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Natural Killer cells in Innate Defense against Infective Pathogens

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Abstract

Infectious diseases cause over 300 million illnesses and more than 5 million deaths each year worldwide. Understanding how components of the host immune system function to control disease-causing pathogens is critically important to develop strategies for preventing and controlling these diseases. With the discovery of innate immune receptors, we are beginning to appreciate the important role of innate immunity in the defense against infectious diseases. NK cells are a critical cell population in innate immunity, providing first line of defense against a variety of pathogens. NK cells mediate protection by direct killing of infected target cells and producing cytokines (mainly IFN-γ and TNF) that shape innate and adaptive immune responses. Recent studies have focused on the mechanisms by which NK cells recognize and respond to viruses, bacteria and parasites, and also the role of NK cells in modulating adaptive immune responses.

Keywords: Natural killer cells; Infective pathogens; Inhibitory receptors; Activating receptors

Abbreviations: MCMV: Murine Cytomegalovirus; OPV: Orthopoxvirus; ECTV: Ectromelia Virus; HIV: Human Immunodeficiency Virus; HCV: Hepatitis C Virus; Mtb: Mycobacterium tuberculosis; ITIM: Immunoreceptor Tyrosine-based Inhibitory Motifs; KIR: Killer cell Immunologobulin-like Receptors; ITAM: Immunoreceptor Tyrosine-based Activation Motif

Introduction

Natural killer (NK) cells are an important component of innate immunity, and serve as a crucial first line of defense against a diverse range of pathogens, such as viruses, bacteria and parasites [1-6]. Derived from the bone marrow, NK cells have wide tissue distribution, with high frequencies of mature NK cells in lung, liver, blood and spleen. They are generally found at low frequencies in lymph nodes and mostly with immature phenotype, however, following local stimulation, mature NK cells can accumulate in these sites [7,8]. NK cell responses are regulated by a balance of activating and inhibitory signals transmitted by cell surface receptors. Unlike B- and T-cell antigen receptors, NK cell receptors are encoded in the germ-line and do not undergo somatic recombination. Extensive work has been done to delineate the responses and functions of NK cells during pathogen infections. The best knowledge of NK cell function in the control of viral infections *in vivo* came from studies of murine cytomegalovirus (MCMV) infection. In the resistant C57BL/6 (B6) mice, NK cell activating receptor Ly49H recognizes m157-a viral encoded protein expressed on infected cell surface, which triggers the cytolytic function of NK cells [9,10]. The exact molecular mechanisms of NK cells during other viral infections are less clear. Further, much less is known about the responses and functions of NK cells during bacterial and parasitic infections. Moreover, NK cells are a heterogeneous population composed of cells that express overlapping subsets of activating and inhibitory receptors, studies have shown that the effector mechanisms that NK cells use may differ in different organs during pathogen infections [11-13]. Furthermore, accumulating evidences show that NK cells are a crucial link between innate and adaptive immune system via cytokine release and cell-cell interaction, which participate in the shaping of adaptive immune response [3,7,14]. This review highlights recent studies on the role of NK cells in the control of viruses, bacteria and parasites, and underscores the important role of NK cells playing in the defense against infectious diseases.

NK cell Recognition and Activation

NK cell function is regulated by inhibitory and activating receptors [15,16]. NK cell inhibitory receptors recognize a wide variety of self-molecules. Upon ligand binding, NK receptors having immunoreceptor tyrosine-based inhibitory motifs (ITIMs) in their cytoplasmic domain prevent NK cell effector function. The Ly49 inhibitory receptors in rodents and the inhibitory killer cell immunologobulin-like receptors (KIR) in primates recognize the MHC class I molecules, the CD94-NKG2A heterodimers in both rodents and primates recognize HLA-E (Qa-1b in mice), a nonclassical MHC class I molecule which binds peptides derived from leader segments of other class I proteins [17,18].

Activating receptors on NK cells can be broadly divided into those that recognize MHC-class-I-like ligands (human KIRs, murine Ly49 families, and CD94-NKG2s) and those that do not (NKG2D, 2B4, NKp30, NKp44 and NKp46) [19]. The activating receptors of the human KIR and murine Ly49 families are highly homologous to their inhibitory counterparts but have truncated cytoplasmic domains lacking ITIMs. These molecules associate with immunoreceptor tyrosine-based activation motif (ITAM)-bearing adapter molecules such as DAP12 and FεRIγ [20,21]. Other activating receptors, including NKG2D, associate with DAP10, an adapter protein containing an activating motif YXXM [22]. In rodent, an NKG2D isoform generated by alternative splicing can also associate with the DAP12 adapter protein in activated mouse NK cells [23,24].

The inhibitory NK receptors (mainly KIR, Ly49, CD94/NKG2A) recognizing self-MHC class I play a predominant role in NK cell tolerance to self. The "missing self hypothesis" states that NK cells scrutinize target cell MHC expression and only respond to target cells lacking the expression of MHC I [25]. The inhibitory receptor/

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MHC I interaction allows them to gain full functionality by directly activating or modifying other signals for developing functional NK cells. Recent works support that NK cell education operates as a rheostat, tuned by a quantitative influence on individual NK cells by the MHC class I alleles present *in vivo* [26]. The inhibitory input that an individual NK cell receives during education quantitatively tunes the responsiveness of individual NK cells. The higher the inhibitory input during education, the more likely it is that it will pass the threshold to respond (i.e. degranulation and IFN-γ expression) under given conditions of stimulation [26]. The role of activating receptors in human NK cell education has also been discovered recently. Fauriat C et al. found that NK cells expressing KIR2DS1 are hyporesponsive against cellular targets from donors homozygous for HLA-C2, the ligand of KIR2DS1. These results suggest that the education of human NK cells via activating receptors is a mechanism to secure tolerance that complements education via inhibitory receptors [20].

The effector function of NK cells is regulated by the signaling balance of activating and inhibitory receptors. When activating receptor/ligand interactions predominate over inhibitory receptor/ligand signals, NK cells are activated and target cells would be lysed. On the other hand, NK cells function is inhibited when activating receptor/ligand signals are weaker than inhibitory receptor/ligand signals [27-29].

NK cell effector functions are stimulated through direct contact with activated dendritic cells (DCs) *in vivo* [30]. In fact, DC/NK-cell interaction is bi-directional and complex, as it could result not only NK cell activation but also in DC maturation or apoptosis, depending on the activation status of both players [31]. Upon stimulation by various pathogens or by TLR ligands, DCs secrete several cytokines such as IL-12, IL-18, IL-15 and type I interferons (IFN-I) which trigger NK cell effector function. DC-derived IL-12 stimulates IFN-γ production by NK cells in different systems [31-33]. Il-18 is known to synergize with IL-12 to induce IFN-γ production by NK cells [31]. DCs use IL-15Rα to present IL-15 *in trans* to NK cells, which is important to trigger NK cell proliferation [34-36]. Lastly, NK cell activity is controlled by IFN-I at various levels. NK cell function cannot be elicited in IFNAR-deficient mice after viral or bacterial infections or injection of TLR ligands [36,37]. IFN-I can be produced by all DC subsets. More recently, studies from Diefenbach's group have shown that system failure of mononuclear phagocytes such as DCs to produce IFN-I in response to microbial stimulation in germ-free mice results in defective NK cell responses [38]. In addition, optimal NK cell activation by DCs also requires direct cell-cell contacts [30,32]. On the other hand, activated NK cells can induce DC maturation, while immature DCs are susceptible to NK cell mediated cytolysis while mature DCs are protected [31,39]. The NK cell activating receptor NKp30 appears to play a central role in DC maturation or apoptosis induced by NK cells [33,40,41].

NK cells and Viral Infection

NK cells play an important role in the control of some, but not all, mouse and human viruses. NK cells can respond to infection either directly or indirectly. They respond directly by recognizing virus-infected cells, and indirectly by interacting with DCs, which express Toll-like receptors (TLRs) and secrete cytokines in response to encounter with pathogens. NK cells use two main effector mechanisms to control viral infections: the secretion of IFN-γ and direct lysis of infected cells through the granule-exocytosis pathway.

NK cell Control of MCMV Infection

NK cells are critical for control of the mouse pathogen MCMV [42-44]. In resistant B6 mice, NK cells recognize MCMV-infected cells mainly by the activating receptor Ly49H [16]. MCMV encodes an MHC class I-like glycoprotein m157, which is expressed on the surface of infected cells and is directly ligated by Ly49H [9,10]. Upon recognition of MCMV-infected cells via Ly49H, NK cells secrete cytokines, such as IFN-γ and TNF-α, and kill infected cells by the release of lytic granules that contain perforin and granzymes. Moreover, during a later phase of infection, $Ly49H^+$ NK cells selectively proliferate, expand from 50% of all NK cells to 90% of all NK cells [45]. Mutant virus with m157 deletion abolishes $Ly49H^+$ NK cell activation after viral infection, gains virulence in B6 mice [46]. Further, Ly49H deficient mice in B6 background are susceptible to MCMV infection, while remain resistant to Leishmania major and ectromelia virus infection [47]. Mouse strains are either resistant or susceptible to MCMV infection. BALB/c mice and FVB/N mice that do not express Ly49H on NK cell surface are susceptible to MCMV infection. $Ly49H^{B6}$ bacterial artificial chromosome transgenes transfer virus resistance in BALB/c and FVB/N mice, and the resistance is correlated with the protein expression level of Ly49H on NK cells [48]. These studies demonstrate Ly49H as a pivotal factor in resistance to MCMV.

New Zealand White (NZW) mice are resistant to MCMV infection, and the resistance is also dependent on NK cells as NK cell depletion results in increased virus titers in multiple organs [49]. New Zealand Black (NZB) mice are susceptible to MCMV infection even though NZW and NZB NK cells display comparable levels of Ly49-related (anti-$Ly49H$ mAb $3D10^+$) receptors. However, the NK cell mediated-resistance in NZW mice is independent of Ly49H and m157 because NZW NK cells Ly49H and other receptors do not bind MCMV-encoded m157. Backcross NZW mice with MCMV-sensitive NZB mouse strains show resistance is mediated by multiple gene products, which remain to be identified [49]. These results indicate that NK cell control of viral infection in NZW genetic system differ from Ly49H-dependent, dominant control previously characterized for the B6 and BALB/c genetic system.

NK cells are also required for the resistance to MCMV in Ma/My mice, Ma/My mice lack the Ly49H receptor, another activating receptor Ly49P encoded on the NK cells in Ma/My mice recognizes the MHC class I molecule $H2\text{-}D^k$ in complex with the viral protein m04 [50]. Different from Ly49H in B6 mice that directly recognize m157 protein encoded by MCMV, Ly49P recognizes MCMV-infected cells requiring $H2\text{-}D^k$ peptide-binding platform. These findings reveal the importance of activating NK cell receptor-MHC class I-peptide complex interactions in the recognition of viral infections.

Another MCMV-susceptible mouse strain 129/J mice lack Ly49H but express two highly related molecules: an inhibitory Ly49I receptor and an activating Ly49U [51]. MCMV m157 binds to the inhibitory Ly49I receptor, preventing NK cell control of MCMV [9]. MCMV encoded m157 may have evolved to provide a selective advantage for the virus by engaging an inhibitory NK cell receptor to prevent NK cell activation. It is intriguing to note that the Ly49I alleles from B6 and 129/J mice both bind selectively to $H\text{-}2K^d$, whereas the Ly49I receptor in B6 mice fails to bind m157. Meanwhile, the activating Ly49H receptor does not recognize any known H-2 ligand, but binds to m157 with high affinity. The observations that m157 binds to both an inhibitory and a highly homologous activating Ly49 receptor suggest the possibility that Ly49H evolved from the inhibitory receptor as a consequence of selection by the pathogen [9,52].

Another NK cell activating receptor NKG2D also plays an important role in the NK cell mediated-protection during MCMV

infection. NKG2D interacts with three different cellular ligands: the retinoic acid early inducible (RAE)-1 family of proteins [53]; the minor histocompatibility antigen H60 [54,55], and the murine UL16-binding protein-like transcript (MULT)-1 glycoprotein [56,57], all of which are regulated by MCMV. The MCMV m145-encoded glocoprotein regulates MULT-1 by preventing plasma membrane residence of MULT-1 [58]. The MCMV m155 protein specifically down-regulates H60 without affecting expression of RAE-1 and MULT-1, an MCMV mutant virus lacking m155 is severely attenuated in BALB/c mice [59]. The MCMV m152-encoded gp40 glycoprotein specifically down-regulates the cell surface expression of all RAE-1 proteins, an m152 deletion mutant virus is less virulent *in vivo* compared with the wild-type virus [60,61].

The ability to generate antigen-specific memory responses is classically regarded as a hallmark of the cells of the adaptive immune system. However, recent studies have shown the NK cells also have adaptive immune features–can be long-lived and generate enhanced responses on secondary encounter with antigen [62-66]. During MCMV infection in B6 mice, Ly49H$^+$ NK cells preferentially proliferate. Following viral clearance, those effector Ly49H$^+$ NK cells undergo a contraction phase resulting in a long-lived memory NK cell pool. These memory NK cells express higher level of Ly49H, KLRG1, CD43 and Ly6C, and a decreased expression of CD27 which indicate that they are more mature than naïve NK cells. More importantly, when adoptively transferred into MCMV-susceptible newborn mice, the memory NK cells significantly protect the newborn mice compared with an equivalent number of naïve NK cells [66]. The memory NK cells generated during MCMV infection clearly demonstrate protective properties which can be parallel with that of the memory CD8 T cells. Understanding the mechanisms and the properties of NK cell memory during viral infections and vaccinations will have major implications on our approach to vaccination strategies for the generation of immunological memory against infectious pathogens.

NK cell Control of Mousepox

Mousepox is another viral disease where an essential role of NK cells in the protection is well established. Mousepox is caused by the mouse Orthopoxvirus (OPV) ectromelia virus (ECTV). Mouse strains can be generally divided into two groups following ECTV infection. Resistant mouse strains such as B6 and 129/J; susceptible mouse strains including DBA/2, DBA/2J, A/J, and BALB/c. To understand the genetic mechanisms involved in mousepox resistance, Brownstein et al. infected a panel of B6 X DBA2/J recombinant inbred strains of mice and mapped four genes involved in the B6 mice resistance to mousepox (Rmp1–Rmp4) [67]. Rmp1 resides in the natural killer (NK) complex (NKC) on chromosome 6 [68]. In recent years, the mechanisms of NK cell-mediated resistance to mousepox are beginning to be uncovered. In resistant B6 mice, the resistance to mousepox requires the direct cytolytic function of NK cells, as well as their ability to boost the adaptive T cell responses [7]. Further, we identified NK cell activating receptor CD94-NKG2E specifically recognize ECTV-infected cells via the targets expressing a specific peptide(s) (either a viral peptide or a peptide derived from an infection-induced cellular protein) bound to the non classical MHC class I Qa-1^b molecular. Another NK cell activating receptor NKG2D acts as a co-stimulator to boost optimal NK cell cytolytic function [69]. However, the peptide(s) bound to the Qa-1^b molecular remain unidentified. Importantly, different from the recognition of MCMV by Ly49-activating receptors, the CD94-NKG2 system is exquisitely conserved between rodents and primates [70], the involvement of activating CD94-NKG2 receptors during other viral infections deserves further in depth investigations.

Another important observation in the mousepox model is that the resistant B6 mice gradually lose their natural resistance to mousepox as they age. Surprisingly, the main reason for the loss of resistance is not of intrinsically defective T cell responses. Instead, the primary reason is because of defects in NK cell responses in the aged mice. In the aged mice, the percentage of total and mature NK cells decreases in blood and spleen, after ECTV infection, the aged NK cells also have defects to migrate to the local draining lymph node to control systemic virus spread, which results in increased early virus replication and spread as well as high mortality rate in the aged mice [8]. These results highlight the importance of NK cells in the control of age-related infectious diseases [71]. Further studies are needed to fully identify NK cell functional changes during physiological ageing process and investigate the mechanisms underlying these changes.

NK cell Control of Influenza Virus Infection

Extensive evidence supports an important role for NK cells during influenza virus (flu) infection. Using anti-asialo GM1 or anti-NK1.1 antibody PK136 to deplete NK cells leads to increased morbidity and mortality in mice with flu infection [72,73]. During the early days of flu infection, NK cells in the lungs become activated and demonstrate high cytotoxic activity followed by production of anti-viral cytokine IFN-γ [72,74]. Furthermore, NKp46, an activating NK cell receptor that recognizes flu haemagglutinin (HA) is critical for NK cell mediated-protection against lethal flu infection in mice [75,76].

In contrast, a recent study reported that increased survival in the NK cell depleted wild-type mice or IL-15$^{-/-}$ mice which lack NK cells due to deficiency of IL-15, a cytokine important for NK cell maintenance was associated with significantly lower lung lesions as well as reduced pulmonary inflammation following lethal flu infection [77]. This study suggested that in some settings, NK cells might contribute to the pathogenesis of flu infection. The discrepancy of the results might be due to a difference in the challenge virus dose, mouse strains used in those studies. Moreover, even though the authors also used anti-asialo GM1 antibody which will not deplete NKT cells to exclude the role of NKT cells as anti-NK1.1 antibody also deplete NKT cells in B6 mice [77], further in depth studies need to be done to explore the role of NKT cells in the pulmonary inflammation during flu infection because NKT cells numbers are also greatly reduced in IL-15$^{-/-}$ mice [78] and NKT cells have been shown to exacerbate pulmonary inflammation [79-81]. Nonetheless, NK cells clearly play an important role during flu infection. Further studies are required to fully dissect the function of NK cells in the defense against flu infection.

NK cell Control of Some Human Viral Infections

Human peripheral NK cells comprise 5-20% of peripheral blood mononuclear cells and can be divided into two distinct subsets characterized by their relative expression of the cell surface markers CD56 and CD16 [82,83]. The CD56^{bright}CD16$^-$ subset, which constitutes less than 10% of peripheral-blood NK cells, has robust cytokines production as IFN-γ, plays an important role in regulating the adaptive immune function but has weaker cytotoxicity compared to CD56^{dim}CD16$^+$ subset, which is the terminal differentiated population with high cytolytic function [84,85]. In addition to the conventional NK cells, a population of CD56$^-$CD16$^+$ NK cells have been found in human immunodeficiency virus (HIV) or hepatitis C virus (HCV) infected patients, which express a similar receptor profile to CD56^{low} NK cell, but have impaired cytolytic function and poor cytokine production upon target cells recognition [86-89].

NK cells are directly involved in HCV infection. In chronic HCV patients, the frequency of circulating NK cells is reduced compared with healthy controls, and is accompanied with subset skewing, with the enrichment of $CD56^{bright}$ subset and a terminally differentiated hypofunctional $CD56^{-}CD16^{+}$ NK cell subset [90-95]. The dysfunctional $CD56^{-}$ NK cells expanded during chronic HCV infection is associated with an impaired ability to respond to antiviral treatment with IFN-α and ribavirin [95]. Jinushi M et al. have demonstrated that NK cells from chronic HCV-infected donors (HCV-NK) were incapable of activating DCs, HCV-NK also showed higher expression of CD94/NKG2A and produced IL-10 and TGF-β when cultured with hepatic cells expressing HLA-E, a ligand for CD94/NKG2A [96]. Further, studies suggest that particular combinations of NK cell inhibitory receptor KIR2DL3 and its ligand HLA-C1 are associated with the clearance of HCV infection [97]. Moreover, lower frequencies of $NKp30^{+}NKp46^{+}$, $CD161^{+}$, and $NKG2D^{+}$ NK cells have been recently associated with the ability to clear HCV following acute infection [98]. Oliviero B et al. observed that different NK cell phenotypic and functional features were associated with different treatment outcome in chronic HCV patients [99]. In the patients achieved sustained virological response (SVR) with treatment of pegylated interferon α/ribavirin, their NK cells displayed higher perforin content, lower CD16 expression and higher proportion of $CD56^{dim}/CD16^{-}$ cells compared with NK cells from non-responder. Moreover, SVR patients displayed higher natural and antibody-dependent NK cell cytotoxicity [99]. These results indicate that early NK cell activation and robust cytolytic function are important in the rapid IFN-α induced elimination of HCV-infected hepatocytes [99].

NK cells also involve in the control of HIV infection, through several pathways such as through secreting perforin and granzyme B to kill target cells; the Fas–FasL pathway to induce apoptosis of infected cells; production of cytokines to regulate immunity; and antibody-dependent cell-mediated cytotoxicity (ADCC) to lyse infected cells [100]. NK cell surface receptors profile is associated with different clinical conditions in HIV patients. In patients with late stage HIV infection, their NK cells are found to contain fewer cytotoxic NK cells with higher expression of inhibitory receptor NKG2A [101]. Furthermore, certain HLA-B antigens have been associated with lack of progression to Acquired Immune Deficiency Syndrome (AIDS) after HIV infection [102]. Subsequent studies observed a protective effect of the combined presence of KIR3DS1 and HLA-Bw4-I80 alleles in patients with chronic HIV-1 infection [103,104]. Further analysis revealed that an increased NK cell KIR3DS1 count generated by copy number variants of KIR3DL1/DS1 was associated with a lower viral set point in the presence of their appropriate ligands. These results suggest that the relative amounts of these activating and inhibitory KIRs play a role in regulating the peripheral expansion of highly antiviral $KIR3DS1^{+}$ NK cells, which may influence the disease progress following HIV-1 infection [105]. Recently, Apps R et al. have shown that increasing HLA-C expression was associated with protection against multiple outcomes in HIV infection, and the protective mechanisms conferred by higher HLA-C expression level occurs partly through an enhanced CTL-mediated immune response [106]. However, it remains to be determined whether higher HLA-C expression also affects NK cell responses in HIV infection.

NK cells and Bacterial Infection

The importance of NK cells in protection against bacterial infection has been controversial. It might depend on different infection dose, infection site and also the type of inflammatory response elicited by different pathogens. NK cells respond to bacterial infection by direct lysing of infected host cells or secreting cytokines to promote inflammation. In addition, NK cell derived IFN-γ can activate macrophages to destroy bacteria. Similarly, macrophages are stimulated to produce NK cell activating cytokines IL-12 and TNF-α when exposed to bacteria, and in turn activate the NK cells to kill these target pathogens [107-109].

In B6 mice infected with *Mycobacterium tuberculosis* (Mtb), the causative agent of human tuberculosis (TB), activated NK cells increase in the lung, and are capable of producing IFN-γ and perforin. However, *in vivo* depletion of NK cells has no influence on bacterial load within the lung [6]. These findings indicate that NK cells are activated during the early response to pulmonary TB and are a source of IFN-γ, even though removal of NK cells does no substantially alter the host control of bacterial burden, NK cells might reduce immunopathology or favor development of protective immune responses. In support of this, Feng C et al. found that NK cell-derived IFN-γ differentially regulated T-independent resistance and granulocyte function in Mtb infection [110]. Human NK cells lyse Mtb-infected monocytes and alveolar macrophages through the NKp46 receptor and NKG2D [111,112]. More recently, when exposed to autologous monocytes and gamma-irradiated Mtb, human NK cells are found to produce IL-22, which inhibits intracellular mycobacterial growth by enhancing phagolysosomal fusion [113]. Further, NK cells lyse Mtb-expanded $CD4^{+}$ regulatory T cells (Tregs) *in vitro* [114]. Using B6 mice model first vaccinated with Bacillus Calmette-Guerin (BCG), followed by challenge with virulent Mtb, Dhiman R et al. showed that NK cells contribute to the efficacy of vaccination against Mtb infection by producing Il-22 and also by direct lysis of inhibitory Tregs that expanded after BCG immunization, induces optimal protective immunity through enhancing Ag-specific T cell responses after challenge with Mtb [14].

Innate immune responses are rapidly triggered upon Listeria monocytogenes (LM) infection and are essential for host survival [115,116]. NK cells represent an important source of IFN-γ at the infectious loci containing infected microphage and inducible nitric oxide synthase-producing DCs (TipDCs) [117-119]. However, NK might not involve in the clearance of LM [120]. As suggested in recent studies, CD8 T cells, rather than NK cells, play a more important role in immunity against LM [121]. In addition, type I IFN is found to hinder host control of LM [122-124]. NK cells are activated by type I IFN, so it is possible that NK cells worsen disease rather than protect from LM infection.

NK cells are also involved in control of other bacterial infection. Mice deficient in the *RAG2* and common γ-chain genes ($RAG^{-/-}\gamma c^{-/-}$) lack B, T and NK cells and serve as a good model to evaluate the function of these cells in immune defense against bacterial infection. $RAG^{-/-}\gamma c^{-/-}$ mice infected with *Shigella flexneri* have higher bacterial titers and compromised survival compared with $RAG^{-/-}$ mice (lack B and T cells, but have NK cells), suggesting that IFN-γ produced by NK might limit infection [125]. $IL\text{-}15^{-/-}$ mice deficient in NK cells are highly susceptible to pulmonary staphylococcal infection. In addition, WT mice depleted of NK cells are similarly susceptible to staphylococcal infection suggest a critical role for NK cells in host defense against pulmonary extracellular bacterial infection [126].

NK cells and Parasitic Infection

Malaria is a serious infectious disease, caused by infection with *Plasmodium* parasites. Immunity against *P. falciparum*, the most dangerous malaria-provoking agent, develops with age over the course of multiple infections and the humoral immunity is crucial

for protection from severe disease. Interactions between NK cells, infected erythrocytes (iRBC) and other immune cells lead to specific NK cell responses to *P. falciparum* [6,127]. NK cells derived from malaria-naïve or infected individuals are shown having cytolytic activity against *P. falciparum*-iRBCs that is possibly mediated by Fas and Granzyme B [128,129]. Mavoungou E, et al. have shown that the interaction of Duffy binding-like (DBL)-1 alpha domain of *P. falciparum*-infected erythrocyte membrane protein-1 (PfEMP-1) and NK natural cytotoxicity receptor (NCR) NKP30 is the key recognition mechanism leading to parasite killing by NK cells [130]. Recently, another study indicates that presence of Hsp70 and absence of HLA-E on the membrane of iRBC prompt NK cell cytotoxicity toward infected host cells [131].

In addition to their up-regulation of CD69 and CD25 activation markers after contact with RBC infected by several different strains of *P. falciparum*, NK cells are one of the first cells to produce IFN-γ in response to *P. falciparum* infection [6,127]. IFN-γ production by human NK cells cultured with iRBCs is dependent on IL-12 and IL-18 derived from myeloid cells in cultures [6]. Moreover, the magnitude of IFN-γ released by NK cells is known to be heterogeneous among individuals, possibly influencing susceptibility to disease [127]. Cerebral malaria is a major, life-threatening complication of *P. falciparum* malaria, and has a high mortality rate [132]. IFN-γ is known to be potentially involved in the pathogenesis of cerebral malaria [133-135]. NK cell depletion resulted in significant protection against cerebral malaria, suggesting involvement of NK cell activity in its pathogenesis [136].

Recently, associations of killer immunoglobulin-like receptors (KIRs) on NK cells with the incidence of malaria pathogenesis have been characterized. Comparison of KIRs between *Plasmodium*-positive and *Plasmodium*-negative Melanesian individuals in the Solomon Islands revealed the trend of parasitic positive individuals to be KIR3DL1/KIR3DS1 heterozygous in pair with KIR2DS4 nondeleted variants in a set of KIR genes in heritable as the AB genotypes [137]. Hirayasu K, et al. found that the combination of KIR2DL3 and its cognate HLA-C1 ligand was significantly associated with the development of cerebral malaria when compared with non-cerebral malaria, which indicates that the NK cell repertoire shaped by the KIR2DL3 -HLA-C1 interaction shows certain functional responses that facilitate development of cerebral malaria [138].

Strategies of Virus to Evade NK cell Immune Surveillance

The eventual outcome of a specific pathogen infection is determined by the battle between host and invading pathogen. Some viruses have evolved strategies to evade NK cell mediated–immune surveillance (Figure 1).

Viral-encoded Proteins Bind to NK cell Inhibitory Receptor

NK cell activation is inhibited by inhibitory signals provided through interaction of receptors on NK cells with self-MHC class I products. Some viruses encode decoy proteins for NK cell inhibitory receptors. Both human and mouse CMV encode their own MHC class

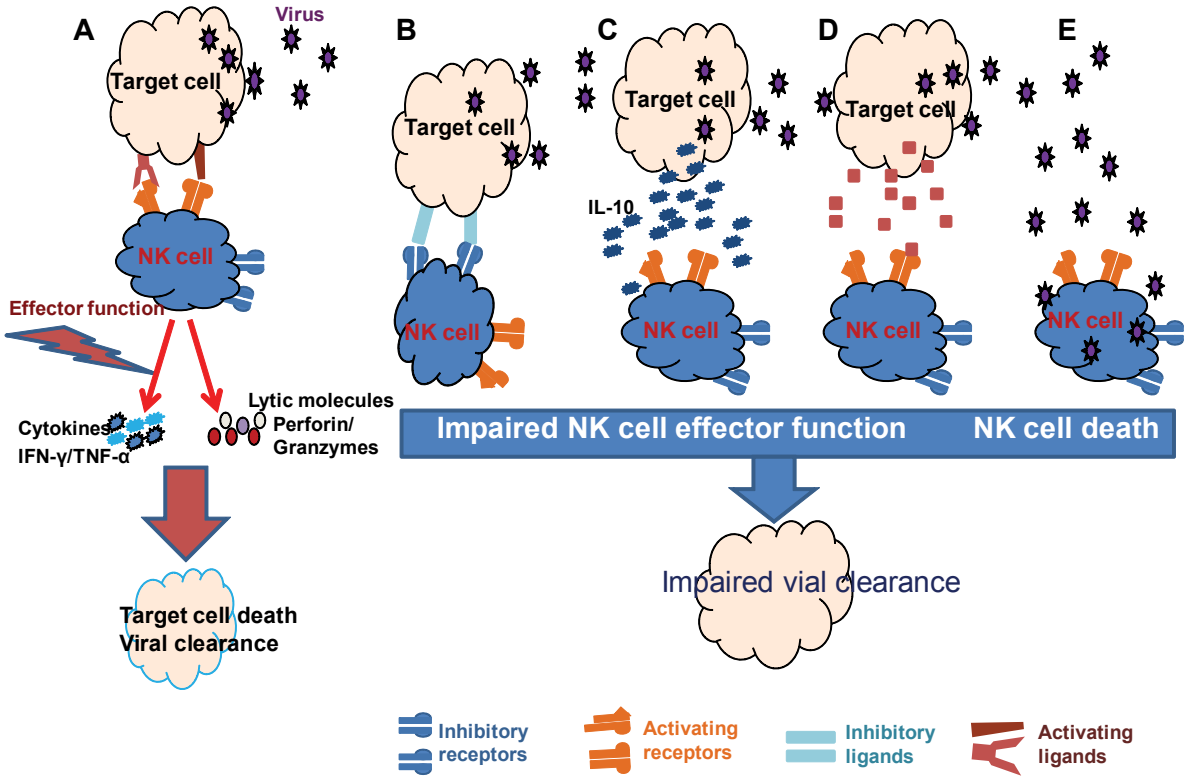

Figure 1: Strategies of viruses to evade NK cell-mediated immune surveillance. A) Upon recognition of virus-infected cells by activating NK cell receptors, NK cells secrete cytokines and kill infected cells to control viral infection. However, viruses have evolved strategies to evade NK cell immune surveillance, such as listed in B-E. **B)** Viruses encode their own MHC class I homolog to inhibit NK cell function through binding to NK cell inhibitory receptors. **C)** Viruses encode anti-inflammatory cytokine IL-10 mimicry to suppress NK cell function. **D)** Viruses encode soluble ligands binding to NK cell activating receptor NKG2D to block NK cell recognition of infected cells. **E)** Viruses directly infect NK cells resulting impaired NK cell function and NK cell apoptosis.

I homolog UL18 [139] and m144 [140], respectively, to inhibit NK cell activity through binding to NK inhibitory receptors. In support of this, NK cells are more effective at restricting replication of a recombinant MCMV with m144 deletion than of wild-type MCMV [140].

Viral Immunoevasion by Encoding Cytokine Mimicry

Cytokines are potent immune response regulators, which play an important role in the outcome during pathogen infection. Several viruses encode cytokine mimicry to escape host immune surveillance. For example, Epstein-Barr virus (EBV) gene BCRF1 encodes a protein homologous to the cellular cytokine IL-10 (vIL-10) with anti-inflammatory properties [141,142]; recent studies show that vIL-10 protects EVB-infected B cells from NK cell mediated elimination [143]. Besides EBV, primate cytomegaloviruses (CMVs), Orf poxvirus, and equine herpes virus type 2 (EHV-2) also encode homologues of human IL-10 [144-146].

Soluble Ligands Secreted by Virus Inhibit NK cell Activity

It is a universal strategy for viruses to escape NK cell recognition by encoding viral proteins to disturb NK cell receptor-ligand interaction. During some viral infections, viruses escape NK-mediated immunosurveillance by interfering NK cells activation and increased shedding of soluble ligands. NKG2D usually is a target of virus for escaping NK cell immune recognition [147]. NKG2D ligands may be either induced or down modulated upon infection by several pathogens [148]. The viral protein UL16 secreted from HCMV binds to ULBP-1, ULBP-2, and MICB, which are members of NKG2D-ligand family, and blocks the activation of NK cells [149,150]. Zoonotic orthopoxviruses encode a protein that is secreted by infected cells and competitively binds to NKG2D, thus blocking the recognition of infected cells by NK cells [151]. HIV-1 escapes NGG2D-mediated immunosurveillance by modulation NKG2D ligands (NKG2DLs) expression and increased shedding of soluble NKG2DLs [152].

Directly Infect NK cells

One of the viral immune-evasion tactics is to infect and kill immune cells, including NK cells. Influenza virus can directly infect NK cells, which results in the impairments of NK cell function and also induces marked apoptosis of NK cells [153,154]. A few viruses, for example, HIV, herpes simplex virus, and ECTV also possess the ability to directly infect NK cells [155-157].

Concluding Remarks

Significant advances have been recently made in understanding the functions of NK cells in innate defense against infective pathogens. NK cell responses have the potential to mediate defense through both direct antiviral and immunoregulatory pathways. NK cell responses are regulated by a balance of activating and inhibitory signals transmitted by cell surface receptors. Other factors such as type I interferon, cross-talk of NK cells with DC and macrophages, and genetic background might also influence NK cell responses during certain pathogen infections. In the battle between host and invading pathogens, virus has also developed several strategies for evading NK cell elimination. Thus, how to reverse the immune suppression of NK cells and boost NK cell activity are crucial for fully usage of NK cells for prevention and treatment of emerging and severe pathogen infections. To achieve this goal, a better molecular definition of the mechanisms by which NK cells participate in innate immunity against these pathogens is required.

References

1. Cerwenka A, Lanier LL (2001) Natural killer cells, viruses and cancer. Nat Rev Immunol 1: 41-49.
2. Vivier E, Tomasello E, Baratin M, Walzer T, Ugolini S (2008) Functions of natural killer cells. Nat Immunol 9: 503-510.
3. Andoniou CE, van Dommelen SL, Voigt V, Andrews DM, Brizard G, et al. (2005) Interaction between conventional dendritic cells and natural killer cells is integral to the activation of effective antiviral immunity. Nat Immunol 6: 1011-1019.
4. Lieke T, Graefe SE, Klauenberg U, Fleischer B, Jacobs T (2004) NK cells contribute to the control of Trypanosoma cruzi infection by killing free parasites by perforin-independent mechanisms. Infect Immun 72: 6817-6825.
5. Artavanis-Tsakonas K, Riley EM (2002) Innate immune response to malaria: rapid induction of IFN-gamma from human NK cells by live Plasmodium falciparum-infected erythrocytes. J Immunol 169: 2956-2963.
6. Junqueira-Kipnis AP, Kipnis A, Jamieson A, Juarrero MG, Diefenbach A, et al. (2003) NK cells respond to pulmonary infection with Mycobacterium tuberculosis, but play a minimal role in protection. J Immunol 171: 6039-6045.
7. Fang M, Lanier LL, Sigal LJ (2008) A role for NKG2D in NK cell-mediated resistance to poxvirus disease. PLoS Pathog 4: e30.
8. Fang M, Roscoe F, Sigal LJ (2010) Age-dependent susceptibility to a viral disease due to decreased natural killer cell numbers and trafficking. J Exp Med 207: 2369-2381.
9. Arase H, Mocarski ES, Campbell AE, Hill AB, Lanier LL (2002) Direct recognition of cytomegalovirus by activating and inhibitory NK cell receptors. Science 296: 1323-1326.
10. Smith HR, Heusel JW, Mehta IK, Kim S, Dorner BG, et al. (2002) Recognition of a virus-encoded ligand by a natural killer cell activation receptor. Proc Natl Acad Sci U S A 99: 8826-8831.
11. Tay CH, Welsh RM (1997) Distinct organ-dependent mechanisms for the control of murine cytomegalovirus infection by natural killer cells. J Virol 71: 267-275.
12. Di Santo JP (2008) Functionally distinct NK-cell subsets: developmental origins and biological implications. Eur J Immunol 38: 2948-2951.
13. Di Santo JP (2008) Natural killer cells: diversity in search of a niche. Nat Immunol 9: 473-475.
14. Dhiman R, Periasamy S, Barnes PF, Jaiswal AG, Paidipally P, et al. (2012) NK1.1+ cells and IL-22 regulate vaccine-induced protective immunity against challenge with Mycobacterium tuberculosis. J Immunol 189: 897-905.
15. Lanier LL (1998) NK cell receptors. Annu Rev Immunol 16: 359-393.
16. Daniels KA, Devora G, Lai WC, O'Donnell CL, Bennett M, et al. (2001) Murine cytomegalovirus is regulated by a discrete subset of natural killer cells reactive with monoclonal antibody to Ly49H. J Exp Med 194: 29-44.
17. Braud VM, Allan DS, O'Callaghan CA, Söderström K, D'Andrea A, et al. (1998) HLA-E binds to natural killer cell receptors CD94/NKG2A, B and C. Nature 391: 795-799.
18. Vance RE, Kraft JR, Altman JD, Jensen PE, Raulet DH (1998) Mouse CD94/NKG2A is a natural killer cell receptor for the nonclassical major histocompatibility complex (MHC) class I molecule Qa-1(b). J Exp Med 188: 1841-1848.
19. Moretta A, Bottino C, Vitale M, Pende D, Cantoni C, et al. (2001) Activating receptors and coreceptors involved in human natural killer cell-mediated cytolysis. Annu Rev Immunol 19: 197-223.
20. Fauriat C, Ivarsson MA, Ljunggren HG, Malmberg KJ, Michaëlsson J (2010) Education of human natural killer cells by activating killer cell immunoglobulin-like receptors. Blood 115: 1166-1174.
21. Trowsdale J, Barten R, Haude A, Stewart CA, Beck S, et al. (2001) The genomic context of natural killer receptor extended gene families. Immunol Rev 181: 20-38.
22. Lanier LL (2001) On guard--activating NK cell receptors. Nat Immunol 2: 23-27.
23. Diefenbach A, Tomasello E, Lucas M, Jamieson AM, Hsia JK, et al. (2002) Selective associations with signaling proteins determine stimulatory versus costimulatory activity of NKG2D. Nat Immunol 3: 1142-1149.

24. Gilfillan S, Ho EL, Cella M, Yokoyama WM, Colonna M (2002) NKG2D recruits two distinct adapters to trigger NK cell activation and costimulation. Nat Immunol 3: 1150-1155.

25. Yokoyama WM, Kim S (2006) Licensing of natural killer cells by self-major histocompatibility complex class I. Immunol Rev 214: 143-154.

26. Brodin P, Kärre K, Höglund P (2009) NK cell education: not an on-off switch but a tunable rheostat. Trends Immunol 30: 143-149.

27. Farag SS, Caligiuri MA (2006) Human natural killer cell development and biology. Blood Rev 20: 123-137.

28. Farag SS, Fehniger TA, Ruggeri L, Velardi A, Caligiuri MA (2002) Natural killer cell receptors: new biology and insights into the graft-versus-leukemia effect. Blood 100: 1935-1947.

29. Lanier LL (2005) NK cell recognition. Annu Rev Immunol 23: 225-274.

30. Fernandez NC, Lozier A, Flament C, Ricciardi-Castagnoli P, Bellet D, et al. (1999) Dendritic cells directly trigger NK cell functions: cross-talk relevant in innate anti-tumor immune responses in vivo. Nat Med 5: 405-411.

31. Walzer T, Dalod M, Robbins SH, Zitvogel L, Vivier E (2005) Natural-killer cells and dendritic cells: "l'union fait la force". Blood 106: 2252-2258.

32. Borg C, Jalil A, Laderach D, Maruyama K, Wakasugi H, et al. (2004) NK cell activation by dendritic cells (DCs) requires the formation of a synapse leading to IL-12 polarization in DCs. Blood 104: 3267-3275.

33. Gerosa F, Gobbi A, Zorzi P, Burg S, Briere F, et al. (2005) The reciprocal interaction of NK cells with plasmacytoid or myeloid dendritic cells profoundly affects innate resistance functions. J Immunol 174: 727-734.

34. Koka R, Burkett P, Chien M, Chai S, Boone DL, et al. (2004) Cutting edge: murine dendritic cells require IL-15R alpha to prime NK cells. J Immunol 173: 3594-3598.

35. Ferlazzo G, Pack M, Thomas D, Paludan C, Schmid D, et al. (2004) Distinct roles of IL-12 and IL-15 in human natural killer cell activation by dendritic cells from secondary lymphoid organs. Proc Natl Acad Sci U S A 101: 16606-16611.

36. Lucas M, Schachterle W, Oberle K, Aichele P, Diefenbach A (2007) Dendritic cells prime natural killer cells by trans-presenting interleukin 15. Immunity 26: 503-517.

37. McCartney S, Vermi W, Gilfillan S, Cella M, Murphy TL, et al. (2009) Distinct and complementary functions of MDA5 and TLR3 in poly(I:C)-mediated activation of mouse NK cells. J Exp Med 206: 2967-2976.

38. Ganal SC, Sanos SL, Kallfass C, Oberle K, Johner C, et al. (2012) Priming of natural killer cells by nonmucosal mononuclear phagocytes requires instructive signals from commensal microbiota. Immunity 37: 171-186.

39. Piccioli D, Sbrana S, Melandri E, Valiante NM (2002) Contact-dependent stimulation and inhibition of dendritic cells by natural killer cells. J Exp Med 195: 335-341.

40. Vitale M, Della Chiesa M, Carlomagno S, Pende D, Aricò M, et al. (2005) NK-dependent DC maturation is mediated by TNFalpha and IFNgamma released upon engagement of the NKp30 triggering receptor. Blood 106: 566-571.

41. Ferlazzo G, Tsang ML, Moretta L, Melioli G, Steinman RM, et al. (2002) Human dendritic cells activate resting natural killer (NK) cells and are recognized via the NKp30 receptor by activated NK cells. J Exp Med 195: 343-351.

42. Loh J, Chu DT, O'Guin AK, Yokoyama WM, Virgin HW 4th (2005) Natural killer cells utilize both perforin and gamma interferon to regulate murine cytomegalovirus infection in the spleen and liver. J Virol 79: 661-667.

43. Andrews DM, Farrell HE, Densley EH, Scalzo AA, Shellam GR, et al. (2001) NK1.1+ cells and murine cytomegalovirus infection: what happens in situ? J Immunol 166: 1796-1802.

44. Bukowski JF, Woda BA, Welsh RM (1984) Pathogenesis of murine cytomegalovirus infection in natural killer cell-depleted mice. J Virol 52: 119-128.

45. Dokun AO, Kim S, Smith HR, Kang HS, Chu DT, et al. (2001) Specific and nonspecific NK cell activation during virus infection. Nat Immunol 2: 951-956.

46. BubiÄ‡ I, Wagner M, KrmpotiÄ‡ A, Saulig T, Kim S, et al. (2004) Gain of virulence caused by loss of a gene in murine cytomegalovirus. J Virol 78: 7536-7544.

47. Fodil-Cornu N, Lee SH, Belanger S, Makrigiannis AP, Biron CA, et al. (2008) Ly49h-deficient C57BL/6 mice: a new mouse cytomegalovirus-susceptible model remains resistant to unrelated pathogens controlled by the NK gene complex. J Immunol 181: 6394-6405.

48. Lee SH, Zafer A, de Repentigny Y, Kothary R, Tremblay ML, et al. (2003) Transgenic expression of the activating natural killer receptor Ly49H confers resistance to cytomegalovirus in genetically susceptible mice. J Exp Med 197: 515-526.

49. Rodriguez M, Sabastian P, Clark P, Brown MG (2004) Cmv1-independent antiviral role of NK cells revealed in murine cytomegalovirus-infected New Zealand White mice. J Immunol 173: 6312-6318.

50. Kielczewska A, Pyzik M, Sun T, Krmpotic A, Lodoen MB, et al. (2009) Ly49P recognition of cytomegalovirus-infected cells expressing H2-Dk and CMV-encoded m04 correlates with the NK cell antiviral response. J Exp Med 206: 515-523.

51. Makrigiannis AP, Pau AT, Saleh A, Winkler-Pickett R, Ortaldo JR, et al. (2001) Class I MHC-binding characteristics of the 129/J Ly49 repertoire. J Immunol 166: 5034-5043.

52. Vidal SM, Lanier LL (2006) NK cell recognition of mouse cytomegalovirus-infected cells. Curr Top Microbiol Immunol 298: 183-206.

53. Cerwenka A, Bakker AB, McClanahan T, Wagner J, Wu J, et al. (2000) Retinoic acid early inducible genes define a ligand family for the activating NKG2D receptor in mice. Immunity 12: 721-727.

54. Malarkannan S, Shih PP, Eden PA, Horng T, Zuberi AR, et al. (1998) The molecular and functional characterization of a dominant minor H antigen, H60. J Immunol 161: 3501-3509.

55. Diefenbach A, Raulet DH (2003) Innate immune recognition by stimulatory immunoreceptors. Curr Opin Immunol 15: 37-44.

56. Diefenbach A, Hsia JK, Hsiung MY, Raulet DH (2003) A novel ligand for the NKG2D receptor activates NK cells and macrophages and induces tumor immunity. Eur J Immunol 33: 381-391.

57. Carayannopoulos LN, Naidenko OV, Fremont DH, Yokoyama WM (2002) Cutting edge: murine UL16-binding protein-like transcript 1: a newly described transcript encoding a high-affinity ligand for murine NKG2D. J Immunol 169: 4079-4083.

58. Krmpotic A, Hasan M, Loewendorf A, Saulig T, Halenius A, et al. (2005) NK cell activation through the NKG2D ligand MULT-1 is selectively prevented by the glycoprotein encoded by mouse cytomegalovirus gene m145. J Exp Med 201: 211-220.

59. Lodoen MB, Abenes G, Umamoto S, Houchins JP, Liu F, et al. (2004) The cytomegalovirus m155 gene product subverts natural killer cell antiviral protection by disruption of H60-NKG2D interactions. J Exp Med 200: 1075-1081.

60. KrmpotiÄ‡ A, Busch DH, BubiÄ‡ I, Gebhardt F, Hengel H, et al. (2002) MCMV glycoprotein gp40 confers virus resistance to CD8+ T cells and NK cells in vivo. Nat Immunol 3: 529-535.

61. Lodoen M, Ogasawara K, Hamerman JA, Arase H, Houchins JP, et al. (2003) NKG2D-mediated natural killer cell protection against cytomegalovirus is impaired by viral gp40 modulation of retinoic acid early inducible 1 gene molecules. J Exp Med 197: 1245-1253.

62. Cooper MA, Elliott JM, Keyel PA, Yang L, Carrero JA, et al. (2009) Cytokine-induced memory-like natural killer cells. Proc Natl Acad Sci U S A 106: 1915-1919.

63. O'Leary JG, Goodarzi M, Drayton DL, von Andrian UH (2006) T cell- and B cell-independent adaptive immunity mediated by natural killer cells. Nat Immunol 7: 507-516.

64. Paust S, Gill HS, Wang BZ, Flynn MP, Moseman EA, et al. (2010) Critical role for the chemokine receptor CXCR6 in NK cell-mediated antigen-specific memory of haptens and viruses. Nat Immunol 11: 1127-1135.

65. Gillard GO, Bivas-Benita M, Hovav AH, Grandpre LE, Panas MW, et al. (2011) Thy1+ NK [corrected] cells from vaccinia virus-primed mice confer protection against vaccinia virus challenge in the absence of adaptive lymphocytes. PLoS Pathog 7:e1002141.

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

67. Brownstein DG, Bhatt PN, Gras L, Jacoby RO (1991) Chromosomal locations

and gonadal dependence of genes that mediate resistance to ectromelia (mousepox) virus-induced mortality. J Virol 65: 1946-1951.

68. Delano ML, Brownstein DG (1995) 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 69: 5875-5877.

69. Fang M, Orr MT, Spee P, Egebjerg T, Lanier LL, et al. (2011) CD94 is essential for NK cell-mediated resistance to a lethal viral disease. Immunity 34: 579-589.

70. Vance RE, Jamieson AM, Raulet DH (1999) Recognition of the class Ib molecule Qa-1(b) by putative activating receptors CD94/NKG2C and CD94/NKG2E on mouse natural killer cells. J Exp Med 190: 1801-1812.

71. Ma Y, Fang M (2013) Immunosenescence and age-related viral diseases. Sci China Life Sci 56: 399-405.

72. Nogusa S, Ritz BW, Kassim SH, Jennings SR, Gardner EM (2008) Characterization of age-related changes in natural killer cells during primary influenza infection in mice. Mech Ageing Dev 129: 223-230.

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

74. Guo H, Topham DJ (2010) Interleukin-22 (IL-22) production by pulmonary Natural Killer cells and the potential role of IL-22 during primary influenza virus infection. J Virol 84: 7750-7759.

75. Gazit R, Gruda R, Elboim M, Arnon TI, Katz G, et al. (2006) Lethal influenza infection in the absence of the natural killer cell receptor gene Ncr1. Nat Immunol 7: 517-523.

76. Mandelboim O, Lieberman N, Lev M, Paul L, Arnon TI, et al. (2001) Recognition of haemagglutinins on virus-infected cells by NKp46 activates lysis by human NK cells. Nature 409: 1055-1060.

77. Abdul-Careem MF, Mian MF, Yue G, Gillgrass A, Chenoweth MJ, et al. (2012) Critical role of natural killer cells in lung immunopathology during influenza infection in mice. J Infect Dis 206: 167-177.

78. Kennedy MK, Glaccum M, Brown SN, Butz EA, Viney JL, et al. (2000) Reversible defects in natural killer and memory CD8 T cell lineages in interleukin 15-deficient mice. J Exp Med 191: 771-780.

79. Scanlon ST, Thomas SY, Ferreira CM, Bai L, Krausz T, et al. (2011) Airborne lipid antigens mobilize resident intravascular NKT cells to induce allergic airway inflammation. J Exp Med 208: 2113-2124.

80. Yu S, Zhao J, Cantorna MT (2011) Invariant NKT cell defects in vitamin D receptor knockout mice prevents experimental lung inflammation. J Immunol 187: 4907-4912.

81. Kok WL, Denney L, Benam K, Cole S, Clelland C, et al. (2012) Pivotal Advance: Invariant NKT cells reduce accumulation of inflammatory monocytes in the lungs and decrease immune-pathology during severe influenza A virus infection. J Leukoc Biol 91: 357-368.

82. Nagler A, Lanier LL, Cwirla S, Phillips JH (1989) Comparative studies of human FcRIII-positive and negative natural killer cells. J Immunol 143: 3183-3191.

83. Caligiuri MA, Zmuidzinas A, Manley TJ, Levine H, Smith KA, et al. (1990) Functional consequences of interleukin 2 receptor expression on resting human lymphocytes. Identification of a novel natural killer cell subset with high affinity receptors. J Exp Med 171: 1509-1526.

84. Cooper MA, Fehniger TA, Caligiuri MA (2001) The biology of human natural killer-cell subsets. Trends Immunol 22: 633-640.

85. Cooper MA, Fehniger TA, Turner SC, Chen KS, Ghaheri BA, et al. (2001) Human natural killer cells: a unique innate immunoregulatory role for the CD56bright subset. Blood 97: 3146-3151.

86. Mavilio D, Lombardo G, Benjamin J, Kim D, Follman D, et al. (2005) Characterization of CD56–/CD16+ natural killer (NK) cells: A highly dysfunctional NK subset expanded in HIV-infected viremic individuals. Proc Natl Acad Sci U S A 102: 2886-2891.

87. Eller MA, Eller LA, Ouma BJ, Thelian D, Gonzalez VD, et al. (2009) Elevated natural killer cell activity despite altered functional and phenotypic profile in Ugandans with HIV-1 clade A or clade D infection. J Acquir Immune Defic Syndr 51: 380-389.

88. Gonzalez VD, Falconer K, Michaëlsson J, Moll M, Reichard O, et al. (2008) Expansion of CD56- NK cells in chronic HCV/HIV-1 co-infection: reversion by antiviral treatment with pegylated IFNalpha and ribavirin. Clin Immunol 128: 46-56.

89. Alter G, Teigen N, Davis BT, Addo MM, Suscovich TJ, et al. (2005) Sequential deregulation of NK cell subset distribution and function starting in acute HIV-1 infection. Blood 106: 3366-3369.

90. Corado J, Toro F, Rivera H, Bianco NE, Deibis L, et al. (1997) Impairment of natural killer (NK) cytotoxic activity in hepatitis C virus (HCV) infection. Clin Exp Immunol 109: 451-457.

91. Norris S, Collins C, Doherty DG, Smith F, McEntee G, et al. (1998) Resident human hepatic lymphocytes are phenotypically different from circulating lymphocytes. J Hepatol 28: 84-90.

92. Bonorino P, Ramzan M, Camous X, Dufeu-Duchesne T, Thélu MA, et al. (2009) Fine characterization of intrahepatic NK cells expressing natural killer receptors in chronic hepatitis B and C. J Hepatol 51: 458-467.

93. Oliviero B, Varchetta S, Paudice E, Michelone G, Zaramella M, et al. (2009) Natural killer cell functional dichotomy in chronic hepatitis B and chronic hepatitis C virus infections. Gastroenterology 137: 1151-1160.

94. Amadei B, Urbani S, Cazaly A, Fisicaro P, Zerbini A, et al. (2010) Activation of natural killer cells during acute infection with hepatitis C virus. Gastroenterology 138: 1536-1545.

95. Gonzalez VD, Falconer K, Björkström NK, Blom KG, Weiland O, et al. (2009) Expansion of functionally skewed CD56-negative NK cells in chronic hepatitis C virus infection: correlation with outcome of pegylated IFN-alpha and ribavirin treatment. J Immunol 183: 6612-6618.

96. Jinushi M, Takehara T, Tatsumi T, Kanto T, Miyagi T, et al. (2004) Negative regulation of NK cell activities by inhibitory receptor CD94/NKG2A leads to altered NK cell-induced modulation of dendritic cell functions in chronic hepatitis C virus infection. J Immunol 173: 6072-6081.

97. Khakoo SI, Thio CL, Martin MP, Brooks CR, Gao X, et al. (2004) HLA and NK cell inhibitory receptor genes in resolving hepatitis C virus infection. Science 305:872-874.

98. Alter G, Jost S, Rihn S, Reyor LL, Nolan BE, et al. (2011) Reduced frequencies of NKp30+NKp46+, CD161+, and NKG2D+ NK cells in acute HCV infection may predict viral clearance. J Hepatol 55: 278-288.

99. Oliviero B, Mele D, Degasperi E, Aghemo A, Cremonesi E, et al. (2013) Natural killer cell dynamic profile is associated with treatment outcome in patients with chronic HCV infection. J Hepatol 59: 38-44.

100. Chung A, Rollman E, Johansson S, Kent SJ, Stratov I (2008) The utility of ADCC responses in HIV infection. Curr HIV Res 6: 515-519.

101. Zhang R, Xu J, Hong K, Yuan L, Peng H, et al. (2007) Increased NKG2A found in cytotoxic natural killer subset in HIV-1 patients with advanced clinical status. Aids 21: S9.

102. Flores-Villanueva PO, Yunis EJ, Delgado JC, Vittinghoff E, Buchbinder S, et al. (2001) Control of HIV-1 viremia and protection from AIDS are associated with HLA-Bw4 homozygosity. Proc Natl Acad Sci U S A 98: 5140-5145.

103. Martin MP, Gao X, Lee JH, Nelson GW, Detels R, et al. (2002) Epistatic interaction between KIR3DS1 and HLA-B delays the progression to AIDS. Nat Genet 31: 429-434.

104. Qi Y, Martin MP, Gao X, Jacobson L, Goedert JJ, et al. (2006) KIR/HLA pleiotropism: protection against both HIV and opportunistic infections. PLoS Pathog 2: e79.

105. Pelak K, Need AC, Fellay J, Shianna KV, Feng S, et al. (2011) Copy number variation of KIR genes influences HIV-1 control. PLoS Biol 9: e1001208.

106. Apps R, Qi Y, Carlson JM, Chen H, Gao X, et al. (2013) Influence of HLA-C expression level on HIV control. Science 340: 87-91.

107. Wolfe SA, Tracey DE, Henney CS (1976) Introduction of “natural” killer’ cells by BCG. Nature 262: 584-586.

108. Guo Y, Niesel DW, Ziegler HK, Klimpel GR (1992) Listeria monocytogenes activation of human peripheral blood lymphocytes: induction of non-major histocompatibility complex-restricted cytotoxic activity and cytokine production. Infect Immun 60: 1813-1819.

109. Wold WS, Gooding LR (1991) Region E3 of adenovirus: a cassette of genes involved in host immunosurveillance and virus-cell interactions. Virology 184: 1-8.

110. Feng CG, Kaviratne M, Rothfuchs AG, Cheever A, Hieny S, et al. (2006) NK cell-derived IFN-gamma differentially regulates innate resistance and neutrophil response in T cell-deficient hosts infected with Mycobacterium tuberculosis. J Immunol 177: 7086-7093.

111. Vankayalapati R, Wizel B, Weis SE, Safi H, Lakey DL, et al. (2002) The NKp46 receptor contributes to NK cell lysis of mononuclear phagocytes infected with an intracellular bacterium. J Immunol 168: 3451-3457.

112. Vankayalapati R, Garg A, Porgador A, Griffith DE, Klucar P, et al. (2005) Role of NK cell-activating receptors and their ligands in the lysis of mononuclear phagocytes infected with an intracellular bacterium. J Immunol 175: 4611-4617.

113. Dhiman R, Indramohan M, Barnes PF, Nayak RC, Paidipally P, et al. (2009) IL-22 produced by human NK cells inhibits growth of Mycobacterium tuberculosis by enhancing phagolysosomal fusion. J Immunol 183: 6639-6645.

114. Roy S, Barnes PF, Garg A, Wu S, Cosman D, et al. (2008) NK cells lyse T regulatory cells that expand in response to an intracellular pathogen. J Immunol 180: 1729-1736.

115. Pamer EG (2004) Immune responses to Listeria monocytogenes. Nat Rev Immunol 4: 812-823.

116. Naper C, Shegarfi H, Inngjerdingen M, Rolstad B (2011) The role of natural killer cells in the defense against Listeria monocytogenes lessons from a rat model. J Innate Immun 3: 289-297.

117. Serbina NV, Salazar-Mather TP, Biron CA, Kuziel WA, Pamer EG (2003) TNF/iNOS-producing dendritic cells mediate innate immune defense against bacterial infection. Immunity 19: 59-70.

118. Kurihara T, Warr G, Loy J, Bravo R (1997) Defects in macrophage recruitment and host defense in mice lacking the CCR2 chemokine receptor. J Exp Med 186: 1757-1762.

119. Kang SJ, Liang HE, Reizis B, Locksley RM (2008) Regulation of hierarchical clustering and activation of innate immune cells by dendritic cells. Immunity 29: 819-833.

120. Teixeira HC, Kaufmann SH (1994) Role of NK1.1+ cells in experimental listeriosis. NK1+ cells are early IFN-gamma producers but impair resistance to Listeria monocytogenes infection. J Immunol 152: 1873-1882.

121. Berg RE, Crossley E, Murray S, Forman J (2005) Relative contributions of NK and CD8 T cells to IFN-gamma mediated innate immune protection against Listeria monocytogenes. J Immunol 175: 1751-1757.

122. Auerbuch V, Brockstedt DG, Meyer-Morse N, O'Riordan M, Portnoy DA (2004) Mice lacking the type I interferon receptor are resistant to Listeria monocytogenes. J Exp Med 200: 527-533.

123. O'Connell RM, Saha SK, Vaidya SA, Bruhn KW, Miranda GA, et al. (2004) Type I interferon production enhances susceptibility to Listeria monocytogenes infection. J Exp Med 200: 437-445.

124. Carrero JA, Calderon B, Unanue ER (2004) Type I interferon sensitizes lymphocytes to apoptosis and reduces resistance to Listeria infection. J Exp Med 200: 535-540.

125. Le-Barillec K, Magalhaes JG, Corcuff E, Thuizat A, Sansonetti PJ, et al. (2005) Roles for T and NK cells in the innate immune response to Shigella flexneri. J Immunol 175: 1735-1740.

126. Small CL, McCormick S, Gill N, Kugathasan K, Santosuosso M, et al. (2008) NK cells play a critical protective role in host defense against acute extracellular Staphylococcus aureus bacterial infection in the lung. J Immunol 180: 5558-5568.

127. Korbel DS, Newman KC, Almeida CR, Davis DM, Riley EM (2005) Heterogeneous human NK cell responses to Plasmodium falciparum-infected erythrocytes. J Immunol 175: 7466-7473.

128. Mavoungou E, Luty AJ, Kremsner PG (2003) Natural killer (NK) cell-mediated cytolysis of Plasmodium falciparum-infected human red blood cells in vitro. Eur Cytokine Netw 14: 134-142.

129. Orago AS, Facer CA (1991) Cytotoxicity of human natural killer (NK) cell subsets for Plasmodium falciparum erythrocytic schizonts: stimulation by cytokines and inhibition by neomycin. Clin Exp Immunol 86: 22-29.

130. Mavoungou E, Held J, Mewono L, Kremsner PG (2007) A Duffy binding-like domain is involved in the NKp30-mediated recognition of Plasmodium falciparum-parasitized erythrocytes by natural killer cells. J Infect Dis 195: 1521-1531.

131. Böttger E, Multhoff G, Kun JF, Esen M (2012) Plasmodium falciparum-infected erythrocytes induce granzyme B by NK cells through expression of host-Hsp70. PLoS One 7: e33774.

132. Marsh K, Forster D, Waruiru C, Mwangi I, Winstanley M, et al. (1995) Indicators of life-threatening malaria in African children. N Engl J Med 332: 1399-1404.

133. Yañez DM, Manning DD, Cooley AJ, Weidanz WP, van der Heyde HC (1996) Participation of lymphocyte subpopulations in the pathogenesis of experimental murine cerebral malaria. J Immunol 157: 1620-1624.

134. Amani V, Vigário AM, Belnoue E, Marussig M, Fonseca L, et al. (2000) Involvement of IFN-gamma receptor-medicated signaling in pathology and anti-malarial immunity induced by Plasmodium berghei infection. Eur J Immunol 30: 1646-1655.

135. Koch O, Awomoyi A, Usen S, Jallow M, Richardson A, et al. (2002) IFNGR1 gene promoter polymorphisms and susceptibility to cerebral malaria. J Infect Dis 185: 1684-1687.

136. Hansen DS, Bernard NJ, Nie CQ, Schofield L (2007) NK cells stimulate recruitment of CXCR3+ T cells to the brain during Plasmodium berghei-mediated cerebral malaria. J Immunol 178: 5779-5788.

137. Taniguchi M, Kawabata M (2009) KIR3DL1/S1 genotypes and KIR2DS4 allelic variants in the AB KIR genotypes are associated with Plasmodium-positive individuals in malaria infection. Immunogenetics 61: 717-730.

138. Hirayasu K, Ohashi J, Kashiwase K, Hananantachai H, Naka I, et al. (2012) Significant association of KIR2DL3-HLA-C1 combination with cerebral malaria and implications for co-evolution of KIR and HLA. PLoS Pathog 8: e1002565.

139. Reyburn HT, Mandelboim O, Valés-Gómez M, Davis DM, Pazmany L, et al. (1997) The class I MHC homologue of human cytomegalovirus inhibits attack by natural killer cells. Nature 386: 514-517.

140. Farrell HE, Vally H, Lynch DM, Fleming P, Shellam GR, et al. (1997) Inhibition of natural killer cells by a cytomegalovirus MHC class I homologue in vivo. Nature 386: 510-514.

141. Moore KW, Vieira P, Fiorentino DF, Trounstine ML, Khan TA, et al. (1990) Homology of cytokine synthesis inhibitory factor (IL-10) to the Epstein-Barr virus gene BCRFI. Science 248: 1230-1234.

142. Salek-Ardakani S, Arrand JR, Mackett M (2002) Epstein-Barr virus encoded interleukin-10 inhibits HLA-class I, ICAM-1, and B7 expression on human monocytes: implications for immune evasion by EBV. Virology 304: 342-351.

143. Jochum S, Moosmann A, Lang S, Hammerschmidt W, Zeidler R (2012) The EBV immunoevasins vIL-10 and BNLF2a protect newly infected B cells from immune recognition and elimination. PLoS Pathog 8: e1002704.

144. Rode HJ, Bugert JJ, Handermann M, Schnitzler P, Kehm R, et al. (1994) Molecular characterization and determination of the coding capacity of the genome of equine herpesvirus type 2 between the genome coordinates 0.235 and 0.258 (the EcoRI DNA fragment N; 4.2 kbp). Virus Genes 9: 61-75.

145. Haig DM, Fleming S (1999) Immunomodulation by virulence proteins of the parapoxvirus orf virus. Vet Immunol Immunopathol 72: 81-86.

146. Kotenko SV, Saccani S, Izotova LS, Mirochnitchenko OV, Pestka S (2000) Human cytomegalovirus harbors its own unique IL-10 homolog (cmvIL-10). Proc Natl Acad Sci U S A 97: 1695-1700.

147. Raulet DH (2003) Roles of the NKG2D immunoreceptor and its ligands. Nat Rev Immunol 3: 781-790.

148. Cerwenka A, Lanier LL (2003) NKG2D ligands: unconventional MHC class I-like molecules exploited by viruses and cancer. Tissue Antigens 61: 335-343.

149. Kubin M, Cassiano L, Chalupny J, Chin W, Cosman D, et al. (2001) ULBP1, 2, 3: novel MHC class I-related molecules that bind to human cytomegalovirus glycoprotein UL16, activate NK cells. Eur J Immunol 31: 1428-1437.

150. Cosman D, Müllberg J, Sutherland CL, Chin W, Armitage R, et al. (2001) ULBPs, novel MHC class I-related molecules, bind to CMV glycoprotein UL16 and stimulate NK cytotoxicity through the NKG2D receptor. Immunity 14: 123-133.

151. Campbell JA, Trossman DS, Yokoyama WM, Carayannopoulos LN (2007) Zoonotic orthopoxviruses encode a high-affinity antagonist of NKG2D. J Exp Med 204: 1311-1317.

152. Matusali G, Tchidjou HK, Pontrelli G, Bernardi S, D'Ettorre G, et al. (2013) Soluble ligands for the NKG2D receptor are released during HIV-1 infection and impair NKG2D expression and cytotoxicity of NK cells. FASEB J 27: 2440-2450.

153. Guo H, Kumar P, Moran TM, Garcia-Sastre A, Zhou Y, et al. (2009) The functional impairment of natural killer cells during influenza virus infection. Immunol Cell Biol 87: 579-589.

154. Mao H, Tu W, Liu Y, Qin G, Zheng J, et al. (2009) Influenza virus directly infects human natural killer cells and induces cell apoptosis. J Virol 83: 9215-9222.

155. Chehimi J, Bandyopadhyay S, Prakash K, Perussia B, Hassan NF, et al. (1991) In vitro infection of natural killer cells with different human immunodeficiency virus type 1 isolates. J Virol 65: 1812-1822.

156. Lusso P, Malnati MS, Garzino-Demo A, Crowley RW, Long EO, et al. (1993) Infection of natural killer cells by human herpesvirus 6. Nature 362: 458-462.

157. Parker AK, Yokoyama WM, Corbett JA, Chen N, Buller RM (2008) Primary naive and interleukin-2-activated natural killer cells do not support efficient ectromelia virus replication. J Gen Virol 89: 751-759.

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