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# NK cells in host responses to viral infections

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Natural killer (NK) cells are cytotoxic innate lymphocytes that play an important role in viral clearance. NK cell responses to viral infections were originally believed to be non-specific and lacked immune memory recall responses. It is now appreciated that NK cell responses to viral infections can be specific and in some cases memory recall responses are established. Increasing evidence also illuminates the complexity of NK cell interactions with both innate and adaptive immune cells. Here, we summarize the evidence for NK cell-specific memory responses to viral infections and the intricate reciprocal interactions between NK cells and other immune cells that dictate their activation and effector functions.

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## Introduction

Natural killer (NK) cells are innate lymphocytes that play an integral role in the host's immune defense against pathogens. NK cells have the unique ability to recognize and lyse target cells without prior exposure. Patients with genetic mutations resulting in diminished NK cell numbers or function succumb to recurrent herpesvirus, varicella virus, and papillomavirus infections [1–4], highlighting the importance of NK cells in controlling certain viral infections. NK cell responses were believed to be non-specific due to expression of germ-line encoded receptors that do not recombine to generate antigen-specific receptors like T and B cells [5]. It was thought that NK cells served to control viral burden by broadly lysing virus-infected cells until the adaptive immune system developed specific anti-viral responses. However, NK cell responses can be specific and they interact with both innate and adaptive immune cells to coordinate appropriate anti-viral responses [reviewed in [6,7]]. Here we summarize recent findings of NK cell specificity through the generation of long-lived memory cells and how NK cells coordinate an anti-viral response with other immune cells.

## NK cell memory

Immunological memory responses are the basis for vaccination and protect the host from secondary encounters with lethal and recurring pathogens. The memory T and B lymphocytes of the adaptive immune system are highly specific and provide quick and robust defenses. These memory response characteristics are now attributed to NK cells in certain situations. First appreciated in studies of delayed contact hypersensitivity, NK cells displaying properties of memory have been demonstrated in response to alloantigens and infectious agents, during homeostatic proliferation, and can be elicited by cytokine stimulation [8–11,12••,13]. Molecular mechanisms governing the generation of memory NK cells are beyond the scope of this article and are reviewed elsewhere [6,7,14].

Viral infections induce the generation of memory cells in the T, B, and now NK cell populations. Studies of mouse cytomegalovirus (MCMV) infection identified a subset of Ly49H+ NK cells in C57BL/6 mice that specifically recognize the MCMV-encoded glycoprotein m157 [15–17]. In 2009, Sun et al. [13] reported the expansion, contraction, and persistence of Ly49H+ NK cells after MCMV infection (Figure 1a). These cells conferred specific protection against MCMV re-challenge and not other heterologous infections, indicating that these are MCMV-specific memory NK cells [13,18••]. The Ly49H-m157 interaction is crucial for host control of MCMV infection. Infection with MCMV$^{G1F}$, a strain in which a m157 variant recognizes both the activating Ly49H and the inhibitory Ly49C receptor, rendered mice more susceptible to low dose infection. Ly49C competed for m157 binding and diminished Ly49H-mediated activation by destabilizing NK cell-MCMV-infected target cell contact. However, cis-interactions of Ly49C with major histocompatibility complex class I (MHC-I) expressed on the NK cells restricted binding of Ly49C to m157 on MCMV-infected cells, thus allowing sufficient Ly49H-mediated activation to provide for limited host protection [19••,20••]. A recent study reported that 50% of Ly49H+ NK cells in C57BL/6 mice co-express the inhibitory receptor NKR-P1B. Expression of NKR-P1B inhibited the proliferation and protection of Ly49H+ cells during MCMV infection, but did not alter secretion of interferon-γ (IFN-γ) and granzymes [21••]. It is unknown

Figure 1
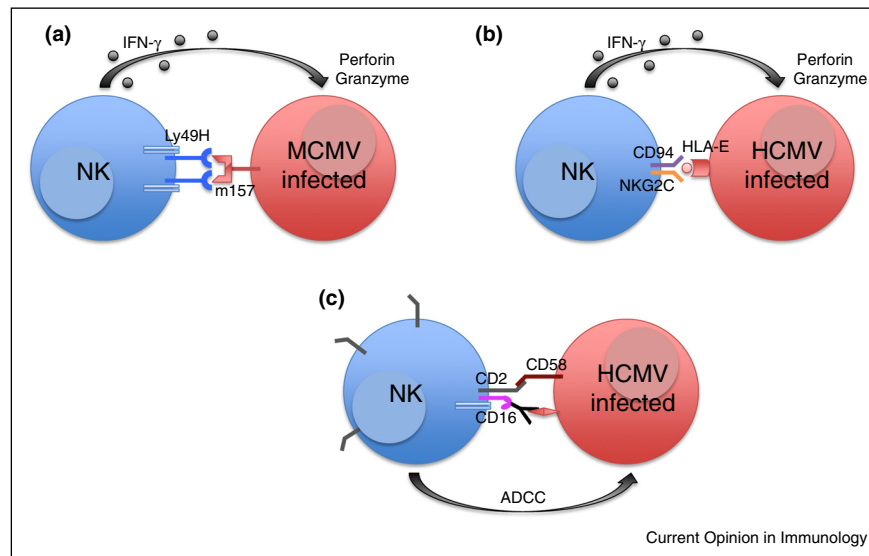


Expansion of NK cells in cytomegalovirus infection. Ly49H-m157 interaction in MCMV infection **(a)** and CD94-NKG2C and HLA-E interaction in HCMV infection **(b)** induces NK cell production of IFN-$\gamma$ and lysis of target cell. NK cells persist as memory cells. **(c)** Synergy of CD2 and CD16 for effective antibody-dependent cell-mediated cytotoxicity (ADCC) of HCMV-infected cells in $KLRC2^{-/-}$ humans.

whether NKR-P1B expression affects the generation of Ly49H$^+$ memory NK cells, although this seems likely. Additionally, animal models of herpes simplex virus, influenza, and simian immunodeficiency virus infection also revealed the existence of memory NK cells. In these studies, NK cells previously exposed to viral antigens conferred enhanced IFN-$\gamma$ production, cytotoxicity, and protection upon re-challenge [9,22–24,25•,26]. The ligand and NK cell receptor(s) responsible for protection against these viruses (other than MCMV) are unknown and identifying them will give scientists insight into controlling these viral infections in humans.

Many investigators have also identified a potential pool of memory NK cells in humans. Gumá *et al.* first reported the expansion and persistence of CD94$^+$NKG2C$^+$ NK cells in human CMV-seropositive, but not in HCMV-seronegative, individuals [27–29]. Other investigators have also described the expansion of NKG2C$^+$ NK cells in chikungunya, hepatitis B and C, Epstein-Barr (EBV), and hanta virus infections [30–33]. However, individuals in these studies were also infected with HCMV, so expansion of the NKG2C$^+$ NK cells likely resulted from subclinical reactivation of HCMV in these patients. Emerging evidence has elucidated the specificity of NKG2C$^+$ NK cell expansion in response to HCMV infection. Björkström *et al.* did not observe expansion of NKG2C$^+$ NK cells or any particular NK cell subset during recurrent herpes simplex virus-2 infection [34] and Hendricks *et al.* found that acute EBV infection in HCMV-seropositive and seronegative individuals did not induce expansion of NKG2C$^+$ NK cells [35••]. Both

studies indicate that the expansion of NKG2C$^+$ NK cells is specific to HCMV and not HSV or EBV infections. Degranulation of NKG2C$^+$ NK cells is triggered by co-culture with HCMV-infected primary human endothelial cells but not HCMV-infected fibroblasts or monocyte-derived dendritic cells [36•]. Further, NK cell expansion is dependent on expression of the NKG2C ligand, HLA-E, on the infected cells and interleukin (IL)-12 produced by myeloid cells (Figure 1b) [37]. Interestingly, HMCV-seropositive individuals possessing a homozygous null allele of *KLRC2* (the gene encoding NKG2C) remain asymptotic and healthy, suggesting that NK cells possess redundant pathways in response to HCMV. In these individuals, the adaptive (or memory) NK cells (defined as FcεRIγ$^-$ and/or Syk$^-$) expressed elevated levels of CD2, which synergized with CD16 to activate NK cells in HCMV infection [38••]. Binding of CD2 to CD58, upregulated on HCMV-infected fibroblasts, is critical to induce CD16-dependent antibody-mediated activation of NKG2C$^+$ NK cells (Figure 1c) [39••]. Further insight into NKG2C$^+$ NK cells are described in a recent review by Rölle and Brodin [40].

## Modulation of the innate immune response
NK cells participate in complex interactions with neutrophils, macrophages, and dendritic cells during viral infections. The appreciation of NK cell interactions with neutrophils has emerged in the past decade with reports describing multiple factors regulating mutual maturation, activation, and effector functions [41,42]. *In vitro* co-culture experiments with human NK cells revealed that IL-15-activated or IL-18-activated NK cells modulated

neutrophil activation and survival via IFN-γ and granu-locyte macrophage colony-stimulating factor (GM-CSF) to perpetuate an immune response [43]. Alternatively, human NK cells may induce neutrophil apoptosis via NKp46 and Fas-dependent mechanisms to limit inflam-mation and further activation of immune responses [44]. In mouse models, IL-22 production by CD3⁻NK1.1⁺ (possibly NK cells, but more likely type 3 innate lym-phocytes), CD3⁺NK1.1⁺, and T cells was necessary for neutrophil recruitment to MCMV-infected tissues to control acute infection [45]. Reciprocally, neutrophils modulate NK cell maturation, activation, function, ho-meostasis, cytokine production, and NK cell licensing [46,47••,48•,49•].

Macrophages secrete cytokines and express ligands to modulate NK cell responses during viral infections [50]. NK cells can readily kill virus-infected macrophages to limit viral burden, as well as cytokines that these virus-infected macrophages secrete. Romo *et al.* found that M1 macrophages were more resistant to HCMV infection than M2 macrophages. M1 macrophages secreted inflam-matory cytokines that triggered autologous NK cells to produce IFN-γ, whereas M2 macrophages produced lim-ited cytokines and did not induce robust NK cell responses [51,52]. Another study found that inflammatory monocytes and NK cells contribute to MCMV control via CD155 and DNAM-1 interactions. The MCMV-encoded protein m20.1 induced downregulation of CD155 in infected monocytes to evade immune detection by the DNAM-1 activating receptor on NK cells [53••]. Further-more, Quillay *et al.* described inhibition of human immu-nodeficiency virus (HIV)-1 infection in the decidua during the first trimester of pregnancy. Decidua NK cells prevented the establishment of HIV-1 infection of de-cidua macrophages in a cell-contact and unknown soluble factor-dependent mechanism [54•]. The intricate cross talk between macrophages and NK cells served to mod-ulate anti-viral immune responses.

Dendritic cells (DC) are potent antigen-presenting cells that initiate the adaptive immune response. NK cells interact with DCs to reciprocally activate and influence subsequent effector functions [55–59]. NK cells are recruited to secondary lymphoid organs to assist in mod-ulating the adaptive immune response [60,61,62•]. *In vitro* IL-2-activated human NK cells induced DC maturation and increased their ability to activate and polarize naïve CD4⁺ T cells. These polarized CD4⁺ T cells potently increased their ability to induce antigen-specific cytotoxic CD8⁺ T cell responses [63,64]. Reciprocally, activated DCs increased NK cell production of IFN-γ and tumor necrosis factor (TNF), which further induced DC matu-ration in a cell contact-dependent manner [65,66].

DC-NK cell interactions vary between different viral infections. *In vitro* and *in vivo* systemic HSV infection

revealed that inflammatory cytokines such as IFN-α and TNF-α from DCs promote NK cell degranulation and IFN-γ production [67••,68]. Engagement of the activat-ing receptor, NKG2D, on NK cells and NKG2D ligands induced on DCs by IL-18 were important for NK cell activation in vaccinia infection, whereas IL-15 from DCs and NKG2D engagement on NK cells were necessary for HIV-specific priming and control of infection in CD4⁺ T cells [69•,70•]. Additionally, DCs stimulated with HIV-1 Gag-virus-like particles induced robust antigen-specific NK cell proliferation, IFN-γ production, and cytotoxicity against HIV-1-infected CD4⁺ T cells [71]. Immune responses are dampened by NK cell-mediated lysis of DCs by limiting viral load and activation of the adaptive immune response. DCs activated by different toll-like receptor ligands upregulated expression of CD155 and CD112, which bind to DNAM-1 on NK cells to induce cytolysis of immature and mature DCs [72]. GM-CSF treatment of DC upregulates CD155 and ICAM-1, which can induce NK cell-mediated lysis of DCs [73•]. NK cells lysed HSV-2 and Dengue virus-infected DCs because expression of HLA class I molecules were downregulated [74,75•].

Certain DC-NK cell interactions favor viral persistence and immune escape. Patients with chronic hepatitis B infection have elevated DC activation, but failed to induce NK cell cytotoxicity in co-culture systems [76,77]. In MCMV infection, IL-10 produced by DCs suppressed DC-NK cell crosstalk, which impaired MCMV-specific CD4⁺ T cell priming and supported viral latency [78]. Of note, HIV opsonized by complement and antibody altered DC cytokine and chemokine responses, which resulted in decreased recruitment of NK cells to the mucosa to control initial HIV infection [79••]. This may result in the poor activation of the adaptive immune response against HIV, which highlights the importance of DC-NK cell responses in controlling viral burden and anti-viral T cell responses. Table 1 lists detailed inter-actions between NK cells and innate cells mentioned in this review.

## Modulation of the adaptive immune response
Besides indirectly modulating adaptive immune responses by limiting or perpetuating recruitment and cytokine production of innate immune cells, NK cells can directly control anti-viral T cell responses [80–82]. Study of persistent lymphocytic choriomeningitis virus (LCMV) infection in mice revealed that viral inoculum doses dictated host NK cell responses. At medium viral doses, NK cells facilitated fatal pathology by lysing activated CD4⁺ T cells, thereby promoting higher viral burden, CD8⁺ T cell exhaustion, and subsequent death of the host. Conversely at high viral doses, NK cells prevented fatal pathology by limiting excessive CD4⁺ and CD8⁺ T cell responses, allowing viral persistence, and survival of the host [83,84•]. In these studies, NK cells altered the

**Table 1**

**Interactions of NK cells with other immune cells. Table specifies the experimental model and the effects of the interactions**

| NK cell cross talk with | Interaction | Experimental model | Reference |
|---|---|---|---|
| Neutrophils | NKp46 and Fas-mediated apoptosis of neutrophils | Human PBMC co-culture Aseptic inflammation | [44] |
| | IL-22 from T, CD3$^+$NK1.1$^+$ T, and CD3$^-$NK1.1$^+$ cells mediated neutrophil recruitment into infected areas | Mouse cytomegalovirus | [45] |
| | TLR-activated neutrophils secreted chemokines and ROS to recruit and activate NK cells | Human PBMC co-culture TLR stimulations | [47••] |
| | IL-8, IL-1β, and IL-18 conditioning of NK cells induced DC maturation and CD4$^+$ T cell activation | | |
| Macrophages/ monocytes | M1 induced NK cells to secrete IFN-γ | Human PBMC co-culture Human cytomegalovirus | [51] |
| | NKp46-, DNAM-1-, 2B4-mediated NK cell degranulation IL-12-activated NK cells lyse M2 readily | Human PBMC co-culture LPS or bacillus Calmette-Guérin | [52] |
| | M1 induced NK cells to secrete IFN-γ NKp46 induced NK cell cytotoxicity 2B4 induced NK cells to secrete IFN-γ DNAM-1 induced NK cell cytotoxicity and IFN-γ secretion | | |
| | DNAM-1 and CD155 control infection CCL2 and iNOS production by monocytes | Mouse cytomegalovirus | [53••] |
| | Cell contact required — unknown receptors Unknown soluble factor | Human immunodeficiency virus | [54•] |
| Dendritic cells | IFN-α and TNF-α from DCs promoted NK cell degranulation and IFN-γ production | Human PBMC co-culture and mouse model of herpes simplex virus | [67••] [68] |
| | IL-18 signaling induced Rae-1 expression on DC NK cells required IL-18 and NKG2D ligation for activation | Mouse Vaccinia | [69•] |
| | DC-derived IL-15 and NKG2D ligands are necessary for NK cell activation to control HIV-infected CD4$^+$ T cells | Human PBMC co-culture Human immunodeficiency virus | [70•] |
| | Gag-VLPs induced DC cytokines that activated NK cells to lyse HIV-infected CD4$^+$ T cells | Human PBMC co-culture and mouse model of human immunodeficiency virus | [71] |
| | HSV-2 viral protein ICP47 mediated downregulation of HLA-C on infected cells resulting in NK cell lysis | Human PBMC co-culture Herpes simplex virus | [74] |
| | Infected DCs downregulated HLA class I and secreted type I IFN and TNF-α to induce NK cell lysis and IFN-γ production NK cell killing via Fas-FasL and perforin-granzyme | Human PBMC co-culture Dengue virus | [75•] |
| | TLR9-matured DCs poorly activated NK cells due to decreased IFN-α and OX40L expression | Human PBMC co-culture from chronic hepatitis B virus patients | [76] |
| | Matured DCs poorly activated NK cells | | [77] |
| | IL-10 suppressed cross talk and NK cell priming of CD4$^+$ T cells NKG2D and NKp46 mediated cross talk | Mouse cytomegalovirus | [78] |
| | HIV exposed-DCs secreted CCL3 and CXCL10 to recruit NK cells for effector functions | Human PBMC co-culture Human immunodeficiency virus | [79••] |
| CD4$^+$ T cells | NK cells lysed activated CD4$^+$ T cells via perforin and not Fas or TNF | Mouse lymphocytic choriomeningitis virus | [84•] |
| | CCL21 and CXCL10 from NK cells recruited T cells to peripheral lymph nodes Perforin-mediated apoptosis was necessary for DC antigen uptake | Mouse model of influenza | [89] |
| | HSV-exposed NK cells upregulated HLA-DQ and HLA-DR to form synapses with CD4$^+$ T cells | Human PBMC co-culture Herpes simplex virus | [91] |
| | IL-21-activated NK cells produced macrophage inhibitory factor to induce differentiation of central memory CD4$^+$ T cells | Mouse study Human biopsies | [92••] |
| | IL-2 from antigen-specific CD4$^+$ T cells was necessary for NK cell activation, IFN-γ production, and cytotoxicity | Simian immunodeficiency virus | [93] |
| | KIR3DS1$^+$ NK cells suppressed HIV-1 replication in infected HLA-F-expressing CD4$^+$ T cell | Human PBMC co-culture Human immunodeficiency virus | [94••] |

cytokine milieu and the polarization of T cell responses. Furthermore, chronic LCMV infection impairs the development of memory CD8+ T cells [85•]. Conversely, depletion of NK cells results in increased antigen presentation, CD4+ T cell expansion, improved CD8+ T cell responses, elevated numbers of follicular helper T cells, and antibody responses, suggesting that NK cells have dual roles in anti-viral responses [86,87••,88•].

A similar phenomenon is observed in influenza infection. In one study, mice infected with a sublethal dose of influenza revealed that NK cells were beneficial. IFN-γ produced by NK cells enhanced DC migration and T cell recruitment to the draining lymph node. NK cell depletion significantly diminished the generation of flu-specific T cells [89]. However, another report suggests that NK cells are detrimental to lethal doses of influenza. Depletion of NK cells resulted in reduced recruitment of innate cells, inflammatory cytokines, and lung pathology [90]. Both models of viral infections suggest that NK cells may have dual functions in modulating the adaptive system.

Emerging evidence suggests that NK-T cell interactions are more complicated than originally perceived. Human NK cells cultured with UV-inactivated HSV-1 and HSV-2 upregulated expression of HLA-DQ and HLA-DR and formed immunological synapses with autologous CD4+ T

cells. This interaction induced CD4+ T cell activation and IFN-γ production [91]. In another study, IL-21 induced expansion of HLA-DR+ CD86+ NKp44− NK cells, which enhanced the development of central memory CD4+ T cells [92••]. Furthermore, CD4+ T cell depletion or IL-2 neutralization in macaque SIV-controllers decreased NK cell activation and cytokine production. Interestingly, anti-retroviral therapy in SIV-non-controllers re-established NK cell activation and cytokine production, suggesting that NK cells and CD4+ T cells cooperate to control SIV infection [93]. A recent study found that HLA-F binding to the activating receptor, KIR3DS1, induces NK cell degranulation and cytokine production. KIR3DS1+ NK cells suppressed viral replication of HIV-1-infected autologous human CD4+ T cells, which had upregulated HLA-F expression [94••].

NK cells indirectly modulate CD8+ T cell responses. MCMV infection with a strain lacking m157 expression abolishes Ly49H+ NK cell recognition and initial viral control. Mice infected with a low dose of the m157-deficient MCMV demonstrated increased viral load, early DC maturation, and elevated amounts of pro-inflammatory cytokines, which resulted in an enhanced early CD8+ T cell response [95]. Conversely, a mouse model of hepatitis B (HBV) infection revealed a positive correlation between HBV-specific CD8+ T cells and NK cells. Depletion of NK cells resulted in diminished CD8+ T

**Figure 2**
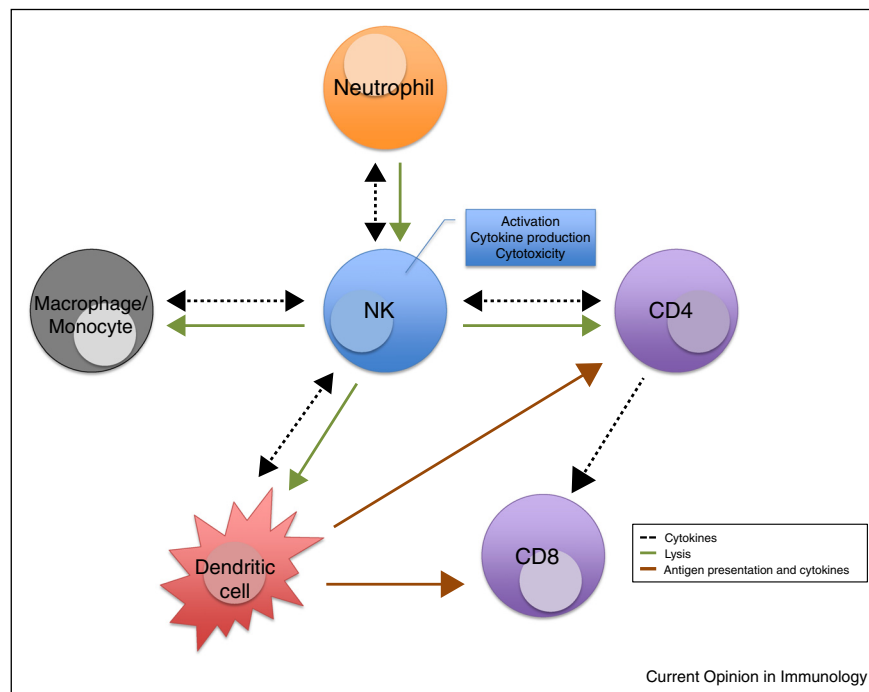


NK cell interactions and their effects on other immune cells. NK cells modulate other immune cells to coordinate anti-viral immune responses. Interactions with neutrophils, macrophages, monocytes, and dendritic cells results in mutual activation or NK cell-mediated lysis to limit responses. NK cells directly or indirectly modulate CD4+ and CD8+ T cell responses.

cell frequencies and adoptive transfer of HBV-exposed NK cells was sufficient to restore CD8+ T cell function [96•]. However, it is unclear whether CD4+ T cells and DCs participate in coordinating NK cell and CD8+ T cell responses in this model. In humans, a study revealed that the elderly have increased percentages of both NKG2C+ NK cells and CD8+ T cells in response to HCMV infection compared with the young [97•], suggesting that NK cells may tune the CD8+ T cell responses to complement their control of viral burden.

## Concluding remarks

NK cells provide immune protection from different viral infections. Evidence in animal models and human studies indicate that NK cells can develop long-lasting antigen-specific memory cells. Identification of the viral antigens and the NK cell receptor(s) responsible for many of these functions remain to be determined. Although specific NK cell responses depend on viral context, they generally require other cells to coordinate effective anti-viral responses (Figure 2). NK cells interact with neutrophils, macrophages, and dendritic cells to regulate the cytokine milieu, initial viral load, and CD4+ T cell responses. NK cells also directly limit CD4+ T cells and their effects on CD8+ T cells. Much more needs to be understood to fully grasp how NK cells respond to viral infections.

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