Molecular mechanisms of human herpes viruses inferring with host immune surveillance

Simon Jasinski-Bergner ¹, Ofer Mandelboim ², Barbara Seliger¹

To cite: Jasinski-Bergner S, Mandelboim O, Seliger B. Molecular mechanisms of human herpes viruses inferring with host immune surveillance. *Journal for ImmunoTherapy of Cancer* 2020;**8**:e000841. doi:10.1136/jitc-2020-000841

Accepted 03 June 2020

ABSTRACT

Several human herpes viruses (HHVs) exert oncogenic potential leading to malignant transformation of infected cells and/or tissues. The molecular processes induced by viral-encoded molecules including microRNAs, peptides, and proteins contributing to immune evasion of the infected host cells are equal to the molecular processes of immune evasion mediated by tumor cells independently of viral infections. Such major immune evasion strategies include (1) the downregulation of proinflammatory cytokines/chemokines as well as the induction of anti-inflammatory cytokines/chemokines, (2) the downregulation of major histocompatibility complex (MHC) class Ia directly as well as indirectly by downregulation of the components involved in the antigen processing, and (3) the downregulation of stress-induced ligands for activating receptors on immune effector cells with NKG2D leading the way. Furthermore, (4) immune modulatory molecules like MHC class Ib molecules and programmed cell death1 ligand 1 can be upregulated on infections with certain herpes viruses. This review article focuses on the known molecular mechanisms of HHVs modulating the above-mentioned possibilities for immune surveillance and even postulates a temporal order linking regular tumor immunology with basic virology and offering putatively novel insights for targeting HHVs.

INTRODUCTION

The molecular mechanisms of virus-related malignant transformation of non-tumorous tissues are diverse and involve molecules encoded by viruses or induced on viral infection. Viruses are able to infect all types of life forms such as animals, plants, fungi, protists, and even microorganisms, like yeast, bacteria, and archaea.^{1–5} Viral infections can predispose a patient to various malignancies which might be mediated by oncogenic viruses like Epstein-Barr virus (HHV4, EBV), human herpes virus 8 (HHV8, Kaposi-Sarkom herpes virus (KSHV)), hepatitis B virus, and certain human papilloma viruses (HPV).

Viruses completely rely on the host cell machinery to propagate and lack an own metabolism and reproduction. The viral particles, also called virions, contain the genetic material (single-stranded/double-stranded

(ss/ds) RNA or ss/dsDNA), a protein coat (capsid) and optional a lipid envelope. The space between the lipid envelope derived from the host cell membranes and the capsid is the tegument, which contains molecules from the infected host cell including, for example, proteins and non-coding RNA species. These molecules may originate from the host cell or by the viruses of the infected host cell and promote the generation of macromolecules required for the next infection cycle.⁶ Furthermore, the tegument contains fluids of the cytoplasm, the endoplasmic reticulum (ER) and/or of the Golgi apparatus.^{7,8}

In ER, the assembly of the classical major histocompatibility complex (MHC) class Ia and non-classical MHC class Ib molecules consisting of the MHC class Ia/b heavy chain (HC), β_2 -microglobulin (β_2 -m), and a peptide derived from cellular proteins, which could theoretically also represent peptides derived from viral proteins or in the case of malignant transformed cells also from tumor antigens. The peptides are generated and processed by different components of the antigen processing and presentation machinery (APM) for their presentation to CD8⁺ cytotoxic T lymphocytes (CTLs) on the cell surface.^{9,10}

The MHC class Ia molecules are physiologically expressed in nucleated cells with the exception of immune privileged tissues like cornea, brain, testis and chorion. In contrast, the MHC class Ib molecules, predominantly HLA-G and HLA-E, exert a physiologically restricted and tightly regulated expression exclusively in immune privileged tissues.^{11,12} Since MHC class Ib molecules represent potent ligands for inhibitory receptors of immune effector cells, the modulation of these molecules has functional relevance for immune responses.^{13,14}

Independently of viral infections in solid and hematopoietic tumor diseases, classical MHC class Ia molecules are downregulated

© Author(s) (or their employer(s)) 2020. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

¹Institute for Medical Immunology, Martin-Luther-Universität Halle-Wittenberg, Halle (Saale), Germany

²Immunology & Cancer Research Center, Hebrew University of Jerusalem, Jerusalem, Israel

Correspondence to

Dr Simon Jasinski-Bergner; simon.jasinski@uk-halle.de

with high frequencies by equal strategies, while non-classical MHC class Ib molecules are induced, and even secreted or shedded into the local tumor microenvironment (TME) strongly contributing to the tumor immune escape.¹¹

Next to antigen presentation toward CTLs, also other molecular mechanisms contribute to successful immune surveillance against viral infections. Despite primary virus infections could elicit host antiviral immune responses, these responses are often insufficient to eliminate the virus. Thus, the ability of viruses to persist suggests that the viruses could subvert antiviral immune responses. For example, the virus mediated reduced expression of NKG2D ligands (NKG2D-Ls) upon viral infection avoids antiviral immune responses of the host immune system.^{15–19}

In addition, the secretion of certain cytokines and/or chemokines on herpes virus infection is altered, which can modulate a strong and effective antiviral immune response against infected cells and/or tissues. It is noteworthy that a number of inhibitory mechanisms mediated by certain herpes viruses have been identified, which prevent the secretion of proinflammatory cytokines or enhance the secretion of anti-inflammatory cytokines.²⁰ Furthermore, the expression and the assembly of MHC class Ia/b and/or APM molecules and the NKG2D-Ls can be induced or reduced by different cytokines.

In this review, the known immune escape mechanisms of human herpes viruses (HHVs) are summarized. The family of dsDNA herpes viruses consists of the α -subfamily (herpes simplex virus, HSV-1, HSV-2, varicella-zoster virus (VZV)), the β -subfamily (cytomegalovirus (CMV), HHV6A, HHV6B, HHV7), and the γ -subfamily (EBV, KSHV), which exerts an oncogenic potential. This separation is based on their host range, genetic organization and replication strategies.²¹ These family members share a common viral morphology and approximately 40 conserved genes important for viral replication.²² Nevertheless, these pathogens differ in their pathogenicity. While the members of the α -subfamily have been identified to act as cofactors for some tumor malignancies resulting in elevated tumor incidences, the members of the γ -subfamily are causative inductors of solid and hematopoietic tumor diseases. Furthermore, CMV as a member of the β -subfamily may infect critical organs including the nervous system, hematological and vascular system, gastrointestinal system and therefore may be accompanied by severe disease outcome in apparently healthy individuals.²³

Following a primary infection, it is characteristically for herpes viruses to persist in the host for an extended duration, considering the herpes viruses as highly successful pathogens.²⁴ A contributing factor of the herpes viruses is their ability to adopt two different modes of life cycle: the latency and the lytic cycles. After such a primary productive infection, the herpes viruses switch to latency, a transcriptional and translational suppressed state. This latent state can be frequently interrupted by lytic

episodes. During such latency, the latency-associated transcripts including coding transcripts resulting in viral peptides and proteins as well as non-coding transcripts like microRNAs (miRs) have been identified to contribute to immune evasion.^{24–27}

Focusing on the MHC class I a/b molecules, APM components, NKG2D-Ls, cytokine and chemokine signaling on viral infection, this review article will highlight the known interfering molecular mechanisms of viral encoded or induced miRs, peptides and proteins. Exactly such processes are affected in tumor cells, also shaping the composition of the TME and therefore representing fundamental steps in immune surveillance or immune escape. Thus, the direct interactions between viral molecules of HHVs and host cell molecules next to indirect mechanisms leading to the induction/reduction of relevant host cell factors on viral infection will be addressed and discussed.

VIRAL PROTEINS INTERFERE WITH THE PEPTIDE PRESENTATION OF MHC CLASS I MOLECULES

Under physiologic conditions, the assembled trimeric MHC class I molecules consisting of the MHC class I HC, non-covalent bound β_2 -m, and processed peptides of 8–12 amino acids in length are transported via the trans-Golgi to the cell surface of nucleated cells and presented to CD8⁺ CTLs.¹¹

After ubiquitination, cellular proteins are degraded into peptides by the multicatalytic proteasome with a correct C-terminus, but a relegated N-terminus. These peptides could be further trimmed by cytosolic or ER-resident aminopeptidases.²⁸ The cytokine interferon (IFN)- γ induces the so-called immunoproteasome, which contains novel active subunits of the proteasome activator (PA)28 and the IFN- γ -inducible proteasomal β -subunits, the low molecular weight proteins (LMP)2, MECL1 and LMP7, replacing their constitutive homologs β 1, β 2, and β 5 during proteasome assembly.²⁹ During the initial viral infection, a rapid induction of the immunoproteasome is crucial, which leads to an altered peptide repertoire.³⁰ Subsequently, the peptides are transported via the heterodimeric transporter associated with antigen processing (TAP)1/TAP2 into the ER, which forms a peptide loading complex with the chaperones calreticulin (CALR), tapasin (TPN) and the protein ERp57, thereby facilitating peptide loading onto MHC class I molecules non-covalently bound to β 2-m.

Reduced or impaired expression of any of these molecules can act as a bottleneck for proper MHC class I surface expression. For example, mutations or deletions of B2M or TAP subunits result in a complete absence of MHC class I molecules on the cell surface.^{31–34} Furthermore, downregulation of MHC class Ia surface levels on reduced expression of one or more APM components represents a potent mechanism for immune escape in tumor cells, but also of viral-infected cells to escape immune surveillance. However, in contrast to tumors,

Table 1 Viral peptides/proteins as well as viral miRs targeting MHC class I and APM components

Targeted mechanisms for downregulation of MHC class I				
	Peptide generation in general	Peptide transport in general	Peptide loading in general	Retention of assembled MHC class I or unknown reductive mechanism
Viral proteins/peptides	vIL-10 (EBV ³⁹) BGLF5 (EBV ⁴¹) EBNA-1 (EBV ⁴²)	ICP47 (HSV-1 ^{35 36}) BNLF2a (EBV ³⁸) vIL-10 (EBV ³⁹) US6 (CMV ⁴⁴)	US3 (CMV ⁴⁵)	ORF66 (VZV ³⁷) BILF1 (EBV ⁴⁰) BDLF3 (EBV ⁴³) US10 (CMV ⁴⁶) US11 (CMV ⁴⁷) US2 (CMV ⁴⁸) U21 (HHV-7 ⁵¹) K3 (KSHV ⁵²) K5 (KSHV ⁵²) LANA1 (KSHV ⁵³)
Viral miRs	miR-US4-1 (CMV ⁷²)	miR-BART17 (EBV ⁷¹) miR-BHRF1-3 (EBV ⁷¹)	n.d.	n.d.

APM, antigen processing and presentation machinery; CMV, cytomegalovirus; EBV, Epstein-Barr virus; KSHV, Kaposi-Sarkom herpes virus; MHC, major histocompatibility complex ; miRs, microRNAs; n.d., not determined; VZV, varicella-zoster virus.

many viral proteins have been identified to interfere with the expression of components of the APM. A summary of such 'immune evasions' is listed in [table 1](#).

The human herpes virus (HHV) 1 (herpes simplex virus 1, HSV-1) produces the protein ICP47 that blocks the peptide loading on the MHC class I HC by direct binding to the TAP 1/2 heterodimer.^{35 36} In HHV-3 (VZV) infected cells, MHC class I complexes were hindered to pass through trans-Golgi to the cell surface, which is mediated by the VZV protein ORF66,³⁷ while HHV-4 (EBV) encodes for the BNLF2a protein blocking the TAP 1/2 heterodimer even more efficient than ICP47 or US6.³⁸ Furthermore, EBV encodes for the protein vIL-10, which downregulates TAP1 and LMP2 expression. Both genes are controlled by a bidirectional promoter.³⁹ The EBV protein BILF1 reduces MHC class Ia surface expression,⁴⁰ and the EBV protein BGLF5 as well as EBNA-1 interfere with the complete peptide generation.^{41 42} Interestingly, the late lytic BDLF3 gene product downregulates both MHC class I and class II molecules.⁴³ The HHV-5 (cytomegalovirus, CMV) encodes for the US6 peptide, which is also able to interfere the peptide transport by blocking the TAP 1/2 heterodimer.⁴⁴ Additionally, CMV encodes for the US3 protein that inhibits the TPN-mediated peptide loading and therefore retains HLA class I molecules within the ER.⁴⁵ While the US10 protein directly binds to MHC class I HC and retaining it in the ER,⁴⁶ the US11 and US2 protein directs the MHC class I HC toward proteasomal degradation.^{47 48} Furthermore, it has been shown that the combination of cytosolic and ER-resident aminopeptidases shapes the pool of antigenic peptides as shown for the immunodominant CMV pp65495-503 CTL epitope.⁴⁹ It is noteworthy that CMV virions can even bind β_2 -m on the cell surface and might use it as receptor for virus entry.⁵⁰

An immune evasion of the HHV-7 viruses is the inhibition of MHC class I presentation by the viral U21 protein.⁵¹ Furthermore, HHV-8 (KSHV) viruses express the K3 and K5 proteins leading to the downregulation of MHC class I molecules.⁵² The similar effect was also reported for LANA1.⁵³

VIRAL MICRORNAS PREVENT IMMUNE SURVEILLANCE BY MHC CLASS I MOLECULES

Not only viral-encoded proteins can counteract immune surveillance by interfering with peptide processing and presentation of MHC class I molecules, also viral-encoded microRNAs (miRs) are reported to hinder the MHC class I mediated immune surveillance. miRs are small single-stranded non-coding RNAs of approximately 19–25 nucleotide (nt) in length⁵⁴ binding sequence specifically to the 3'-untranslated region (UTR), but less frequent to the 5'-UTR and the coding sequence (CDS) of target mRNAs.⁵⁵ The miR binding to the target mRNA results in translational inhibition leading to mRNA storage⁵⁶ or in most cases to mRNA decay.⁵⁷ Only the seed regions of the miRs between the second to seventh nt exert perfect complementary sequence homology to the target mRNA sequences, but the impact of their length and the resulting target repression is currently controversially discussed.⁵⁸ Furthermore, miRs redundantly regulate mRNAs and one single miR may control the fate of many different target mRNAs.⁵⁷

Some of the miRs affect tumor biologic relevant cellular functions, like cell proliferation, cell migration, invasion, angiogenesis, apoptosis inducibility, immune cell recognition and others. Therefore, based on their target genes, some miRs can be grouped into oncogenic, tumor suppressive or immune modulatory miRs.⁵⁹

Interestingly, some of these miRs are functionally incorporated into the RNA-induced silencing complex (RISC) complex.⁶⁰ So far, more than 250 viral miRs have been identified, predominantly encoded by herpes viruses, but also by polyomaviruses, ascoviruses, and adenoviruses.⁶¹ Herpes viruses encode and express not only own miRs binding to certain host mRNAs, they further alter the whole host cell miR transcriptome on infection⁶¹ and/or during the process of viral-induced malignant transformation.⁶² In the case of EBV, the viral-mediated induction of the oncogenic miR-155 in host B cells is one major molecular mechanism for immortalization and malignant transformation.^{63 64} On the other hand, the EBV-encoded miR-BART-1 targets the tumor suppressor gene PTEN, which is associated with tumor metastasis.⁶⁵ The viral miR BART16 targets the transcriptional coactivator CREBBP mRNA and thereby inhibits type I IFN signaling and other target genes of this important transcriptional coactivator,⁶⁶ affecting the whole host cell transcriptome for a putative shift toward immortalization and malignant transformation. If secreted factors, like hormones, cytokines, and chemokines, are affected on viral infection, an impact even on non-infected host cells/tissues/organs including immune effector cells could be possible. Indeed, KSHV downregulates the tumor suppressive miRs miR-221, miR-222, and the let7 family members of the infected host cell.⁶⁷

The herpes viruses express miRs during the lytic phase and even during the latency.^{68 69} Currently, the tumor biologic and tumor immunologic targets of these viral miRs are identified. So far, there is no proof that the viruses do encode for additional miR processing enzymes or for additional RISC components, since the viral-encoded miRs use the miR processing machinery of the infected host cells.⁷⁰

Furthermore, EBV targets the mRNA of TAP2 by miR-BART17 and miR-BHRF1-3.⁷¹ The CMV virus encodes for miR-US4-1 negatively regulating the ER-resident aminopeptidase ERAP1 involved in the peptide shaping/trimming for later presentation on MHC class I molecules.⁷² It is postulated that more herpes virus-encoded miRs will be identified impairing the function of the MHC class I APM in the future. All so far reported viral-encoded proteins and regulatory miRs affecting the MHC class I-mediated antigen presentation are summarized in [table 1](#).

VIRAL PROTEINS RESTRAIN THE ACTIVITY OF IMMUNE EFFECTOR CELLS

The current research does not only proof the inhibition of the MHC class I-dependent antigen presentation by viral proteins, but rather the disruption of the interaction between (infected/tumor) target cell and immune effector cells. Such disruption could be arranged by reduction of certain host cell proteins acting as ligands for activating receptors on immune effector cells or by enhancing the expression of viral and/or host molecules leading to the inhibition of immune effector cells. This

includes an enhanced expression of immune modulatory molecules, like non-classical MHC class Ib molecules, in the host cell. Actually, the expression of non-classical MHC class Ib molecules is strongly induced in solid and hematopoietic tumor malignancies offering a strong mechanism for immune evasion.¹³

Indeed, HHV-1 induces HLA-G expression on infection in human neuronal cells.⁷³ While HLA-G is a ligand for the inhibitory receptors ILT-2, ILT-4, and KIR2DL4, which are present on NK cells, CTLs, B cells, macrophages and dendritic cells,⁷⁴ HLA-E binds to the inhibitory receptors CD94/NKG2A, -B and -C on NK cells and CTLs.⁷⁵ For both immune modulatory molecules, a strictly controlled gene expression has been reported, which includes also miRs. Those HLA-G negative regulating miRs were also classified as tumor suppressive miRs^{13 76 77} and might also be downregulated on viral infections. Indeed, CMV infection interferes the regulation between miR-376a and HLA-E.⁷¹ Furthermore, the HCMV genome encodes for different NK cell modulators, like UL135, UL141, UL142, and UL148 thereby inhibiting NK cell activation and recognition.⁷⁸ UL141 inhibits the expression of the activating ligands CD155 and CD112, the activating receptor CD226 (DNAM-1), TRAIL-R1 and -R2, while UL142 and UL148A target specifically MICA and UL148 the expression of LFA-3.

Next to the viral-mediated enhancement of MHC class Ib molecules, the checkpoint molecule programmed cell death1 ligand 1 (PD-L1) is induced on several viral infections including HIV, HCV, and HHV1.^{79 80} There exist more immune inhibitory molecules, which are directly or indirectly induced on viral infections. For example, HHV1 induces transforming growth factor- β (TGF- β) secretion of infected host cells.⁸¹ TGF- β induces among others HLA-G, but inhibits MHC class Ia and APM components gene expression.⁸² Such mechanisms are strongly required for the further processes of viral infection and immune evasion.

A second strategy is the reduced expression of molecules that act as ligands for activating immune cell receptors including among others different NKG2D-Ls, namely the major histocompatibility complex class I-related molecules (MIC) A and B as well as the UL16-binding proteins (ULBP) 1–6, also known as retinoic acid early transcript 1 (RAET1) proteins.^{83 84} In analogy to the tightly controlled cell surface expression of the MHC class Ia/b molecules, the NKG2D-Ls exert also strongly regulated cell surface expression to avoid respective immune responses by NKG2D expressing NK cells and CTLs.^{85 86} Various pathophysiological situations, such as viral infection, oxidative stress, genotoxic drugs, tissue damage, heat shock, inflammatory cytokines, and malignant transformation are known inducers for NKG2D-L surface expression.⁵⁹

HHV-1-infected cells show reduced surface levels of MICA and ULBP2,⁸⁷ as well as ULBP1 and -3.⁸⁸ VZV-infected cells reported to show equal effects by downregulating ULBP2 and ULBP3.⁸⁸ EBV infection decreased MICA, MICB, and ULBP4 surface levels.⁸⁹

Table 2 Viral peptides/proteins as well as viral miRs and other mechanisms leading to downregulation of the NKG2D ligands

	NKG2D ligands							
	MICA	MICB	ULBP1	ULBP2	ULBP3	ULBP4	ULBP5	ULBP6
Viral proteins/peptides	UL142 (CMV ⁹²) US18 (CMV ⁹⁴) US20 (CMV ⁹⁴) U21 (HHV-7 ⁹⁵) K5 (KSHV ⁹⁶)	UL-16 (CMV ⁹¹) U21 (HHV-7 ⁹⁵) K5 (KSHV ⁹⁶)	UL-16 (CMV ⁹⁰) U21 (HHV-7 ⁹⁵)	UL-16 (CMV ⁹⁰)	UL142 (CMV ⁹³)	n.d.	UL-16 (CMV ⁹⁰)	UL-16 (CMV ⁹⁰)
viral miRs	miR-BART7 (EBV ¹⁰⁰)	miR-BART2-5p (EBV ⁹⁹) miR-UL122 (CMV ¹⁰¹) miR-K12-7 (KSHV ⁹⁹)	n.d.	miR-H8 (HSV-1 ⁹⁸)	miR-H8 (HSV-1 ⁹⁸)	n.d.	n.d.	n.d.
Downregulation on unspecified mechanism	HSV-1 ⁸⁷ ; EBV ⁸⁹	EBV ⁸⁹	HSV-1 ⁸⁸	HSV-1 ⁸⁷ ; VZV ⁸⁸	HSV-1 ⁸⁸ ; VZV ⁸⁸	EBV ⁸⁹	n.d.	n.d.

CMV, cytomegalovirus; EBV, Epstein-Barr virus; HSV-1, herpes simplex virus 1; KSHV, Kaposi-Sarkom herpes virus; miRs, microRNAs; n.d., not determined; VZV, varicella-zoster virus.

The many possibilities of the herpes viruses to downregulate NKG2D-L surface expression include viral-encoded proteins, binding to the NKG2D-Ls and causing a functional inhibition as well as viral miRs or a combination of them.

The CMV encodes for the UL16 protein, which is able to bind many ULBPs with the exception of ULBP3 and ULBP4.⁹⁰ Even MICB can be bound and retained by UL16.⁹¹ Next to UL16, the viral UL142 protein binds and retains MICA as well as ULBP3.^{92–93} MICA is further targeted by the CMV gene products US18 and US20.⁹⁴ The immune evasion by U21 of HHV7 not only inhibits MHC class I antigens, but it also contributes to the downregulation of MICA, MICB, and ULBP1.⁹⁵ Furthermore, the KSHV protein K5 causes a downregulation of MICA and MICB.⁹⁶ The viral proteins/peptides targeting NKG2D-L mRNAs are summarized in table 2.

VIRAL-ENCODED MIRS ENABLE IMMUNE EVASION BY TARGETING NKG2D-L TRANSCRIPTION

In analogy to the prevention of the antigen presentation by MHC class I molecules, the herpes viruses can also block the NKG2D-Ls via the expression of miRs. Indeed, current studies identified a number of viral miRs directly targeting the NKG2D-Ls or indirectly leading to a reduction of their surface levels. In addition, various host cell-encoded oncogenic miRs have been described, which can be induced after malignant transformation or as an indirect result of viral infection, such as miR-17-5p, miR-20a, miR-93 directed against MICA, miR-10b against MICB, and miR-650 against ULBP1.⁵⁹ The literature even lists more human miRs targeting NKG2D-Ls, but these miRs

have not yet been classified as oncogenic based on their functional activity.

In addition to these host cell miRs, the viral miR EBV-miR-BART-6 directly targets Dicer in the host cells,⁹⁷ which has an impact on the whole miR transcriptome in the host cell and even on the processing of viral encoded miRs themselves. HHV-1 encodes for miR-H8, which reduces the surface levels of ULBP2 and ULBP3.⁹⁸ The EBV-miR-BART2-5p directly targets MICB,⁹⁹ while EBV-miR-BART7 targets MICA.¹⁰⁰ MICB expression is also repressed by the CMV-miR-UL122¹⁰¹ and by KSHV-miR-K12-7.⁹⁹ The viral encoded miRs targeting NKG2D-L mRNAs are summarized in table 2.

HERPES VIRUS-MEDIATED INTERFERENCE OF THE INTERACTION BETWEEN INFECTED HOST CELLS AND IMMUNE EFFECTOR CELLS BY TARGETING HOST CELL CYTOKINES AND CHEMOKINES

For an early antiviral response, the secretion of certain proinflammatory cytokines is required, including among others IFN- γ , TNF- α , IL-1 β , IL-2, IL-6, IL-12, IL-18, and IL-23,^{102–105} leading to the activation of phagocytic cells like macrophages, but also to the activation of CTLs and NK cells. As a consequence of these proinflammatory cytokines, proinflammatory chemokines, like CXCL8, CCL2 (MCP-1), CCL3, CCL4, CCL5 (Rantes), CCL11, CXCL10, are released and recruit other immune effector cells.¹⁰⁶ A viral intervention at this point is crucial and is to be affiliated functionally and temporally before CTLs interact with MHC class I presented antigens or NK cells interact with the infected cell via NKG2D-Ls and/or other molecules. This putative intervention may include the

block of proinflammatory cytokines/chemokines and/or the increased secretion of anti-inflammatory cytokines/chemokines. A respective summary of targeted cytokines and chemokines is listed in [table 3](#).

HHV-1 represses several proinflammatory cytokines, including IL-6, TNF- α , IFN- α/β , CCL5 (Rantes), and IL-12, IL-23 by the tegument localized proteins VP16, ICP4 and ICP27,¹⁰⁷ which underlines the relevance of these molecules for an early immune evasion.

EBV inhibits the IFN- γ downstream signaling pathway by its immediate-early protein BZLF1.¹⁰⁸ Furthermore, EBV lytic transactivator Zta was characterized as a potent suppressor of IFN- β production,¹⁰⁹ while the EBV LMP1 protein inhibits TNF- α .¹¹⁰ The EBV protein LMP1 induces the secretion of the anti-inflammatory cytokine IL-10,¹¹¹ whereas the EBV miR-BHRF1-2-5p blocks the proinflammatory IL-1 signaling.¹¹²

CMV disrupts multiple levels of the IFN- α signal transduction pathway¹¹³ and the IFN- β response with its US9 protein.¹¹⁴ Also targeting the TNF- α ¹¹⁵ as well as the IFN- γ induced gene expression by the CMV-encoded protein UL23 has been reported.¹¹⁶

The β -subfamily and γ -subfamily of the herpes viruses encode for own viral chemokines and even viral chemokine receptors known to bind and interfere with the functions of the host cell chemokines.¹¹⁷ The CMV UL21.5 mRNA is also packed within the virion, and its protein binds and blocks the function of CCL5 (Rantes),¹¹⁸ whereas the CMV-encoded protein US28 blocks CCL5 function.¹¹⁹ KSHV expresses the viral chemokine vCCL2, which is a broad-spectrum chemokine receptor antagonist, which might impair the recruitment of antiviral immune cells to the site of infection.^{117 120} The KSHV infection is further accompanied by a reduced secretion of TNF- α and IL-1.¹²¹

CONCLUSION

This review summarizes for the first time the combined mechanisms for immune evasion strategies of herpes viruses with focus on cytokine/chemokine signaling, thereby interfering the MHC class I-mediated antigen presentation and the interaction with immune effector cells via NKG2D-L ([figure 1](#)). While the cytokine/chemokine signaling and the NKG2D-based interactions reflect parts of the innate immunity also, the adaptive immunity is targeted by viral molecules including antigen processing and presentation via MHC class I molecules. It is noteworthy that also other subareas of the immune system are targeted by viral molecules encoded by HHVs that have not been addressed within this study.

The cytokine/chemokine signaling is a very early reaction to viral infection and might explain the presence of the respective inhibiting viral factors in the tegument. Such factors are present as protein encoding mRNAs or already as peptides/proteins. In the case of viral-based cytokine and chemokine inhibition, the

Table 3 Viral peptides/proteins as well as viral miRs and unknown mechanisms leading to modulation of host cell cytokines/chemokines									
Herpes viruses									
α -subfamily			β -subfamily			γ -subfamily			
HSV-1	HSV-2	VZV	CMV	HHV-6A	HHV-6B	HHV-7	EBV	KSHV	
Downregulation of proinflammatory cytokines/IL-23, TNF- α , chemokines by viral protein/peptide and viral miR			IFN- α and IFN- β by US9 ¹¹⁴ ; TNF- α and IFN- γ by UL23 ^{115 116} ; CCL5 (Rantes) by UL21.5 and US28 ^{118 119}	n.d.	n.d.	n.d.	IFN- γ by BZLF1 ¹⁰⁸ ; by Zta ¹⁰⁹ ; TNF- α by LMP1 ¹¹⁰ ; IL-1 by miR-BHRF1-2-5p ¹¹²	TNF- α and IL-1 ¹¹²	

CMV, cytomegalovirus; EBV, Epstein-Barr virus; HSV, herpes simplex virus; IFN, interferon; IL, interleukin; KSHV, Kaposi-Sarkom herpes virus; miR, microRNA; n.d., not determined; TGF, transforming growth factor; VZV, varicella-zoster virus.

Figure 1 Selected immune evasion strategies of herpes viruses in the cellular context of infected host cell and immune effector cells. APM, antigen processing and presentation machinery; CTLs, cytotoxic T lymphocytes; HLA, human leukocyte antigen; IL, interleukin.

involvement of respective viral miRs is not yet well investigated. In contrast, the involvement of viral miRs as well as peptides/proteins in the different steps of the complex MHC class I-mediated antigen presentation as well as in the NKG2D-Ls-based immune effector cell interaction is well studied and understood. A temporal order in the establishment of the strategies enabling the immune evasion on infection with herpes viruses is summarized in [figure 2](#) and highlights the downregulation of proinflammatory cytokines and/or chemokines as first step based on the fact that already the virions contain molecules directly targeting a proper cytokine and chemokine signaling. Only after host cell infection and viral DNA transcription leading to viral miRs and after translation of viral mRNAs to viral peptides and/or proteins, other mechanisms of correct immune surveillance are targeted including inter alia MHC class I antigen presentation as well as NKG2D interaction.

Unfortunately, only a little is known whether the reported molecular interactions between the viral miRs/peptides/proteins with immunological relevant targets in the host cell differ between primary infection, latency, reinfection, and so on, or whether they differ if different target cell types infected by the same virus, for example, EBV-infected B cells compared with infected epithelial cells of the respiratory tract. Further clinical

studies are necessary to investigate and validate the clinical relevance of the reported in vitro studies.

Furthermore, it is important to consider the information of the viral-encoded immunomodulatory molecules in the context of coexpressed viral-encoded oncogenes. Already mentioned were the indirect mechanisms, like the induction of the human-encoded oncogenic miR-155 in host B cells by EBV. But, additionally, the herpes viruses are known to encode for genes exerting an oncogenic potential and such factors are not only limited to the strongly cancer-associated two members of the γ -subfamily of the human herpes viruses, namely, EBV and KSHV. In fact, even HSV-1 and HSV-2 are reported to act as cofactors for malignant transformation in several tumor malignancies including thyroid tumors, prostate cancer, and elevated incidences for melanoma, as well as cervical cancer in combination with HPV.^{122–125} As a major cause for a putative malignant transformation mediated by HSV-1/2, the oncogenic and antiapoptotic viral protein ICP10PK is discussed.¹²⁶ VZV is also speculated to elevate the risk for certain malignancies mediated by its antiapoptotic IE63 protein.^{127–128} The oncogenic potential of EBV is well characterized. It is highly associated with the Burkitt's lymphoma, Hodgkin's lymphoma, and nasopharyngeal carcinoma. LMP1 was so far identified as

Figure 2 Schematic summary of the highlighted mechanisms leading to immune evasion with postulated temporal order. APM, antigen processing and presentation machinery; HLA, human leukocyte antigen; miR, microRNA.

the major EBV oncogene.¹²⁹ The Roseoloviruses (HHV-6/7) were at least detected in some hematopoietic malignancies.^{130–131} In contrast, the KSHV is the causative inductor of the Kaposi's sarcoma by inhibiting the apoptosis via the viral-encoded proteins LANA, viral Bcl-2, and K13.^{132–133} Many malignancies induced by the herpes viruses occur in combination with immune deficiencies. The ability of the herpes viruses to prevent complete elimination by the host immune system is therefore a possible neuralgic point for putative therapies.

All of the addressed mechanisms for immune surveillance are also targeted in tumor cells independently of viral infections and therefore the authors want to underline the strong connection between tumor immunology and virology.

Acknowledgements The authors want to thank Maria Heise and Nicole Ott for secretarial assistance. Figure 1 was created with BioRender.

Contributors SJ-B and BS designed the review article. SJ-B, OM, and BS wrote the manuscript.

Funding This work was funded by the German-Israeli Foundation (GIF; I-37-414.11-2016) and Dr Werner Jackstädt Foundation.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is

properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Simon Jasinski-Bergner <http://orcid.org/0000-0001-6300-7371>

Ofer Mandelboim <http://orcid.org/0000-0002-9354-1855>

REFERENCES

- Attar N. Viral evolution: animal viruses in pieces. *Nat Rev Microbiol* 2016;14:606–7.
- Roossinck MJ. Metagenomics of plant and fungal viruses reveals an abundance of persistent lifestyles. *Front Microbiol* 2014;5:767.
- Berjón-Otero M, Koslová A, Fischer MG. The dual lifestyle of genome-integrating virophages in protists. *Ann N Y Acad Sci* 2019;1447:97–109.
- Maaty WS, Steffens JD, Heinemann J, et al. Global analysis of viral infection in an archaeal model system. *Front Microbiol* 2012;3:411.
- Brüssow H. Bacteria between protists and phages: from antipredation strategies to the evolution of pathogenicity. *Mol Microbiol* 2007;65:583–9.
- Amen MA, Griffiths A. Packaging of non-coding RNAs into herpesvirus virions: comparisons to coding RNAs. *Front Genet* 2011;2:81.
- Homman-Loudiyi M, Hulténby K, Britt W, et al. Envelopment of human cytomegalovirus occurs by budding into Golgi-derived vacuole compartments positive for gB, Rab 3, trans-Golgi network 46, and mannosidase II. *J Virol* 2003;77:3191–203.
- Wild P, Kaech A, Schraner EM, et al. Endoplasmic reticulum-to-Golgi transitions upon herpes virus infection. *F1000Res* 2017;6:1804.
- Reeves E, James E. Antigen processing and immune regulation in the response to tumours. *Immunology* 2017;150:16–24.
- Rock KL, Reits E, Neefjes J. Present yourself! by MHC class I and MHC class II molecules. *Trends Immunol* 2016;37:724–37.
- Bukur J, Jasinski S, Seliger B. The role of classical and non-classical HLA class I antigens in human tumors. *Semin Cancer Biol* 2012;22:350–8.

- 12 Friedrich M, Jasinski-Bergner S, Lazaridou M-F, *et al.* Tumor-Induced escape mechanisms and their association with resistance to checkpoint inhibitor therapy. *Cancer Immunol Immunother* 2019;68:1689–700.
- 13 Jasinski-Bergner S, Stoeckl C, Bukur J, *et al.* Clinical relevance of miR-mediated HLA-G regulation and the associated immune cell infiltration in renal cell carcinoma. *Oncoimmunology* 2015;4:e1008805.
- 14 Seliger B, Jasinski-Bergner S, Quandt D, *et al.* HLA-E expression and its clinical relevance in human renal cell carcinoma. *Oncotarget* 2016;7:67360–72.
- 15 Ghadially H, Brown L, Lloyd C, *et al.* MHC class I chain-related protein A and B (MICA and MICB) are predominantly expressed intracellularly in tumour and normal tissue. *Br J Cancer* 2017;116:1208–17.
- 16 Dassa L, Seidel E, Oiknine-Djian E, *et al.* The human cytomegalovirus protein UL148A downregulates the NK cell-activating ligand MICA to avoid NK cell attack. *J Virol* 2018;92:e00162–18.
- 17 Schmiedel D, Tai J, Levi-Schaffer F, *et al.* Human herpesvirus 6B downregulates expression of activating ligands during lytic infection to escape elimination by natural killer cells. *J Virol* 2016;90:9608–17.
- 18 Bauman Y, Mandelboim O. MicroRNA based immunoevasion mechanism of human polyomaviruses. *RNA Biol* 2011;8:591–4.
- 19 Bauman Y, Nachmani D, Vitsenshtein A, *et al.* An identical miRNA of the human JC and BK polyoma viruses targets the stress-induced ligand ULBP3 to escape immune elimination. *Cell Host Microbe* 2011;9:93–102.
- 20 Mogensen TH, Paludan SR. Molecular pathways in virus-induced cytokine production. *Microbiol Mol Biol Rev* 2001;65:131–50.
- 21 Whitley RJ. *Herpesviruses*, 1996.
- 22 Owen DJ, Crump CM, Graham SC. Tegument assembly and secondary envelopment of alphaherpesviruses. *Viruses* 2015;7:5084–114.
- 23 Rafailidis PI, Mourtoukou EG, Varbobitis IC, *et al.* Severe cytomegalovirus infection in apparently immunocompetent patients: a systematic review. *Virol J* 2008;5:47.
- 24 Sehrawat S, Kumar D, Rouse BT. Herpesviruses: harmonious pathogens but relevant cofactors in other diseases? *Front Cell Infect Microbiol* 2018;8:177.
- 25 Naqvi AR, Shango J, Seal A, *et al.* Herpesviruses and microRNAs: new pathogenesis factors in oral infection and disease? *Front Immunol* 2018;9:2099.
- 26 Tang S, Bertke AS, Patel A, *et al.* Herpes simplex virus 2 microRNA miR-H6 is a novel latency-associated transcript-associated microRNA, but reduction of its expression does not influence the establishment of viral latency or the recurrence phenotype. *J Virol* 2011;85:4501–9.
- 27 Barbu MG, Condrat CE, Thompson DC, *et al.* MicroRNA involvement in signaling pathways during viral infection. *Front Cell Dev Biol* 2020;8:143.
- 28 Kloetzel PM, Ossendorp F. Proteasome and peptidase function in MHC-class-I-mediated antigen presentation. *Curr Opin Immunol* 2004;16:76–81.
- 29 Ferrington DA, Gregerson DS. Immunoproteasomes: structure, function, and antigen presentation. *Prog Mol Biol Transl Sci* 2012;109:75–112.
- 30 McCarthy MK, Weinberg JB. The immunoproteasome and viral infection: a complex regulator of inflammation. *Front Microbiol* 2015;6:21.
- 31 Benitez R, Godelaine D, Lopez-Nevot MA, *et al.* Mutations of the beta2-microglobulin gene result in a lack of HLA class I molecules on melanoma cells of two patients immunized with MAGE peptides. *Tissue Antigens* 1998;52:520–9.
- 32 Feenstra M, Rozemuller E, Duran K, *et al.* Mutation in the beta 2M gene is not a frequent event in head and neck squamous cell carcinomas. *Hum Immunol* 1999;60:697–706.
- 33 Chen HL, Gabrilovich D, Tampé R, *et al.* A functionally defective allele of TAP1 results in loss of MHC class I antigen presentation in a human lung cancer. *Nat Genet* 1996;13:210–3.
- 34 Ritz U, Drexler I, Sutter D, *et al.* Impaired transporter associated with antigen processing (TAP) function attributable to a single amino acid alteration in the peptide TAP subunit TAP1. *J Immunol* 2003;170:941–6.
- 35 York IA, Roop C, Andrews DW, *et al.* A cytosolic herpes simplex virus protein inhibits antigen presentation to CD8+ T lymphocytes. *Cell* 1994;77:525–35.
- 36 Röder G, Geironsen L, Bressendorff I, *et al.* Viral proteins interfering with antigen presentation target the major histocompatibility complex class I peptide-loading complex. *J Virol* 2008;82:8246–52.
- 37 Abendroth A, Lin I, Slobodman B, *et al.* Varicella-Zoster virus retains major histocompatibility complex class I proteins in the Golgi compartment of infected cells. *J Virol* 2001;75:4878–88.
- 38 Hislop AD, Rensing ME, van Leeuwen D, *et al.* A CD8+ T cell immune evasion protein specific to Epstein-Barr virus and its close relatives in old World primates. *J Exp Med* 2007;204:1863–73.
- 39 Zeidler R, Eissner G, Meissner P, *et al.* Downregulation of TAP1 in B lymphocytes by cellular and Epstein-Barr virus-encoded interleukin-10. *Blood* 1997;90:2390–7.
- 40 Zuo J, Currin A, Griffin BD, *et al.* The Epstein-Barr virus G-protein-coupled receptor contributes to immune evasion by targeting MHC class I molecules for degradation. *PLoS Pathog* 2009;5:e1000255.
- 41 Rowe M, Glaunsinger B, van Leeuwen D, *et al.* Host shutoff during productive Epstein-Barr virus infection is mediated by BGLF5 and may contribute to immune evasion. *Proc Natl Acad Sci U S A* 2007;104: :3366–71.
- 42 Levitskaya J, Sharipo A, Leonchiks A, *et al.* Inhibition of Ubiquitin/proteasome-dependent protein degradation by the Gly-Ala repeat domain of the Epstein-Barr virus nuclear antigen 1. *Proc Natl Acad Sci U S A* 1997;94:12616–21.
- 43 Quinn LL, Williams LR, White C, *et al.* The missing link in Epstein-Barr virus immune evasion: the BDLF3 gene induces ubiquitination and downregulation of major histocompatibility complex class I (MHC-I) and MHC-II. *J Virol* 2016;90:356–67.
- 44 Hewitt EW, Gupta SS, Lehner PJ. The human cytomegalovirus gene product US6 inhibits ATP binding by TAP. *Embo J* 2001;20:387–96.
- 45 Park B, Kim Y, Shin J, *et al.* Human cytomegalovirus inhibits tapasin-dependent peptide loading and optimization of the MHC class I peptide cargo for immune evasion. *Immunity* 2004;20:71–85.
- 46 Furman MH, Dey N, Tortorella D, *et al.* The human cytomegalovirus US10 gene product delays trafficking of major histocompatibility complex class I molecules. *J Virol* 2002;76:11753–6.
- 47 Wiertz EJ, Jones TR, Sun L, *et al.* The human cytomegalovirus US11 gene product dislocates MHC class I heavy chains from the endoplasmic reticulum to the cytosol. *Cell* 1996;84:769–79.
- 48 Wiertz EJ, Tortorella D, Bogoy M, *et al.* Sec61-mediated transfer of a membrane protein from the endoplasmic reticulum to the proteasome for destruction. *Nature* 1996;384:432–8.
- 49 Urban S, Textoris-Taube K, Reimann B, *et al.* The efficiency of human cytomegalovirus pp65⁽⁴⁹⁵⁻⁵⁰³⁾ CD8+ T cell epitope generation is determined by the balanced activities of cytosolic and endoplasmic reticulum-resident peptidases. *J Immunol* 2012;189:529–38.
- 50 Grundy JE, McKeating JA, Ward PJ, *et al.* Beta 2 microglobulin enhances the infectivity of cytomegalovirus and when bound to the virus enables class I HLA molecules to be used as a virus receptor. *J Gen Virol* 1987;68:793–803.
- 51 Hudson AW, Blom D, Howley PM, *et al.* The ER-luminal domain of the HHV-7 immunoevasin U21 directs class I MHC molecules to lysosomes. *Traffic* 2003;4:824–37.
- 52 Coscoy L, Ganem D. Kaposi's sarcoma-associated herpesvirus encodes two proteins that block cell surface display of MHC class I chains by enhancing their endocytosis. *Proc Natl Acad Sci U S A* 2000;97:8051–6.
- 53 Kwun HJ, da Silva SR, Qin H, *et al.* The central repeat domain 1 of Kaposi's sarcoma-associated herpesvirus (KSHV) latency associated-nuclear antigen 1 (LANA1) prevents cis MHC class I peptide presentation. *Virology* 2011;412:357–65.
- 54 Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell* 2004;116:281–97.
- 55 Nielsen AF, Gloggnitzer J, Martinez J. MicroRNAs cross the line: the battle for mRNA stability enters the coding sequence. *Mol Cell* 2009;35:139–40.
- 56 Chan S-P, Slack FJ. microRNA-Mediated silencing inside P-bodies. *RNA Biol* 2006;3:97–100.
- 57 Di Leva G, Garofalo M, Croce CM. MicroRNAs in cancer. *Annu Rev Pathol* 2014;9:287–314.
- 58 Mullany LE, Herrick JS, Wolff RK, *et al.* MicroRNA seed region length impact on target messenger RNA expression and survival in colorectal cancer. *PLoS One* 2016;11:e0154177.
- 59 Jasinski-Bergner S, Mandelboim O, Seliger B. The role of microRNAs in the control of innate immune response in cancer. *J Natl Cancer Inst* 2014;106:dju257.
- 60 Stark TJ, Arnold JD, Spector DH, *et al.* High-resolution profiling and analysis of viral and host small RNAs during human cytomegalovirus infection. *J Virol* 2012;86:226–35.
- 61 Skalsky RL, Cullen BR. Viruses, microRNAs, and host interactions. *Annu Rev Microbiol* 2010;64:123–41.
- 62 Bondada MS, Yao Y, Nair V. Multifunctional miR-155 pathway in avian oncogenic virus-induced neoplastic diseases. *Noncoding RNA* 2019;5:24.

- 63 Linnstaedt SD, Gottwein E, Skalsky RL, *et al.* Virally induced cellular microRNA miR-155 plays a key role in B-cell immortalization by Epstein-Barr virus. *J Virol* 2010;84:11670–8.
- 64 Wood CD, Carvell T, Gunnell A, *et al.* Enhancer control of microRNA miR-155 expression in Epstein-Barr virus-infected B cells. *J Virol* 2018;92:e00716–8.
- 65 Cai L, Ye Y, Jiang Q, *et al.* Epstein-Barr virus-encoded microRNA BART1 induces tumour metastasis by regulating PTEN-dependent pathways in nasopharyngeal carcinoma. *Nat Commun* 2015;6:7353.
- 66 Hooykaas MJG, van Gent M, Soppe JA, *et al.* Ebv microRNA BART16 suppresses type I IFN signaling. *J Immunol* 2017;198:4062–73.
- 67 O'Hara AJ, Wang L, Dezube BJ, *et al.* Tumor suppressor microRNAs are underrepresented in primary effusion lymphoma and Kaposi sarcoma. *Blood* 2009;113:5938–41.
- 68 Jurak I, Silverstein LB, Sharma M, *et al.* Herpes simplex virus is equipped with RNA- and protein-based mechanisms to repress expression of ATRX, an effector of intrinsic immunity. *J Virol* 2012;86:10093–102.
- 69 Pratt ZL, Kuzembayeva M, Sengupta S, *et al.* The microRNAs of Epstein-Barr virus are expressed at dramatically differing levels among cell lines. *Virology* 2009;386:387–97.
- 70 Wang M, Yu F, Wu W, *et al.* Epstein-Barr virus-encoded microRNAs as regulators in host immune responses. *Int J Biol Sci* 2018;14:565–76.
- 71 Albanese M, Tagawa T, Bouvet M, *et al.* Epstein-Barr virus microRNAs reduce immune surveillance by virus-specific CD8+ T cells. *Proc Natl Acad Sci U S A* 2016;113:E6467–75.
- 72 Kim S, Lee S, Shin J, *et al.* Human cytomegalovirus microRNA miR-US4-1 inhibits CD8(+) T cell responses by targeting the aminopeptidase ERAP1. *Nat Immunol* 2011;12:984–91.
- 73 Mégret F, Prehaud C, Lafage M, *et al.* Modulation of HLA-G and HLA-E expression in human neuronal cells after rabies virus or herpes virus simplex type 1 infections. *Hum Immunol* 2007;68:294–302.
- 74 Lemaoult J, Zafaranloo K, Le Danff C, *et al.* HLA-G up-regulates ILT2, ILT3, ILT4, and KIR2DL4 in antigen presenting cells, NK cells, and T cells. *Faseb J* 2005;19:1–23.
- 75 Braud VM, Allan DS, O'Callaghan CA, *et al.* HLA-E binds to natural killer cell receptors CD94/NKG2A, B and C. *Nature* 1998;391:795–9.
- 76 Jasinski-Bergner S, Reches A, Stoeck C, *et al.* Identification of novel microRNAs regulating HLA-G expression and investigating their clinical relevance in renal cell carcinoma. *Oncotarget* 2016;7:26866–78.
- 77 Nachmani D, Zimmermann A, Oiknine Djian E, *et al.* MicroRNA editing facilitates immune elimination of HCMV infected cells. *PLoS Pathog* 2014;10:e1003963.
- 78 Patel M, Vlahava V-M, Forbes SK, *et al.* HCMV-Encoded NK Modulators: Lessons From *in vitro* and *in vivo* Genetic Variation. *Front Immunol* 2018;9:2214.
- 79 Chentoufi AA, Kritzer E, Tran MV, *et al.* The herpes simplex virus 1 latency-associated transcript promotes functional exhaustion of virus-specific CD8+ T cells in latently infected trigeminal ganglia: a novel immune evasion mechanism. *J Virol* 2011;85:9127–38.
- 80 Schönrich G, Raftery MJ. The PD-1/CD-137 axis and virus infections: a delicate balance. *Front Cell Infect Microbiol* 2019;9:207.
- 81 Méndez-Samperio P, Hernandez M, Ayala HE. Induction of transforming growth factor-beta 1 production in human cells by herpes simplex virus. *J Interferon Cytokine Res* 2000;20:273–80.
- 82 Guan Z, Song B, Liu F, *et al.* TGF- β induces HLA-G expression through inhibiting miR-152 in gastric cancer cells. *J Biomed Sci* 2015;22:107.
- 83 Schmiedel D, Mandelboim O. NKG2D Ligands-Critical targets for cancer immune escape and therapy. *Front Immunol* 2018;9:2040.
- 84 Conejo-Garcia JR, Benencia F, Courrèges MC, *et al.* Letal, a tumor-associated NKG2D immunoreceptor ligand, induces activation and expansion of effector immune cells. *Cancer Biol Ther* 2003;2:446–51.
- 85 Stern-Ginossar N, Mandelboim O. An integrated view of the regulation of NKG2D ligands. *Immunology* 2009;128:1–6.
- 86 Bauer S, Groh V, Wu J, *et al.* Activation of NK cells and T cells by NKG2D, a receptor for stress-inducible MICA. *Science* 1999;285:727–9.
- 87 Schepis D, D'Amato M, Studahl M, *et al.* Herpes simplex virus infection downmodulates NKG2D ligand expression. *Scand J Immunol* 2009;69:429–36.
- 88 Campbell TM, McSharry BP, Steain M, *et al.* Varicella-Zoster virus and herpes simplex virus 1 differentially modulate NKG2D ligand expression during productive infection. *J Virol* 2015;89:7932–43.
- 89 Rancan C, Schirrmann L, Hüls C, *et al.* Latent membrane protein LMP2A impairs recognition of EBV-infected cells by CD8+ T cells. *PLoS Pathog* 2015;11:e1004906.
- 90 Zöller T, Wittenbrink M, Hoffmeister M, *et al.* Cutting an NKG2D ligand short: cellular processing of the peculiar human NKG2D ligand ULBP4. *Front Immunol* 2018;9:620.
- 91 Wu J, Chalupny NJ, Manley TJ, *et al.* Intracellular retention of the MHC class I-related chain B ligand of NKG2D by the human cytomegalovirus UL16 glycoprotein. *J Immunol* 2003;170:4196–200.
- 92 Chalupny NJ, Rein-Weston A, Dosch S, *et al.* Down-Regulation of the NKG2D ligand MICA by the human cytomegalovirus glycoprotein UL142. *Biochem Biophys Res Commun* 2006;346:175–81.
- 93 Bennett NJ, Ashiru O, Morgan FJE, *et al.* Intracellular sequestration of the NKG2D ligand ULBP3 by human cytomegalovirus. *J Immunol* 2010;185:1093–102.
- 94 Fielding CA, Aichele R, Stanton RJ, *et al.* Two novel human cytomegalovirus NK cell evasion functions target MICA for lysosomal degradation. *PLoS Pathog* 2014;10:e1004058.
- 95 Schneider CL, Hudson AW. The human herpesvirus-7 (HHV-7) U21 immunoevasin subverts NK-mediated cytotoxicity through modulation of MICA and MICB. *PLoS Pathog* 2011;7:e1002362.
- 96 Thomas M, Boname JM, Field S, *et al.* Down-Regulation of NKG2D and Nkp80 ligands by Kaposi's sarcoma-associated herpesvirus K5 protects against NK cell cytotoxicity. *Proc Natl Acad Sci U S A* 2008;105:1656–61.
- 97 Iizasa H, Wulff B-E, Alla NR, *et al.* Editing of Epstein-Barr virus-encoded BART6 microRNAs controls their dicer targeting and consequently affects viral latency. *J Biol Chem* 2010;285:33358–70.
- 98 Enk J, Levi A, Weisblum Y, *et al.* Hsv1 microRNA modulation of GPI anchoring and downstream immune evasion. *Cell Rep* 2016;17:949–56.
- 99 Nachmani D, Stern-Ginossar N, Sarid R, *et al.* Diverse herpesvirus microRNAs target the stress-induced immune ligand MICB to escape recognition by natural killer cells. *Cell Host Microbe* 2009;5:376–85.
- 100 Wong T-S, Chen S, Zhang M-J, *et al.* Epstein-Barr virus-encoded microRNA BART7 downregulates major histocompatibility complex class I chain-related peptide A and reduces the cytotoxicity of natural killer cells to nasopharyngeal carcinoma. *Oncol Lett* 2018;16:2887–92.
- 101 Nachmani D, Lankry D, Wolf DG, *et al.* The human cytomegalovirus microRNA miR-UL112 acts synergistically with a cellular microRNA to escape immune elimination. *Nat Immunol* 2010;11:806–13.
- 102 Trinchieri G. Interleukin-12: a proinflammatory cytokine with immunoregulatory functions that bridge innate resistance and antigen-specific adaptive immunity. *Annu Rev Immunol* 1995;13:251–76.
- 103 Sekiyama KD, Yoshida M, Thomson AW. Circulating proinflammatory cytokines (IL-1 beta, TNF-alpha, and IL-6) and IL-1 receptor antagonist (IL-1ra) in fulminant hepatic failure and acute hepatitis. *Clin Exp Immunol* 1994;98:71–7.
- 104 Dinarello CA. IL-18: a TH1-inducing, proinflammatory cytokine and new member of the IL-1 family. *J Allergy Clin Immunol* 1999;103:11–24.
- 105 Duvallet E, Semeraro L, Assier E, *et al.* Interleukin-23: a key cytokine in inflammatory diseases. *Ann Med* 2011;43:503–11.
- 106 Zlotnik A, Yoshie O. The chemokine superfamily revisited. *Immunity* 2012;36:705–16.
- 107 Mogensen TH, Melchjorsen J, Malmgaard L, *et al.* Suppression of proinflammatory cytokine expression by herpes simplex virus type 1. *J Virol* 2004;78:5883–90.
- 108 Morrison TE, Mauser A, Wong A, *et al.* Inhibition of IFN-gamma signaling by an Epstein-Barr virus immediate-early protein. *Immunity* 2001;15:787–99.
- 109 Wong NHM, Yuen K-S, Chan C-P, *et al.* Suppression of IFN- β production by Epstein-Barr virus lytic transactivator Zta. *J Immunol* 2017;198:214.15.
- 110 Chuang H-C, Lay J-D, Chuang S-E, *et al.* Epstein-Barr virus (EBV) latent membrane protein-1 down-regulates tumor necrosis factor-alpha (TNF-alpha) receptor-1 and confers resistance to TNF-alpha-induced apoptosis in T cells: implication for the progression to T-cell lymphoma in ebv-associated hemophagocytic syndrome. *Am J Pathol* 2007;170:1607–17.
- 111 Herbst H, Foss HD, Samol J, *et al.* Frequent expression of interleukin-10 by Epstein-Barr virus-harboring tumor cells of Hodgkin's disease. *Blood* 1996;87:2918–29.
- 112 Skinner CM, Ivanov NS, Barr SA, *et al.* An Epstein-Barr virus microRNA blocks interleukin-1 (IL-1) signaling by targeting IL-1 receptor 1. *J Virol* 2017;91:e00530–17.

- 113 Miller DM, Zhang Y, Rahill BM, *et al.* Human cytomegalovirus inhibits IFN- α -stimulated antiviral and immunoregulatory responses by blocking multiple levels of IFN- α signal transduction. *J Immunol* 1999;162:6107–13.
- 114 Choi HJ, Park A, Kang S, *et al.* Human cytomegalovirus-encoded US9 targets MAVS and sting signaling to evade type I interferon immune responses. *Nat Commun* 2018;9:125.
- 115 Baillie J, Sahlender DA, Sinclair JH. Human cytomegalovirus infection inhibits tumor necrosis factor α (TNF- α) signaling by targeting the 55-kilodalton TNF- α receptor. *J Virol* 2003;77:7007–16.
- 116 Feng L, Sheng J, Vu G-P, *et al.* Human cytomegalovirus UL23 inhibits transcription of interferon- γ stimulated genes and blocks antiviral interferon- γ responses by interacting with human N-myc interactor protein. *PLoS Pathog* 2018;14:e1006867.
- 117 Pontejo SM, Murphy PM, Pease JE. Chemokine subversion by human herpesviruses. *J Innate Immun* 2018;10:465–78.
- 118 Wang D, Bresnahan W, Shenk T. Human cytomegalovirus encodes a highly specific RANTES decoy receptor. *Proc Natl Acad Sci U S A* 2004;101:16642–7.
- 119 Pleskoff O, Tréboute C, Brelot A, *et al.* Identification of a chemokine receptor encoded by human cytomegalovirus as a cofactor for HIV-1 entry. *Science* 1997;276:1874–8.
- 120 Sozzani S, Luini W, Bianchi G, *et al.* The viral chemokine macrophage inflammatory protein-II is a selective Th2 chemoattractant. *Blood* 1998;92:4036–9.
- 121 Gregory SM, Wang L, West JA, *et al.* Latent Kaposi's sarcoma-associated herpesvirus infection of monocytes downregulates expression of adaptive immune response costimulatory receptors and proinflammatory cytokines. *J Virol* 2012;86:3916–23.
- 122 Jensen K, Patel A, Larin A, *et al.* Human herpes simplex viruses in benign and malignant thyroid tumours. *J Pathol* 2010;221:193–200.
- 123 Thomas F, Elguero E, Brodeur J, *et al.* Herpes simplex virus type 2 and cancer: a medical geography approach. *Infect Genet Evol* 2011;11:1239–42.
- 124 Haverkos H, Rohrer M, Pickworth W. The cause of invasive cervical cancer could be multifactorial. *Biomed Pharmacother* 2000;54:54–9.
- 125 Golais F, Mrázová V. Human alpha and beta herpesviruses and cancer: passengers or foes? *Folia Microbiol* 2020;65:439–49.
- 126 Wales SQ, Li B, Laing JM, *et al.* The herpes simplex virus type 2 gene ICP10PK protects from apoptosis caused by nerve growth factor deprivation through inhibition of caspase-3 activation and XIAP up-regulation. *J Neurochem* 2007;103:365–79.
- 127 Malavige GN, Rohanachandra LT, Jones L, *et al.* IE63-specific T-cell responses associate with control of subclinical varicella zoster virus reactivation in individuals with malignancies. *Br J Cancer* 2010;102:727–30.
- 128 Alibek K, Baiken Y, Kakpenova A, *et al.* Implication of human herpesviruses in oncogenesis through immune evasion and suppression. *Infect Agent Cancer* 2014;9:3.
- 129 Raab-Traub N. Novel mechanisms of EBV-induced oncogenesis. *Curr Opin Virol* 2012;2:453–8.
- 130 Loutfy SA, Fawzy M, El-Wakil M, *et al.* Presence of human herpes virus 6 (HHV6) in pediatric lymphomas: impact on clinical course and association with cytomegalovirus infection. *Virol J* 2010;7:287.
- 131 Seror E, Coquerel B, Gautheret-Dejean A, *et al.* Quantitation of human herpes virus 6 genome in children with acute lymphoblastic leukemia. *J Med Virol* 2008;80:689–93.
- 132 Friberg J, Kong W, Hottiger MO, *et al.* P53 inhibition by the LANA protein of KSHV protects against cell death. *Nature* 1999;402:889–94.
- 133 Cheng EH, Nicholas J, Bellows DS, *et al.* A Bcl-2 homolog encoded by Kaposi sarcoma-associated virus, human herpesvirus 8, inhibits apoptosis but does not heterodimerize with Bax or Bak. *Proc Natl Acad Sci U S A* 1997;94:690–4.