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Roles of natural killer cells in antiviral immunity
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Natural killer (NK) cells are important in immune defense against virus infections. This is predominantly considered a function of rapid, innate NK-cell killing of virus-infected cells. However, NK cells also prime other immune cells through the release of interferon gamma (IFN-γ) and other cytokines. Additionally, NK cells share features with long-lived adaptive immune cells and can impact disease pathogenesis through the inhibition of adaptive immune responses by virus-specific T and B cells. The relative contributions of these diverse and conflicting functions of NK cells in humans are poorly defined and likely context-dependent, thereby complicating the development of therapeutic interventions. Here we focus on the contributions of NK cells to disease in diverse virus infections germane to human health.

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Introduction
The prevention and control of virus infections involves a complex interplay between diverse cell types of the innate and adaptive immune systems. Natural killer (NK) cells are a type of innate lymphoid cell (ILC) that unquestionably play an important role in immune defense against infection in both mice and humans. The contribution of NK cells to cytolytic killing of virus-infected cells is well-established and prominently featured in immunology textbooks. Likewise, the importance of early and potent production of pro-inflammatory cytokines like interferon gamma (IFN-γ) by NK cells is widely accepted. More recently, there is increasing evidence that NK cells play a key regulatory role in shaping adaptive immune responses to control infection [1]. In this capacity, NK cells have been shown to kill both antigen-presenting cells [2,3] and virus-specific T cells [4,5,6,7,8,9,10], and can produce anti-inflammatory cytokines like interleukin-10 (IL-10) to suppress immunity [11–13]. NK cells can also play a beneficial regulatory role in stimulating adaptive immunity [14]. Finally, a series of recent intriguing studies have questioned the ‘innate’ nature of NK cells by advancing the concept of long-lived memory NK cells that can contribute to viral control during latent infections or following re-infection [15–17].

In general, while the significance of NK cells in host defense against virus infection is clear, the relative contributions of their diverse and often conflicting functions (Figure 1) to antiviral immunity is poorly defined in humans. Therefore, it is difficult to determine whether NK cell activity is beneficial or detrimental during vaccination [18], and whether strategies to cure chronic infection should aim to enhance or subvert NK cells. This uncertainty is almost undoubtedly compounded by the context-dependence of NK cell activity in different virus infections. In order to complement more in-depth summaries of the regulatory [1], antiviral [19], and memory functions [20] of NK cells, this review focuses on highlighting what is presently known about the potential involvement of NK cells in different types of virus infections relevant to human disease.

DNA viruses
Herpesviridae: Since 1989, it has been clear that rare individuals genetically deficient in NK cells or the functional activity of NK cells display heightened susceptibility to severe diseases conferred by infection with herpesviruses [21], including cytomegalovirus (CMV), varicella zoster virus (VZV), Epstein-Barr virus (EBV), and herpes simplex virus (HSV). This is paralleled by the increased susceptibility of mice lacking NK cells or
Contributions of NK cells to antiviral immunity. NK cells have the potential to (a) recognize and kill virus-infected cells or release antiviral pro-inflammatory cytokines that can inhibit virus replication. These activities can be protective, but can also contribute to (b) pathological damage of host tissues. Inflammation and viral antigens can also trigger the development of (c) long-lived memory NK cells that may protect against reinfection or prevent viral reactivation from latency. By contrast, (d) NK cell promotion or inhibition of adaptive immune cells (e.g. T and B cells) or other innate cells (e.g. dendritic cells) can shape the overall immune response against the virus which can have consequences for (e) viral control, disease pathogenesis, and infection outcome.

In this context, the MCMV model was used to reveal the long-lived nature of NK cells with features of adaptive immune cells [15]. Infection of susceptible mice triggered the clonal expansion of NK cells expressing the MCMV-specific activating receptor, Ly49H. Following contraction, a small population of these cells persisted long-term in mice and demonstrated enhanced recall function against infection compared to unprimed Ly49H-expressing NK cells. In humans, an analogous population of CD94/NKG2C-expressing NK cells characterized by epigenetic changes in the IFNG locus [26] and other immune loci [27**,28**] becomes prominent after HCMV infection [29,30]. Together, these results suggest NK cells have evolved to recognize and control herpesvirus infections in a sustained fashion that leaves a phenotypical and functional imprint on the NK cell repertoire in infected individuals.

Despite the clear importance of NK cells in immune defense against herpesviruses, several groups have uncovered regulatory functions of NK cells in these infections. Removal of NK cells enhanced antiviral T cells responses during MCMV infection [31], which has been attributed to crosstalk between NK cells and antigen-presenting cells like dendritic cells [2,32–34] as well as production of IL-10 by NK cells [11]. Additionally, there is some speculation that severe T cell-mediated pathology in the absence of cytotoxic function in hemophagocytic lymphohistiocytosis patients, who suffer severe pathology during uncontrolled virus infections, arises as a consequence of both loss of cytotoxic-mediated elimination of virus infected cells and NK cell-mediated cytotoxic regulation of adaptive immunity [35]. NK cell subversion of antiviral T cells also appeared to be important in preventing development of autoimmune inflammatory conditions associated with persistent herpesvirus infections [36**]. However, it is unclear to what extent these regulatory functions of NK cells contribute to the antiviral responses against herpesvirus in humans, where-in absence of NK cells is associated with loss of viral control [21*]. A recently developed model of EBV infection of humanized mice, in which NK cells prevented mononucleosis-like disease by targeting infected cells [37], may be useful in trying to parse out the relative contributions of NK cell functions to human disease.

Papovaviridae: The condition of NK cell deficiency in humans is also associated with a loss of control of human papillomavirus (HPV) infection [38], suggesting that this virus may demonstrate herpesvirus-like susceptibility to NK cell-mediated antiviral function. In addition, the virus-like particles of HPV in vaccines aimed at preventing HPV-induced cancers are potent stimulants of human NK cell activity and crosstalk with dendritic cells [39]. This is not surprising given the vital role of NK cells in antitumor immunity and the propensity of HPV to trigger carcinogenesis. Thus, HPV may represent a useful model to examine the induction and function of virus-specific memory NK cells in humans.

Polyomaviridae: A microRNA encoded by two human polyoma viruses, JC and BK, targets the transcripts of a ligand for the activating NK cell receptor, NKG2D, in order to prevent NK cell-mediated lysis of infected cells [40]. Similarly, mouse models of polyomavirus infection have revealed a role for NK cells in preventing virus-induced tumor development [41] that is subverted when virus-induced inflammation curtails the expression of a ligand for NKG2D [42]. Together, these studies establish that NK cells are important players in immune defense against tumor-promoting DNA viruses via elimination of either transformed cells during these infections.

Poxviridae: NK cells were discovered shortly before the eradication of smallpox, the major poxvirus contributing to human disease. Therefore, little is known about the
role of NK cells in smallpox pathogenesis. However, ectromelia virus provides a mouse model of smallpox and vaccinia virus is similar enough to smallpox that it served as the active component for vaccination and facilitated global smallpox eradication. In each of these viral infections, NK cells have been shown to play a crucial early role in viral control that involves IFN-γ and the cytolytic protein, perforin [22,43–45]. Moreover, both viruses encode proteins that interfere with NK cell function [46–48]. More recently, memory NK cells that can mediate protection against re-infection were shown to be induced following vaccinia virus administration in mice [17]. Thus, like other DNA viruses, poxviruses appear to be susceptible to the antiviral effects of NK cells and drive the development of memory NK cells that may provide lasting protection.

**Adenoviridae:** Similar to other DNA viruses, there is evidence that human adenoviruses evade NK cell antiviral functions by sequestering or preventing up-regulation of ligands of activating NK-cells receptors on infected cells [49,50]. Nevertheless, NK cells play a critical role in eliminating adenoviral vectors in the liver [51–53], which may be beneficial during natural adenovirus infection but can also inhibit the efficacy of adenovirus-mediated gene transfer.

**Hepadnaviridae:** Hepatitis B virus (HBV) infection can result in various infectious pathologies ranging from acute to chronic infections associated with liver disease. Dysfunction of NK cells in infected individuals, driven predominately by heightened expression levels of IL-10 and TGF-β has been associated with failure to control HBV replication and chronic infection [54,55], consistent with a potential direct antiviral role of NK cells against HBV. However, NK cells can also kill virus-specific CD8T cells in a TRAIL-dependent manner in chronically infected individuals [56], thereby suppressing the ability of antiviral T cells to control infection. Moreover, the killing of infected hepatocytes by NK cells also contributes to liver damage and development of disease, whereas NK-cell killing of activated stellate cells in HBV-infected individuals may prevent the development of fibrosis [56,57]. These reports suggest NK cells play both beneficial and detrimental roles during HBV infection but the overall contribution of these functions to disease severity remains unclear.

**RNA viruses**

**Arenaviridae:** By contrast to the vital role of NK cells in control of herpesvirus infection, NK cells do not suppress replication of lymphocytic choriomeningitis virus (LCMV) in mice [22], even in the absence of adaptive immune cells [58]. For this reason, the LCMV model was a valuable tool for uncovering the functional contribution of NK cell regulatory function to disease pathogenesis without a confounding contribution of NK cells to direct viral control. NK cells are potently activated by the inflammatory cytokine milieu (e.g. type I IFN) during LCMV infection, resulting in suppression of virus-specific CD4 and CD8T cell responses as well as antigen-presenting cell function [4,9,59,60,61**]. Ironically, type I IFN is also critical for protecting antiviral T cells from NK-cell mediated cytolysis [7,8**]. Importantly, NK cell inhibition of antiviral T and B cells could prevent fatal immunopathology [4] and facilitate viral persistence during chronic LCMV infection [4,9,60,61**]. Similar regulatory functions of NK cells during acute LCMV infection contributed to diminished virus-specific memory T-cell and B-cell responses [62**]. Whether NK cells play a similar role in determining disease outcome during infections of humans with Lassa, Machupo, and other arenaviruses remains to be explored. There is some in vitro evidence that lassa-virus infected APCs stimulate NK cell cytolytic function, which is inhibited by viral nucleoprotein as a viral evasion strategy [63].

**Flaviviridae:** A number of studies have shown that establishment and maintenance of chronic hepatitis C virus (HCV) infection is associated with NK cell dysfunction [57], consistent with an important antiviral function of these cells against this major human pathogen. Similar to HBV infection, chronic HCV-induced NK cell activity has the potential to potentiate or limit liver damage and fibrosis depending on the interactions between NK cells and hepatocytes, stellate cells, or other leukocytes. By contrast to chronic HBV infection, depletion of NK cells did not appear to enhance the responses of antiviral CD8T cells [5**], suggesting immunoregulatory functions of NK cells may be less pronounced in this type of chronic viral infection.

The relevance of NK cells to pathogenesis of a number of vector-borne flaviviruses, including dengue virus, West Nile virus, and yellow fever virus, has been reported. Notably, the yellow fever vaccine 17D (YF-17D) is typically a highly efficacious vaccine, but a recent study found reduced vaccine efficacy in a cohort of vaccine recipients that was associated with an inflamed innate compartment that included highly activated NK cells [64**]. The high frequency of activated NK cells correlated with poor vaccine responses, including weaker induction of neutralizing antibodies, which suggests a potential role for regulatory NK cells in controlling responses to the YF-17D vaccine or even natural yellow fever virus infection. Alternatively, it remains possible that these activated NK cells with an exhausted-like phenotype may be poor candidates for the induction of memory NK cells, which may be critical in immune defense against this virus. Preliminary studies in mouse models of dengue and West Nile virus infections largely support the concept of direct antiviral functions of NK cells against these pathogens, which is bolstered by reports of viral strategies to evade NK cell mediated attack [65,66].
Orthomyxoviridae: There are conflicting reports concerning the role of NK cells in pathogenesis of influenza A virus infection. Most of the data from animal models suggests that NK cells may be directly antiviral [67], able to recognize and kill virus-infected cells through interactions with influenza hemagglutinin and the receptor, NKp46 [68,69]. This has been extended to the idea that influenza vaccines stimulate NK cell memory that may be beneficial during subsequent viral infection [70]. By contrast, one report asserted that NK cells suppress influenza-specific T cells and modulate antiviral defense in a regulatory capacity [71]. How these disparate functions fit with the apparent contribution of human NK cells to immunity during influenza infection remains to be determined.

Paramyxoviridae: Respiratory syncytial virus (RSV) is a life-threatening pediatric pathogen associated with severe acute lung pathology. In a mouse model of RSV infection, NK cells made IFN-γ that contributed both to the lung disease [72] and to the failure of adaptive immunity to control infection [73]. These limited results suggest that NK cells may not only be dispensable for control of RSV infection, but may in fact be undesirable in RSV immunity in order to limit pathology and optimize adaptive anti-RSV immune responses.

Filoviridae: Although there are few studies of NK cells in Ebola virus infection in humans, the repertoire of host NK cell receptors, or killer immunoglobulin-like receptors (KIRs), has been linked to fatal outcome of Ebola [74]. This may relate to the potential of human NK cells to recognize and kill Ebola virus-infected DCs in vitro [75]. In fact, immunization of mice with Ebola virus-like particles could protect against lethal Ebola virus challenge in an NK cell-dependent and perforin-dependent manner [76,77], highlighting a possible direct antiviral role for NK cells against this important human pathogen as well as the potential value in vaccine-induced generation of Ebola-specific memory NK cells.

Retroviridae: The role of NK cells in retrovirus infection has been widely studied and yet it remains unclear due to the overall complexity in understanding the correlates of protection against these viruses [19]. In the case of infection with human T-cell leukemia virus type 1 (HTLV-1), the sum of available evidence suggests that NK cells are not involved in control of HTLV-1 infection or disease outcome [78]. By contrast, genetic studies have revealed an association between the presence of NK cell receptors (e.g., KIRs) and slower progression toward AIDS disease [79]. This is most likely due to NK cell-mediated killing of infected cells, since the protective KIR alleles are associated with enhanced NK cell cytolysis in vitro [80] and HIV appears to mutate in order to escape NK cell-mediated KIR-facilitated immune pressure [81]. HIV also exerts multiple effects on infected cells in order to subvert NK cell-mediated killing [82–85]. Nevertheless, the activation of NK cells or the lack of certain inhibitory NK cell receptors has been positively correlated with AIDS progression [86], suggesting that these cells may promote disease while trying to combat the infection. Other studies have highlighted an inverse relationship between NK cells and antiviral T cells [87], which suggests an element of NK-cell regulation of adaptive immunity at play in the determination of pathogenesis of HIV infection. In fact, NK-cell mediated suppression of adaptive immunity has been observed at distinct stages of Friend retrovirus infection of mice, whereas other time points reveal NK cell control of retrovirus replication that was recently shown to be suppressed by regulatory T cells [88,89]. These studies highlight the potentially complex relationship between NK cells and virus in disease pathogenesis.

There has been extensive analysis of changes in NK cell phenotype in function in nonhuman primate models of simian immunodeficiency virus (SIV) infection [90]. Although NK cells appear capable of antiviral activity against SIV, the distribution, phenotype, and functionality are compromised in chronic SIV infection [91–93]. A recent and very exciting study not only revealed the presence of functional SIV antigen-specific NK cells present in infected macaques, but highlighted the potential to stimulate virus-specific memory NK cells in macaques through adenoaviral vector-mediated vaccination [94*]. In combination with the realization that HIV-specific memory NK cells could be generated in conventional mice [16] and that distinct memory-like populations of NK cells are present in the blood of HIV-infected but seronegative individuals [95], these studies highlight the incredible potential of developing means to elicit retrovirus-specific memory NK cell responses through immunization that may prevent infection.

Rhabdoviridae and Togaviridae: Although vesicular stomatitis virus (VSV) is a human pathogen, its current importance to human health is in the use of VSV as an oncolytic anti-tumor treatment [96]. As antitumor effector cells, NK cells and VSV would appear to be on the same team against tumors. However, the direct antiviral functions of NK cells against VSV and other oncolytic viruses can limit the antitumor functionality via rapid clearance of the virus itself [97,98]. Thus, there may be cases in humans where reduced durability of vaccine or therapeutic viral vectors may be a detrimental consequence of NK cell antiviral functions. By contrast, there is a clear beneficial role for NK cells in therapy with oncolytic togaviruses, like Sindbis, which stimulate both direct antitumor functions of the NK cells as well as the positive feedback stimulation of other arms of the immune response via NK cell-derived IFN-γ [99].

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\textbf{Bunyaviridae:} In an analogous manner to HCMV, infection of humans with hantavirus stimulates a rapid and sustained expansion of NKG2C-expressing NK cells [106]. It remains unclear whether this expanded population of NK cells is contributing to viral control, or causing tissue damage associated with hantavirus hemorrhagic fever. IL-15 rather than virally encoded factors appears to be the driving force in this NK cell expansion, suggesting there may not be specific NK cell recognition of hantavirus via an NK cell receptor as was the case for MCMV. Nonetheless, this may represent another instance of the induction of long-lived NK cells with features of adaptive immune cells.

\textbf{Picornaviridae and Coronaviridae:} Depletion of NK cells or low levels of NK cell cytolytic function is associated with increased virus replication and more severe disease during infections with coxsackie virus, encephalomyocarditis virus, and Thieiler’s murine encephalitis virus [101–103]. NK cells have been similarly implicated in direct inhibition of virus replication and stimulation of liver damage during mouse hepatitis virus (MHV) infection [104,105]. Whether NK cells also play a direct antiviral role in human infections with picornaviruses (coxsackie) or coronaviruses (SARS) is not known.

\textbf{Summary}

In conclusion, there are clear instances in humans where NK cells play an important role in combatting virus infection, most notably against DNA viruses. This function can be detrimental when NK cells cause immunopathology or when NK cells are too effective at eliminating viral vectors in oncotherapy and gene therapy trials. There are also defined instances of long-lived memory NK cells that may contribute to immunity and health in ways that are not currently apparent. Importantly, the regulatory function of human NK cells cannot be overlooked in the interpretation of experimental results and evaluation of factors contributing to disease. However, current clinical practices must largely favor strategies to stimulate or induce only the antiviral functions of NK cells. The value of activating NK cells in chronic infection has been realized during therapeutic vaccination of SIV-infected macaques [106], restoration of HIV-specific T cell responses in human HIV infection [107], ribavirin/interferon therapy of chronic hepatitis C virus infection in human patients [108], IL-15-based potentiation of anti-HIV immune responses in humanized mice [109], and probiotic enhancement of control of influenza virus infection in mice [110]. Nevertheless, there are also reports that subversion of NK cell function can enhance adaptive immune responses that facilitate better control of virus replication in chronic infection [5*,36,111*]. Moreover, attempts to subvert the regulatory function in order to enhance adaptive immunity may have detrimental consequences for NK cell-mediated host resistance against latent herpesviruses and other viral pathogens present in most healthy adults. Continued evaluation of the specific context-dependent roles of NK cells in human virus infection will be necessary to guide attempts to modulate NK cells in therapy or prevention of infection.

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