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Immune escape of γ -herpesviruses from adaptive immunity

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SUMMARY

Epstein-Barr virus (EBV) and Kaposi's sarcoma-associated herpesvirus (KSHV) are two γ -herpesviruses identified in humans and are strongly associated with the development of malignancies. Murine γ -herpesvirus (MHV-68) is a naturally occurring rodent pathogen, representing a unique experimental model for dissecting γ -herpesvirus infection and the immune response. These γ -herpesviruses actively antagonize the innate and adaptive antiviral responses, thereby efficiently establishing latent or persistent infections, and even promoting development of malignancies. In this review, we summarize immune evasion strategies of γ -herpesviruses. These include suppression of MHC-I- and MHC-II-restricted antigen presentation, impairment of dendritic cell functions, downregulation of costimulatory molecules, activation of viral-specific regulatory T cells, and induction of inhibitory cytokines. There is a focus on how both γ -herpesvirus-derived and host-derived immunomodulators interfere with adaptive antiviral immunity. Understanding immune-evasive mechanisms is essential for developing future immunotherapies against EBV- and KSHV-driven tumors.

Keywords

Immune escape; γ -herpesviruses; EBV; KSHV; MHV-68; viral immunomodulators

INTRODUCTION

Persistent viral infection depends on the balance between host immune responses and viral immune evasion. To establish a persistent infection efficiently, viruses have evolved a number of strategies to avoid immune elimination. These include: hiding in certain cell types to escape encounters with the immune system; inhibiting their replication to limit antigen production; subverting cytokine-mediated intercellular communication; and increasing the generation of viral mutants. Latency is a successful mechanism of evasion for all herpesviruses, allowing them to survive in their hosts for a lifetime. Two γ -herpesviruses have been identified in humans: Epstein-Barr virus (EBV) [1] and Kaposi's sarcoma-associated herpesvirus (KSHV) [2]. EBV and KSHV are strongly associated with a range of malignancies, mostly in immune suppressed populations [3].

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EBV, also called human herpesvirus 4 (HHV-4), belongs to the genus *Lymphocryptovirus*. Its genome, ~172 kbp [4], encodes 86 proteins [5]. EBV undergoes lytic replication mainly in epithelial cells of the oropharynx, subsequently establishes latent infection in B cells, and can reactivate periodically from latency. EBV is an orally transmitted ubiquitous virus and infects more than 90% of the adult population worldwide. In healthy individuals, EBV can cause infectious mononucleosis, and is a significant risk factor for Burkitt's lymphoma and nasopharyngeal carcinoma. In AIDS and other immunocompromised patients, EBV is directly associated with the development of malignancies, such as non-Hodgkin's lymphoma, CNS lymphomas and post-transplant lymphoproliferative disease [6].

KSHV, also called human herpesvirus 8 (HHV-8), belongs to the genus *Rhadinovirus*. Like EBV, its linear dsDNA consists of 160 to 170 kbp and is stably maintained in latently infected B cells [7]. Its genome contains a central unique region of 140.5 kbp with at least 81 ORFs [8]. KSHV, a unique human tumor virus, has pirated numerous genes from host cells, which may help the virus to escape from the immune system and provoke host cell proliferation [9]. This virus can be transmitted both sexually and through body fluids, such as saliva [10], in addition to bloodborne transmission, which is important in the setting of intravenous drug abuse. The prevalence of KSHV infection is not as high as EBV and is greatly dependent on regional and social factors, such as intravenous drug use. Prevalence ranges from 2 to 40% in the general population, 20 to 50% in HIV-infected individuals without Kaposi's sarcoma, and over 90% in patients with Kaposi's sarcoma and other KSHV associated diseases [11]. KSHV is etiologically linked to the development of Kaposi's sarcoma, primary effusion lymphoma and multicentric Castleman's disease [10].

Murine γ -herpesvirus (MHV-68) is a naturally occurring rodent pathogen, originally isolated from two species of free living small rodents: *Apodemus flavicollis* (yellow-necked-mouse) and *Clethrionomys glareolus* (bank vole) [12]. Later studies indicated this virus is endemic in wood mice (*Apodemus sylvaticus*) in the UK, suggesting this may be the natural host species [13]. MHV-68 belongs to the genus *Rhadinovirus* and is genetically closely related to EBV and KSHV [14, 15]. Its genome contains a region of ~118 kbp with at least 80 genes, of which more than 60 ORFs are homologous to those of KSHV [15]. MHV-68 initially replicates in the lung after intranasal infection [16] and then establishes lifelong latency, primarily in B cells [17], but also in dendritic cells (DCs), macrophages [18] and lung epithelial cells [19]. MHV-68 provides an important model to explore the γ -herpesvirus infections and host responses [20-26].

These γ -herpesviruses evade the immune response by producing certain viral proteins and non-coding RNAs. Gammaherpesvirus-derived immunomodulators can interfere with antigen presentation, attenuate IFN signaling, alter host chemokine networks, inhibit complement-mediated effector activity, and block apoptotic and autophagic pathways. These help viral escape from innate and adaptive antiviral responses [27-32]. In addition, suppression of antiviral responses by regulatory T cells (Tregs) is a host factor associated with viral persistence and the development of malignancies [33]. In this review, we summarize how γ -herpesviruses escape from adaptive immunity by releasing viral immunomodulators and by manipulating the immunological environment of the host.

INTERFERENCE WITH MHC CLASS I-RESTRICTED ANTIGEN PRESENTATION

CD8⁺ T cells play a critical role in the control of viral infections by recognizing viral peptides presented by MHC class I (MHC-I) molecules. Downregulation of MHC-I expression on the cell surface is an important strategy for γ -herpesviruses to avoid being recognized by CD8⁺ T cells. Antigenic peptides are generated in the cytosol by the proteasome, shuttled into the ER and loaded onto newly synthesized MHC-I molecules. This process is controlled by the peptide-loading complex (PLC), which contains TAP (TAP₁ and TAP₂, transporters associated with antigen processing), tapasin (a transmembrane glycoprotein), ERp57 (an oxidoreductase) and CRT (calreticulin, a glycoprotein chaperone) [34]. The peptide-MHC-I complex is transported to the cell surface where it will be recognized by CD8⁺ T cells. Gammaherpesviruses effectively interfere with the adaptive antiviral response by producing immunomodulators that act at various stages during MHC-I-mediated antigen presentation (Figure 1).

Inhibition of MHC-I molecule transcription by KSHV vIRF1

Activation of the IFN-mediated antiviral pathway is one of the major defensive strategies for the host immune system. KSHV-encoded IFN regulatory factors 1 to 4 (vIRF1 to 4) are homologous to cellular IRFs. Generally, the vIRFs function as negative regulators for the antiviral response and apoptosis mediated by cellular IRFs [35]. vIRF1 and vIRF3 contribute to viral immune evasion by interfering with MHC-I and MHC-II antigen presentation pathways, respectively. vIRF1 (KSHV k9) functions as a repressor of IFN-mediated signal transduction, inhibiting the expression of IFN-inducible genes by blocking IRF1- and IRF3-mediated transcription. vIRF1 downregulates basal and IFN-induced MHC-I transcription in lymphatic endothelial cells through its interaction with the transcriptional coactivator p300 [35]. Moreover, vIRF1 can antagonize the upregulation of MHC-I transcription induced by KSHV-encoded vFLIP (viral FLICE inhibitory protein) [36].

Degradation of cellular mRNA by KSHV SOX, EBV BGLF5 and MHV-68 muSOX

Viral infection often results in a global shutoff of host cellular gene expression, which confers a selective advantage to the virus by facilitating redirection of cellular resources toward virus replication and by dampening immune stimulatory signals. SOX, a shutoff factor for host gene expression, is encoded by KSHV ORF37 and named after its functions shutoff and exonuclease [37]. SOX induces host mRNA degradation by hyperadenylation of the transcripts, thereby retaining host mRNAs in the nucleus. SOX also induces relocalization of cytoplasmic poly(A)-binding proteins into the nucleus, and these proteins are important for stability and translation of cytoplasmic mRNAs. Therefore, SOX may prevent nascent mRNA export and deplete preexisting cytoplasmic mRNAs [38, 39]. BGLF5, an EBV-derived DNase, displays a high degree of homology to KSHV SOX at the amino acid level. BGLF5 can promote mRNA degradation and induce host MHC-I gene shutoff [40]. Both BGLF5 and SOX have also been reported to have intrinsic RNase activity [41, 42]. Impairment of endogenous antigen recognition by virus-specific CD8⁺ T cells is observed following expression of BGLF5 or SOX [43]. MuSOX, a SOX homolog from

MHV-68, mimics all known activities of SOX and BGLF5, underscoring functional conservation within the γ -herpesviruses [44].

Retardation of antigen processing by EBV EBNA1, KSHV LANA1 and MHV-68 mLANA

The proteasome is a protein complex that functions to degrade unneeded or damaged proteins by proteolysis. The ubiquitin-proteasome system degrades intracellular proteins into peptide fragments that can be presented by MHC-I molecules [45]. Some viral proteins employ effective strategies to escape from CD8⁺ T cell recognition by self-inhibition of antigen processing. EBNA1 (Epstein-Barr nuclear antigen 1), a virus episome maintenance protein, regulates the replication of episomes in synchrony with cellular DNA, allowing proper segregation during cell division [46]. EBNA1-specific CD8⁺ T cell responses are present in the majority of EBV-infected healthy individuals, but the number of EBNA1-specific CD8⁺ T cells is significantly decreased in nasopharyngeal carcinoma patients [47]. Loss of EBNA1-specific memory CD8⁺ and CD4⁺ T cells are also observed in patients progressing to AIDS-related non-Hodgkin lymphoma [48]. These data suggest that EBNA1-specific T-cell immunity is important for control of EBV-associated malignancies. EBNA1 restricts its own proteasomal degradation. A glycine-alanine repeat (GAR) domain of EBNA1 plays an important role in interfering with antigen processing by proteasome and MHC-I-restricted presentation [49, 50]. In addition, the GAR domain also regulates EBNA1 synthesis by inhibiting its own translation [51].

KSHV LANA (latency-associated nuclear antigen) tethers viral DNA to chromosomes during mitosis to ensure correct partition of the viral genome into progeny cells [52]. It also plays a critical role in maintaining latency by repressing Rta (replication and transcription activator)-mediated transactivation, resulting in decreased lytic cycle replication [53]. Although LANA1 does not share amino acid homology with EBNA1, the QED central repeat domain of LANA1 has similar function in immune evasion by inhibiting its own proteasomal degradation and retarding its own translation [54]. mLANA encoded by MHV-68 ORF73 is homologous to KSHV LANA [15], and is involved in the establishment and maintenance of latency [55]. Similar to EBNA1 and LANA1, mLANA is also associated with inhibition of its own protein degradation and synthesis [56].

Impairment of peptide-MHC-I assembly by MHV-68 mK3 and EBV BNLF2a

MHC-I molecule consists of two polypeptide chains, heavy α chain (HC) and β 2-microglobulin (β 2m). MHV-68-encoded K3 (mK3) protein is a homolog of KSHV-encoded K3 and K5 (kK3 and kK5), having E3 ubiquitin ligase activity. kK3 and kK5 induce rapid endocytosis and lysosomal degradation of cell surface glycoproteins (see next section). In contrast, mK3 is predominantly expressed in the ER membrane where it ubiquitinates the cytoplasmic tails of newly synthesized H-2D^b glycoproteins for proteasomal degradation. This leads to the rapid degradation of nascent MHC-I molecules [57]. mK3 can also degrade the TAP and tapasin [58]. The mK3-induced reduction of MHC-I expression is sufficient to block antigen presentation [59]. However, mK3 fails to interfere with the assembly of MHC-I molecule in TAP/tapasin deficient cells, suggesting that the ubiquitination is dependent on TAP/tapasin [60].

BNLF2a, an EBV lytic cycle protein, inhibits TAP-mediated import of antigenic peptides into the ER by suppressing the binding of both ATP and peptide to TAP [61]. BNLF2a is a membrane-associated protein, composed of two specialized domains. Its C-terminal tail anchor mediates membrane integration and ER retention, and its cytosolic N-terminus inhibits TAP function [62].

Interference with cell surface expression of peptide-MHC-I complexes by EBV BILF1 and KSHV K3/K5

Once antigenic peptide is loaded onto MHC-I molecule, the peptide-MHC-I complex dissociates from the PLC and then leaves the ER to the cell surface. EBV-encoded BILF1, a lytic cycle protein, is a G-protein coupled receptor and localizes predominantly in the plasma membrane [63]. BILF1 can downregulate the expression of MHC-I molecules on the cell surface by enhancing their endocytosis and promoting lysosomal degradation [64]. BILF1 selectively downregulates cell surface expression of HLA-A, -B and -E, while HLA-C expression is less affected [65]. kK3 and kK5 (also termed MIR1 and MIR2, modulator of immune recognition) are two KSHV-encoded membrane-bound E3 ubiquitin ligases [66]. kK3 and kK5 lead to ubiquitination of the cytosolic tail of MHC-I molecules, thus enhancing their endocytosis from the cell surface. Subsequently, the internalized MHC-I molecules are delivered to endolysosomal vesicles where they undergo degradation [67, 68]. kK3 and kK5 display different specificities in downregulation of HLA alleles. kK3 downregulates the expression of HLA-A, -B, -C and -E, whereas kK5 downregulates HLA-A and -B significantly, HLA-C weakly, but not HLA-E [69].

INTERFERENCE WITH MHC CLASS II-RESTRICTED ANTIGEN PRESENTATION

CD4⁺ T helper cells are important for the induction and maintenance of effective CD8⁺ T cell response and humoral immunity by recognizing antigens presented by MHC-II molecules [70]. Generally, peptide antigens presented by MHC-II are derived from exogenous proteins that are endocytosed, degraded in lysosomes, then delivered to the MHC-II loading compartment (MIICs) [71]. In addition, endogenous antigens can be presented through autophagy by the fusion of autophagosomes with MIICs [72]. These antigenic peptides in MIICs are loaded onto MHC-II molecules and the peptide-MHC-II complexes are then transported to the cell surface where they will be recognized by CD4⁺ T helper cells. Gammaherpesviruses encode a variety of immunomodulators to interfere with MHC-II-restricted antigen presentation (Figure 2).

Attenuation of MHC-II expression by KSHV vIRF3 and EBV BZLF1

As a master regulator, the class II transactivator (CIITA) promotes expression of MHC-II molecules at the transcriptional level [73]. The CIITA gene is under the control of several promoters. Promoter I (PI) and PIII direct the specific constitutive expression of CIITA with a preferential use in DCs and B cells, respectively. In contrast, PIV mediates the IFN- γ -inducible expression of CIITA [74]. STAT1 and IRF1 are required for the function of PIV [75].

SOCS (suppressor of cytokine signaling) can inhibit the JAK/STAT signaling pathway, and SOCS1 and SOCS3 play important roles as regulators of adaptive immunity [76]. KSHV infection triggers transcriptional upregulation of SOCS3 in human endothelial cells, which results in a reduction of HLA-DR at the transcriptional level. This is because SOCS3 inhibits IFN- γ -induced phosphorylation of STAT1 and transcription of CIITA [77]. vIRF3 (also called LANA2) is expressed in latently infected primary effusion lymphoma cells functioning as an oncogene and is required for the cell survival [78]. vIRF3 downregulates the surface expression of MHC-II on KSHV-infected lymphoma cells by inhibiting the activity of CIITA PIV and PIII [79]. In addition, vIRF3 interacts with cellular IRF5, thereby blocking IRF5-mediated IFN promoter activation and interfering with IRF5-mediated regulation of cell proliferation. This contributes to immune evasion and sustained proliferation of primary effusion lymphoma cells [80, 81].

BZLF1 (BamH fragment Z left frame 1, also called Zta, ZEBRA or EB1), the EBV immediate-early lytic protein, is a transcription factor that activates lytic cycle cascade leading to switch from latency to lytic cycle [82]. BZLF1 reduces IFN- γ receptor α (IFN- γ R α) expression at both the mRNA and protein levels, and thus reduces IFN- γ -induced MHC-II expression [83]. BZLF1 also inhibits transcription of the MHC-II gene by binding to and repressing CIITA PIII [84]. In addition, BZLF1 downregulates surface CD74 (a chaperone for MHC-II antigen presentation) post-transcriptionally [85].

Blockade of TCR and MHC-II engagement by EBV gp42

EBV gp42 (also called BZLF2), a lytic-phase protein, functions as an entry mediator in a complex with glycoproteins gH and gL during B cell infection [86]. gp42 triggers fusion of the EBV envelope with the host cell membrane by binding to MHC-II molecules on the surface of B cells [87]. gp42 has two forms, full length type II membrane protein and a shorter soluble protein, and both of them can bind to immature MHC-II protein or peptide-MHC-II complex. gp42 does not affect peptide-loading on MHC-II molecules, but can block the interaction of TCR with peptide-MHC-II complex, thereby inhibiting antigenic recognition by CD4⁺ T helper cells [88, 89].

Limited presentation of EBNA1 antigen to CD4⁺ T helper cells

EBNA1 can be processed and loaded onto MHC-II molecules as an endogenous antigen [90], and this process requires autophagy [91]. EBNA1 is predominantly located in the nucleus, which restricts its accessibility to the autophagy pathway. In consequence, limited EBNA1 epitopes are presented on the surface of infected cells for CD4⁺ T cell recognition [92].

IMPAIRMENT OF DC FUNCTIONS AND DOWNREGULATION OF COSTIMULATORY MOLECULES

DCs are professional antigen-presenting cells (APCs) and are essential for the initiation of immune responses as messengers between innate and adaptive immunity [93]. DCs are very efficient at antigen processing for both MHC-I and -II pathways by capturing antigens in infected tissues and then migrating to lymphoid organs to prime T cells. Interference with

the function of DCs is a common feature of γ -herpesviruses. EBV inhibits the development of DCs by promoting apoptosis of their monocyte precursors, leading to reduced numbers of mature DCs [94]. Monocyte-derived DCs in patients with Kaposi's sarcoma have been shown to be functionally impaired [95]. Cytokines including IL-10, released by primary effusion lymphoma cells, can suppress DC differentiation [96]. KSHV inhibits monocyte differentiation into DCs [97] and reduces DC migration by downregulating CCR6 and CCR7 expression on the cell surface and by inducing cytoskeleton modifications [98]. KSHV also downregulates DC-SIGN (dendritic cell-specific ICAM-3 grabbing nonintegrin), a receptor for virus attachment, thereby decreases endocytic activity of DCs and inhibits antigen-specific activation of CD8⁺ T cells [99].

Costimulation provided by APCs as signal 2 is essential to induce full activation of T cells and prevent them from becoming refractory to antigenic stimulation. The most important costimulatory pathways include CD28/CD80-CD86, CD40L/CD40, CD27/CD70, 4-1BB/4-1BBL and OX-40/OX-40L [100]. The CD28/CD80-CD86 pathway is crucial in the antiviral CD8⁺ T cell response and immune surveillance against MHV-68 [101]. Interaction of ICAM-1 (intercellular adhesion molecule 1) with LFA-1 (lymphocyte function-associated antigen 1) also provides an important costimulatory signaling for T cell activation [102]. Viruses have evolved the ability to downregulate these costimulatory molecules. kK5 can downregulate CD86 and ICAM-1 expression on B cells by inducing their endocytosis and degradation, thereby impairing the ability to activate T cells [103]. Moreover, the kK5-triggered downregulation of CD86 and ICAM-1 expression on the BJAB (a B lymphoma cell line) results in a reduced natural killer (NK) cell-mediated cytotoxicity [104]. kK5 also protects KSHV-infected cells against NK cytotoxicity by decreasing expression of the ligands for NK cell activating receptors, MICA (MHC class I polypeptide-related sequence A), MICB and AICL (activation-induced C-type lectin) [105]. This strategy is very important for evasion from NK cytotoxicity because downregulation of MHC-I molecules renders KSHV-infected cells sensitive to NK-mediated recognition and killing.

Unlike many viral infections, MHV-68 infection does not upregulate the expression of CD80, CD86, MHC-I, and MHC-II molecules on immature DCs, indicating that MHV-68 cannot induce DC maturation. Furthermore, LPS and poly I:C stimulations fail to promote the expression of these molecules on MHV-68-infected immature DCs, suggesting that MHV-68 can block DC maturation [106].

REGULATORY T CELLS INDUCED BY γ -HERPESVIRUS INFECTIONS

Tregs play an important role in the maintenance of immunologic homeostasis by suppressing immune responses in infection and autoimmunity [107]. Tregs are composed of phenotypically and functionally distinct populations, and their differentiation and function are controlled by specific signals in the immune environment. Tregs suppress immune responses by several mechanisms, including direct cell-cell contact, modulation of APC functions, and production of anti-inflammatory cytokines such as IL-10, TGF- β and IL-35 [108]. Consequently, Tregs can play a dual role in infectious diseases by preventing immunopathology and impeding pathogen clearance.

EBV-specific Tregs

Enhanced number and function of Tregs are observed in many disease conditions associated with the γ -herpesviruses. $CD4^+CD25^{high}Foxp3^+$ Tregs increase in the peripheral blood of EBV positive patients with nasopharyngeal carcinoma and suppress the proliferation of autologous $CD4^+CD25^-$ T cells [109]. Reactivation of EBV-specific $CD8^+$ T cells in transplant patients results in an expansion of $CD8^+$ Tregs that show upregulated Foxp3 expression, produce both IL-10 and IFN- γ , and suppress proliferation of noncognate $CD4^+$ T cells via cell-cell contact [110]. $CCR4^+Foxp3^+$ Tregs are abundantly present in the infiltrating cells in age-related EBV-positive B cell lymphoproliferative disorder [111]. EBNA1 upregulates production of the chemokine CCL20 by EBV positive Hodgkin's lymphoma cells and thereby increases the migration of $CD4^+Foxp3^+$ Tregs [112]. EBNA1 can induce both Th1 and $CD4^+CD25^+Foxp3^+GITR^+$ Tregs *in vitro*, and the Tregs display suppressive activity by cell-cell contact or partially by soluble inhibitory factors [113]. Taken together, these EBV-specific Tregs may be associated with immune escape of tumor cells and affect the clinical progression of malignancies. In contrast, it has also been reported that an increase in $CD4^+CD25^+FOXP3^+$ Tregs correlates with EBV infection, but has no impact on survival in patients with classical Hodgkin lymphoma [114].

MHV-68-specific Tregs

$CD8^+$ Tregs can be induced in a range of different systems and exhibit different phenotypes and functions. Naturally occurring $CD8^+CD122^+$ Tregs mediate suppression through IL-10 [115]. HIV-specific IL-10-positive $CD8^+$ Tregs mediate suppression through direct cell-cell contact [116]. In MHV-68-infected mice, IL-10-producing $CD8^+$ T cells account for 1% of total $CD8^+$ T cells, of which around 10% are specific to ORF61₅₂₄₋₅₃₁, a dominant epitope of MHV-68. In the absence of $CD4^+$ T cell help, a similar situation to AIDS patients, the population of IL-10-producing $CD8^+$ T cells increases up to 4.5% of total $CD8^+$ T cells during the chronic phase of MHV-68 infection, and these cells function as Tregs [117]. IL-10-producing $CD8^+$ Tregs are partially responsible for erosion in immune surveillance against MHV-68, which leads to spontaneous viral reactivation in the lungs of $CD4^+$ T cell-depleted mice [118]. The $CD8^+$ Tregs suppress proliferation of naïve $CD8^+$ T cells *in vitro* in a cell contact-independent manner, and the suppression cannot be antagonized by blockade of IL-10R, suggesting the existence of suppressive factors besides IL-10 [117]. Interestingly, it is also reported that MHV-68 can reduce the frequency and activity of naturally occurring $CD4^+CD25^+$ Tregs following infection [119].

INDUCTION AND PRODUCTION OF IL-10 IN γ -HERPESVIRUS INFECTIONS

IL-10 plays a pivotal role in controlling inflammation by suppressing the functions of APCs and T cells and the production of inflammatory cytokines [120]. Accordingly, IL-10 plays a dual role in infectious disease. In acute virus infections, such as influenza virus, effector $CD8^+$ and $CD4^+$ T cells attenuate lung inflammation by producing IL-10, thus preventing immunopathology [121]. In persistent virus infections, such as HIV, IL-10 inhibits virus-specific T cells, thereby impeding pathogen control [122]. It has been demonstrated that γ -herpesvirus infections can induce IL-10 production. The percentage of IL-10-expressing cells in EBV-positive cases of Hodgkin's disease is significantly higher than in EBV-

negative cases [123]. B cell lines derived from EBV positive Burkitt's lymphoma, especially those from patients with AIDS, constitutively secrete large quantities of IL-10 [124]. High levels of IL-10 expression are also induced by EBV infection of B lymphocytes [125]. IL-10 and viral IL-6 (vIL-6) have been shown to be autocrine growth factors for autonomous proliferation of KSHV-infected primary effusion lymphoma cell lines [126]. MHV-68 infection also results in increased levels of IL-10 [127]. MHV-68-infected mice show elevated IL-10 expression in DCs, which interferes with the ability of DCs to activate T cells, and this action can be partially reversed by blocking IL-10 [128]. It is notable that IL-10 can be encoded not only by the host cells (cIL-10), but also by some viruses (vIL-10). IL-10-like ORFs have been identified in multiple members of the two families *Herpesviridae* and *Poxviridae*. Several γ -herpesviruses, including EBV, rhesus lymphocryptovirus, equine herpesvirus 2 and ovine herpesvirus 2, have been shown to encode IL-10 homologs (vIL-10) [129]. The acquisition of IL-10-like sequences likely equips the viruses with a powerful tool to modulate host immune function.

cIL-10 induced by γ -herpesvirus-derived immunomodulators

LMP1 (latent membrane protein 1) is a key factor for EBV-mediated transformation of primary B cells and plays multiple roles in EBV induced immune escape [130]. LMP1 induces high levels of IL-10 secretion by CD4⁺ T cells from EBV sero-positive individuals, and thus inhibits T cell proliferation and IFN- γ secretion induced both by mitogen and recall antigen [131]. LMP2A can upregulate IL-10 production in mitogen-stimulated primary B cells and B cell lymphomas, and the increased IL-10 promotes the survival of these cells [132]. BZLF1 activates both transcription and translation of human IL-10 (hIL-10) in B cells by binding directly to specific DNA sequences in the hIL-10 promoter [133]. EBERs are EBV-encoded non-coding RNAs with ~170 nucleotides, are expressed at high levels in infected cells, and play a role in the pathogenesis of this infection [134]. EBERs also induce IL-10 expression in Burkitt's lymphoma cells, and the IL-10 acts as an autocrine growth factor for Burkitt's lymphoma [135].

MicroRNAs (miRNAs) are a class of short (~20-23 nucleotides), single-stranded and non-coding RNAs that regulate gene expression post-transcriptionally. Gammaherpesvirus-encoded miRNAs and their contribution to pathogenesis and tumorigenesis have recently been reviewed [136]. KSHV encodes over 25 miRNAs, and these miRNAs participate in a highly complex network of interactions with the cellular and viral transcriptomes [137, 138]. Of these, miR-K12-3 and miR-K12-7 can induce the transcription and secretion of IL-10 and IL-6 by macrophages [139].

MHV-68-encoded M2, a latency-associated protein, induces an antigen-specific CD8⁺ T cell response, which contributes to the control of latency establishment in the infected animal [22]. However, M2 has also been reported to play a role in MHV-68 latency establishment and reactivation in splenic B cells [140]. M2 increases the pool of germinal center B cells by inhibiting apoptosis of the infected cells [141], and suppresses IFN-mediated antiviral activity by downregulating STAT1/2 signaling [142]. In addition, M2 induces B cells to secrete high levels of IL-10, which leads to the proliferation and differentiation of M2-expressing B cells [143].

vIL-10 encoded by EBV

In addition to inducing IL-10 expression by host cells, EBV encodes vIL-10, a product of the lytic phase BCRF-1 gene [144]. vIL-10 shares 84% amino acid identity with hIL-10, while the identity between hIL-10 and murine IL-10 is 73% [145]. vIL-10, together with BNLF2a, contributes to immune evasion during the early phase of infection [146]. vIL-10 downregulates TAP1 and bli/LMP2 (a subunit of the proteasome) at the mRNA level, thereby resulting in a reduction of MHC-I expression [147] (Figure 1). vIL-10 inhibits IFN- γ synthesis by activated mouse Th1 clones and human peripheral blood mononuclear cells [148]. It reduces antigen-specific T cell proliferation by downregulating basal and IFN- γ - or IL-4-induced MHC-II expression on monocytes [149] (Figure 2). Like hIL-10, vIL-10 is also a potent growth factor for activated B cells [150]. However, vIL-10 does not stimulate the proliferation of thymocytes [151] and mast cells [152] and does not upregulate MHC-II on B cells [153]. Substitution of isoleucine at position 87 with alanine (corresponding to the vIL-10 residue) abrogates the immunostimulatory activity of cIL-10 but preserves its immunosuppressive activity [145]. These data suggest that vIL-10 may derive from a captured and mutated cIL-10 gene, and the alteration is beneficial to the virus by disrupting host immune responses.

CONCLUSIONS

Gammaherpesviruses establish persistent infections and trigger the development of malignancies by antagonizing the adaptive antiviral responses in their hosts. Immune evasion mechanisms are associated with the suppression of MHC-I- and MHC-II-restricted antigen presentation, impairment of DC functions, downregulation of costimulatory molecules, activation of viral-specific Tregs, and induction of inhibitory cytokines, such as IL-10. By summarizing the literature above, we aim to gain a clearer picture regarding how γ -herpesviruses escape from adaptive immunity by the concerted actions of γ -herpesvirus-derived immunomodulators and host-derived regulatory factors.

Gammaherpesvirus infections utilize an exceptionally broad array of strategies to evade the immune response, involving multiple viral and host proteins. These are potential targets for drug development, as inhibition of these pathways has the potential to attenuate the infection. However in order to have a significant impact on disease, it may be necessary to target multiple pathways simultaneously. Progress in this area has been hampered by the lack of tractable animal models to study EBV and KSHV infection and immunity *in vivo*. The MHV-68 model offers a system in which the effects of potential therapies on infection, pathogenesis and the immune response can be monitored very readily. Other factors for consideration are that the outcomes of γ -herpesvirus infections depend not only on the properties of the virus and its immunomodulators, but also on the presence of other pathogens such as HIV and the individual immune response of the host. Accordingly, more in-depth study of immune modulation during γ -herpesvirus infection is necessary, and will likely ultimately lead to new therapeutic approaches for this important class of infection.

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Abbreviations used

CIITA	class II transactivator
DC	dendritic cell
EBNA	Epstein-Barr nuclear antigen
IRF	IFN regulatory factor
KSHV	Kaposi's sarcoma-associated herpesvirus
LANA	latency-associated nuclear antigen
MHV-68	murine γ -herpesvirus
Treg	regulatory T cell

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Figure 1.

Gammaherpesviruses inhibit MHC-I-restricted antigen presentation. vIRF1 interacts with the transcriptional coactivator p300 and thereby interferes with the MHC-I transcription. BGLF5, SOX and muSOX promote the degradation of host mRNAs and shutoff of MHC-I gene expression. EBNA1, LANA1 and mLANA escape being processed by the proteasome and inhibit their own translation. BNLF2a shuts down TAP-mediated import of antigenic peptides. mK3 directs immature MHC-I molecules to the cytosol and also degrades TAP and tapasin. BILF1, kK3 and kK5 trigger endocytosis of cell surface MHC-I molecules and promote their lysosomal degradation. vIL-10 downregulates TAP1 and bli/LMP2 (a subunit of proteasome) at the mRNA level.

Figure 2.

Gammaherpesviruses inhibit MHC-II-restricted antigen presentation. SOCS3 expression is upregulated by KSHV infection, which inhibits IFN- γ -induced phosphorylation of STAT1, thereby downregulating the transactivation of CIITA gene. BZLF1 and vILF3 bind to the promoters of CIITA genes and thus interfere with its transactivation. BZLF1 reduces IFN- γ R α expression at both the mRNA and protein level, and in that way shuts down the entire IFN- γ -induced CIITA signaling cascade. gp42 blocks TCR and MHC-II engagement. vIL-10 reduces IFN- γ synthesis and inhibits both basal and IFN- γ -induced expressions of MHC-II.