Immune evasion of natural killer cells by viruses

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Summary

Natural killer (NK) cells are important in the host resistance to viral infections. They are among the first cells to sense the release of proinflammatory cytokines, as well as the downregulation of surface MHC class I molecules and molecules induced by viral invasion of cells. Various viral functions have evolved to counter NK cell responses illustrating the evolutionary struggles between viruses and NK cells. Ligands for NK cell receptors are primary targets for viral immunoevasion. In order to counteract NK cell activation via the "missing self"-axis, viruses encode proteins which serve as ligands for inhibitory NK cell receptors. Viruses also downmodulate the ligands for the activating NK cell receptors and encode soluble ligands which block these receptors. In addition to viral immunoregulatory proteins, regulatory RNAs can also inhibit the expression of ligands for NK cell receptors. Improving our understanding of viral regulation of NK cell function could be essential for designing more efficient measures in the prophylaxis and treatment of virus-induced pathology.

Introduction

Natural killer (NK) cells control viral replication during the time preceding the induction of the adaptive immune response. They are activated through soluble mediators and by direct cell-to-cell contact. Also, by interacting with dendritic cells (DCs), NK cells are involved in regulation of the adaptive immunity [1,2]. NK cells control the infection by cytolysis and secreting proinflammatory cytokines [3]. The activation of NK cells is regulated through the integration of signals from a number of inhibitory and activating receptors [4], many of which employ MHC class I or class I-like proteins as their ligands. Furthermore, in order to become fully functional during ontogenesis, individual NK cells must engage self-reactive inhibitory receptors specific for appropriate MHC class I molecules [5,6]. NK cell receptors, which utilize MHC class I as their ligands, include the human killer cell Ig-like receptor (KIR) family, the mouse Ly49 family, human and mouse CD94/NKG2 heterodimers and leukocyte Ig-like receptors (LIR) [7]. Other activating NK cell receptors include natural cytotoxicity receptors (NCRs) and NKG2D, among others [8]. While normal cellular ligands for NCRs remain unknown, the NKG2D receptor recognizes several different ligands induced by cellular stress and infection [9].

Viruses have acquired numerous mechanisms aimed at subverting or evading the NK cell immune surveillance. Apart from interfering with NK cell receptors and their ligands, viruses affect NK cell responses by regulating apoptosis, modulating cytokines and chemokines, and by compromising DC functions [10,11]. Here we review the unique relationship between NK

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cells and viruses, with a focus on viral strategies for interfering with the expression of ligands for NK cell receptors (Table 1).

Viral avoidance of NK cells activation via "missing self" axis

Viruses downregulate surface MHC class I molecules in order to avoid recognition by CD8^{+} T cells [12]. However, the loss of MHC class I molecules renders the cells susceptible to NK cells as described by the "missing-self" hypothesis [13]. To avoid NK cell-mediated control, viruses encode surrogate ligands for inhibitory NK cell receptors and/or are able to differentially regulate MHC class I molecules by downmodulating those that present viral peptides to CD8^{+} T cells, while sparing those that serve as ligands for inhibitory NK cell receptors [14].

The human cytomegalovirus (HCMV) MHC class I homolog, UL18, was originally described as a decoy ligand for the inhibitory NK cell receptor [15]. The fact that its receptor, LIR-1, was found only on a minor subset of NK cells makes this finding controversial [16]. Later on, it was reported that UL18 could both activate and inhibit NK cell response [16,17]. Its inhibitory function is dependent on the interaction with the LIR-1 molecule [18*]. The mode of activation by UL18 still remains unknown, although it is LIR-1 independent [19*]. Of note, the UL18 sequence and its affinity for LIR-1 vary among clinical HCMV isolates [20,21]. The cellular receptor for mouse cytomegalovirus (MCMV) MHC class I homolog, m144, remains unknown, although mutant viruses lacking this gene show enhanced NK cell sensitivity *in vivo* [22]. However, in our recent study the virus lacking *m144* acted more like the wild type (wt) MCMV strain [23]. The basis for this discrepancy is unclear, but it could be attributed to the use of different viral strains.

Although the "missing self" hypothesis assumes that NK cells can sense the altered expression of MHC class I molecules [13], recent studies showed that the "missing self" axis can also be activated via non-classical MHC molecules [24]. The Nkrp1b and d receptors mediate inhibition via the recognition of Ocil/Clr molecules [25,26]. It has been postulated that the Nkrp1-Ocil/Clr receptor-ligand recognition system may represent an alternative mechanism for discriminating between normal and damaged cells [24]. Recently, it has been shown that cellular Ocil/Clr-b are subject to downmodulation by rat CMV (RCMV) [27*]. This should make the RCMV-infected cells susceptible to the control by NK cell killing due to the lack of inhibition. To avoid this, RCMV encodes its own homolog of Ocil/Clr-b, RCMV C-type lectin-like (RCTL), which serves as a viral ligand for Nkrp1b [27*]. While downmodulation of MHC class I molecules is aimed at protecting the infected host cells against CD8^{+} T cells, the rationale for cells undergoing RCMV infection to selectively downmodulate the ligand for the inhibitory receptor that could sensitize them to NK cell killing, remains elusive. Since NK cells possess no stimulatory receptors for Ocil/Clr-b, the selective pressure for the virus to downmodulate the ligand is unlikely [25,26]. The explanation for the loss of Ocil/Clr-b could be a default reaction of cells to stress induced by infection.

Differential modulation of MHC class I expression by viruses

HLA-E and mouse Qa-1 are MHC class Ib molecules that are loaded with a peptide derived from a conserved signal sequence of MHC class Ia molecules and are recognized by CD94/ NKG2 receptors. Only cells that synthesize MHC class Ia molecules generate a functional ligand for the CD94/NKG2 receptors. While KIRs and Ly49 NK receptors directly survey surface MHC class Ia, the HLA-E-CD94/NKG2A ligand-receptor interaction is therefore an indirect monitoring system for the MHC class Ia expression. Thus, viral functions that spare the expression of HLA-E/Qa-1 should be an optimal strategy to evade both NK and CD8^{+} T cells.

The HCMV UL40 derived peptide, identical to nonameric HLA-C leader sequence, binds to HLA-E and upregulates its surface expression [28,29]. Although the published data on the efficacy of HCMV US2 and US11 in downmodulation of individual HLA class I molecules are not consistent, it is well established that these proteins spare the inhibitory receptor ligand HLA-E, while targeting HLA-A for degradation [30]. A similar function was attributed to the HIV Nef, causing internalization and lysosomal degradation of HLA-A and HLA-B, but having little or no effect on HLA-C and HLA-E [31]. Similar selectivity was described for Kaposi's sarcoma herpes virus (KSHV) K5 protein [32].

The functional effect on HLA-E expression has some caveats, however. Although the ability of viruses to preserve HLA-E seems to be an attractive mechanism to avoid NK cells via the inhibitory CD94/NKG2A receptor, its functional impact is questionable since the activating receptor CD94/NKG2C also binds HLA-E [33]. In HCMV-infected humans, either healthy or aviremic HIV-1 infected, a substantial increase of CD94/NKG2C$^+$ over CD94/NKG2A$^+$ cells was observed [34,35]. Furthermore, co-cultivation of peripheral blood mononuclear cells from HCMV-positive donors with virus-infected fibroblasts resulted in the expansion of CD94/NKG2C$^+$ cells [36*]. This function was independent of HCMV UL16, UL18 and UL40, but could be impaired if the virus is lacking MHC class I inhibitors, suggesting that the engagement of inhibitory receptors via MHC class I prevail over activation via CD94/NKG2C.

Viral interference with NK cell activation via NKG2D

The ligand engagement by some activating NK cell receptors, such as NKG2D, can cause activation of NK cells even if target cells express normal levels of MHC class I. NKG2D serves as an activating and co-stimulatory receptor on NK cells and CD8$^+$ T lymphocytes, respectively [9]. NKG2D ligands are usually not constitutively expressed on normal cells but can be induced upon infection or stress [9,37].

NKG2D serves as a target for viral subversion. ULBP-1 and -2, as well as MICB, members of NKG2D-ligand family in humans, can bind to HCMV protein UL16 [38,39] resulting in the retention and sequestration of these ligands [40,41] (Figure 1b). MICA is not exempt from regulation by HCMV [42]. However, only expression of full-length MICA is affected, whereas the truncated form is resistant. The truncated allele is the most common allele in human population, suggesting that polymorphism in the MICA represent an advantage in the ability of the host to control virus infection [43]. Subsequent studies demonstrated that the product of the HCMV *UL142* gene downregulates full-length MICA [44*]. Of note is that the laboratory strain AD169, which lacks the UL/b' region, containing 14 genes among which is *UL142*, also downregulates MICA [42]. Therefore, it seems that HCMV developed two independent mechanisms affecting MICA whereas HIV Nef downmodulates cell surface expression of MICA, ULBP-1 and ULBP-2 [45].

The significance of viral immunoevasins for NKG2D has been also extensively studied in mice whose ligands for the NKG2D receptor, RAE-1 family, H60 and MULT-1, are subject for downregulation by several MCMV proteins (Table 1). Regarding susceptibility to MCMV, most laboratory mouse strains are MCMV-sensitive, characterized by the inability to mount a NK cell response against MCMV [11]. Why these mouse strains fail to generate an efficient virus control via NKG2D and other activating receptors, had been an enigma for a long time, especially keeping in mind that the cellular ligands for NKG2D are inducible by infection [9]. We hypothesized that the virus actively compromises NK cells by downmodulating NKG2D ligands. By using a systemic approach, we characterized the first MCMV gene involved in the downmodulation of NKG2D ligands [46]. Unlike cells infected with wt MCMV, cells infected with the mutant virus lacking the *m152* gene expressed NKG2D ligands.

The deletion of *m152* converted the virus from NK cell-resistant to NK cell-sensitive *in vivo* (Figure 1a).

Others expanded our data showing that *m152*/gp40 is involved in the regulation of the members of RAE-1 family [47]. Later on, we and others characterized additional ORFs encoding proteins responsible for the downmodulation of NKG2D ligands [23,48–50]. It turned out that MCMV possesses not only efficient but also redundant mechanisms to avoid expression of NKG2D ligands, suggesting strong selective pressure enforced by NK cells. The product of *m145* gene is involved in downmodulation of MULT-1, whereas the m155 protein is responsible for the regulation of H60. The deletion of either of these two MCMV genes resulted in the reconstitution of the corresponding NKG2D ligand on the surface of infected cells and increased virus sensitivity to NK cell control *in vivo* (Figure 1a).

The molecular mechanisms by which three MCMV immunoevasins interfere with the NKG2D ligands are so far poorly understood. However, some mechanisms have been elucidated from previous studies. For example, the m152 protein has originally been identified for its ability to retain MHC class I complexes in the endoplasmic reticulum-Golgi intermediate compartment (ERGIC)/*cis* Golgi compartment [51]. Our unpublished results suggest that m152 might also cause the downmodulation of RAE-1 molecules by the same mechanism (SJ, unpublished). However, from our data it seems that RAE-1 isoforms express differential susceptibility to m152. With respect to H60, Lodoen *et al.* have reported that it is degraded in MCMV-infected cells in proteasome-dependent pathway via m155 [50]. We have shown that the acquisition of endo-b-N-acetylglucosaminodase H resistance and the half-life of H60 is not affected in the presence of m155, suggesting that m155 affects H60 after it exits the ERGIC/*cis* Golgi compartment [48]. This discrepancy should be clarified by further studies. However, H60 is not only regulated by m155, but also by m138 [49**], an originally described MCMV receptor for Fc portion of IgG [52]. We have previously shown that the virus lacking *m138* is attenuated *in vivo* in normal as well as in immunoglobulin deficient mice, suggesting an additional immunoevasive function of the m138 protein [53]. We tested the ability of the virus lacking the *m138* to downregulate ligands for the activating NK receptors and reported that two NKG2D ligands, MULT-1 and H60, are subject to downmodulation by m138 [49**]. Recently, others have demonstrated that this viral immunoevasin is able to target the costimulatory molecule B7-1 [54]. m138 interferes with the recycling pathway of surface MULT-1 and leads to its degradation in lysosomes [49**]. The ability of inhibitors of clathrin-dependent endocytosis to rescue the expression of MULT-1 in MCMV-infected cells suggests that m138 interferes with this endocytic pathway although the modes of interaction and the synergistic effect with m145 remain unanswered. Interestingly, although both MULT-1 and H60 are regulated by m138, it appears that distinct N-terminal domains within the fcr-1 ectodomain are involved in downregulation of these ligands.

Immunoevasion of NKG2D by regulatory RNA

Upon entering target cells, DNA viruses transcribe their DNA not only into protein encoding messenger RNA (mRNA), but also into noncoding regulatory RNA, such as microRNA (miRNA). Although noncoding RNAs were known to be involved in the regulation of gene expression, the potential significance of this mechanism in the regulation of immune response was unknown until recently. Stern-Ginossar *et al.* provided evidence that virus can use miRNA to thwart NK cells [55**]. They used an algorithm to predict miRNA targets and showed that HCMV-derived miRNA (miR-UL112) displays sequence complementarity to the 3′-UTR of mRNA encoding a human ligand for the NKG2D receptor, MICB (Figure 1c). When expressed in recombinant lentivirus vector this miRNA protects infected cells from NKG2D-dependent lysis by preventing translation of MICB mRNA. Similar observations were observed during authentic virus infection. The fact that MICB protein is also downmodulated by HCMV UL16

again indicates a strong selective pressure on the virus for the development of redundant immunoevasion mechanisms against NKG2D. As compared to the immunoevasion by viral proteins, regulatory RNA may have some advantages due to its mechanism of action involving only a small amount of nucleic acid of poor immunogenicity. This could play a role in latently infected cells undergoing reactivation in fully immunocompetent host.

Evasion of NK cells by virally encoded soluble ligands for NKG2D receptors

Unlike CMVs, zoonotic orthopoxviruses secrete a protein, distantly related to class I molecules, that serves as a competitive antagonist of the NKG2D receptor [56**] (Figure 1d). Having in mind the dual function of NKG2D for NK and T cells, one could speculate that the strategy adopted by the zoonotic orthopoxviruses is less selective as compared to the downmodulation of cellular ligands by CMVs. By downmodulating NKG2D ligands only on infected cells, the CMVs are limiting its immunomodulatory potential to infected target cells; in the case of orthopoxviruses, a secreted soluble competitive inhibitor is likely to attenuate the response to any pathogen otherwise controlled via NKG2D. Similarly, some tumors evade NK cell activation by releasing soluble MICA, which results in downmodulation and inactivation of the NKG2D receptor [57]. Thus, perhaps these different strategies have broader implications for viral immunoevasion of NKG2D.

MCMV interference with activating Ly49 NK cell receptors

Some NK cell receptors are specific for viral proteins. The first described one was the *Cmv1^r* locus, which encodes Ly49H, an activating NK cell receptor [58–60]. Unlike most of other Ly49 receptors the ligand for Ly49H is not an MHC class I molecule but a product of the MCMV *m157* gene [61,62]. However, as predicted, m157 adopts MHC class I-like protein fold and its intra- and intermolecular interactions within and between domains enable this protein to be even more compact than classical MHC class I [63**]. Recently, additional genetic loci have also been implicated in the NK cell-dependent resistance. Vidal and colleagues have shown that the genetic resistance in *Cmv3$^+$* mice maps to Ly49P in MCMV-resistant MA/My mice, and that NK cell-mediated resistance to infection in these mice involves epistatic recognition of a viral protein in the context of the MHC H-2^k molecule [64]. Although the molecular nature of target recognition remains unknown, it is likely that the recognition of H-2D^k molecules depends on the viral peptide. These conclusions are corroborated by Brown and colleagues [65]. Altogether, by its specificity for MHC class I allele and viral protein, Ly49P represents another highly specific mechanism of NK cell-mediated control. An additional locus, *Cmv4*, is also suggested to encode an NK cell activating receptor and mediate MCMV resistance in PWK mice [66].

On the first glance, it makes no sense that viruses encode ligands for an activating NK cell receptor. Indeed, m157 is also a ligand for the inhibitory NK cell receptor Ly49I [62], which was perhaps its primary function. Two independent studies have shown that *m157* is subject for mutation under selective pressure of Ly49H$^+$ NK cells [67,68]. Therefore, for Ly49P it could be speculated that the virus would not "tolerate" the genes encoding its viral ligand, and that Ly49P must have an inhibitory counterpart with specificity for H-2D^k and a so far undefined viral peptide.

NCRs as putative targets for viral immunoevasins

NCRs are represented by activating receptors NKp30, NKp44 and NKp46 (mice express only NKp46) [69,70]. Unlike other NK cell receptor families, which include inhibitory and activating isoforms, NCRs share no such heterogeneity. While cellular ligands for NCRs remain unknown, it has been reported that viral hemaglutinin can bind NKp46 and NKp44 [71,72]. Mice lacking the NKp46 activating receptor are much more sensitive to influenza virus

infection [73**]. It remains to be tested whether NKp46 receptor or its cellular ligands are subjects for viral immunoevasion. Since most mouse strains fail to mount a NK cell response to MCMV, it is possible that, similarly to NKG2D, there may be an MCMV mechanism to prevent NK cell activation via NCRs. Consistent with this speculation, it has been shown that pp65, a tegument protein of HCMV, can antagonize NKp30 activation by causing its dissociation from the adaptor molecule CD3ζ [74]. Moreover, the downmodulation of NKp30 and NKp46 ligands, but not of NKp44, on T-cell blasts, is reported in patients infected with HIV [75].

More question than answers

It is generally believed that the major function of viral NK cell immunoevasion is to enable the virus to replicate and spread before the onset of the specific immune response. However, in the case of herpesviruses such as MCMV, the most explored viral model in NK cell research, one can challenge this simplified view. In spite of a plethora of immunoregulatory functions, MCMV does not cause significant disease in immunocompetent hosts. Although data published so far indicate an important role of NK cells in shaping the CD8$^+$ T cell response, the lessons obtained in so-called MCMV-sensitive mice, indicate that inefficient early NK cell response cannot be a decisive factor for the generation of the adaptive immunity. Namely, Ly49H$^-$ mice, such as BALB/c, can control the infection and establish latency. Does this suggest that NK cells are not essential for surveillance of the primary CMV infection? However, based on the attenuation of mutant viruses lacking NK cell immunoevasins, we can conclude that they are nevertheless important in virus control. A better understanding of the linkage between NK cell functions and viral immunoevasins might require additional considerations. Two major parameters are at the present in use for the assessment of the role of immunoevasins *in vivo*: (a) NK cell-dependent virus control in tissues after primary infection and (b) survival after challenge infection. Are the results obtained by these approaches really sufficient for reaching conclusions about the significance of viral immunoevasins for the pathogenesis of MCMV infection in natural conditions? We think they are not. The right question may be why it is so important to limit NK cell response and is this good for the virus or for the host, or for both. Our knowledge about the natural virus spread and the putative significance of the viral immunoregulatory mechanisms is still limited. Are these viral genes developed during the evolution to assist herpesviruses in horizontal and vertical spread? Another important role of these immunoevasins could be to allow sufficient antigenic load and optimal priming and shaping of specific immune response required for maintenance of viral latency. Altogether, new experimental approaches are needed to answer questions about the importance of viral immunoevasins for balancing the immune response, the function that is equally important for the virus and its host. Of equal importance is also the question about the putative role of immunoevasins in the prevention of immunopathology, particularly in the case of chronic infections. Although the deletion of individual viral immunoevasion genes usually results in altered sensitivity to NK cells *in vivo*, it is questionable whether we would be able to get the full picture by using the individual mutants. Do we need the viruses lacking sets of these immunoevasins to assess their function in the context of primary and chronic infection? We also need to understand the meaning of redundancy of viral immunoevasins. Bearing in mind that numerous NK cell receptors are also expressed on T cells and some other cells, we need to focus our efforts on the role of immunoevasins in these cells as well.

Thanks to new high-throughput technologies, we are constantly learning about new viral genes involved in the regulation of immune response, but their role in natural infection and viral pathogenesis will remain without complete answers without more sensitive and more specific approaches for monitoring immune surveillance *in vivo*.

Acknowledgments

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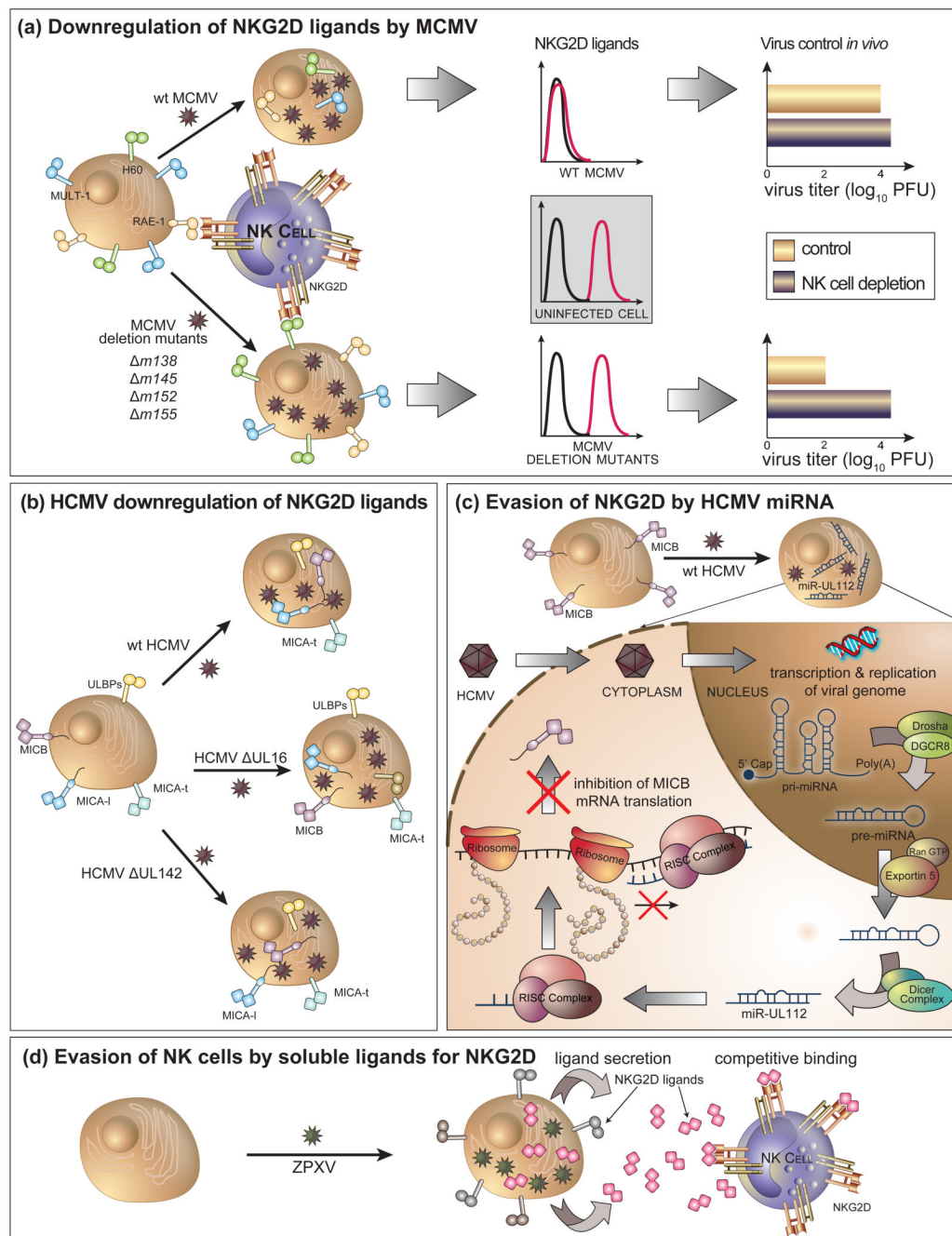
Figure 1. A schematic overview of viral interereference with NK cell activation via NKG2D
(a)MCMV downmodulates ligands for the NKG2D receptor. *m145*, *m152*, *m155* affect cell
surface expression of MULT-1, RAE-1 family and H60, respectively. *m138* is the first
described MCMV protein with a dual function on NKG2D ligands, affecting both MULT-1
and H60. The figure shows that the deletion of either of these viral proteins results in the
reconstitution of the surface expression of the respective ligands and the conversion of the virus
from being NK cell-resistant to become NK cell-sensitive. **(b)** HCMV acts in a similar manner
as MCMV, also exploiting different mechanisms. HCMV UL16 downmodulates ULBP-1 and
-2, and also MICB whereas UL142 downmodulates full-length MICA. The truncated form of
MICA shows resistance to downmodulation by HCMV. **(c)** After virus enters the cell, its

genome is transcribed into mRNA but also noncoding RNA molecules. By using the cellular machinery, HCMV expresses its own miRNAs, including miR-UL112, which forms the RISC complex and binds the 3′ UTR region of MICB. In this way, miR-UL112 inhibits the translation of MICB mRNA, thus preventing it in reaching the cell surface and signaling. **(d)** Orthopoxviruses utilize a previously undescribed mode of interference with NKG2D signaling. They secrete a soluble protein, named OMCP, which competitively binds to NKG2D and antagonizes the function of cellularly expressed ligands.

Table 1

Common viral interference with NK cell receptor ligands.

Virus	Viral immunoevasin	Mode of function	References
Interference with "missing self" axis			
HCMV	UL18	Binding to NK cell inhibitory receptor LIR-1	[15]
MCMV	m144	Unknown	[22]
MCMV	m157	Binding to Ly49I	[62]
RCMV	r144	Unknown	[76]
RCMV	RCTL	Binding to inhibitory receptor Nkrp1b	[27*]
Differential regulation of MHC class I			
HCMV	US2, US11	Downmodulate HLA-A but spare HLA-E; act differentially on other HLA molecules	[77–79]
HCMV	UL40	UL40 leader peptide loads HLA-E and provides inhibitory signal to NK cells	[28,29]
MCMV	m04/gp34	Binds MHC class I and rescues its expression on the cell surface, possible NK cell decoy	[80,81]
KSHV	K5	Downmodulates HLA-A and HLA-B and weakly HLA-C, but shows no effect on HLA-E	[82]
HIV	Nef	Downmodulates HLA-A and -B	[31]
Interference with ligands for activating NK cell receptors			
HCMV	UL16	Downmodulates ULBP-1, -2 and MICB	[38,39]
HCMV	UL141	Downmodulates CD155	[83]
HCMV	UL142	Downmodulates full length MICA	[44*]
HCMV	miR-UL112	Prevents translation of MICB mRNA	[55**]
HCMV	UL83/pp65	Abolishes activation via NKp30 by dissociating adaptor molecule CD3ζ	[74]
MCMV	m138	Viral FcγR, downmodulates MULT-1 and H60, interferes with clathrin-dependent endocytosis	[49**]
MCMV	m145	Downmodulates MULT-1	[23]
MCMV	m152/gp40	Downmodulates RAE-1 family members	[47]
MCMV	m155	Downmodulates H60	[48,50]
KSHV	K5	Induces endocytosis of CD86 and CD54	[32]
Zoonotic orthopoxvirus	OMCP	Competitively binds to NKG2D	[56**]
Other			
MCMV	m157	Binds to Ly49H and activates NK cells	[61,62]
MCMV	unknown	Activates Ly49P in context of H-2D^k	[64]
influenza virus	HA	Binds to NKp46	[72]
HCV	E2	Binds to CD81	[84]
HTLV	p12I	Downmodulates ICAM-1 and -2 and reduces NK cell adherence to HTLV-infected CD4$^+$ T cells	[85]