

Immune Evasion by Betaherpesviruses

Subjects: Virology

Contributor: Daniel Sausen

The human immune system boasts a diverse array of strategies for recognizing and eradicating invading pathogens. Human betaherpesviruses, a highly prevalent subfamily of viruses, include human cytomegalovirus (HCMV), human herpesvirus (HHV) 6A, HHV-6B, and HHV-7. These viruses have evolved numerous mechanisms for evading the host response.

Keywords: betaherpesvirus ; immune evasion ; viral evasion ; immune response ; HCMV ; HHV-6A ; HHV-6B ; HHV-7

1. Introduction

Betaherpesviruses, a widespread subfamily of viruses within the herpesviridae family, are nearly ubiquitous in the global population ^{[1][2][3]} and include human cytomegalovirus (HCMV), human herpesvirus (HHV) 6A, HHV-6B, and HHV-7 ^[4].

Like other herpesviridae, betaherpesviruses are comprised of four primary sections: the double-stranded viral DNA, the capsid, the tegument, and the envelope. The capsid surrounds the DNA core, while the tegument is a protein-filled area surrounding the capsid. The envelope, the most exterior structural component of herpesviridae, is studded with glycoprotein spikes ^{[4][5]}. Tegument proteins are involved in a wide variety of viral activities, including virion assembly, gene expression, egress, and immune evasion ^{[6][7][8]}. Envelope glycoproteins play a particularly prominent role in protection and in mediating viral entry ^{[9][9][10]}.

The tropism of HCMV ^{[11][12][13]}, HHV-6 ^{[14][15][16][17]}, and HHV-7 ^[17] has been reviewed in depth elsewhere. Specific cellular receptors and viral proteins play an important role in the determination of viral tropism and are also detailed in the aforementioned reviews. HCMV can infect a variety of different cell types in vivo and in vitro, including epithelial cells, endothelial cells, fibroblasts, and smooth muscle cells ^[18]. While many receptors contribute to viral entry in HCMV, there are two models of viral entry, one for fibroblasts and one for epithelial and endothelial cells ^[13]. In fibroblasts, the cellular platelet-derived growth factor- α receptor (PDGFR α) interacts with the HCMV gH/gL/gO trimer complex (TC), which activates glycoprotein B (gB) to fuse the viral envelope with the cell membrane ^[13]. In epithelial and endothelial cells, the cellular receptor neuropilin2 (Nrp2) interacts with the HCMV gH/gL/pUL128L pentamer complex (PC) to stimulate viral endocytosis followed by TC activation of gB, which facilitates viral entry ^[13]. Once viral entry is accomplished, local spread is mediated by direct cell-to-cell transmission ^[13]. However, HCMV primarily establishes latency in cells arising from myeloid progenitors. HCMV has been found to infect dendritic cells latently as well as peripheral mononuclear blood cells, including monocytes and CD34+ progenitor cells ^[11]. Infection begins following exposure to contaminated saliva, mucosa, skin lesions, or genital secretions ^[1]. HCMV disease associations include transplant rejection, retinitis, and serious birth defects ^{[19][20][21]}. HCMV can also present as a mono-like illness ^[22].

HHV-6 also infects a broad range of cells in vivo and in vitro, although it preferentially infects activated CD4+ T lymphocytes. In vivo, HHV-6 can infect tissues ranging from the brain to the liver ^[14] as well as a variety of additional cell types including endothelial cells, NK cells, and myeloid cells ^{[23][24]}. HHV 6 is composed of two related but distinct viruses, HHV-6A and HHV-6B ^[25]. HHV-6A but not HHV-6B has been shown to infect endometrial cells ^[26]. However, HHV-6A and HHV-6B differ in their replicative ability within specific transformed T-lymphocyte cell lines ^{[15][16]}. For example, HHV-6A is most commonly maintained in HSB-2 or JJhan T cell lines while HHV-6B is preferentially maintained in Molt3 or MT4 ^{[15][23]}. In addition, a recent study showed that HHV-6A_{GS} was capable of transcribing the viral genes U7 and U23 in the T cell lines Peer and Jurkat while HHV-6B_{PL1} could not. Both HHV-6A and HHV-6B infect Molt3 and SupT1 T cells ^[27]. HHV-6A uses the cell surface receptor CD46 to mediate viral entry, while HHV-6B uses CD134 ^{[14][17]}. HHV-7 has similar tropism to HHV-6, selectively infecting CD4+ T cells. However, HHV-7 can be observed in various tissues in vivo, including the skin, salivary glands, and other organs ^[17]. Like HCMV, contaminated saliva, mucosa, skin lesions, or genital secretions leads to HHV-6 and HHV-7 infection ^[1]. The primary disease associated with HHV-6 is exanthem subitum, commonly known as roseola or sixth disease, a self-limited disease seen in infants aged 6 months to 2 years of age ^[14]. More serious disease associations include seizures, encephalitis/encephalopathy, retinitis, and hepatitis ^{[14][28]}.

Complications including graft versus host disease and lower respiratory tract infections have been reported in the setting of organ transplantation [29]. HHV-6 has also been associated with neurodegenerative disorders such as multiple sclerosis [30][31] and Alzheimer's disease [32], although a definitive link has yet to be established. HHV-7 is a sparsely researched virus with limited disease associations at this time, although it is also thought to cause exanthem subitum [17]. It, too, has been associated with encephalitis/encephalopathy [28] and more tenuously with Alzheimer's disease [32]. Betaherpesviruses have also been associated with multiple sclerosis [33][34][35][36] and chronic fatigue syndrome [37][38], although these associations have been questioned in the past [39][40][41].

2. Innate Immune Response Pathways

A primary mechanism to induce the innate immune response begins when pathogen associated molecular patterns (PAMPs) are detected by pattern recognition receptors (PRRs), including toll-like receptors (TLRs), NOD-like receptors (NLRs), RIG-I-like receptors, and cGAS-STING [42][43]. Pattern recognition receptor activation stimulates signal transduction pathways that culminate in the activation of transcription factors including NF- κ B and interferon regulatory factors. These transcription factors drive the production of antimicrobial peptides, proinflammatory cytokines, chemokines, and type I interferons [42]. Type I Interferon (IFN) binds the interferon α receptor (IFNAR), which initiates the janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway [44] by phosphorylating JAK [45]. Phosphorylated JAK recruits STAT, a transcription factor [44], which is then phosphorylated and dimerizes. Dimerized STAT translocates to the nucleus [45], which leads to the production of interferon stimulated genes, or ISGs [44] (**Figure 1**). Betaherpesviruses have developed numerous methods of evading this pathway as will be discussed shortly.

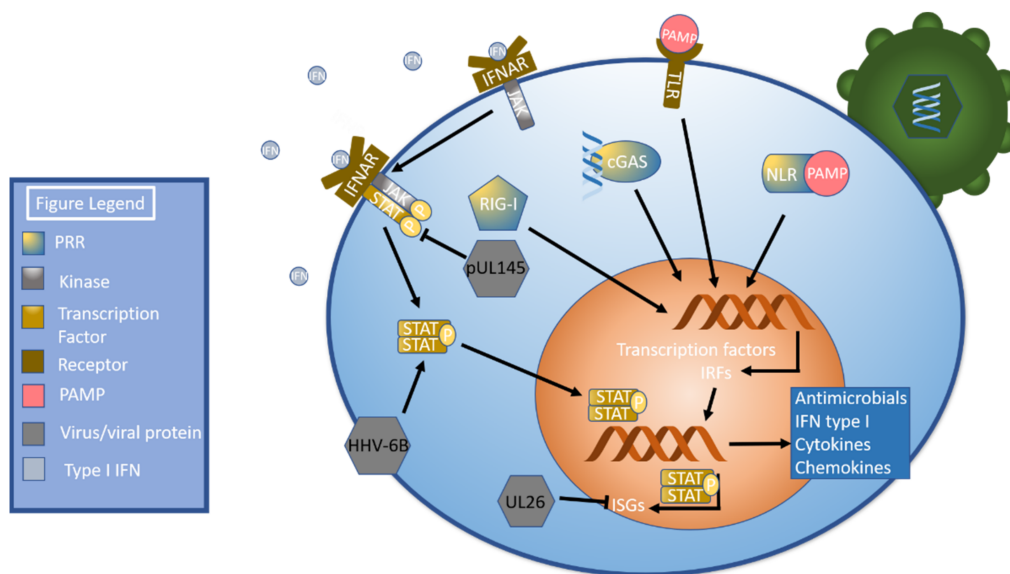


Figure 1. Pathogen Sensing, Interferon (IFN), and the JAK-STAT Pathway. Pathogen invasion triggers several pattern recognition receptors (PRRs), including NOD-like receptors (NLRs), RIG-I-like receptors (RIG-I), cGAS, and TLRs (toll-like receptors). These PRRs activate signal transduction pathways that culminate in the production of transcription factors and interferon regulatory factors, which in turn leads to the production of antimicrobial peptides, proinflammatory cytokines, chemokines, and type I IFN. Type I IFN then binds to the interferon α receptor (IFNAR), which phosphorylates JAK. Phosphorylated JAK recruits STAT, which is then phosphorylated, dimerizes, and translocates to the nucleus. Once in the nucleus, STAT upregulates the transcription of ISGs. The HCMV protein pUL145 inhibits STAT, while HHV-6B has been shown to upregulate STAT. The HCMV protein UL26 inhibits ISGs and ISGylation.

3. Immune Cell Responses

The immune system has numerous effector cells. Key cell types include but are not limited to natural killer cells, T cells, and dendritic cells [46]. These cells have a variety of immune functions ranging from cytokine secretion to antigen presentation and cytotoxic effect [47][48]. Betaherpesviruses must successfully contend with each of them in order to successfully establish and maintain an infection.

4. Autophagy and Apoptosis

Apoptosis can be triggered by both intra- and extracellular signals. Cell death mediated by external signaling, termed extrinsic apoptosis, is characterized by the binding of several different molecules including FAS/CD95L and TNF related

apoptosis inducing ligand (TRAIL). These bind to the receptors CD95 and TRAIL receptors 1 and 2, respectively [49]. When stimulated, these molecules recruit FADD, which recruits procaspases to create a death-inducing signaling complex (DISC). Once created, DISC facilitates autoproteolytic cleavage and activation of caspases. Activated caspases cleave molecules such as lamin A, poly (ADP-ribose) polymerase (PARP), and inhibitor of caspase-activated DNase (ICAD) to stimulate apoptosis [50]. The intrinsic pathway is triggered following exposure to stressors such as DNA damage or nutrient deprivation. These stressors cause the proteins BAX and BAK to dissociate from BCL2 and damage the mitochondrial membrane, leading to perforation of the mitochondrial membrane and subsequent release of mitochondrial contents [51]. **Figure 2** details the apoptotic pathways.

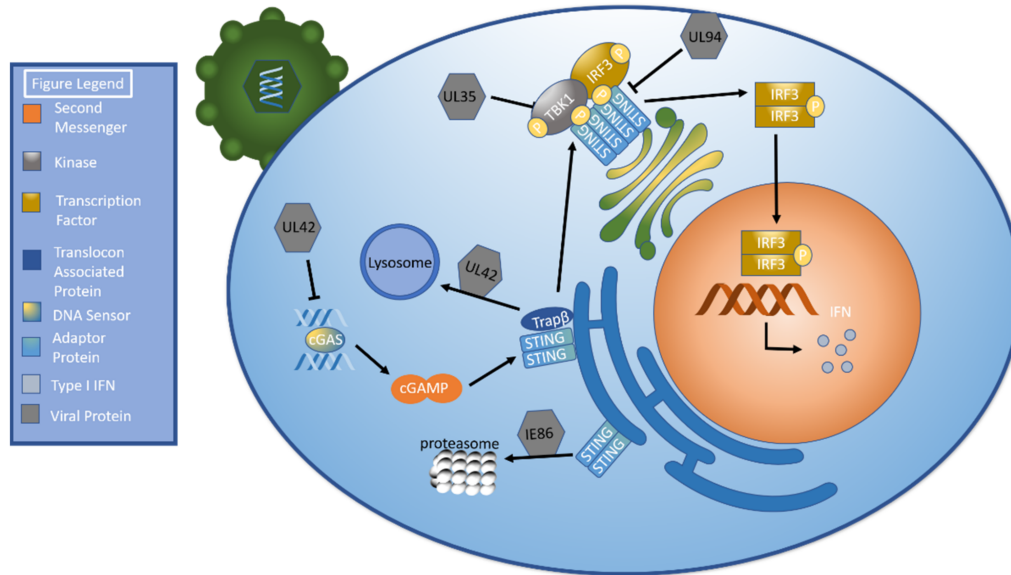


Figure 2. AKT and Apoptosis. There are two apoptotic pathways: extrinsic and intrinsic. The extrinsic pathway begins when ligands such as FAS ligand (FASL) or TRAIL bind their corresponding cellular receptors. The adaptor protein FADD is recruited to the receptor. FADD recruits procaspases to create the death-inducing signaling complex (DISC). Once DISC has formed, it facilitates autoproteolytic cleavage and caspase activation. Activated caspases cleave target molecules and stimulate apoptosis. The intrinsic pathway is initiated when the cell is exposed to stressors. The pro-apoptotic proteins BAK and BAX dissociate from BCL2 and disrupt the mitochondrial membrane, resulting in release of mitochondrial contents and apoptosis. The AKT pathway, which can be initiated through either EGFR or integrin stimulation, begins with receptor-mediated activation of PI3K. PI3K activation results in the formation of PIP₃, which activates PDK1, which in turn activates AKT. AKT activates mTOR, which promotes cell survival. The human cytomegalovirus (HCMV) protein pUL7 and HCMV miRNAs inhibit FOXO. HCMV gB interacts with the EGFR while gH interacts with integrins to stimulate AKT.

Viruses are obligate intracellular parasites, meaning they require living cells for their survival. Thus, it stands to reason that viruses have strategies to subvert the apoptotic pathway. In fact, Arcangeletti et al., determined that both HCMV and HHV-6A significantly altered the expression levels of numerous apoptosis-associated genes, with HCMV having a greater influence on apoptotic genes than HHV-6A [52].

Monocytes are essential to HCMV persistence and dissemination [53]. However, monocytes have a relatively short lifespan of only a few days [54]. HCMV has been shown to induce monocyte differentiation into longer-lived macrophages that support HCMV replication [53]. Recent research has shed light on the effect of modulating the AKT signaling pathway on monocyte survival [55]. In brief, PI3K activation leads to the formation of PIP₃, which activates 3-phosphoinositide-dependent kinase 1 (PDK1). PDK1 phosphorylates and activates AKT. AKT stimulates mTOR signaling, which leads to activation of anabolic pathways as shown in **Figure 2** [56]. Of note, both EGFR [57] and integrins [58] have been shown to stimulate AKT signaling.

Cojohari et al., first described how HCMV induces AKT within 15 min of infection to allow monocyte survival beyond 48 h, which is accomplished by altering expression of the AKT modulating factors PI3K, PTEN, and SHIP1. Moreover, HCMV activation of the AKT pathway was stronger than that induced by macrophage colony stimulating factor (M-CSF) under physiologic conditions [59]. It was later shown by Peppenelli et al., that the viral glycoproteins gB and gH interacted with epidermal growth factor receptor (EGFR) and $\alpha\beta 3$ integrin, respectively, to stimulate the AKT pathway. These interactions increased myeloid leukemia sequence 1 (Mcl-1) and heat shock protein 27 (HSP27) to deter apoptosis within monocytes [60]. Mahmud et al. further expanded on this research, determining that gB may have a more significant effect on AKT

signaling given that monocytes treated with gB inhibitors alone had lower survivability than those treated with gH alone. While soluble gB and gH could stimulate monocyte survival, monocytes did not survive as well as when infected by HCMV. This may indicate that co-stimulation by gB and gH is necessary to fully potentiate AKT stimulation. Additionally, they showed that gB binds EGFR and that gH binds integrin $\beta 1$ but not $\beta 3$ in monocytes. This finding contrasts with the above findings of Peppenelli et al., who found that gH binds $\alpha \beta 3$ integrin. One potential explanation for this discrepancy is that Peppenelli studied fibroblasts while Mahmoud studied monocytes. Interestingly, treatment with either an integrin or EGFR inhibitor blocked signaling through both integrin $\beta 1$ and EGFR, implying some degree of signal crosstalk. Elimination of this crosstalk blocked HCMV-mediated AKT signaling. EGFR inhibition resulted in abrogated upregulation of MCL-1 and HSP27, which are anti-apoptotic proteins generated by the AKT signaling cascade. The simultaneous activation of EGFR and integrin $\beta 1$ results in noncanonical activation of AKT signaling. Lastly, inhibition of SHIP was shown to downregulate the pro-survival proteins Mcl-1 and HSP27 [61]. This contrasts with its normal inhibitory function [60]; however, aberrant SHIP function has been previously demonstrated in cancer cells [62].

FOXO is a pro-apoptotic protein family targeted by AKT to promote cell survival [63] and represents another point at which HCMV can regulate apoptosis. HCMV protein pUL7 stimulates the phosphorylation, translocation to the cytoplasm, and inactivation of FOXO3a through the MAPK pathway. Telomerized human fibroblast cells treated with pUL7 had significantly lower levels of FOXO3a downstream targets BCL2L11 (BIM) and CDKN1B (p27). mRNA expression and protein levels of FOXO3a were unchanged, indicating that regulation occurred via phosphorylation rather than inhibition or degradation, but pUL7 did decrease mRNA levels of the pro-apoptotic protein BCL2L11 [64].

miRNAs represent another means of FOXO3a targeting and subsequent anti-apoptotic regulation. Transfection of HEK293T cells with HCMV miR-US5-1 and miR-UL112-3p was found to target the 3' UTR of FOXO3a, which caused FOXO3a transcript and protein levels to decrease [64].

Autophagy is essential to cellular function. Not only does this process dispose of worn cellular components, but their breakdown is an important source of energy and materials to synthesize new components [65]. Autophagy is also integral to the normal immune response with functions including but not limited to antigen presentation and pathogen destruction [66].

Viruses are known to manipulate the autophagic process for their survival and benefit [66]. Romeo et al., noted autophagosomes, which are involved in the autophagic process, in both infected and nearby uninfected cells as well as an increase in lipidated LC3II, a marker of autophagic flux, in HSB-2 cells after infection with HHV-6A. By comparison, HHV-6B was found to block autophagy in infected Molt-3 cells. Autophagy blockage was confirmed by the relative paucity of autophagolysosomes in both infected and nearby uninfected cells as well as the accumulation of p62, a protein that is normally degraded by autophagy. The two were found to differentially regulate the unfolded protein response [67], which is associated with endoplasmic reticulum stress. Endoplasmic reticulum stress triggers autophagy, which can help restore the endoplasmic reticulum to its baseline state. If the stressor is too severe, apoptosis ensues [68]. While HHV-6A increased expression of immunoglobulin heavy chain binding protein (BiP), an anti-apoptotic protein, HHV-6B upregulated C/EBP homologous protein (CHOP), a pro-apoptotic protein. This was accomplished by modulating expression levels of the upstream factors inositol requiring enzyme 1 alpha (IRE1 α), activating transcription factor 4 (ATF4), and activating transcription factor 6 (ATF6) [67].

Autophagy dysregulation has also been shown to play a role in inhibiting dendritic cell formation and monocyte survival in HHV-6B infection. HHV-6B extracted from patients with exanthem subitum was able to inhibit monocyte differentiation into dendritic cells and decrease overall monocyte survival. The addition of sodium 4-phenylbutyrate, which reduces endoplasmic reticulum stress by preventing protein aggregation and acting as chaperone to stabilize folded proteins, attenuated the HHV-6B-mediated inhibition of monocyte differentiation and improved monocyte survival [69]. A general summary of betaherpesvirus immunoevasive strategies can be found in the table below (**Table 1**). A graphical summary of pathways discussed above with a listing of key immunoevasive strategies can also be found below (**Figure 3**).

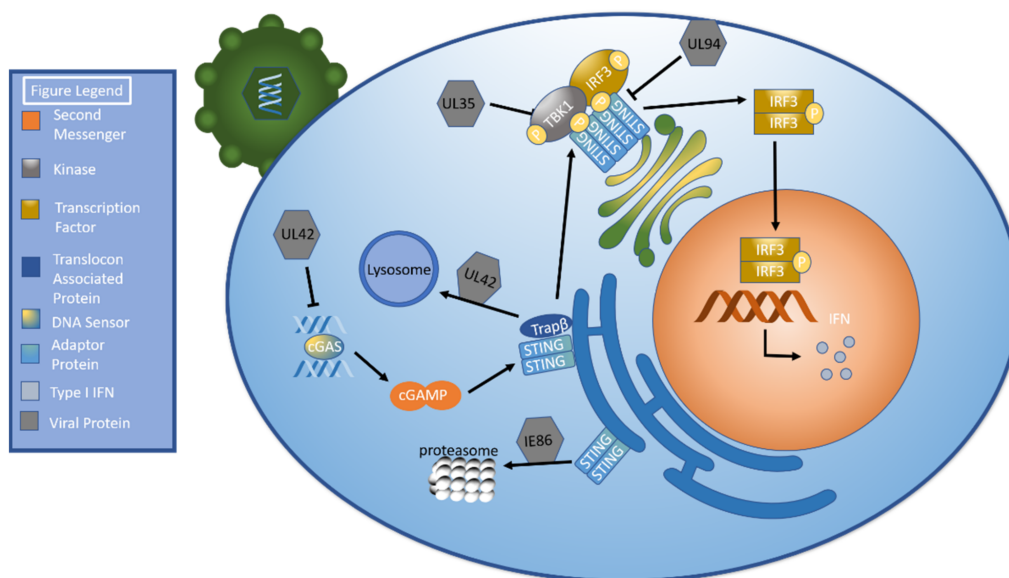


Figure 3. Summary of Key Pathways and Associated Immunoevasive Methods. The immune response to betaherpesviruses begins with the detection of pathogen-associated molecular patterns (PAMPs) by pattern recognition receptors (PRRs), including cGAS and toll-like receptors (TLRs). The cGAS/cGAMP/STING signaling axis results in the production of interferon (IFN) while TLRs can generate both IFN and other defensive compounds. IFN results in STAT activation, which stimulates production of interferon-stimulated genes (ISGs). Betaherpesvirus manipulation of cell survival is an integral element in their success as pathogens. Apoptosis may be stimulated by either intrinsic (BAK/BAX mediated mitochondrial perforation) or extrinsic (FAS ligand/CD95 binding, TRAIL/TRAILR binding) signals. The PI3K/AKT/mTOR signaling pathway represents a major pro-survival cascade. Immunoevasive methods are listed below.

Table 1. Summary of Betaherpesvirus Immunoevasive strategies.

Virus	Immunoevasive Strategy	Associated References
HCMV	UL35: Decrease TBK/IRF3 phosphorylation	[70]
	UL42: Inhibit cGAS' ability to bind HCMV DNA	[71]
	Inhibit cGAS oligomerization	
	Facilitate TRAPβ degradation (lysosome)	
	UL94: Inhibit STING dimerization	[72]
	Prevent STING from recruiting TBK1	
	IE86: Facilitate STING degradation via proteasome	[73][74]
	US7: Facilitate TLR3 and TLR4 proteasomal degradation	[75]
	US8: Inhibit TLR3 and TLR4 by destabilization	[75]
	IE1: Suppress CpG motifs to avoid ZAP detection	[76]
pUL145	UL26: Inhibit ISG15/ISGylation	[77]
	pUL145: Downregulate STAT	[78]

Virus	Immuno-evasive Strategy	Associated References
	UL147a: Target MICA for lysosomal degradation	[79]
	UL148a: Target MICA for lysosomal degradation	[80]
	gB: Interact with epidermal growth factor receptor to stimulate the AKT pathway	[59][60][61]
	gH: Interact with $\alpha\beta 3$ integrin to stimulate the AKT pathway	[59][60][61]
	pUL7: Stimulate phosphorylation, translocation to cytoplasm, and inactivation of FOXO3a	[64]
	miR-US5-1 and miR-UL112-3p: FOXO3a inhibition	[64]
	Downregulate CIITA	[81]
	Downregulate MHC class I expression	[82]
	Alter expression of apoptotic genes	[52]
	HHV-6A	[83]
		[83]
		[83]
		[24]
		[84]
		[85]
		[86]
		[52]
		[67]
		[67]
	HHV-6B	[83]
		[83]

Virus	Immuno-evasive Strategy	Associated References
	Inhibit TLR signaling	[87]
	Inhibit autophagy	[67][69]
	Upregulate CHOP via modulating expression of IRE1 α , ATF4, and ATF6	[67]
	Inhibit monocyte survival and differentiation into dendritic cells	[69]
	Increase ROS to upregulate PD-L1, influence STAT phosphorylation	[88]
	Downregulate NKG2D ligands	[89]
	Infect NK cells and alter miRNA and transcription factor expression	[24]
HHV-7	U21: Targets MCH class I complex for lysosomal degradation, target UBPL1 for lysosomal degradation, decrease MICA and MICB concentration, post-transcriptional modification of MICA and MICB	[90][91][92][93]
	Slight decrease in cGAS expression	[83]

5. Latency and Reactivation

Upon infection, betaherpesviruses establish lifelong latency in the human host. The virus can subsequently be reactivated under certain conditions and enter a lytic phase. Latency and reactivation play an important role in betaherpesviruses' evasion of the human immune system, and there are many facets to the control of these processes [4].

6. Vaccination Efforts

Betaherpesviruses express numerous glycoproteins that serve as essential components of their fusion machinery [94][95][96]. Recently, these glycoproteins have been assessed as potential targets in vaccination efforts.

Of the betaherpesviruses, efforts to create a vaccine against human cytomegalovirus have been the most robust. As was mentioned previously, HCMV is associated with congenital infection and a relatively high risk of associated birth defects, including but not limited to cognitive impairment, cerebral palsy, bilateral hearing loss, and death [21][97]. HCMV infection also causes significant complications in transplant patients, such as transplant-associated vasculopathy, hepatitis, retinitis, infection, and graft rejection [98][99].

The HCMV glycoprotein B (gB) has been examined as a potential target for vaccination efforts. Nelson et al., recently examined a lipid nanoparticle vaccine (LNPV) containing a nucleoside modified mRNA transcript encoding full length gB protein in comparison to vaccines containing gB ectodomain (gB protein with antigenic domain 3 removed) with a squalene adjuvant and full length gB with an MF59-like squalene-based adjuvant. Three doses of each vaccine were delivered to New Zealand White rabbits four weeks apart. While the three vaccines were equivalent in their maximal immunogenicity and elicited IgG affinity for gB, the LNPV demonstrated enhanced response longevity relative to the other two. In addition, the LNPV was able to generate antibodies with a broader spectrum of gB peptide binding abilities [100].

A second effort at targeting gB for vaccine development found that HCMV-neutralizing antibodies primarily targeted antigenic domain 5 [101]. Using this information, a nanoparticle vaccine was created that increased titers of neutralizing antibodies by 100-fold in comparison to gB extracellular domain vaccine [101], presumably by increasing the number of copies of antigen presented and by presenting the antigens in a well-ordered manner that may more closely resemble the pathogen surface [101][102].

While gB is frequently targeted for HCMV vaccine generation, other promising targets have emerged. The gH/gL/UL128/UL130/UL131 pentamer, a glycoprotein complex required for entry into epithelial and endothelial cells but not fibroblasts [95], is one such target. A recent series of experiments by Chiuppesi et al., used a modified vaccinia virus ankara (MVA) vector to deliver an antigen including the pentamer complex, the strong T cell stimulator [103] phosphoprotein 65, and gB. The antigen stimulated a potent immune response involving both humoral and cell-mediated immunity [104]. A separate study using a guinea pig/guinea pig cytomegalovirus model demonstrated that a disabled infectious single-cycle viral vaccine expressing the pentamer complex was 97% effective in preventing congenital guinea pig cytomegalovirus infection [105]. Notably, the guinea pig is an accepted animal model for human congenital cytomegalovirus infection [106][107]. A more comprehensive review of cytomegalovirus vaccination principles and recent advances in HCMV vaccine technology can be found elsewhere [108][109][110].

While it has not received the same degree of attention as HCMV, there have been some recent efforts to develop a vaccine for HHV-6B. HHV-6 expresses several envelope glycoproteins, including glycoproteins H, L, Q1, and Q2, or gH, gL, gQ1, and gQ2, respectively [111][112]. These glycoproteins complex to form a gH/gL/gQ1/gQ2 tetramer that facilitates viral entry by binding CD46 during HHV-6A infection and CD134 during HHV-6B infection [113][114]. A recent study by Wang et al., assessed the efficacy of the gH/gL/gQ1/gQ2 tetramer in conjunction with the common vaccine adjuvants aluminum hydroxide gel adjuvant (alum) and D35, a CpG oligodeoxynucleotide adjuvant. N-[1-(2,3-Dioleoyloxy)propyl]-N,N,N-trimethylammonium methylsulfate was mixed with the D35. A series of three injections given to hSIRPα-DKO mice stimulated the development of both cell-mediated and humoral immunity as measured by cytokine production (specifically IFN-γ and IL-13) and antibody production, respectively [115]. A PubMed search did not reveal any research into developing a vaccine against HHV-7.

References

1. Cohen, J.I. Herpesvirus latency. *J. Clin. Invest.* 2020, 130, 3361–3369.
2. Ablashi, D.V.; Berneman, Z.N.; Kramarsky, B.; Asano, Y.; Choudhury, S.; Pearson, G.R. Human herpesvirus-7 (HHV-7). *Vivo* 1994, 8, 549–554.
3. Campadelli-Fiume, G.; Mirandola, P.; Menotti, L. Human herpesvirus 6: An emerging pathogen. *Emerg. Infect. Dis.* 1999, 5, 353–366.
4. Pellett, P.E.; Roizman, B. Herpesviridae. In *Fields Virology*, 6th ed.; Knipe, D.M., Howley, P.M., Eds.; Lippincott Williams & Wilkins: Philadelphia, PA, USA, 2013; pp. 1802–1822.
5. Close, W.L.; Anderson, A.N.; Pellett, P.E. Betaherpesvirus Virion Assembly and Egress. *Adv. Exp. Med. Biol.* 2018, 1045, 167–207.
6. Tomtishen, J.P., 3rd. Human cytomegalovirus tegument proteins (pp65, pp71, pp150, pp28). *Virol. J.* 2012, 9, 22.
7. Full, F.; Ensser, A. Early Nuclear Events after Herpesviral Infection. *J. Clin. Med.* 2019, 8, 1408.
8. Guo, H.; Shen, S.; Wang, L.; Deng, H. Role of tegument proteins in herpesvirus assembly and egress. *Protein Cell* 2010, 1, 987–998.
9. Nishimura, M.; Novita, B.D.; Kato, T.; Handayani Tjan, L.; Wang, B.; Wakata, A.; Lystia Poetranto, A.; Kawabata, A.; Tang, H.; Aoshi, T.; et al. Structural basis for the interaction of human herpesvirus 6B tetrameric glycoprotein complex with the cellular receptor, human CD134. *PLoS Pathog.* 2020, 16, e1008648.
10. Connolly, S.A.; Jardetzky, T.S.; Longnecker, R. The structural basis of herpesvirus entry. *Nat. Rev. Microbiol.* 2021, 19, 110–121.
11. Gugliesi, F.; Coscia, A.; Griffante, G.; Galitska, G.; Pasquero, S.; Albano, C.; Biolatti, M. Where do we Stand after Decades of Studying Human Cytomegalovirus? *Microorganisms* 2020, 8, 685.
12. Nguyen, C.C.; Kamil, J.P. Pathogen at the Gates: Human Cytomegalovirus Entry and Cell Tropism. *Viruses* 2018, 10, 704.
13. Gerna, G.; Kabanova, A.; Lilleri, D. Human Cytomegalovirus Cell Tropism and Host Cell Receptors. *Vaccines* 2019, 7, 70.
14. Agut, H.; Bonnafous, P.; Gautheret-Dejean, A. Laboratory and clinical aspects of human herpesvirus 6 infections. *Clin. Microbiol. Rev.* 2015, 28, 313–335.
15. Mori, Y. Recent topics related to human herpesvirus 6 cell tropism. *Cell Microbiol.* 2009, 11, 1001–1006.
16. Dockrell, D.H. Human herpesvirus 6: Molecular biology and clinical features. *J. Med. Microbiol.* 2003, 52, 5–18.

17. Agut, H.; Bonnafous, P.; Gautheret-Dejean, A. Update on infections with human herpesviruses 6A, 6B, and 7. *Med. Mal. Infect.* 2017, 47, 83–91.
18. Scrivano, L.; Sinzger, C.; Nitschko, H.; Koszinowski, U.H.; Adler, B. HCMV spread and cell tropism are determined by distinct virus populations. *PLoS Pathog.* 2011, 7, e1001256.
19. Landolfo, S.; Gariglio, M.; Gribaudo, G.; Lembo, D. The human cytomegalovirus. *Pharmacol. Ther.* 2003, 98, 269–297.
20. Dutt, K.; Ezeonu, I. Human retinal and brain cell lines: A model of HCMV retinitis and encephalitis. *DNA Cell Biol.* 2006, 25, 581–596.
21. Minsart, A.F.; Rypens, F.; Smiljkovic, M.; Kakkar, F.; Renaud, C.; Lamarre, V.; Boucher, M.; Boucoiran, I. Prenatal findings, neonatal symptoms and neurodevelopmental outcome of congenital cytomegalovirus infection in a university hospital in Montreal, Quebec. *J. Perinat. Med.* 2020, 48, 234–241.
22. Cohen, J.I.; Corey, G.R. Cytomegalovirus infection in the normal host. *Medicine* 1985, 64, 100–114.
23. Tang, H.; Mori, Y. Glycoproteins of HHV-6A and HHV-6B. *Adv. Exp. Med. Biol.* 2018, 1045, 145–165.
24. Rizzo, R.; Soffritti, I.; D'Accolti, M.; Bortolotti, D.; Di Luca, D.; Caselli, E. HHV-6A/6B Infection of NK Cells Modulates the Expression of miRNAs and Transcription Factors Potentially Associated to Impaired NK Activity. *Front. Microbiol.* 2017, 8, 2143.
25. Ablashi, D.; Agut, H.; Alvarez-Lafuente, R.; Clark, D.A.; Dewhurst, S.; DiLuca, D.; Flamand, L.; Frenkel, N.; Gallo, R.; Gompels, U.A.; et al. Classification of HHV-6A and HHV-6B as distinct viruses. *Arch. Virol.* 2014, 159, 863–870.
26. Marci, R.; Gentili, V.; Bortolotti, D.; Lo Monte, G.; Caselli, E.; Bolzani, S.; Rotola, A.; Di Luca, D.; Rizzo, R. Presence of HHV-6A in Endometrial Epithelial Cells from Women with Primary Unexplained Infertility. *PLoS ONE* 2016, 11, e0158304.
27. Hansen, A.S.; Bundgaard, B.B.; Biltoft, M.; Rossen, L.S.; Hollsberg, P. Divergent tropism of HHV-6AGS and HHV-6BPL1 in T cells expressing different CD46 isoform patterns. *Virology* 2017, 502, 160–170.
28. Ongradi, J.; Ablashi, D.V.; Yoshikawa, T.; Stercz, B.; Ogata, M. Roseolovirus-associated encephalitis in immunocompetent and immunocompromised individuals. *J. Neurovirol.* 2017, 23, 1–19.
29. Hill, J.A. Human herpesvirus 6 in transplant recipients: An update on diagnostic and treatment strategies. *Curr. Opin. Infect. Dis.* 2019, 32, 584–590.
30. Leibovitch, E.C.; Jacobson, S. Evidence linking HHV-6 with multiple sclerosis: An update. *Curr. Opin. Virol.* 2014, 9, 127–133.
31. Soldan, S.S.; Berti, R.; Salem, N.; Secchiero, P.; Flamand, L.; Calabresi, P.A.; Brennan, M.B.; Maloni, H.W.; McFarland, H.F.; Lin, H.C.; et al. Association of human herpes virus 6 (HHV-6) with multiple sclerosis: Increased IgM response to HHV-6 early antigen and detection of serum HHV-6 DNA. *Nat. Med.* 1997, 3, 1394–1397.
32. Itzhaki, R.F.; Golde, T.E.; Heneka, M.T.; Readhead, B. Do infections have a role in the pathogenesis of Alzheimer disease? *Nat. Rev. Neurol.* 2020, 16, 193–197.
33. Tarlinton, R.E.; Martynova, E.; Rizvanov, A.A.; Khaiboullina, S.; Verma, S. Role of Viruses in the Pathogenesis of Multiple Sclerosis. *Viruses* 2020, 12, 643.
34. Friedman, J.E.; Lyons, M.J.; Cu, G.; Ablashi, D.V.; Whitman, J.E.; Edgar, M.; Koskiniemi, M.; Vaheeri, A.; Zabriskie, J.B. The association of the human herpesvirus-6 and MS. *Mult. Scler.* 1999, 5, 355–362.
35. Zabalza, A.; Vera, A.; Alari-Pahissa, E.; Munteis, E.; Moreira, A.; Yelamos, J.; Llop, M.; Lopez-Botet, M.; Martinez-Rodriguez, J.E. Impact of cytomegalovirus infection on B cell differentiation and cytokine production in multiple sclerosis. *J. Neuroinflammation* 2020, 17, 161.
36. Nora-Krukke, Z.; Chapenko, S.; Logina, I.; Millers, A.; Platkajis, A.; Murovska, M. Human herpesvirus 6 and 7 reactivation and disease activity in multiple sclerosis. *Medicina* 2011, 47, 527–531.
37. Sepulveda, N.; Carneiro, J.; Lacerda, E.; Nacul, L. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome as a Hyper-Regulated Immune System Driven by an Interplay Between Regulatory T Cells and Chronic Human Herpesvirus Infections. *Front. Immunol.* 2019, 10, 2684.
38. Chapenko, S.; Krumina, A.; Kozireva, S.; Nora, Z.; Sultanova, A.; Viksna, L.; Murovska, M. Activation of human herpesviruses 6 and 7 in patients with chronic fatigue syndrome. *J. Clin. Virol.* 2006, 37 (Suppl. 1), S47–S51.
39. Simpson, S., Jr.; Taylor, B.; Burrows, J.; Burrows, S.; Dwyer, D.E.; Taylor, J.; Ponsonby, A.L.; Blizzard, L.; Dwyer, T.; Pittas, F.; et al. EBV & HHV6 reactivation is infrequent and not associated with MS clinical course. *Acta Neurol. Scand.* 2014, 130, 328–337.
40. Soto, N.E.; Straus, S.E. Chronic Fatigue Syndrome and Herpesviruses: The Fading Evidence. *Herpes* 2000, 7, 46–50.

41. Buchwald, D.; Ashley, R.L.; Pearlman, T.; Kith, P.; Komaroff, A.L. Viral serologies in patients with chronic fatigue and chronic fatigue syndrome. *J. Med. Virol.* 1996, 50, 25–30.
42. Kumar, S.; Ingle, H.; Prasad, D.V.; Kumar, H. Recognition of bacterial infection by innate immune sensors. *Crit. Rev. Microbiol.* 2013, 39, 229–246.
43. Paludan, S.R.; Pradeu, T.; Masters, S.L.; Mogensen, T.H. Constitutive immune mechanisms: Mediators of host defence and immune regulation. *Nat. Rev. Immunol.* 2021, 21, 137–150.
44. Ivashkiv, L.B.; Donlin, L.T. Regulation of type I interferon responses. *Nat. Rev. Immunol.* 2014, 14, 36–49.
45. Murray, P.J. The JAK-STAT signaling pathway: Input and output integration. *J. Immunol.* 2007, 178, 2623–2629.
46. Iwasaki, A.; Medzhitov, R. Control of adaptive immunity by the innate immune system. *Nat. Immunol.* 2015, 16, 343–353.
47. Thery, C.; Amigorena, S. The cell biology of antigen presentation in dendritic cells. *Curr. Opin. Immunol.* 2001, 13, 45–51.
48. Hammer, Q.; Romagnani, C. About Training and Memory: NK-Cell Adaptation to Viral Infections. *Adv. Immunol.* 2017, 133, 171–207.
49. Galluzzi, L.; Vitale, I.; Abrams, J.M.; Alnemri, E.S.; Baehrecke, E.H.; Blagosklonny, M.V.; Dawson, T.M.; Dawson, V.L.; El-Deiry, W.S.; Fulda, S.; et al. Molecular definitions of cell death subroutines: Recommendations of the Nomenclature Committee on Cell Death 2012. *Cell Death Differ.* 2012, 19, 107–120.
50. Lee, E.W.; Seo, J.; Jeong, M.; Lee, S.; Song, J. The roles of FADD in extrinsic apoptosis and necroptosis. *BMB Rep.* 2012, 45, 496–508.
51. Orzalli, M.H.; Kagan, J.C. Apoptosis and Necroptosis as Host Defense Strategies to Prevent Viral Infection. *Trends Cell Biol.* 2017, 27, 800–809.
52. Arcangeletti, M.C.; D'Accolti, M.; Maccari, C.; Soffritti, I.; Conto, F.; Chezzi, C.; Calderaro, A.; Ferri, C.; Caselli, E. Impact of Human Cytomegalovirus and Human Herpesvirus 6 Infection on the Expression of Factors Associated with Cell Fibrosis and Apoptosis: Clues for Implication in Systemic Sclerosis Development. *Int. J. Mol. Sci.* 2020, 21, 6397.
53. Smith, M.S.; Bentz, G.L.; Alexander, J.S.; Yurochko, A.D. Human cytomegalovirus induces monocyte differentiation and migration as a strategy for dissemination and persistence. *J. Virol.* 2004, 78, 4444–4453.
54. Van Furth, R.; Cohn, Z.A. The origin and kinetics of mononuclear phagocytes. *J. Exp. Med.* 1968, 128, 415–435.
55. Goyal, A.; Wang, Y.; Graham, M.M.; Doseff, A.I.; Bhatt, N.Y.; Marsh, C.B. Monocyte survival factors induce Akt activation and suppress caspase-3. *Am. J. Respir Cell Mol. Biol.* 2002, 26, 224–230.
56. Dibble, C.C.; Cantley, L.C. Regulation of mTORC1 by PI3K signaling. *Trends Cell Biol.* 2015, 25, 545–555.
57. Li, X.; Wu, C.; Chen, N.; Gu, H.; Yen, A.; Cao, L.; Wang, E.; Wang, L. PI3K/Akt/mTOR signaling pathway and targeted therapy for glioblastoma. *Oncotarget* 2016, 7, 33440–33450.
58. Wan, H.; Xie, T.; Xu, Q.; Hu, X.; Xing, S.; Yang, H.; Gao, Y.; He, Z. Thy-1 depletion and integrin beta3 upregulation-mediated PI3K-Akt-mTOR pathway activation inhibits lung fibroblast autophagy in lipopolysaccharide-induced pulmonary fibrosis. *Lab. Invest.* 2019, 99, 1636–1649.
59. Cojohari, O.; Peppenelli, M.A.; Chan, G.C. Human Cytomegalovirus Induces an Atypical Activation of Akt To Stimulate the Survival of Short-Lived Monocytes. *J. Virol.* 2016, 90, 6443–6452.
60. Peppenelli, M.A.; Arend, K.C.; Cojohari, O.; Moorman, N.J.; Chan, G.C. Human Cytomegalovirus Stimulates the Synthesis of Select Akt-Dependent Antiapoptotic Proteins during Viral Entry To Promote Survival of Infected Monocytes. *J. Virol.* 2016, 90, 3138–3147.
61. Mahmud, J.; Miller, M.J.; Altman, A.M.; Chan, G.C. Human Cytomegalovirus Glycoprotein-Initiated Signaling Mediates the Aberrant Activation of Akt. *J. Virol.* 2020, 94.
62. Kerr, W.G. Inhibitor and activator: Dual functions for SHIP in immunity and cancer. *Ann. N. Y. Acad. Sci.* 2011, 1217, 1–17.
63. Zhang, X.; Tang, N.; Hadden, T.J.; Rishi, A.K. Akt, FoxO and regulation of apoptosis. *Biochim. Biophys. Acta* 2011, 1813, 1978–1986.
64. Hancock, M.H.; Crawford, L.B.; Perez, W.; Struthers, H.M.; Mitchell, J.; Caposio, P. Human Cytomegalovirus UL7, miR-US5-1, and miR-UL112-3p Inactivation of FOXO3a Protects CD34(+) Hematopoietic Progenitor Cells from Apoptosis. *mSphere* 2021, 6.
65. Mizushima, N.; Komatsu, M. Autophagy: Renovation of cells and tissues. *Cell* 2011, 147, 728–741.

66. Shibutani, S.T.; Saitoh, T.; Nowag, H.; Munz, C.; Yoshimori, T. Autophagy and autophagy-related proteins in the immune system. *Nat. Immunol.* 2015, 16, 1014–1024.
67. Romeo, M.A.; Masuelli, L.; Gaeta, A.; Nazzari, C.; Granato, M.; Gilardini Montani, M.S.; Faggioni, A.; Cirone, M. Impact of HHV-6A and HHV-6B lytic infection on autophagy and endoplasmic reticulum stress. *J. Gen. Virol.* 2019, 100, 89–98.
68. Qi, Z.; Chen, L. Endoplasmic Reticulum Stress and Autophagy. *Adv. Exp. Med. Biol.* 2019, 1206, 167–177.
69. Romeo, M.A.; Gilardini Montani, M.S.; Falcinelli, L.; Gaeta, A.; Nazzari, C.; Faggioni, A.; Cirone, M. HHV-6B reduces autophagy and induces ER stress in primary monocytes impairing their survival and differentiation into dendritic cells. *Virus Res.* 2019, 273, 197757.
70. Fabits, M.; Goncalves Magalhaes, V.; Chan, B.; Girault, V.; Elbasani, E.; Rossetti, E.; Saeland, E.; Messerle, M.; Pichlmair, A.; Lisnic, V.J.; et al. The Cytomegalovirus Tegument Protein UL35 Antagonizes Pattern Recognition Receptor-Mediated Type I IFN Transcription. *Microorganisms* 2020, 8, 790.
71. Fu, Y.Z.; Guo, Y.; Zou, H.M.; Su, S.; Wang, S.Y.; Yang, Q.; Luo, M.H.; Wang, Y.Y. Human cytomegalovirus protein UL42 antagonizes cGAS/MITA-mediated innate antiviral response. *PLoS Pathog.* 2019, 15, e1007691.
72. Zou, H.M.; Huang, Z.F.; Yang, Y.; Luo, W.W.; Wang, S.Y.; Luo, M.H.; Fu, Y.Z.; Wang, Y.Y. Human Cytomegalovirus Protein UL94 Targets MTA to Evade the Antiviral Immune Response. *J. Virol.* 2020, 94.
73. Kim, J.E.; Kim, Y.E.; Stinski, M.F.; Ahn, J.H.; Song, Y.J. Human Cytomegalovirus IE2 86 kDa Protein Induces STING Degradation and Inhibits cGAMP-Mediated IFN-beta Induction. *Front. Microbiol.* 2017, 8, 1854.
74. Lee, J.K.; Kim, J.E.; Park, B.J.; Song, Y.J. Human cytomegalovirus IE86 protein aa 136-289 mediates STING degradation and blocks the cGAS-STING pathway. *J. Microbiol.* 2020, 58, 54–60.
75. Park, A.; Ra, E.A.; Lee, T.A.; Choi, H.J.; Lee, E.; Kang, S.; Seo, J.Y.; Lee, S.; Park, B. HCMV-encoded US7 and US8 act as antagonists of innate immunity by distinctively targeting TLR-signaling pathways. *Nat. Commun.* 2019, 10, 4670.
76. Lin, Y.T.; Chiweshe, S.; McCormick, D.; Raper, A.; Wickenhagen, A.; DeFillipis, V.; Gaunt, E.; Simmonds, P.; Wilson, S.J.; Grey, F. Human cytomegalovirus evades ZAP detection by suppressing CpG dinucleotides in the major immediate early 1 gene. *PLoS Pathog.* 2020, 16, e1008844.
77. Goodwin, C.M.; Schafer, X.; Munger, J. UL26 Attenuates IKKbeta-Mediated Induction of Interferon-Stimulated Gene (ISG) Expression and Enhanced Protein ISGylation during Human Cytomegalovirus Infection. *J. Virol.* 2019, 93.
78. Le-Trilling, V.T.K.; Becker, T.; Nachshon, A.; Stern-Ginossar, N.; Scholer, L.; Voigt, S.; Hengel, H.; Trilling, M. The Human Cytomegalovirus pUL145 Isoforms Act as Viral DDB1-Cullin-Associated Factors to Instruct Host Protein Degradation to Impede Innate Immunity. *Cell Rep.* 2020, 30, 2248–2260 e2245.
79. Seidel, E.; Dassa, L.; Schuler, C.; Oiknine-Djian, E.; Wolf, D.G.; Le-Trilling, V.T.K.; Mandelboim, O. The human cytomegalovirus protein UL147A downregulates the most prevalent MICA allele: MICA*008, to evade NK cell-mediated killing. *PLoS Pathog.* 2021, 17, e1008807.
80. Dassa, L.; Seidel, E.; Oiknine-Djian, E.; Yamin, R.; Wolf, D.G.; Le-Trilling, V.T.K.; Mandelboim, O. The Human Cytomegalovirus Protein UL148A Downregulates the NK Cell-Activating Ligand MICA to Avoid NK Cell Attack. *J. Virol.* 2018, 92.
81. Sandhu, P.K.; Buchkovich, N.J. Human Cytomegalovirus Decreases Major Histocompatibility Complex Class II by Regulating Class II Transactivator Transcript Levels in a Myeloid Cell Line. *J. Virol.* 2020, 94.
82. Abdelaziz, M.O.; Ossmann, S.; Kaufmann, A.M.; Leitner, J.; Steinberger, P.; Willmsky, G.; Raftery, M.J.; Schonrich, G. Development of a Human Cytomegalovirus (HCMV)-Based Therapeutic Cancer Vaccine Uncovers a Previously Unsuspected Viral Block of MHC Class I Antigen Presentation. *Front. Immunol.* 2019, 10, 1776.
83. Bortolotti, D.; Gentili, V.; Caselli, E.; Siculo, M.; Soffritti, I.; D'Accolti, M.; Barao, I.; Rotola, A.; Di Luca, D.; Rizzo, R. DNA Sensors' Signaling in NK Cells During HHV-6A, HHV-6B and HHV-7 Infection. *Front. Microbiol.* 2020, 11, 226.
84. Caselli, E.; Campioni, D.; Cavazzini, F.; Gentili, V.; Bortolotti, D.; Cuneo, A.; Di Luca, D.; Rizzo, R. Acute human herpesvirus-6A infection of human mesothelial cells modulates HLA molecules. *Arch. Virol.* 2015, 160, 2141–2149.
85. Caselli, E.; D'Accolti, M.; Soffritti, I.; Zatelli, M.C.; Rossi, R.; Degli Uberti, E.; Di Luca, D. HHV-6A in vitro infection of thyrocytes and T cells alters the expression of miRNA associated to autoimmune thyroiditis. *Virol. J.* 2017, 14, 3.
86. Gustafsson, R. Human Herpesvirus 6A Induces Dendritic Cell Death and HMGB1 Release without Virus Replication. *Pathogens* 2021, 10, 57.
87. Murakami, Y.; Tanimoto, K.; Fujiwara, H.; An, J.; Suemori, K.; Ochi, T.; Hasegawa, H.; Yasukawa, M. Human herpesvirus 6 infection impairs Toll-like receptor signaling. *Virol. J.* 2010, 7, 91.
88. Romeo, M.A.; Gilardini Montani, M.S.; Benedetti, R.; Giambelli, L.; D'Aprile, R.; Gaeta, A.; Faggioni, A.; Cirone, M. The cross-talk between STAT1/STAT3 and ROS up-regulates PD-L1 and promotes the release of pro-inflammatory/immune

suppressive cytokines in primary monocytes infected by HHV-6B. *Virus Res.* 2021, 292, 198231.

89. Schmiedel, D.; Tai, J.; Levi-Schaffer, F.; Dovrat, S.; Mandelboim, O. Human Herpesvirus 6B Downregulates Expression of Activating Ligands during Lytic Infection To Escape Elimination by Natural Killer Cells. *J. Virol.* 2016, 90, 9608–9617.
90. May, N.A.; Glosson, N.L.; Hudson, A.W. Human herpesvirus 7 u21 downregulates classical and nonclassical class I major histocompatibility complex molecules from the cell surface. *J. Virol.* 2010, 84, 3738–3751.
91. Hudson, A.W.; Howley, P.M.; Ploegh, H.L. A human herpesvirus 7 glycoprotein, U21, diverts major histocompatibility complex class I molecules to lysosomes. *J. Virol.* 2001, 75, 12347–12358.
92. Schneider, C.L.; Hudson, A.W. The human herpesvirus-7 (HHV-7) U21 immunoevasin subverts NK-mediated cytotoxicity through modulation of MICA and MICB. *PLoS Pathog* 2011, 7, e1002362.
93. Dirck, A.T.; Whyte, M.L.; Hudson, A.W. HHV-7 U21 exploits Golgi quality control carriers to reroute class I MHC molecules to lysosomes. *Mol. Biol. Cell* 2020, 31, 196–208.
94. Wille, P.T.; Wisner, T.W.; Ryckman, B.; Johnson, D.C. Human cytomegalovirus (HCMV) glycoprotein gB promotes virus entry in trans acting as the viral fusion protein rather than as a receptor-binding protein. *mBio* 2013, 4, e00332-13.
95. Liu, J.; Jardetzky, T.S.; Chin, A.L.; Johnson, D.C.; Vanarsdall, A.L. The Human Cytomegalovirus Trimer and Pentamer Promote Sequential Steps in Entry into Epithelial and Endothelial Cells at Cell Surfaces and Endosomes. *J. Virol.* 2018, 92.
96. Tang, H.; Wang, J.; Mahmoud, N.F.; Mori, Y. Detailed study of the interaction between human herpesvirus 6B glycoprotein complex and its cellular receptor, human CD134. *J. Virol.* 2014, 88, 10875–10882.
97. Rawlinson, W.D.; Boppana, S.B.; Fowler, K.B.; Kimberlin, D.W.; Lazzarotto, T.; Alain, S.; Daly, K.; Doutre, S.; Gibson, L.; Giles, M.L.; et al. Congenital cytomegalovirus infection in pregnancy and the neonate: Consensus recommendations for prevention, diagnosis, and therapy. *Lancet Infect. Dis.* 2017, 17, e177–e188.
98. Legendre, C.; Pascual, M. Improving outcomes for solid-organ transplant recipients at risk from cytomegalovirus infection: Late-onset disease and indirect consequences. *Clin. Infect. Dis* 2008, 46, 732–740.
99. Griffiths, P.; Baraniak, I.; Reeves, M. The pathogenesis of human cytomegalovirus. *J. Pathol.* 2015, 235, 288–297.
100. Nelson, C.S.; Jenks, J.A.; Pardi, N.; Goodwin, M.; Roark, H.; Edwards, W.; McLellan, J.S.; Pollara, J.; Weissman, D.; Permar, S.R. Human Cytomegalovirus Glycoprotein B Nucleoside-Modified mRNA Vaccine Elicits Antibody Responses with Greater Durability and Breadth than MF59-Adjuvanted gB Protein Immunization. *J. Virol.* 2020, 94.
101. Perotti, M.; Marcandalli, J.; Demurtas, D.; Sallusto, F.; Perez, L. Rationally designed Human Cytomegalovirus gB nanoparticle vaccine with improved immunogenicity. *PLoS Pathog.* 2020, 16, e1009169.
102. Lopez-Sagaseta, J.; Malito, E.; Rappuoli, R.; Bottomley, M.J. Self-assembling protein nanoparticles in the design of vaccines. *Comput. Struct. Biotechnol. J.* 2016, 14, 58–68.
103. Kern, F.; Bunde, T.; Faulhaber, N.; Kiecker, F.; Khatamzas, E.; Rudawski, I.M.; Pruss, A.; Gratama, J.W.; Volkmer-Engert, R.; Ewert, R.; et al. Cytomegalovirus (CMV) phosphoprotein 65 makes a large contribution to shaping the T cell repertoire in CMV-exposed individuals. *J. Infect. Dis.* 2002, 185, 1709–1716.
104. Chiuppesi, F.; Nguyen, J.; Park, S.; Contreras, H.; Kha, M.; Meng, Z.; Kaltcheva, T.; Iniguez, A.; Martinez, J.; La Rosa, C.; et al. Multiantigenic Modified Vaccinia Virus Ankara Vaccine Vectors To Elicit Potent Humoral and Cellular Immune Responses against Human Cytomegalovirus in Mice. *J. Virol.* 2018, 92.
105. Choi, K.Y.; El-Hamdi, N.S.; McGregor, A. Inclusion of the Viral Pentamer Complex in a Vaccine Design Greatly Improves Protection against Congenital Cytomegalovirus in the Guinea Pig Model. *J. Virol.* 2019, 93.
106. Coleman, S.; Hornig, J.; Maddux, S.; Choi, K.Y.; McGregor, A. Viral Glycoprotein Complex Formation, Essential Function and Immunogenicity in the Guinea Pig Model for Cytomegalovirus. *PLoS ONE* 2015, 10, e0135567.
107. Roark, H.K.; Jenks, J.A.; Permar, S.R.; Schleiss, M.R. Animal Models of Congenital Cytomegalovirus Transmission: Implications for Vaccine Development. *J. Infect. Dis.* 2020, 221, S60–S73.
108. Plotkin, S.A.; Wang, D.; Oualim, A.; Diamond, D.J.; Kotton, C.N.; Mossman, S.; Carfi, A.; Anderson, D.; Dormitzer, P.R. The Status of Vaccine Development against the Human Cytomegalovirus. *J. Infect. Dis.* 2020, 221, S113–S122.
109. Inoue, N.; Abe, M.; Kobayashi, R.; Yamada, S. Vaccine Development for Cytomegalovirus. *Adv. Exp. Med. Biol.* 2018, 1045, 271–296.
110. Plotkin, S.A. Preventing Infection by Human Cytomegalovirus. *J. Infect. Dis.* 2020, 221, S123–S127.
111. Akkapaiboon, P.; Mori, Y.; Sadaoka, T.; Yonemoto, S.; Yamanishi, K. Intracellular processing of human herpesvirus 6 glycoproteins Q1 and Q2 into tetrameric complexes expressed on the viral envelope. *J. Virol.* 2004, 78, 7969–7983.

112. Tang, H.; Hayashi, M.; Maeki, T.; Yamanishi, K.; Mori, Y. Human herpesvirus 6 glycoprotein complex formation is required for folding and trafficking of the gH/gL/gQ1/gQ2 complex and its cellular receptor binding. *J. Virol.* 2011, 85, 11121–11130.
113. Tang, H.; Serada, S.; Kawabata, A.; Ota, M.; Hayashi, E.; Naka, T.; Yamanishi, K.; Mori, Y. CD134 is a cellular receptor specific for human herpesvirus-6B entry. *Proc. Natl. Acad. Sci. USA* 2013, 110, 9096–9099.
114. Mori, Y.; Seya, T.; Huang, H.L.; Akkapaiboon, P.; Dhepakson, P.; Yamanishi, K. Human herpesvirus 6 variant A but not variant B induces fusion from without in a variety of human cells through a human herpesvirus 6 entry receptor, CD46. *J. Virol.* 2002, 76, 6750–6761.
115. Wang, B.; Hara, K.; Kawabata, A.; Nishimura, M.; Wakata, A.; Tjan, L.H.; Poetranto, A.L.; Yamamoto, C.; Haseda, Y.; Aoshi, T.; et al. Tetrameric glycoprotein complex gH/gL/gQ1/gQ2 is a promising vaccine candidate for human herpesvirus 6B. *PLoS Pathog.* 2020, 16, e1008609.

Retrieved from <https://encyclopedia.pub/entry/history/show/36530>