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Modulation of natural killer cell activity by viruses

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Summary

Since their discovery, our understanding of NK cells has evolved from branding them marginal innate immunity cells to key players in anti-viral and anti-tumor immunity. Importance of NK cells in control of various viral infections is perhaps best illustrated by the existence of plethora of viral mechanisms aimed to modulate their function. These mechanisms include not only virally encoded immunoevasion proteins but also viral miRNA. Moreover, the evidence has been accumulated supporting the role of viral immunoevasion of NK cells in viral pathogenesis *in vivo*.

Introduction

NK cells have a prominent role in early virus control. Upon activation NK cells control infection either through the lysis of infected cells, or by release of antimicrobial cytokines. This latter function enables them to influence adaptive immune responses as well. NK cells survey their surroundings through numerous inhibitory and activating receptors – integration of these signals determines the activity of an NK cell. More recent data indicate that NK cells may even acquire memory-like function enabling them to respond differently upon recall challenge [1–3].

Importance of NK cells in control of viral infection is best illustrated by the sheer number of viral evasion mechanisms. These mechanisms include regulation of apoptosis, interference with ADCC, modulation of cytokines and chemokines and function of APCs. Even more numerous are viral techniques dedicated to control of engagement of NK cell receptors. The viruses can downmodulate ligands for activating NK cell receptors, provide competitors and surrogates for cellular ligands, interfere with their translation or target the activating receptors directly.

Despite a remarkable increase in knowledge about relationship between NK cells and viruses there are still many outstanding issues. In this review we will highlight recent progress and current understanding of most important viral immunosubversive mechanisms directed at NK cells with emphasis on receptor – ligand interactions and their impact on overall immunity.

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Conflicts of interest

The authors do not claim any conflict of interest.

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1. Direct interactions with NK cells

In the course of viral infection, NK cells play a crucial role during the early times post infection. Although the most employed viral evasion techniques are indirect, avoiding NK cell detection, some viruses have opted for a more direct approach and target NK cells *per se*. Influenza virus can directly infect human NK cells via clathrin and caveolin dependent endocytosis and induce apoptosis [4], a finding which was confirmed *in vivo* [5]. As viral transmission happens in the first few days post infection, evasion of innate immunity and especially NK cells is paramount to influenza virus.

Cross-linking of CD81, tetraspanin involved in the regulation of NK cell recruitment, by recombinant HCV envelope protein E2 alters IFN- γ production and cytotoxic activity of NK cells [6]. However, *in vivo* data did not support this finding as E2 failed to crosslink CD81 when it was a part of a virion [7]. More recent *in vitro* data using HCV viral particles showed that engagement of NK cell CD81 results in altered cytokine secretion pattern and reduced antiviral activity [8]. However, only immobilized HCV viral particles were able to inhibit IFN- γ secretion and therefore it remains to be seen whether these new data will be corroborated by *in vivo* findings. Other examples of direct interactions of viruses and NK cells are mentioned later in the text.

2. Viral functions that promote engagement of inhibitory NK cell receptors

To avoid recognition by MHC I restricted T cells, many viruses downregulate MHC I. However, the lack of MHC I molecules is quickly detected by NK cells through lack of engagement of their inhibitory receptors and thus leading to prevalence of activating ones. But not all MHC I molecules are fit to display peptides to CD8⁺ T cells and viruses were quick to exploit this loophole. In addition to selective downmodulation of MHC I molecules, viruses are also employing MHC surrogates that are not recognized by cytotoxic T lymphocytes but are able to engage inhibitory NK cell receptors (reviewed in detail in [9]) (Table 1).

Among viruses cytomegaloviruses (CMVs) are masters of MHC I exploitation in order to avoid both CD8 and NK cell recognition. Murine CMV (MCMV) encodes 3 regulators of MHC I molecules: m152 which arrests the maturation of MHC molecules at the level of ERGIC compartment, m06 which redirects MHC I to lysosomes for degradation and m04 which forms a complex with MHC I and actually allows it to reach the cell surface (reviewed in [10,11]). The current findings about m04 *modus operandi* and role are pretty controversial. On one hand it has been shown that m04 can inhibit MHC I presentation [12] while others report that m04 antagonizes the action of m152 and enhances recognition of infected cells by virus specific CD8⁺ T cells [13]. In addition, m04 is essential for recognition of infected cells by activating Ly49P receptor but only in complex with H2-D^k molecules [14]. Since Ly49 family of receptors contain both inhibitory and activating variants which can recognize the same ligand it is plausible that m04 has originally evolved as immunoevasin directed at inhibitory Ly49 receptors in order to prevent “missing-self” recognition. Resistance of mice bearing Ly49P receptor could be a consequence of fierce and ongoing evolutionary battle between viruses and the host where the host currently has the upper hand.

HCMV encodes several proteins aimed at regulation of MHC I molecules. Peptide loading is prevented by US6 which binds to TAP, US3 and US10 retain HLA molecules in ER while US2 and UL11 target HLA-A but not HLA-E for degradation [15]. Although each protein is able to reduce class I surface expression independently, recently it was shown that US2 and US3 coordinate their function so that cells co-expressing both proteins are more successful in MHC I downregulation [16].

HLA-E molecules in humans and Qa-1 in mouse present only peptides derived from leader sequence of other MHC I molecules. To account for this HCMV encodes gpUL40 whose leader sequence is identical to leader sequences of classical MHC I molecules [17,18]. HLA-E and Qa-1 molecules are ligands of inhibitory CD94/NKG2 family of receptors and by maintaining the expression of HLA-E NK cell mediated killing is successfully prevented even in the absence of other MHC I molecules on the infected cell surface. However, HLA-E molecules are not without controversy as they too can be recognized by activating CD94/NKG2 receptors in addition to inhibitory variants. In HCMV infected and HCMV and HIV-1 co-infected patients Guma and colleagues noticed an expansion of NK cells bearing activating CD94/NKG2C receptors which outnumbered NK cells with inhibitory CD94/NKG2A variants. By co-culturing NK cells from HCMV infected patients with infected fibroblasts, it was demonstrated that expansion of CD94/NKG2C⁺ NK cells is independent of the UL16, UL18, and UL40 HCMV genes, but was impaired upon infection with a mutant lacking the US2-11 gene region responsible for MHC class I inhibition [19]. More recently, similar result was observed in children infected with HCMV which had higher levels of NKG2C⁺ cells [20]; moreover percentages of NKG2C⁺ cells correlated with the titers of anti-HCMV IgG antibodies. However, the mechanism behind this interesting phenomenon remained undefined.

Unlike other viruses, flaviviruses upregulate all MHC I alleles indiscriminately which may be a consequence of nature of flaviviruses when it comes to choosing their host (Fig 1). Dengue virus upregulates MHC I expression through TAP dependent and TAP independent mechanisms and this enhanced MHC I expression is associated with increased binding of inhibitory NK cell receptors and subsequent reduced susceptibility to NK cell lysis [21]. The role of NK cells in the control of Dengue virus infection is not yet clear and current reports send conflicting messages. However, strong evolutionary pressure of NK cells on the Dengue virus is evident in the fact that the virus has opted for upregulation of MHC I in order to escape NK cell recognition even though this tactic renders it sensitive to CTL lysis.

Viral MHC I Surrogates

In addition to differential regulation of MHC I expression, viruses employ MHC homologues or surrogates of both classical and non-classical MHC I molecules (Table 1.). A successful MHC I surrogate must be able to engage inhibitory NK cell receptors while avoiding to elicit T cell responses. MHC surrogates are perhaps best represented by HCMV gpUL18 which shares only a moderate sequence homology to MHC I but binds inhibitory receptor LIR-1 with 1000-fold higher affinity than HLA-E molecules (reviewed in [22]). Although the expression of US6 could negatively regulate gpUL18 due to its high structural homology to MHC I, gpUL18 restores TAP mediated peptide translocation while preventing association of other MHC I molecules and TAP [23]. Thus, gpUL18 is a unique immune evasion protein enabling resistance to both arms of the immune response: it ensures its own long life on the cell surface while serving as an MHC surrogate and preventing both CD8 and NK cell recognition. However, gpUL18 is also not free of controversy as it can activate LIR-1 negative NK cells which comprise the majority of NK cell pool (reviewed in [22]).

3. Viral functions that prevent engagement of activating NK cell receptors

In addition to inhibitory receptors ensuring “missing-self” recognition and preventing autoimmunity, NK cells possess a plethora of activating receptors. As viral infection or transformation poses a stress to the cell, stress molecules appear on the cell surface alerting NK cells of suspicious behavior. Since “to attack or not to attack” decision relies on the sum of signals from inhibitory and activating NK cell receptors, it is important for the viruses to actively prevent engagement of activating receptors to ensure the prevalence of inhibitory

signals. Such prevention can be achieved by directly targeting the receptors or indirectly by interfering with ligands.

3.1. Viral interference with NKG2D receptor

NKG2D, one of the best characterized NK receptors, can override inhibitory signals in the absence of missing-self recognition. It is expressed on a vast majority of NK cells and also serves as co-stimulatory receptor on CD8+ T cells. Broad range and heterogeneity of NKG2D ligands exerts a significant selective pressure on viruses. CMVs have developed multiple strategies for interference with NKG2D-mediated activation of NK cells (Table 2). MCMV encodes several proteins that negatively regulate NKG2D ligands; m145 affects surface portion of MULT-1, m152 targets RAE-1 family and H60 is targeted by m155 (reviewed in [10]). Surface portions of H60, MULT-1 and RAE-1 ϵ are additionally downregulated by *m138/fcr-1* [10,24] (Figure 2A). Deletions of either of these genes results in the enhanced susceptibility of the MCMV infected cells to NK cell control. Not all RAE-1 isoforms are equally susceptible to MCMV regulation suggesting host escape from viral immunoevasion [24,25]. Mature form of RAE-1 δ is more resistant to MCMV than RAE-1 γ which could be the consequence of the absence of PLWY motif from RAE-1 δ as compared to RAE-1 α , β , γ . More recent studies, which have demonstrated direct interactions between m152 and RAE-1 proteins, also confirmed quantitative differences in binding depending on particular RAE-1 isoforms [26]. However, the presence or absence of PLWY motif could not on its own fully explain the differences in affinity of RAE-1 isoforms to m152.

HCMV employs two different strategies: MICB, ULBP-1 and ULBP-2 are prevented from reaching the cell surface by UL16 (reviewed in [27]), while newly synthesized full-length MICA is retained in the cis-Golgi by UL142 [28,29]. Very recently crystal structure of UL16 in complex with MICB revealed that UL16 mimics a central binding motif of otherwise structurally unrelated NKG2D thus enabling the virus to disable several diverse NKG2D ligands [30]. In addition to targeting already synthesized proteins, HCMV also employs miRNA miR-UL-122 which prevents translation of MICB [31]. Although putative binding site for miR-UL-122 is found in 3'-UTR of MICA, miR-UL-122 does not cause its significant downregulation. The recognition sequence for miR-UL-122 is conserved among different MICB alleles. Similar recognition sites are targets for EBV miR-BART2-5p and KSHV miR-K12-7 [32] [33] (Figure 2B). Therefore an interesting question is why the host would keep a highly conserved untranslated sequence just for the purpose of viral immunoevasion. Though not expressed on the cell surface of normal, healthy cells, MICA and MICB genes are transcribed in all cells [34]. Translation and subsequent appearance of these proteins on the cell surface is held in check by cellular miRNAs and histone acetylation. However, infection with HCMV causes displacement of histone acetylases and induces transcription of *MICA* and *MICB* mRNA rising it to the levels that exceed repression abilities of cellular miRNAs. Thus the host has ensured a mechanism for recognizing threat and quickly reacting to it without the need for *de novo* transcription which was then, in turn, successfully exploited by the viruses.

Finally, zoonotic orthopox viruses, as well as some tumors, employ saturation of the receptor tactic. By secreting soluble NKG2D ligands they provide competitor for the receptor [35]. In addition to competition for the receptor, binding of the soluble ligand results in internalization of the receptor and thus diminished the amount of available NKG2D receptors even more (Fig 2B). Other examples of viral immunoevasion directed at NKG2D are listed in table 2.

3.2. Viral interference with Ly49 receptors

Most Ly49 receptors are inhibitory receptors, recognizing MHC I molecules. To account for downregulation of MHC I, viruses encode many MHC-like molecules able to engage Ly49 receptors (Table 2). The first such interaction described is that between Ly49H receptor present in MCMV resistant C57Bl/6 mice and MCMV encoded m157 protein (reviewed in [27]). Another mouse strain, MA/My, ensures its MCMV resistance through Ly49P receptor which recognizes H-2D^k-m04 complexes [14]. Wild derived PWK mouse strain contain *Cmv4* locus which confers resistance to MCMV through as of yet undefined receptor and mechanism (reviewed in [27] (table 2, figure 2C).

Taking all of this into consideration, it will not come as a surprise that the comparison of the extracellular domains of several activating and inhibitory Ly49 receptors showed extensive homology indicating that they might have evolved from common ancestral gene. It is very likely that activating Ly49 and KIR receptors have evolved from inhibitory analogues through chromosome duplication and genetic recombination complemented by loss of ITIM [36].

Do these results suggest that CMV was instrumental for the evolution of Ly49? Virus driven evolution of its hosts on the population level is certainly not unknown and some examples have already been pointed out in this review. Other examples of virus driven diversification of receptors include differential expression of an activating KIR3DS1 which leads to a better control of HIV virus [37], higher IFN- γ and CD107a expression in unstimulated NK cells in individuals possessing KIR3DS1 gene [38], influence of distinct allelic combinations of the KIR3DL1 and HLA-B on AIDS progression [39], better clearance of HCV in patients which possess KIR2DL3 and HLA-C I alleles [40] or resistance to HCV in drug users which, along with KIR2DL, KIR2DL3 and HLA-C1 molecules also possess activating KIR2DS4 [41] and others.

What about cross-specificity of virus-specific receptors to other viruses? Could evolutionary driven virus specific receptors bring advantage to the host during the infection or co-infection with a different virus? Recent data indicates just that. NK cells of HIV-1 patients co-infected with HSV-2 showed more efficient degranulation after *in vitro* stimulation than NK cells from HIV mono-infected controls [42]. Additionally, differences in viral load connected to the number of NK cells expressing NKp30, NKp46, KIR3DL1 and KIR3DS1 activating receptors in HIV monoinfected individuals were not observed in HSV-2 co-infected patients. Obviously, the reaction of NK cells to HSV-2 infection affected NK mediated immunity to HIV-1.

3.3. Viral interference with NCR-1

Natural cytotoxicity receptors (NCRs) are a group of activating receptors expressed almost exclusively on NK cells. Humans express 3 NCR receptors – NKp30, NKP44 and NKP46 while mice possess only one – NCR1. Despite intensive research in the recent years, cellular ligands remain elusive.

The role of NCRs in viral infections is currently best understood for Influenza virus. Hemagglutinins (HA) of Influenza virus and hemagglutinin-neuraminidase of Sendai virus are recognized by NKp44 and NKp46 [43,44]. NCR1 knock-out mice are more sensitive to Influenza virus than their wild-type counterparts [45]. In contrast, recent reports show that free HA, which is released along with new virions from the infected cells and UV-inactivated virions can inhibit NK cell cytotoxicity by entering the cell and inducing ζ -chain degradation in lysosomes [46]. As NKp30 and NKp46 rely on the ζ chain for signal transduction, signalling from these two receptors is efficiently blocked (Table 2). Importance of NCR receptors in influenza infection is underscored by yet another

immuno-evasion tactic this virus directs against NCRs – modification of HA through addition of more glycosylation sites resulting in weaker recognition of HA by NKp46 [47]. HA is therefore yet another example of the constant evolutionary battle between viruses and their hosts – it is essential for the viral entry into the cell, ligand for activating NK cell receptor and, at the same time, successful inhibitor of the same receptor.

All the viruses implicated in the immuno-evasion of NCRs so far can generally be described as hit-and-run viruses concerned only with temporary immuno-evasion in order to ensure their spread to new hosts. What about viruses that establish latency, such as CMVs? HCMV tegument protein pp65, similarly to influenza HA, causes dissociation of ζ -chain from NKp30 and prevents signal transduction [48]. Reduced or defective NCR expression during HCV or HIV infection is associated with a decrease in NK cell cytotoxicity [49,50] (Table 2).

3.4. Viral interactions with other NK cell receptors

As our knowledge about NK cell receptors increases, so does our knowledge of new viral immuno-evasive techniques as viruses do not fail to target any receptor (Table 2). Kaposi's Sarcoma Herpes Virus (KSHV) encodes a multi-talented immuno-evasin – K5. In addition to targeting NKG2D ligands MICA and MICB, it also downregulates AICL - ligand of activating NK cell receptor NKp80 [51]. Low passage strains of HCMV encode UL141 which sequesters CD155 (also known as PVR (poliovirus receptor) in the ER. CD155 is a ligand for activating NK cell receptors CD96 and DNAM-1 (CD226) [52]. As CD226 is present on almost all NK cells, downregulation of its ligand is a powerful immuno-evasion tactic. Additionally, CD155 is constitutively present on many cells and can therefore cause activation of NK cells in the absence or when inhibitory signals are diminished. DNAM-1 also recognizes PVRL2 (CD112), while interaction of PVR (CD155) and PVRL2 with TIGIT can directly inhibit NK cells and indirectly T cells [53].

Future perspectives—Nowadays a multitude of viral immuno-evasion techniques directed at NK cells are known and have been confirmed *in vitro* and somewhat *in vivo*. Recently few studies have suggested that NK cells can even acquire certain type of memory features [1,2]. If NK cell memory is biologically relevant in control of chronic infections or reinfections, one would expect that viruses, which have already invested a lot of effort into NK evasion, would have means to cope with this function of NK cells as well. The challenging issue is the fact that SCID mice which possess otherwise normal NK cell response succumb to MCMV infection by generation of escape mutants [54]. In such situations, the function of specific memory cells is questionable. Although existence of memory NK cells has a solid experimental background several questions arise. What would be advantage of such function if we take into account that constitutive frequency of NK cells with potential to recognize infected cells is high enough to respond without clonal expansion characteristic for specific T and B cell responses? Perhaps the most difficult challenge for the viruses is the necessity to simultaneously avoid T cell and NK cell response, the functions that are sometimes mutually exclusive such as downmodulation of MHC I. In that context it would be interesting to investigate how the viral immuno-evasins impact the generation of memory NK cells and how this function impacts the T cell response during chronic/latent viral infections. By using rhesus monkey CMV lacking MHC I inhibitors US2-11, Hansen and colleagues have recently demonstrated that these viral regulators are required for viral replication and dissemination during superinfection [55]. Since MHC I downregulation should sensitize the virus to missing self recognition by NK cells, it is likely that this function of viral MHC class I inhibitors can be achieved only in concert with other immuno-evasins which simultaneously prevent NK cell activation. These issues require intensive further studies.

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Figure 1. Viral functions that promote engagement of inhibitory receptors

Normal, healthy cells display MHC I molecules on their cell surface presenting cellular peptides which are not recognized by CD8⁺ T cell receptor. MHC I molecules are ligands for inhibitory NK cell receptors and their expression on the cell surface ensures tolerance through prevalence of inhibitory signals. In order to avoid detection by CD8⁺ T cells viruses may be tempted to downregulate all MHC I molecules from the cell surface. However this would render them sensitive to NK cells through "missing-self" recognition. Dengue virus causes upregulation of MHC I molecules thus enforcing inhibition of NK cells but risking detection by CD8⁺ T cells. HCMV selectively downregulates MHC I molecules capable of presenting peptides to CD8⁺ T cells while leaving HLA-E molecules capable of engaging inhibitory NK cell receptors. As HLA-E display peptides derived from leader sequences of other MHC I molecules, HCMV encodes gpUL40 whose leader sequence is similar to leader sequences of other MHC I molecules for loading into HLA-E. In addition HCMV also encodes MHC surrogate gpUL18 which is a ligand for inhibitory LIR-1 receptor.

Figure 2. Examples of viral interference with function of activating NK cell receptors

A) Viral interference with NKG2D receptor. NKG2D ligands are not expressed on healthy cells, only on those that are stressed, transformed or undergoing infection. Binding of NKG2D to its ligands can cause NK cell activation even in the presence of inhibitory signals. MCMV encodes 4 regulators of NKG2D ligands: m145 downmodulates MULT-1, m152 downmodulates RAE-1 family of molecules, while H60 is targeted by m155. Additionally, m138 targets H60, MULT-1 and RAE-1 ϵ . EBV, KSHV and HCMV target MICB by microRNAs. ZPXV produce soluble NKG2D ligands and thus saturate NKG2D receptors on NK cells. **B)** Herpesviral regulation of MICB via miRNAs. EBV, KSHV and HCMV encode microRNA, small RNAs that, after processing and loading into RISC

complex, bind to 3'-UTR of MICB messenger RNA and prevent efficient translation of MICB mRNA. **C) MCMV interactions with Ly49 receptors.** MCMV encodes MHC I homologue m157 which, in some MCMV sensitive mice serves as a ligand for inhibitory Ly49I receptor. However, some mouse strains, during the course of the evolution with MCMV, have developed activating Ly49H receptor capable of recognizing m157. In MA/My mice resistance is conferred through the recognition of m04/MHC I complexes on the cell surface. As there is no evolutionary advantage for the virus to develop and keep protein displayed on the infected cell surface which is recognized by an activating receptor, it is quite possible that inhibitory Ly49 receptor specific for the m04/MHC I complexes is waiting to be found.

Table 1

Viral proteins affecting engagement of inhibitory NK cell receptors

Virus	Immuneovasin	Target	Action	References
Regulators of MHC I expression				
MCMV	m04	MHC I	binding to MHC I in the ER and allowing them to reach cell surface	[56]
MCMV	m06	MHC I	targeting MHC I for degradation	[57]
MCMV	m152	MHC I	retention of MHC I in ERGIC compartment	[58]
HCMV	US2, US11	HLA I	differentially targeting MHC I for degradation	[59,60]
HCMV	US3, US10	HLA I	retention of MHC I in ER	[61,62]
HCMV	US6	HLA I	prevention of peptide loading into MHC I molecules	[63,64]
HCMV	gpUL40	HLA-E	providing leader sequence for loading into HLA-E	[17]
HIV	p24aa14-22a	HLA-E	stabilization of HLA-E	[65]
HIV	Nef	HLA-A, HLA-B	acceleration of HLA-A and B endocytosis	[66]
KSHV	K3	HLA I	endocytosis of all HLA I molecules	[67]
KSHV	K5	HLA A, HLAB, HLA C	endocytosis of HLA-A and HLA-B, HLA-C is affected only weakly	[67]
Viral MHC I surrogates				
HCMV	gpUL18	LIR-1	binding to inhibitory receptor LIR-1 with higher affinity than HLA-E	[68,69]
MCMV	m144	unknown	possible ligand for inhibitory receptors	[70]
RCMV	RCTL	NKR-P1A	homologue of Ocil	[71]
RCMV	ORFr144	unknown	unknown	[72]
MCV	MC080R	unknown	unknown	[73]

Table 2

Viral proteins affecting engagement of activating NK cell receptors

Virus	Immune-evasin	Target	Action	References
Interference with NKG2D receptor				
MCMV	m138	H60, MULT-1, RAE-1ε	interference with endocytic pathways	[10,24]
MCMV	m145	MULT-1	intracellular retention	[10]
MCMV	m152	RAE-1	intracellular retention	[74]
MCMV	m155	H60	intracellular retention	[10,75]
HCMV	UL16	MICB, ULBP-1, ULBP-2	intracellular retention	[76,77]
HCMV	UL142	MICA	downregulation of full-length MICA	[28,29]
HCMV	miR-UL-122	MICB	interference with translation	[31]
EBV	miR-BART2-5p	MICB	interference with translation	[33]
KSHV	miR-K12-7	MICB	interference with translation	[33]
KSHV	K5	MICA, MICB	ubiquitylation of full-length MICA and targeting to unknown compartment, downmodulation of MICB	[78]
HIV	Nef	MICA, ULBP-1, ULBP-2	downmodulation	[79]
ZPXV	soluble NKG2D ligands	NKG2D	saturation of receptor	[35]
Interference with Ly49 receptors				
MCMV	m157	Ly49H, Ly49I	ligand for activating Ly49H and inhibitory Ly49I receptors	[27]
MCMV	m04	Ly49P	in complex with MHC I engages Ly49P and putative inhibitory Ly49 receptor	[14]
Interference with natural cytotoxicity receptors				
Influenza virus	HA	NKp30, NKp46	ζ-chain degradation in lysosomes	[80]
HCMV	pp65	NKp30	dissociation of ζ-chain from NKp30	[48]
Interference with other NK cell receptors				
KSHV	K5	AICL	downregulation of NKp80 ligand AICL	[78]
HCMV	UL141	CD155	sequestration of CD155 in the ER, prevention of NK cell activation via activating receptors CD96 and DNAM-1	[52]