due to passive death of activated lymphocytes. In contrast, self-tolerance is maintained either because self-antigens are ignored by the immune system or because they actively terminate immune responses. If the mechanisms that maintain homeostasis and self-tolerance are indeed largely distinct, then the next question that arises is what are the features of foreign and self-antigens that trigger these distinct regulatory processes. This question, too, cannot be answered with certainty. It is tempting to speculate that the key differences are that most foreign antigens, such as microbes, are short-lived and responses to them are often accompanied by innate immune reactions, whereas self-antigens are permanent, and their recognition is not associated with innate immune responses. Therefore, the type of homeostatic processes that terminate an immune response may vary according to the nature of the antigen and attendant stimuli and may not be strictly related to whether the antigen is foreign or self. Indeed, it is possible that responses to some foreign antigens, for example, viruses, that are able to persist in the absence of substantial inflammation may be limited by the same mechanisms that normally function to maintain self-tolerance and that tolerance to certain self-antigens may result from the elimination of activated lymphocytes by passive cell death.

Future studies should start to define the types of immune responses, conditions of antigen exposure, and forms of foreign and self-antigens that trigger different mechanisms of homeostasis and self-tolerance, as well as the biochemical basis of these regulatory processes. The ability to combine transgenic and gene knockout animal models with in vivo and biochemical analyses holds great promise for providing valuable answers to these fundamental questions.

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Viral Strategies of Immune Evasion

Hidde L. Ploegh

The vertebrate body is an ideal breeding ground for viruses and provides the conditions that promote their growth, survival, and transmission. The immune system evolved and deals with this challenge. Mutually assured destruction is not a viable evolutionary strategy; thus, the study of host-virus interactions provides not only a glimpse of life at immunity's edge, but it has also illuminated essential functions of the immune system, in particular, the area of major histocompatibility complex–restricted antigen presentation.

The immune system is commonly divided into two major branches: innate and adaptive immunity (Fig. 1). The innate response to an invading pathogen involves the rapid recognition of general molecular patterns such as carbohydrates or other posttranslational modifications present on the pathogens themselves or in the infected cell. Eosinophils, monocytes, macrophages, natural killer cells, and soluble mediators—such as components of the complement cascade and acute phase reactants—are either bactericidal or activate cellular functions that eradicate pathogens. Viral infections also induce a potent antiviral response mediated by interferons. Confrontation of the innate immune system with pathogens leads to its activation and prepares the adaptive arm of the immune system to respond appropriately. Adaptive immunity is conveyed by both cellular and humoral elements. Through their antigen specific receptors, B and T lymphocytes interact with pathogens or fragments derived from them, presented on antigen-presenting cells. The activated

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B lymphocytes produce antibodies, for which the activation of T cells and the interleukins secreted by them are generally required. These antibodies, together with components of the complement system, flag pathogens for recognition by specialized cells that can destroy them. Infected cells can likewise be targeted for destruction by T lymphocytes or natural killer (NK) cells. The interconnections that exist between innate and adaptive immunity are crucial: cells and soluble mediators of both systems interact for greater efficacy and survival value to the individual.

These defenses are not perfect. The host's strategies select for escape variants of pathogens that are no longer susceptible to timely immune recognition and attack. Molecular analysis of virus genomes reveals numerous virus-encoded homologs of cellular immune regulators. In many cases, the evasive maneuvers specified by the viral genome remain to be linked directly to the virulence of the pathogen in question. This is particularly true for those viruses that are human pathogens, but where no relevant animal model is available. Here, I focus on mechanisms used by viruses to subvert normal host defenses. Other aspects of viral evasion are reviewed elsewhere (*1*–*5*).

Antigen Presentation

Initiation of an immune response requires that antigenic fragments of pathogen-derived proteins be presented by the products of the major histocompatibility complex (MHC). MHC class I products sample the cytosolic compartment and its topological equivalents and present peptides to antigen-specific receptors on CD8 T cells. Entry into the class I–restricted pathway of antigen presentation through other routes is also possible. Phagocytes and dendritic cells, for example, can ingest materials, including host cells that express viral antigens, and have them processed and presented by class I products (*6*). MHC class II products mostly focus on peptides generated in the endocytic pathway.

MHC Class I–Restricted Antigen Presentation

Class I–restricted antigen presentation is linked to the biosynthesis and intracellular trafficking of MHC molecules. Most nucleated cells transcribe and express class I genes. The class I heavy and light (β2-microglobulin) chains are inserted into the endoplasmic reticulum (ER) in signal sequence–dependent fashion (Figs. 2 and 3). Free light chains are secreted, and misfolded heavy chains are destroyed. The third subunit of the MHC class I molecule is the short antigenic peptide itself. Without its peptide cargo, class I molecules are unstable and dissociate. Cytosolic proteins targeted for destruction through the attachment of ubiquitin are rapidly destroyed by the proteasome to yield peptides of 8 to 12 residues,

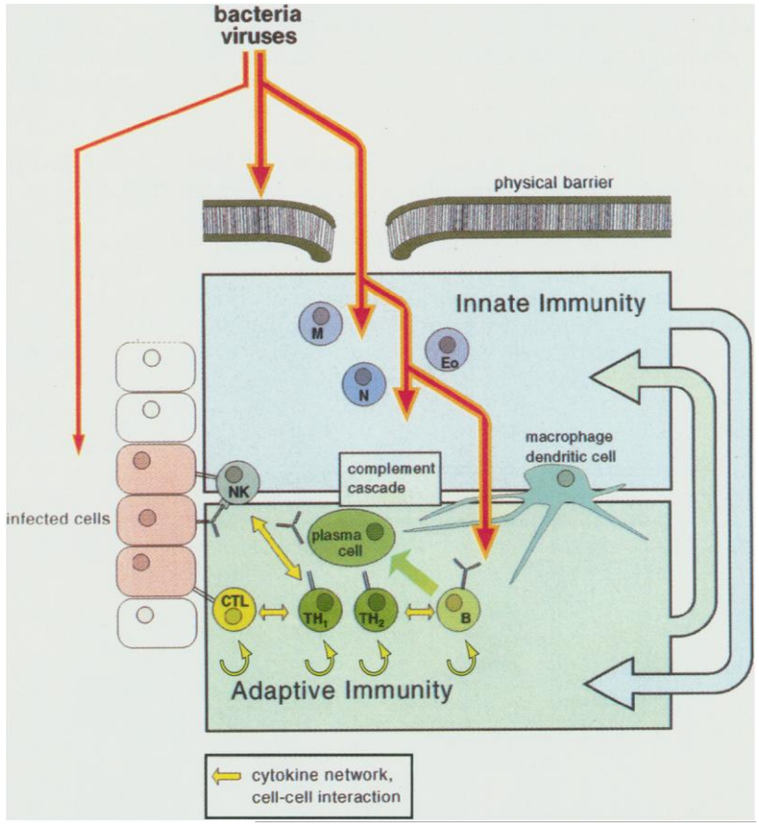

Fig. 1. The immune system. M, monocyte; N, neutrophil; Eo, eosinophil; NK, natural killer cell; CTL, cytotoxic T cell; Th1, inflammatory T cell; Th2, T helper cell; B, B lymphocyte. Infected cells (on the left) are denoted in pink.

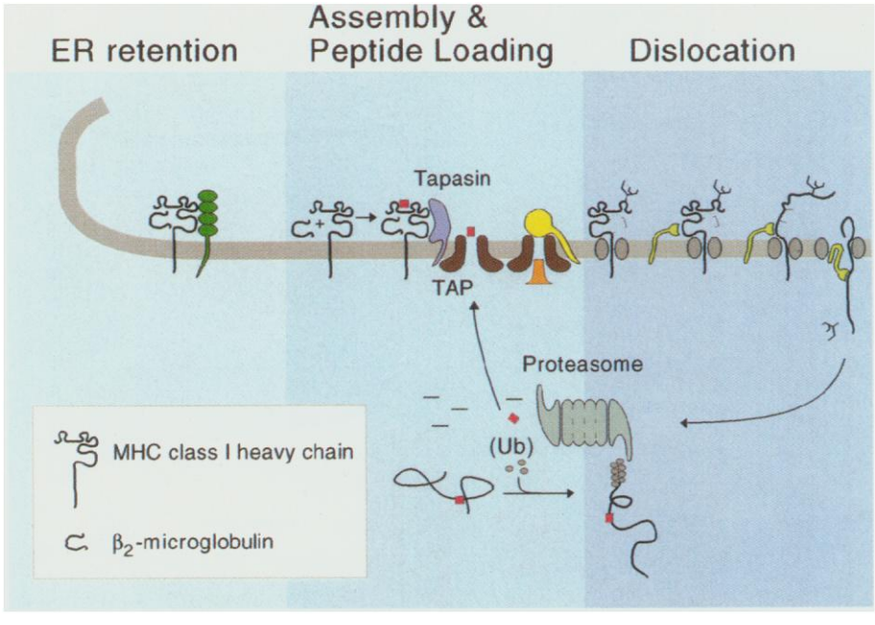

Fig. 2. Interference with class I MHC biosynthesis in the ER. The various viral gene products responsible for interference are shown in red. Ub, ubiquitin.

appropriate for class I–restricted antigen presentation. In response to interferon-γ (IFN-γ), produced upon triggering of the innate immune system, three proteasome β subunits, LMP2, LMP7, and MECL1, are induced and replace constitutively expressed β subunits, presumably to tune proteasomal specificity or activity to the demands of the immune response. The peptides are translocated by an MHC-encoded peptide transporter, TAP, which is physically linked to the class I molecule through the ER-resident protein tapasin, an arrangement that facilitates peptide loading. When properly assembled and loaded with peptide, class I molecules are then released from the ER. They enter the secretory pathway and are displayed at the cell surface.

Because cellular protein turnover is a constitutive process, most class I molecules on normal cells will be occupied by peptides derived from the cell's own proteins. Only when pathogen-derived proteins make their appearance in the cytosol can there be a contribution of pathogen-derived peptides to the surface-displayed pool of MHC-peptide complexes.

Evasion of MHC Class I Antigen Presentation

If the eradication of virus-infected cells relies on the activity of class I–restricted $CD8^+$ cytotoxic T lymphocytes (CTLs), then pathogens that attenuate class I expression would have a selective advantage: through elimination of class I molecules from the cell surface, the infected cell becomes temporarily invisible to CTLs and allows the pathogen the time to proliferate. Of course, a pathogen must select which of the many effector mechanisms of the immune system it inhibits, often reducing one at the expense of augmenting another. This applies to both innate and adaptive immunity. Elimination of surface class I expression as a strategy for deceiving the immune system is not without risk to the virus: NK cells can recognize cells deficient in self-MHC products.

Every step in the assembly and trafficking of the class I complex presents a suitable target for this strategy (Figs. 2 and 3). A number of viruses can down-regulate the transcription of class I genes, and in doing so, prevent expression of class I products (5). Other components of the class I presentation pathway such as TAP and the LMPs are also targets for transcriptional control (7). Even their partial down-regulation could frustrate T cell recognition of the infected cell.

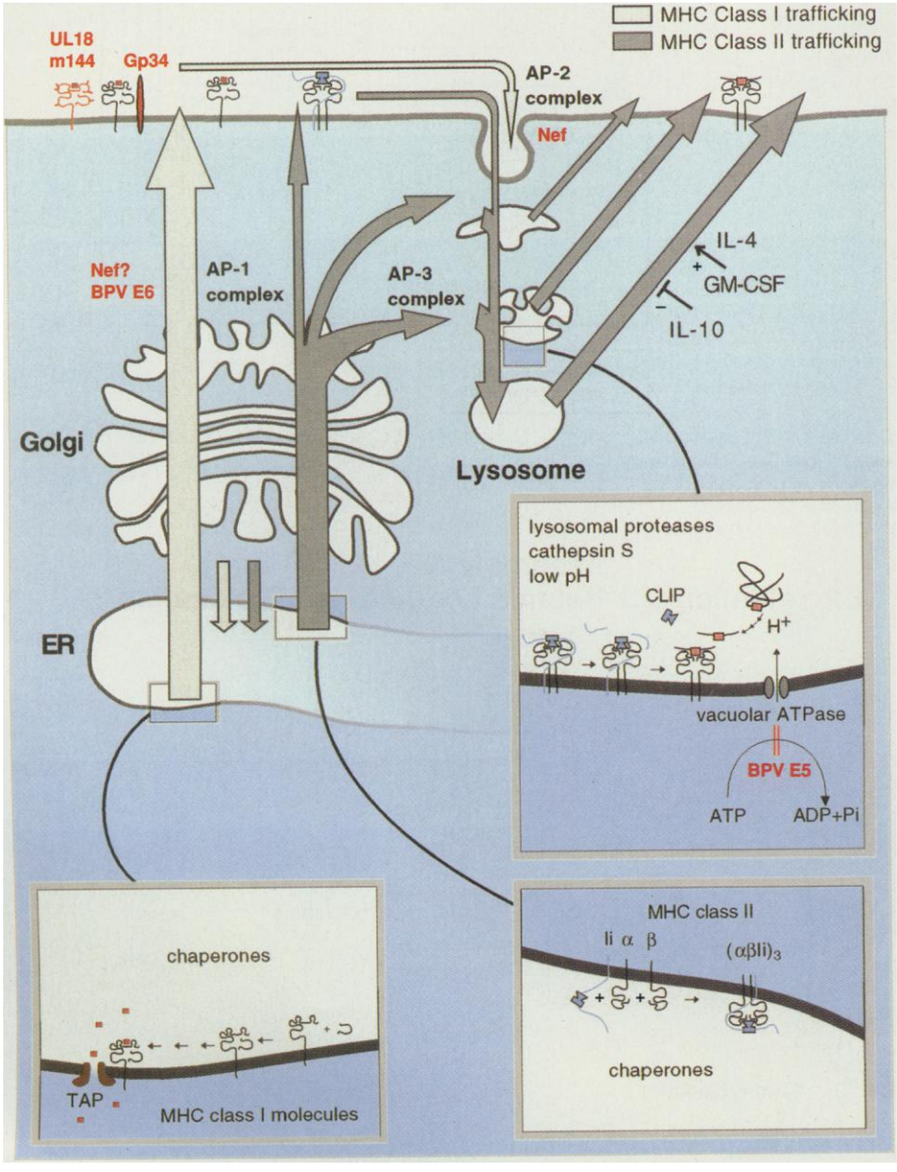

Fig. 3. Trafficking pathways of MHC class I and MHC class II molecules. Points of interference for viral and bacterial gene products are shown in red.

Proteolysis

The first step in the generation of an antigenic peptide is proteolysis of cellular proteins. There are two examples of interference with cytosolic proteolysis (Fig. 2). In human cytomegalovirus (HCMV)–infected cells, expression of the viral phosphoprotein, pp65, inhibits the generation of HCMV-specific T cell epitopes (8). The second example is the Epstein-Barr virus (EBV)–encoded EBNA-1 protein which contains a Gly-Ala repeat that interferes with its proteasomal proteolysis (9).

A single amino acid substitution can eliminate the proteolytic cleavage site required for the generation of a mouse leukemia virus–derived epitope and thus thwart CTL recognition (*10*). Presumably, the polymorphism of the MHC evolved in part to accommodate these types of escape strategies, maximizing the likelihood that, for a given pathogen, at least some peptides can be presented by the MHC alleles present in the population.

Although unrelated to the generation of peptide epitopes per se, MHC products are exploited in a fundamentally different way by human immunodeficiency virus (HIV). Certain types of peptides that are sequence variants of the nominal peptide antigens recognized by antigen-specific receptors on T cells can act as antagonists. In infected individuals, variants of HIV evolve in which peptide epitopes recognized by HIV-specific T cells have sustained exactly the type of mutation that transforms these peptide ligands into antagonists (*11*, *12*), thus actively silencing HIV-specific T lymphocytes.

Peptide Transport

The peptides that are produced in the cytosol are delivered to the lumen of the ER by the peptide transporter, the TAP complex, so that class I heterodimers may bind them. Herpes simplexvirus type 1 (HSV-1) and HSV-2 each encode a polypeptide inhibitor of TAP, the ICP47 product (Fig. 2) (*13*). The ICP47 protein competes with peptides for the single peptide binding site on the TAP complex (*13*). HCMV has likewise targeted TAP, but its US6, a type I membrane protein, attacks the TAP complex from the ER-lumenal side (Fig. 2) (*14*). TAP polymorphisms, which largely involve substitutions in the cytosolic domain, were perhaps selected for in response to these assaults.

Retention and Destruction of Class I Molecules

Even if assembly and peptide loading of class I molecules are completed successfully, the final complex must be delivered to the cell surface if T cells are to recognize them. Some viruses detain properly assembled class I molecules at the site of synthesis (Fig. 2); the adenovirus E3-19K type I membrane glycoprotein (*15*) forces retention through an ER-retrieval signal in its cytoplasmic tail. HCMV engages in similar behavior; the US3 product binds to class I molecules and sequesters them in the ER (*16*). Murine CMV (MCMV) is subtly different; its m152 gene product, gp40, likewise causes intracellular retention, but does so in the cis-Golgi compartment, a reaction independent of gp40's cytoplasmic tail (*17*). More unusual is the mechanism of action of the HCMV products US2 and US11. Either product can bind to class I molecules and redirect the class I heavy chains to the cytosol, a reaction referred to as dislocation, in an apparent reversal of the process by which the nascent chain is inserted in the ER membrane (*18*). The US2 product is itself destroyed in a sequence of events that mimics that seen for the class I heavy chains, and an association between US2 and class I heavy chains may be maintained until these substrates encounter the proteasome. Most likely, the action of US2 and US11 serves to accelerate the rate constant of the dislocation reaction, while conferring specificity to the process by interacting selectively with class I products. This type of reaction has meanwhile been observed for other misfolded ER-resident proteins in the absence of viral accessories and may well be a more general mechanism by which eukaryotic cells purge their ER of defective polypeptides (*19*).

In HIV-infected cells, the action of the Vpu product abolishes expression of class I molecules before their egress from the ER (*20*). Vpu is also capable of down-regulating CD4. The mechanisms involved have not been molecularly defined, but are distinct from those described for the herpesviruses.

Internalization of Class I Molecules

Class I molecules may be retained in or purged from the ER, but even when they reach the cell surface, they are not safe from viral proteins that compromise or modify their function. An MCMV-encoded glycoprotein, gp34, can override the m152-imposed ER retention and is delivered to the cell surface in a complex with fully assembled class I molecules (Fig. 3) (*21*). Although these complexes could compromise CTL recognition or could silence NK cells, the function of gp34 remains to be defined. Internalization of class I molecules from the cell is a viable strategy to avoid detection by T cells. The HIV Nef protein modifies the endocytic machinery so that the coreceptor CD4 is cleared from the cell surface (*22*) and down-modulates surface expression of class I molecules (*23*). Nef may interact with the adaptor complex AP-2, a set of proteins that links cargo molecules such as receptors to the coat proteins of the vesicles that transport them (*24*). Nef presumably modifies the AP-2 complex to facilitate endocytosis of CD4 and class I molecules (*25*). Notwithstanding the sensitivity of CD8 T cells, this down-regulation appears sufficiently effective to block killing by class I–restricted anti-HIV CTLs in vitro (*26*). More generally, the possibility that virus-infected cells manage to reorganize intracellular trafficking and accelerate endocytosis is likely to extend to proteins other than MHC products or coreceptors such as CD4.

Natural Killer Cells

NK cells destroy a variety of virus-infected cells early during infection. NK cells are constitutively present in animals that have never been previously immunized or infected, and they are not MHC restricted and do not express T cell receptors. NK cells are normally prevented from killing their targets by inhibitory signals provided through interaction of receptors on NK cells with self-MHC products (*27*). Should the virus be successful in eliminating class I expression, how then does the infected cell avoid inviting NK cells to attack?

Both mouse and human CMV encode their own class I homologs, m144 and UL18, respectively, which ostensibly serve as a decoys for NK cells (*28*, *29*). Antibodies against a C-type lectin (CD94) expressed on NK cells block the protective effect of UL18, implicating CD94 as a potential receptor for UL18 (*3*). A separate receptor for UL18, termed leukocyte immunoglobulin-like receptor-1 or LIR-1 (*30*), contains two immunoreceptor tyrosine-based inhibitory motifs—also found in the inhibitory NK receptors or KIRs—believed to mediate the inhibitory signal. LIR-1 is expressed on cells other than NK cells, including monocytes, suggesting that UL18-mediated immune regulation may occur at several points in the innate response. The MCMV class I homolog (m144) has been implicated directly in virus virulence in vivo (*28*). MCMV lacking m144 is cleared more efficiently by NK cells, as confirmed by restored pathogenicity of the mutant virus in NK-depleted animals.

Class II–Restricted Antigen Presentation

The MHC class II–restricted pathway of antigen presentation focuses largely on events in the endocytic pathway (Fig. 3) (*31*). Endosomal and lysosomal proteases destroy internalized protein antigens and generate peptide fragments appropriate for presentation by MHC class II molecules. The MHC class II proteins are delivered to the endocytic pathway through diversion from the constitutive secretory pathway by signals carried in the cytoplasmic tail of an accessory polypeptide, the invariant chain or Ii. The invariant chain is destroyed by proteases to yield an Ii remnant called CLIP, which is removed by a catalyst or "peptide editor" that is itself a class II–like protein called H-2M (mouse) or HLA-DM (human). Peptide-loaded class II molecules are then transferred to the cell surface for recognition by CD4 T cells.

Transcription of class II molecules can be manipulated by pathogens: in HCMV-infected cells the Jak/Stat pathway seems compromised and expression of class II molecules cannot be up-regulated (*32*). Endothelial cells are particularly responsive to cytokines that induce expression of class II molecules such as IFN-γ and might be one of the cell populations targeted by HCMV to block induction of the transcriptional transactivator CIITA and, hence, the class II presentation machinery (*33*).

Interference with Trafficking Along the Endocytic Pathway

Pathogens can rearrange the intracellular trafficking machinery without causing overt cytopathic effects. They could modify the endocytic pathway either directly or through control of cytokine production. In-

terleukin-10 (IL-10) appears capable of preventing the surface display of MHC class II molecules by inhibition of their recruitment from intracellular compartments to the cell surface (*34*). The IL-10 homolog encoded by EBV could thus conceivably impede the display of peptide-loaded class II molecules, and so delay the call for T cell help. The E6 protein of BPV interacts with components of the AP-1 adaptor complex (*35*), which could affect the intracellular distribution of class II products or the antigens destined for presentation by them. The adaptor complex AP-3 may be essential for orchestrating traffic involving endocytic compartments (*36, 37*) and may allow further dissection of the steps targeted by the E6 products of bovine papilloma virus (BPV) or HIV Nef. The E5 product of BPV can replace a subunit of the vacuolar H^+ adenosine triphosphatase responsible for acidification of endosomes and lysosomes (*38*). Even a slight elevation of endosomal pH might spare certain antigens from proteolysis and thus prevent their presentation. This strategy is realistic because the *Helicobacter pylori* VacA toxin inhibits acidification of the endosomal system in a very similar manner (*39*), thus thwarting Ii-dependent antigen presentation.

Negative Cytokine Regulation

Cytokines are secreted proteins that regulate immune and inflammatory responses, and many viruses would benefit from antagonism of cytokine activity. Cytokines can be either positive or negative regulators of the immune response, and for this reason, some viruses encode their own cytokines. EBV encodes a protein homologous to the cellular cytokine IL-10 (*40*), which is a negative regulator of IL-12, itself a cytokine that both promotes IFN-γ production and has a profound impact on the development of Th1- and Th2-like cytokine-producing cells. The recent identification of a second chain of the IL-10 receptor may shed new light on the activity of this viral cytokine (*41*), which binds to the IL-10 receptor some 100 times weaker than does cellular IL-10. EBV-encoded IL-10 can also down-regulate TAP expression, as does its cellular counterpart (*42*).

Viruses may also neutralize cytokine activities. Adenoviruses encode at least four genes that antagonize the effects of tumor necrosis factor (TNF). The products of these genes are found at different locations within the infected cell, suggesting that they may act independently to interrupt different stages of TNF-induced biological activities, but their mechanism of action remains to be determined. The effort that adenoviruses expend at neutralizing TNF strongly suggests its importance in the control of adenovirus infection.

In contrast to the focus on TNF neutralization displayed by adenoviruses, the poxviruses and herpesviruses may have a broader need for cytokine modulation. Both encode functional cytokine receptors. EBV encodes a soluble, neutralizing receptor for CSF-1 (macrophage colony-stimulating factor), although no role for CSF-1 during EBV infection has thus far been defined (*43*). Four other herpesviruses carry membrane-bound receptors for chemokines (*2*).

Members of the poxvirus family collectively encode an impressive array of soluble cytokine receptors that bind and block the activity of IFN-γ, the α and β IFNs, TNF, and IL-1. These latter cytokines are among the most potent regulators of inflammation and immune function. The use of mutant poxviruses containing single gene disruptions has confirmed the importance of the soluble cytokine antagonists in animal models (*2*). The incorporation of soluble receptors for broad-spectrum cytokines into the genomes of poxviruses, whose infections elicit strong inflammatory responses (vesicular skin lesions with polymorphonuclear infiltrates), underscores the potential utility of antagonism of these cytokines in the treatment of chronic inflammatory conditions in the clinic.

In some cases, presumably as a result of intense selective pressure, the viral cytokine receptor functions better than its host homolog. In poxviruses, a soluble chemokine receptor (p35) has been identified that exhibits an affinity for its ligands at least 10 times greater than that of its cellular counterpart (*44*). This enhanced affinity is all the more unusual because, as a rule, all cellular chemokine receptors contain multiple transmembrane segments thought to compose the ligand-binding site; the soluble viral receptor equivalent thus must bind the same ligand in a completely different manner.

A different form of cytokine regulation is manifested by measles virus. The virus binds specifically to CD46, a cellular complement-regulatory protein found on monocytes, which are a prime target for measles virus infection in vivo. When measles virus binds and cross-links CD46, the production of IL-12 by monocytes is inhibited (*45*) and may account in part for the generalized immunosuppression of cell-mediated responses typically seen in measles virus–infected patients. Understanding the mechanisms of the interaction of viruses and the host immune response can reveal useful information on both symptomatic treatment of virus infection and ultimately aid in the design of "intelligent" vaccines.

Inhibition of Apoptosis

Apoptosis is a form of cell death that is a normal aspect of B and T cell maturation. It can also function as a protective mechanism, in that parasite-infected cells killed by such immune watchdogs as CTL and NK cells undergo apoptotic death. Virus infection can also induce apoptosis more directly and may restrict virus infection by killing off the host cell before the release of progeny virions. Because viruses require cellular machinery to complete their replicative cycle and reproduce, they have again risen to the challenge of the host immune response by employing methods that interfere with apoptotic cell death.

One of the more intriguing examples of apoptotic interference involves a poxvirus protein termed crmA, which resembles a serine protease inhibitor (serpin) but functionally inhibits Asp-specific cysteine proteases (caspases), such as the IL-1β converting enzyme (ICE). This caspase inhibition is probably how crmA blocks apoptosis induced by CTL, TNF, or Fas. The exact mechanisms of crmA-mediated inhibition are still unclear, but may involve inhibition of Granzyme-B, an Asp-Xaa–specific serine protease released by CTLs that proteolytically activates apoptosis-inducing proteins, and inactivation of FLICE, a caspase that is part of the death-inducing signal complex (DISC) associated with the cytoplasmic tail of Fas. Several members of the herpesvirus family [including equine herpesvirus-2, Kaposi's sarcoma virus or HHV8, and molluscum contagiosum virus (MCV)] encode FLICE-inhibitory proteins or v-FLIPS that interfere with recruitment and activation of FLICE (*46*). In this manner, v-FLIPs protect against cell death induced by activation of members of the TNF-receptor family.

An unusual example of inhibition of apoptosis is provided by the MC066L gene of MCV. The virus replicates in human epidermis and causes benign lesions in immunocompetent individuals. Apoptosis of damaged epidermal cells is postulated as a mechanism for controlling neoplasms and can be inhibited by glutathione peroxidase, a selenoenzyme capable of inactivating cellular peroxidases that can induce apoptosis. The MC066L gene of MCV encodes a true selenoprotein that protects ultraviolet- or peroxidase-sensitive cells from apoptosis, indicating that it can function in a manner similar to its cellular counterpart (*47*).

Concluding Remarks

More than 50 different virus genes have been identified as immune modulators; this collection is certainly incomplete. Many of these modulators have similar targets, but

show little if any structural similarity. The different layers of protection that are targeted by immune evasive strategies necessitate this complexity, but also illustrate the shared characteristics of immune responses directed against pathogens. The study of these proteins has increased understanding of basic immune processes, viral pathogenesis, and ways in which vaccines, gene targeting vectors, and biologicals can be designed and administered. Although the emergence of new viral diseases is a constant reminder that these pathogens are usually one step ahead of the host, the study of viral immune evasion helps to close that gap.

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