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Immune responses to viruses

Scott N. Mueller, Barry T. Rouse

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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 muscosa and causes warts and may transform cells, inducing cancers such as cervical cancer. Viruses such as West Nile 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 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 (i.e., 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]

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

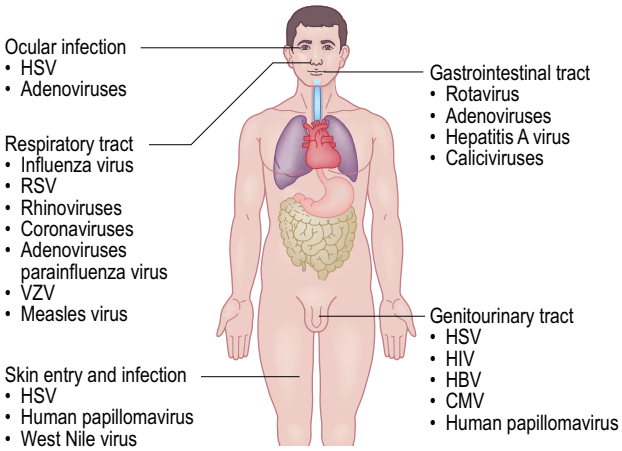

Fig. 27.1 Common routes of entry and infection for human viral pathogens. CMV, cytomegalovirus; HBV, hepatitis B virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; RSV, respiratory syncytial virus; VZV, varicella-zoster virus.

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, and occur well before the onset of adaptive immunity (Chapter 3). The innate immune defenses are initiated via pathogen recognition receptors of the Toll-like receptor (TLR) family or a family of DExD/H box RNA helicases (Table 27.2).[3] These cellular sensors promote the expression of type I (α/β) interferons (IFN) and a variety of IFN-stimulated genes and inflammatory cytokines.[4] TLRs are cell surface or endosomal membrane-bound proteins expressed by numerous cells including dendritic cells (DC), macrophages, lymphocytes, and parenchymal cells.[5] 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). The more recently described non-TLR RNA helicases, retinoic acid-inducible gene I (RIG-I) and melanoma differentiation-associated gene (MDA-5), mediate cytoplasmic recognition of viruses.[6] It is thought that other cytoplasmic sensors of viruses are also likely to exist such as the recently discovered cytosolic dsDNA sensor DAI (DNA-dependent activator of IFN).

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. Type I IFNs also activate natural killer (NK) cells and induce other cytokines such as interleukin (IL)-12 that promote NK responses. NK cells produce proinflammatory

KEY CONCEPTS

MAJOR ANTIVIRAL INNATE DEFENSE MECHANISMS

- Acting to block infection:
  - Natural antibodies
  - Complement components
  - Some chemokines
- Acting to protect cells from infection
  - Interferon-α/β
  - Interferon-γ
- 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
  - Transforming growth factor-β
  - Chemokines

Table 27.2 Sensors of viral infection

Toll-like receptors	
TLR3	dsRNA
	MCMV
	VSV
	LCMV
TLR7 and TLR8	ssRNA
	Influenza virus
	HIV
	VSV
TLR9	dsDNA
	HSV1/2
	MCMV
TLR2	MV hemagglutinin protein
	HSV-1
	HCMV
TLR4	MMTV envelope protein
	RSV
DExD/H box RNA helicases	
RIG-I	Influenza virus
	Paramyxoviruses
	JEV
	HCV
MDA-5	Poly(I:C)
	Measles virus
	Picornaviruses
DAI	Cytosolic dsDNA

dsRNA, double-strand RNA; HCMV, HCV, hepatitis C virus; HIV, human immunodeficiency virus; HSV1/2, 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; RSV, respiratory syncytial virus; ssRNA, single-strand RNA; TLR, Toll-like receptor; VSV, vesicular stomatis virus.

cytokines, they can kill infected cells and interact with DC, and are an important component of innate defense against viruses (Chapter 18). NK cells are regulated by an array of activating and inhibitory receptors whose expression and function are just beginning to be understood.[7] 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 resistence 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. Many other leukocytes are involved in innate defense, including macrophages, DC, neutrophils and perhaps T cells expressing γδ T-cell receptors for antigen (Chapter 3).

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

In addition to IFN-α/β, several other 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 complement proteins (Chapter 20). Some viruses may be directly inactivated by complement activation or be destroyed by phagocytic cells that bind and ingest complement-bound virions. Several cytokines and chemokines induced by virus infection also play a role in defense. These include the cytokines 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 (Chapter 10). 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[9] (Chapter 11). Not only are these components of innate immunity involved in mediating initial protection against viruses, several components (such as the TLRs and type I IFN and IL-12) serve to shape the nature and effectiveness of the subsequent adaptive response to viral antigens.

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. As all viruses replicate within cells and many of them 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 and HIV infections. 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). 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.[10] 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. 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[11] (Chapter 2). Some activated B cells become short-lived plasma cells while others move the edges of the B-cell follicles and interact with antigen-specific helper CD4 T cells via presention 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[12] (Chapter 8). 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.[13] 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.[14]

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.[15] 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.

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

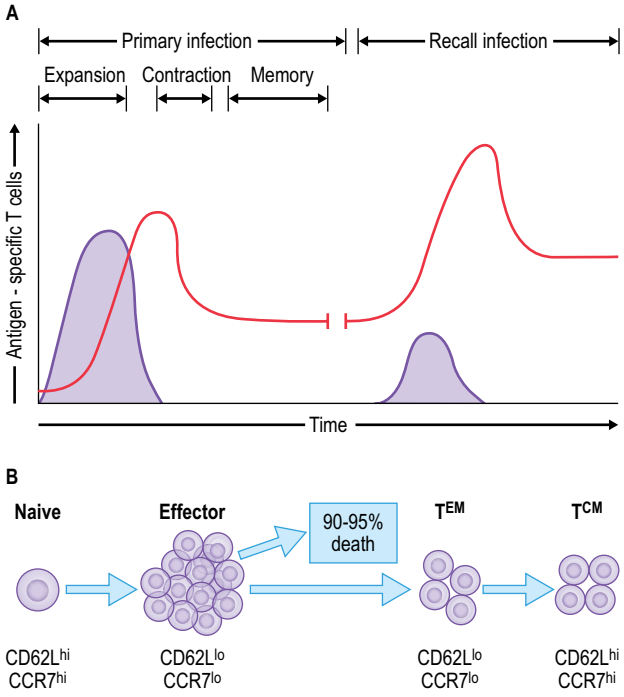

Fig. 27.2 Expansion/contraction/memory phases of adaptive immunity and memory cell subsets. (A) Dynamics of primary and secondary (recall) T-cell responses to viral infection. Both primary and recall T-cell responses undergo expansion and contraction phases, followed by stable immune memory. Recall responses 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.

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-α/β and IL-12) are required to program the development of functional effector lymphocytes.[16] 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. The topic of memory and homeostasis as it relates to antiviral immunity is further discussed later in this chapter.

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

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.

(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-priming.[17] Recent experiments in mice have also demonstrated a role for transfer of antigen between DC[18] 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.[19]

During the past few years there have been major advances in the techniques to quantify antigen-specific T-cell responses. The most revolutionary of these has been the use of MHC class I and class II tetramers to directly visualize antigen-specific CD8 and CD4 T-cell responses, respectively.[20] Many recent studies have used MHC class I tetramers to analyze virus-specific CD8 T-cell responses both in animal models and in humans. These studies demonstrated the significant size of CD8 T-cell responses to viruses and that the majority of the activated CD8 T cells seen at the peak of the response are virus-specific.

CTL function by recognizing virus-infected cells and killing them (Chapter 18). 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 10 and 11). 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 nonrejuvenating cells such as nerve cells.

CD4 T cells are also involved in antiviral defense. They are important, though not always essential, 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.[11, 21] CD4 T cells also function as antiviral effector cells, and generate stable memory cell populations similar to those of CD8 T cells.[22] 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 reports indicate that CD4 T cells undergo less expansion during virus infections, resulting in an effector pool smaller than that observed with CD8 T cells. CD4 T cells are activated by recognizing viral peptides. However, these are larger than those involved in CD8 T-cell recognition and are associated with class II MHC molecules present on more specialized cells such as APC (Chapter 6). 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 17). 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. Additionally, an IL-17-producing subset of effector CD4 T cells has also been described (Th17), with potential roles in immune pathogenesis.[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 (i.e., measles and smallpox viruses).[24, 25] It is now understood that memory is defined by the persistence of specific lymphocytes and antibody-producing plasma cells, rather than persisting antigen inducing 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.[26] This maintenance of humoral immunity also involves a population of homeostatically maintained memory B cells. However, the precise relationship between memory B cells and long-lived plasma cells in maintaining humoral immunity is uncertain. The pool of memory T cells is regulated by low-level homeostatic division controlled by the cytokines IL-7 and IL-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.[27]

Immunological memory is defined by a pool of antigen-specific cells whose increased frequency enables rapid control of viral reinfection (Fig. 27.2).[28] Recent studies identified a population of IL-7 receptor-alpha-expressing effector cells as the precursors of this memory pool.[29] This population of cells, which constitutes ~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.[30] 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. 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.[31] 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 are largely present in the lymph nodes and spleen. The current model predicts that effector T cells form the T_{EM} subset; 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; however, exactly when this help is required during the differentiation of effector and memory T cells is uncertain.[21]

Recent studies have suggested 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. These differences may define the physiological raison d'être for these two memory T-cell subsets. Indeed, protection from localized viral infections such as HSV-1, influenza, and vaccinia virus in mice is more dependent upon T_{EM} cells.[32–34] However, studies suggest that memory in peripheral tissues may be less effective, or wane over time. This appears to be the case in the respiratory tract,[32] explaining 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 evasion strategies to circumvent aspects of the immune system, allowing them time to replicate further or escape detection[35] (Table 27.3). 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 (i.e., influenza virus), or within hosts during chronic infection through the generation of viral escape mutants (i.e., HIV).

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.[36] Two well-studied examples of this are CMV and EBV. T-cell responses to these viruses are prominent and readily 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.[37]

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.[38] 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. This altered T-cell function is hierarchical and appears to correlate directly with antigen levels, resulting in functional T-cell defects ranging from reduced cytokine production and altered proliferative capacity (exhaustion) to death (deletion) of the responding T cells[38] (Fig. 27.3). This is in stark contrast to normal memory T-cell development which occurs in the

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.

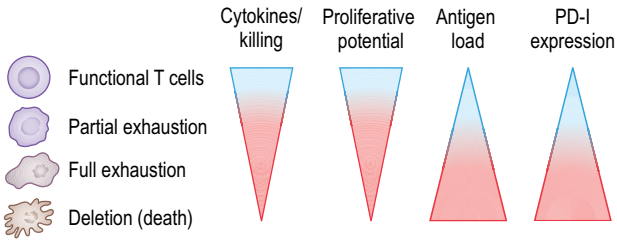

Fig. 27.3 Hierarchical model of T-cell exhaustion during persistent viral infection. T-cell function (cytokine production, killing, and proliferative potential) is negatively influenced by increasing levels of antigen. Low levels of persistent antigen may lead to partial loss of function and intermediate 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).

absence of persisting antigen (see previous section). Recent studies have demonstrated that signaling through programmed death (PD)-1 on effector CTL causes exhaustion during chronic infections.[39] This pathway may be essential for preventing excessive immunopathology by effector T cells, yet appears to contribute directly to failed immunity to HIV infection,[40] and other chronic human viral infections.[39] These studies implicate this pathway as a potential therapeutic target.

IMMUNOPATHOLOGY AND AUTOIMMUNITY

Immune responses against virus-infected cells often result in tissue damage, especially if cell killing is involved. If this effect is brief and without long-term consequences, it is usually judged as an immunoprotective event. A prolonged tissue-damaging effect resulting from an immune reaction against viruses is considered immunopathology.[41] Such situations most commonly involve persistent viruses, themselves at best modestly cytodestructive in the absence of an immune reaction. Chronic tissue damage initiated by viruses may also result in the response becoming autoreactive. Accordingly, some autoimmune diseases may be initiated or exacerbated by virus infections, although this notion has yet to be proved in the case of any human autoimmune disease.[42] 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, though no specific one tied to the disease. 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.[42]

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 immunopathology 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, but 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 diseases such as SLE and rheumatoid arthritis also result 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

Table 27.4 Lesions resulting from immunopathology

Primarily involving CD8 T cells acting as cytotoxic T lymphocyte or sources of proinflammatory cytokines
Murine lymphocytic choriomeningitis virus
Hepatitis B virus-induced chronic hepatitis
Coxsackie B virus-induced diabetes
Coxsackie B virus-induced myocarditis
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
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
Dengue hemorrhagic fever

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

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 also a likely explanation for acute hepatitis caused by some other hepatitis virus strains. The mechanisms involved in hepatitis B infection have been carefully analyzed in a mouse model in which the whole HBV was expressed as a transgene.[43] In this model, CD8 cells organized the immunopathology reaction, but the process appeared complex. Initially, CTL-mediated cell 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, primary 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.[44]

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.[42] In both instances, CD8 T cells mainly orchestrate events, but tissue damage may result from the bystander effects of cytokines. This is especially likely in the diabetes model, as the coxsackievirus cannot be demonstrated in islet cells. The diabetes model is of interest, however, because the events observed closely resemble those that occur in an autoimmune model of diabetes. However, attempts to relate viral infection directly to the etiology of human diabetes have so far failed.[42]

Immunopathological reactions against virus can also involve CD4 T cells.[41] One well-studied example involves persistent infection with Theiler's virus in mice[45] (Fig. 27.4). This infection causes a demyelinating syndrome that resembles the experimental autoimmune disease experimental allergic encephalomyelitis (EAE). In both situations, CD4 T cells that produce Th1 cytokines appear to be pathologic. 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 involving CD4 T cells of the Th1 phenotype is stromal keratitis caused by herpes simplex virus infection (Fig. 27.5).[46] The pathogenesis of this immunopathology 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 (IL-1, IL-6, IL-12, and CXCL8) and chemokines, recruitment of inflammatory cells (such as neutrophils), and neovascularization of the avascular cornea all precede immunopathology.[46] Recent work has also highlighted the role of Th17 CD4 T cells in autoimmune inflammation and immunopathology, and the role of TGF-β and IL-23 in driving these cells.[23] Whether this IL-17/IL-23 axis is important for viral pathoogenesis remains to be determined.

A further mechanism of viral-induced immunopathology and autoimmunity is molecular mimicry.[47] Molecular mimicry represents shared antigenic epitopes, either B-cell or T-cell antigens, between the host and virus (Chapter 50). 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. Tissue damage can be the bystander consequence of a dysregulated immune response to infection. The magnitiude of the response can be influenced by the activity of one or more types of regulatory T cells (Tregs) (Chapter 16). Recent research has emphasized the role of

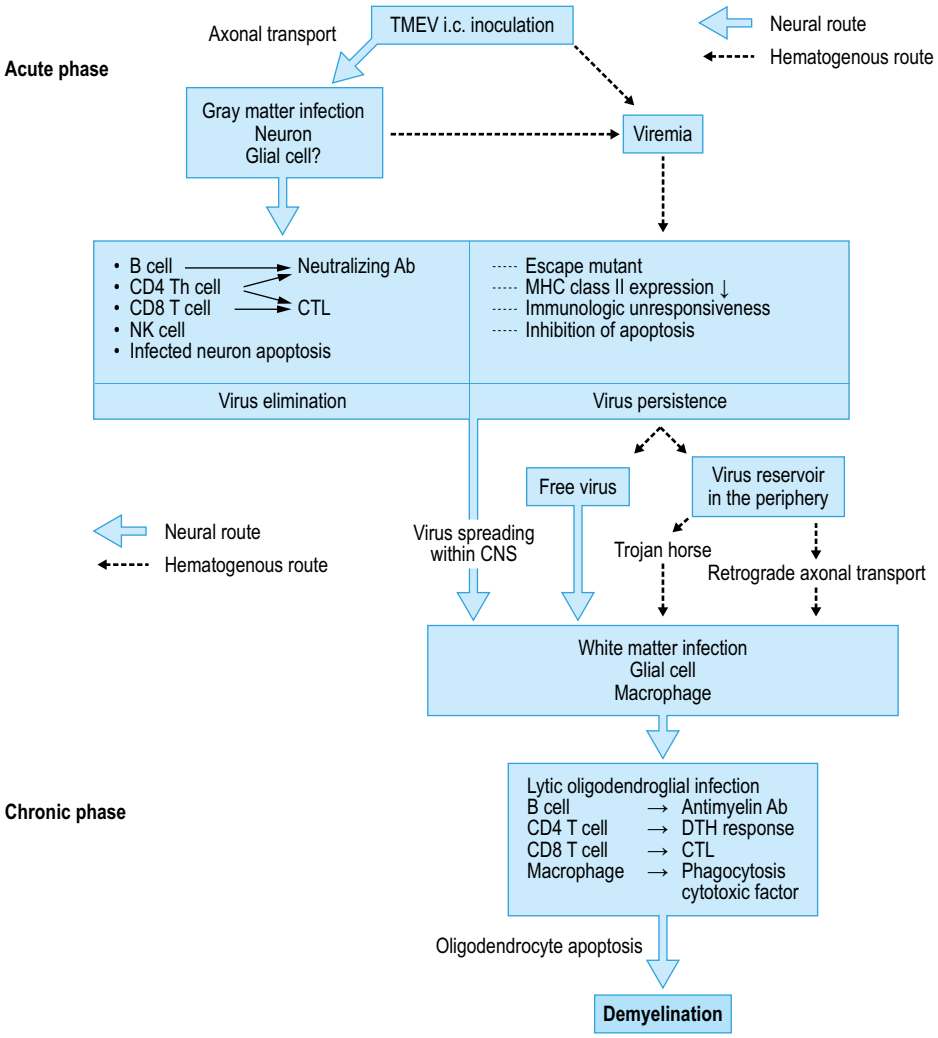

Fig. 27.4 Possible scheme of events set off by virus infection, such as Theiler's virus that results in demyelination. Ab, antibody; CNS, central nervous system; CTL, cytotoxic T cell; DTH, delayed-type hypersensitivity; i.c., intracerebral; MHC, major histocompatibility complex; NK, natural killer; Th, helper T cell. (Courtesy of Dr Robert Fujinami, University of Utah.)

natural $CD4^+CD25^+FoxP3^+$ Tregs, which are considered important for controlling the onset of autoimmune disease. These Tregs can also influence the magnitude of the protective immune response to viruses.[48] Natural $FoxP3^+$ Tregs, or other types of regulatory T cells that produce an abundance of the 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 such as HCV and HIV.[48] 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.

CONCLUSIONS

Humans are infected by several pathogenic viruses, the number of which would be far greater but for the presence of innate and adaptive mechanisms of immunity. As it is, relatively few cause major clinical problems or lethality, except when the immune response is impaired, absent, or dysfunctional. However, during immune defects pathogenic viruses become more consequential and viruses that are unremarkable agents in immunocompetent persons become highly significant. An excellent example is cytomegalovirus infection. A high proportion of the population is infected, yet only those individuals who are immunosuppressed in connection

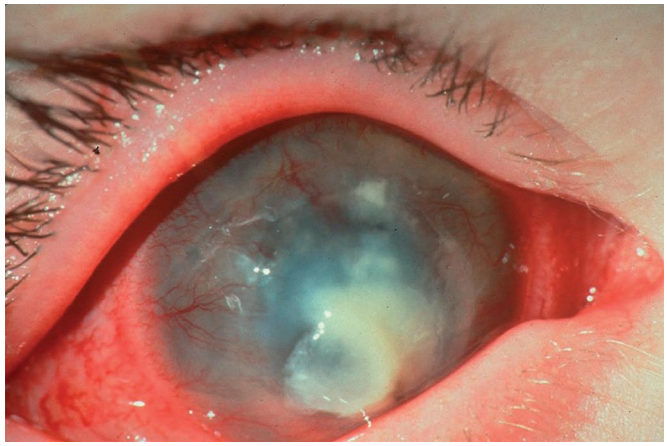

Fig. 27.5 Example of herpetic stromal keratitis (HSK) in the human eye after herpes simplex virus-1 (HSV-1) infection. Inflammation of the eye and eyelid can be observed, as well as neovascularization, and substantial necrosis, ulceration, and opacity of the cornea.

KEY CONCEPTS

PHASES OF IMMUNITY AFFECTED BY REGULATORY T CELLS

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

with cancer treatment, transplantation, or acquired immunodeficiency syndrome (AIDS) caused by HIV display complications. This is true for many common bacterial and viral agents, such as HSV, whose infections become far more frequent and severe in AIDS patients.

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.

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