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Roseoloviruses and their modulation of host defenses

Amy W Hudson

Human cytomegalovirus (HCMV), the prototypical human β-herpesvirus, encodes approximately 40 known gene products that function to subvert our host defense mechanisms. From HCMV, we have learned about interferon signaling, cytokine function, chemokine signaling, natural killer (NK) cells' cytotoxicity toward tumors and virus-infected cells, antigen processing and presentation, and protective initiation of the apoptotic signaling cascade. With each successive discovery of novel host evasion mechanism encoded by the cytomegaloviruses, we illuminate what these herpesviruses have learned over the course of their 100 MYr-long evolution with their hosts. As much as we have learned from HCMV, the other members of the human β-herpesvirus family, HHV-6 and HHV-7, are closely-related and yet largely unexplored. These viruses likely have much yet to teach us.

Addresses
Department of Microbiology and Molecular Genetics, Medical College of Wisconsin, 8701 Watertown Plank Rd, Milwaukee, WI 53226, United States

Corresponding author: Hudson, Amy W (ahudson@mcw.edu)

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Introduction

To achieve optimal reproduction and spread, viruses realign host cellular processes to create a more hospitable environment. Over the course of their co-evolution, viruses have pushed their hosts to develop and fortify an arsenal of sophisticated defense mechanisms. Mammalian hosts, for example, are able to immediately sense the introduction of foreign viral products. Recognition of these viral products provokes rapid upregulation of host innate immune response genes, including soluble cytokines and chemokines, which together influence almost every other aspect of the host response to pathogens. Shortly after cytokine release and signaling, host natural killer (NK) cells are activated to recognize and destroy virus-infected cells. The adaptive immune response then ensues, usually eliminating the virus-infected cells with cytotoxic T cells and neutralizing antibodies. If all else fails, individual infected host cells are programmed to undergo selfless sacrifice – apoptosis for the greater good.

The intimate relationships that occur between hosts and viruses that establish long-lived, latent, or persistent infections have further pushed the evolution of the host defense network. Herpesviruses, for example, after primary lytic infection, remain latent or persistent within the host throughout the life of the host. In so doing, they must necessarily interact with and evade host defense mechanisms. It is therefore not surprising that herpesviruses devote as much as half of their large (~125-240 kB) genomes to counteracting host defenses.

Here, we illustrate the individual cunning of the β-herpesviruses. Human cytomegalovirus (HCMV), one of the most stealthy, successful, and well-studied human β-herpesviruses, is an example of a virus that has fought - and seems to be winning - a long evolutionary battle to live, propagate and disseminate in the face of extensive and sophisticated defense mechanisms. But HCMV is not the only β-herpesvirus that seems to be winning this battle. Human herpesviruses-6A, -6B and -7 are arguably equally as ''successful'' as HCMV. While HCMV infects 50-80% of the US population by age 40, HHV-6A, HHV-6B, and HHV-7 infect over 90% of the population before the age of 6 [1,2]. Like HCMV, HHV-6A, -6B, and -7 also remain latent or persistent throughout the life of their hosts. HCMV, HHV-6A and -6B, and HHV-7 share a core set of essential β-herpesvirus genes involved in DNA replication, packaging, and encapsidation. The other, ''non-essential'' genes in the β-herpesvirus genomes are largely devoted to escaping host defenses. Indeed, our current understanding of host defense mechanisms is derived in part from the what we have learned from HCMV, and distantly related murine CMV. Study of these viruses has shed light upon interferon signaling, cytokine function, chemokine signaling, NK cytotoxicity toward tumors and virus-infected cells, antigen processing and presentation, and protective initiation of the apoptotic signaling cascade. With each discovery of novel host evasion mechanism encoded by cytomegaloviruses, we illuminate what these herpesviruses have learned over their 100 MYr-long evolution with their hosts. As much as we have learned from HCMV, the closely-related and largely unexplored HHV-6A,

HHV-6B, and HHV-7 would seem to have much still to teach us.

The host interferon response

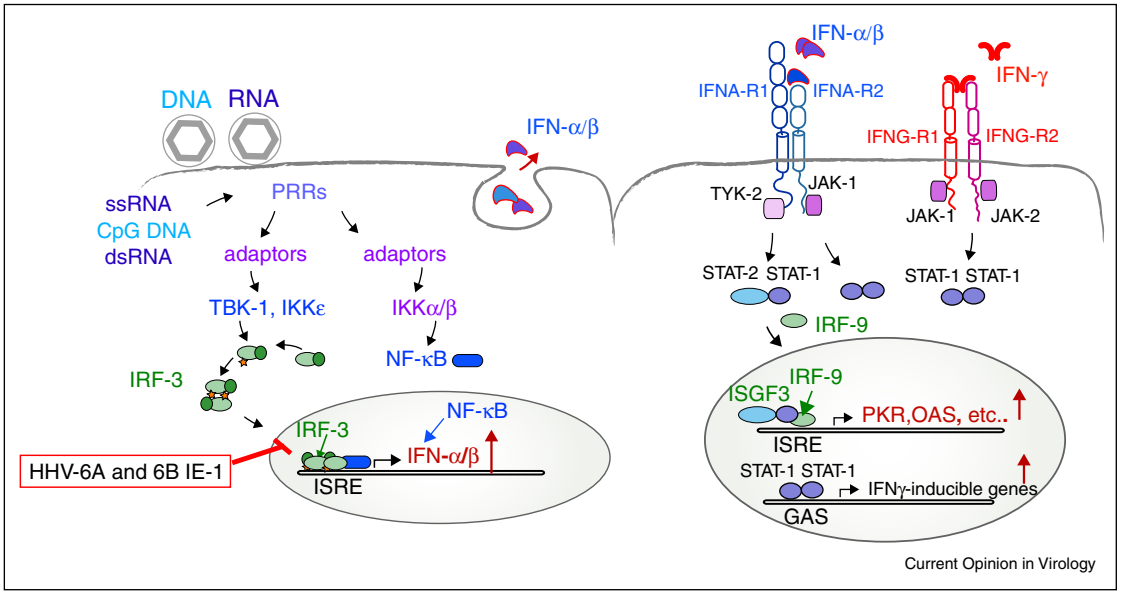
After recognition of uniquely foreign viral products such as dsRNA or cytosolic DNA by pattern recognition receptors, host signaling cascades lead to the IκB kinase- NFκB-, and IRF3/7/9-induced transcription of type I interferons (IFNα and IFNβ) (See Figure 1). Type I interferons signal through IFN receptors, JAK/STAT adaptor kinases, and ultimately use the STAT1/STAT2/IRF9 complex to induce transcription of myriad interferon-inducible genes. These interferon-responsive gene products, which include protein kinase R (PKR) and 2'-5' oligoadenylate synthase (OAS), induce an anti-viral state in the host, preventing viruses from usurping cellular protein synthesis machinery for the production of viral proteins. Type II interferon (IFN-γ), or ''immune'' interferon, is released by immune cells in response to cytokines. IFN-γ then stimulates the launch of an effective adaptive immune response, activating T and B lymphocytes.

To minimize the inhospitable environment they encounter upon entering the host cell, viruses encode multiple means of quelling the innate immune response. HCMV, for example, encodes 7 protein products that hamper the host interferon response (Table 1). HHV-6A and -6B have also been shown to impair interferon signaling: Jaworska, et al. have shown that the **HHV-6A and -6B IE-1** proteins may either prevent or disrupt the dimerization of IRF3, reducing the presence of IRF3 in the nucleus, and reducing transcription of IRF3-inducible genes downstream of IFNβ signaling [3••] (Figure 1).

Cytokine and chemokine signaling

Cellular proinflammatory cytokines IL-1β and TNFα participate in the host defense against viruses through recruitment of inflammatory cells and activate signaling cascades involved in both the innate and adaptive immune response. TNFα is secreted by activated macrophages, and binds to TNF receptors (TNFR) expressed on most tissues (for review, see [4]). TNFR signaling activates NFκB, and can induce fever, apoptosis, and inflammation, thus viruses benefit from developing means to downregulate the functions of inflammatory cytokines like TNFα and IL-1β. Lymphocyte trafficking to sites of infection depends upon the local presence of chemokines, chemoattractant cytokines which attract immune cells and play a role in the activation of their effector mechanisms.

Figure 1



The interferon response. Viral products (e.g.,single-stranded RNA, CpG DNA, or dsRNA) are sensed by pattern recognition receptors (e.g.,TLRs, RIG-I, IFI16, mda5) and a signaling cascade ensues, involving adaptor proteins, ultimately leading to interferon regulatory factor-3 (IRF-3) phosphorylation, which allows dimerization, translocation to the nucleus, and, with βcatenin and p300, binding to the interferon-stimulated response element (ISRE) to upregulate transcription of the type I interferons IFNα/β. IFNα or β is secreted and binds to IFNA-Receptors on neighboring cells, inducing another signaliing cascade mediated by JAK-1, TYK-2, and STATs. STAT-1, STAT-2, and IRF-9 comprise the interferon-stimulated gene factor-3 (ISGF3), which bind to ISRE and upregulate type I IFN-inducible genes, such as PKR and OAS. Also shown is the Type II IFN signaling pathway, induced by IFN-γ, mediated by JAK-1, -2, and STAT-1 homodimers. Type II IFN signaling results in upregulation of genes possessing an interferon-gamma activating sequence (GAS) element. HHV-6A and -6B IE-1 proteins prevent the dimerization of IRF-3, inhibiting interferon signaling.

Table 1

Listing of HCMV gene products and their function in evasion of host defenses. Note that only 4 of the HCMV genes possess positional homologs in the roseoloviruses (italic), suggesting that the roseolovirus gene products that participate in evasion of host defenses are likely to be unique to the roseoloviruses. ORFs possessing positional homologs in HHV-6 are in italics.

ORF	Function	Positional homolog in HHV6	References
	IFN response		
UL83	*Impairs localization of interferon regulatory factors*	*U54*	*[43,44]*
UL83	Inhibits IFI16-mediated DNA sensing		[45]
UL123 (IE1)	Interferes with Type I and Type II IFN signaling; sequesters STAT2		[46,47]
UL122 (IE2)			[48,49]
TRS1	Bind to dsRNA and prevent PKR-induced shutoff of protein synthesis		[50–53]
IRS1	Bind to dsRNA and prevent PKR-induced shutoff of protein synthesis		[50–53]
ORF94	Reduces OAS expression and impairs OAS function		[54]
	Cytokine response		
UL144			[55,56]
UL144	Binds to BTLA, mimicking the function of HVEM, inhibiting T cell proliferation		[57]
UL111a			[58,59]
UL21.5	Soluble CC chemokine receptor that functions as a decoy to modulate host response		[60]
US27	7-tm GPCR homolog; no ligand found, function unknown		[61,62]
US28	7-tm GPCR homolog; signals constitutively in response to multiple CC chemokines		[62–66]
UL33	*7-tm GPCR homolog; heteroligomerizes with US28 and regulates CCR5 and CXCR4*	*U12*	*[62,67]*
UL78	*7-tm GPCR homolog; heteroligomerizes with US28 and regulates CCR5 and CXCR4*	*U51*	*[62]*
UL146			[68]
UL147			[69]
UL128			[70,71]
	Class I MHC antigen presentation		
US2	Binds to class I MHC molecules and results in retrotranslocation and degradation		[72]
US11	Binds to class I MHC molecules and results in retrotranslocation and degradation		[73]
US3	Binds to class I MHC molecules and impedes trafficking from the ER to the Golgi		[74–77]
US6	Blocks the TAP transporter, impeding peptide entry into the ER, affecting stability of class I		[78,79]
	NK response		
UL16	Binds to ULBP1, ULBP2, ULBP6, and MICB and downregulates these NK activating ligands		[28,29,33–36]
US18	Induce the lysosomal degradation of MICA		[80]
US20	Induce the lysosomal degradation of MICA		[80]
UL142	Retains MICA in the Golgi		[81,82]
UL141	Sequesters CD155 and CD112, activating ligands for DNAM-1 or CD96		[83,84]
miR-UL112	miRNA that targets and downregulates MICB		[85]
UL18 Class I	homolog; acts as a decoy NK-inhibitory receptor; also binds LIR-1 inhibitory receptor		[86,87]
UL83	Binds to NKp30 NK activating receptor and suppresses signaling		[88]
	Apoptosis		
UL123 (IE1)	Activates Akt, which acts on IkK to release NFkB to activate tx of anti-apoptotic genes		[89]
UL122 (IE2)	Inhibits NFkB's DNA-binding activity		[48,49,90]
UL141	Binds to TRAIL receptors,retaining them, reducing TRAIL-dependent NK-mediated killing		[91]
UL36	A class I MHC homolog that is a viral inhibitor of caspase-8-induced apoptosis (vMIA)		[92,93]
UL37	Binds to Bax and prevents Bax from arriving in the mitochondria, reducing its activity		[94,95]
UL38	*Prevents apoptosis; mechanism unknown*	*U19*	*[96,97]*
UL28	Induces caspase-dependent apoptosis by activating caspases 8 and 10, independent of TNFR		[98]
miR-UL70-3p	Silences pro-apoptotic genes MOAP1, PHAP, and ERN1		[99]
miR-UL148D	Silences pro-apoptotic genes MOAP1, PHAP, and ERN1		[99]

To minimize cytokine effects, viruses encode multiple means of usurping chemokine and cytokine signaling pathways. HCMV, for example, encodes 12 protein products that may affect chemokine signaling (Table 1). Eight of these HCMV genes encode G-protein coupled receptors or chemokines, as predicted from their sequence homology. HHV-6A, HHV-6B, and HHV-7 possess positional and structural homologs of two of these HCMV genes, UL33 and UL78. **HHV-6B** and **HHV-7 U12** and **U51** gene products are positional and structural homologs of HCMV UL33 and UL78, respectively. Both **HHV-7 U12 and U51** have been shown to be functional chemokine receptors that act as ligands for CCL22 and CCL19 [5••]. **HHV-7** U21 and U51 share ~66% and 50% homology with their HHV-6A and -6B GPCR counterparts, while HHV-6A and HHV-6B chemokine receptors are 94% identical. HHV-6B U12 was shown to be a functional chemokine receptor for CCL2, CCL4, and

CCL5 [6]. HHV-6A U51A signals constitutively and also inducibly responds to CCL2, CCL5, CCL7, CCL11, and CCL13 [7,8].

HHV-6B U83 is a secreted β-chemokine shown to have monospecific β-chemotactic activity for CCR2 [9••,10••]. The **HHV-6A** homolog of **U83** (U83A) shares 86% identity with **HHV-6B U83**, and has β-chemokine activity for CCR1, CCR4, CCR5, CCR6, and CCR8 [11••]. Catusse, et al. have shown that U83A can functionally bind to CCR5 with higher affinity than human chemokines, displacing their binding, inhibiting chemotaxis of human leukocytes, and inhibiting infection by HIV-1 strains that use CCR5 as a co-receptor [12]. The functionality of these HHV-6 gene products in the context of HHV-6 infection has not yet been investigated, largely due to the historical lack of a genetically manipulable BAC system for HHV-6. Interestingly, HHV-7 does not contain a U83 homolog.

T cell activation

The T cell response is critical in the adaptive immune response to virus infection. Since HHV-6A, HHV-6B, and HHV-7 predominantly infect $CD4^+$ T-cells, an activated T cell response directed against HHV-6A, -6B and -7-infected cells might be complicated by infection of the T cells themselves. HHV-6A and HHV-6B encode two proteins that could affect T-cell proliferation during HHV-6A or -6B infection. The **HHV-6B U54** gene product, for example, was recently shown to inhibit IL-2 gene expression [13••]. IL-2 is necessary for growth and proliferation of T cells as they differentiate during the adaptive immune response. Iampietro et al., found that the U54-encoded tegument protein interacts with the phosphatase calcineurin to prevent the dephosphorylation of NFAT, which blocks its nuclear translocation [13••]. Nuclear translocation of NFAT is necessary for its activation of NFAT-inducible genes, which include IL-2. Interestingly, despite 80% amino acid identity, **HHV-6A U54** does not inhibit IL-2 gene expression [13••]. The function of **HHV-7 U54**, which shares only 44% identity with HHV-6B U54, has not been investigated. HHV-6A, -B, and -7 U54 are the positional homologs of HCMV UL82/83.

HHV-6A U24 encodes a unique tail-anchored protein that downregulates the CD3 T cell receptor signaling complex from the cell surface [14••,15••]. The physiological benefit of downregulating CD3 during HHV-6A infection is unclear, but Sullivan and Coscoy suggest three possibilities: 1) U24 expression might prevent T cell activation, which would, in turn, reduce the release of cytokines and potentially dampen the adaptive immune response. 2) reducing surface expression of the T cell receptor in infected cells might prevent reactivation, helping to maintain a latent state. Expression profiling analysis suggests that U24 is an early gene product [16], but further experimentation is necessary to ascertain whether U24 maintains expression during latency. 3) Sullivan and Coscoy note that pretreatment of cells with an anti-CD3 antibody enhances HHV-6 replication, thus in downregulating CD3, perhaps U24 reduces HHV-6A titers so that they do not induce large-scale immune activation [17]. With the availability of the BAC genetic system for manipulation of the HHV-6A genome, future investigation aimed at elucidating the physiological benefit of CD3 downregulation to HHV-6A may to illuminate the novel pathophysiological features of HHV-6 infection [18]. **HHV-6B U24** is quite similar to **HHV-6A U24**, but **HHV-7 U24** shares only 30% identity with HHV-6A U24 [19]. **HHV-6A and HHV-7 U24** remain uncharacterized.

Antigen processing and presentation to cytotoxic T cells

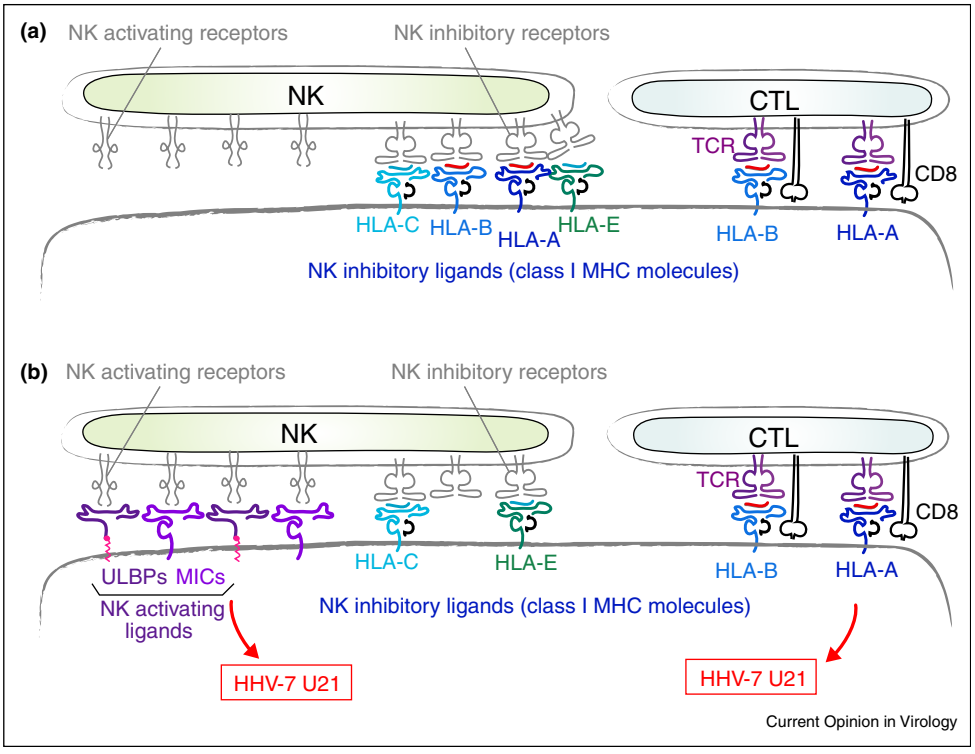
To identify virus-infected cells, class I MHC molecules present peptide antigens derived from intracellular proteins – host and viral antigens alike – for scrutiny by cytotoxic T cells. Peptides generated in the cytosol are transported into the ER via TAP transporters, and are loaded onto newly-assembled class I MHC molecules (in humans, termed HLA-A, HLA-B and HLA-C) in the ER. Once assembled, the peptide-bound class I molecules travel *via* the secretory pathway to the plasma membrane, where they present self- or virus-derived peptides to cytotoxic T lymphocytes.

NK cell function

Before an adaptive cytotoxic T cell response can develop, NK cells participate in the innate immune response against virus infection. NK cells recognize and kill virus-infected cells and tumor cells through recognition of NK *activating* ligands. NK activating ligands are not expressed constitutively, but instead are induced by virus infection or in response to cell stressors (e.g. DNA damage) (See Figure 2). The NK cell integrates the activating and inhibitory signals it receives in formulating a decision to kill its target. Class I MHC molecules are *inhibitory ligands* for NK cells, thus the function of the four different HCMV gene products in downregulating class I molecules (Table 1), would seemingly serve to enhance NK cytotoxicity toward virus-infected cells. Strategically, however, several of these viral proteins have been shown to downregulate some HLA alleles (HLA-A and HLA-B) and not others (e.g. HLA-C) [20,21], leaving some class I alleles remaining on the cell surface to act as NK inhibitory ligands. This tactic is practiced by other viruses as well; HIV Nef and HHV-8 K3 proteins are also selective for HLA-A and HLA-B alleles [22,23].

None of the four HCMV gene products that affect class I MHC molecules possess positional homologs in the roseoloviruses. However, HHV-7 encodes a unique

Figure 2



T- and NK-cell recognition of virus-infected cells. (a) Classical class I MHC molecules, (blue, HLA-A, HLA-B, and HLA-C) present peptides to CD8+ T cells. T cell receptors (TCR, purple), with a co-receptor (CD8, black), can recognize peptides presented in the context of class I molecules and secrete perforin and granzymes to kill a target cell. Both classical (blue) and non-classical class I MHC molecules (green, HLA-E, e.g.) can act as inhibitory ligands for NK cell receptors. (b) When a virus infects a cell, NK activating ligands (purple, ULBPs, MICs) are upregulated. NK cells integrate the inhibitory and activating signals they receive. If activating signals predominate, NK cells can secrete perforin and granzymes to kill a target cell. HHV-7 U21 downregulates classical and non-classical class I molecules, as well as NK activating ligands, presumably escaping both T- and NK-cytotoxicity.

protein that reduces cell surface expression of class I MHC molecules. The **HHV-7 U21** gene product binds to and reroutes class I MHC molecules to lysosomes [24••,25••]. Interestingly, U21 can associate with and reroutes all class I gene products, including HLA-A, HLA-B, HLA-C, as well as the non-classical class I molecules HLA-E and HLA-G. U21 can even reroute the murine class I molecule H-2K^{b} [26]. Given the ability of U21 to reduce surface expression of NK-inhibitory class I MHC molecules, we surmised that HHV-7 must encode other novel means of preventing NK activation.

In addition to the selective downregulation of NK-inhibitory class I MHC molecules, another viral strategy to escape NK engagement involves downregulation of NK-*activating* ligands from the cell surface (Figure 2). Cellular NK-activating ligands were first discovered when investigators queried the binding partners of the HCMV UL16 gene product [27] (Table 1). UL16 was found to bind to two members of a family of cellular proteins termed UL16-binding proteins, or ULBPs, sequestering them in the ER [28,29]. UL16 was also found to associate with MICB (MHC class I chain-related protein B) [29]. Both MICs and ULBPs share structural similarity with class I MHC molecules [30–32]. HMCV UL16 binds to ULBP1, ULBP2, ULBP6, and MICB, and traps these activating ligands intracellularly, reducing NK engagement of HCMV-infected cells [33–36].

The same **HHV-7** gene product that binds to and downregulates class I MHC molecules, **HHV-7 U21,** also downregulates NK activating ligands MICA, MICB, and reroutes ULBP1 to lysosomes [37••], thus U21 appears to have dual-function, downregulating class I MHC molecules as well as NK activating ligands. While HCMV encodes 7 proteins and a miRNA that are devoted to downregulating the NK response, only U21 has been identified to affect NK function in HHV-7. It is not known how HHV-7 (or HHV-6) has evolved to cope with the other NK activating ligands CD155, CD112, ULBP2-6, or NKp30, all of which are targets of HCMV proteins (Table 1). **HHV-6A and HHV-6B U21**, which share only ~30% identity with

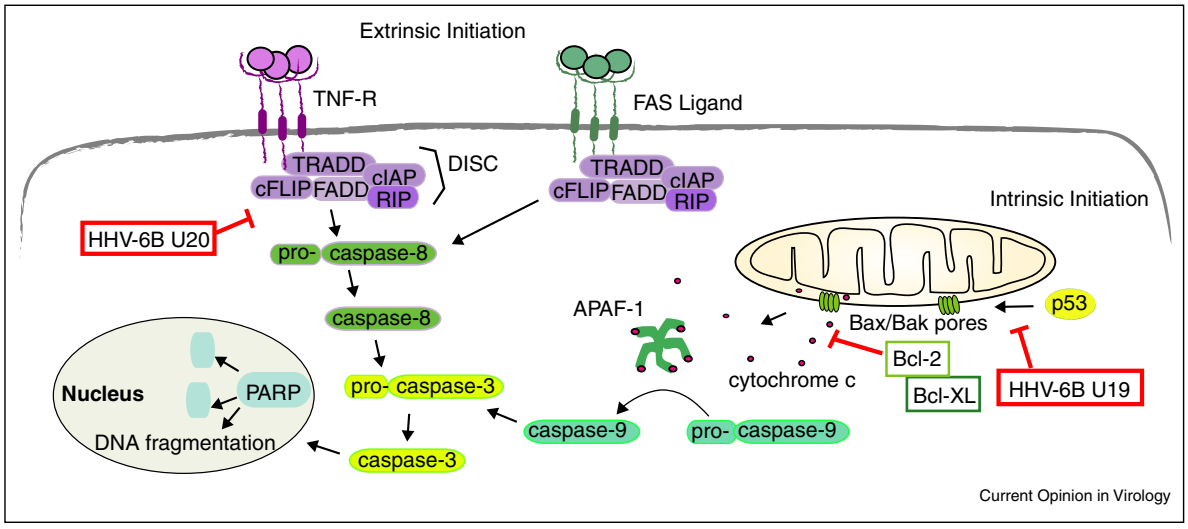
HHV-7 U21, can also bind to and reroute class I MHC molecules to the lysosomal compartment, but the affinity of HHV-6A and -6B U21 for class I MHC molecules is considerably weaker; it is therefore possible that HHV-6 U21 molecules assume an entirely different function [38••]. If so, one would assume that HHV-6A and -6B must encode other means of reducing NK cytotoxicity toward HHV-6-infected cells.

Apoptosis

The host response can also include the induction of apoptosis, as a means to prevent the virus from spreading. The signal to initiate apoptosis can come from within the infected cell, initiated by infection-induced stimuli such as DNA damage or other infection-induced cell stress, or the signal can come from the external environment, in the form of TNF-family binding to cell surface TNF'death' receptors (See Figure 3). Host cell-intrinsic stimuli are sensed by BH3-only domain-containing proteins of the Bcl-2 family such as **Bim** and **Bad**. Activation of these proteins result in insertion of proapoptotic Bcl-2 family members such as pore-forming **Bax** and **Bak**, into the mitochondrial membrane (for review, see [39]). Release of cytochrome c from mitochondria into the cytosol activates **caspase-9** and results in formation of a complex of **APAF-1, cytochrome c**, and **caspase-9**, called the apoptosome, which mediates cleavage of downstream **caspases-3 and -7**, which in turn induce the effects of apoptosis, a result of degradation of many downstream cellular proteins involved in DNA repair and cell maintenance. Host-cell-extrinsic stimuli, such as TNF-family cytokine members TNFα, Fas ligand, and TRAIL, induce apoptosis through a death-induced signaling complex (DISC) assembled on the TNF-receptor family of death domain containing receptors. Death-domain-containing adaptors such as fas-associated death domain (**FADD**) and TNFR-associated death domain (**TRADD**) mediate activation of **caspase-8**, which can then activate **caspases-3 and -7**, converging upon the same effectors as the intrinsic pathway. Initiation of the apoptotic cascade results in dire consequences to the cell, and is therefore tightly regulated by anti-apoptotic members of the BH3-domain family, such as **Bcl-2** and **Bcl-X_L**, or mitochondrial inhibitors of apoptosis (**MIAs**)(for review see [40]). Thus, for a virus to inhibit the apoptotic program, it would either need to upregulate anti-apoptotic proteins, or inhibit the pro-apoptotic cascade. Not surprisingly, HCMV encodes at least 4 proteins and 2 miRNAs that possess these qualities.

Like HCMV, **HHV-6B** manipulates both the extrinsic and intrinsic apoptotic cascades: **HHV-6B U20** expression impairs PARP cleavage and cleavage of caspase-3 and caspase-8, preventing extrinsically-induced apoptosis through an unknown mechanism [41••]. **HHV-6B U19**, the positional homolog of HCMV **UL38**, was recently shown to impair intrinsic, p53-mediated apoptosis [42••].

Figure 3



The extrinsic and intrinsic apoptotic cascades. Extrinsic signals, such as TNFα and Fas signal through trimeric TNF Receptors or TNFR-like receptors through a death-inducing signaling complex (DISC) to cleave and activate caspases, beginning with caspase-8, and ultimately converging upon activation of effector caspases and nucleases. The intrinsic pathway is initiated in the mitochondria, which integrate intracellular apoptotic signals (e.g., DNA damage, ER stress), inducing permeabilization of the mitochondria by Bax/Bak channels. Mitochondrial cytochrome c, when in the cytosol, forms an'apoptosome' with APAF-1, which activates caspase cleavage to induce DNA fragmentation and cell death. HHV-6B U19 and U20 prevent both extrinsic and intrinsic apoptosis.

Table 2

Listing of HHV-6A, HHV-6B, and HHV-7 gene products and their function in evasion of host defenses. ORFs possessing positional homologs in HCMV are in italics.

ORF	Function	HCMV ORF	References
	IFN response		
6A, 6B IE-1	Prevent or disrupt the dimerization of IRF3, reducing transcription of IRF3-inducible genes		[3••]
	Cytokine response		
7 U12	*Positional and structural homolog of UL33*	*UL33*	*[5••]*
7 U51	*Positional and structural homolog of UL78*	*UL78*	*[5••]*
6A U83	β-Chemokine having chemotactic activity for CCR2		[9,10]
6B U83	Chemotactic activity for CCR2, CCR4, CCR5, CCR6, and CCR8		[11]
	Class I MHC antigen presentation		
7 U21	Binds to class I MHC molecules and reroutes them to lysosomes		[20,21,26]
	NK response		
7 U21	Binds to NK activating ligands and reroutes them to lysosomes		[37]
	Apoptosis		
6B U19	*Impairs intrinsic, p53-mediated apoptosis; mechanism unknown UL38*		*[42]*
6B U20	Impairs extrinsic PARP cleavage and cleavage of caspase-3 and -8; mechanism unknown		[41]
	T cell response		
6A U24	Downregulates CD3 T cell receptor		[16,17]
6B U54	*Impairs expression of IL-2*	*UL82/83*	*[13]*

HHV-7 U20 shares only 20% identity with **HHV-6B U20**, and does not seem to affect PARP cleavage (S. Konrad and A. Hudson, unpublished results), and **HHV-7 U19** remains uncharacterized.

Summary

Given the similarity of β-herpesvirus family members HHV-6A, HHV-6B, and HHV-7 to the prototypical β-herpesvirus HCMV, and the sheer number of HCMV proteins (~39) that have been described to escape the host arsenal of defense, the 3 proteins from HHV-7 (U12, U51, and U21) and the 6 proteins from HHV6A or HHV6B (IE1, U19, U20, U24, U54, and U83) seem paltry in comparison (Table 2). With the arsenal of proteins encoded by HCMV found to impair the host response, one wonders how, with so few means of doing so themselves, HHV-6A, -6B, and -7 are able to survive in the face of host defenses? Is the lifestyle of the roseoloviruses so different from HCMV that they do not require such an arsenal of host evasion proteins? Do the roseoloviruses encode fewer host evasion proteins because the few that they encode are far more effective than those encoded by HCMV? Or do the roseoloviruses encode many more, as yet unidentified, means of escape? It seems likely that some additional gene products from HHV-6A, HHV-6B, and HHV-7 are also involved in host evasion, with as-yet undiscovered mechanisms remaining to be elucidated.

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- • of special interest
- •• of outstanding interest

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