focus especially in lesions of AID.[22] When Th17 T cells are the principal mediators of tissue damage, there is an abundance of neutrophils recruited to the inflammatory sites, with such cells mainly responsible for the tissue damage.

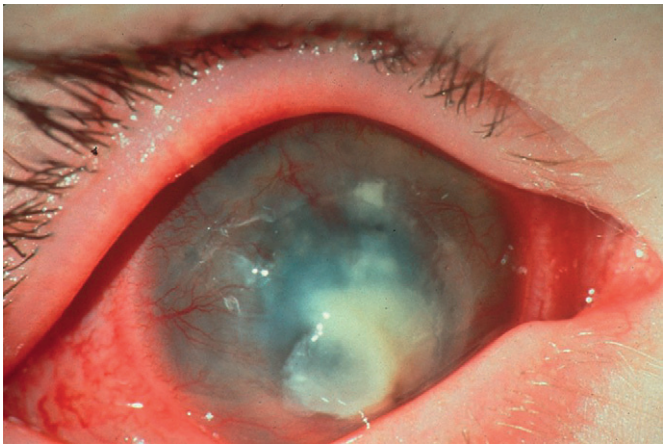

**Fig. 27.5 Example of herpetic stromal keratitis (HSK) in the human eye after herpes simplex virus-1 (HSV-1) infection.** Inflammation of the eye and eyelid can be observed, as well as neovascularization, and substantial necrosis, ulceration, and opacity of the cornea.

A further mechanism of viral-induced immunopathology and autoimmunity is molecular mimicry.[38] Molecular mimicry represents shared antigenic epitopes, either B- or T-cell antigens, between the host and virus (Chapter 48). The idea began for streptococci and their association with rheumatic fever. With human autoimmune disease, there is little direct support for viral molecular mimicry; however, some animal models have been used to prove the theoretical case, using a model where a viral antigen is expressed as a self-protein in the islet cells of the pancreas. In this model subsequent infection with the virus induces diabetes. However, this is not true mimicry and may be more closely related to viral antigen persistence in a model such as Theiler's disease.

Recently it has become apparent that immunopathology can result from an imbalance in the types of functional effector T cells induced.[37] Tissue damage can be the bystander consequences of a dysregulated immune response to infection. The magnitude of the response can be influenced by the activity of one or more types of regulatory T cells (Tregs) (Chapter 15). Recent research has emphasized the role of natural $CD4^+CD25^+FoxP3^+$ Tregs, which are considered important for controlling the onset of autoimmune disease. These Tregs can also influence that magnitude of the protective immune response to viruses.[43] Natural $FoxP3^+$ Tregs, or other types of regulatory T cells that produce an abundance of anti-inflammatory cytokines IL-10 and TGF-β, are known to be involved in limiting excessive immunopathology associated with ongoing immune responses to persistent viral infection. Evidence for this has been reported in several viral infections, including HCV, HIV, and influenza virus.[43] It is interesting to note that Treg function may be both beneficial to the host, by limiting immunopathology, and detrimental, due to reduced local T-cell responses and thus prolonged viral persistence.

KEY CONCEPTS

**Phases of immunity affected by regulatory T cells (Tregs)**

- Interference with antigen presentation by dendritic cells
- Inhibition of T-cell proliferation
- Inhibition of molecules involved in tissue-specific migration of effector cells
- Inhibition of T-cell effector functions in lymphoid and nonlymphoid tissues

## Translational research opportunities

Reversing T-cell exhaustion in patients suffering from chronic infections or cancer will be a key clinical target in the near future. The discovery of multiple inhibitory receptors on exhausted T cells (including PD-1, LAG-3, 2B4, TIM-3, etc.) provides the opportunity to selectively improve T-cell function through blockade of these inhibitory receptors. This may be combined with blockade of immunosuppressive cytokines (such as IL-10), or enhancement of signals stimulatory to the response (such as IL-7 therapy), as well as with more traditional anti-viral therapies and vaccination. The challenge that lies ahead will be in determining which combination of inhibitory and stimulatory signals will need to be manipulated in different diseases and in different groups of patients.

The design of new generation vaccines to target diseases such as HIV and influenza virus may require tailor-made solutions for patients who respond poorly to vaccination, or respond improperly through adverse effects such as autoimmune reactions. High throughput approaches now allow for the generation of a molecular signature of vaccination or infection. Such systems biology approaches are expected to result in novel screening for immune protection parameters after vaccination. In the near future this should also assist in the formulation of new vaccines containing key immune activators, such as those that stimulate certain subsets of T cells, or induce appropriate homing molecule expression on these cells to direct them to tissues where they are required to mediate protection (such as mucosal sites, or the skin).

ON THE HORIZON

**Clinically needed research opportunities**

- Overcoming immune dysfunction during chronic viral infections essential for successful viral clearance.
- Improving the efficacy of vaccines to viruses using systems biology approaches.
- Therapies for reducing immunopathology during viral infections.

In some individuals viral infections cause mild, or sometimes debilitating, tissue damage. Factors that influence whether a viral infection results in immunopathology varies from individual to individual. These factors include age, the route of infection, pre-existing immunity, host genetics and the host's viral burden or virome. Our knowledge of the influence of these factors on the outcome of viral infection is expected to improve rapidly in the coming decade. Recent advances have shed considerable light on the various pro-inflammatory and anti-inflammatory mediators produced during viral infections. These represent key targets for novel therapies in the near future via the use of small-molecule inhibitors or treatment with endogenous chemical mediators such as resolvins or protectins.

## Conclusions

Humans are infected by many pathogenic viruses. In most cases, these infections are controlled by the immune system with limited damage to the host. However, certain viruses, particularly in cases where the host's immune system is impaired, can cause significant damage to the host's tissues. As our understanding of the mechanisms underlying innate immune defenses, antigen presentation, T- and B-cell responses, and Tregs continues to improve, so too does the ability to design better vaccines and therapies to boost the immune control of viral infections. Although this remains a challenging goal, particularly for many human viruses such as HIV, HCV, and HSV, these rapid advances continue to provide many avenues for further investigation.

## Acknowledgments

Barry T. Rouse is supported by grants from the National Institutes of Health and Scott N. Mueller by the Australian Research Council.

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