VIRAL SUBVERSION OF THE IMMUNE SYSTEM

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Abstract: The continuous interactions between host and viruses during their co-evolution have shaped not only the immune system but also the countermeasures used by viruses. Studies in the last decade have described the diverse arrays of pathways and molecular targets that are used by viruses to elude immune detection or destruction, or both. These include targeting of pathways for major histocompatibility complex class I and class II antigen presentation, natural killer cell recognition, apoptosis, cytokine signalling, and complement activation. This paper provides an overview of the viral immune-evasion mechanisms described to date. It highlights the contribution of this field to our understanding of the immune system, and the importance of understanding this aspect of the biology of viral infection to develop efficacious and safe vaccines.

1. INTRODUCTION

The continuous interactions between hosts and viruses during their co-evolution have shaped not only the immune system but also the countermeasures used by viruses. The evasion strategies that viruses have devised are highly diverse, ranging from the passive to the active. Passive evasion strategies comprise hiding inside the infected host cell in a dormant form or creating a broad antigenetic diversity among the progeny virions during each replication cycle (as exploited, for example, by retroviruses), thus evading or staying one step ahead of the immune response. Active mechanisms include interferences with pathways for major histocompatibility complex (MHC)
class I and class II antigen presentation, natural killer (NK) cell recognition, cytokine signalling, apoptosis of infected cells, and complement activation. In this review, the authors provide an overview of the different active mechanisms that viruses use to evade host immune responses. Due to space constraints, those mechanisms will be presented concisely in pairs of associated figures and tables. The basic concepts of the components of the immune system targeted by the viruses are described in the figures, while viral strategies are listed in the corresponding tables. To save space, viruses are cited using the abbreviations of the International Committee for Taxonomy of Viruses.

2. VIRAL INTERFERENCE WITH MHC CLASS I PATHWAY

CD8-positive cells play an important role in immunity against viruses. Just how important these cells are is demonstrated by the evolution of viral strategies for blocking the genesis or the display of viral peptide-MHC class I complexes on the surface of viral infected cells. To enhance the understanding of this field, the manner in which viral proteins are processed for recognition by virus-specific CD8+ T cells is briefly described (Figure 1). In the infected cells, peptides are generated from by-products of proteasomal degradation. Most of the substrates consist of defective ribosomal products (DRiPs). Peptides are then transported into the endoplasmic reticulum (ER) by the TAP protein. Here, MHC class I molecules are folded through the actions of general purpose molecular chaperones working with a dedicated chaperone (Tapasin) that tethers MHC class 1 to TAP. After peptide binding, MHC class I molecules dissociate from TAP, leave the ER and migrate to the plasma membrane through the Golgi complex. As viral peptide-MHC class I complexes accumulate on the cell surface, they have a greater chance of triggering activation by CD8+ T cells with a cognate receptor. Viruses have been shown to interfere with virtually every step of T cell antigen processing and presentation (Figure 1 and Table 1). The viral proteins involved in such mechanisms have been called VIPRs (pronounced “viper”) for viral proteins interfering with antigen presentation. They are listed in Table 1 together with their mechanism of action. For an excellent review on this subject, see that of Yewdell and Hill (2002).
Figure 1. Viral interference with MHC class I pathway.

The classical MHC class I pathway is depicted with reference to viral interfering proteins listed in Table 1. Peptides are derived from DRiPs through the action of proteasomes and transported into the ER by the TAP protein. Nascent MHC class I molecules bind to TAP via tapasin. Binding of peptide to MHC class I molecules releases them from the ER. Peptide-MHC class I molecules then migrate to the cell surface. VIPRs have been shown to interfere with virtually every step of T cell antigen processing and presentation, namely (1) prevention of peptide degradation; (2) inhibition of peptide translocation in the ER, the inhibitory viral protein being either on the cytosolic side (2a) or in the lumen of the ER (2b); (3) retention of MHC class I molecules in the ER (3a) or in the transGolgi network (TGN) (3c), or by targeting of ER MHC class I molecules for degradation by the proteasomes (3b); (4) reduction of peptide-MHC class I complexes exposed on the cell surface by inhibition of their migration to the cell surface, by increasing their endocytosis from the cell surface and by increasing their degradation into lysosomes; and (5) inhibition of T CD8+ cell recognition of cell surface peptide-MHC class I complexes. The VIPRs acting at those steps are listed in Table 1.
### Table 1. Viral interference with the MHC class I pathway.

| Site | Virus | Viral gene or protein | Mechanism of action | Source |
|------|-------|----------------------|---------------------|--------|
| 1    | HHV-4 | EBNA-1               | Contains a sequence that renders it resistant to proteasome degradation and self inhibition of synthesis | [1; 2] |
| 1    | HHV-5 | UL83                 | Inhibits generation of antigenic peptides from a 72 kDa transcription factor by phosphorylation of the latter | [3] |
| 2a   | HHV-1 | ICP47                | Prevents peptide translocation by interacting with both TAP 1 and TAP 2 on the cytosolic side of the ER | [4; 5] |
| 2a   | BoHV-1| ICP47                | Prevents peptide translocation by interacting with both TAP 1 and TAP 2 on the cytosolic side of the ER | [6] |
| 2b   | HHV-5 | US6                  | Binds to TAP in the ER lumen and prevents peptide transport | [7; 8; 9] |
| 3a   | Adeno-virus | E19 | Retains MHC-I in the ER by binding to the α1 and α2 regions (could also inhibit peptide loading of the MHC-I) | [10; 11; 12; 13] |
| 3a   | HHV-5 | US3                  | Retains MHC-I in the ER | [14; 15] |
| 3a   | MuHV-1| m4                   | Forms extensive complexes with MHC-I in the ER | [16] |
| 3b   | HHV-5 | US2, US3             | Targets class 1 heavy chains for degradation by the proteasome | [17] |
| 3b   | MuHV-4| K3                   | Targets class 1 heavy chains for degradation by the proteasome and subverts TAP/Tapasin associated class I | [18; 19] |
| 3b   | HIV-1 | Vpu                  | Destabilizes newly synthesized class I molecules and targets for degradation | [20] |
| 3b   | HTLV-1| p12(I)               | Targets class 1 heavy chains for degradation by the proteasome | [21] |
| 3c   | MuHV-1| m152                 | Retains MHC-I within the ER-transGolgi intermediate compartment | [22] |
| 4    | HIV, SIV | nef | Prevents the MHC-I from reaching the cell surface (specific targeting of HLA A and B locus) | [23; 24; 25] |
| 4    | EHV-1 | ?                    | Accelerates endocytosis of class 1 complexes | [26] |
| 4    | HHV-8 | K3, K5               | Enhanced endocytosis of MHC-I from the surface | [27] |
| 5    | MuHV1 | m4                   | Targets the MHC-I to lysosomes | [28] |

**NOTES:** (1) Site of action. Numbers refer to paths identified in Figure 1. (2) International Committee for Taxonomy of Viruses (ICTV) abbreviations.

**SOURCES:** [1] Levitskaya et al., 1995. [2] Yin, Mauory and Fahraeus, 2003. [3] Gilbert et al., 1993. [4] Galocha et al., 1997. [5] Ahn et al., 1996. [6] Hinkle, Hill and Srikumaran, 1998. [7] Hengel et al., 1996, 1997. [8] Ahn et al., 1997. [9] Lehner et al., 1997. [10] Cox, Bennink and Yewdell, 1991. [11] Burgert and Kvist, 1987. [12] Jeffries and Burgert, 1990. [13] Bennett et al., 1999. [14] Ahn et al., 1996. [15] Jones, et al., 1996. [16] Kavanagh, Koszinowski and Hill, 2001. [17] Wiertz et al., 1996. [18] Boname and Stevenson, 2001. [19] Lybarger et al., 2003. [20] Kerkau et al., 1997. [21] Johnson et al., 2001. [22] Ziegler et al., 1997. [23] Reusch et al., 1999. [24] Le Gall et al., 1998. [25] Cohen et al., 1999. [26] Rappocciolo, Birch and Ellis, 2003. [27] Hewitt et al., 2002. [28] Kleijnen et al., 1997.
Viral mechanisms interfering with NK cell functions fall into five categories, namely (1) expression of virally encoded MHC class I homologues that serve as NK cell decoys and ligate inhibitory receptors to block NK cytotoxicity; (2) selective modulation of MHC class I allele expression. Some viruses are able to down-regulate MHC class I molecules that are efficient for presentation of viral peptides to CD8+ cytotoxic T cells (such as HLA-A and HLA-B) without affecting or even increasing the expression of HLA-C and HLA-E, the dominant ligands for NK cell inhibitory receptors; (3) through the various mechanisms listed in Table 2, some viruses are capable of inhibiting the function of NK activatory receptor; (4) other viruses interfere with the cytokine pathways relevant to NK cell activation by producing virally encoded cytokine-binding proteins or cytokine antagonist; and (5) viruses can also directly inhibit NK cells by infecting them or by using viral envelope proteins to ligate NK cell inhibitory receptor.
3. VIRAL EVASION OF NATURAL KILLER CELLS

NK cells are lymphocytes that, in contrast to B and T cells, do not undergo genetic recombination events to increase their affinity for particular ligands, and are therefore considered as part of the innate immune system. They are capable of mediating cytotoxic activity and producing cytokines after ligation of a variety of germline-encoded receptors. Like CD8+ T cells, NK cells mediate direct lysis of target cells by releasing cytotoxic granules containing perforin and granzymes, or by binding to apoptosis-inducing receptors on the target cells. Several receptors that can activate NK cells have been identified, among which some recognize viral proteins (Orange et al., 2002). Due to the possible consequences of NK cell activation, normal host cells must inhibit NK activity. Various inhibitory receptors are consistently expressed by a subset of NK cells. These receptors bind to host MHC class I molecules and transmit inhibitory signals to the NK cells.

As noted above, many viruses have acquired effective means of avoiding T cell antigen presentation, thus avoiding T cell adaptive immune response. However, by eluding T cells, the viruses might have increased their susceptibility to NK cell-mediated defences. Consequently, in addition to the inhibition of T cell antigen presentation, some viruses have also acquired mechanisms to evade the action of NK cells. These mechanisms fall into five categories, presented in Figure 2; the viruses known to have acquired such mechanisms are listed Table 2. For an excellent review of the viral evasion of NK cells, see Orange et al. (2002).

Table 2. Viral evasion of natural killer cells.

| Site | Virus | Viral gene | Mechanism of action | Source |
|------|-------|------------|---------------------|--------|
| 1    | HHV-5 | UL18       | Homologue of MHC class I, binds to ILT-2 | [1; 2; 3; 4] |
| 1    | MuHV-1 | m144       | Homologue of MHC class I | [5; 6; 7] |
| 1    | MuHV-1 | m157       | Homologue of MHC class I, binds to Ly49-1 | [8; 9; 10] |
| 1    | MuHV-2 | r144       | Homologue of MHC class I | [11] |
| 1    | MOCV  | MC80R      | Homologue of MHC class I | [12] |
| 2    | HHV-5 | US2, US11  | Cytosolic degradation of MHC class I, with exception of HLA-C and HLA-E | [13; 14; 15; 16] |
| 2    | HHV-5 | US2, US3, US6, US11 | Degradation or intracellular retention of MHC class I but not IL-18 | [17] |
| 2    | HHV-5 | UL40       | Enhances surface expression of HLA-E | [18; 19; 20] |
| 2    | MuHV-1 | m04        | Forms complexes with MHC class I molecules intracellularly and on the cell surface | [21] |
| 2    | HIV   | Nef        | Induces the endocytosis of MHC class I with exception of HLA-C and HLA-E | [22; 23] |
## Viral subversion of the immune system

| Site (1) | Virus (2) | Viral gene | Mechanism of action | Source |
|---------|-----------|------------|---------------------|--------|
| 2       | SIV       | Nef        | Induces the endocytosis of MHC class I with exception of HLA-C and/or HLA-E | [22; 24] |
| 2       | HHV-8     | K5         | Induces the endocytosis of HLA-A and HLA-B | [19; 25] |
| 3       | HHV-5     | ?          | Decreases surface expression of the CD2 ligand LFA-3 | [26] |
| 3       | HHV-5     | UL16       | Blocks the interaction of NKG2D-DAP10 and ULBP | [27; 28; 29] |
| 3       | MuHV-1    | m152       | Decreases surface expression of H60 (NKG2D ligand) | [30] |
| 3       | HHV-8     | K5         | Mediates ubiquitination and decreases surface expression of ICAM-1 and B7-2 | [25; 31; 32] |
| 3       | HIV, HTLV | ?          | Mediates sialylation of cell surface receptors in infected cells | [33] |
| 3       | HIV       | Tat        | Inhibits LFA-1 mediated Ca^{2+} influx through binding of L-type Ca^{2+} channel | [34; 35] |
| 4       | MuHV-1    | m131/129   | Putative chemokine homologue | [36; 37] |
| 4       | HHV-8     | vMIP-1, vMIP-2 | Chemokine antagonists | [38; 39] |
| 4       | HHV-5     | UL111a     | Viral IL-10 homologue | [40] |
| 4       | HHV-4     | BCRF1      | Viral IL-10 homologue | [41] |
| 4       | ECTV      | p13        | IL-18 binding protein | [42] |
| 4       | MOCV      | MC54L      | IL-18 binding protein | [43] |
| 4       | HPV       | E6, E7     | IL-18 binding protein and antagonistic binding to IL-18 Rα | [44; 45] |
| 4       | MuHV-4    | hvCKBP     | Chemokine binding protein | [46] |
| 4       | VACV      | vCKBP      | Chemokine binding protein | [47] |
| 5       | HIV       | /          | Infects NK cells | [48] |
| 5       | HHV-1     | /          | Infects NK cells | [49] |
| 5       | HCV       | E2         | Binds to CD81 | [50; 51] |

**Notes:** (1) Site of action. Numbers refer to paths identified in Figure 2. (2) International Committee for Taxonomy of Viruses (ICTV) abbreviations.

**Sources:** [1] Beck and Barrell, 1988. [2] Reyburn et al., 1997. [3] Leong et al., 1998. [4] Cosman et al., 1997. [5] Farrell et al., 1997. [6] Kubota et al., 1999. [7] Cretney et al., 1999. [8] Smith, Idris and Yokoyama, 2001. [9] Mandelboim et al., 2001. [10] Arase et al., 2002. [11] Kloover et al., 2002. [12] Senkevich and Moss, 1998. [13] Schust et al., 1998. [14] Gewurz et al., 2001. [15] Machold et al., 1997. [16] Lopez-Botet, Llano and Ortega, 2001. [17] Park et al., 2002. [18] Tomasec et al., 2000. [19] Ishido et al., 2000. [20] Wang et al., 2002. [21] Kavanagh et al., 2001. [22] Le Gall et al., 1998. [23] Cohen et al., 1999. [24] Swigut et al., 2000. [25] Coscoy, Sanchez and Ganem, 2001. [26] Fletcher, Prentice and Grundy, 1998. [27] Sutherland, Chalupny and Cosman, 2001. [28] Kubin et al., 2001. [29] Cosman et al., 2001. [30] Krmpotic et al., 2002. [31] Ishido et al., 2000. [32] Coscoy and Ganem, 2001. [33] Zheng and Zucker-Franklin, 1992. [34] Zocchi et al., 1998. [35] Poggi et al., 2002. [36] Fleming et al., 1999. [37] Saederup et al., 2001. [38] Kledal et al., 1997. [39] Immjerdingen, Damaj and Maghazachi, 2001. [40] Kotenko et al., 2000. [41] Moore et al., 1990. [42] Born et al., 2000. [43] Xiang and Moss, 1999. [44] Lee et al., 2001. [45] Cho et al., 2001. [46] Parry et al., 2000. [47] Alcam et al., 1998. [48] Chehimi et al., 1991. [49] York and Johnson, 1993. [50] Tseng and Klimpel, 2002. [51] Crotta et al., 2002.
Figure 3. Viral inhibition of MHC class II antigen presentation.

MHC class II α and β chains and the invariant chain (Li) are expressed constitutively or in response to IFN-γ stimulation. These molecules assemble in the ER to form the α-β-Li complexes that are then transported from the ER through the Golgi apparatus to the TGN, where the complexes are sorted to endosomes in response to signals present in the cytoplasmic tail of Li. In early endosomes, Li is progressively degraded by low-pH proteases so that fragments of it remain bound to the peptide-binding groove formed by the α-β chains. The MHC class II complexes then traffic into more acidic late endosomes and prelysosomal compartments known as MHC class II loading compartment (MIIC). Viral antigens can reach the endocytic pathway by phagocytosis, endocytosis or recycling of internal vesicles (site of virus assembly). Antigens delivered into the endocytic pathway are degraded by acid-dependent proteases to form peptides that are delivered to MIIC and loaded onto MHC class II α-β dimers. Exchange of peptide antigens for Li fragments occurs in collaboration with class II-like α-β dimers called DM. From the MIIC, peptide-loaded class II moves to the cell surface for presentation to CD4+ T cells. Viral mechanisms interfering with MHC class II antigen presentation fall into 5 categories: (1) inhibition of the IFN-γ transduction cascade leading to the expression of MHC class II; (2) Inhibition of the association of the α and β chains with the Li chains; (3) redirecting the α and β chains and DM for degradation by the proteasome; (4) preventing MHC class II from reaching the endocytic compartment; and (5) interfering with MHC class II processing and acidification of the endosome.
4. VIRAL INHIBITION OF MHC CLASS II ANTIGEN PRESENTATION

CD4-positive cells can recognize viral antigens expressed on virus-infected cells expressing MHC class II molecules to act cytolytically, to produce antiviral cytokines or to coordinate the antiviral immune response. MHC class II molecules are expressed constitutively by thymic epithelial cells, activated T cells and professional antigen-presenting cells, while in other cells, such as fibroblasts, keratinocytes, endothelial, epithelial and glial cells, their expression require IFN-γ stimulation. The latter induces the expression of MHC-II molecules through a complex cascade of factors (reviewed in Hegde, Chevalier and Johnson, 2003).

From the recent literature, it appears that viral inhibition of MHC class II antigen presentation is designed to prevent presentation of endogenous viral antigens in virus-infected cells rather than presentation of exogenous antigens in professional antigen-presenting cells.

Table 3. Viral inhibition of MHC class II antigen presentation.

| Site (1) | Virus (2) | Viral gene | Mechanism of action | Source |
|---------|-----------|------------|---------------------|--------|
| 1       | Adeno-virus | E1A        | Interferes with MHC class II upregulation (INF γ signal transduction cascade) | [1]    |
| 1       | HHV-5      | ?          | Interferes with MHC class II upregulation (INF γ signal transduction cascade) | [2; 3] |
| 2       | HHV-5      | US3        | Bounds to α/β subunits of MHC class II complexes in the ER reducing their association with Li | [4]    |
| 3       | HHV-5      | US2        | Targets the MHC class II α and DM-α molecules for degradation by the proteasome | [5]    |
| 4       | HHV-1      | ?          | Redistributes MHC class II molecules away from the endocytic pathway | [6]    |
| 4       | HIV        | Env        | Redistributes MHC class II molecules away from the endocytic pathway | [7]    |
| 5       | HIV        | Nef        | Interference with MHC class II processing | [8]    |
| 5       | SIV        | Nef        | Interference with MHC class II processing | [9]    |
| 5       | HHV-1      | gB         | Interference with molecular co-players of MHC class II (DR and DM) processing | [10]   |
| 5       | HPV/BPV    | E5         | Interference with MHC class II processing, and acidification of the endosomes | [11; 12] |
| 5       | BPV        | E6         | Interacts with AP-1, the TGN-specific clathrin adaptator complex | [11; 13] |

NOTES: (1) Site of action. Numbers refer to paths identified in Figure 3. (2) International Committee for Taxonomy of Viruses (ICTV) abbreviations.

SOURCES: [1] Leonard and Sen, 1996. [2] Miller et al., 1999. [3] Miller et al., 1998. [4] Hegde et al., 2002. [5] Tomazin et al., 1999. [6] Lewandowski, Lo and Bloom, 1993. [7] Rakoff-Nahoum et al., 2001. [8] Stumptner-Cuvelette et al., 2001. [9] Schindler et al., 2003. [10] Neumann, Eis-Hubinger and Koch, 2003. [11] Tortorella et al., 2000. [12] Andresson et al., 1995. [13] Tong et al., 1998.
To enhance the understanding of this field, Figure 3 illustrates how viral peptides are processed for presentation in association with MHC class II molecules on the surface of an infected host cell. Some of the viral mechanisms acquired by viruses to interfere with this process are listed in Table 3. For an excellent review of this topic, see Hegde, Chevalier and Johnson (2003).

**Figure 4.** Viral interference with cytokines, chemokines and their receptors.

The strategies acquired by viruses to interfere with or to exploit host cytokines, chemokines and their receptors can be classified into 5 categories: (1) some viruses encode membrane anchored molecules able to bind host chemokine and eventually transduce a signal. Because these viral molecules have sequence similarity with host cellular receptors, they have been called chemokine receptors; (2) other viruses encode soluble proteins capable of binding to chemokines and preventing their action on target cells. Because these viral proteins are not homologues of host cellular proteins, they have been called chemokine binding protein rather than chemokine receptor; similarly, (3) viral encoded membrane anchored cytokine receptors; and (4) soluble cytokine receptors or soluble cytokine binding proteins have been described; (5) viruses are known to encode homologues of cytokines or chemokines.
5. **VIRAL INTERFERENCE WITH CYTOKINES, CHEMOKINES AND THEIR RECEPTORS**

Viral infection induces the production of cytokines and chemokines playing crucial roles in inducing the migration and activation of immune cells to areas of infection; in immune regulation; in anti-viral defence; as well as in the capacity of target cells to support virus replication. For example, cytokines such as interferons (IFN) and tumour necrosis factor (TNF) induce intracellular pathways that activate an anti-viral state or apoptosis, and thereby contribute to limit viral replication. A very large number of cytokines induce mechanisms that enhance immune recognition, or immune responses that protect against viral infection. Finally, some anti-viral cytokines mediate killing of infected cells by NK cells or cytotoxic T lymphocytes. Therefore, it is not surprising to find that cytokines, chemokines and their receptors are targets of viral immune-evasion strategies. The different strategies developed by viruses to interfere with or to exploit host cytokines, chemokines or their receptors are illustrated in Figure 4. Example of viruses known to have acquired such strategies are listed in the accompanying Table 4. For an excellent review of this topic, see the recent review by Alcami (2003).

### Table 4. Viral interference with cytokines, chemokines and their receptors.

| Site (1) | Virus (2) | Viral gene | Mechanism of action | Source |
|----------|-----------|------------|---------------------|--------|
| 1        | HHV-8     | ORF74      | Viral chemokine receptor, induces cell proliferation *in vitro* and tumours in transgenic mice | [1]    |
| 1        | HHV-5     | US28       | Viral chemokine receptor | [2]    |
| 1        | HHV-5     | US27       | Viral chemokine receptor | [3]    |
| 1        | SCMV      | E3-7       | Cluster of five HCMV US28 homologues | [4]    |
| 1        | MuHV-1    | m33        | Viral chemokine receptor | [5]    |
| 1        | HHV-6     | U51        | Viral chemokine receptor | [6]    |
| 1        | FWPV      | FPV 021, 027, 206 | Viral chemokine receptor | [7]    |
| 1        | SWPV      | SPV146     | CXCR1 homologue | [3]    |
| 1        | SPPV      | Q2/3L      | CC-chemokine receptor | [3]    |
| 1        | YLDV      | 7L, 145R   | CCR8 homologues | [8]    |
| 1        | LSDV      | LSDV011    | CC-chemokine receptor homologue | [9]    |
| 2        | EHV-1     | gG (vCKBP4) | Secreted or membrane anchored C-, CC-, CXC-chemokine binding protein | [10]   |
| 2        | EHV-3     | gG (vCKBP4) | Secreted or membrane anchored C-, CC-, CXC-chemokine binding protein | [10]   |
| 2        | BoHV-1    | gG (vCKBP4) | Secreted or membrane anchored C-, CC-, CXC-chemokine binding protein | [10]   |
| 2        | BoHV-5    | gG (vCKBP4) | Secreted or membrane anchored C-, CC-, CXC-chemokine binding protein | [10]   |
| Site | Virus | Viral gene | Mechanism of action | Source |
|------|-------|-----------|---------------------|--------|
| 2    | RanHV-1 | gG (vCKBP4) | Secreted or membrane anchored C-, CC-, CXC-chemokine binding protein | [10] |
| 2    | CapHV-1 | gG (vCKBP4) | Secreted or membrane anchored C-, CC-, CXC-chemokine binding protein | [10] |
| 2    | CerHV-1 | gG (vCKBP4) | Secreted or membrane anchored C-, CC-, CXC-chemokine binding protein | [10] |
| 3    | MYXV   | vCKBP1    | Secreted C-, CC-, CXC-chemokine binding protein | [11] |
| 3    | VACV   | vCKBP2    | Secreted C-chemokine binding protein | [12; 13] |
| 3    | CPXV   | H5R       | Secreted C-chemokine binding protein | [12; 13] |
| 3    | MYXV   | M-T1      | Secreted C-chemokine binding protein | [12; 13] |
| 3    | MuHV-4 | vCKBP3    | Secreted C-, CC-, CXC-, CX3C-chemokine binding protein | [14] |
| 3    | VACV   | A41L      | vCKBP2 homologue | [15] |
| 4    | HHV-5  | UL144     | Membrane TNFR homologue | [16] |
| 5    | CPXV   | CrmB      | Secreted TNF inhibitor | [17] |
| 5    | MYXV   | MT-2      | Secreted TNF inhibitor | [18] |
| 5    | CPXV   | CrmC      | Secreted TNF inhibitor | [19] |
| 5    | CPXV   | CrmD      | Secreted TNF inhibitor | [20] |
| 5    | CPXV   | CrmE      | Secreted TNF inhibitor, also expressed at the cell surface | [21] |
| 5    | VACV   | CrmE      | Surface | [22] |
| 5    | LCDV1  | ORF167L   | Homology to domain of TNFR | [23] |
| 5    | SFV    | T2        | TNF-R homologue | [24; 25] |
| 5    | ECTV   | E13       | Secreted; blocks binding of CD30 to CD30L and induces reverse signalling in cells expressing CD30L | [26] |
| 5    | VACV   | vCD30     | Secreted; blocks binding of CD30 to CD30L and induces reverse signalling in cells expressing CD30L | [27] |
| 5    | VACV   | B16R      | Secreted receptor for interleukin-1 β | [28] |
| 5    | MYXV   | MT-7      | Secreted receptor for IFN-γ | [29] |
| 5    | VACV   | B8R       | Secreted receptor for IFN-γ | [30] |
| 5    | VACV   | B19R      | Secreted and cell surface binding protein for IFN-α/β | [31] |
| 5    | HHV-4  | BARF1     | Secreted binding protein for CSF1 | [32] |
| 5    | ORFV   | GIF       | Secreted binding protein for GM-CSF/IL2 | [33] |
| 5    | MOCV   | MC54      | Secreted binding protein for IL18 | [34] |
| 5    | ECTV   | E19       | Secreted binding protein for IL18 | [35] |
| 5    | MOCV   | MC51, MC53 | Secreted binding proteins for IL18 | [36] |
| 6    | VACV   | C11R      | Viral epidermal growth factor homologue | [37] |
| 6    | ORFV   | A2R       | Viral vascular endothelial growth | [38] |
| 6    | HHV-4  | BCRF1     | Viral IL-10 homologue | [39] |
| 6    | HHV-5  | UL111a    | Viral IL-10 homologue | [40] |
| 6    | ORFV   | vIL-10    | Viral IL-10 homologue | [41] |
| 6    | EHV-2  | E7        | Viral IL-10 homologue | [42] |
| 6    | SaHV-2 | ORF13     | Viral IL-17 homologue | [43] |
| 6    | HHV-8  | K2        | Viral IL-6 homologue | [44] |
| 6    | VACV   | A39R      | Viral semaphorin, binds semaphorin receptor VESPR | [45] |
Viral subversion of the immune system

### 6. VIRAL MANIPULATION OF THE CELL DEATH PROGRAMME

Replication of viruses may stimulate suicide of the host cell directly or via recognition by immune effector cells. These cells (cytolytic T cells and NK cells) induce cell death by secretion of cytotoxic cytokines such as TNFs and by processes requiring direct cell-cell contact, such as release of perforin and granzyme. This form of programmed cell death is called apoptosis. Apoptosis is an orchestrated biochemical process that leads ultimately to the demise of the cell, initiated by both internal sensors (intrinsic pathway,
mitochondria dependent) and external stimuli (extrinsic pathway, death receptor mediated).

Figure 5. Viral inhibition of apoptosis.

Apoptosis can be initiated by two main pathways. The extrinsic pathway is triggered by death ligands binding to their cognate death receptors. These receptors then multimerize and their death domains (DDs) interact with the DDs of adaptor proteins that bind to pro-caspase 8 and/or pro-caspase 10 to form the DISC. This ends with pro-caspase cleavage in their active form. These caspases can then cleave Bid and activate the effector caspase cascade. On the other end, internal sensors initiate the intrinsic pathway via a process that results in hetero-oligomeric pores formation in the outer membrane of the mitochondria. Factors such as cytochrome c, Smac and Omi are then released in the cytoplasm where cytochrome c promotes formation of the apoptosome, resulting in autocatalytic activation of caspase 9, which initiates the effector caspase cascade. Caspases activation is negatively regulated by IAP, which are counter-balanced by proapoptotic Smac and Omi. Viral mechanisms of apoptosis inhibition fall into 4 main categories: (1) modulating of death receptors signalling; (2) regulation of caspase; (3) mimicking Bcl-2; and (4) blinding the internal sensors.

In the case of replicating viruses, apoptosis can be viewed as an altruistic defence mechanism by which the host infected cell commits suicide in order to prevent virus spread in the infected host. Indeed, premature cell death would enable viruses to maximally replicate or to establish latency. Apoptosis is a complex and highly regulated process. Many viruses have acquired mechanisms to inhibit this important biological process, by
targeting different steps. These mechanisms of viral inhibition of apoptosis can be classified into four main classes: modulation of death receptor signalling; caspase regulation; Bcl-2 mimicking; and internal sensors blinding. They are described in Figure 5. Viral proteins inhibiting apoptosis are listed in Table 5, together with their mechanism of action. For an excellent review of this subject, see Benedict, Norris and Ware (2002).

**Table 5. Viral inhibition of apoptosis.**

| Site | Virus (1) | Viral gene (2) | Mechanism of action | Source |
|------|-----------|----------------|---------------------|--------|
| 1    | adenovirus | E3-6.7         | Complexes with 10.4 and 14.5 resulting in downmodulation of TRAIL receptor 1 and 2 | [1]    |
| 1    | adenovirus | E3-10.4        | Inhibits TNF and FasL induced apoptosis | [2; 3] |
| 1    | adenovirus | E3-14.5        | Inhibits TNF and FasL induced apoptosis | [2; 3] |
| 1    | adenovirus | E3-14.7        | Inhibits TNF induced apoptosis | [4; 5] |
| 1    | BoHV-4    | ORF71          | Inhibits TNF and FasL induced apoptosis (viral homologue of cFLIP) | [6]    |
| 1    | EHV-2     | E8             | Inhibits TNF and FasL induced apoptosis (viral homologue of cFLIP) | [7]    |
| 1    | SaHV-2    | ORF71          | Inhibits TNF and FasL induced apoptosis (viral homologue of cFLIP) | [8]    |
| 1    | HHV-8     | K13            | Inhibits TNF and FasL induced apoptosis (viral homologue of cFLIP) | [9]    |
| 1    | MOCV      | MC159          | Inhibits TNF and FasL induced apoptosis (viral homologue of cFLIP) | [7; 10]|
| 1    | HHV-5     | UL36           | Prevents caspase 8 activation | [11]   |
| 1    | MYXV      | MT-2           | TNF-R homologue      | [12; 13]|
| 1    | HHV-4     | LMP1           | Interacts with TRAFs and TRADD | [14; 15]|
| 1    | SFV       | T2             | TNF-R homologue      | [16; 17]|
| 1    | VACV      | CrmE           | TNF-receptor         | [18]   |
| 1    | CPXV      | CrmB           | TNF-receptor         | [19]   |
| 1    | CPXV      | CrmC           | TNF-receptor         | [20]   |
| 1    | CPXV      | CrmD           | TNF-receptor         | [21]   |
| 1    | CPXV      | CrmE           | Secreted TNF inhibitor, also expressed at the cell surface | [22]   |
| 1    | LCDV1     | ORF167L        | Homology to domain of TNFR | [23]   |
| 1    | HHV-5     | UL144          | Membrane TNFR homologue | [24]   |
| 2    | ASFV      | A224L          | IAP-related protein  | [25; 26]|
| 2    | Baculo-   | P35            | Inhibits caspase 1, 3, 6, 8 and 10 | [27 – 29]|
| 2    | virus     | IAP            | Inhibits caspase 3, 6 and 7 | [27; 30]|
| 2    | CPXV      | CrmA           | Inhibits caspase 1, 4, 5 and 11 | [31 – 33]|
| 2    | VACV      | SPI-2          | Inhibits caspase 1, 4, 5 and 11 | [34]   |
| 2    | ECTV      | SPI-2          | Inhibits caspase 1, 4, 5 and 11 | [35]   |
| Site | Virus(1) | Viral gene | Mechanism of action | Source |
|------|----------|------------|---------------------|--------|
| 3    | Adeno-    | E1B-19K    | Bcl-2-related protein | [36; 37] |
| 3    | HHV-4     | BHRF1      | Bcl-2-related protein | [38; 39] |
| 3    | HHV-4     | BALF1      | Bcl-2-related protein | [40]   |
| 3    | HHV-8     | HHV-8      | Bcl-2-related protein | [41]   |
| 3    | SaHV-2    | ORF16      | Bcl-2-related protein | [42; 43] |
| 3    | MuHV-4    | m11        | Bcl-2-related protein | [44]   |
| 3    | AS芙V     | A179L      | Bcl-2-related protein | [45]   |
| 3    | HHV-1     | US3        | Prevents virus induced apoptosis via a post-translational modification of Bad | [46]   |
| 3    | HHV-1     | US5        | Cooperates with US3 | [46]   |
| 3    | HHV-5     | UL37       | Appears to be functionally similar to Bcl-2 | [47]   |
| 3    | HHV-4     | LMP1       | Up-regulates Bcl-2 and other cell survival proteins | [14; 15] |
| 3    | HIV       | Nef        | Prevents apoptosis via phosphorylation of Bad | [48]   |
| 3    | HTLV-1    | Tax        | Activates the Bcl-xL promoter while repressing transcription of Bax | [49]   |
| 4    | Adeno-    | E1B-55K    | Binds to p53 and functionally inactivates it | [50]   |
| 4    | HPV       | E6         | Targets p53 for degradation | [51 – 53] |
| 4    | SV-40     | Large T    | Binds to p53 and inactivates it | [54; 55] |
| 4    | HBV       | pX         | Complexes p53 and inhibits p53-mediated transcriptional activation | [56]   |

NOTES: (1) Site of action. Numbers refer to paths identified in Figure 5. (2) International Committee for Taxonomy of Viruses (ICTV) abbreviations.

SOURCES: [1] Benedict et al., 2001. [2] Gooding et al., 1991. [3] Shisler et al., 1997. [4] Gooding et al., 1988. [5] Li, Kang and Horowitz, 1998. [6] Wang et al., 1997. [7] Bertin et al., 1997. [8] Glykofrydes et al., 2000. [9] Sturzl et al., 1999. [10] Shisler and Moss, 2001. [11] Skaletskaya et al., 2001. [12] Macen et al., 1996. [13] Xu, Nash and McFadden, 2000. [14] Kawanishi, 1997. [15] Henderson et al., 1991. [16] Smith et al., 1990. [17] Smith et al., 1991. [18] Reading, Khanna and Smith, 2002. [19] Hu, Smith and Pickup, 1994. [20] Smith et al., 1996. [21] Loparev et al., 1998. [22] Saravia and Alcamí, 2001. [23] Tidona and Darai, 1997. [24] Benedict et al., 1999. [25] Chacon et al., 1995. [26] Nogal et al., 2001. [27] Clem, 2001. [28] Clem, Fechheimer and Miller, 1991. [29] Bertin et al., 1996. [30] Crook, Clem and Miller, 1993. [31] Dbaibo and Hannun, 1998. [32] Tewari and Dixit, 1995. [33] Zhou et al., 1997. [34] Dubbelstein and Shenk, 1996. [35] Turner et al., 2000. [36] Sundarajan and White, 2001. [37] Henry et al., 2002. [38] Henderson et al., 1993. [39] Kawanishi, 1997. [40] Marshall et al., 1999. [41] Sarid et al., 1997. [42] Nava et al., 1997. [43] Derfuss et al., 1998. [44] Wang, Garvey and Cohen, 1999. [45] Afonso et al., 1996. [46] Jerome et al., 1999. [47] Goldmacher et al., 1999. [48] Wolf et al., 2001. [49] Tsukahara et al., 1999. [50] Teodoro and Branton, 1997. [51] Thomas and Banks, 1998. [52] Thomas and Banks, 1999. [53] Pan and Griep, 1995. [54] Lane and Crawford, 1979. [55] Linzer and Levine, 1979. [56] Wang et al., 1995.
Complement is part of the innate immune system and is activated in a cascade manner through two main pathways, known as the classical and the alternative pathways. The classical pathway is activated by the recognition proteins C1q or mannose-binding lectin, which bind respectively to charge clusters or neutral sugars on targets. In contrast, activation of the alternative pathway is a default process that proceeds unless down-regulated by specific mechanisms. Complement activation results in cleavage and activation of C3 and deposition...
of opsonic C3 fragments on surfaces. Subsequent cleavage of C5 leads to assembly of the membrane attack complex (C5b,6,7,8,9), which disrupts lipid bilayers. Viruses have developed different strategies acting at different stages of the complement cascade in order to evade complement-mediated destruction. These are listed in Table 6, and are referred to in this figure. These strategies fall into three main categories: (1) some viruses interfere with the classical pathway by avoiding complement binding to antibody-antigen complexes, either by shedding or internalization of these complexes from the cell surface or by expressing virally-encoded Fc receptor on the cell surface; (2) other viruses encode and express functional homologue of cellular regulators of complement activation (RCA), protecting their lipid envelope and the membrane of the infected cell; and (3) some viruses can incorporate host complement RCA in their envelope and/or up-regulate expression of these proteins in infected cells.

Complement activation on host cells is prevented by several membrane regulators of complement activation (RCA), the activity of which is predominantly restricted to complement of the same species, a phenomenon called homologous restriction. These proteins down-regulate complement activity at two steps in the classical and the alternative pathways: complement receptor 1 (CD35) and decay-accelerating factor (CD55) inhibit the formation and accelerate the decay of the classical pathway and alternative pathway C3-activating enzymes (C3 convertases); complement receptor 1 and membrane cofactor protein (CD46) act as cofactors for Factor I (a serum protease), which catabolizes C4b and C3b, thereby inhibiting formation of the C3 convertases C4b2a and C3bBb; finally, at the end of the complement cascade, CD59 and possibly also homologous restriction factor (C8-binding protein) prevent the formation of the membrane attack complex.

In general, micro-organisms lack mammalian RCA and thus cannot restrict complement deposition and amplification on their surfaces. However, the toxicity of the complement system has selected viruses that have acquired countermeasures. The viral strategies to evade complement-mediated destruction are summarized in Table 6. For a recent review of this topic, see that of Favoreel et al. (2003).

| Site | Virus | Viral gene | Mechanism of action | Source |
|------|-------|------------|---------------------|--------|
| 1    | SuHV-1| gE-gI      | Shedding of viral protein-antibody complexes | [1]    |
| 1    | SuHV-1| gB-gD      | Internalization of viral protein-antibody complexes | [2]    |
| 2    | HHV-1  | gE-gI      | Fc receptor activity | [3]    |
| 2    | HHV-3  | gE-gI      | Fc receptor activity | [4]    |
| 2    | SuHV-1| gE-gI      | Fc receptor activity | [1]    |
| 2    | HHV-5  | UL118-UL119| Fc receptor activity | [5]    |
| 2    | HHV-5  | TRL11/IRL11| Fc receptor activity | [6]    |
| 2    | MuHV-1 | Fcr1       | Fc receptor activity | [7]    |
### Table: Viral subversion of the immune system

| Site (1) | Virus (2) | Viral gene | Mechanism of action | Source |
|---------|-----------|------------|---------------------|--------|
| 2       | S         | TGEV       | Fc receptor activity | [8]    |
| 2       | S         | MHV        | Fc receptor activity | [8]    |
| 2       | S         | BCoV       | Fc receptor activity | [8]    |
| 3       | CPXV      | IMP        | Downregulates chemotactic proteins C3a, C4a, C5a | [9]    |
| 4       | VACV      | VCP        | Cofactor for factor I | [10]   |
| 4       | VARV      | SPICE      | Cofactor for factor I | [11]   |
| 5       | VACV      | VCP        | Binds to C4b | [10]    |
| 5       | VARV      | SPICE      | Binds to C4b | [11]    |
| 5       | SaHV-2    | ORF4       | Inhibits formation and accelerates decay of classical and alternative C3 convertases | [12] |
| 6       | VACV      | VCP        | Cofactor for factor I | [10]    |
| 6       | VARV      | SPICE      | Cofactor for factor I | [11]    |
| 6       | HHV-4     | ?          | Cofactor for factor I? | [13] |
| 7       | HHV-1,    | gC1, gC2  | Binds human C3b | [14]    |
| 7       | VACV      | VCP        | Binds to C3b | [10]    |
| 7       | VARV      | SPICE      | Binds to C3b | [11]    |
| 7       | SaHV-2    | ORF4       | Inhibits formation and accelerates decay of classical and alternative C3 convertases | [12] |
| 7       | SuHV-1    | gC         | Binds species-specific C3b | [15] |
| 7       | BoHV-1    | gC         | Binds species-specific C3b | [15]   |
| 7       | EHV-1     | gC         | Binds species-specific C3b | [15] |
| 7       | EHV-2     | gC         | Binds species-specific C3b | [15] |
| 8       | HHV-1     | gC1        | Inhibits Factor D binding | [16] |
| 9       | HHV-1     | gC1        | Inhibits C5 binding | [16] |
| 10      | CPXV      | IMP        | Downregulates chemotactic proteins C3a, C4a, C5a | [9] |
| 11      | SaHV-2    | ORF15      | Homologue of CD59 | [17] |
| 12      | HHV-5     | ?          | Upregulation of CD55 and CD46 | [18] |
| 12      | SuHV-2    | ?          | Incorporation of cellular complement regulators | [19] |
| 12      | VACV      | ?          | Incorporation of cellular complement regulators | [20] |
| 12      | HIV       | ?          | Incorporation of cellular complement regulators | [21] |
| 12      | HTLV      | ?          | Incorporation of cellular complement regulators | [22] |
| 12      | SINV      | ?          | Incorporation of sialic acids | [23] |

**NOTES:**

1. Site of action. Numbers refer to paths identified in Figure 6.
2. International Committee for Taxonomy of Viruses (ICTV) abbreviations.

**SOURCES:**

[1] Favoreel et al., 1997. [2] Favoreel et al., 1999. [3] Watkins, 1964. [4] Ogata and Shigeta, 1979. [5] Litley, Ploegh and Toirabassi, 2001. [6] Atalay et al., 2002. [7] Thale et al., 1994. [8] Oleszak et al., 1993. [9] Howard et al., 1998. [10] Kotwal et al., 1990. [11] Rosengard et al., 2002. [12] Fodor et al., 1995. [13] Mold et al., 1988. [14] Friedman et al., 1984. [15] Huemer et al., 1993. [16] Kostavasili et al., 1997. [17] Rother et al., 1994. [18] Spiller et al., 1996. [19] Maeda et al., 2002. [20] Vanderplasschen et al., 1998. [21] Saifuddin et al., 1995. [22] Spear et al., 1995. [23] Hirsch, Griffin and Winkelman, 1981.
8. CONCLUSION

During the millions of years they have been co-evolving with their host, viruses have learned how to manipulate host immune control mechanisms. The review of the immune evasion strategies acquired by viruses revealed several fascinating aspects of this field. First, it is remarkable that individual virus families have targeted many common immunological principles. Second, the analysis of viral immunoregulatory proteins revealed that they belong to two classes: those encoded by genes with and those encoded by genes without sequence homology to cellular genes. While the former indicates that viruses have “stolen” genes from the host that were subsequently modified for the benefit of the virus, the latter suggests acquisitions through a mechanism of convergent evolution.

Viruses are obligate parasites that live “on the edge”. On the one hand, they need to impair the immune response of their host to be able to replicate and to avoid eradication; but, on the other hand, they need to respect the host immune response in order to ensure their host’s (and hence their own) survival. In other words, the perfect adaptation of a virus to its host would represent a virus able to complete its biological cycle without inducing clinical symptoms. Further studies are required to determine the roles of viral immune-evasion mechanisms in this delicate equilibrium. Indeed, most of the studies cited in this review have investigated the ability of viral genes to interfere with the host immune response in vitro. However, only in vivo experiments will be able to determine the real biological functions of these viral immune-evasion mechanisms. A beautiful example supporting this statement has been provided by the study of vaccinia virus IL-1β receptor. Indeed, while this viral product was thought to contribute to the pathogenicity of the virus, it is interesting to observe that deletion of the corresponding gene enhanced virus virulence and the onset of fever, suggesting that the purpose of at least some of the immune-evasion mechanisms is to reduce immunopathology caused by viral infection (Alcami and Smith, 1996).

In conclusion, this review highlights the complexity and the importance of viral immune-evasion strategies in the host-virus relationship.

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