Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Virology

Roles of natural killer cells in antiviral immunity

Stephen N Waggoner[1,2,3,4], Seth D Reighard[1,2,3], Ivayla E Gyurova[1,4], Stacey A Cranert[1], Sarah E Mahl[1], Erik P Karmele[1], Jonathan P McNally[1], Michael T Moran[1,2], Taylor R Brooks[1], Fazeela Yaqoob[1,2] and Carolyn E Rydyznski[1,2]

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.

Addresses
[1] Center for Autoimmune Genomics and Etiology (CAGE), Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States
[2] Immunology Graduate Program, University of Cincinnati, Cincinnati, OH, United States
[3] Medical Scientist Training Program, University of Cincinnati, Cincinnati, OH, United States
[4] Pathobiology and Molecular Medicine Graduate Program, University of Cincinnati, Cincinnati, OH, United States

Corresponding author: Waggoner, Stephen N (Stephen.Waggoner@cchmc.org)

Current Opinion in Virology 2016, **16**:15–23

This review comes from a themed issue on **Viral immunology**

Edited by **Liisa K Selin** and **Allan J Zajac**

For a complete overview see the Issue and the Editorial

Available online 16th November 2015

http://dx.doi.org/10.1016/j.coviro.2015.10.008

Introduction

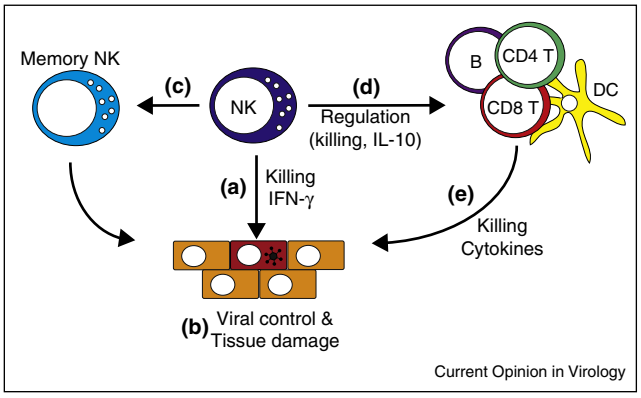
The prevention and control of virus infections involves a complex interplay between diverse cell types of the innate and adaptive immune systems. Natural killer (NK) cells are a type of innate lymphoid cell (ILC) that unquestionably play an important role in immune defense against infection in both mice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

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 [5••], 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 adenoviral 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 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].

Bunyaviridae: In an analogous manner to HCMV, infection of humans with hantavirus stimulates a rapid and sustained expansion of NKG2C-expressing NK cells [100]. 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.

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 Theiler'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.

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.

Acknowledgements

The authors are supported by National Institutes of Health grants DA038017 and AI118179, the Cincinnati Children's Research Foundation, the Alpha Omega Alpha Honor Medical Society, the Albert J. Ryan Foundation, the CancerFree KIDS Pediatric Cancer Research Alliance, and The Ellison Medical Foundation. Our apologies to colleagues whose work could not be cited due to space limitations.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Welsh RM, Waggoner SN: **NK cells controlling virus-specific T cells: rheostats for acute vs. persistent infections**. *Virology* 2013, **435**:37-45.

2. Andrews DM, Estcourt MJ, Andoniou CE, Wikstrom ME, Khong A, Voigt V, Fleming P, Tabarias H, Hill GR, van der Most RG *et al.*: **Innate immunity defines the capacity of antiviral T cells to limit persistent infection**. *J Exp Med* 2010, **207**:1333-1343.

3. Ferlazzo G, Morandi B, D'Agostino A, Meazza R, Melioli G, Moretta A, Moretta L: **The interaction between NK cells and dendritic cells in bacterial infections results in rapid induction of NK cell activation and in the lysis of uninfected dendritic cells**. *Eur J Immunol* 2003, **33**:306-313.

4. Waggoner SN, Cornberg M, Selin LK, Welsh RM: **Natural killer cells act as rheostats modulating antiviral T cells**. *Nature* 2012, **481**:394-398.

5. •• Peppa D, Gill US, Reynolds G, Easom NJ, Pallett LJ, Schurich A, Micco L, Nebbia G, Singh HD, Adams DH *et al.*: **Up-regulation of a death receptor renders antiviral T cells susceptible to NK cell-mediated deletion**. *J Exp Med* 2013, **210**:99-114.
Using blood and liver biopsies from hepatitis patients, the authors demonstrate a critical regulatory function of human NK cells during chronic HBV infection that hampers antiviral CD8 T cell responses.

6. Nielsen N, Odum N, Urso B, Lanier LL, Spee P: **Cytotoxicity of CD56(bright) NK cells towards autologous activated CD4+ T cells is mediated through NKG2D, LFA-1 and TRAIL and dampened via CD94/NKG2A**. *PLoS One* 2012, **7**:e31959.

7. • Crouse J, Bedenikovic G, Wiesel M, Ibberson M, Xenarios I, Von Laer D, Kalinke U, Vivier E, Jonjic S, Oxenius A: **Type I interferons protect T cells against NK cell attack mediated by the activating receptor NCR1**. *Immunity* 2014, **40**:961-973.

8. • Xu HC, Grusdat M, Pandyra AA, Polz R, Huang J, Sharma P, Deenen R, Kohrer K, Rahbar R, Diefenbach A *et al.*: **Type I interferon protects antiviral CD8(+) T cells from NK cell cytotoxicity**. *Immunity* 2014, **40**:949-960.
In a mouse model of chronic LCMV infection [7•,8•], the authors highlight the important role of type I IFN signaling in inducing in T cells a resistance to NK cell-mediated attack.

9. Lang PA, Lang KS, Xu HC, Grusdat M, Parish IA, Recher M, Elford AR, Dhanji S, Shaabani N, Tran CW *et al.*: **Natural killer cell activation enhances immune pathology and promotes chronic infection by limiting CD8+ T-cell immunity**. *Proc Natl Acad Sci U S A* 2012, **109**:1210-1215.

10. Cerboni C, Zingoni A, Cippitelli M, Piccoli M, Frati L, Santoni A: **Antigen-activated human T lymphocytes express cell-surface NKG2D ligands via an ATM/ATR-dependent mechanism and become susceptible to autologous NK- cell lysis**. *Blood* 2007, **110**:606-615.

11. Lee SH, Kim KS, Fodil-Cornu N, Vidal SM, Biron CA: **Activating receptors promote NK cell expansion for maintenance, IL-10 production, and CD8 T cell regulation during viral infection**. *J Exp Med* 2009, **206**:2235-2251.

12. Perona-Wright G, Mohrs K, Szaba FM, Kummer LW, Madan R, Karp CL, Johnson LL, Smiley ST, Mohrs M: **Systemic but not local infections elicit immunosuppressive IL-10 production by natural killer cells**. *Cell Host Microbe* 2009, **6**:503-512.

13. De Maria A, Fogli M, Mazza S, Basso M, Picciotto A, Costa P, Congia S, Mingari MC, Moretta L: **Increased natural cytotoxicity receptor expression and relevant IL-10 production in NK cells from chronically infected viremic HCV patients**. *Eur J Immunol* 2007, **37**:445-455.

14. Krebs P, Barnes MJ, Lampe K, Whitley K, Bahjat KS, Beutler B, Janssen E, Hoebe K: **NK-cell-mediated killing of target cells triggers robust antigen-specific T-cell-mediated and humoral responses**. *Blood* 2009, **113**:6593-6602.

15. Sun JC, Beilke JN, Lanier LL: **Adaptive immune features of natural killer cells**. *Nature* 2009, **457**:557-561.

16. Paust S, Gill HS, Wang BZ, Flynn MP, Moseman EA, Senman B, Szczepanik M, Telenti A, Askenase PW, Compans RW *et al.*: **Critical role for the chemokine receptor CXCR6 in NK cell-mediated antigen-specific memory of haptens and viruses**. *Nat Immunol* 2010, **11**:1127-1135.

17. Gillard GO, Bivas-Benita M, Hovav AH, Grandpre LE, Panas MW, Seaman MS, Haynes BF, Letvin NL: **Thy1+ NK [corrected] cells from vaccinia virus-primed mice confer protection against vaccinia virus challenge in the absence of adaptive lymphocytes**. *PLoS Pathog* 2011, **7**:e1002141.

18. Rydyznski CE, Waggoner SN: **Boosting vaccine efficacy the natural (killer) way**. *Trends Immunol* 2015, **36**:536-546.

19. Jost S, Altfeld M: **Control of human viral infections by natural killer cells**. *Annu Rev Immunol* 2013, **31**:163-194.

20. Min-Oo G, Kamimura Y, Hendricks DW, Nabekura T, Lanier LL: **Natural killer cells: walking three paths down memory lane**. *Trends Immunol* 2013, **34**:251-258.

21. • Orange JS: **Natural killer cell deficiency**. *J Allergy Clin Immunol* 2013, **132**:515-525 quiz 526.

This review describes the nature of a number of rare human disease conditions in which the lack of NK cells or their functional activity impairs control of infection.

22. Bukowski JF, Woda BA, Habu S, Okumura K, Welsh RM: **Natural killer cell depletion enhances virus synthesis and virus-induced hepatitis in vivo**. *J Immunol* 1983, **131**:1531-1538.

23. Scalzo AA, Fitzgerald NA, Wallace CR, Gibbons AE, Smart YC, Burton RC, Shellam GR: **The effect of the Cmv-1 resistance gene, which is linked to the natural killer cell gene complex, is mediated by natural killer cells**. *J Immunol* 1992, **149**:581-589.

24. Tay CH, Welsh RM: **Distinct organ-dependent mechanisms for the control of murine cytomegalovirus infection by natural killer cells**. *J Virol* 1997, **71**:267-275.

25. Jonjic S, Babic M, Polic B, Krmpotic A: **Immune evasion of natural killer cells by viruses**. *Curr Opin Immunol* 2008, **20**:30-38.

26. Luetke-Eversloh M, Hammer Q, Durek P, Nordstrom K, Gasparoni G, Pink M, Hamann A, Walter J, Chang HD, Dong J *et al.*: **Human cytomegalovirus drives epigenetic imprinting of the IFNG locus in NKG2Chi natural killer cells**. *PLoS Pathog* 2014, **10**:e1004441.

27. •• Lee J, Zhang T, Hwang I, Kim A, Nitschke L, Kim M, Scott JM, Kamimura Y, Lanier LL, Kim S: **Epigenetic modification and antibody-dependent expansion of memory-like NK cells in human cytomegalovirus-infected individuals**. *Immunity* 2015, **42**:431-442.

28. •• Schlums H, Cichocki F, Tesi B, Theorell J, Beziat V, Holmes TD, Han H, Chiang SC, Foley B, Mattsson K *et al.*: **Cytomegalovirus infection drives adaptive epigenetic diversification of NK cells with altered signaling and effector function**. *Immunity* 2015, **42**:443-456.

Together, these studies [27••,28••] uncover a myriad of epigenetic changes that occur in human NK cells in response to virus infection, and which may demarcate discrete functional subsets of human NK cells.

29. Guma M, Angulo A, Vilches C, Gomez-Lozano N, Malats N, Lopez-Botet M: **Imprint of human cytomegalovirus infection on the NK cell receptor repertoire**. *Blood* 2004, **104**:3664-3671.

30. Beziat V, Liu LL, Malmberg JA, Ivarsson MA, Sohlberg E, Bjorklund AT, Retiere C, Sverremark-Ekstrom E, Traherne J, Ljungman P *et al.*: **NK cell responses to cytomegalovirus infection lead to stable imprints in the human KIR repertoire and involve activating KIRs**. *Blood* 2013, **121**:2678-2688.

31. Su HC, Nguyen KB, Salazar-Mather TP, Ruzek MC, Dalod MY, Biron CA: **NK cell functions restrain T cell responses during viral infections**. *Eur J Immunol* 2001, **31**:3048-3055.

32. Robbins SH, Bessou G, Cornillon A, Zucchini N, Rupp B, Ruzsics Z, Sacher T, Tomasello E, Vivier E, Koszinowski UH *et al.*: **Natural killer cells promote early CD8 T cell responses against cytomegalovirus**. *PLoS Pathog* 2007, **3**:e123.

33. Stadnisky MD, Xie X, Coats ER, Bullock TN, Brown MG: **Self MHC class I-licensed NK cells enhance adaptive CD8 T-cell viral immunity**. *Blood* 2011, **117**:5133-5141.

34. Mitrovic M, Arapovic J, Jordan S, Fodil-Cornu N, Ebert S, Vidal SM, Krmpotic A, Reddehase MJ, Jonjic S: **The NK cell response to mouse cytomegalovirus infection affects the level and kinetics of the early CD8+ T-cell response**. *J Virol* 2012, **86**:2165-2175.

35. Sepulveda FE, Maschalidi S, Vosshenrich CA, Garrigue A, Kurowska M, Menasche G, Fischer A, Di Santo JP, de Saint Basile G: **A novel immunoregulatory role for NK-cell cytotoxicity in protection from HLH-like immunopathology in mice**. *Blood* 2015, **125**:1427-1434.

36. •• Schuster IS, Wikstrom ME, Brizard G, Coudert JD, Estcourt MJ, Manzur M, O'Reilly LA, Smyth MJ, Trapani JA, Hill GR *et al.*: **TRAIL+ NK cells control CD4+ T cell responses during chronic viral infection to limit autoimmunity**. *Immunity* 2014, **41**:646-656.

Using a mouse model of CMV infection, the authors reveal that NK cells promote viral latency in the salivary gland and prevent autoimmune disease by impairing virus-specific CD4 T cell responses.

37. Chijioke O, Muller A, Feederle R, Barros MH, Krieg C, Emmel V, Marcenaro E, Leung CS, Antsiferova O, Landtwing V *et al.*: **Human natural killer cells prevent infectious mononucleosis features by targeting lytic epstein-barr virus infection**. *Cell Rep* 2013, **5**:1489-1498.

38. Kamili QU, Seeborg FO, Saxena K, Nicholas SK, Banerjee PP, Angelo LS, Mace EM, Forbes LR, Martinez C, Wright TS *et al.*: **Severe cutaneous human papillomavirus infection associated with natural killer cell deficiency following stem cell transplantation for severe combined immunodeficiency**. *J Allergy Clin Immunol* 2014, **134**:1451-1453 e1451.

39. Langers I, Renoux V, Reschner A, Touze A, Coursaget P, Boniver J, Koch J, Delvenne P, Jacobs N: **Natural killer and dendritic cells collaborate in the immune response induced by the vaccine against uterine cervical cancer**. *Eur J Immunol* 2014, **44**:3585-3595.

40. Bauman Y, Nachmani D, Vitenshtein A, Tsukerman P, Drayman N, Stern-Ginossar N, Lankry D, Gruda R, Mandelboim O: **An identical miRNA of the human JC and BK polyoma viruses targets the stress-induced ligand ULBP3 to escape immune elimination**. *Cell Host Microbe* 2011, **9**:93-102.

41. Mishra R, Chen AT, Welsh RM, Szomolanyi-Tsuda E: **NK cells and gammadelta T cells mediate resistance to polyomavirus-induced tumors**. *PLoS Pathog* 2010, **6**:e1000924.

42. Mishra R, Polic B, Welsh RM, Szomolanyi-Tsuda E: **Inflammatory cytokine-mediated evasion of virus-induced tumors from NK cell control**. *J Immunol* 2013, **191**:961-970.

43. Delano ML, Brownstein DG: **Innate resistance to lethal mousepox is genetically linked to the NK gene complex on chromosome 6 and correlates with early restriction of virus replication by cells with an NK phenotype**. *J Virol* 1995, **69**:5875-5877.

44. Parker AK, Parker S, Yokoyama WM, Corbett JA, Buller RM: **Induction of natural killer cell responses by ectromelia virus controls infection**. *J Virol* 2007, **81**:4070-4079.

45. Fang M, Lanier LL, Sigal LJ: **A role for NKG2D in NK cell-mediated resistance to poxvirus disease**. *PLoS Pathog* 2008, **4**:e30.

46. Born TL, Morrison LA, Esteban DJ, VandenBos T, Thebeau LG, Chen N, Spriggs MK, Sims JE, Buller RM: **A poxvirus protein that binds to and inactivates IL-18, and inhibits NK cell response**. *J Immunol* 2000, **164**:3246-3254.

47. Jacobs N, Bartlett NW, Clark RH, Smith GL: **Vaccinia virus lacking the Bcl-2-like protein N1 induces a stronger natural killer cell response to infection**. *J Gen Virol* 2008, **89**:2877-2881.

48. Melo-Silva CR, Tscharke DC, Lobigs M, Koskinen A, Wong YC, Buller RM, Mullbacher A, Regner M: **The ectromelia virus SPI-2 protein causes lethal mousepox by preventing NK cell responses**. *J Virol* 2011, **85**:11170-11182.

49. Yawata N, Selva KJ, Liu YC, Tan KP, Lee AW, Siak J, Lan W, Vania M, Arundhati A, Tong L *et al.*: **Dynamic change in natural killer cell type in the human ocular mucosa in situ as means of immune evasion by adenovirus infection**. *Mucosal Immunol* 2015 http://dx.doi.org/10.1038/mi.2015.47. (epub ahead of print).

50. McSharry BP, Burgert HG, Owen DP, Stanton RJ, Prod'homme V, Sester M, Koebernick K, Groh V, Spies T, Cox S *et al.*: **Adenovirus E3/19K promotes evasion of NK cell recognition by intracellular sequestration of the NKG2D ligands major histocompatibility complex class I chain-related proteins A and B**. *J Virol* 2008, **82**:4585-4594.

51. Liu ZX, Govindarajan S, Okamoto S, Dennert G: **NK cells cause liver injury and facilitate the induction of T cell-mediated immunity to a viral liver infection**. *J Immunol* 2000, **164**: 6480-6486.

52. Ruzek MC, Kavanagh BF, Scaria A, Richards SM, Garman RD: **Adenoviral vectors stimulate murine natural killer cell responses and demonstrate antitumor activities in the absence of transgene expression**. *Mol Ther* 2002, **5**:115-124.

53. Zhu J, Huang X, Yang Y: **A critical role for type I IFN-dependent NK cell activation in innate immune elimination of adenoviral vectors in vivo**. *Mol Ther* 2008, **16**:1300-1307.

54. Lunemann S, Malone DF, Hengst J, Port K, Grabowski J, Deterding K, Markova A, Bremer B, Schlaphoff V, Cornberg M *et al.*: **Compromised function of natural killer cells in acute and chronic viral hepatitis**. *J Infect Dis* 2014, **209**:1362-1373.

55. Ju Y, Hou N, Meng J, Wang X, Zhang X, Zhao D, Liu Y, Zhu F, Zhang L, Sun W *et al.*: **T cell immunoglobulin- and mucin-domain-containing molecule-3 (Tim-3) mediates natural killer cell suppression in chronic hepatitis B**. *J Hepatol* 2010, **52**:322-329.

56. Schuch A, Hoh A, Thimme R: **The role of natural killer cells and CD8(+) T cells in hepatitis B virus infection**. *Front Immunol* 2014, **5**:258.

57. Rehermann B: **Pathogenesis of chronic viral hepatitis: differential roles of T cells and NK cells**. *Nat Med* 2013, **19**: 859-868.

58. Welsh RM, O'Donnell CL, Shultz LD: **Antiviral activity of NK 1.1+ natural killer cells in C57BL/6 scid mice infected with murine cytomegalovirus**. *Nat Immun* 1994, **13**:239-245.

59. Waggoner SN, Taniguchi RT, Mathew PA, Kumar V, Welsh RM: **Absence of mouse 2B4 promotes NK cell-mediated killing of activated CD8+ T cells, leading to prolonged viral persistence and altered pathogenesis**. *J Clin Invest* 2010, **120**:1925-1938.

60. Cook KD, Whitmire JK: **The depletion of NK cells prevents T cell exhaustion to efficiently control disseminating virus infection**. *J Immunol* 2013, **190**:641-649.

61. •• Cook KD, Kline HC, Whitmire JK: **NK cells inhibit humoral immunity by reducing the abundance of CD4+ T follicular helper cells during a chronic virus infection**. *J Leukoc Biol* 2015, **98**:153-162.

In a mouse model of chronic LCMV infection, the authors show that NK cell inhibition of CD4 T cells restricts antiviral B cell responses and thereby promotes viral persistence.

62. •• Rydyznski C, Daniels KA, Karmele EP, Brooks TR, Mahl SE, Moran MT, Li C, Sutiwisesak R, Welsh RM, Waggoner SN: **Generation of cellular immune memory and B-cell immunity is impaired by natural killer cells**. *Nat Commun* 2015, **6**:6375.

In mouse models of acute infection, the authors discovery that suppressive functions of NK cells limit the induction and memory T and B cells, in part by impairing the germinal center response and undermining the development of neutralizing antibodies.

63. Russier M, Reynard S, Carnec X, Baize S: **The exonuclease domain of Lassa virus nucleoprotein is involved in antigen-presenting-cell-mediated NK cell responses**. *J Virol* 2014, **88**:13811-13820.

64. •• Muyanja E, Ssemaganda A, Ngauv P, Cubas R, Perrin H, Srinivasan D, Canderan G, Lawson B, Kopycinski J, Graham AS *et al.*: **Immune activation alters cellular and humoral responses to yellow fever 17D vaccine**. *J Clin Invest* 2014, **124**:3147-3158.

In volunteer yellow fever vaccine recipients in Africa and Europe, the authors demonstrate that an active immune environment, including activated and exhausted NK cells, is deterimental to vaccine-induced T and B cell responses. This is a clear extension of discoveries in mouse models to the human population, which reveals the potential for identification of individuals who will be poor vaccine responders and highlights the potential for interventions targeting this innate immune state to enhance vaccine efficacy.

65. Wang T, Welte T: **Role of natural killer and Gamma-delta T cells in West Nile virus infection**. *Viruses* 2013, **5**:2298-2310.

66. Petitdemange C, Wauquier N, Rey J, Hervier B, Leroy E, Vieillard V: **Control of acute dengue virus infection by natural killer cells**. *Front Immunol* 2014, **5**:209.

67. Stein-Streilein J, Guffee J: **In vivo treatment of mice and hamsters with antibodies to asialo GM1 increases morbidity and mortality to pulmonary influenza infection**. *J Immunol* 1986, **136**:1435-1441.

68. Glasner A, Zurunic A, Meningher T, Lenac Rovis T, Tsukerman P, Bar-On Y, Yamin R, Meyers AF, Mandeboim M, Jonjic S *et al.*: **Elucidating the mechanisms of influenza virus recognition by Ncr1**. *PLoS One* 2012, **7**:e36837.

69. Gazit R, Gruda R, Elboim M, Arnon TI, Katz G, Achdout H, Hanna J, Qimron U, Landau G, Greenbaum E *et al.*: **Lethal influenza infection in the absence of the natural killer cell receptor gene Ncr1**. *Nat Immunol* 2006, **7**:517-523.

70. Dou Y, Fu B, Sun R, Li W, Hu W, Tian Z, Wei H: **Influenza vaccine induces intracellular immune memory of human NK cells**. *PLoS One* 2015, **10** e0121258.

71. Ge MQ, Ho AW, Tang Y, Wong KH, Chua BY, Gasser S, Kemeny DM: **NK cells regulate CD8+ T cell priming and dendritic cell migration during influenza A infection by IFN-gamma and perforin-dependent mechanisms**. *J Immunol* 2012, **189**:2099-2109.

72. Li F, Zhu H, Sun R, Wei H, Tian Z: **Natural killer cells are involved in acute lung immune injury caused by respiratory syncytial virus infection**. *J Virol* 2012, **86**:2251-2258.

73. Tregoning JS, Wang BL, McDonald JU, Yamaguchi Y, Harker JA, Goritzka M, Johansson C, Bukreyev A, Collins PL, Openshaw PJ: **Neonatal antibody responses are attenuated by interferon-gamma produced by NK and T cells during RSV infection**. *Proc Natl Acad Sci U S A* 2013, **110**:5576-5581.

74. Wauquier N, Padilla C, Becquart P, Leroy E, Vieillard V: **Association of KIR2DS1 and KIR2DS3 with fatal outcome in Ebola virus infection**. *Immunogenetics* 2010, **62**:767-771.

75. Fuller CL, Ruthel G, Warfield KL, Swenson DL, Bosio CM, Aman MJ, Bavari S: **NKp30-dependent cytolysis of filovirus-infected human dendritic cells**. *Cell Microbiol* 2007, **9**:962-976.

76. Warfield KL, Perkins JG, Swenson DL, Deal EM, Bosio CM, Aman MJ, Yokoyama WM, Young HA, Bavari S: **Role of natural killer cells in innate protection against lethal ebola virus infection**. *J Exp Med* 2004, **200**:169-179.

77. Williams KJ, Qiu X, Fernando L, Jones SM, Alimonti JB: **VSVDeltaG/EBOV GP-induced innate protection enhances natural killer cell activity to increase survival in a lethal mouse adapted Ebola virus infection**. *Viral Immunol* 2015, **28**:51-61.

78. Cook LB, Elemans M, Rowan AG, Asquith B: **HTLV-1: persistence and pathogenesis**. *Virology* 2013, **435**:131-140.

79. Bashirova AA, Thomas R, Carrington M: **HLA/KIR restraint of HIV: surviving the fittest**. *Annu Rev Immunol* 2011, **29**:295-317.

80. Alter G, Martin MP, Teigen N, Carr WH, Suscovich TJ, Schneidewind A, Streeck H, Waring M, Meier A, Brander C *et al.*: **Differential natural killer cell-mediated inhibition of HIV-1 replication based on distinct KIR/HLA subtypes**. *J Exp Med* 2007, **204**:3027-3036.

81. Alter G, Heckerman D, Schneidewind A, Fadda L, Kadie CM, Carlson JM, Oniangue-Ndza C, Martin M, Li B, Khakoo SI *et al.*: **HIV-1 adaptation to NK-cell-mediated immune pressure**. *Nature* 2011, **476**:96-100.

82. Shah AH, Sowrirajan B, Davis ZB, Ward JP, Campbell EM, Planelles V, Barker E: **Degranulation of natural killer cells following interaction with HIV-1-infected cells is hindered by downmodulation of NTB-A by Vpu**. *Cell Host Microbe* 2010, **8**:397-409.

83. Matusali G, Potesta M, Santoni A, Cerboni C, Doria M: **The human immunodeficiency virus type 1 Nef and Vpu proteins downregulate the natural killer cell-activating ligand PVR**. *J Virol* 2012, **86**:4496-4504.

84. Nolting A, Dugast AS, Rihn S, Luteijn R, Carrington MF, Kane K, Jost S, Toth I, Nagami E, Faetkenheuer G *et al.*: **MHC class I chain-related protein A shedding in chronic HIV-1 infection is associated with profound NK cell dysfunction**. *Virology* 2010, **406**:12-20.

85. Kulkarni S, Savan R, Qi Y, Gao X, Yuki Y, Bass SE, Martin MP, Hunt P, Deeks SG, Telenti A *et al.*: **Differential microRNA regulation of HLA-C expression and its association with HIV control**. *Nature* 2011, **472**:495-498.

86. Martin MP, Qi Y, Gao X, Yamada E, Martin JN, Pereyra F, Colombo S, Brown EE, Shupert WL, Phair J *et al.*: **Innate partnership of HLA-B and KIR3DL1 subtypes against HIV-1**. *Nat Genet* 2007, **39**:733-740.

87. Tomescu C, Duh FM, Hoh R, Viviani A, Harvill K, Martin MP, Carrington M, Deeks SG, Montaner LJ: **Impact of protective killer inhibitory receptor/human leukocyte antigen genotypes on natural killer cell and T-cell function in HIV-1-infected controllers**. *AIDS* 2012, **26**:1869-1878.

88. Littwitz E, Francois S, Dittmer U, Gibbert K: **Distinct roles of NK cells in viral immunity during different phases of acute Friend retrovirus infection**. *Retrovirology* 2013, **10**:127.

89. Littwitz-Salomon E, Akhmetzyanova I, Vallet C, Francois S, Dittmer U, Gibbert K: **Activated regulatory T cells suppress effector NK cell responses by an IL-2-mediated mechanism during an acute retroviral infection**. *Retrovirology* 2015, **12**:66.

90. Takahashi Y, Mayne AE, Khowawisetsut L, Pattanapanyasat K, Little D, Villinger F, Ansari AA: **In vivo administration of a JAK3 inhibitor to chronically siv infected rhesus macaques leads to NK cell depletion associated with transient modest increase in viral loads**. *PLoS One* 2013, **8** e70992.

91. Schafer JL, Li H, Evans TI, Estes JD, Reeves RK: **Accumulation of cytotoxic CD16+ NK cells in simian immunodeficiency virus-infected lymph nodes associated with in situ differentiation and functional anergy**. *J Virol* 2015, **89**:6887-6894.

92. Schafer JL, Ries M, Guha N, Connole M, Colantonio AD, Wiertz EJ, Wilson NA, Kaur A, Evans DT: **Suppression of a natural killer cell response by simian immunodeficiency virus peptides**. *PLoS Pathog* 2015, **11** e1005145.

93. Albrecht C, Malzahn D, Brameier M, Hermes M, Ansari AA, Walter L: **Progression to AIDS in SIV-infected rhesus macaques is associated with distinct KIR and MHC class I polymorphisms and NK cell dysfunction**. *Front Immunol* 2014, **5**:600.

94. •• Reeves RK, Li H, Jost S, Blass E, Li H, Schafer JL, Varner V, Manickam C, Eslamizar L, Altfeld M *et al.*: **Antigen-specific NK cell memory in rhesus macaques**. *Nat Immunol* 2015, **16**: 927-932.

The authors made the important discovery that SIV and SHIV infection of macaques triggers the generation of functional viral antigen-specific NK cells. Importantly, SIV-specific memory NK cells were also induced in macaques following immunization with an adenoviral vector. These NK cells appeared to mediate antigen-specific effector functions via the NKG2 family of receptors.

95. Lima JF, Oliveira LM, Pereira NZ, Mitsunari GE, Duarte AJ, Sato MN: **Distinct natural killer cells in HIV-exposed seronegative subjects with effector cytotoxic CD56(dim) and CD56(bright) cells and memory-like CD57(+)NKG2C(+)CD56(dim) cells**. *J Acquir Immune Defic Syndr* 2014, **67**:463-471.

96. Barber GN: **Vesicular stomatitis virus as an oncolytic vector**. *Viral Immunol* 2004, **17**:516-527.

97. Altomonte J, Wu L, Meseck M, Chen L, Ebert O, Garcia-Sastre A, Fallon J, Mandeli J, Woo SL: **Enhanced oncolytic potency of vesicular stomatitis virus through vector-mediated inhibition of NK and NKT cells**. *Cancer Gene Ther* 2009, **16**:266-278.

98. Alvarez-Breckenridge CA, Yu J, Price R, Wojton J, Pradarelli J, Mao H, Wei M, Wang Y, He S, Hardcastle J *et al.*: **NK cells impede glioblastoma virotherapy through NKp30 and NKp46 natural cytotoxicity receptors**. *Nat Med* 2012, **18**:1827-1834.

99. Granot T, Venticinque L, Tseng JC, Meruelo D: **Activation of cytotoxic and regulatory functions of NK cells by Sindbis viral vectors**. *PLoS One* 2011, **6** e20598.

100. Bjorkstrom NK, Lindgren T, Stoltz M, Fauriat C, Braun M, Evander M, Michaelsson J, Malmberg KJ, Klingstrom J, Ahlm C *et al.*: **Rapid expansion and long-term persistence of elevated NK cell numbers in humans infected with hantavirus**. *J Exp Med* 2011, **208**:13-21.

101. Godeny EK, Gauntt CJ: **Murine natural killer cells limit coxsackievirus B3 replication**. *J Immunol* 1987, **139**:913-918.

102. McFarland HI, Bigley NJ: **Sex-dependent, early cytokine production by NK-like spleen cells following infection with the D variant of encephalomyocarditis virus (EMCV-D)**. *Viral Immunol* 1989, **2**:205-214.

103. Paya CV, Patick AK, Leibson PJ, Rodriguez M: **Role of natural killer cells as immune effectors in encephalitis and demyelination induced by Theiler's virus**. *J Immunol* 1989, **143**:95-102.

104. Zou Y, Chen T, Han M, Wang H, Yan W, Song G, Wu Z, Wang X, Zhu C, Luo X *et al.*: **Increased killing of liver NK cells by Fas/Fas ligand and NKG2D/NKG2D ligand contributes to hepatocyte necrosis in virus-induced liver failure**. *J Immunol* 2010, **184**:466-475.

105. Welsh RM, Haspel MV, Parker DC, Holmes KV: **Natural cytotoxicity against mouse hepatitis virus-infected cells II. A cytotoxic effector cell with a B lymphocyte phenotype**. *J Immunol* 1986, **136**:1454-1460.

106. • Vargas-Inchaustegui DA, Xiao P, Demberg T, Pal R, Robert-Guroff M: **Therapeutic envelope vaccination in combination with antiretroviral therapy temporarily rescues SIV-specific CD4(+) T-cell-dependent natural killer cell effector responses in chronically infected rhesus macaques**. *Immunology* 2015, **145**:288-299.

107. • Jost S, Tomezsko PJ, Rands K, Toth I, Lichterfeld M, Gandhi RT, Altfeld M: **CD4+ T-cell help enhances NK cell function following therapeutic HIV-1 vaccination**. *J Virol* 2014, **88**:8349-8354.

In Refs. [106•,107•], the authors show that therapies that restore virus-specific T cells have the capability of enhacing antiviral NK cell responses.

108. Werner JM, Serti E, Chepa-Lotrea X, Stoltzfus J, Ahlenstiel G, Noureddin M, Feld JJ, Liang TJ, Rotman Y, Rehermann B: **Ribavirin improves the IFN-gamma response of natural killer cells to IFN-based therapy of hepatitis C virus infection**. *Hepatology* 2014, **60**:1160-1169.

109. Seay K, Church C, Zheng JH, Deneroff K, Ochsenbauer C, Kappes JC, Liu B, Jeng EK, Wong HC, Goldstein H: **In vivo activation of human NK cells by treatment with an interleukin-15 superagonist potently inhibits acute in vivo HIV-1 infection in humanized mice**. *J Virol* 2015, **89**:6264-6274.

110. Kawahara T, Takahashi T, Oishi K, Tanaka H, Masuda M, Takahashi S, Takano M, Kawakami T, Fukushima K, Kanazawa H *et al.*: **Consecutive oral administration of Bifidobacterium longum MM-2 improves the defense system against influenza virus infection by enhancing natural killer cell activity in a murine model**. *Microbiol Immunol* 2015, **59**:1-12.

111. Waggoner SN, Daniels KA, Welsh RM: **Therapeutic depletion of**
• **natural killer cells controls persistent infection**. *J Virol* 2014, **88**:1953-1960.
In a mouse model of chronic infeciton, the authors demonstate that there could be beneficial effects for viral control associated with removal of regulatory NK cells and associated enhancement of antiviral T cell responses.