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VIRUSES must be extremely successful predators as they depend on living cells for replication. Almost all living species represent prey for a viral invader. Viruses have coevolved with their hosts and therefore have limited pathogenicity in an immunocompetent natural host. In turn, probably as a result of the constant evolutionary pressure from viral invaders, higher vertebrates have developed a complex immune system. Only in the last decade have we caught a glimpse of what viruses do beyond invading cells for replication. For millions of years viruses have ‘studied’ cell biology and immunology the hard way, to acquire and defend an ecological niche. It is remarkable that, in the process, individual virus families have targeted many common immunological principles.

Viruses that belong to different families are subject to different constraints. Owing to the low fidelity of RNA polymerase, the genome size of RNA viruses is limited. Although this confers the advantage of being able to use mutation to escape immune control, there is little room in the genome to allow immune defences to be encoded by individual genes. The proteins encoded by RNA viruses are therefore multifunctional. This particular constraint is less rigid for DNA viruses as their genome size allows a larger number of genes to be devoted to host control. In the case of herpesviruses and poxviruses, these genes probably account for >50% of the total genome.

Viruses can exist in two forms: extracellular virion particles and intracellular genomes. Virions are more resistant to physical stress than genomes but are susceptible to humoral immune control. Virus genomes can be maintained in host cells by limited gene expression and can evade the host immune response. Nevertheless, to exist as a species, virus replication and transfer to a new host are essential. These processes are associated with the production of antigenic proteins that make the virus vulnerable to immune control mechanisms ‘warning’ the host of the presence of an invader. However, viruses have evolved strategies to evade such immune control mechanisms, and the list of these strategies forms the ‘Who’s who’ of today’s immunology.

During the millions of years they have coexisted with their hosts, viruses have learned how to manipulate host immune control mechanisms. Viral gene functions provide an overview of many relevant principles in cell biology and immunology. Our knowledge of viral gene functions must be integrated into virus–host interaction networks to understand viral pathogenesis, and could lead to new anti-viral strategies and the ability to exploit viral functions as tools in medicine.

There are two classes of viral immunoregulatory proteins: those encoded by genes with and those encoded by genes without sequence homology to cellular genes. Viral homologs of host genes involved in the immune system are mainly found in large DNA viruses (herpesviruses and poxviruses) and their existence suggests that viruses have ‘stolen’ genes from the host that were subsequently modified for the benefit of the virus. Viral genes without sequence similarity to cellular genes might represent a paradigm for co-evolution or could simply be examples of proteins for which the host homologs have not yet been identified. These proteins might possess specific motifs or particular folding properties required for interaction with the host cellular machineries.

In this review and the accompanying poster we provide an overview of the different mechanisms that viruses use to evade host immune responses. The basic concepts of virus immune evasion will be discussed, with some examples to illustrate particular points; however, space constraints have not allowed a comprehensive review of all immune-evasion strategies. The strategies are listed in the accompanying tables and are discussed in more detail in the references given throughout the text.

Inhibition of humoral responses

Antigenic variability was one of the first viral immune-evasion strategies to be identified. Because of the low fidelity of RNA polymerases, viral RNA genomes comprise a collection of RNA species (quasispecies) with random mutations. Therefore, in RNA viruses the generation and selection of variants with different antigenic properties that can evade recognition by neutralizing antibodies is common. Genetic
The complement system is a major non-specific host defense mechanism\textsuperscript{1–3}. Viruses encode homologs of complement regulatory proteins that are secreted and block complement activation and neutralization of virus particles (Table 1; Box 1). The cowpox virus (CPV) complement inhibitor, termed inflammation modulatory protein (IMP), blocks immunopathological tissue damage at the site of infection, presumably by inhibiting production of the macrophage chemotactic factors C3a and C5a (Ref. 3). Viruses protect the membranes of infected cells and the lipid envelopes of virus particles from complement lysis by encoding homologs of inhibitors of the membrane-attack complex. Viruses such as HIV, human cytomegalovirus (HCMV) and vaccinia virus (VV) utilize a clever strategy, ‘borrowing’ host cellular factors, including CD59, which normally protects cells from complement lysis, and incorporating them into the viral envelope.

Lastly, some viruses encode Fc receptors\textsuperscript{1} (Table 1). Antibodies bound to infected cells or virus particles might therefore be bound at the Fc region, thereby inhibiting Fc-dependent immune activation of complement and phagocytes. Fc receptors probably have additional functions \textit{in vivo}\textsuperscript{4}.

### Interference with interferons

Interferons (IFNs) were discovered because of their ability to protect cells from viral infection. The key role of both type I (α and β) and type II (γ) IFNs as one of the first anti-viral defense mechanisms is highlighted by the fact that anti-IFN strategies are present in most viruses (Table 2). Viruses block IFN-induced transcriptional responses and the janus kinase (JAK)/signal transducers and activators of transcription (STAT) signal transduction pathways, and also inhibit the activation of IFN effector pathways that induce an anti-viral state in the cell and limit virus replication. This is mainly achieved by inhibiting double-stranded (ds)-RNA-dependent protein kinase (PKR) activation, the

### Box 1. Abbreviations in Tables

2′,5′-OA, 2′,5′-oligoadenylate; 2′,5′OS, 2′,5′ OA synthetase; 3β-HSD, 3β-hydroxysteroid dehydrogenase; AHV, alcelaphine herpesvirus; ASFV, African swine fever virus; BHV, bovine herpesvirus; BP, binding protein; BPV, bovine papilloma virus; CaPV, capripox virus; CCI, chemokine inhibitor; CCPH, complement control protein homolog; CK, chemokine; CKBP, chemokine-binding protein; CP, complement control protein CPV, cowpox virus; Crm, cytokine response modifier; CSF, colony-stimulating factor; dsRNA, double stranded RNA; EBER, EBV-encoded small RNA; EBV, Epstein–Barr virus; EGF, epidermal growth factor; EHV, equine herpesvirus; eIF-2, eukaryotic translation initiation factor 2α; EMCV, encephalomyocarditis virus; ER, endoplasmic reticulum; ESPR, virus-encoded semaphorin protein receptor; EV, ectromelia (mouspox) virus; FLIP, FLICE inhibitory protein; GF growth factor; GM-CSF, granulocyte–macrophage CSF; gp, glycoprotein; HBV, hepatitis B virus; HCMV, human cytomegalovirus; HCV, hepatitis C virus; HHV, human herpesvirus; HHV-8, human herpesvirus 8 or Kaposi’s sarcoma-associated herpesvirus; HPIV, human parainfluenza virus; HPV, human papilloma virus; HTLV, human T cell leukemia virus; HIV, herpes simplex virus; HVS, herpesvirus saimiri; IFN, interferon; Ig, immunoglobulin; IL, interleukin; IRF, interferon regulatory factor; JAK, janus kinase; LMP, latent membrane protein; LT, lymphotoxin; MCH, murine cytomegalovirus chemokine; MCMV, murine cytomegalovirus; MCV, molluscum contagiosum virus; MeV, measles virus; MGF, myxoma growth factor; MHC, major histocompatibility complex; MHV-68, murine gammaherpesvirus 68; MIP, macrophage inflammatory protein; MPV, murine polyoma virus; MV, myxoma virus; NF-κB, nuclear factor κB; NFAT, nuclear factor activated T cell; NK, natural killer; ORF, open reading frame; OV, Orf virus; PKR, dsRNA-dependent protein kinase; R, receptor; RANTES, regulated upon activation normal T cell expressed and secreted; RCMV, rat cytomegalovirus; RID, receptor internalization and degradation complex; SEMA, semaphorin; Serpin, serine protease inhibitor; SeV, Sendai virus; SFV, Shope fibroma virus; SPI, serine protein inhibitor; SPV, swinepox virus; STAT, signal transducers and activators of transcription; SV, simian virus; TAP, transporters associated with antigen processing; TAR, transacting response element; TNF, tumor necrosis factor; TPV, Tanapox virus; V, viral; VaV, variola (smallpox) virus; VEGF, vascular endothelial growth factor; VV, vaccinia virus.

### Table 1. Viral inhibition of humoral immunity (complement and antibodies)

| Function/Activity                        | Gene/Protein                  | Virus              | Mechanism                                                                 | Refs |
|-----------------------------------------|-------------------------------|--------------------|----------------------------------------------------------------------------|------|
| Inhibition of soluble complement factors | vCP/C21L, IMP, SPICE, gc, ORF4, CCPH, gp120-gp41 | VV, CPV, VaV, HSV-1, HSV-2 HVS, HIV-8, MHV-68 | Viral homologs of C4BP, CR1, CD46 or CD55 | 1–3  |
| Blockade of formation of membrane-attack complex | ORF15 Host proteins CD59, CD55 or CD46 | HVS W, HIV, HTLV, HCMV | Viral CD59 homolog Host proteins incorporated into virion envelope | 1,3,34 |
| Viral IgG Fc receptors                   | gE-gl, gE, Fcr1, S peplomer   | HSV-1, HSV-2, MCMV, coronavirus | Binding of IgG and inhibition of Fc-dependent immune activation | 1,4,34 |
phosphorylation of eukaryotic translation initiation factor 2α (eIF-2α) and the RNase L system, which might degrade viral RNA and arrest translation in the host cell.

Poxviruses encode soluble versions of receptors for IFN-α and -β (IFN-α/βR) and IFN-γ (IFN-γR), which also block the immune functions of IFNs. The VV-secreted IFN-α/βR is also localized at the cell surface to protect cells from IFN (Table 3). Additionally, several viruses inhibit the synthesis or activity of factors required for its production, such as interleukin (IL)-1β and IL-12 (Table 4): CPV cytokine response modifier (Crm A) inhibits caspase-1, which processes the mature forms of IL-1β and IL-18 (Refs 2,6); various poxviruses encode soluble IL-18-binding proteins (IL-18BPs)6–10; measles virus (MeV) binds CD46 in macrophages and inhibits IL-12 production1; and herpesviruses and poxviruses express IL-10 homologs that diminish the Th1 response by downregulating the production of IL-12 (Refs 1,11,12).

### Inhibition and modulation of cytokines and chemokines

Cytokines play a key role in the initiation and regulation of the innate and adaptive immune responses, and viruses have learned how to block cytokine production, activity and signal transduction (Tables 3 and 4). African swine fever virus (ASFV) replicates in macrophages and encodes an IκB homolog that blocks cytokine expression mediated by nuclear factor (NF)-κB and the nuclear factor activated T cell (NFAT) transcription factors13. Many viruses block signal transduction by ligands of the tumor necrosis factor (TNF) family, whereas others deliberately induce some cytokine pathways; for example, the Epstein–Barr virus (EBV) latent membrane protein 1 (LMP1) recruits components of the TNF receptor (TNFR) and CD40 transduction machinery to mimic cytokine responses that could be beneficial for the virus, such as cell proliferation14 (Table 4).

One of the most interesting mechanisms identified in recent years is the mimicry of cytokines (virokines) and cytokine receptors (viroceptors) by large DNA viruses (herpesviruses and poxviruses)1,2,11,15,16 (Table 3). The functions of these molecules in the animal host are diverse. Soluble viral cytokine receptors might neutralize cytokine activity and cytokine homologs might redirect the immune response for the benefit of the virus. Alternatively, viruses that infect immune cells might use these homologs to induce signaling pathways in the infected cell that promote virus replication.

The herpesvirus cytokine homologs vIL-6 and vIL-17 might have immunomodulatory activity but might also increase proliferation of cells that are targets for viral replication11,11. Viral semaphorin homologs have uncovered a role for the semaphorins family – previously known as chemoattractants or chemorepellents involved in axonal guidance during development – in the immune system, and have identified a semaphorin receptor in macrophages that mediates cytokine production16.

Secreted cytokine receptors or binding proteins are mainly encoded by poxviruses6,11,15,18. These proteins were originally identified as

### Table 2. Viral interference with IFN

| Function/Activity | Gene/Protein | Virus | Mechanism | Refs |
|-------------------|-------------|-------|-----------|------|
| Inhibition of JAK/STAT pathway | E1A | Adenovirus | Decreases the levels of STAT1 and p48 | 1,7,42 |
| | EBNA-2 | EBV | Downregulates IFN-induced transcription | 1,7 |
| | Unknown | HCMV | Reduces levels of JAK1 and p48; involvement of proteasome | 7 |
| | Unknown | HPV-2 | Targets STAT2 for degradation | 7 |
| | Unknown | HPV-3, SeV | Blocks STAT1 phosphorylation | 7 |
| | E7 | HPV-16 | Binds to p48 | 7 |
| | T antigen | MPV | Binds to and inactivates JAK1 | 7 |
| | V protein | SV5 | Targets STAT1 for proteasome-mediated degradation | 7 |
| IFN-induced transcription | IRF homolog | HHV-8 | Represses transcriptional responses to IFNs | 1,7 |
| | Capsid protein | HBV | Inhibits MxA gene expression | 7 |
| Inhibition of PKR activity | α3, NSP3, E3L, OV20.0L, NS1 | Reovirus, rotavirus, influenza virus, VV | Bind dsRNA and prevent PKR activation | 2,5–7 |
| | VAI RNA, EBER RNA, TAR RNA | Adenovirus, EBV, HIV | RNA that binds to, but fails to activate, PKR | 5,7,42 |
| | PK2, N55A and E2, US11, Tat | Baculovirus, HCV, HSB, HIV | Bind to and inhibit PKR | 5,7 |
| | Unknown | Poliovirus | Induced degradation of PKR | 5,7 |
| | Unknown | Influenza virus | Induction of p58IPK, a cellular inhibitor of PKR | 5,7 |
| Inhibition of eIF-2α phosphorylation and translational arrest | K3L | VV | eIF-2α homolog, prevents eIF-2α phosphorylation, also inhibits PKR | 2,5–7 |
| | ICP34.5 | HSV | Redirects protein phosphatase 1 to dephosphorylate and reactivate eIF-2α | 7 |
| Inhibition of 2’5′ OS/RNase L system | α3, NSP3, E3L, OV20.0L, NS1 | Reovirus, rotavirus, VV, influenza virus | Bind dsRNA and prevent activation of 2’5′OS/RNase L | 2,6,7 |
| | Unknown | EMCV, HIV | Induce RNase L inhibitor, which antagonizes 2’5′OA binding to RNase L | 7 |
| | Unknown | HSV | Synthesis of 2’5′ OA antagonists | 7 |
| Function/Activity | Gene/Protein | Virus | Mechanism | Refs |
|------------------|--------------|-------|-----------|------|
| vTNFR | M-T2 | MV, SFV | Secreted, binds rabbit TNF | 2,11,15,18 |
| CrmB | CPV, VaV | Secreted, binds TNF and LT-α | 2,11,15,18 |
| CrmC | CPV, VV | Secreted, binds TNF | 2,18 |
| CrmD | CPV, EV | Secreted, binds TNF and LT-α | 19 |
| CrmE | CPV | Secreted, binds TNF | 2|
| Unknown | VV | TNFR at the surface of VV-infected cells | 20 |
| UL144 | HCVM | TNFR homolog, unknown function | 34 |
| vIL-1βR | B15R | VV | Secreted, binds IL-1β, blocks febrile response | 2,11,18 |
| vIFN-γR | M-T7, B8R | MV, VV, CPV | Secreted, binds IFN-γ from various species | 2,6,11,15 |
| vIFN-α/βR | B18R | VV | Secreted and cell surface, binds type I IFN from various species | 2,6,11 |
| vCSF-1R | BARF-1 | EBV | Secreted, binds CSF-1 | 1 |
| vGM-CSF/IL-2BP | GIF | OV | Secreted, binds GM-CSF and IL-2 | 21 |
| vIL-18BP | MC54 | MCV | Secreted, binds IL-18, inhibits IL-18-induced IFN-γ production | 8,9 |
| | D7L | EV, VV, CPV, VaV | Secreted, binds IL-18, inhibits IL-18-induced IFN-γ production | 9,10 |
| vIFN-γ/IL-2/IL-5BP | Unknown | TPV | 35 kDa, secreted, binds IFN-γ, IL-2 and IL-5 | 2,18 |
| vCKBP | vCKBP-I, M-T7 | MV | Secreted, binds C, CC and CXC CKs through heparin-binding site | 2,15,16,18 |
| | vCKBP-II, B29R | MV, VV, VaV | Secreted, binds CC CKs | 2,15,16,18 |
| | G3R, C5R, H5R | CPV, MV, SFV | Secreted, binds CC CKs | 2,15,16,18 |
| & | vCKBP-III, M3 | M-T1, S-T1 | Secreted, binds CC CKs | 2,15,16,18 |
| vCKR | ORF74 | HHV-8, HV5, MCV, EH2 | Secreted, binds CC, CXC, C and CXC3 CKs | 29 |
| | US28, E1 | HCVM, EH2 | HCV US28 binds CC CKs, mediates cell migration and decreases local concentration of RANTES; EH2 E1 binds eotaxin | 16,22,26,43 |
| | US27, E6 | HCVM, EH2 | Unknown | 16,22 |
| | U12, UL33, M33, R33 | HHV, MCV, HCVM, RCMV | Secreted, binds cell migration and decreases local concentration of RANTES; EH2 E1 binds eotaxin | 16,22 |
| | U51, UL78, M78 | HHV, MCV, MCMV | Secreted, binds CC and CXC CKs and induces downregulation of RANTES transcription | 16,22,25 |
| | K2R | SPV | IL-8 CKR homolog | 16,18 |
| | Q2/3L | CaPV | CC CKR homolog | 16,18 |
| vCK | vMIP-I | HHV-8 | CCR8 agonist, Th2 chemoattractant, angiogenic activity | 16,22 |
| | vMIP-II | HHV-8 | C, CC, CXC and CXC3 CK antagonist | 16,22,44 |
| | vMIP-III | HHV-8 | Unknown | 16,22 |
| | U83 | HHV-6 | CC CK agonist | 16,22 |
| | MCK-1/2, m131 | MCMV | CC CK agonist, chemoattraction of monocytes, promotes monocyte-associated viremia in vivo | 16,22,23 |
| | vCX/1/UL146 | HCMV | CXC CK agonist, chemoattraction of neutrophils | 16 |
| | vCX/2/UL147 | HCMV | Unknown | 16 |
| | MGC-1/MC148 | MCV | Specific CCR8 antagonist, interference with monocyte function | 16,44 |
| | Tat | HIV | Partial CK similarity, chemoattractant for monocytes | 24 |
| vGF | C11R, MGF | VV, HV5 | EGF an TGF-α homolog, stimulates cell growth, virulence factor | 11,15 |
| vVEGF | A2R | OV | Angiogenic factor | 11,45 |
| vIL-10 | BCRF-1, IL-10 | EBV, HV5 | IL-10 activity, downregulates Th1 response | 1,11 |
| vIL-17 | ORF13 | HV5 | T cell mitogen | 1,11 |
| vIL-α | K2 | HHV-8 | Angiogenic factor, B-cell growth factor | 1,5 |
| vSEMA | A39R | VV, EV | Semaphorin homolog, binds semaphorin receptor vESPR | 17 |
| | AHV-SEMA | AHV | Semaphorin homolog | 17 |

* M. Saraiva and A. Alcami, unpublished.
Table 4. Viral inhibitors and modulators of cytokine activity

| Function/Activity                        | Gene/Protein | Virus          | Mechanism                                                                 | Refs |
|----------------------------------------|--------------|----------------|---------------------------------------------------------------------------|------|
| Inhibition of TNF signaling            | E3 14.7K, E3 10.4/15.4K, E1B 19K | Adenovirus      | Prevent TNF cytolysis and block phospholipase A2 activation               | 42   |
| Mimicry of TNFR/CD40 signaling         | LMP-1        | EBV            | Recruits death-domain-containing proteins and induces signals of the TNFR/CD40 pathway | 14   |
| lxB homolog                            | A238L        | ASFV           | Inhibition of NFxB/NFAT signaling                                       | 13   |
| Inhibition of maturation of cytokines  | CrmA, SPI-2, B13R, SERP-2     | CPV, VV, M     | Inhibition of IL-1β converting enzyme (ICE, caspase-1), inhibition of IL-1β, and possibly IL-18, cleavage | 2,15,18 |
| Inhibition of IL-12 production         | Hemagglutinin | MeV            | Binds to CD46 and blocks induction of IL-12 by macrophages              | 1    |

Inhibitors of apoptosis

Apoptosis or programmed cell death can be triggered by a variety of inducers, including ligands of the TNF family, irradiation, cell-cycle inhibitors or infectious agents such as viruses. Apoptosis can be considered an innate cellular response to limit viral propagation, and viruses express proteins that block the death response (Table 5); however, apoptosis might also facilitate virus dissemination, and viral pro-apoptotic mechanisms have been described. In addition, cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells kill virus-infected cells by inducing apoptosis via secretion of cytokines such as TNF, the release of perforin and granymes, or the activation of Fas in the target cell.

The cellular proteins implicated in the control of apoptosis are targeted by viral anti-apoptotic mechanisms. Viruses inhibit activation of caspases, encode homologs of the anti-apoptotic protein Bel2, block apoptotic signals triggered by activation of TNF receptor family members by encoding death-effector-domain-containing proteins, and inactivate IFN-induced PKR and the tumor suppressor p53, both of which promote apoptosis. An alternative mechanism is provided by the glutathione peroxidase of molluscum contagiosum virus (MCV), which provides protection from peroxide- or UV-induced apoptosis, and perhaps from peroxides induced by TNF, macrophages or neutrophils.

Evading CTLs, NKs, and modulating MHC function

How to achieve persistence in the face of a vigorous host immune response is a problem that must be solved by viruses that establish lifelong infections. Cellular proteins are degraded by the proteasome, the complex major intracellular protease, and the resulting peptides are translocated by transporting associated with antigen processing (TAP) molecules into the endoplasmic reticulum (ER), where they contribute to the assembly of MHC class I molecules. MHC class I molecules indicate the composition of cellular proteins to cells of the immune system. The presentation of foreign peptides activates and attracts cytolytic CD8+ T cells. Interference with antigen processing e.g. Epstein–Barr nuclear antigen A1 (EBNA1)] or TAP function e.g. herpes simplex virus (HSV) infected cell protein 47 (ICP47) and HCMV US6 and pp65] prevents peptide generation and
transport either specifically or generally (Table 6). Viruses use various mechanisms to modify the maturation, assembly and export of MHC class I molecules. To date, no cellular homologs have been found for the proteins and functions that target peptide processing, transport and MHC maturation. With few exceptions, the viral proteins bind their target molecule directly. There is only limited functional homology and no sequence homology among the different viral effectors. Nevertheless, the general outcome of these functions is the same: downregulation of MHC class I molecules or of some MHC class I alleles. The study of MHC class I regulation has revealed additional genes in herpesviruses of different species, which might affect many cell types or only those tissues relevant for virus maintenance.

Although the downregulation of MHC class I expression prevents CD8+ T-cell recognition, cells that downregulate these molecules become targets for NK cells. NK cells, the first line of cellular defense against viruses, have receptors for certain MHC molecules. Some of these receptors silence the cytolytic machinery of NK cells and act as killer cell inhibitory receptors (KIR). Other receptors, designated leukocyte immunoglobulin-like receptors (LIR), are expressed mainly on monocytes and B cells. Engagement of an NK receptor can alternatively result in NK activation as not all receptors have immunoreceptor tyrosine-based inhibitory motifs (ITIMs) in their intracellular domains. The HCMV protein UL18 and the MCMV m144 protein, which are homologous to MHC class I, could be associated with NK killing, and UL18 is instrumental in the identification of LIR-1. In addition, the HCMV UL40 protein provides a peptide selectively required for the maturation of the HLA-E molecule, an NK target. However, clinical isolates of HCMV confer a much stronger NK resistance than the laboratory strains sequenced and tested so far, and this resistance is unrelated to MHC class I expression and LIR-1. Clinical isolates carry additional genes, and in vitro propagation has probably led to a loss of certain NK-specific gene functions.

Effects on MHC class II expression fall into two classes, namely effects on transcription and post-translational effects. Adenovirus, MCMV and HCMV affect MHC class II transcription but the target in the signal cascade, although known to be different for these viruses, has not been defined and the viral gene or genes responsible are unknown. At the post-translational level, the HCMV US2 protein, which affects MHC class I, apparently also translocates the DRα and the DMα chain into the cytosol for degradation by the proteasome. Another target involved in interference with MHC class II function is the shuttling between endosomal peptide loading and surface expression. Human papilloma virus (HPV) and HIV Nef affect vesicle traffic as well as the function of the endocytic machinery. Accordingly, in addition to MHC class II, other proteins that use this pathway, for example the CD4 molecule, are also affected.
Future perspectives
An understanding of the functions of the viral immunoregulatory genes isolated to date is now emerging. However, we do not yet know whether the list is complete (Table 7). Additionally, it is unclear when and why a virus deploys one specific function rather than another. Many questions therefore remain unanswered, including which genes are needed during primary infection to ‘conquer the territory’; which genes are required to support active replication; and which genes are required to ensure transmission to a new host in the face of a vigorous host immune response? Moreover, why is there such complexity and functional redundancy? Is there a hierarchy in terms of general importance or do some functions operate only in certain tissues? Is complexity and redundancy a viral strategy that enables viruses to infect individuals resistant to some functions? Are the functions of an individual viral gene modulated by its genetic context, and is there any evidence for cooperativity? To date, we only have limited information because the construction of virus mutants and the in vivo testing of the predicted gene function is still in its infancy and, additionally, owing to the species specificity of many viruses, this information can only be gathered from some animal models.

The identification of novel immune-evasion strategies and the analysis of their functions in the context of a viral infection should lead to a better understanding of the immune system and the interaction of viruses with their hosts. This will help us to treat virus-induced pathology, to design safer and more immunogenic virus vectors as vaccines or gene delivery systems, and to identify new strategies for immune modulation.

Table 6. Viral interference with MHC functions

| Function/Activity       | Gene/Protein | Virus    | Mechanism                                                                 | Refs |
|------------------------|--------------|----------|---------------------------------------------------------------------------|------|
| Effect on MHC class I  | E3/19K       | Adenovirus| Binding and retention of class I in ER                                     | 1,11,32,33,42 |
| Effect on MHC class I  | US3          | HCMV     | Binding and retention of class I in ER                                     | 1,11,32–34 |
| Effect on MHC class I  | US2, US11    | HCMV     | Relocation of heavy chain into ER for degradation                         | 1,11,32–34,49 |
| Effect on MHC class I  | m4           | MCMV     | Binds class I molecules                                                   | 1,11,32–34 |
| Effect on MHC class I  | m6           | MCMV     | Binding of class I molecules and transport to lysosomes for degradation   | 1,11,32–34 |
| Effect on MHC class I  | m152         | MCMV     | Retains class I in ER-Golgi intermediate compartment                     | 1,11,32–35 |
| Effect on MHC class II | E1A          | Adenovirus| Interferes with class II upregulation (IFN-γ signal transduction cascade) | 1,11,32,33 |
| Effect on MHC class II | US11         | HCMV     | Interference with class II function                                       | 1,11,32,33 |
| Effect on MHC class II | US2          | HCMV     | Interference with class II upregulation (IFN-γ signal transduction cascade) | 1,11,32–34 |
| Effect on MHC class II | ORF14        | HSV      | Class II binding                                                          | 1,11,32,33 |
| Effect on MHC class II | E5, E6       | HPV, BPV | Interference with class II processing, E5 acidification of endosomes, E6 interaction with AP complex | 1,11,32,33 |
| Effect on NK cells     | Nef          | HIV      | Interference with class II processing                                      | 1,11,32,33 |
| Effect on NK cells     | ICP-47       | HSV      | Prevents peptide binding to TAP in cytosol                                | 1,11,32,33 |
| Effect on NK cells     | US6          | HCMV     | Prevents peptide transport through TAP pore                               | 1,11,32–34 |
| Effect on antigen      | EBNA-1       | EBV      | A Gly–Ala repeat motif prevents proteosomal degradation                    | 1,11,32,33 |
| Processing             | pp65         | HCMV     | Modulates processing of another HCMV protein                              | 1,11,32–34 |
| Effect on NK cells     | UL18, r144   | HCMV     | Class I homolog, inhibits NK cell lysis                                   | 1,11,32–34 |
| Effect on NK cells     | MC80         | MCMV     | Class I homolog, function unknown                                         | 1,11,32,33 |
| Effect on NK cells     | UL40         | HCMV     | UL40 peptide causes HLA-E upregulation                                    | 39,40 |

Table 7. Other viral immune evasion mechanisms

| Function/Activity             | Gene/Protein | Virus | Mechanism                                                                 | Ref. |
|-------------------------------|--------------|-------|---------------------------------------------------------------------------|------|
| Inhibition of inflammation   | SERP-1       | MV    | Secreted serpin, potent anti-inflammatory properties                      | 15   |
| vCD2                          | 3β-HSD       | VV    | Synthesis of steroids with immunosuppressive properties                  | 2    |
|                               | EP402R, 8DR  | ASFV  | Adhesion molecules responsible for erythrocyte hemadsorption; immunosuppressive; may modulate T-cell activation | 50   |
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