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Review Article

Human Herpesviridae Methods of Natural Killer Cell Evasion

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Human herpesviruses cause diseases of considerable morbidity and mortality, ranging from encephalitis to hematologic malignancies. As evidence emerges about the role of innate immunity and natural killer (NK) cells in the control of herpesvirus infection, evidence of viral methods of innate immune evasion grows as well. These methods include interference with the ligands on infected cell surfaces that bind NK cell activating or inhibitory receptors. This paper summarizes the most extensively studied NK cell receptor/ligand pairs and then describes the methods of NK cell evasion used by all eight herpesviruses through these receptors and ligands. Although great strides have been made in elucidating their mechanisms, there is still a disparity between viruses in the amount of knowledge regarding innate immune evasion. Further research of herpesvirus innate immune evasion can provide insight for circumventing viral mechanisms in future therapies.

1. Introduction (Herpesviridae and Disease)

The human herpes family of viruses includes human cytomegalovirus (HCMV), Kaposi's sarcoma herpesvirus (KSHV), herpes simplex virus types 1 and 2 (HSV-1, 2), varicella zoster virus (VZV), Epstein-Barr virus (EBV), and human herpesvirus 6 and 7 (HHV6, 7). These viruses share similar characteristics: all contain linear double-stranded DNA, are enveloped, and undergo latent and lytic lifecycles. However, there are important differences between these viruses in terms of infection niche and immune evasion strategies for persistent infection.

Herpesviridae evasion of adaptive immune responses has been previously described [1–4]. This paper will focus on herpesvirus innate immune evasion, specifically viral evasion of the natural killer (NK) cells response. Reviews on broad interactions between viruses and NK cells can be found in references [5–8]. The role of NK cells in controlling herpes viral infections become apparent in consideration that multiple herpes infections have been documented in patients lacking NK cells [9] and evidence of NK activation during viral infection [10–13].

2. NK Cells and Activation

NK cells are important innate immune cells involved in the regulation of viral infection [14, 15]. They are a lymphocyte subset of the innate immune system that kills without prior exposure and sensitization to antigens via release of granzymes, perforin, TRAIL, and FAS ligand [16]. NK cells are regulated through surface receptor interactions with ligands expressed on stressed cells, such as virally infected or malignantly transformed cells. NK cells possess both activating and inhibitory cell surface receptors; it is the balance of ligand interactions with these receptors that determine NK cell activation. The structures, functions, and signaling mechanisms of these receptors and their ligands are comprehensively reviewed in references [16–21]. In addition to receptor-mediated regulation, cytokines induced during viral infection (IL-15, IL-12, IL-8, IFN-α, and IFN-β) can

indirectly activate NK cells as well [6]. A summary of the receptors present on NK cells and associated ligands most relevant to immune evasion by human herpesviruses is provided below.

2.1. Activating Receptors and Ligands

2.1.1. Natural Killer Group 2 Member D (NKG2D) Receptor. NKG2D is a receptor found prominently on NK cells that provides activation signals through the coreceptor DAP-10 upon ligand binding. The ligands that bind NKG2D include (1) the MHC-I-like molecules MHC-class-I-polypeptide-related sequence A (MICA) and B (MICB), (2) UL16 binding proteins (ULBP1–4 and 6), and (3) retinoic acid early transcript 1G (RAET1G). This interaction with multiple activating ligands is unique to NKG2D and does not occur with the other NK cell activating receptors [22, 23]. Investigators have proposed that this development of multiple activating ligands is a coevolutionary responses to viral or tumor pressure [22]. The structures of MICA and MICB are similar to MHC-I with alpha domains; however, they do not engage β2-microglobulin [24–26]. Surface expression of these ligands is normally absent or low on healthy cells and increases upon events of cellular stress such as viral infection, DNA damage, oxidative stress, and oncogenic stress [22, 27–30]. MICA is noted to have a large polymorphic distribution, with over 73 alleles identified [31]. A subset group of MICA alleles contains a frameshift mutation resulting in a premature stop codon and subsequent truncation of the cytoplasmic C-terminus. Interestingly, the MICA allele $*008$ encodes a truncated protein and is the most frequently distributed MICA allele in various populations across the world [32–39]. ULBP1–4 and RAET1 have alpha1 and alpha2 domains similar to MICA/B; however, unlike MICA/B, they do not contain alpha3 domains and their mRNA is expressed at low levels even in normal cells without corresponding surface expression [23, 40].

2.1.2. Natural Cytotoxicity Receptors (NCRs). The NCRs contain immunoglobulin (Ig)-like domains and include NKp30, NKp44, NKp46, and NKp80 [41, 42]. A role for NCRs has been implicated in the prognosis of leukemia [43, 44] and the recognition/killing of various solid tumors [45, 46]. Only NKp30 has a confirmed ligand, the tumor ligand B7-H6 [47, 48]. Additional ligands for the NCRs are unknown, although possible ligands have been identified and include nuclear factor BAT3 [49] and a number of viral hemagglutinin proteins and heparan sulfate structures [50, 51].

2.1.3. DNAX Accessory Molecule-1 (DNAM-1). DNAM-1 is a member of the Ig super family that recognizes CD112 (nectin-2) and the poliovirus receptor [17]. Similar to other activating receptors, there is expression of DNAM-1 ligands on various tumors resulting in DNAM-1-mediated killing alone or in concert with other receptors [52–56]. Aberrations in DNAM-1 expression or DNAM-1 expressing NK cells have also been linked to a variety of autoimmune diseases [57–59].

2.2. Inhibitory Receptors and Ligands. The primary inhibitory receptors include the killer Ig-like inhibitory receptors (KIRs) and CD94-NKG2A lectin-like inhibitory receptor. The KIRs and CD94-NKG2A bind to MHC-I molecules and diminish NK cell activation. There has been no evidence to date for their binding to MHC-II molecules. The receptor-ligand interactions for both KIRs and CD94-NKG2A are MHC-I isotype specific [60–62]. In accordance with the "Missing Self" hypothesis first proposed by Karre et al., the lack of MHC-I on target cells removes the inhibitory signals from NK cells, thus leading to unopposed activation [63, 64].

2.2.1. Killer Ig-Like Inhibitory Receptors (KIRs). The KIRs are members of the Ig superfamily that recognize MHC-I molecules of the HLA-C isotype on surrounding cells [17, 19]. The absence of HLA-C on tumor and virus infected cells can result in loss of NK cell inhibition [21, 65, 66].

2.2.2. Leukocyte Ig-Like Receptor (LIR)-1. Like the KIRs, LIR-1 contains Ig domains and binds MHC-I, but with a lower affinity than other inhibitory receptors [17, 19]. LIR-1 expression is more variable on NK cells than other immune cells [17].

2.2.3. CD94-NKG2A Lectin-Like Inhibitory Receptor. This receptor is a C-lectin-like heterodimer that recognizes MHC-I molecules of the HLA-E isotype. Ligation of HLA-E by CD94-NKG2A leads to inhibition of NK cells, yet HLA-E ligation can activate NK cells if CD94 is complexed to NKG2C or -E [17, 19]. Similar to KIRs, the CD94-NKG2A complex results in loss of NK cell inhibition in the absence of HLA-E. However, the uninhibited activity is not as strong as that mediated by KIRs [65].

3. Herpesviridae Methods of NK Cell Evasion

Human herpesviruses have evolved multiple mechanisms to dampen NK cell cytotoxicity, interacting with many of the factors influencing the balance of NK cell activation and inhibition. A summary of these mechanisms is provided in Table 1. A number of methods employed by human herpesviruses hinder the expression of NK cell ligands on infected cells. This method of immune evasion has been studied in different members of the herpesvirus family, defining marked similarities and stark differences between family members. Multiple mechanisms offset the indirect NK cell activation prompted by lack of MHC-I surface expression. As many human herpesviruses diminish MHC-I presentation of viral antigens to avoid detection by cytotoxic T lymphocytes, these mechanisms may offset the loss of NK cell inhibition from "Missing Self" [64, 67].

3.1. CMV. The HCMV product UL18 is an MHC-I homologue that binds the inhibitory NK cell receptor LIR, possibly as a means of increasing the inhibitory signal [80, 81]. However, inhibition via this ortholog is controversial [101–103]. CMV also encodes UL40, which stabilizes and promotes surface expression of the HLA-E isotype. This

Table 1: Summary of known interactions between NK cell receptors, ligands, and herpesvirus immunoevasins.

Major receptors	Ligand	Virus	Immunoevasin	Mechanism	References
Activating					
NKG2D	MICA	HCMV	UL142	Internal retention	[68, 69]
		KSHV	K5	Ubiquitination/sequestration	[70, 71]
		HSV	?	?	[72, 73]
		HHV-7	U21	?	[74]
	MICB	HCMV	UL16	Internal retention	[23, 75–77]
		HCMV	miR-UL112	Translational downregulation	[78]
		KSHV	K5	Ubiquitination/sequestration	[70, 71]
		KSHV	miRK12-7	Translational downregulation	[79]
		HSV	?	?	[72, 73]
		EBV	miR-BART2-5p	Translational downregulation	[79]
		HHV-7	U21	?	[74]
	ULBP1–4	HCMV	UL16	Internal retention	[23, 75–77]
		HSV	?	?	[72]
		HHV-7	U21	Lysosomal degradation	[74]
NCRs	AICL	KSHV	K5		[71]
DNAM-1	PVR	?	?		
	CD112	?	?		
Inhibitory					
LIR-1, KIRs, CD94/NKG2A	MHC-I	HCMV	UL18	MHC-I homologue	[80, 81]
		HCMV	UL40	Signal prolongation	[82–84]
		HCMV	US2, US3, US6, US11	Retention/degradation	[64, 67]
		KSHV	K5, K3	Endocytosis	[85–87]
		HSV	ICP47	TAP interference	[88–90]
		EBV	vIL-10	IL-10 homolog	[91]
		EBV	BNLF2a	TAP interference	[92, 93]
		EBV	BILF1	Endocytosis/degradation	[94]
		HHV-6	U21 analogues	Lysosomal degradation	[95]
		HHV-7	U21	Lysosomal degradation	[96–98]
		VZV	ORF66	Internal retention	[99, 100]

diminishes NK cell activation by increased ligation of the CD94-NKG2A receptor [82–84]. US11 targets HLA-A; US2 and US3 target HLA-A and HLA-G while sparing HLA-E; US6 targets HLA-A,G, and E for degradation to diminish cytotoxic T-cell detection [64, 67, 104].

In addition to inducing an inhibitory response, HCMV also suppresses activating ligands that bind NKG2D. HCMV UL16 binds MICB, ULBP1, and ULBP2 to sequester these proteins in the ER of infected cells but is unable to bind to RAET1G [23, 75–77, 105]. The crystal structure of UL16-MICB complex has been characterized in reference [106]. The HCMV protein UL142 blocks surface expression of some MICA alleles by interacting with the cytosolic carboxyl-terminal region of the transmembrane protein and retaining it in the golgi network, limiting surface expression of the activating ligand. HCMV UL142 cannot downmodulate truncated forms of MICA lacking the intracellular carboxy terminus. It is interesting that, of the >70 MICA allelic forms, the MICA∗008 truncated form is present in a majority of the population and may provide a selective advantage [68, 70]. There is also evidence that HCMV encodes the microRNA mIR-UL112 that decreases MICB production to escape NKG2D detection [78, 107].

In summary, HCMV has multiple means of NK cell ligand manipulation. UL18 is a mock MHC-I molecule that takes advantage of NK cell inhibitory receptors, while UL40 prolongs the inhibitory signals of actual host MHC-I molecules. UL16 retains NKG2D ligands (except MICA and ULBP3) to prevent activation, while UL142 downmodulates MICA in an allele-dependent manner. All of the methods of immune evasion used by CMV are more comprehensively reviewed in references [2, 108].

3.2. KSHV. KSHV encodes proteins that target MHC-I to prevent viral antigen presentation to T-lymphocytes as does HCMV; however, the molecular mechanisms differ. KSHV K3 and K5 are E3 ubiquitin ligases that transfer ubiquitin to the cytoplasmic tails of proteins [70, 85]. The K5 protein

targets HLA-A and HLA-B for endocytosis from cell surfaces, while the K3 protein targets HLA-A, B, C, and E [85–87]. No interactions with HLA-G are known.

Like UL142 of CMV, the KSHV protein K5 also blocks surface expression of MICA and MICB but is unable to downregulate the MICA∗008 allele due to the absence of a cytoplasmic tail and lysine ubiquitin sites [71]. Ubiquitinated MICA proteins are endocytosed from the infected cell surface and retained in cytoplasmic vesicles without increased degradation [71]. K5-mediated downmodulation protects infected cells from NK cell cytotoxicity [71]. K5 also downmodulates the activating ligands B7-2, AICL, and ICAM-1 by a similar mechanism [71, 109]. In contrast to acute lytic infection, chronic infection with KSHV results in higher levels of MHC-I, MICA/B, PVR, and CD112 expression [110]. Akin to HCMV, KSHV encodes the microRNA miRK-12-7 inhibiting MICB expression [79]. Additionally, KSHV has been reported to infect NK cells, leading to downmodulation of the activating NCRs and NKG2D receptors on NK cell surfaces [110].

To summarize, KSHV is similar to CMV in that both viruses encode proteins downmodulating MHC-I and MICA/B. The mechanism by which KSHV proteins function diverges from HCMV proteins in that KSHV K3 and K5 ubiquinate and promote endocytosis of targeted proteins, whereas HCMV UL142 and UL16 prevent protein maturation and surface expression. Similar to HCMV UL142, KSHV K5 downmodulation of MICA is allele dependent. The mechanistic basis is the absence of ubiquitin sites in the truncated cytoplasmic tail. To date, there is no evidence of KSHV mechanisms affecting the expression of the ULBP or RAET ligands. KSHV specific immune evasion is reviewed in more detail in [70, 111].

3.3. HSV-1 and 2. The exact mechanisms by which HSV-1 modulates NK cell inhibitory and activating ligands are less studied than those for HCMV and KSHV. The HSV-1 and 2 US12 gene product (infected cell protein 47, ICP47) downmodulates MHC-I surface expression by suppressing MHC-I transport from the ER [64, 72]. ICP47 binds to the transporter associated with antigen presentation (TAP) and in doing so inhibits MHC-I antigen loading and expression of antigenic peptides generated by proteasomal degradation that then translocate from the cytosol to the ER lumen [88–90, 112]. Cells engineered to express ICP47 failed to express antigenic peptides [90]. Interestingly, HSV-1 induces expression of certain HLA-G isoforms while decreasing the surface expression of others [113].

The consequences of MHC-I downmodulation on NK cell recognition of HSV-1 and HSV-2 infected cells are controversial. Studies using antibody blocking of KIRs and MHC-I in conjunction with exogenous ICP47 expression suggest that the protective properties of MHC-I via KIR inhibitory signaling are rendered ineffective upon infection with HSV-1 [64]. However, some studies utilizing ICP47 deleted recombinant HSV-1 and anti-KIR antibodies suggest that NK cell inhibitory effects of MHC-I molecules are not significant enough alone to diminish cytotoxicity and that the viral product ICP47 is not necessary in inducing susceptibility to NK cell killing [73]. There are yet other findings that suggest a qualitative change in MHC-I molecules, such as the binding site shape presented to NK cells during HSV infection rather than the quantity of molecules presented, may contribute to NK recognition and killing [114].

There are few studies examining the influence of HSV-1 and HSV-2 infection upon the NK cell activating ligands. Experiments utilizing HSV-1 recombinants deleted of all IE genes except for ICP0 were able to induce NK cell induced lysis of human fibroblasts. Fibroblasts expressing ICP0 yielded similar results [73]. Infection with these recombinants also demonstrated an upregulation of unknown ligands binding to NCRs with cytotoxicity dependent upon their presence, yet this only occurred at low multiplicities of infection (MOIs). ICP0-independent mechanisms were reported at higher MOIs [73]. In contrast, studies of HSV effects on NKG2D ligands demonstrated decreased surface expression of MICA in HeLa and U373 cells infected with HSV-1 or HSV-2 with no difference in total protein levels [72]. Interestingly, this HSV-mediated downmodulation of MICA occurs with both the full-length and the truncated protein encoded by the MICA∗008 allele. This diverges significantly from the inability of HCMV and KSHV to downmodulate truncated MICA variants. Down-modulation of MICA was reported with ICP0 deleted recombinant HSV but not with PAA blocking of late gene expression, suggestive that this phenomenon is dependent on late-gene expression [72].

These studies together suggest HSV-1 and HSV-2 employ both early and late gene modulation of NK activating ligands, each with potentially different consequences for virus-infected cells. ICP0 might be sufficient to trigger NK cell cytotoxicity at low MOIs through upregulation of NCR ligands, which would be deleterious for virus survival. Yet at higher MOIs mechanisms other than ICP0 contribute to infected cell susceptibility. MICA downmodulation was shown to be independent of ICP0 expression and may be caused by late gene products. As posited by Schepis et al., HSV-1 may cause infected cells to be particularly susceptible to NK cell-mediated killing early in infection due to ICP0 upregulation of NCR ligands while attempting immunoevasion later in infection by NKG2D ligand and MHC-I downregulation [72]. Although HSV-1 and HSV-2 microRNAs have been documented, none have been found to interfere with NK cell pathways.

3.4. EBV. As with the previously described human herpesviruses, EBV has methods of interfering with MHC-I to prevent presentation of viral antigens to cytotoxic T cells. During active B-cell infection, EBV expresses a viral homolog of interleukin-10 (vIL-10) [91] and BNLF2a, a lytic-phase viral protein [92, 93]; both have been reported to downregulate the expression of TAP and in turn decrease surface MHC-I. BILF1 is a protein also expressed during lytic EBV infection that mediates both increased endocytosis/degradation and decreased exocytosis/presentation of MHC-I [94]. Downmodulation of all isotypes of MHC-I during EBV lytic infection, as well as subsequent decrease in inhibitory binding to KIRs and CD94-NKG2A, results

in increased sensitivity to NK cell-mediated killing [115]. Instead of downregulation of activating ligands to offset this decrease in inhibition, the same studies found an increase in ULBP1 and CD112 expression that contributed to NK cell activation [115]. The only reported mechanism to possibly offset this indirect NK cell activation is a microRNA (miR-BART2-5p) inhibiting MICB expression [79]. EBV may possibly interfere with NKG2D activation through down-modulation of the NKG2D receptor itself via indoleamine-2, 3-dioxygenase metabolites, although the functional consequences have yet to be reported [116]. Similar to KSHV, EBV can infect NK cells, causing aberrantly high expression of the inhibitory CD94-NKG2A receptor but diminished expression of the KIRs [117].

3.5. HHV-6 and HHV-7. The involvement of NK cells in the control of HHV-6 and HHV-7 infection has been documented through studies of IL-2 and IL-15 enhancement of cytotoxicity [118–120]. However, the only documented HHV-7 protein involved in NK cell ligand modulation is U21, a transmembrane protein capable of downmodulating both MHC-I and MICA/B. U21 binds and redirects MHC-I trafficking to lysosomal compartments most similarly to HCMV MHC-I interfering proteins [96–98]. The effect on NK cell killing through this method has not been established. U21 also binds to ULBP1 for redirection to lysosomes and decreases surface MICA and MICB by an undefined mechanism that results in decreased NK cell cytotoxicity [74]. The A and B variants of HHV-6 express proteins analogous to U21 that also bind MHC-I for lysosome redirection [95], but the effect on NK cells or identification of mechanisms affecting activating ligands has not been established.

3.6. VZV. Although NK cells have long been implicated in the control of VZV infection [121–123], specific interactions with infected cells through NK cell receptors have not been extensively studied. VZV downregulates MHC-I on infected cell surfaces via the viral protein kinase ORF66, leading to retention of MHC-I molecules in the golgi [99, 100]. However, any functional consequences of ORF66 on NK cell recognition and killing have not been demonstrated. Likewise, no methods of VZV interference with NK cell activating ligands have been reported to date.

4. Conclusion

Human herpesviruses possess multiple mechanisms for evading both innate and adaptive immune responses. A summary of NK cell receptors, their ligands, and viral mechanisms interfering with each is provided in Table 1. A primary point of interest is the diversity of NK cell evasion mechanisms employed by human herpesviruses. Other than mechanisms shared by the highly similar HSV-1 and HSV-2, the human herpesviruses have evolved different mechanisms for subverting the immune response. It is also notable that these immunoevasion mechanisms do not group with herpesvirus subfamilies. For example, HCMV (a betaherpesvirus) and KSHV (a gammaherpesvirus) both encode microRNA's targeting MICB yet downmodulate MICA via different mechanisms. The NK cell evasion mechanisms are unique to each human herpesvirus likely reflecting selection pressures encountered in the various infection niches occupied by the viruses. The lack of well-defined mechanisms of NK cell immunoevasion by given herpesviruses (i.e., HSV and VZV) is puzzling. There is well-documented persistence of HSV in patients with NK cell defects and the importance of NK cell involvement in the control of disease. Continuing research will likely reveal as yet unknown mechanisms of immunoevasion by the alpha herpesviruses.

Human herpesviruses cause substantial morbidity and mortality. HSV-1 is regarded as one of the most common causes of viral encephalitis, an infection carrying significant risk of mortality [124, 125]. EBV, HCMV, and KSHV infections have the potential to not only cause severe manifestations during acute infection, but also the development of hematologic or solid malignancies [126, 127]. A variety of herpesviruses also cause cutaneous and ocular infections with potential for life-long morbidity [128–130]. Thorough knowledge of specific viral immune evasion mechanisms may provide avenues for developing more effective therapies against disease related to human herpesviruses. Understanding NK cell evasion may improve oncolytic herpesvirus therapies for cancer [131–133]. Insight into viral abilities to evade the immune system may also yield better markers for clinical prognosis and monitoring of active and latent infection [117, 134]. Continued research into these mechanisms of NK cell evasion will not only deepen basic understandings of human herpesviruses but may also serve to ultimately alleviate disease burden and guide strategies for clearance of persistent infection in immunocompromised patients.

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