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Viral immune evasion: a masterpiece of evolution

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Abstract Coexistence of viruses and their hosts imposes an evolutionary pressure on both the virus and the host immune system. On the one hand, the host has developed an immune system able to attack viruses and virally infected cells, whereas on the other hand, viruses have developed an array of immune evasion mechanisms to escape killing by the host's immune system. Generally, the larger the viral genome, the more diverse mechanisms are utilized to extend the time-window for viral replication and spreading of virus particles. In addition, herpesviruses have the capacity to hide from the immune system by their ability to establish latency. The strategies of immune evasion are directed towards three divisions of the immune system, i.e., the humoral immune response, the cellular immune response and immune effector functions. Members of the herpesvirus family are capable of interfering with the host's immune system at almost every level of immune clearance. Antibody recognition of viral epitopes, presentation of viral peptides by major histocompatibility complex (MHC) class I and class II molecules, the recruitment of immune effector cells, complement activation, and apoptosis can all be impaired by herpesviruses. This review aims at summarizing the current knowledge of viral evasion mechanisms.

Keywords Immune evasion · Virus · Antigen presentation · Lymphocytes · Human cytomegalovirus

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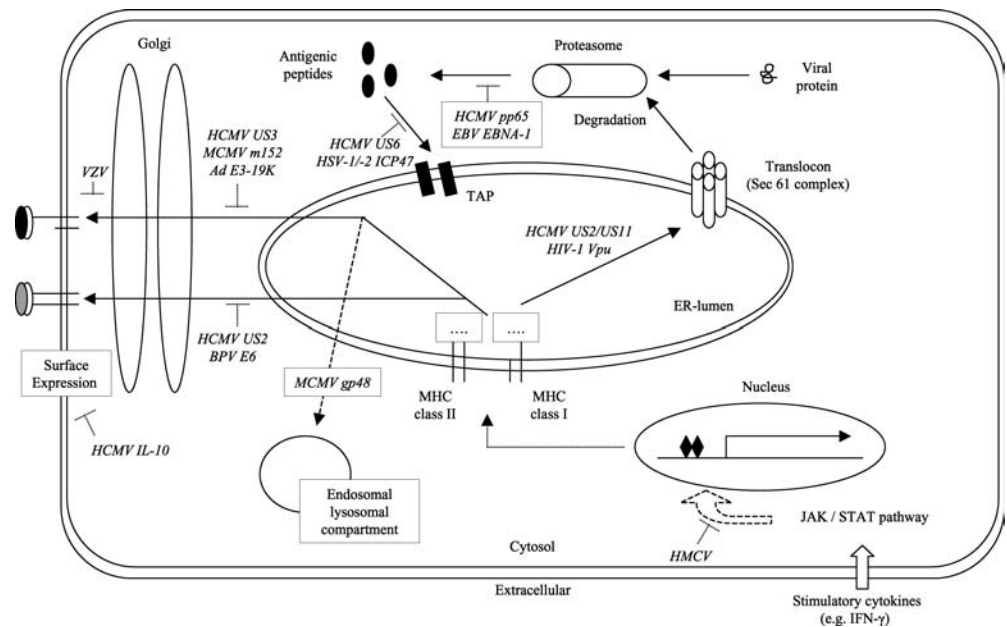
Introduction

Coexistence of a virus and its immunocompetent host requires a balance between the rates of viral replication and viral clearance by the immune system for mutual survival. The host's immune system employs a variety of strategies to eliminate the virus, whereas the virus has developed an array of immune evasion mechanisms to escape its elimination by the host's immune system.

Viruses with small coding capacity, such as picornaviruses, myxoviruses and retroviruses, constantly change their envelope glycoproteins, which results in immune evasion through the restriction of immunodominant peptides in the context of major histocompatibility complex (MHC) class I molecules. Viruses with larger coding capacity can express a wider array of proteins with specific effects on immune recognition and other immune effector functions. Thus, DNA viruses such as poxviruses, herpesviruses and adenoviruses utilize diverse mechanisms to extend the time-window for viral replication and spreading of virus particles. Herpesviruses have the additional capacity to hide from the host's immune system by their ability to establish latency.

The β -herpesviruses are slowly growing viruses with a restricted host range. They tend to establish latency in hematopoietic progenitor cells and persistently infect epithelial and glandular cells. Human cytomegalovirus (HCMV) usually causes infected cells to enlarge (cytomegali). HCMV is a ubiquitous pathogen, carried by 70–100% of healthy adults, in whom infection is generally subclinical. The virus can cause severe morbidity and mortality in immunocompromised hosts. Various cell types, such as fibroblasts, smooth muscle cells, endothelial cells, epithelial cells, monocytes and granulocytes, are infected during acute (lytic) infection. Infection of monocytes is non-lytic and results in latent infection. To reactivate from latency in order to complete the viral life cycle, HCMV takes advantage of situations when the immune system becomes activated (Söderberg-Nauclér et al 1997a, b, 2001; Zhuravskaya et al. 1997).

Fig. 1 Viral gene products block the MHC antigen-presentation pathway at multiple levels



The mechanisms for viral immune evasion can broadly be divided into three categories. These mechanisms include strategies that (1) enable the virus to avoid recognition by the humoral immune response, for example by changing its immunodominant epitopes, (2) interfere with the functioning of the cellular immune response, for example by disabling peptide presentation or impairment of natural killer (NK) cell functions, and (3) interfere with immune effector functions, for example the expression of cytokines or the blockage of apoptosis. The mechanisms underlying these viral evasion strategies are discussed below.

Impairment of the humoral immune response

Influenza virus is a typical example of a virus that effectively evades anti-viral B-cell immunity. Influenza virus type A infections can lead to large epidemics worldwide, each caused by a single virus variant. The human body can rapidly clear the virus by developing protective immunity towards it, mainly by directing neutralizing antibodies against the major surface protein of the influenza virus, hemagglutinin. Influenza virus type A has evolved two forms of antigenic variation to prevent running out of potential hosts (Gorman et al. 1992). First, antigenic drift is caused by point mutations in the genes encoding the hemagglutinin and neuraminidase. This can lead to the escape of viral variants from antibody neutralization by impairment of binding of the antibody to the epitope due to the change of critical residues at sites of interaction (Pruett and Air 1998). Although the virus evades neutralization by antibodies, severe disease will not develop, since the unaltered epitopes are still being recognized. Second, in the process of antigenic shift, RNA segments are exchanged between viral strains in a secondary host, which can lead to major changes in the

hemagglutinin protein on the viral surface. In such case, antibodies produced in response to previous infections cannot recognize the virus, and severe influenza pandemics can occur (Claas and Osterhaus 1998; de Jong et al. 1997; Gorman et al. 1992).

Impairment of the cellular immune response

Cell-mediated immune responses, in particular CD8⁺ CTL responses, play a major role in the elimination of virus infections (Barouch and Letvin 2001; Harty et al. 2000). Therefore, viruses frequently interfere with the activation of CD8⁺ and CD4⁺ T cells by blocking presentation of antigen in the context of MHC class I and class II molecules, respectively. Each step within the MHC class I and II biogenesis and transportation pathways is an inviting (and important) target for manipulation by viruses (Fig. 1).

Interference with proteasomal degradation

Peptides that are presented in the context of MHC class I molecules result from the degradation of viral proteins by proteasomes in the cytosol (Arrigo et al. 1988; Glynne et al. 1991; Kelly et al. 1991; Martinez and Monaco 1991). Proteasomal degradation is dependent on proteolytic cleavage of specific sequences within the protein. By altering parts of its genome and thereby the viral proteins, a virus can escape processing of these proteins into peptides. In a study with murine leukemia virus, a single amino acid change in a proteolytic cleavage site abolished productive processing of an immunodominant CTL epitope (Ossendorp et al. 1996).

The Epstein-Barr virus (EBV)-encoded nuclear antigen (EBNA)-1 escapes CTL detection and encodes

a mechanism to inhibit the generation of epitopes (Levitskaya et al. 1995). The Gly-Ala co-repeat (GAR) in EBNA-1 is a *cis*-acting inhibitor of ubiquitin-proteasome proteolysis (Levitskaya et al. 1997; Sharipo et al. 2001). The GAR domain is suggested to form β -sheets, that are resistant to unfolding and block entry into the proteasomal complex (Sharipo et al. 2001).

Expression of the HCMV matrix protein pp65 (UL83) results in phosphorylation of several HCMV proteins (Gilbert et al. 1993, 1996; Schmolke et al. 1995). Phosphorylation of threonine residues within immediate-early (IE) intermediate proteins may severely restrict access of the protein to proteasomal degradation or divert the protein into a different degradation pathway.

Interference with peptide transport by the transporter associated with antigen presentation

Peptides pass the membrane of the endoplasmic reticulum (ER) through translocation by the transporter associated with antigen presentation (TAP), for assembly into ternary MHC class I complexes (Androlewicz et al. 1993; Neefjes et al. 1993; Shepherd et al. 1993; van Endert et al. 1994).

Expression of the HCMV-encoded unique short 6 (US6) gene product, a type I transmembrane protein with a protein core of M_r 21,000 and a single N-linked glycosylation site, results in inhibition of TAP via its ER luminal face and retains the peptides without affecting peptide binding to TAP (Ahn et al. 1996a, 1997; Hengel et al. 1997). The interaction of the ER luminal domain of US6 with TAP stabilizes a conformation in TAP1 that is unable to bind ATP, which is a prerequisite for peptide transport (Hewitt et al. 2001). Although TAP2 is still capable of binding ATP, peptide translocation is inhibited. It is hypothesized that the ER-resident chaperone calnexin retains the immature gpUS6 molecules in the ER by high-affinity binding, since the protein itself does not contain the C-terminal KKXX consensus motif for ER retention of transmembrane proteins (Hengel et al. 1997; Jackson et al. 1990; Sadasivan et al. 1996). US6 protein synthesis starts during the early phase of infection and it reaches peak levels at 72 h post infection. The presence of US6 in the late phase of viral replication may limit the presentation of abundantly expressed structural viral antigens, such as glycoprotein B (Hengel et al. 1997).

HSV 1 and 2 encode the IE cytoplasmic protein ICP47, which blocks presentation of viral peptides to MHC class-I-restricted cells by blocking the peptide-binding site of TAP through competition with peptides (Ahn et al. 1996b; Früh et al. 1995; Hill et al. 1995; Tomazin et al. 1996; York et al. 1994).

Several other viruses, such as bovine herpes virus-1 (BHV-1) and pseudorabies virus (PrV) are also able to block TAP (Ambagala et al. 2000; Hinkley et al. 1998; Koppers-Lalic et al. 2001).

Retention of MHC class I molecules in subcellular compartments

The expression of the HCMV US3 protein impairs maturation and intracellular transport of MHC class I heavy chains by the formation of a complex with β_2m -associated class I heavy chains prior to peptide loading in the ER (Ahn et al. 1996a; Jones et al. 1996). Although this association does not prevent peptide loading, complete MHC class-I-peptide complexes are retained in the ER, resulting in the loss of MHC class I heavy-chain expression on the cell surface. US3 is an IE gene encoding a glycoprotein with a relatively short intracellular half-life (Jones et al. 1996). Since IE genes are independent of viral protein synthesis, US3 might be expressed during the latent stage of the virus and might be necessary for escape from immune surveillance during the latent phase and early stages of infection (Ahn et al. 1996a).

The murine CMV (MCMV) gene products of *m06* (gp48) and *m152* (gp40) both inhibit antigen presentation to CD8⁺ CTLs (Krmpotić et al. 2002). Gp40 retains mouse MHC class I complexes in the ERGIC/*cis*-Golgi compartments, a process that requires the luminal part of the protein (Ziegler et al. 1997, 2000). Gp48 binds MHC class I molecules and redirects their transport into lysosomes, where the complexes are degraded (Reusch et al. 1999). Another MCMV gene, *m4*, encodes a glycoprotein (gp34) which is expressed at the cell surface in association with MHC class I molecules, thus inhibiting CTLs without blocking class I surface expression (Kavanagh et al. 2001). Gp34 and gp40 inhibit antigen presentation in a complementary and cooperative fashion.

Varicella-Zoster virus (VZV) retains MHC class I molecules in Golgi compartments of infected cells, but the mechanism(s) responsible for this interference with MHC class I transport have not yet been identified (Abendroth et al. 2001).

The adenoviral E3-19k gene product is synthesized on membrane-bound ribosomes in the host cell and is subsequently translocated through the rough ER and glycosylated (Persson et al. 1980). In the ER, the protein binds to MHC class I heavy chains with high affinity, inhibiting terminal glycosylation of MHC class I antigens, thereby preventing their translocation to the cell surface (Andersson et al. 1985; Burgert and Kvist 1985; Pääbo et al. 1983). Gamma-interferon (IFN- γ) can overcome this effect by the induction of MHC class I expression. Tumor necrosis factor (TNF)- α cannot and even significantly increases the expression of the viral protein by interference with the functioning of NF- κ B.

The cytoplasmic HIV-1 Nef polypeptide is responsible for downregulation of MHC class I molecules (Schwartz et al. 1996). Nef is expressed in the earliest stages of viral infection and is suggested to physically connect the MHC class I molecules to clathrin-coated pits, involved in endocytosis at the plasma membrane and the *trans*-Golgi network. CD4 is downregulated by Nef by the same mechanism (Mangasarian et al. 1997).

Destruction of MHC class I heavy chains in the context of viral evasion

In addition to mechanisms that interfere with MHC class I expression on the cell surface, such as withdrawal of peptides or intracellular retention of the MHC complexes, a more radical approach is utilized by HCMV. Expression of HCMV gene products US2 and US11 result in degradation of MHC class I molecules (Wiertz et al. 1996a; Wiertz et al. 1996b).

In cells expressing US2 or US11, the MHC class I molecules are transported from the ER back into the cytosol, where they are degraded by the proteasome with a half-time of less than 1 min. Prior to their degradation by proteasomes, the class I heavy chains are deglycosylated by a host N-glycanase (Wiertz et al. 1996b). US2 and US11 are both type I membrane glycoproteins that are confined to the ER. A specific interaction of the luminal domains of gpUS2 and gpUS11 with MHC class I heavy chains ensures that only class I molecules (and certain MHC class II chains, see below) and not other membrane or secretory proteins are directed for degradation. It has been shown that a functional ubiquitin system is essential for dislocation of MHC class I molecules, and that binding of US11 precedes the required polyubiquitination (Kikkert et al. 2001; Shamu et al. 2001). The heavy chain degradation intermediate can be found in association with the Sec61 complex, which suggests the retrograde transport to occur through the same protein-conducting channel that allowed the original membrane insertion of the heavy chain (Wiertz et al. 1996a). This route of degradation is normally used in cells to degrade class I heavy chains that fail to assemble into multimeric complexes, either due to misfolding or to incapability to bind peptides (Wiertz et al. 1996a; Hughes et al. 1997). A distinction between US2/US11-mediated degradation and degradation of misfolded proteins is the difference in kinetics. Class I molecules are degraded rapidly in US2/US11-expressing cells, whereas misfolded proteins may be retained in the ER for hours before they are disposed of (Furman et al. 2002). The US2 ER-luminal domain forms an Ig-like fold, which allows a tight interaction with class I molecules (HLA-A) (Gewurz et al. 2001a, b). This association does not significantly alter the conformation of the class I molecules. The recently found ability of newly translated US2 to target pre-existing heavy chains, suggests that US2 recruits factors that stimulate dislocation, rather than triggering dislocation of heavy chains while still located in the Sec61 pore (Furman et al. 2002; Gewurz et al. 2001a).

Although the production of two proteins with similar functions by a single virus seems redundant, in mouse models the proteins differ in their ability to attack allelic forms of mouse heavy chain (Machold et al. 1997). US11 degrades H-2 Kb, Db, Dd and Ld efficiently. US2 is most effective in degrading Db and Dd, possibly as a consequence of interacting with different regions of the class I heavy chain in the process of dislocation.

Truncation experiments have shown that US2 and US11 have different targeting mechanisms (Furman et al. 2002). US2 requires both transmembrane and cytosolic domains to function, whereas US11 does not require its cytoplasmic tail to target heavy chains for destruction. It has been shown recently that US11 exhibits a superior ability to degrade MHC class I molecules in primary human dendritic cells (Rehm et al. 2002).

The HIV-1 Vpu gene product is a small integral membrane phosphoprotein with three established functions (Schubert and Strebel 1994). These are (1) downregulation of MHC class I molecules (Kerkau et al. 1997), (2) augmentation of viral particle release from the plasma membrane of HIV-1-infected cells (Kerkau et al. 1997), and (3) degradation of the viral co-receptor CD4 (Margottin et al. 1996; Schubert et al. 1998). The abolished expression of class I molecules is accomplished by interference with an early step in class I biogenesis, before egression from the ER. This probably occurs through a process involving phosphorylation of the cytoplasmic tails, similar to the induction of proteolysis of nascent CD4 (Kerkau et al. 1997; Schubert and Strebel 1994).

Human herpesvirus 7 (HHV-7) encodes the U21 protein, which binds to and diverts properly folded class I molecules from the ER to a lysosomal compartment (Hudson et al. 2001).

Karposi's sarcoma-associated herpesvirus (KSHV) or HHV-8 encodes K3 and K5 zinc finger membrane proteins that remove MHC class I molecules from the cell surface (Ishido et al. 2000). The proteins do not affect expression or intracellular transport of class I molecules, but their expression induces rapid endocytosis of the molecules. Recently, it has been shown that K3 not only directs internalization, but also targets MHC class I complexes to a dense endocytic compartment on the way to lysosomes in a ubiquitin-proteasome-dependent manner (Lorenzo et al. 2002).

Induction of functional paralysis of dendritic cells

Dendritic cells (DCs) are professional antigen-presenting cells with a crucial role in the generation and maintenance of immune responses. Immature DCs in peripheral tissues take up and process antigens, an event that triggers their differentiation into mature DCs. Mature DCs have a reduced Ag-processing capacity and an increased cell surface expression of MHC and co-stimulatory molecules. Their additionally altered expression of chemokine receptors facilitates migration to the T-cell areas of lymph nodes.

MCMV can infect immature DCs and thus induces a functional paralysis (Andrews et al. 2001). Cell surface expression of MHC and co-stimulatory molecules on the infected DCs is reduced. They remain unresponsive to maturation stimuli, lose their capacity to secrete IL-12 or IL-2 and are unable to prime an effective T-cell response (Andrews et al. 2001; Lehner and Wilkinson 2001).

When HCMV also induces this functional paralysis of DCs, it would provide a further explanation of the low CTL response against immediate-early proteins of the virus, such as pp65 (Gilbert et al. 1993, 1996). Recently, it has been shown that late HCMV-infected cells can secrete soluble factors, such as TGF- β 1, which interfere with the maturation of DCs (Arrode et al. 2002). As a result, the cross-presentation of the pp65 protein and the establishment of a CD8⁺ T-cell response was blocked. Therefore, recognition of the virus by DCs has to occur early after infection to be able to activate CTLs directed against IE proteins.

Downregulation of MHC class II expression

Although CD8⁺ T cells have been shown to be important in the control of viral disease, CD4⁺ T cells play a key role in the early activation of CD8⁺ T cells and in B-cell development. Little is known about the targets of viral proteins in the MHC class II peptide presentation pathway, which focuses largely on events in the endocytotic pathway.

HCMV and MCMV are able to interfere with CD4⁺ T-cell recognition of infected cells by inhibition of MHC class II expression on endothelial and epithelial cells (Buchmeier and Cooper 1989; Heise et al. 1998; Scholz et al. 1992; Sedmak et al. 1995).

HCMV-infected cells stimulated with IFN- γ could not induce expression of MHC class II molecules, caused by a decrease in Janus kinase 1 (JAK1) protein levels (Miller et al. 1998), probably through the enhancement of JAK1 protein degradation by the proteasome. Downstream CIITA, an IFN- γ -induced transcription factor of MHC class II molecules in the JAK/Stat pathway, is also impaired.

VZV has a similar effect on IFN- γ -stimulated expression of cell surface MHC class II molecules. VZV infection inhibits the expression of Stat1 α and JAK2, thus inhibiting transcription of IFN regulatory factor 1 and the MHC class II transactivator (Abendroth et al. 2000).

Recently, it was found that HCMV uses different mechanisms in infected macrophages to downregulate MHC class II molecules at early (E) and late (L) times after infection (Odeberg et al. 2001). A structural component is probably responsible for the early inhibition of HLA class II expression and Ag presentation, since the effect was independent of virus-replication. The late effect was dependent on active virus-replication and expression of US1-US9 or US11. Ag presentation and T-cell proliferation was also found to be inhibited by undefined soluble factors, excluding IL-10 and TGF- β 1, produced by the HCMV-infected cells.

The expression of HCMV protein US2 causes degradation of two essential proteins in the MHC class II antigen presentation pathway; the HLA-DM- α and HLA-DR- α chains (Tomazin et al. 1999). Expression of US2 reduced or abolished the ability to present antigens to CD4⁺ T cells. US2 may thus allow HCMV-infected

macrophages to remain invisible to CD4⁺ T cells, a property important after virus reactivation.

Bovine papillomavirus (BPV) produces the zinc finger E6 protein, which can interact with the clathrin adaptor (AP)-1 protein complex (Tong et al. 1998). AP-1 is required for clathrin-mediated cellular transport. E6 might affect the intracellular distribution of class II products or the antigens destined for presentation in context of MHC class II.

Circumvention of NK cell-mediated killing

In accordance with the concept of the "missing self" hypothesis, downregulation of MHC class I complexes on the cell membrane by viral proteins results in elimination of the infected cells by NK cells (Ljunggren and Kärre 1990). NK cells express both activating and inhibitory surface receptors, such as CD94 and immunoglobulin-like transcript (ILT)-2 (Blery et al. 2000; Colonna et al. 1999). Herpes simplex virus (HSV) and HCMV induce NK cell cytotoxicity by downregulation of HLA-C molecules *in vitro* (Huard and Früh 2000). Furthermore, HCMV avoids NK cell-mediated killing by expression of MHC homologues that engage killer cell inhibitory receptors (KIRs) and function as viral decoys to prevent NK-mediated cytotoxicity (Fahnestock et al. 1995; Farrell et al. 1997; Reyburn et al. 1997).

Both HCMV and MCMV encode MHC class I heavy-chain homologues (Beck and Barrel 1988; Farrell et al. 1997; Rawlinson et al. 1996; Reyburn et al. 1997). HCMV encodes gpUL18, an extensively glycosylated type I TM glycoprotein exhibiting an amino acid sequence identity of approximately 21% with human polymorphic MHC class I molecules. UL18 forms three domains typical for MHC class I molecules (Farrell et al. 1997). MCMV encodes m144, a type I transmembrane glycoprotein whose extracellular region shares approximately 25% amino acid sequence identity with the corresponding part of mouse MHC class I extracellular regions. Both MHC homologues are able to bind β_2m (Browne et al. 1990; Chapman and Bjorkman 1998), but only gpUL18 can bind endogenous peptides, since M144 has a deletion within the counterpart of its α 2 domain (Fahnestock et al. 1995). Antibodies to CD94, an inhibitory receptor on most NK and subsets of T cells, abolish target cell protection mediated by gpUL18 (Reyburn et al. 1997). A separate receptor for UL18 has been identified: LIR-1 (leukocyte immunoglobulin-like receptor-1). LIR-1 is related to human NK inhibitory receptors and is mainly expressed on B cells and monocytes, but only on a subset of NK cells. Therefore, the HCMV MHC homologue UL18 might exert its primary effects on other host cells than NK cells (Chapman et al. 1999). The capability of UL18 to circumvent NK cell mediated killing is controversial (Cosman et al. 1999). Whereas Reyburn and co-workers have demonstrated protection of UL18 transfectants from NK cell killing, Leong and co-workers (1998) could not observe this protection. Recently,

Odeberg and co-workers concluded that the lower susceptibility of HCMV-infected endothelial cells and macrophages to NK lysis is not dependent on downregulation of HLA class I molecules nor on the expression of the HCMV class I homologue UL18 (Odeberg et al. 2002).

HCMV UL16 binds to ULBPs and MICB. Both ULBPs and MICB are members of the MHC class I family. The ULBP and MICB molecules are ligands for the NK activating receptor, NKG2D/DAP10, and this interaction is blocked by a soluble form of UL16 (Cosman et al. 2001).

Other studies showed that the non-classical MHC class I molecule HLA-E, an inhibitor of NK cell-mediated lysis, is upregulated by HCMV (Tomasec et al. 2000). Surface expression of HLA-E depends on binding of conserved peptides, derived from MHC class I molecules. A similar peptide is present in the leader sequence of the HCMV gpUL40 (Tomasec et al. 2000).

In addition to downregulation of MHC class I expression on the plasma membrane, the MCMV gene product m152/gp40 plays a role in controlling NK cell activation. Expression of gp40 results in downregulation of the surface expression of H-60, the high-affinity ligand for the NKG2D receptor, which results in prevention of NK cell activation (Kärre 2002; Krmpotić et al 2002). Thus, gp40 is capable of inhibiting both the adaptive and the innate immune response.

Downregulation of transcription of proteins involved in the MHC class I peptide presentation pathway

In adenovirus (Ad)12-transformed cell lines, proteins involved in the MHC class I peptide presentation pathway, including Tap2, LMP2, and LMP7, exhibit a >100-fold reduction in their steady state mRNA levels, with both mRNA and protein products barely detectable (Rotem-Yeduhar et al. 1996). TAP1, class I heavy chains and β_2m genes show a two- to tenfold reduction in their steady state mRNA levels, with gene expression varying among individual cell lines. MHC class I transcription is downregulated through strong DNA-binding activity of the repressor COUP-TFII and weak binding of the activator NF- κ B to, respectively, the R2 and R1 binding sites of the class I enhancer (Hou et al. 2002). COUP-TFII is upregulated in Ad12-transformed cells (Smirnov et al. 2001). The diminished NF- κ B binding is due to the reduced phosphorylation of p50 (Kuscher and Ricciardi 1999).

Antigenic variation of T-cell epitopes

Antigenic variation has its impact on the cellular immune response. The efficiency of processing and presentation of CTL epitopes is determined by the sequence of the epitope, but also by the residues surrounding it in the protein. Therefore, variation in a relatively broad region can lead to alteration of peptide binding to MHC or reduction in the affinity of peptide-MHC interaction,

which results in unstable peptide-MHC complexes. For example, in HIV-infected individuals variants evolve in which peptide epitopes are mutated in such a way that these epitopes function as antagonists, actively silencing HIV-specific T-lymphocytes (Klenerman et al. 1995). This phenomenon is also described for amino acid changes within the core molecule of hepatitis B virus (HBV) (Bertoletti et al. 1994).

Inhibition of tapasin

In addition to the capability of the adenoviral gene product E3-19k to retain the MHC class I molecules in the ER by binding to the heavy chains and preventing translocation, the protein has a second mechanism to affect MHC class I expression. E3-19k is capable of binding to both class I and TAP, acting as a competitive inhibitor of tapasin (Bennet et al. 1999). E3-19k cannot substitute for tapasin, but it can independently bind to either class I or TAP, thereby causing a decrease in association between these molecules and a delay in class I maturation.

Downregulation of CD4 expression

Recognition of an antigenic determinant-containing MHC complex by the T-cell receptor requires the co-expression of CD4 or CD8 molecules on the surface of T cells. HIV-1 Vpu, Env and Nef have all been implicated in modulating the levels of cell surface CD4 on infected cells (Chen et al. 1996; Fujita et al. 1996). The proteins use different mechanisms to downmodulate CD4 at different time points during the infection. Vpu induces degradation of CD4 by the proteasome after retranslocation from the ER to the cytosol (Kerkau et al. 1997; Margotin et al. 1996; Schubert and Strebel 1994; Schubert et al. 1998). Nef blocks transport of MHC class I molecules to the cell surface via a PI3 kinase-dependent pathway, probably by diverting the MHC class I proteins in intracellular organelles (Swann et al. 2001). Env forms a complex with CD4 in the ER (Piguet et al. 1999).

Downregulation of the T-cell receptor

Some viruses are capable of avoiding immune recognition by downregulation of the CD3/T-cell receptor (TCR) complexes on T cells. Human herpesvirus (HHV)-6A, but not HHV-6B, is able to downregulate the TCR complex at a transcriptional level, but the mechanism is still unknown (Furukawa et al. 1994; Lusso et al. 1991b).

Viral interference with immune effector functions

Viral interference with cytokine synthesis and function

Cytokines are important modulators of the immune response. IL-10 is an important cytokine with strong

immunosuppressive and anti-inflammatory activities. On the other hand, IL-10 is a cofactor for the growth and differentiation of B cells, mast cells and mouse T cells. IL-10 is secreted by activated T cells, B cells and monocytes, and binds to its specific receptor expressed on all hematopoietic cells (de Waal Malefyt et al. 1991a; Liu et al. 1994; Matthes et al. 1993; Yssel et al. 1992). IL-10 inhibits proliferation of activated human T cells and their IL-2 production (de Waal Malefyt 1991b), induces T-cell anergy, and inhibits the secretion of lipopolysaccharide-induced pro-inflammatory cytokine (de Waal Malefyt et al. 1991a). IL-10 decreases plasma membrane expression of MHC class II molecules (de Waal Malefyt et al. 1991a; Koppelman et al. 1997), downregulates cell adhesion, and downregulates expression of co-stimulatory molecules and TAP (Zeidler et al. 1997). IL-12, which promotes IFN- γ production and has a profound impact on the development of Th1- and Th2-like cytokine producing cells, is negatively regulated by IL-10 (Holland and Zlotnik 1993).

A homologue of the immune modulator IL-10 was discovered in the genome of HCMV (Kotenko et al. 2000). CMV IL-10 also possesses potent immunosuppressive properties, such as the inhibition of proliferation of mitogen-stimulated peripheral blood mononuclear cells (PBMCs) and the inhibition of proinflammatory cytokine synthesis in PBMCs and monocyte cultures (Spencer et al. 2002). CMV IL-10 was observed to decrease cell surface expression of both MHC class I and class II complexes, while increasing expression of the non-classical MHC allele HLA-G. Despite the low homology of this viral IL-10 to endogenous cellular IL-10, CMV IL-10 is suggested to bind to the cellular human IL-10 receptor, through which it mediates its activity (Kotenko et al. 2000; Spencer et al. 2002).

EBV expresses the BCRF1 protein, which is a biologically active homologue of IL-10 (Zdanov et al. 1997). Despite extensive sequence homology with human IL-10, it does not stimulate the proliferation of B cells, suggesting that viral IL-10 homologues may retain only a subset of human IL-10 activities that are advantageous for the virus (Spencer et al. 2002). Other viruses are capable of inducing the production of IL-10. Bovine leukemia virus (BLV) proteins Tax and gp51 induce IL-10 secretion by monocytes and macrophages (Pyeon et al. 1996). HIV proteins Tat and gp120 induce IL-10 production through the activation of host transcription factors, including NF- κ B (Howcroft et al. 1993). MCMV is shown to induce IL-10 production in infected cells, which causes a decrease in the expression of MHC class II on macrophages (Redpath et al. 1999).

There are also examples of viruses that can decrease the production of immunoactivating factors. HBV inhibits both IFN- α production and the capacity of infected cells to respond to IFN (Foster et al. 1991). Adenoviruses encode at least three genes that antagonize the effects of TNF (Gooding et al. 1990; Wold et al. 1994).

Another level of interference with cytokine functioning occurs at the level of cytokine receptors. The Shope

fibroma virus genome contains a genetic sequence with extensive homology (24%) to the binding portion of the mammalian TNF receptor (TNFR). This homologous gene codes for a soluble protein called T2, which cleverly serves as a TNF receptor decoy molecule (Smith et al. 1990). A T2-like protein is also expressed by myxoma virus (Upton et al. 1991). Myxoma virus and swinepox encode gene products functioning as homologues of the IFN- γ receptor, MT7 and C61 respectively (Upton et al. 1992). Other examples of viral gene products that bind to cytokines are swinepox K2R (binds to IL-8), HBV PreS2 (binds to IL-6), and vaccinia and cowpox B15R (binds to IL-1 β) (Evans 1996). Expression of receptor homologues in viruses seems to have the purpose of withdrawing these activating cytokines of the immune response from the environment.

G-Protein-coupled receptors

G-Protein-coupled receptors (GCRs) link the binding of an extracellular ligand (hormones, neurotransmitters and chemoattractant chemokines) to processes within the cell by their activation of associated G proteins (Murphy 1994a). Binding of a ligand to its receptor triggers a pathway of signaling molecules, resulting in the increase of intracellular Ca²⁺ levels. This results in amplification of the initial signal transduced by the ligand-GCR interaction into complex cellular processes, such as chemotaxis (Bokoch 1995). Chemokines are structurally related 70- to 90-amino-acid polypeptides that regulate the trafficking and activation of mammalian leukocytes and thus may be important mediators of inflammation (Baggiolini and Dahinden 1994; Kelner et al. 1994). Chemokines can be divided in three subfamilies: α (C-X-C) chemokines, which act primarily on neutrophils (chemotaxis), β (C-C) chemokines, which act on monocytes, lymphocytes, basophils and eosinophils (chemoattraction and degranulation), and γ chemokines, which act upon lymphocytes.

Some viruses encode GCR homologues, which may mimic the functions of cellular GCR, but the role of the expression of viral GCRs in the biology of a viral infection is largely unknown. Viral GCRs are ubiquitous and a number of suggestions regarding the function in viral pathogenesis have been made (Rosenkilde et al. 2001), including (1) immune evasion by sequestering chemokines in order to limit the recruitment of further effector cells, (2) tissue targeting and dissemination of the virus, (3) reactivation of a latent virus (Murphy 1994b), (4) modulation of cellular reprogramming (cellular activation and proliferation could lead to an increase in the amount of potential targets).

HCMV encodes four GCR homologues, UL33, UL78, US27 and US28 (Chee et al. 1990a, b). US28 appears to be functional in many different aspects. US28 is expressed early after infection (Vieira et al. 1998) and shows highest homology (33%) to the CC chemokine receptor CCR1 (Neote et al. 1993a). US28 is capable of

binding the CC chemokines RANTES, MCP-1, MCP-3, MIP-1 α and MIP-1 β (Billstrom et al. 1998; Gao and Murphy 1994; Neote et al. 1993a, b), as well as the membrane-associated CX3C chemokine fractalkine (Kledal et al. 1998). Transient expression of US28 leads to constitutive activation of both phospholipase C and NF- κ B signaling and here fractalkine acts as an inverse agonist (Casarosa et al. 2001). In this way the homeostasis of infected cells might be modulated via US28. The interaction US28-fractalkine has been suggested to play a role in the dissemination of the virus and cell targeting. It might also present an initial interaction between virus and target cell, and thus enhances and possibly mediates the cell fusion process (cell entry) (Kledal et al. 1998). The lower-affinity US28-CC binding might function as a means to prohibit recognition of the US28 receptor by the immune system (shielding).

Expression of US28 leads to internalization of RANTES and MCP-1 in fibroblasts and endothelial cells, which suggests that the receptor functions as a CC-chemokine sink, enabling HCMV-infected cells to evade immune surveillance (Bodaghi et al. 1998). US28 is also a co-receptor for several HIV strains and can elicit cell-to-cell fusion with several types of viral envelope proteins (Pleskoff et al. 1997). Additionally, transient high-level expression of US28 in smooth muscle cells induces chemokinesis in the presence of MCP-1 and chemotaxis within a RANTES-gradient (Streblov et al. 1999). This might provide a link between HCMV and the development of vascular diseases. US28 is transcribed during both latent and productive HCMV infection, which might prove a role in the dissemination of latent HCMV (Beisser et al. 2001).

Experiments with rat and mouse homologues of HCMV UL33 (R33 and M33, respectively) showed that these molecules are essential for targeting and/or replication of RCMV/MCMV in salivary glands, and thus indicates their importance for general virulence, since spreading of the virus between individuals occurs through saliva (Beisser et al. 1998; Davis-Poynter et al. 1997).

UL78 can probably also influence virulence. The rat homologue R78 is suggested to play an important role in both CMV replication *in vitro* and the pathogenesis of viral infection *in vivo* (Beisser et al. 1999).

US27 is located immediately upstream of US28 in the genome of HCMV and has approximately 40% sequence homology to US28 (Bodaghi et al. 1998). US27 does not bind any of the chemokines known to interact with US28, although the proteins have a similar cellular distribution (Rosenkilde et al. 2001; Vieira et al. 1998).

In contrast to most human chemokine receptors, only a small amount of the virally encoded US28, US27, UL33 is expressed on the cell surface. Most receptors accumulate in endosomal compartments, where viral envelope formation occurs late in infection. The targeting of receptors to the virus envelope implies that they function as IE genes, possibly changing the functional state of the cell through the various signaling cascades and altering gene expression (Rosenkilde et al. 2001).

The HCMV gene *UL146* has been found to encode the fully functional chemokine vCXCL-1, a 117-amino-acid glycoprotein that is secreted as a late gene product (Penfold et al. 1999). This virus-encoded α chemokine may ensure recruitment of neutrophils, providing for efficient dissemination during HCMV infection.

Interference with cellular signaling

Virus replication and spread in a host population depends on highly specific interactions of viral proteins with infected cells, which result in subversion of multiple cellular signal transduction pathways. For instance, viral proteins cause cell cycle progression of the infected host cell, in order to establish a cellular environment favourable for virus replication. Of equal importance for successful propagation of a virus is virus-mediated attenuation of a host's immune response. HCMV inhibits interferon-stimulated antiviral and immunoregulatory responses by blocking multiple levels of the interferon-signal transduction. As a consequence, the virus decreases the expression of JAK-1 and p48 (Miller et al. 1999), which results in inhibition of MHC class I and II expression. HCMV infection alters the expression of many cellular genes, including IFN-stimulated genes (ISGs). The envelope glycoprotein B (gB), a critical mediator of HCMV entry, has been identified as a trigger (Simmen et al. 2001). Interaction of gB with its unidentified cellular receptor is the principal mechanism by which HCMV alters cellular gene expression early during infection, independent of viral replication.

Many of the signaling pathways controlling the aspects of cell behavior are regulated by cellular tyrosine kinases, especially those of the Src family (Erpel and Courtneidge 1995). EBV expresses the membrane-associated protein LMP2A during latent infection. In EBV-infected cells expressing LMP2A, the tyrosine kinase signal cascade is not triggered, probably due to binding of the constitutively tyrosine phosphorylated LMP2A to domains of Src family kinases. In cells not expressing LMP2A, triggering of the cascade leads to reactivation of EBV, resulting in lytic infection (Miller et al. 1994, 1995). HVS also targets the Src-related kinase signaling by encoding a tyrosine kinase interacting protein (Tip). Tip inhibits Lck-mediated signal transduction in T cells, which results in blockage of signaling of the T-cell receptor and downregulation of surface molecules, such as CD2 and CD4 (Biesinger et al. 1995; Jung et al. 1995).

Inhibition of apoptosis

Apoptosis is the process of programmed cell death. Apoptosis is a normal event in the maturation of B and T cells, as well as in their effector function of killing of infected cells without causing inflammation. It is often induced by activation of so-called death receptors, all belonging to the TNFR superfamily. Examples are Fas

(CD95), TNFR-1 and TNFR-related apoptosis-mediated protein (TRAMP). Death signals are conducted through a cytoplasmic motif, called the death domain (DD). Upon receptor activation, this DD interacts with the DD of the adaptor molecules FADD (Fas-associated death domain protein) and/or TRADD (TNFR-associated protein), thereby recruiting them to the membrane (Nagata 1997). A receptor-associated death-inducing signaling complex (DISC) is formed by association of oligomerized CD95 and FADD with the ICE-like protease FLICE (Fas-associated death-domain-like IL-1 β -converting enzyme), also known as caspase-8, Mch5 or MACH, and CAP3 (cytotoxicity-dependent APO-1-associated protein 3) (Kischkel et al. 1995). Association of these proteins occurs through the death-effector domains (DED) of FADD and FLICE, resulting in subsequent proteolytic activation of other members of the ICE-family. Active caspase-8 dissociates from the DISC to start the cascade of caspases, which constitute the execution phase of apoptosis (Martin and Green 1995; Medema et al. 1997). To avoid inappropriate cell death, death-receptors have to be tightly controlled by a variety of inhibitory signals. Viruses also evolved several distinct strategies to avoid killing of infected cells by the host, including the production of caspase inhibitors, Bcl-2 homologues and FLIPs (FLICE-inhibitory proteins) (Irmeler et al. 1997). Cellular FLIPs are highly expressed in tumor cells, T lymphocytes and myocytes, which suggest a critical role of FLIPs as endogenous modulators of apoptosis. Their viral counterparts, v-FLIPs, are encoded by several γ -herpesviruses (KSHV/HHV-8 and HVS), as well as the tumorigenic human molluscipoxvirus (Senkevich et al. 1996). V-FLIPs are proteins consisting of two DED motives, that interact with the DED of FADD and/or caspase-8, which results in inhibition of caspase-8 recruitment and activation by Fas, thereby acting as dominant-negative inhibitors. All FLIP-encoding γ -herpesviruses also encode a Bcl-2 homologue, which provides two complementary anti-apoptotic functions. It is conceivable that two such molecules were developed to block apoptosis in different reacting cell types (Peter and Kramer 1998). Thus, FLIPs facilitate viral spread and persistence, and contribute to the transforming capacities of some herpesviruses (Thome et al. 1997). Besides the production of FLIPs, interference with death signaling can also be achieved on the receptor level. The adenoviral protein E3-10.4/14.5K triggers internalization of cell-surface Fas and its destruction in lysosomes (Shisler et al. 1997; Tollefson et al. 1998). In addition, cowpox virus-encoded CrmA is a member of the family of serine protease inhibitors (serpins) that efficiently inhibits caspase-1 and -8, thereby interrupting the cascade of caspase activation (Zhou et al. 1997).

Interference with the complement system

An important effector mechanism of the immune system is the classical complement system, which eliminates

infected cells by activating the complement cascade, resulting in the formation of pores in the target cells. Host cells are protected against the action of the complement system by expression of regulators of complement activation (RCA) on their membranes. These RCA downregulate complement activity by inhibiting formation and promoting the decay of C3-activating enzymes (C3 convertases) and by preventing the formation of the membrane attack complex (Vanderplasschen et al. 1998).

Viral interference with the complement system can be achieved on different levels. First, some viruses can express structural viral proteins that mimic the function of cellular RCA. HSV-1-encoded glycoprotein C induces the dissociation of the alternative pathway C3 convertase (Friedman et al. 1984; Harris et al. 1990). Second, some viruses, such as the enveloped vaccinia virus, are able to incorporate host RCA into their envelope by budding through the plasma membrane or into intracellular vacuoles. Third, some viruses can secrete a soluble protein that blocks complement activation. Vaccinia virus secretes a complement-control protein (VCP), which shares amino acid similarity with mammalian RCA and is capable of binding proteins in the C3 convertase pathway (McKenzie et al. 1992; Sahu et al. 1998). Variola virus is a member of the same genus as vaccinia virus (*Orthopoxvirus*) and is the causative agent of smallpox. Variola encodes a homologue of VCP, named smallpox inhibitor of complement enzymes (SPICE). SPICE is more specific for human complement than VCP and is a nearly 100-fold more potent inactivator of C3b (Rosengard et al. 2002).

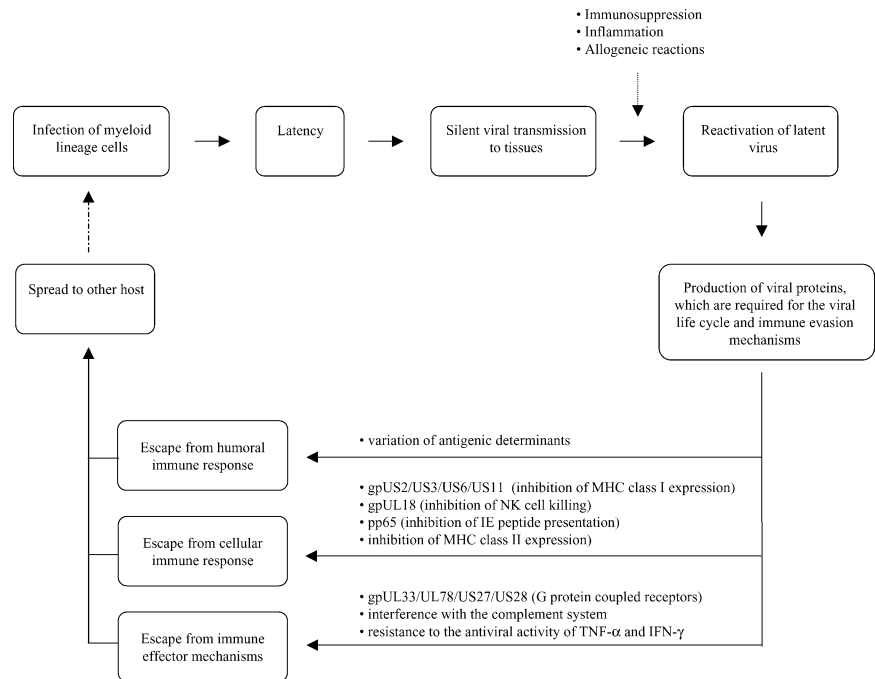
Infected cells can also be lysed by antibody-dependent complement-mediated lysis. Binding of antibodies to epitopes on the surface of an infected cell results in the activation of the complement pathway and lysis of the cell. Some viruses produce molecules that bind to the Fc region of host immunoglobulins. These virally encoded Fc receptors (v-FcRs) may prevent antiviral immunoglobulin G (IgG) from neutralizing free virus and engaging in antibody-dependent activity against infected cells (Lubinski et al. 1998).

HCMV and MCMV induce Fc-binding activity in infected cells, possibly by inducing the expression of cellular Fc-receptors (Furukawa et al. 1975; Thäle et al. 1994). Recently, it has been demonstrated that the HCMV open reading frame (ORF) TRL11/IRL11 encodes a type I membrane glycoprotein of M_r 34,000 that possesses IgG Fc-binding capabilities (Lilley et al. 2001).

The HSV v-FcR is a heterodimer of the gE and gI glycoproteins, and binding to IgG results in inhibition of cell lysis (Baucke and Spear 1979; Dubin et al. 1991; Johnson et al. 1988).

In addition to these mechanisms to inhibit the complement pathway, the Epstein-Barr virus (EBV)-encoded major outer membrane glycoprotein gp350 is able to bind to complement receptor type 2 (CR2) (Nemerow et al. 1987). This interaction triggers endocytosis of the virus (Tanner et al. 1987). A complex of three EBV-

Fig. 2 Schematic presentation of HCMV infection and viral immune evasion throughout the human body



encoded glycoproteins, gH, gL and gp42, is essential for cell entry into B cells (Molesworth et al. 2000). In B cells, entry requires the interaction of gp42 with mHC class II molecules, which function as co-receptors.

Infection of epithelial cells requires gH-gL complexes that lack gp42. EBV originating in B cells contains little gp42 and, consequently, infects B cell less efficiently. Conversely, EBV from epithelial cells carries high levels of gp42 and preferentially infects B cells. Gp42 thus may act as a molecular switch that influences tropism of EBV to epithelial cells and B cells (Borza and Hutt-Fletcher 2002).

Predisposition of an infected cell to superinfection

Manipulation of the immune system by a virus can lead to superinfections with other viruses or bacteria that are taking advantage of the downmodulated immune system. Opportunistic infections, such as HCMV and *Pneumocystis carinii* infections in AIDS patients, are believed to occur as a consequence of the destruction of the immune system by HIV. The other way around, the HCMV chemokine-receptor homologue US28 has been suggested to serve as a cofactor for HIV-1 entry into cells that are already infected by HCMV (Pleskoff et al. 1997). Furthermore, HHV-6 infects B cells latently infected with EBV more efficiently than EBV-negative B cells (Ablashi et al. 1988; Flamand et al. 1993). HHV-6 infection of some EBV-containing B-cell lines can induce the EBV lytic replication cycle. HHV-6A also induces CD4 expression in CD3⁺ CD4⁻ CD8⁺ lymphocytes, which renders these cells more susceptible to HIV-1 infection (Lusso et al. 1991a). Another example is observed in the enhanced expression of human papillomavirus (HPV)

RNA encoding the viral oncoproteins E6 and E7, which has been demonstrated in HHV-6-infected, HPV-transformed cervical epithelial cells (Chen et al. 1994). Cooperation is also observed between viruses within a single species. For example, infection of peripheral blood lymphocytes from healthy adults with HHV-7 can result in reactivation of latent HHV-6, which can overgrow the input of HHV-7 (Frenkel and Wyatt 1992). In summary, viruses of different species can cooperate for mutual survival of both strains in the host.

Concluding remarks

Evolution has put an immense pressure on viruses to develop mechanisms to avoid viral elimination by the host's immune response. One of the most sophisticated viruses in this respect known today is HCMV. HCMV's ability to cause infections in myeloid lineage cells may have favored the development of a broad range of immune evasion strategies. While infection of differentiated macrophages results in a permissive infection and the production of new viral progeny, infection of monocytes is restricted to immediate early gene expression. The choice of infecting a cell type that traffics out to the tissues while the virus is silent is ideal for hiding from the immune system during dissemination of the virus. When T cells are activated – for example, during an allogeneic response or an inflammatory reaction – these cells produce IFN- γ and TNF- α , which are important factors for reactivation of latent HCMV (Söderberg-Nauclér et al 1997b, 2001). IFN- γ and TNF- α specifically induce differentiation of monocytes into macrophages, which are highly permissive to HCMV infection. HCMV is resistant to the antiviral activities of these cytokines. As

a consequence of reactivation and inhibition of the replication cycle, viral proteins produced will enter the MHC presentation pathway. At this point, the virus turns on its functions to avoid immune recognition (Fig. 2). To avoid detection of the early produced proteins, the viral protein pp65 specifically inhibits presentation of IE peptides. Since pp65 is present in the virus particle and is delivered into the cells at the time of viral fusion, the virus will immediately hide from immunological surveillance, until other immune evasion proteins are produced.

MHC class I molecules will be retained in the ER by gpUS3. Peptide transportation by TAP will be inhibited by gpUS6, and gpUS2 and gpUS11 will mediate translocation of MHC molecules back into the cytoplasm for degradation by the proteasome. After losing MHC class I expression on their cell surface, the virus must circumvent NK cell-mediated killing. The surface expression of HLA-E and HLA-G, induced by gpUL40 and CMV IL10 respectively, are upregulated for this purpose. It remains uncertain whether this evasion of NK cell-mediated killing is achieved by the expression of the MHC class I homologue UL18, since the lower susceptibility of HCMV-infected endothelial cells and macrophages to NK lysis is not dependent on downregulation of HLA class I molecules nor on the expression of the HCMV class I homologue UL18 (Odeberg et al. 2002). Furthermore, HCMV is able to inhibit an important pathway of NK-cell activation mediated by NKG2D through the expression of UL16 (Cosman et al. 2001).

At the same time, MHC class II expression is downregulated by the expression of US2, which causes the degradation of two essential proteins in the MHC class II antigen presentation pathway. IFN- γ -induced MHC class II expression is inhibited by interference of the JAK/Stat pathway. Downregulation of MHC class II inhibits Th cell activation and thereby indirectly the antibody production by plasma cells.

The virus increases Fc receptor production in infected cells to eliminate viral-specific antibodies. In addition, the virus can change its antigenic determinants to circumvent elimination of the virus by the humoral immune response.

Finally, HCMV produces the GCR homologues UL33, UL78, US27 and US28, which might function as eliminators of chemotactic factors, thus inhibiting further accumulation of inflammatory cells at the site of local viral infection.

All these strategies will be used by the virus to secure production of new viral progeny and spread to other hosts. Although it seems as if the virus is always one step ahead of its host, viral coexistence may have affected the evolution of our own immune system. For example, one can hypothesize that NK cells developed to take care of virally infected cells and tumor cells that have lost their MHC class I expression. Thus, the study of the mechanisms involved in the induction of immunosuppression, i.e. viral immune evasion strategies, will help us understand aspects of cellular and immunological function and will aid the improvement of immunotherapies preventing and treating viral infections.

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