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Mutually assured destruction: the cold war between viruses and natural killer cells

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Natural killer (NK) cells play a multitude of antiviral roles that are significant enough to provoke viral countereffortsto subvert their activity. As innate lymphocytes, NK cells provide a rapid source of pro-inflammatory antiviral cytokines and bring to bear cytolytic activities that are collectively meant to constrain viral replication and dissemination. Additionally, NK cells participate in adaptive immunity both by shaping virus-specific T-cell responses and by developing adaptive features themselves, including enhanced antibody-dependent effector functions. The relative importance of different functional activities of NK cells are poorly understood, thereby obfuscating clinical use of these cells. Here we focus on opposing efforts of NK cells and viruses to gain tactical superiority during infection.

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Introduction

There is strong evidence that natural killer (NK) cells make crucial contributions to host defense during virus infection. In humans, genetic lesions that result in functional or cellular deficiencies of NK cells are strongly linked to heightened susceptibility to herpesvirus and papillomavirus infections [1–3]. Absence or dysfunction of NK cells likewise contributes to loss of viral control and altered pathogenesis of virus infection in mice [4], most notably in the context of murine cytomegalovirus (MCMV) infection. NK cells also play a role in pathogenesis of simian immunodeficiency virus (SIV) infection in non-human primates [5••]. The antiviral activities of NK cells span production of pro-inflammatory cytokines, like interferon gamma (IFN-γ) [6], and lysis of infected cells [7]. NK cells also shape adaptive antiviral responses by editing the available pool of antigen-presenting cells [8] and directly inhibiting T-cell responses [9]. Remarkably, NK cells can also develop memory-like features of antiviral T cells [10,11] and are capable of cooperating with B cells to suppress virus replication via antibody-dependent cellular cytotoxicity (ADCC) [12]. While the relative importance of these diverse functions of NK cells in virus infection remains undefined, the evolutionary trade-offs exhibited by viruses to facilitate suppression or evasion of NK cell effector function [13,14] highlights the strong antiviral potential of these cells. In this review, we highlight contributions made by NK cells to pathogenesis of virus infection and describe mechanisms used by viruses to fight back.

Innate functions of NK cells during virus infection

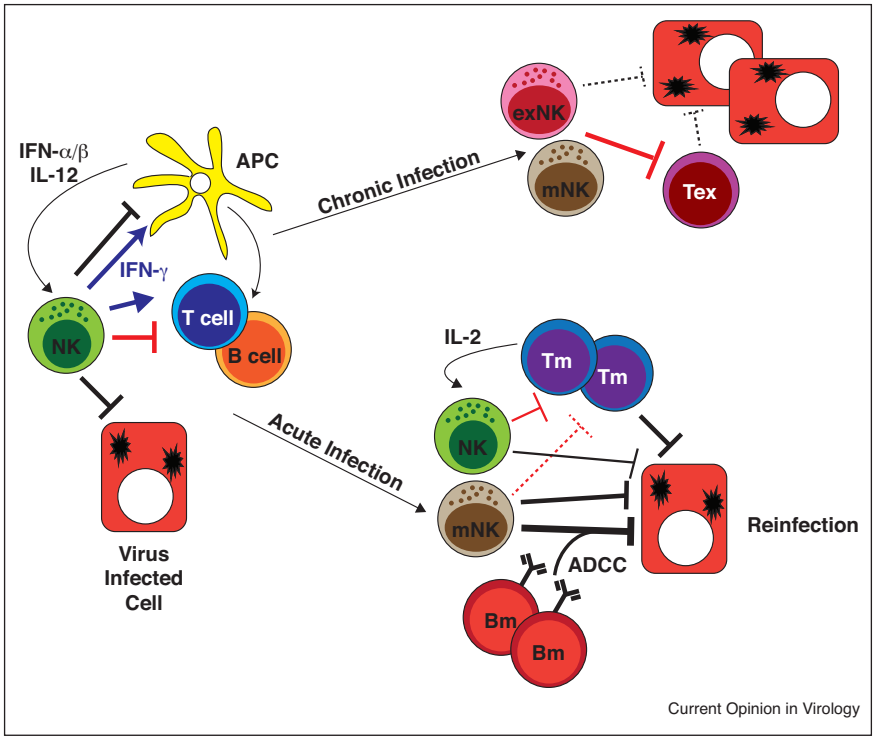
Proinflammatory cytokine release

NK cells provide a crucial, early source of IFN-γ that is necessary for host defense against multiple viruses, including MCMV [6], vaccinia virus [15], herpes simplex virus-2 (HSV-2) [16•], ectromelia virus (ECTV) [17•], and influenza virus [18••]. NK-cell derived IFN-γ promotes non-cytolytic control of virus replication [19] and enhances antiviral T-cell responses [20] (Figure 1). Notably, activated NK cells make additional cytokines (e.g. tumor necrosis factor alpha, TNF-α), growth factors (e.g. Granulocyte-macrophage colony-stimulating factor, GM-CSF), and inflammatory chemokines (e.g. RANTES) [21,22••], with the potential to influence antiviral immunity.

The closely related but distinct lineage of type 1 innate lymphoid cells (ILC1) [23] are an additional source of early IFN-γ after virus infection. In fact, tissue resident ILC1 in the liver and at other sites of initial virus replication confer IFN-γ-dependent control of MCMV infection [24]. The context-dependent requirements and potential overlap of NK cell or ILC1 antiviral IFN-γ production, particularly where both cells are implicated in viral control at initial sites of virus entry [6,18••,24,25], remains to be determined.

Antiviral IFN-γ production by NK cells is driven by the pro-inflammatory cytokine milieu elicited by virus infection. This frequently includes interleukin-12 (IL-12) and

Figure 1



Contributions of NK cells to acute, chronic, and secondary infections with viruses.
During acute challenge with new virus, NK cells contribute to host immunity by secreting proinflammatory cytokines (e.g. IFN-γ), lysing virus-infected cells, and exerting immunosuppressive effects indirectly via antigen-presenting cells (APC) or directly on T and B cells. Establishment of chronic infection is associated with functional and phenotypic exhaustion of both T (Tex)and NK cells (exNK), where some NK cells contribute to maintenance of T cell exhaustion and viral persistence. Viral exposure is associated with development of memory NK cells (mNK), T cells (Tm), and B cells (Bm). Following resolution of acute infection, re-exposure to the original virus prompts more potent antiviral and ADCC responses of mNK cells, altered capacity of naïve NK or mNK cells to suppress Tm, and amplification of NK cell responses by Tm-derived cytokines (e.g. IL-2).

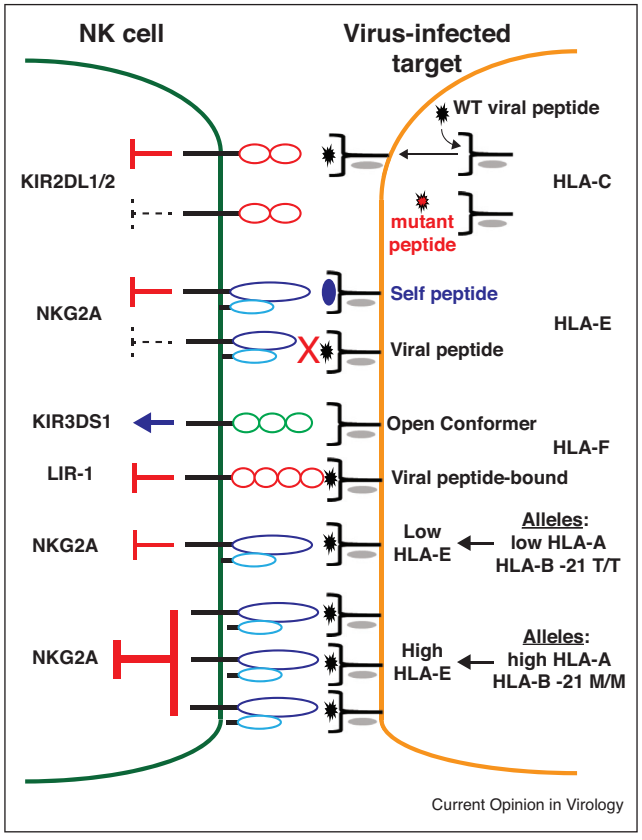
IL-18 induction of IFN-γ [26,27], although type I IFN and coordination among innate cells is important as well [28] (Figure 1). Mechanistically, type I IFN critically primes IL-18 production by inflammatory monocytes, which in turn elicits antiviral IFN-γ production by NK cells during HSV-2 infection [16•]. In addition, NK cells can promote coordination among innate leukocytes to enhance their own antiviral function. Infected dendritic cells trigger initial release of IFN-γ by NK cells in draining lymph node after ECTV infection, thereby simulating chemokine (C-X-C motif) ligand 9 (CXCL9) expression by inflammatory monocytes and subsequent recruitment of CXCR3-expressing NK cells to constrain viral dissemination [17•]. Recent work in cancer immunology reveals the capacity of NK cells to stimulate inflammatory dendritic cell (DC) recruitment into tumors [29,30], highlighting the intriguing possibility that similar mechanisms exist at sites of virus infection.

Direct lysis of virus-infected cells

While inflammatory cytokines can enhance IFN-γ-producing and cytolytic functions of NK cells, variegated expression of an array of germline encoded receptors that recognize viral, self, or altered self ligands ultimately controls killing of virus-infected cells by NK cells (reviewed in [7]) (Figure 2). Natural Killer Group 2D (NKG2D) provides an activating signal upon recognition of stress-induced ligands on infected cells [17•,31–33]. NKp46 stimulates NK-cell activation in response to viral ligands encoded by parainfluenza [34], metapneumovirus [35], reovirus [36], and influenza A [37,38] viruses. In C57BL/6 mice, the Ly49H receptor directly recognizes the m157 gene product of MCMV [39–41], whereas human NK cell responses against CMV are driven largely by NKG2C [42••] and activating killer cell immunoglobulin-like receptors (KIRs) [43,44]. Notably, the recent discovery that NKG2C recognized CMV UL40-derived peptides [42••] underscores the phenomenon of receptor driven expansion of specific subsets of NK cells expressing virus-specific recognition receptors in mice [45–47], humans [48], and non-human primates [49].

Variable engagement of NK cell receptors by viral peptide-containing class I human leukocytes antigen (HLA)

Figure 2



NK cell sensitivity to viral modulation of HLA.
A) Wild type viral peptides bind to HLA-C and suppress NK-cell cytotoxicity upon interaction with KIR2DL1/2 on NK cells. Certain viral variants decrease HLA-C expression or produce mutant peptides with reduced binding affinity to HLA-C, resulting in reduced KIR2DL1/2-mediated inhibition of NK cells. B) Expression of HLA-E bound self-peptides on uninfected cells protects from NK-cell killing via NKG2A inhibitory signaling. Certain viral peptides displayed on HLA-E of virus-infected cells obstruct HLA-E interaction with NKG2A, rendering virus-infected cells susceptible to NK-cell cytotoxicity. C) Open conformers of HLA-F preferentially interact with KIR3DS1 and activate NK cells. HLA-F occupation by viral peptides leads to preferential interaction with LIR-1, thereby suppressing NK cell activity. D) Host alleles promoting low HLA-A expression coupled with specific HLA-B alleles provoke low expression of HLA-E and weaker NKG2A control of NK cells. Alternatively, alleles associated with high HLA-A expression and HLA-B alleles associated with education via NKG2A render high HLA-E expression and strong NKG2A modulation of NK cell function.

and major histocompatibility complex (MHC) molecules is another mechanism controlling NK cell effector function in responses to virus infection (Figure 2). This concept is reinforced by the strong correlations between various KIR/HLA combinations and outcomes of virus infection, including those with hepatitis C virus (HCV) and HIV-1 [50,51]. Preservation of surface expression of HLA-C can limit viral elimination by NK cells via engagement of inhibitory KIR [52], yet KIR2DL2/S2 is implicated in protection against HIV in the context of specific HLA-C alleles. Expression of KIR2DL2/S2 in combination with HLA-C•14:03 or HLA-C•12:02 correlated with reduced viral load and increased NK-cell mediated elimination of infected CD4 T cells [53•]. Mechanistically, low HIV peptide affinity with these HLA subtypes resulted in reduced inhibitory signaling via KIR2DL2. In a similar vein, downmodulation of HLA-C does not always equate to enhanced NK cell antiviral function. Korner *et al.* witnessed impaired antiviral function of KIR2DL + NK cells against HIV-1-infected T cells that had downregulated HLA-C, revealing that NK cells are sensitive to virus-induced changes in HLA expression, but that the response to reduced HLA depends on genetics of HLA-KIR interaction [54•].

Activating KIR are also associated with pathogenesis of virus infection [55] (Figure 2). KIR2DS2 stimulates NK cell function upon recognition of a well-conserved flavivirus helicase peptide bound to HLA-C•0102, thereby implicating KIR2DS2 in immunity to HCV [56•]. In a similar fashion, KIR3DS1 is associated with delayed progression to AIDS in HIV-1 infection [50]. Recently, open-conformers of HLA-F were revealed as high-affinity ligands for KIR3DS1 that trigger NK cell cytokine production and degranulation [57••]. Moreover, activated and HIV-infected CD4 T cells exhibit increased expression of HLA-F. However, peptide-bound HLA-F preferentially binds leukocyte immunoglobulin-like receptor 1 (LIR-1), potentially providing an inhibitory signal to LIR-1 expressing NK cells [58•]

The inhibitory receptor NKG2A that interacts with the non-classical MHC receptor HLA-E (Figure 2), has emerged as a potent regulator of antiviral NK cell function [59,60]. Barker *et al.* [61•] discovered that a conserved HIV-1 peptide bound to HLA-E renders infected T cells highly susceptible to NK cell killing by limiting NKG2A-derived inhibitory signals. In addition, elegant genetic work reveals that expression of the NKG2A ligand HLA-E is driven by a combination of genetic alleles that dictate HLA-A and HLA-B expression and ultimately determine HIV-1 control [62••]. High expression levels of HLA-A promote HLA-E expression by providing a source of HLA-E stabilizing peptides, thereby provoking a strong NKG2A inhibitory signal and weak NK cell antiviral responses. Moreover, HLA-B haplotypes that characterize strong education of NK cells via NKG2A [63] exacerbate the effect of HLA-A expression on HLA-E/NKG2A inhibitory signaling [62••].

NK cell migration to sites of virus replication

Migration of NK cells to sites of virus replication and specific regions of lymphoid tissues is implicated in both viral control and determination of disease pathology [64,65]. Recent studies revealed that NK cell migration into the B-cell zone of lymph nodes during SIV infection is associated with better viral control and non-pathogenic

infection in the natural SIV host species, the African Green Monkeys [5••]. Depletion of NK cells in these animals significantly increased burden of SIV in lymph nodes, highlighting the potential antiviral role of NK cells in natural SIV hosts. In contrast, SIV infection of macaques is associated with reduced NK cell migration to B-cell follicles, poor viral control, and development of AIDS [5••]. Of note, NK cell localization within the follicle is a shared feature of MCMV and lymphocytic choriomeningitis virus (LCMV) infections of mice [66,67], reflecting the general importance of NK migration to sites of infection to mediate viral elimination or control.

NK cell participation in antiviral adaptive immunity

NK-cell regulation of adaptive immunity

Perforin-dependent and IL-10-dependent immunoregulatory mechanisms of NK cells are implicated in restraint of antiviral responses by T and B cells [9,68,69] (Figure 1). This immunoregulatory activity of NK cells crucially determines immune exhaustion, viral persistence, and immunopathology during chronic infection with LCMV [70–72]. Moreover, NK cell suppression affects development of T and B cell memory responses after acute virus infection [73]. However, neither the generation of memory T cells after adenovirus immunization nor the recall of these memory T cells after LCMV challenge was measurably impacted by NK cells [74•]. Collective results from several labs indicate that induction of NK cell regulatory function is a shared feature of many virus infections [72,75–79], but that differential gene expression, including that of NKG2A, may tune the regulatory capacity of NK cells and the susceptibility of T cells to this effect [74•,80,81]. In fact, NKG2A has emerged as a crucial negative regulator of the immunosuppressive capacity of NK cells [80–82], which highlights an alternative explanation for links between NKG2A and virus infection outcome [62••]. Distinct subsets of NK cells may differ in their regulatory capacity, in part due to how they are educated during development [22••]. A critical new finding concerning the immunoregulatory role of NK cells in virus infection recently emerged from investigation of HIV-1-infected individuals who do or do not develop broadly neutralizing antibodies (bnAbs) against HIV-1. Induction of bnAbs was associated with high expression of *RAB11FIP5* and dysfunction of NK cells [83••]. These data extend past mouse studies into humans and reveal the potential utility of targeting NK cells to enhance vaccine-elicited antibody responses [73,84•].

Adaptive features of NK cells

The recognition that subsets of NK cells can clonally expand and form pools of memory-like cells in response to virus infection or immunization has revolutionized NK cell research (reviewed in [85]) (Figure 1). NK cells with adaptive features are observed in MCMV [46], HCMV [42••,86,87], vaccinia virus [88], and SIV [49,89] infection, as well as after cytokine, hapten, or vaccine administration [89–92]. Although a wealth of studies reveal precise epigenetic [93•,94], metabolic [95], and transcription factors [96–98] involved in generation of antiviral NK cells with adaptive features, the mechanisms governing antigen-specific induction of these memory NK cells remain unclear. Recent evidence points to HCMV UL40-derived peptides as drivers of NKG2C + NK cell expansion [42••]. In the case of influenza A virus, NK cell expression of IFN-γ varies in a viral strain-dependent manner linked to differential type I IFN, CD54, and CD112 expression [18••]. Likewise, peptides derived from HCV and HIV alter KIR interaction with HLA, resulting in enhanced activation of NK cell subsets expressing particular KIR [56•,99–102]. The importance of viral peptide-HLA interaction with KIR is reinforced by observations of HIV adaptation to KIR [103,104]. Alteration of HLA interactions with NK cell receptors by viral peptides may also explain the observation of NK cell specificity for SIV-derived antigens in SIV-infected or SHIV-infected, as well as Ad26 based SIV vaccine immunized resus macaques [89]. Notably, another type of adaptive NK cell demarcated by reduced expression of FcεRγ, SYK, and/or EAT-2 expands in CMV infected individuals, but appears to do so in response to antibody-dependent signals [86,87,105]. Remarkably, this NK cell subset displays enhanced antibody-dependent effector functions that reflect cooperation between innate (NK) and adaptive (B-cell) memory cells (Figure 1).

Antibody-dependent cellular cytotoxicity (ADCC)

ADCC involves CD16-dependent recognition and killing of antibody-opsonized targets by NK cells [12] (Figure 1). This mechanism couples NK cells to antibody production by B cells, and represents a possible correlate of protection against infections, including those with HIV-1 [106–108]. Notably, the education of NK cells by self-specific HLA-binding receptors [109,110] contributes to the capacity of mature NK cells to mediate ADCC [63,111•]. Some pathogens, including HSV-1, express viral antigens (gE) with the capacity to bind Fc domains of immunoglobulin molecules (IgG-Fc) to block ADCC. However, a recent study revealed that HSV-1 gE binding to IgG-Fc forms a molecular bridge between NK cells and infected cells that promotes NK cell-mediated lysis and clearance of HSV-1-infected cells [112••]. Bacteria-derived proteins are capable of similar cross-linking, potentially highlighting a common mechanism of immune defense.

Viral subversion of NK cell functions

Virus infection of NK cells

Some viruses may evade innate immunity by directly infecting NK cells. HSV [113,114], Epstein-Barr virus [115], and human herpesvirus 6 [116] were all previously shown to productively infect NK cells, while influenza and vaccinia viruses can establish non-productive infections in these cells [117,118]. HIV also infects CD4 + NK

cells [119], although more recent work suggests this may reflect infection of CD4 + ILC1, which are subsequently depleted from the gut [120]. More recently, another herpesvirus, varicella zoster virus (VZV), was shown to preferentially infect CD56dim NK cells, thereby driving CD57 expression, loss of cell-surface CD16, and impairment of NK-cell function [121•].

Viral evasion of NK cells

Many viruses work to actively suppress or avoid NK cell activation (reviewed in Ref. [122]). During HIV-1 infection, viral gene products actively subvert NK-cell responses [123,124] while the virus itself appears to evolve in response to NK cell mediated pressure [103,104]. Most, if not all, members of the herpesvirus family suppress NK cells through a myriad of methods (reviewed in Ref. [14]). These mechanisms often reflect complicated evolutionary relationships between virus and host. For example, MCMV m157 binds to Ly49H [39] promoting viral resistance in a singular strain of inbred mice (C57BL/6), yet many MCMV isolates have mutations in m157 that evade Ly49H recognition [125] or promote interaction with inhibitory Ly49C receptors [126]. Another MCMV protein, m12, acts as a decoy immunoevasin by engaging with both inhibitory NKR-P1B and activating NKR-P1A/C receptors to modulate NK cell cytotoxic function [127••]. Remarkably, gain-of-function and loss-of-function mutations in m12 reveal evolution of host-virus interaction.

NK cell exhaustion

Persistent virus infections are known to promote dysfunction of virus-specific T cells [128] (Figure 1). This phenomenon led to the discovery that blockade of programmed death-1 (PD-1) interactions with its ligand, PD-L1, can rescue exhausted T cells in the context of chronic virus infection [129] and cancer, with the latter finding revolutionizing the cancer clinic [130]. NK cells also undergo functional exhaustion during chronic inflammation [131] and may contribute to clinical responses following PD-1 blockade [132,133•]. However, TIGIT [134•], IL1R8 [135•], and TIM3 [136] also appear to be highly relevant checkpoint receptors in NK cell functional exhaustion. Furthermore, a wealth of new studies indicate that metabolism stringently regulates the function of NK cells [137–143], which can limit their antiviral capacity in the context of CMV or HCV infection [144,145•].

Conclusions

NK cells play a variety of roles in response to virus infection. These activities include both independent and cooperative, multi-lineage functions that span innate and adaptive immunity. The clinical importance of NK cell function is clearly seen both from disease in patients who lack NK cells as well as from the evolutionary sacrifices made by many viruses to manipulate NK-cell functional activity. An improved understanding of context-specific contributions of NK cells in virus infection will be necessary to develop means to therapeutically modulate NK cells during infection.

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