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Cross-regulation between herpesviruses and the TNF superfamily members

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Abstract

Herpesviruses have evolved numerous strategies to subvert host immune responses so they can coexist with their host species. These viruses ‘co-opt’ host genes for entry into host cells and then express immunomodulatory genes, including mimics of members of the tumour-necrosis factor (TNF) superfamily, that initiate and alter host-cell signalling pathways. TNF superfamily members have crucial roles in controlling herpesvirus infection by mediating the direct killing of infected cells and by enhancing immune responses. Despite these strong immune responses, herpesviruses persist in a latent form, which suggests a dynamic relationship between the host immune system and the virus that results in a balance between host survival and viral control.

The immune system has evolved to provide protection against the many pathogens that are encountered throughout the lifetime of an individual. In turn, the selective pressure that is exerted by the immune system has shaped the evolution of pathogens. This co-evolutionary relationship between host and pathogen is particularly clear for viruses that establish persistent infections, such as herpesviruses (BOX 1). Indeed, analyses of viral genome sequences have shown that herpesvirus genomes encode sequence homologues of host proteins that have a role in the immune system, and many viral gene products have immunomodulatory function. These ‘co-opted’ genes allow the virus to manipulate detection and clearance by the host innate and adaptive immune systems, and this is thought to favour viral replication or persistence in the host. In addition, many host proteins that have basic cellular functions are active during viral infection and might be beneficial to the virus, and other host proteins might facilitate viral infection by performing functions that are unrelated to their normal role (for example, by acting as receptors for the entry of the virus into host cells). Phylogenetic analysis has shown that the evolution of herpesvirus genomes is closely linked to the evolution of host genomes, such that the divergence of herpesvirus species correlates with the divergence of vertebrate orders¹. The factors that drive virus-host co-evolution are unclear, although immunomodulation by the virus might be involved.

Both innate and adaptive immune responses can exert strong selective pressure on herpesviruses in infected individuals. For example, infection of mice that lack an adaptive immune system with mouse cytomegalovirus (MCMV) results in the rapid accumulation of mutations in selected viral genes, which allows the viral mutants that escape detection by cells of the innate immune system to thrive and overwhelm the host². However, herpesvirus

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genomes are remarkably stable in immunocompetent individuals, perhaps because viral latency can only be maintained if mutations of the genome are limited and sufficient viral replicative capacity is retained.

Many viruses, including herpesviruses, have evolved mechanisms to interfere with recognition by innate and adaptive immune cells. However, host recognition of viruses is never completely blocked; viruses must therefore also evade effector immune responses, particularly those that are mediated by cytokines, including interferons (IFNs), chemokines and tumour-necrosis factor (TNF)-related cytokines, in order to propagate. The TNF superfamily of ligands and receptors is involved in signalling pathways that are important during development and host defence³⁻⁵, in which they have crucial roles in the regulation of cell survival and death in immune, nervous and ectodermal tissues. Because of this important role in host defence, the TNF superfamily network exerts a strong selection pressure on viruses to evolve strategies that evade responses that are mediated by these host proteins. Indeed, herpesviruses, poxviruses, adenoviruses and other pathogens use multiple strategies to manipulate signalling pathways through TNF superfamily members — for example, viruses express orthologues of TNF receptors (TNFRs) and of their downstream signalling components and target genes that interfere with host signalling pathways⁶⁻⁸. One of the best-known TNFR mimics is the protein M-T2, which is expressed by the poxvirus myxoma virus and was shown to be a virus virulence factor, as infection of rabbits with a M-T2-deficient virus resulted in attenuated disease⁹. The unique ability of herpesviruses to establish lifelong infections depends on the virus taking advantage of many host-cell processes, including manipulation of host TNFR pathways, to evade clearance by the immune system.

In this review we discuss several aspects of the manipulation of host TNFR pathways by herpesviruses, including the use of host receptors, such as the TNFR herpesvirus entry mediator (HVEM; also known as TNFRSF14), for viral entry into cells, and the expression of viral mimics of host TNFRs to manipulate host-cell signalling. In addition, we discuss the recent studies which show that the host counteracts viral-evasion strategies through the co-stimulatory TNFR OX40 (also known as TNFRSF4), and that lymphotoxin- β receptor (LT β R), a key homeostatic regulator of lymphoid organs, limits the spread of herpesviruses from infected cells and maintains splenic architecture and productive immune responses. The selective targeting of the cytokine pathways that are involved in homeostatic processes by herpesviruses suggests an intimate host-pathogen relationship.

Box 1 Infection by herpesviruses

Herpesviruses are a family of large, double-stranded DNA viruses that infect organisms in a species-specific manner. Primary infection can be subclinical or can result in disease, especially in the context of a compromised immune system. There are eight human herpesviruses, which are divided into three subfamilies on the basis of their genomic structure (see table). These viruses are remarkably diverse in terms of their biological properties and pathogenesis, despite similarities between virus subfamilies regarding virion properties and strategies of viral replication¹⁵⁵.

Herpesvirus virions consist of the DNA genome packaged in an icosahedral capsid that is surrounded by a layer of proteins (known as the tegument) and by an outermost lipid bilayer that contains approximately 12 viral glycoproteins. A subset of these glycoproteins mediates the binding of a virus to host receptors and the entry into host cells through fusion of the virion envelope with a cell membrane. Although the replicative strategies are similar among

Viral glycoprotein A glycoprotein that is found in the outer envelope of viruses. Of the 12 glycoproteins that are found in the outer envelope of herpesviruses, gB, gH and gL are the most highly conserved and are thought to be important for virus–host-cell membrane fusion.

various herpesviruses, cell tropisms and strategies for maintaining latent infections and for evading host immune responses differ and contribute to the biological distinctions of the herpesviruses. Common to all herpesviruses is a characteristic latent phase and a lytic replicative cycle, during which the virus can be detected in the infected host. Even after immunity is established, the virus can be released persistently from mucosal tissues. The large genomes of herpesviruses encode a range of proteins that function as immune modulators that are active during the viral life cycle and that interfere with antigen presentation, with detection by the innate immune system and with other signalling pathways. Many of these immune modulators mimic the action of host proteins, thereby allowing the virus to survive and disseminate.

Subfamily	Formal name	Common name	Disease manifestations
Alphaherpesvirinae	Human herpesvirus 1 (HHV-1)	Herpes simplex virus type 1	Mucocutaneous lesions (orofacial, genital, other), keratitis and encephalitis
	Human herpesvirus 2 (HHV-2)	Herpes simplex virus type 2	Mucocutaneous lesions (orofacial, genital, other), encephalitis and meningitis
	Human herpesvirus 3 (HHV-3)	Varicella-zoster virus	Chicken pox and zoster (shingles)
Betaherpesvirinae	Human herpesvirus 5 (HHV-5)	Cytomegalovirus	Transplant- and AIDS-related disease, and intrauterine infections that cause mental retardation and hearing loss
	Human herpesvirus 6 (HHV-6)	HHV-6	Roseola
	Human herpesvirus 7 (HHV-7)	HHV-7	Roseola
Gammaherpesvirinae	Human herpesvirus 4 (HHV-4)	Epstein-Barr virus	Infectious mononucleosis; cofactor in various malignancies (Burkitt's lymphoma, AIDS-associated lymphoma, Hodgkin's lymphoma, nasopharyngeal carcinoma)
	Human herpesvirus 8 (HHV-8)	Kaposi's sarcoma-associated virus	Kaposi's sarcoma, Castleman's disease and primary effusion lymphoma

Entry of herpes simplex virus into host cells

The first encounter between a virus and its host, and an important opportunity for the immune system to resist infection and viral dissemination, is the entry of the virus into the host cell. In general, many glycoproteins in the envelope of a herpesvirus must interact with many cell-surface receptors for host-cell invasion to occur (TABLE 1). Most herpesviruses make their initial contact with the host-cell surface by binding to heparan-sulphate proteoglycans, and this increases the efficiency of virus entry. The viral ligands for heparan sulphate are glycoprotein

Latent phase A phase of a virus life cycle that is characterized by the absence of most or all viral-gene transcription despite the presence of the viral genome in host cells.

Lytic replicative cycle A phase of a virus life cycle that is characterized by active viral-gene transcription and viral-particle production and that commonly results in cell death.

B (gB) and usually at least one other glycoprotein. entry of the virus into the host cell requires fusion of the viral envelope with the host-cell membrane; this is mediated by the binding of the conserved glycoproteins (gB, gH and gL) and usually one or more non-conserved glycoproteins to specific cell-surface receptors¹⁰. The viral ligands that are used for binding to cell-surface entry receptors and, for some herpesviruses, the composition of the gH- and gL-containing complexes on the surface of the virion determine the host-cell receptors that are used for entry, the cell tropism of the virus and ultimately viral pathogenesis^{11,12}.

Attachment and fusion

The requirement of numerous receptors and ligands for the entry of herpes simplex virus (HSV; used here when referring to both HSV-1 and HSV-2) into host cells illustrates the complexity of the viral-entry process (FIG. 1). similarly to other herpes-viruses, HSV-1 first attaches to the host cell through the interaction of gB or gC with heparan-sulphate chains on cell-surface proteoglycans (the HSV-2 ligands for heparan sulphate are gB and gG)^{13,14}. These interactions with heparan sulphate are reversible and are not solely sufficient for viral entry; the action of four HSV glycoproteins is also required, specifically the interaction of HSV gD (which is unique to a subset of the alphaherpesviruses) and gB with a cell-surface receptor, and the participation of a gH-gL heterodimer in membrane fusion. The gD receptors include HVEM (a member of the TNFR super-family), nectin-1 and nectin-2 (also known as PVRL1 and PVRL2, respectively, and are cell-adhesion molecules that belong to the immunoglobulin superfamily), and heparan-sulphate chains that have been modified by particular 3-*O*-sulphotransferases¹⁵. recently, gB was shown to bind to paired immunoglobulin-like type 2 receptor- α (PILR α) and have a role in HSV entry¹⁶; this interaction seems to be independent of gB binding to heparan sulphate.

It is not yet clear how the five HSV glycoproteins (gB, gC, gD, gH and gL) mediate fusion of the viral envelope with the host-cell membrane, an event that can occur either at the cell surface or after endocytosis of the virus. It has been shown that gD can assume multiple conformations depending on whether or not it is bound to HVEM or nectin-1 (REF. 17). The binding of gD to one of its receptors is thought to trigger a change in its conformation that allows it to interact with the gH-gL heterodimer or with gB and activate their fusion activity. Although less is known about the gB-PILR α interaction, it also has a role in triggering fusion activity in some cell types.

Expression of viral-entry receptors and cell tropism

The cell-surface receptors that can mediate HSV entry are expressed by various cell types, including epithelial cells and neurons (which are the main targets for HSV infection *in vivo*). several lines of evidence indicate that, of the gD-binding receptors, nectin-1 is preferentially used by HSV for the infection of these cells. Accordingly, antibodies that are specific for nectin-1, but not those that are specific for HVEM, can inhibit the infection of cultured neuronal and epithelial cells by HSV¹⁸⁻²⁰. Moreover, mutations in gD that specifically abrogate HVEM binding do not interfere with the infection of neuronal and epithelial cells, whereas mutations that specifically affect nectin-1 binding do²¹. Finally, in nectin-1- deficient mice, intravaginal infection of HSV-2 is less efficient than in wild-type mice and neurological disease is attenuated, whereas in HVEM-deficient mice HSV infection is largely unchanged. However, the role of HVEM as an entry receptor should not be ignored, as mice that are deficient in both nectin-1 and HVEM are resistant to HSV-2 infection through an intravaginal route²².

Heparan sulphate A ubiquitously expressed glycosaminoglycan found on most proteoglycans. Most herpesviruses target and use heparan sulphate as a receptor for initial attachment to host cells.

HVEM may be more important for the infection of leukocytes than for the infection of epithelial cells and neurons, as HVEM-specific antibodies partially blocked the infection of activated human T cells¹⁹, and gD mutants that can bind HVEM but not nectin-1 can still mediate the infection of Jurkat T cells²¹. Finally, antibodies that are specific for either HVEM or PILR α inhibited HSV infection of CD14⁺ monocytes, which indicates that both receptors are required for the infection of these cells¹⁶. Nevertheless, it is unclear how HSV infection of leukocytes may contribute to viral pathogenesis *in vivo*.

In addition to the use of HVEM by HSV as a receptor for entry into host cells, other viruses (such as feline immunodeficiency virus, rabies virus, and avian leukosis and sarcoma virus) are now known to enter cells by binding to members of the TNFR superfamily (OX40, nerve growth factor receptor (NGFR) and avian TNF-related apoptosis-inducing ligand receptor (TRAILR; also known as TNFRSF10A)). These viruses can target the structurally conserved cysteine-rich domain 1 (CRD1) that is present in TNFRs²³.

Activation of HSV entry receptors

Ligation of HVEM and PILR α by their cellular ligands triggers positive- and negative-signalling pathways that regulate immune effector cells. Binding of these receptors by HSV glycoproteins is also thought to induce some degree of signalling, and this could prime the cell for downstream events that are involved in viral replication and/or initiate host protective responses. Signalling is not absolutely necessary for HSV entry into host cells, as deletion of the cytoplasmic domains of HVEM, PILR α or nectin-1 does not abrogate this event^{16,19,24}. It remains to be determined whether binding of gD to HVEM or of gB to PILR α has immunomodulatory effects and how this might benefit the virus *in vivo*. However, the recent discovery that HVEM has many cellular ligands raises the possibility that immunomodulatory selective pressure is involved in the evolution of these viral-entry strategies.

The complex interactions between HVEM, PILR α and their ligands

The cellular and viral ligands that interact with HVEM include the TNF superfamily members LT α and LIGHT (also known as TNFSF14), the immunoglobulin-domain-containing cell-surface receptors B and T lymphocyte attenuator (BTLA) and the recently identified CD160, and HSV gD²⁵⁻²⁸ (FIG. 2a). Activation of HVEM by LIGHT leads to co-stimulation of several cell types, including T cells and antigen-presenting cells, whereas ligation of T-cell-expressed BTLA or CD160 by HVEM results in inhibition of T-cell proliferation and effector function²⁸⁻³⁰. Although the interaction stoichiometry and the relative positions of HVEM and BTLA or CD160 on opposing membranes are not clear, the trimeric TNF-related ligands LIGHT and LT α are thought to induce HVEM trimerization, whereas HVEM and BTLA bind as heterodimers in solution³¹⁻³³. Interestingly, LIGHT increases the binding of BTLA to HVEM, and there is some evidence that HVEM can interact in a ternary complex with BTLA and LIGHT^{34,35}. These data, and the ubiquitous expression of these proteins, have led to the proposal that HVEM binds LIGHT and BTLA in a multimeric complex that contains three heterodimers of BTLA or CD160 with HVEM bound to a trimer of LIGHT molecules^{28,30,33,34}. It is unclear whether HSV gD can participate in a ternary complex with HVEM and additional ligands and whether this complex can induce signalling. Nevertheless, the structure of HVEM bound to gD shows that these two proteins form a heterodimer, as do HVEM and BTLA^{30,33,36}, which indicates that gD-containing complexes may exist. Still, it is unclear whether such complexes are necessary for the activation of any of these proteins.

Cysteine-rich domain (CRD). A protein domain that is present in several copies in most tumour-necrosis factor receptors (TNFRs) and that contains up to six cysteine residues, which form up to three disulphide bonds. CRDs are named according to their position in TNFRs and typically CRD2 and CRD3 are required for binding of the receptors to members of the TNF superfamily.

PILR α is one of a pair of inhibitory and activating receptors that are expressed by dendritic cells (DCs), macrophages, natural killer cells and nervous-system cells^{16,37,38}. The cytoplasmic domain of PILR α contains an immunoreceptor tyrosine-based inhibitory motif and triggers inhibitory responses, whereas the related receptor, PILR β , interacts with an adaptor molecule that contains an immunoreceptor tyrosine-based activation motif (ITAM) and transduces activating signals³⁹. The cellular ligand for both PILR α and PILR β is the leukocyte-expressed protein CD99 (FIG. 2b), and natural killer cells that express PILR β are activated to kill target cells that express CD99 (REF. 37). CD99 is highly expressed on activated T cells⁴⁰, indicating that PILR β and/or PILR α might regulate T-cell activation. The selective ligation of gB with the inhibitory receptor PILR α , as mentioned earlier, suggests a mechanism whereby surface-expressed gB potentially deactivates natural killer cells and prevents lysis of HSV-infected cells.

Signal transduction induced by HSV

As an early event in infection, HSV-1 induces the activation of nuclear factor- κ B (NF- κ B), which seems to be necessary for efficient viral replication⁴¹⁻⁴³. More specifically, a purified soluble form of gD, or gD expressed by fibroblasts, was shown to induce NF- κ B activation in U293 and THP-1 tumour cell lines, and this activation was decreased or inhibited by the presence of a gD-specific blocking antibody or by the expression of a mutant form of gD that cannot bind to HVEM^{44,45}. Although these results indicate that gD is one viral factor that can activate NF- κ B, gD has also been implicated in the inhibition of T-cell activation, as discussed later. At present, it is difficult to provide an explanation for these apparently contradictory observations.

In epithelial cells, HSV-1 and HSV-2 trigger inositol-1,4,5-trisphosphate-mediated release of Ca²⁺ from endoplasmic reticulum Ca²⁺ stores, and this is necessary for the phosphorylation of focal adhesion kinase^{46,47}. Ca²⁺-activated focal adhesion kinase seems to be required for the transport of viral capsids to the nuclear pore, as blocking the Ca²⁺ activation of this enzyme significantly inhibits the establishment of viral infection immediately after entry. Viral mutants that lack gD, gB, gH or gL can still bind to host cells, presumably through the remaining viral glycoproteins that are present in the virions, but these mutants fail to enter cells and fail to trigger the release of Ca²⁺ stores. Therefore, cell binding of one or more of these viral glycoproteins is not sufficient for the Ca²⁺ response. Downregulation of nectin-1 expression in human cervical epithelial cells using small interfering RNA prevented viral entry and the subsequent Ca²⁺ response. By contrast, downregulation of HVEM using the same mechanism had no effect on viral entry or on Ca²⁺ mobilization. However, human cervical epithelial cells may not express HVEM⁴⁷. Therefore, gD binding to HVEM is presumably not responsible for Ca²⁺-mediated capsid transport in these cells, even though intracellular Ca²⁺ mobilization has been associated with HVEM signalling in monocytes in response to LIGHT⁴⁸.

HVEM-mediated viral entry is probably more important in other cell types, and HVEM may engage signalling mechanisms that are different to those engaged by nectin-1. gD binding to HVEM may have an additional immunomodulatory role, as recombinant soluble gD or fibroblasts expressing gD alone could inhibit T-cell proliferation⁴⁹. Furthermore, HSV-

Immunoreceptor tyrosine-based inhibitory motif (ITIM). A short peptide motif (Ile/Val/Leu/Ser-X-Tyr-X-X-Leu/Val; in which X denotes any amino acid) that is present in the cytoplasmic domain of inhibitory receptors. When the tyrosine residue is phosphorylated, ITIMs recruit lipid or tyrosine phosphatases that mediate the inhibitory function of these receptors.

Immunoreceptor tyrosine-based activation motif A structural motif containing tyrosine residues, which is found in the cytoplasmic tails of several signalling molecules. The motif has the form Tyr-X-X-(Leu/Ile), in which X denotes any amino acid, and the tyrosine is a target for phosphorylation by SRC tyrosine kinases and subsequent binding of proteins containing SRC-homology 2 domains.

Nuclear factor- κ B (NF- κ B). A family of transcription factors (including NF- κ B1 (also known as p50), NF- κ B2 (also known as p52), cREL, RELA and RELB) that is important for pro-inflammatory and anti-apoptotic responses and for the development of lymphoid tissues. Each of these responses is mediated by canonical and non-canonical signalling pathways.

infected fibroblasts could inhibit the activation and effector functions of T cells⁵⁰. Both CD4⁺ and CD8⁺ T cells have been isolated from skin lesions containing reactivated HSV-2, although HSV-2-specific cytotoxic T-cell recruitment to these lesions and localization at peripheral nerve endings seem to best correlate with viral clearance⁵¹⁻⁵³. Mutant HSV that expressed a form of gD that cannot bind HVSM was as effective as wild-type HSV at inhibiting T-cell activity⁵², which suggests that other inhibitory pathways may be engaged by the virus (for example, through the interaction between gB and PILR α).

Herpesvirus mimicry of TNFR pathways

Signalling through TNFR superfamily members has diverse outcomes, including caspase-induced apoptosis in response to signalling downstream of death receptors, inflammation and co-stimulation in response to TNFR-induced canonical NF- κ B activation, and the provision of developmental and homeostatic signals in response to non-canonical NF- κ B activation⁵ (FIG. 3a). TNFR signalling pathways are commonly targeted by viruses both to prevent the infected cell from triggering apoptotic cascades and to promote the induction of survival pathways^{6, 8, 54-56}. Examples of herpesvirus proteins that activate all or part of the TNFR signalling pathways include Epstein-Barr virus (EBV) LMP1 (latent membrane protein 1), Kaposi's sarcoma-associated virus (KSHV) K1, K15 and vFLIP (viral caspase-8 (FLICE)-like inhibitory protein), and CMV UL144 (FIG. 3b-f). Although the function of each of these viral gene products during infection is not completely understood, they are thought to regulate cell transformation, viral latency and immune evasion. So, these proteins induce different signalling pathways that, however, share features of ligand-independent signalling, TNFR-associated factor (TRAF) recruitment and NF- κ B activation, which ultimately lead to the induction of expression of pro-survival factors and consequently the inhibition of apoptosis. Although none of these proteins has been shown to influence pathogenesis in natural human infections, it should be noted that studying them in the context of a natural infection remains a challenge.

EBV LMP1

LMP1 is a six-transmembrane-domain protein that is associated with lipid rafts and that oligomerizes to form a receptor complex that signals constitutively using the TNFR signalling apparatus⁵⁷⁻⁶⁰. The cytoplasmic domain of LMP1 contains a binding site with a TRAF recruitment motif (known as carboxy (C)-terminal activator region 1 (CTAR1)) and a TNFR-associated via death domain (TRADD)- and receptor-interacting protein 1 (RIP1)-binding site (known as CTAR2). CTAR1 and CTAR2 can recruit several TRAF molecules directly and indirectly, respectively; of these TRAF molecules, TRAF3 is specifically required for the activation of the JUN N-terminal kinase (JNK) and activator protein 1 (AP1) pathway, for the activation of the NF- κ B components RELA and RELB and for the production of immunoglobulins by B cells⁶¹⁻⁶³. By driving these signalling pathways, LMP1 functions as a constitutively active mimic of the TNFR family member CD40, resulting in the activation of survival pathways and in the provision of proliferative signals for B-cell transformation. EBV-transformed B-cell lymphomas that express LMP1 have constitutively active NF- κ B, protein kinase B (PKB; also known as AKT) and signal transducer and activator of transcription 3 (STAT3), and inhibition of the constitutive activation of these molecules using specific inhibitors against NF- κ B, PKB and STAT3 restrains B-cell lymphoma growth and

Death receptor A cell-surface receptor that can mediate cell death following ligand-induced trimerization. The best-studied members of the death-receptor family include tumour-necrosis factor (TNF) receptor 1, CD95 and two receptors for TNF-related apoptosis-inducing ligand (TRAILR1 and TRAILR2).

Lipid raft A cholesterol- and glycosphingolipid-rich region of the plasma membrane that provides ordered structure to the lipid bilayer and can include or exclude specific signalling molecules and complexes.

Activator protein 1 A transcription factor complex composed of a heterodimer of JUN and FOS subunits that is necessary for the induction of interleukin-2 transcription in T cells. JUN and FOS subunits are members of a family of leucine-zipper-containing proteins that are induced following activation of extracellular-signal-regulated kinase and JUN N-terminal kinase.

survival⁶⁴. It is unclear whether LMP1 activates the Janus kinase (JAK)-STAT signalling pathway directly or indirectly following the transcription of LMP1-responsive genes such as interleukin-10 (*IL10*)^{59,65}. LMP1 also activates PKB and numerous other signalling pathways, and together with other EBV proteins that are expressed during viral latency, LMP1 promotes the differentiation of infected naive B cells into long-lived memory B cells, in which the virus remains in a latent state⁶⁶.

LMP1-mediated activation of the transcription factors AP1, RELA and RELB is known to involve the coordination of a large number of adaptor molecules and signalling pathways. TRAF6, IL-1R-associated kinase 1 (IRAK1) and IκB kinase-β (IKKβ) are all essential for LMP1-mediated phosphorylation and nuclear localization of the NF-κB RELA-p50 heterodimers, which trigger the canonical NF-κB pathway^{59,67-70}. The recruitment of TRAF3 to the CTAR1 of LMP1 also activates NF-κB-inducing kinase and IKKα to activate the processing of the NF-κB p100 subunit to p52, which allows the formation of RELB-p52 heterodimers and, consequently, the activation of the non-canonical NF-κB pathway⁷¹. In mouse embryonic fibroblasts, but not in B cells, LMP1 activates AP1 through the direct association of TRAF1 with its CTAR1 or through the indirect association of TRAF2 with TRADD through CTAR2 (REFS 72,73). LMP1-mediated AP1 activation also requires the activation of TRAF6-dependent TGFβ-activated kinase 1 (TAK1), and the downstream mitogen-activated protein kinases JNK and p38 (REFS 74,75). Finally, LMP1-mediated activation of the phosphoinositide 3-kinase pathway that leads to the activation of PKB requires the CTAR1 of LMP1, which indicates that TRAF proteins are involved in this pathway⁷⁶.

KSHV K1

The KSHV protein K1 self-associates through its single extracellular immunoglobulin domain to initiate ligand-independent constitutive signalling⁷⁷. The cytoplasmic domain of K1 contains an ITAM, which is phosphorylated, possibly by spleen tyrosine kinase (SYK), and functions in the recruitment of LYN, SYK, phospholipase Cγ 2, the p85 subunit of phosphoinositide 3-kinase, VAV1, SRC homology 2 (SH2)-domain-containing phosphatase 1 (SHP1), SHP2, RAS GTPase-activating protein and growth-factor-receptor-bound protein 2 (REFS 78,79). These proteins can activate several transcription factors, including AP1, Ca²⁺-signal-driven nuclear factor of activated T cells (NFAT) and PKB-signal-driven forkhead-box-containing proteins, which are all involved in preventing apoptosis^{59,80}. In addition, K1 activates NF-κB in B cells in a process that requires the K1 cytoplasmic ITAM and LYN⁸¹. Together these signalling pathways ensure the survival of infected cells and promote the expression of many host genes, including vascular-endothelial growth factor (VEGF) *in vitro*. In a mouse model of infection using a recombinant variant of mouse gammaherpesvirus 68 that expresses KSHV K1, expression of K1 was shown to increase latent viral load, tumour formation and the inflammatory response^{82,83}.

KSHV K15

The KSHV protein K15 is a multi-transmembrane-domain protein that associates with lipid rafts and initiates constitutive signalling through SH2- and SH3-binding motifs in its cytoplasmic domain^{59,84}. Although none of these domains is required for the binding of SRC family kinases *in vitro*, the C-terminal tyrosine-containing motif is required for SRC-kinase-mediated phosphorylation of K15. Once phosphorylated, K15 activates extracellular signal-regulated kinase 2 (ERK2) through RAS and MAPK/ERK kinase 1 (MEK1) or through MEK2

Mitogen-activated protein kinase A family of serine/threonine kinases that are activated by various mitogenic stimuli and lead to the activation of extra-cellular-signal-regulated kinase, JUN N-terminal kinase or p38.

Phosphoinositide 3-kinase (PI3K). A lipid kinase that generates phosphatidylinositol-3,4,5-trisphosphate, which can be bound by pleckstrin homology domain-containing proteins, such as protein kinase B. PI3K activation is often associated with survival signals and the activity of anti-apoptotic proteins.

and the JNK pathway, which together lead to AP1 activation. K15 also activates NF- κ B, although the mechanism of activation is unclear. However, K15 binds TRAF1, TRAF2 and TRAF3 *in vitro*, and the C-terminal tyrosine of K15 is required for TRAF2 binding and NF- κ B activation^{59,84}. K15 signalling induces the expression of many cytokines and chemokines, including IL-6 and IL-8, and, as with K1, this leads to VEGF expression *in vitro* and could contribute to angiogenesis *in vivo*⁸⁵. Therefore, KSHV triggers many signalling pathways through K1 and K15, which may act together with other KSHV proteins, including the viral homologues of IL-6 and CD200, to establish a state that promotes tumour formation in patients with Kaposi's sarcoma⁸⁶.

CMV UL144

The UL144 protein of human CMV (HCMV) is encoded within the (U_L)/b' region of the virus genome and was originally described as a homologue of HVEM^{87,88}. Although the (U_L)/b' region is not necessary for the replication of HCMV in certain cell types *in vitro* and is absent from many laboratory strains of the virus, it contains most of the viral immunomodulatory genes and is required for the virus to evade host immune responses⁸⁹. UL144 binds the HVEM ligand BTLA^{30,35} but does not interact with any TNF-related ligands^{87,90}, presumably because UL144 has only two CRDs. Exposure of T cells to HVEM-Fc or UL144-Fc fusion proteins inhibited T-cell proliferation, possibly through binding of the fusion proteins to T-cell-expressed BTLA^{27,35,91,92}. Interestingly, UL144 seems to have a stronger inhibitory activity than HVEM despite having lower affinity for BTLA, probably owing to the selective binding of UL144 to BTLA and not to the TNF ligands LIGHT or LT α (REF. 35). As UL144 competes with HVEM for binding BTLA^{35,93}, HVEM and UL144 may bind and activate BTLA similarly, and HCMV may use UL144 to inhibit T-cell responses through BTLA.

Although it was previously reported that UL144 cannot induce apoptosis or activate NF- κ B⁸⁷, a recent report has shown that UL144 recruits TRAF6 and constitutively activates NF- κ B⁹⁰. It is unclear whether UL144 binds to TRAF6 directly or indirectly through an intermediate protein, as the cytoplasmic domain of UL144 does not contain a canonical TRAF-binding site. The cytoplasmic domain of UL144 is conserved between strains of HCMV, in contrast to the significant sequence variability in the extracellular domain⁸⁸, which suggests that the cytoplasmic domain has a role in signalling. Interestingly, both UL144 and LMP1 induce the expression of CC-chemokine ligand 22 (CCL22), which implies that this chemokine has an important role during infection with herpesviruses of different subfamilies^{90,94}. However, more studies need to be carried out to determine which signalling molecules act downstream of UL144, the relevance of virus-induced NF- κ B activation, and how UL144 interacts with BTLA (in *cis* or in *trans*) during infection.

Although the impact of UL144 on immune function during HCMV infection in lymphoid organs and in the periphery is unclear (owing to technical difficulties in assessing UL144 expression in various human tissues that are targeted by the virus), a recent report has identified HVEM-BTLA co-signalling as an important pathway for regulating the homeostasis of splenic CD8 α^- and CD8 α^+ DC subsets, which preferentially activate CD4 $^+$ and CD8 $^+$ T cells, respectively^{95,96}. Importantly, mice that are deficient in either HVEM or BTLA have increased numbers of CD8 α^- DCs, whereas mice that are deficient in LT α , LT β or LT β R have decreased numbers of CD8 α^- DCs. In addition, mice that lack all three components (HVEM, LIGHT and LT β) show an additional decrease in the number of the CD8 α^+ DCs. Taken together, these observations suggest that these TNF ligands and receptors regulate DC

SRC family kinases A group of structurally related cytoplasmic and membrane-associated enzymes that is named after its prototypical member, SRC. In haematopoietic cells, SRC kinases are the first protein tyrosine kinases to become activated after stimulation through the immunoreceptor. They phosphorylate ITAMs of the immunoreceptors, thereby providing binding sites for SRC homology 2 (SH2)-domain-containing molecules, such as SYK.

homeostasis at many levels. CMV infects DCs and inhibits their maturation and effector function by decreasing their expression of MHC molecules, co-stimulatory molecules and cytokines, which leads to the inhibition of T-cell activation^{97,98}. It is also possible that CMV regulates DC function by direct UL144-mediated activation of DC-expressed BTLA, which results in inhibition of DC function. It is unclear whether similar DC subsets are present in humans, and it remains to be determined whether UL144 influences the frequencies or activation of these cells *in vivo*.

Herpesvirus subversion of death receptors

Expression of death receptors and ligands

The death receptors CD95 (also known as FAS), TRAILR1, TRAILR2 and TNFR1 (also known as TNFRSF1A) are crucial for the induction of apoptosis of infected cells^{99,100}. Not surprisingly therefore, many viruses, including herpesviruses, regulate the expression of death receptors. The EBV protein BZLF1 inhibits the expression of TNF-induced genes and decreases *TNFR1* promoter activity, which results in decreased *TNFR1* transcription during lytic reactivation of the virus¹⁰¹. CMV also reduces the cell-surface expression of TNFR1 by inducing the relocalization of TNFR1 from the cell surface to the trans-Golgi network¹⁰². By contrast, herpesviruses can also increase the expression of death receptors, possibly to allow for cytotoxic T-cell-mediated clearance of infected cells^{103,104}. CMV induces TRAILR expression *in vitro* and EBV induces CD95 expression through signalling downstream of LMP1 and through activation of NF-κB. Moreover, type I IFNs that are produced in response to CMV infection cause the induction of TRAIL expression by DCs¹⁰⁵, and the CMV immediate-early 2 (IE2) gene product has been shown to induce the expression of CD95 ligand by human retinal pigment epithelial cells¹⁰⁶. These observations indicate that increased expression of death-receptor ligands might be used by the virus to induce fratricide of uninfected, virus-specific effector T cells, thereby limiting detection by the immune system⁸.

Regulation of death-receptor signalling

The apoptotic signalling cascade that is induced by several members of the TNFR superfamily is regulated at many levels and has many steps that viruses can exploit^{6,8}. In addition to the regulation of the expression of the death receptors and ligands themselves, a common mechanism that is used by herpesviruses to block apoptosis is the induction of expression of cellular FLIP or vFLIP^{107,108}. FLIP proteins bind to FAS-associated via death domain (FADD), which prevents the oligomerization of pro-caspase-8 with the death-induced signalling complex of death receptors, and inhibits subsequent apoptosis^{107,109,110}. EBV infection protects BJAB cells from CD95- and TRAIL-induced apoptosis, partly owing to the ability of LMP1 to induce the expression of cellular FLIP¹¹¹. Similarly, the CMV protein IE2 induces the expression of cellular FLIP in human retinal pigment epithelial cells, and this also contributes to protection from CD95- and TRAIL-mediated apoptosis¹¹². HSV induces the expression of both cellular FLIP and cellular inhibitor of apoptosis protein 2 (cIAP2) following gD-mediated activation of NF-κB⁴⁴. HCMV and MCMV also encode proteins (UL36 and M36) that prevent caspase-8 activation by binding to pro-caspase-8, similarly to FLIP, although these viral proteins share no sequence homology with FLIP^{113,114}. Another protein encoded by MCMV (M45) blocks TNF-induced apoptosis in a manner that is independent of caspase activation and instead occurs through the binding of M45 to the TNFR adaptor protein RIP1 (REF. 115). Taken together, these observations suggest that herpesviruses have evolved numerous mechanisms to subvert death-receptor-induced apoptosis.

Fatricide A form of cell killing in which one of a group of similar cells kills another member or members of the group.

Recently, several studies have been published that examine the function of KSHV vFLIP beyond its known role as an inhibitor of apoptotic cascades. KSHV vFLIP protects the human myeloid leukaemia cell line TF-1 from growth-factor-withdrawal-induced apoptosis through the induction of NF- κ B activation¹¹⁶. NF- κ B activation by KSHV vFLIP in primary effusion lymphoma requires direct binding by TRAF2 and TRAF3, and correlates with the binding of IKK γ (REF. 117). vFLIP recruits the IKK α -IKK β -IKK γ complex, in addition to heat-shock protein 90, resulting in the activation and nuclear translocation of RELA-p50 heterodimers¹¹⁸. vFLIP binds p100 directly, and this activates IKK α -mediated ubiquitylation and processing of p100 to p52 independently of RIP1 and NF- κ B-inducing kinase¹¹⁹. vFLIP signalling induces the transcription of many genes, including those that encode the anti-apoptotic proteins cellular FLIP, cIAP1 and cIAP2, and the cytokines and chemokines IL-6, IL-8 and CXC-chemokine ligand 3 (CXCL3)^{120,121}. Interestingly, the NF- κ B-activating function of vFLIP might be more relevant than its anti-apoptotic function, as vFLIP-transgenic mice have normal CD95-mediated apoptosis of thymocytes, but increased DNA binding by NF- κ B in lymphoid tissues¹²².

As previously mentioned, KSV K1 activates the phosphoinositide 3-kinase pathway to protect cells from apoptosis and inhibits CD95, but not TRAILR, signalling¹²³. EBV protects cells from CD95-induced apoptosis through a small non-polyadenylated RNA that binds IFN-inducible dsRNA-dependent protein kinase (PKR) and prevents cleavage of poly(ADP-ribose) polymerase, and CMV RNA β 2.7 stabilizes the mitochondrial membrane, thereby preventing chemically induced apoptosis^{124,125}. Together, these examples show that herpesviruses have evolved many different mechanisms to interfere with death-receptor signalling and prevent host-cell apoptosis, thereby allowing for the eventual spread of the virus.

Regulation of herpesviruses by TNFR pathways

The TNFR superfamily proteins control numerous important pathways that limit pathogen infection through the induction of inflammatory responses and the direct lysis of infected cells (FIGS 3a,4a). Recent studies indicate that members of the TNFR superfamily might also have important roles in limiting virus infection by augmenting T-cell co-stimulation (for example, through OX40-mediated co-stimulation) and by regulating IFN production (for example, through LT β R signalling). Indeed, OX40 enhances immunity to infection with MCMV, and LT β R signalling limits MCMV replication through the production of IFN and helps to maintain splenic architecture during viral infection.

Control of viral transmission by OX40

Previously, OX40 was shown to contribute to antiviral immunity by inducing T-cell expansion and effector responses through co-stimulatory signalling¹²⁶⁻¹²⁸. OX40 not only synergizes with signals from other co-stimulatory receptors to induce naive T-cell stimulation, but also signals to increase effector T-cell proliferation, cytolytic activity and cytokine production^{129,130}. During HSV-induced herpesvirus stromal keratitis in mice, OX40 is expressed by corneal CD4⁺ T cells, although OX40 ligand does not seem to be expressed by the tissue-associated antigen-presenting cells¹³¹. OX40 stimulation of CD4⁺ T cells increases the clonal expansion and cytolytic activity of EBV-specific CD8⁺ T cells *in vitro*¹³². MCMV stimulates the proliferation of virus-specific CD8⁺ T cells, the numbers of which change during the acute and persistent phases of infection¹³³. Notably, OX40-deficient mice have decreased CD4⁺ and CD8⁺ T-cell responses in the persistent phase of viral infection, whereas T-cell responses in the acute phase are equivalent to those of wild-type mice. Together, these data indicate that OX40 signalling might be important in secondary responses to herpesviruses, and that CD4⁺ T cells receive OX40 signals to provide help for CD8⁺ T-cell expansion (FIG. 3b). MCMV replicates in the salivary glands and is persistently shed from this location in C57Bl/6 mice; similarly, herpesviruses can be readily detected in human saliva. A recent report showed

that during MCMV infection of salivary glands, the immunosuppressive cytokine IL-10 is expressed by a significant percentage of salivary-gland-infiltrating CD4⁺ T cells. OX40 ligation on these T cells reduced IL-10 expression and resulted in viral clearance from the salivary glands (but not from visceral organs), which indicates that OX40 activation can directly inhibit IL-10-mediated immune suppression, and that both the IL-10 and OX40 signalling pathways can be modulated to alter the course of viral dissemination¹³⁴. Interestingly, several herpesviruses, including HCMV and EBV, encode homologues of IL-10. These homologues are thought to inhibit or skew effector T-cell responses or to promote B-cell survival, although the contribution of these viral genes to the pathogenesis of human disease is yet to be shown^{135,136}.

Cooperative relationship between LTβR, IFNβ and CMV

At present, it is not clear which innate immune receptor is responsible for detecting herpesvirus infection. Moreover, receptor use might depend on cell type. In conventional and plasmacytoid DCs, Toll-like receptor 9 (TLR9) might be used by MCMV, and this probably leads to the activation of IFN-regulatory factor 3 (IRF3), IRF7 and IRF9 (REFS 137-139). Recent reports indicate that DAI (DNA-dependent activator of IRFs; also known as ZBP1) might be a cytosolic sensor of HSV DNA and that a dominant-negative mutation of TLR3 increases susceptibility to HSV-induced encephalitis in humans, which suggests that multiple sensors are used to detect herpesvirus in host cells^{140,141}.

An important outcome of virus detection is the production of type I and type II IFNs, which inhibit virus replication. Herpesviruses can block both IFN production and their downstream effects; for example, HCMV blocks the induction of IFN production and triggers cytopathic effects in fibroblasts *in vitro*, an effect that is countered by the TNF superfamily members LTαβ and LIGHT¹⁴². Blockade of HCMV-induced cytopathology depends on IFNβ production, and this requires both LTβR signalling through NF-κB and HCMV infection in IFN-producing cells. Lack of LTβR signalling in mice that had been infected with MCMV resulted in uncontrolled infection and lethality¹⁴³, and defective IFNβ production was linked to a blockade of LTβR signalling in stromal cells (the site of primary infection) (FIG. 4c). The LTβR pathway regulates the early TLR-independent type I IFN response in the spleen, which is the main source of serum IFN during the first few hours after infection¹⁴⁴. In mice this LTβR-induced early IFNβ production was recently shown to be activated by LTαβ that is produced by naive B cells, and in humans IL-2-activated natural killer cells also express high levels of cell-surface LTαβ and can activate LTβR signalling to induce IFNβ production by CMV-infected fibroblasts^{143,145}. Type I IFNs and IFNγ have crucial roles in establishing and maintaining the latency of herpesviruses^{146,147}, and the cooperation of LTβR and IFNβ may be one mechanism by which latency is initiated.

Another way in which MCMV manipulates the LTβR pathway is by influencing the organization of the splenic microarchitecture. LTβR signalling is required for the formation and maintenance of the microarchitecture of lymphoid organs, in part through the regulation of the tissue-organizing chemokines CCL19, CCL21 and CXCL13. B-cell-expressed LTαβ has an important role in the expression of these stromal chemokines. MCMV infection disrupts the splenic architecture 3-4 days after infection, specifically through a decrease in CCL21 protein levels that is caused by a loss of *Ccl21* mRNA¹⁴⁸. As a result, T cells do not properly localize in the splenic white pulp. However, T-cell localization to the splenic white pulp could be reinstated through enforced LTβR signalling during infection. This virus-induced dysregulated homeostasis is transient, as the expression of CCL21 is restored following viral clearance at 7-10 days after infection. This transient remodelling of the host environment may provide a selective advantage for the virus over host adaptive immune responses.

Lymphocytic choriomeningitis virus (LCMV), which is a small RNA virus of the arenavirus family and is often used as a model virus infection in mice, is associated with disorganization of lymphoid tissue. Late after infection, when the CD8⁺ T-cell response is reaching its peak, the expression of all of the tissue-organizing chemokines is lost^{149,150}. The broad loss of chemokine production results in poor immune responses to other pathogens and is due to damage to the stroma caused by cytotoxic-T-cell-mediated clearance of the virus, rather than by a virus-mediated cytopathic mechanism. So, LCMV infection induces immune pathology, whereas the strategies used by herpesviruses, such as CMV, that target homeostatic processes seem to create a niche for viral persistence and latency.

Concluding remarks

From the initial point of entry of herpesviruses into host cells to the induction of downstream effectors, these viruses target multiple components of the TNF signalling pathways. The HVEM-BTLA pathway stands out as a common target of both alphaherpesviruses and betaherpesviruses: the envelope gD of HSV mimics BTLA binding, whereas UL144 of HCMV and HVEM are orthologues. HSV and HCMV diverged a long time ago, but retained specific but distinct mechanisms for targeting the HVEM-BTLA pathway. The findings that herpesviruses in evolutionarily distant vertebrates encode HVEM-like molecules^{151,152} (J.R.S. and C.F.W., unpublished observations) and that BTLA is present in many forms in these host species¹⁵³, and therefore probably represents an ancient inhibitory pathway, support the idea that the HVEM-BTLA pathway exerts an important selective pressure that influences pathogen evolution. The discovery that diverse viral pathogens, such as equine infectious anaemia virus (a lentivirus), target the host-specific equivalent of HVEM to enter host cells¹⁵⁴ suggests that HVEM binding confers some benefit to these pathogens.

The important role of HVEM in regulating host immune-cell functions might also explain why targeting this molecule would benefit the virus. This is supported by the finding that activation of inhibitory signalling through BTLA by the UL144 protein of HCMV modulates immune responsiveness. The dual advantage of targeting a receptor for both entry and immunomodulation may act as the key selective pressure to retain and evolve these viral-entry strategies. Indeed, other immunoregulatory TNFRs, such as OX40, TRAILR and NGFR, are also used by diverse pathogens to enter host cells²³. A clear understanding of the entry mechanisms that are used by viruses might therefore provide clues to finding new strategies for modulating undesired immune responses in the clinical setting.

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Figure 1. Herpes simplex virus entry receptors and ligands

Herpes simplex virus (HSV) contains on its surface five glycoproteins that are used for its entry into host cells, gB, gC, gD, gH and gL. gB and gC mediate the initial attachment of virus particles to heparan-sulphate moieties on host cell-surface proteoglycans. gB binding to paired immunoglobulin-like type 2 receptor- α (PILR α) and gD binding to herpesvirus entry mediator (HVEM), nectin-1, nectin-2 or 3-*O*-sulphotransferase-modified heparan sulphate trigger membrane fusion, which is mediated by gB and the gH-gL heterodimer, and release of the viral nucleocapsid into the host-cell cytoplasm. Viral-gene transcription occurs following the release of viral DNA into the cell nucleus.

Figure 2. Co-stimulatory and inhibitory signalling by HVEM and PILR α

a | Herpesvirus entry mediator (HVEM) binds the trimeric tumour-necrosis factor (TNF) proteins lymphotoxin- α (LT α) and LIGHT through cysteine-rich domain 2 (CRD2) and CRD3 in its extracellular domain, and this leads to co-stimulatory signalling in many cell types. HVEM binds the immunoglobulin proteins B and T lymphocyte attenuator (BTLA) and CD160 through its amino (N)-terminal CRD1, and this activates inhibitory signalling in T cells. Herpes simplex virus (HSV) glycoprotein D (gD) also binds the CRD1 of HVEM using its N-terminal loop, which facilitates the entry of the virus into HVEM-expressing cells. Although the TNF and immunoglobulin ligands bind distinct regions of HVEM, gD can compete with LIGHT and BTLA for binding to HVEM. **b** | Paired immunoglobulin-like type 2 receptor- α (PILR α)

and PILR β are inhibitory and co-stimulatory receptors for CD99, respectively. Only PILR α binds HSV gB, which is present as a trimer on the HSV virion.

Figure 3. Tumour-necrosis-factor-receptor-like signalling of viral proteins

a | In general, tumour-necrosis factor (TNF) ligands initiate TNF-receptor (TNFR) signalling through ligand-induced trimerization, which leads to the oligomerization of the associated adaptor proteins. Death receptors, such as CD95, first recruit FAS-associated via death domain (FADD) directly or through the adaptor TNFR1-associated via death domain (TRADD) and then recruit caspase-8 and caspase-3, which ultimately leads to DNA cleavage and apoptosis. Non-apoptotic TNFRs that recruit TNFR-associated factor 2 (TRAF2) activate the IκB kinase-α (IKKα)-IKKβ-IKKγ complex, leading to the formation of RELA-p50 nuclear factor-κB (NF-κB) heterodimers. By contrast, the TNFRs that recruit TRAF3 generally activate IKKα-IKKα complexes, leading to the degradation of p100 to p52 and the formation of RELB-p52 NF-κB heterodimers. TNFR1 can activate apoptotic cascades by associating with TRADD, and NF-κB signalling by associating with TRAF2. Lymphotoxin-β receptor (LTβR) activates both RELA- and RELB-containing NF-κB complexes through the recruitment of both TRAF2 and TRAF3. **b-e** | Epstein-Barr virus (EBV) latent membrane protein 1 (LMP1), Kaposi's sarcoma-associated virus (KSHV) K15 and viral caspase-8 (FLICE)-like inhibitory protein (vFLIP) all recruit cellular TRAFs to activate NF-κB, whereas KSHV K1-mediated activation of NF-κB requires the SRC family kinases. Some of these virus-encoded proteins also activate mitogen-activated protein kinase (MAPK) and Ca²⁺ pathways to induce the expression of activator protein 1 (AP1) and nuclear factor of activated T cells (NFAT), leading to the transcription of many host genes that are necessary for host and virus survival. vFLIP (as well as cellular FLIP) blocks apoptosis by inhibiting the death-inducing signalling complex downstream of TNFR signalling. **f** | The human cytomegalovirus (HCMV) protein UL144 may have signalling activity and thereby induce the expression of NF-κB. In addition, it binds B

and T lymphocyte attenuator (BTLA), which induces inhibitory signalling. CTAR, C-terminal activator region; DED, death effector domain; ERK, extracellular signal-regulated kinase; GRB2, growth-factor-receptor-bound protein 2; HSP90, heat-shock protein 90; IRAK1, interleukin-1 receptor-associated kinase 1; JNK, JUN N-terminal kinase; MEK, MAPK/ERK kinase; PI3K, phosphoinositide 3-kinase; PKB, protein kinase B; PLC γ 2, phospholipase C γ 2; RASGAP, RAS GTPase-activating protein; RIP1, receptor-interacting protein 1; SHP, SH2-domain-containing protein tyrosine phosphatase; SYK, spleen tyrosine kinase; TAK1, transforming-growth-factor- β -activated kinase 1.

Figure 4. The role of tumour-necrosis factor receptors in the control of viral replication

a | Death receptors, such as CD95 and tumour-necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) receptor, mediate signalling in virus-infected cells to induce apoptosis and viral clearance. **b** | Co-stimulatory TNF receptors (TNFRs), such as OX40, that are present on cytotoxic T lymphocytes induce signalling to promote the proliferation, cytokine production and lytic activity of virus-specific effector T-cell populations, which reduces viral load. **c** | Lymphotoxin-β receptor (LTβR) signalling in cytomegalovirus-infected cells induces interferon-β (IFNβ) expression, which limits viral replication and induces the antiviral state in other cells. CD95L, CD95 ligand; DAI, DNA-dependent activator of IRFs; IRF, IFN-regulatory factor; NF-κB, nuclear factor-κB; OX40L, OX40 ligand; TCR, T-cell receptor; TLR, Toll-like receptor.

Table 1
Human herpesvirus glycoproteins and their cellular receptors

Human herpesvirus	Initial binding Viral glycoprotein	Host molecule	Entry Viral glycoprotein	Host receptor	Refs
HSV-1	gB, gC	Heparan-sulphate proteoglycans	gB	PILR α	14,16,19 156,157
			gD	HVEM, nectin-1, nectin-2, 3-O-sulphotransferase-modified heparan sulphate	
HSV-2	gB, gC	Heparan-sulphate proteoglycans	gD	HVEM, nectin-1, nectin-2, 3-O-sulphotransferase-modified heparan sulphate	14,19 156,157
VZV	gB	Heparan-sulphate proteoglycans	Mannose-6-phosphate-containing gB, gE, gH, gI	Mannose-6-phosphate receptor	14 158-160
EBV	gp220 and gp350	CD21	gE	Insulin-degrading enzyme	161
CMV	gB, gM	Heparan-sulphate proteoglycans	gH, gL, gp42	MHC class II, others?	14,162,163
HHV-6	Unknown	Heparan-sulphate proteoglycans?	gB, gH	EGFR, $\alpha_4\beta_3$ -integrin	14,164-166
HHV-7	gB, gp65	Heparan-sulphate proteoglycans	gH, gL, gQ	CD46	14,167
KSHV	Unknown	Heparan-sulphate proteoglycans	Unknown	CD4	14,168,169
			gB, gH, gL	$\alpha_3\beta_1$ -integrin	
				Cysteine transporter	

CMV, cytomegalovirus; EBV, Epstein-Barr virus; EGFR, epidermal growth factor receptor; gX, glycoprotein X; HHV, human herpesvirus; HSV, herpes simplex virus; HVEM, herpesvirus entry mediator; KSHV, Kaposi's sarcoma-associated virus; PILR α , paired immunoglobulin-like type 2 receptor- α VZV, varicella-zostervirus.