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MINIREVIEW

Molecular Anatomy of Viral Persistence†

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The concept that persistent viral infections exist and are not uncommon is one of the remarkable and interesting advances in modern virology. Understanding how viruses can persist in their hosts and what the consequences are in terms of producing disease requires new insights. Yet, much current thinking is based on information gathered over the past century from studies of acute viral infections. These began with the primary observations of Beijerinck and Ivanovski (5, 18) that material responsible for tobacco mosaic disease passed through the pores of a Pasteur-Chamberlin filter without losing infectivity and that this soluble residue of filtration replicated when reintroduced onto healthy tobacco leaves. Correspondingly, Loeffler and Frosch (20) determined the same series of events for the pathogen causing bovine foot-and-mouth disease. These observations provided the basis for defining viruses as subcellular entities that could cause a distinct, often pathognomonic form of tissue destruction. Documentation during the years that followed and up to the present affirmed that many diseases with a proven viral cause were accompanied by cellular necrosis and inflammatory infiltrates. Thus, the histopathologic hallmarks of acute infection, tissue destruction, cell necrosis, and lymphoid infiltration, have served as signals to begin attempts to isolate virus. Accordingly, when these hallmarks are not present, the problem is assumed to originate from a source other than viral.

However, we are now aware of significant differences between persistent and acute virus infections. For example, their histopathologic pictures often differ dramatically. Lymphoid cell infiltration and destruction of virally infected cells, the signs of acute infection, need not occur and frequently do not, with persistent infections. Another example lies with immune responses; the immune system consists of humoral (antibody) and cellular (lymphocyte, monocyte) components that function to protect the host from invading microbes. Immunization, primarily developed and used most successfully against agents causing acute infection in humans and domestic animals, has been focused toward enhancing antibody responses to glycoprotein or structural protein antigens present on surface virions, although cytotoxic T lymphocytes (CTL) also play roles in control of acute infection (24). However, the dilemma in protection from persistent infections is more complex. The viruses often are cell associated, and surface glycoproteins are usually not expressed or are expressed to minimal degrees on such persistently infected cells (29). In this scenario, antibodies are not efficient in lysing infected cells. Further, several million antibody molecules are needed, along with effector molecules of the complement system, to destroy virally infected cells (38, 39), an ineffective system. To better handle persistent infection, the organism uses the other effector arm of the immune response consisting of lymphocytes that can detect the low levels of viral antigens expressed on infected cells. These lymphocytes are cytotoxic for virally infected cells. Indeed, CTL are believed to require no more than 100 viral protein (peptide) molecules (10, 41) for activation. In vivo, CTL can recognize viral sequences expressed in cells that antiviral antibodies are unable to detect (30). CTL are effective against nonglycosylated immediate-early or early proteins of a virus, i.e., herpes simplex virus and cytomegalovirus, that are transcribed many hours before structural viral proteins are made and prior to assembly of the viruses (9, 19). Further, CTL can recognize infected cells as foreign and destroy them during the latent period of virus infection when the late-acting genes (that encode structural viral proteins) are blocked. CTL effectively and efficiently recognize and lyse a virally infected cell expressing regulatory proteins (i.e., Nef of human immunodeficiency virus [HIV], T antigen [T-Ag] of simian virus 40) and proteins of the replicative complex (i.e., NS, NP of influenza virus, NP of lymphocytic choriomeningitis virus [LCMV], Pol and Gag of HIV), all usually made early in the infectious cycle (Table 1). Thus, the cellular arm of the host's immune system provides an advantage for controlling persistent infection. The strategic advantage to the host in its battle with viruses is that the CTL effector arm can eliminate potential factories (cells) before they produce a finished infectious product.

Several principles have been important in forming conclusions about viral persistence. First, Sigurdsson (37), in studies of visna virus-infected sheep, introduced the concept of a slow virus infection, i.e., a long incubation period from the time of initial infection to the clinical manifestation of illness. Gajdusek and Gibbs (13) described a similar scenario of long incubation time for humans with Kuru or Creutzfeldt-Jakob disease, although it is still controversial whether the transmissible agent is a virus or a modified protein (prion). Nevertheless, a major implication of Gajdusek's work was that other human illnesses of undetermined etiology might be caused by persistent virus infections. Later it was shown that replication of noncytopathic viruses in differentiated cells in culture could abrogate the luxury function of such cells without affecting their vital functions (cloning efficiency, growth, levels of total RNA, DNA, protein, and vital enzymes) (reviewed in reference 27). For example, replication of LCMV in differentiated neuroblastoma cells abrogated the synthesis and degradation of acetylcholine by inducing decreases in the cellular content of enzymes that synthesize (acetylase) or degrade (esterase) acetylcholine, yet infected and uninfected cells were indistinguishable under the microscope and showed normal growth character-

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TABLE 1. Viral peptide sequences that serve as epitopes for CTL[a]

Virus[b]	Protein	Position	MHC-restricting allele	Sequence
LCMV	GP	278	D^b	VENPGGYCL
LCMV	GP	34	D^b	AVYNFATCGIFA
LCMV	NP	397	D^b	QPQNGQFIHFY
LCMV	NP	119	L^d	PQASGVYMG
LCMV	NP	93	$H\text{-}2^k$	VGRLSAEE
MCMV	IEp89	168	L^d	YPHFMPTNL
HSV-1	gB	497	K^b	TSSIEFARLQF
VSV	N	53	K^b	GYVYQGL
Sendai virus	NP	324	K^d	FAPGNYPAL
SV40	T-Ag	207	D^b	AINNYAQKL
SV40	T-Ag	223	D^b	CKGVNKEYL
SV40	T-Ag	489	D^b	QGINNLDNLRDYLDG
Adenovirus	E1A	235	D^b	GPSNTPPEI
Influenza virus	HA	202	K	RTLYQNVGTYVSVGTSTLNK
Influenza virus	HA	523	K^d	VYQILAIYATVAGSLSLAIMMAG
Influenza virus	HA	158	$H\text{-}2^d$	SFYRNVVWLIKK
Influenza virus	NP	147	K^d	TYQRTRALVRTGMDP
Influenza virus	NP	365	D^b	IASNENMETMESSTL
Influenza virus	NP	50	K^k	SDYEGRLIQNSLI
Influenza virus	NP	335	HLA Aw68	SAAFEDLRVLSFIRG
Influenza virus	NP	383	HLA B27	SRYWAIRTRSGG
Influenza virus	M	57	HLA A2	KGILGFVFTLTV
HIV-1	Nef	73	HLA A3	QVPLRPMTYK
HIV-1	p24	253	HLA B8	NPPIPYGEITKAWII
HIV-1	p24	181	HLA B14	PQDLNTMLNTVGG
HIV-1	p24	265	HLA B27	KRWIILGLNKIVRYN
HIV-1	p24	140	HLA C3W	GQMVHQAISPRTL
HIV-1-IIIB	gp	315	D^d	RIQRGPGRAFVTIGK
HIV-1-MN	gp	315	D^d	RIHIGPGRAFYTTKN
HIV-1-SC	gp	315	D^d	SIHIGPGRAFYATGD
HTLV-1	gp46	196	DR-2	LDHILEPSIPWKSK
HTLV-1	Tax	18	HLA A2	YVFGDCVQ
EBV	EBNA6	290	BW44	EENLLDFVRFMGVMSSCNNP

[a] Data were compiled from the work of many laboratories, including those of B. Askonas, J. Berzofsky, T. Braciale, F. Ennis, L. Gooding, S. Koenig, U. Koszinowski, D. McFarlin, A. McMichael, M. Oldstone, K. Rosenthal, S. Tevethia, A. Townsend, B. Walker, L. Whitton, and R. Zinkernagel.

[b] Abbreviations: MCMV, murine cytomegalovirus; HSV-1, herpes simplex virus type 1; SV40, simian virus 40; EBV, Epstein-Barr virus.

istics. Investigators working with a wide number of RNA and DNA viruses have found similar alterations in luxury, i.e., differentiated, functions without perturbation of vital functions in such diverse sites as immune, neural, and endocrine cells infected with viruses specific for human and nonhuman species. These in vitro observations have been extended in in vivo models (27). In such instances, viruses growing in differentiated cells alter the function of those cells without lysing them or causing infiltrating lymphoid cells to accumulate in the area. Unlike in vitro experiments, when the lowering of the differentiated product (growth hormone, insulin, thyroglobulin, etc.) occurs in vivo, it disturbs normal homeostasis and disease occurs.

From these and other studies two essential ingredients have been identified upon which the current understanding of persistent virus infection rests (Table 2). The first is a unique component(s) or strategy of viral replication that ensures a nonlytic phenotype. The second is an immune response that is ineffectual in recognizing and clearing virus and/or virus-infected cells. Unfortunately, our knowledge of how viral genes and cellular factors interact to cause persistence is incomplete in most instances. For herpesviruses, a block at the level of immediate-early genes and also perhaps early gene expression appears to stop the activation of late genes, which are essential for productive virus infection (4, 25, 33). Considerable effort has gone into mapping which immediate-early gene(s), viral *cis* elements, and cellular transcriptional activating factors determine cell (tissue)-specific expression and activation of these viruses. With HIV, the role of the cell cycle and the influence of various cytokines in interacting with transcriptional activating factors associated with upregulation of HIV transcripts have been mapped (15, 34). In other instances, the production of deletion mutants, including defective interfering viruses, has

TABLE 2. Mechanisms for the occurrence of viral persistence

A. Avoid immunologic surveillance
  1. Remove recognition molecules on infected cells
     Alter viral protein expression
        Directly: virus itself
        Indirectly: antiviral antibody-induced capping and modulation
     Alter MHC expression
        Directly: adenovirus E3 19-kDa protein, cytomegalovirus UL18 67-kDa protein
        Indirectly: infection and the release of cytokines
     Alter expression of lymphocyte adhesion molecules
  2. Abrogate lymphocyte/macrophage function
        Immunosuppression
        Cytokines alter transcription of host gene(s)
        Mimic cytokine activity
           Epstein-Barr virus BCRFI: interleukin-10
  3. Hide in cells lacking MHC expression (neurons)

B. Nonlytic phase of viral replication
  1. Generate mutants or variants
  2. Diminish expression of viral genes or their products

been uncovered in vitro and suspected in vivo, although their role as regards cause or association is still under active debate (17). But we still do not know the biochemical functions or interrelationships of most genes in viruses that establish persistence or their involvement with factors that regulate cellular transcription.

Viral persistence occurs as an evasion of the host's immune surveillance system. Since the raison d'etre of the immune system is recognizing and then purging foreign materials like viruses from the host, the continued presence of virus is equated with a partial or total malfunction of the appropriate immune response. In evolving strategies to accomplish persistence, viruses have developed a number of tricks. Table 2 lists several ways viruses can avoid immunologic surveillance and examples of how certain viruses use some of these mechanisms. Because CTL likely play an important role in the control of viral persistence, we will focus on two dramatic examples of how viruses avoid CTL recognition.

CTL recognize proteolytic fragments of viral proteins that are presented at the cell surface by major histocompatibility complex (MHC) glycoprotein molecules (41, 43, 45). MHC molecules are divided into class I and class II, with class I molecules recognized by a CTL subset that bears the CD8 surface marker and class II molecules recognize by CTL or T-helper cells that bear the CD4 surface marker. MHC class I utilizes primarily a cytosolic pathway and is found on nearly all cells in the body (an exception being neurons). CTL recognize viral peptide bound to the MHC glycoprotein (Fig. 1). The bound peptide sequence is linear and occurs as a consequence of proteolytic fragmentation of a viral protein usually synthesized within the cell. The number of peptides per viral protein able to complex with the MHC glycoprotein in a manner that allows CTL recognition is limited and ranges from one to generally no more than three peptides per viral protein. Further, the size of the peptide has been mapped experimentally and consists of 5 to 9 amino acids. This mapping utilized recombinant technology, overlapping peptides to narrow the region under study, single amino acid truncations from the amino or carboxy termini to decipher the minimal requirement for CTL recognition, and functional lysis of target cells expressing peptide complexed with MHC. Solving the three-dimensional structure of the MHC class I molecule revealed two alpha helixes that border a floor of beta sheaths in which the peptide would reside (Fig. 1). Recently, direct isolation of viral peptide, processed by MHC glycoprotein from the infected cell (35, 42), confirmed earlier findings as to the size of added peptide binding to the MHC (32, 44). Studies of influenza A virus-infected cells led to recovery of a single 9-amino-acid peptide (35), and work with vesicular stomatitis virus (VSV)-infected cells identified an 8-amino-acid peptide of VSV N protein (42) restricted by specific MHC class I molecules. Table 1 lists viral peptide sequences that serve as epitopes for CTL. The data on hand do not yet enable one to search a viral protein sequence for the particular peptide sequence that is MHC restricted and will become a CTL epitope. Hence, identification of peptides recognized by CTL still requires experimental analysis. The recent report by Falk et al. (12) may provide important insights into motifs of peptides bound to MHC molecules and thus lead us a step closer to solving this puzzle. Once the MHC glycoprotein-peptide complex is on the cell surface, it is recognized by a CTL according to the latter's receptor composed of alpha and beta chains. If not recognized, the MHC complex likely dissociates, MHC glycoproteins recycle, and the peptide is degraded.

The MHC heavy chain and its associated light chain (β_2-microglobulin) are encoded by different genes. Their synthesis and assembly occur at the rough endoplasmic reticulum (ER), and it is currently believed that the assembled MHC molecule does not migrate to the cell surface until a specific peptide binds within the MHC α_1 and α_2 domains (Fig. 1). During this scenario, the β_2-microglobulin is conceived of assisting to lock the peptide within the MHC groove, causing a change in conformation that allows the complexed molecule to leave the ER.

There are at least two ways by which the cell surface concentrations of MHC-peptide complexes can be reduced by viruses. First, many subgenera of human adenoviruses are known to downregulate surface expression of MHC class I antigens in infected cells. The early adenovirus protein, E19 (or a homolog), forms a complex with the nascent class I molecules in the ER and prevents that MHC protein from reaching the cell surface. Deletion studies and site-specific mutagenesis indicate that the carboxy terminus of E19 is responsible for anchoring the E19-MHC complex to the ER membrane, since removal of that sequence allows MHC transport from the ER (26). Critical for the retention process are lysines at positions -3 and -4 at the carboxy end of the E19 protein. These biochemical observations account for the process whereby tumors induced by adenovirus type 12, upon transfer into an immunocompetent host, escape immunologic surveillance and continue to grow. That is, these tumors fail to express their endogenous MHC antigens. However, when the adenovirus type 12-induced tumors that evaded host immunologic surveillance are transfected with an exogenous murine MHC gene (whose product does not bind with E19) and then are transferred into immunocompetent animals syngeneic for the transfected gene, MHC expression on the cell surface occurs, and the tumor is rejected. Other adenovirus-induced tumors grow as well as MHC-negative tumors in culture but express endogenous MHC molecules. When transplanted in vivo the MHC$^+$ tumors, as expected, are destroyed by the host immune system.

The second example of decreased MHC class I expression is by human cytomegalovirus (HCMV) (8). Analysis of the HCMV nucleotide sequence reveals the presence of an open

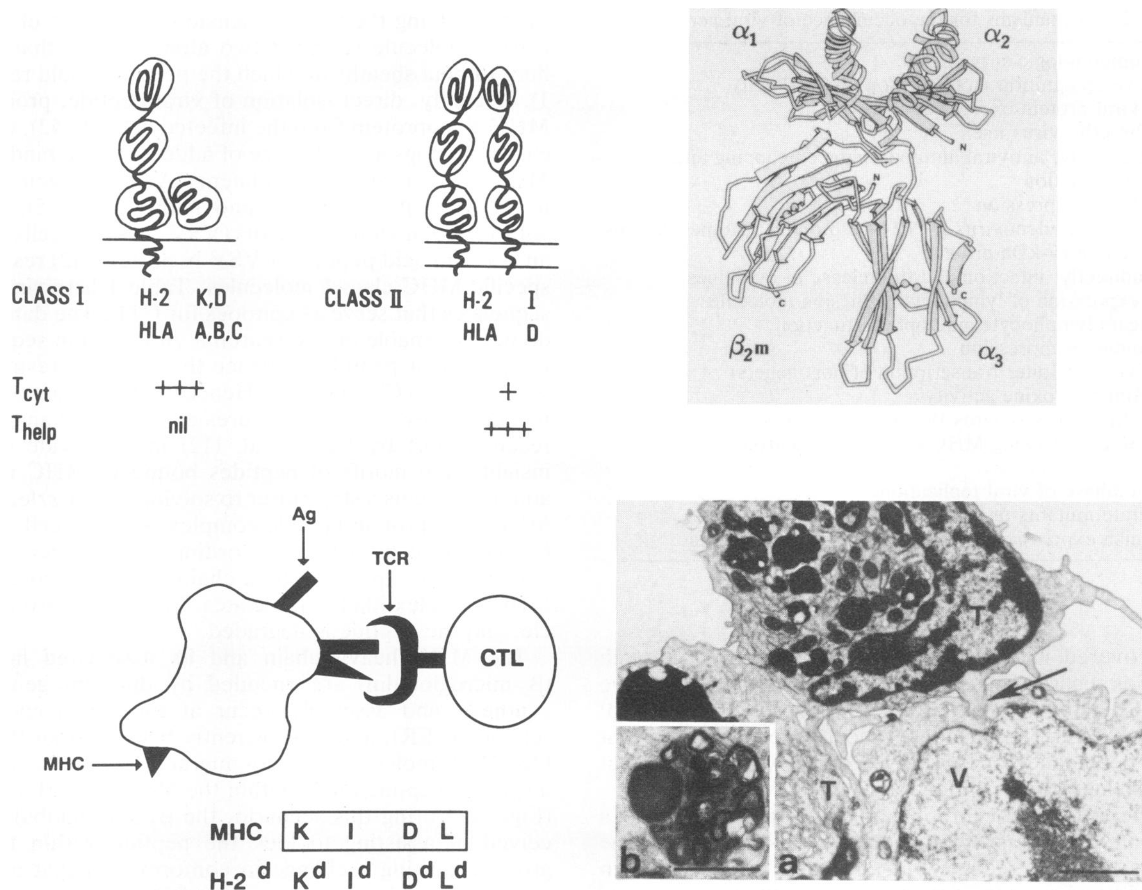

FIG. 1. Cartoons and a photograph to explain principles of the CTL-virus-infected cell interaction. The upper left drawing schematically shows MHC class I and II molecules and lists different functions in terms of cytotoxic (Tcyt) or helper (Thelp) T-cell activity. The upper right panel shows a sketch of the three-dimensional X-ray crystallographic structure of HLA-A2 (6). Viral peptide formed in the infected cells binds in the groove between the α_1 and α_2 arms. The lower left panel depicts the MHC-peptide complex recognized by the receptor (TCR) of CTL. Further, the MHC class I alleles and how they are represented in Table 1 are shown. The lower right panel is a photograph of an electron micrograph showing the interaction of a cloned LCMV-specific CTL pushing a process (arrow) deep into the cytoplasm of a virus-infected cell (V). Note the close cell-cell contact that is essential for CTL-mediated lysis. After contact, a variety of proteolytic enzymes (perforin, etc.) are released by the CTL from granules (inset b) that cause approximately 9- to 15-nm lesions (holes) in the membranes of the target cell.

reading frame whose predicted translation product has homology with the heavy chain of the MHC class I glycoprotein. Interestingly, HCMV virions bind to β_2-microglobulin, and HCMV-infected cells fail to synthesize mature cellular class I MHC molecules, but mRNA levels remain unaltered. By this treachery, the HCMV MHC homolog presumably competes for and sequesters β_2-microglobulin, thus preventing its binding to the MHC heavy chain. As a consequence, the MHC protein can be prevented from reaching the surfaces of infected cells, rendering such cells free from recognition by virus-specific CTL.

Viruses have additional strategies to avoid immunosurveillance. Instead of rendering infected cells invisible to CTL, viruses can infect cells of the immune system and abrogate their function. Most, if not all, viruses associated with persistence are known to infect lymphocytes and/or monocytes. The resulting interaction between the virus and lymphoid cell may totally disable specific immune responsiveness, as has been shown for several RNA viruses (measles virus, LCMV, and HIV) and DNA viruses (HCMV and hepatitis B virus) (reviewed in reference 22). These observations speak to the concept that a common mechanism by which viruses can initiate persistence is infection of effector T cells that ordinarily participate in clearing the virus. The result would be a selective advantage for the virus by restricting immunosuppression against itself, although in some instances, such as infection with HIV, the lymphocyte defect can lead to generalized immunosuppression and severe disease. The best-studied model for dissecting this concept is that of persistent infection by LCMV (2, 3, 7, 11, 21, 31, 36). During the persistent state, LCMV CTL are often selectively suppressed without generalized immunosuppression. For example, animals persistently infected with LCMV since birth can generate crisp CTL or antibody responses against many other, unrelated infectious agents. Inoculation of wild-type LCMV into fully immunocompetent hosts leads to development of CTL (CTL^+) and the clearance of virus (lack of persistence, P^{nil}). However, when mice are infected in utero or at birth, before they become fully immunocompetent, they lack or have low levels of CTL and develop persistent infection. Viral variants are selectively generated and/or amplified in lymphocytes of such persistently infected mice, and these variants have the unique ability to cause persistent infection when inoculated into

adult, immunocompetent mice. Hence, such viral variants are $CTL^{nil}P^{+}$. After reassorting the two RNA segments of LCMV of $CTL^{+}P^{nil}$ and $CTL^{nil}P^{+}$ virus (21), cloning and sequencing studies (36) in two independent laboratories established that a single amino acid mutation in the LCMV glycoprotein at residue 260 which changed a phenylalanine to a leucine determined whether the virus was cleared (CTL are generated) or not (21, 36). Other studies indicated that the immunosuppressive variants effect is at the induction stage, likely affecting either antigen processing, glycoprotein cleavage (the mutation occurs close to the cleavage site of the LCMV glycoprotein precursor into gpl and gp2 molecules), or a cytokine or other cellular factor. Thus, this and the earlier examples strongly indicate that investigation of and understanding virus peptide processing in infected cells and their interaction with lymphocytes and/or monocytes will prove pivotal in understanding how viruses avoid immunologic surveillance and adopt strategies favoring their persistence. Since, at least in model systems, persistent infections can be terminated by gene transfer (16, 40; MHC gene in adenovirus-induced tumors) or by immunocytotherapy (1, 28; adoptive transfer of virus-specific MHC-restricted CTL), there is the therapeutic possibility that once the unique defect in the immune system allowing persistence is uncovered, reconstitution may provide an option for successful treatment and control of persistent viral infections.

Humans are continually exposed to a wide spectrum of microorganisms. Many of these agents have been identified as the cause of acute disease, and this number grows. Several of these viruses cause tissue injury and elicit an immune response against themselves which often complements and accentuates cell and tissue destruction. Yet it is likely that we are bathed with many other microbial agents that establish a more advantageous symbiotic relationship for the microbe and the host. In such a relationship the virus would have a "safe house" in which to live throughout most if not the entire life span of the infected host. To establish such a relationship, the virus must employ a nonlytic strategy of replication as well as precise plans for escaping immunologic surveillance. The outcome would be a persistent infection without cell destruction or an associated inflammatory response. However, viral replication may alter a cell's differentiated function and thus may well be linked to diseases not traditionally attributed to viruses. Hence persistent viral infection may play a hitherto unsuspected role in diseases of the nervous, endocrine, and immune systems. Disorders of neurotransmitters, cytokines, or hormones would result. Yet, the customary hallmarks of viral infection (cell lysis and inflammatory infiltration) would not occur and should no longer be required as evidence of viral causation. It may well be that as we enter the 21st century and learn how to establish and maintain cultured differentiated cells such as neurons, oligodendrocytes, β-islet cells, etc., as has been done with lymphocytes and T-cell growth factor (14, 23), we will uncover new viral foes or rediscover old ones.

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ADDENDUM IN PROOF

A registry of viral CTL epitopes is being kept by the author. Data on viral amino acid sequence, MHC- restricting element, and virus protein should be sent to the author. The registry will be made available on request.

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