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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

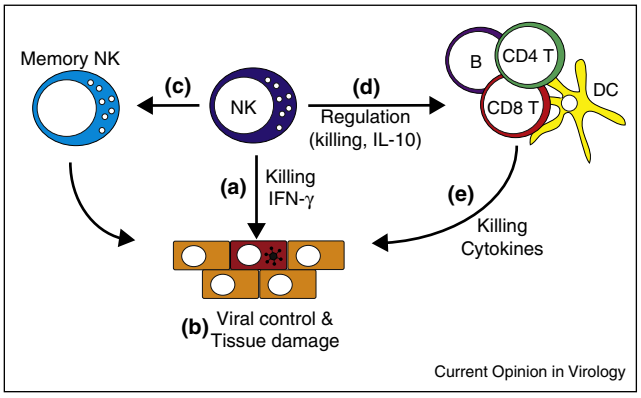
The prevention and control of virus infections involves a complex interplay between diverse cell types of the innate and adaptive immune systems. Natural killer (NK) cells are a type of innate lymphoid cell (ILC) that unquestionably play an important role in immune defense against infection in both mice 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

Figure 1



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.

particular NK-cell receptors to murine CMV (MCMV) infection [22,23], wherein infected cells are targets of NK-cell cytolytic attack and the antiviral effects of IFN-γ [24]. Notably, several herpesviruses encode genes that promote evasion of NK-cell antiviral function [25]. Together, these data provide compelling evidence for the importance of the direct antiviral functions of NK cells during herpesvirus infection.

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, wherein 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