Natural Killer Cells and Innate Immunity in HIV-2 Infection

Definition

This entry describes what is known about the function and activity of the innate immune cell populations natural killer (NK) cells and natural killer T cells (NKT) in HIV-2 infection.

Introduction

In contrast to the extensive efforts made to learn more about HIV-1 in the fields of epidemiology, geographical distribution, and viral pathogenesis, very little work has been carried out to understand the interactions between the HIV-2 and the host immune system. Although both cellular and humoral immune responses to HIV-1 have been shown to play a part during acute infection, these activities are impaired during chronic infection, leading to disease progression and eventually death (Zhang et al. 2003).

Studies of HIV-2-infected individuals have shown that the majority experiences a slower and more prolonged disease course than seen in HIV-1 infection: therefore, a better understanding of the interactions between HIV-2 and the host immune response may be useful in providing insights for therapeutic and vaccine strategies. One way viruses are attacked early in infection is through the action of natural killer (NK) cells, which are one of the key components of the innate immune response to infections (Biron and Brossay 2001). These cells are naturally activated in response to infection without the requirement for prior sensitization and may play an important role in the outcome of viral infections. NK cells provide the first line of defense in the early stage of many infections, including HIV, and continue to render a critical service in nonspecific host defense mechanisms. However, little is known about NK cell function in HIV-2 infection.

Natural Killer Cells

Natural killer (NK) cells are large granular lymphocytes forming about 15 % of the total lymphocyte population. There are two main subpopulations of NK cells. These are $CD56^{bright}$, which produce cytokines and form about 10 % of the NK cell population (Cooper et al. 2001), and $CD56^{dim}$, which exhibit cytotoxicity and form about 90 % of the NK cell population. They respond to bacterial, parasite, and viral infection, as well as to tumor cells, without the need for prior antigen sensitization. Early studies showed evidence that the nonadaptive immune response mediated by NK cells played a role in bacterial, parasite, tumor, and viral immunity (Fehniger et al. 1998). NK cells exert their activities by the use of both inhibiting and activating receptors expressed on their surface. In addition to direct stimulation through activating receptors, NK cells are indirectly activated during the initial stages of viral infection by cytokines secreted by various cells of the immune system (Biron and Brossay 2001). Infection stimulates the direct production of innate cytokines such as interferon (IFN)-α, IFN-β, interleukin-2, interleukin-12, and interleukin-15. In response to these cytokines, NK cells release cytolytic granules that directly lyse infected cells. They also rapidly produce IFN-γ, tumor necrosis factor alpha (TNF-α), granulocyte-monocyte colony-stimulating factor (GM-CSF), and chemokines such as macrophage inflammatory protein-1α (MIP-1α), MIP-1β, and RANTES to prevent further infection of new cells and also suppress viral replication in already infected cells (Scott-Algara and Paul 2002). As a result, the cytokines and chemokines produced during viral infection in vivo may serve not only to induce an antiviral state in nearby cells but also to enhance NK cell activity within circulating leukocytes. In addition, the activated NK cells play a role in modulating hematopoietic cell growth, reviewed in Cooper et al. (2001), and their functions further enhance the adaptive immune response.

Natural Killer Cell Development

Natural killer cells develop within the microenvironment of the bone marrow (BM) with CD34+ hematopoietic stem cells expressing growth factors (c-KIT and FLT3l), cytokine receptors (IL2Rβ and IL-15Rα), as well as other lymphoid development transcriptional factors (Yu et al. 1998).

Numerous studies have identified IL-15 as the most important soluble factor for the development of human and murine NK cells (Cooper et al. 2001). Interleukin-15 induces differentiation of human hematopoietic progenitor cells (HPCs) into NK cells in the absence of other cytokines in vitro. Interleukin-2 was also identified to play a role with IL-15 in inducing the

differentiation of bipotential cells into NK cells, whereas IL-7 and stem cell factor (SCF) support further maturation and differentiation of NK cells. The recently described cytokine, IL-21, in combination with IL-15, was also reported to induce the development of CD56+16+ NK cells from BM HPCs (Parrish-Novak et al. 2000). The induction of IL-15 results in the development of NK cells that are $CD56^{bright}$ cells (Cooper et al. 2001). These produce immunoregulatory cytokines or chemokines upon stimulation. The development of $CD56^{dim}$ cells might have a distinct precursor that has not yet been identified.

Location and Subsets of Natural Killer Cells

As well as forming about 15 % of circulating lymphocytes, NK cells have a similar frequency in the spleen. Natural killer cells have also been identified in the lungs, gastrointestinal tract, and liver, together with populations of NKT cells at these sites (Norris et al. 1999). They are however not commonly found in unstimulated lymph nodes and do not circulate through the lymphatic system.

The cell surface density of the CD56 receptor allows classification of NK cells into two functionally distinct NK cell subsets. About 10 % of NK cells are $CD56^{bright}$ CD16+ (Cooper et al. 2001) and the majority (90 %) are $CD56^{dim}$CD16+, exhibiting high cytotoxic activity.

The $CD56^{bright}$ NK cells secrete high levels of cytokines that are useful in preventing viral infection after stimulation with monokines (Cooper et al. 2001). They show low-density expression of CD16 and are of low natural cytotoxicity as well as low antibody-dependent cellular cytotoxicity (ADCC) (Cooper et al. 2001). They also exhibit potent lymphokine-activated killer (LAK) activity. The expression of inhibitory receptors also varies in this subset of NK cells. The inhibitory CD94/NKG2A C-type lectin NK receptors (NKR) are highly expressed but they have low expression of killer immunoglobulin-like receptors (KIR). The cytokine and chemokine receptors expressed include high-affinity interleukin-2 receptors (IL-2Rαβγ), c-kit, and CC-chemokine receptor 7(CCR7) (Andre et al. 2000). The adhesion molecule L-selectin, in combination with CCR7, is involved in trafficking to secondary lymph nodes and is predominantly found on $CD56^{bright}$ NK cells.

In contrast $CD56^{dim}$ NK cells have a more granular morphological structure than $CD56^{bright}$ NK cells and produce lower levels of NK-derived cytokines (Cooper et al. 2001). They are potent mediators of ADCC, LAK activity, and natural cytotoxicity. The $CD56^{dim}$ NK cell subsets have low levels of expression of cytokine receptors (e.g., IL-2Rβγ) and chemokine receptors (e.g., CXCR1 and CX3CR1) (Campbell et al. 2001). They however lack L-selectin but highly express PEN5-P-selectin glycoprotein ligand-1 (PSGK-1) adhesion molecules.

Natural Cytotoxicity Receptors

There are other distinct receptors that have been identified on the surface of NK cells. They allow NK cells to recognize their target cells in a manner that is quite different from that of T cells and B cells, which depend on the presence of foreign antigen. These include the natural cytotoxicity receptors (NCRs): NKp30, NKp44, and NKp46. NKp 30 and NKp46 are uniquely expressed on resting NK cells, and their blockage impairs lysis of target cells by NK cells (De Maria et al. 2001). Their ligands, however, have not yet been identified, although it has recently been suggested NKp30 and NKp46 interact with dendritic cells and hemagglutinin, respectively (Ferlazzo et al. 2002). NKp44 is expressed when NK cells are activated and facilitates killing of targets cells during NK cell activation.

Other receptors called killer cell immunoglobulin-like short-tail (KIR-S) activating receptors in humans also contribute to the cytolytic activity of NK cells. Most activating NK cell receptors are transmembrane molecules with short cytoplasmic domains that lack intrinsic signaling features. They are associated with adaptor signaling proteins through charged amino acid residues of their transmembrane domains. The activating receptors KIR2DS, Ly49D/H, NKp44, and CD94/NKG2C associate with KARAP/DAP12 signal-transducing adaptor proteins (LaBonte et al. 2006), whereas CD16, NKp30, and NKp46 couple to the FcεR1γ and CD3ζ transmembrane adaptor proteins. The activating receptors recognize both MHC Class I and non-MHC Class I ligands. There are also a number of other coreceptors, which are implicated in the activation of NK cells. These include 2B4 (CD244) NKp80 and NTB-A (Biassoni et al. 2001) and CD48, CD58, and CD84 and SLAM/CD150 belonging to the CD2 subfamily of Ig-SF. They work in combination with NCRs in mediating NK cytotoxicity.

Natural Killer Inhibitory Receptors

Natural killer cells use a set of activating and inhibitory receptors to identify cells that lack MHC Class I expression. The balance between the engagements of these receptors by the target cells may result in cytolysis. Thus, NK cells do not lyse healthy MHC Class I positive cells because the presence of MHC Class I molecules usually engages inhibitory receptors on NK cells. The upregulation or downregulation of MHC Class I molecules, as may occur in tumors or infected cells, plays a major role in the ability of NK cells to lyse infected or target cells or become inhibited from cytolysis, depending on which type of these molecules is engaged by NK cells.

There are three different groups of inhibitory receptors identified for classical MHC Class I molecules on target cells. The first family of the inhibitory receptors is the killer cell immunoglobulin-like receptors (KIRs) with different numbers of immunoglobulin-like domains (Borrego et al. 2002). They include CD158a (KIR2DLI), CD158b (KIR2DL2), CD158e (KIR3DL1), and CD158k, which recognize different alleles of HLA-A, HLA-B, and HLA-C molecules. The second is the leucocytes Ig-like receptor (ILT2/LIR1/CD85j) family found in human cells. The third family of inhibitory receptors is the lectin-like heterodimers, represented by CD94/NKG2, which are found in both rodents and human.

Natural Killer Cell Activity in Viral Infection

Natural killer cells are important in controlling intracellular pathogens. In viral infection, NK cells provide an important early defense against pathogens, while T cells, which are responsible for adaptive immunity, are undergoing a process of activation. The importance of NK cell functions in the defense against pathogens was appreciated from observations such as in an adolescent case of a selective NK cell defect which led to recurrent herpes virus infection in the patient (Biron and Brossay 2001). Loss of NK cell function also resulted in severe infection by cytomegalovirus (MCMV) in mice (Biron and Brossay 2001). Thus, NK cells play a major role in controlling microbial infections at a very early stage in infection before the adaptive immune response mediated by T lymphocytes sets in.

One way in which NK cells control infection is by direct lysis of infected cells. This involves the release of cytolytic granules, perforin, and granzyme A in close contact with the infected cells. However, it has been shown in CMV infection that NK cells could function even in the absence of perforin to mediate cytotoxicity (Seaman 2000), acting through the secretion of soluble factors which enhance the immune response of the host. These factors include cytokines such as IFN-γ, TNF-α, IL-10, IL-13, and GM-CSF. The production of such effector cytokines by NK cells is initially induced by early innate cytokine secretion in response to infection, such as IL-12, IL-15, and IL-21 (Cooper et al. 2001), and plays a major role in the early development of antiviral immune responses by recruiting other cells of the immune system to the sites of infection. These early innate-induced cytokines not only activate NK cells but also stimulate their development and differentiation.

Natural killer cells also produce substantial amounts of IFN-γ in response to pathogenic/viral infections (He et al. 2004). This cytokine promotes a Th1 response, which in turn promotes adaptive cellular immunity as well as the effective production of antibodies that fix complement, all of which are important in host defense against intracellular infections. Moreover, NK cells are also known to support the production of cytokines that promote Th2 responses, which include the production of IgE and IgG4 and the activation of eosinophils. The capacity of NK cells to secrete IL-5 has been shown to be important in the eosinophilic response to allergen in the peritoneal cavity. Allergen-induced eosinophilic airways inflammation in the mice is also under the influence of IL-5 produced by NK cells (Kiessling et al. 1977). Thus the promotion of Th2 responses by NK cells contributes to host defense against extracellular parasites. NK cells also attack viral-infected cells by the use of fas ligands and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) receptors as well as soluble TRAIL (Hayakawa et al. 2004).

The extent of NK cell activation is known to vary in different infections. Infection of mice with murine CMV promotes the production of IL-12, IFN-αβ, and IL-18 by dendritic cells (DC) that enhances IFN-γ secretion by NK cells to defend the host (Andrews et al. 2003), with IFN-αβ mainly required for cytotoxicity. In contrast, infection with lymphocytic choriomeningitis virus (LCMV) activates NK cells through the release of IFN-αβ mainly from DC and other monocytes which promote natural cytotoxicity. Infection with this virus actually suppresses the production of IL-12 by DC and subsequently the secretion of IFN-γ by NK cells respectively (Biron and Brossay 2001), making the role of adaptive cytokine production less important in the control of LCMV.

Type 1 interferons are the primary cytokines that provide the first line of immune defense against viral infections and are known to enhance the activity of NK cells during infection. They are encoded by 13 α-genes that are responsible for the secretion of 12 IFN-α subtypes and one β-gene for the IFN-β cytokine (Smith et al. 2005). Infection of mice with murine cytomegalovirus (MCMV) induces innate cytokine IFN-αβ secretion within 2 days of infection that stimulates NK cell function by promoting cytolytic activity as well as IFN-γ secretion. IFN-γ secretion in turn enhances T-cell polarization in

the lymph node leading to an expansion of $CD4^+$ T cells during infection. This demonstrates the cascade effect of the innate immune response in the early control of viral infection.

NK Cell Function in HIV-1 Infection

HIV-1 infection is associated with significant changes in the distribution of NK subsets in the circulation, together with the appearance of a dysfunctional subset of NK cells that are CD3-CD56-CD16+ and are rarely found in healthy individuals (Alter and Altfeld 2009). It is thought that accumulation of this aberrant subset accounts for the decline in NK function observed with HIV-1 disease progression. Generally, HIV-1-infected individuals with long-term nonprogression exhibit normal values of NK cells as well as normal NK functional activity (Scott-Algara and Paul 2002). A restoration of NK cell numbers has also been noted in individuals on highly active antiretroviral therapy (HAART) (Parato et al. 2002), which may support the hypothesis that continued HIV-1 replication plays a role in impaired NK cell function with disease progression. It has been suggested that infection of NK cells by the virus may favor the persistence of the virus in the host (Valentin et al. 2002). Viral proteins may also contribute to the inhibition of NK cell activities. Whereas the env, nef, and vpu proteins induce a strong reduction in the lytic activity of NK cells (Kottilil et al. 2006), the tat protein blocked L-type calcium channels, thus interfering with NK cell activation. High viremia has been associated with the upregulation of inhibitory and downregulation of activating receptor expressions on the surface of NK cells (Kottilil et al. 2006). Nevertheless, the mechanisms underlying the low activity and the deregulation of receptor expression of NK cells may be complex, as cytolytic activity has also been observed to correlate with low plasma viral load in some cases (Ahmad et al. 2001).

Enhanced cytolytic activity by NK cells with increased levels of perforin and granzyme A expression has been demonstrated in HIV-1-infected patients following IFN-α administration (Portales et al. 2003). The administration of IL-12 has also been used in early HIV-1 infection to increase the number of NK cells and their activity in patients. A reduced level of IL-15 may contribute to the impaired function of NK cells during chronic infection. However, in vitro costimulation of infected cells with IL-12 and IL-15 resulted in suppression of viral replication by NK cells that produce CC chemokines (Ferlazzo and Munz 2004). Interleukin-18 is produced by macrophages and has an antiviral effect, which is mainly mediated by inducing IFN-γ secretion from NK cells (Pien et al. 2000).

HIV-2 Infection

There are close similarities between the genetic structure of HIV-1 and HIV-2, the main difference being that HIV-2 expresses a vpx gene which in HIV-1 is vpu (Guyader et al. 1987). HIV-2 is closely related to SIV_{sm} which infects sooty mangabeys in West Africa, overlapping with the distribution of the HIV-2 epidemic. Currently, eight HIV-2 groups, A-H, have been reported, thought to have arisen from eight different cross-species transmissions from sooty mangabeys to humans (Chen et al. 1997), analogous to the HIV-1 groups. Unlike HIV-1 with various epidemic subtypes and circulating recombinant forms (CRFs), HIV-2 is characterized by an epidemic of only two groups (A and B) and six non-epidemic groups (C-H) (van der Loeff et al. 2006).

The Epidemiology of HIV-2 Infection

HIV-2 was first isolated from three AIDS patients from West Africa (Guinea Bissau, Senegal, and Cape Verde) in 1986 (Brun-Vezinet et al. 1987) and has subsequently been found predominantly in heterosexual populations in West Africa. Outside West Africa, HIV-2 infection also occurs in Angola and Mozambique (De Cock and Brun-Vezinet 1989). Sporadic cases of HIV-2 infection have also been identified in Europe, mainly Portugal, in the Americas, and in India, but also in other places such as Brazil and South Korea.

In recent years, several surveillance studies have revealed a declining trend in HIV-2 prevalence in the region of origin. In West Africa from 1985 to 1996, HIV-2 infection in blood donors has decreased in nine out of ten nations (Bouckenooghe and Shandera 1999). There was also decline in HIV-2 infection rates in a survey carried out from 1988 to 2003 in 23,363 patients aged 15 years or older in the Gambia from 7.0 % to 4.0 % (van der Loeff et al. 2006). Between 1988 and 1992, Ivory Coast witnessed a drop in HIV-2 infection rates from 2.6 % to 1.5 % during a survey of 19,701 women of reproductive age (Eholie and Anglaret 2006). Similar declines have been reported in men in Guinea Bissau, with a decrease in HIV-2 prevalence from 9.1 % to 4.7 % in a period of 9 years from 1987, accompanied by a decline among pregnant women from 8.3 % to 3.3 % in 14 years from 1987 (van der Loeff et al. 2006).

Transmission of HIV-2 Infection

Although HIV-2 can be transmitted by the same routes as HIV-1, transmission usually occur through heterosexual contact. HIV-2 can also be vertically transmitted from mother to child as well as through blood transfusions, but transmissions through homosexual contact and in intravenous drug users (IVDU) are not common (van der Loeff et al. 2006). Human immunodeficiency virus type 2-infected patients show lower rates of transmission and lower plasma viral burdens than HIV-1 in infected subjects in asymptomatic stage of the disease. The mortality rate is also significantly lower than HIV-1 in subjects with CD4 counts >500 cells/μl but similar at lower CD4 counts (van der Loeff et al. 2006). The plasma viral load is much lower in HIV-2, but the proviral load is similar to patients with HIV-1 at the same stage of disease. This may be due to the increased sensitivity of HIV-2 to the recently described host restriction factor TRIM-5α (Ylinen et al. 2005), which restricts the activity of retroviruses after cell entry.

HIV-2 Pathogenesis and Progression to Disease

HIV-2 infects cells of the immune system and the central nervous system, resulting in disease that occurs in very similar stages to those found in HIV-1 infection. However, HIV-2-infected individuals have a much slower disease progression and longer survival, with some individuals never progressing to AIDS (Mota-Miranda et al. 2001). The asymptomatic phase lasts for much longer periods in the majority of HIV-2-infected individuals, sometimes more than 27 years. Longitudinal studies in Caio, Guinea Bissau, have indicated that the majority of HIV-2-infected people do not progress to AIDS (van der Loeff et al. 2006).

Toward the last stage of the disease, defined as AIDS, HIV-2-infected individuals show the same clinical manifestations as seen in HIV-1 infection, with a few exceptions. Researchers in Ivory Coast found that extrapulmonary tuberculosis (TB) was less frequent in HIV-2 infection, whereas multiorgan cytomegalovirus (CMV) infections, HIV encephalitis, and cholangitis were more frequent in HIV-2 compared with HIV-1 infection (Abouya et al. 1995). In an 11-year study in Senegal, researchers found that oral candidiasis and chronic fever were more frequent in HIV-1 infection and that bacterial and cryptococcal meningitis was found only in 59 HIV-2-infected patients (Ndour et al. 2000). On the other hand, chronic diarrhea, especially those caused by bacterial infections, were observed more frequently HIV-2 AIDS patients (Ndour et al. 2000). Studies in the Gambia showed that Kaposi's sarcoma (KS) is less frequent in HIV-2 than in HIV-1 infection, but that wasting syndrome was more frequent in HIV-2 (Martinez-Steele et al. 2007).

Natural Killer Cell Function in HIV-2 Infection

Previous studies of adaptive responses in HIV-2 infection have highlighted the strong broadly neutralizing antibody responses in HIV-2-infected subjects (Rodriguez et al. 2007) and the preservation of HIV-2-specific CD4+ T-cell function in subjects with a normal CD4+ T-cell count (Duvall et al. 2006), both of which contrast with findings in HIV-1 infection.

Only one study comparing NK cell numbers and function between HIV-1 and HIV-2 infection has been reported. In a cross-sectional study of 30 HIV-1- and 30 HIV-2-infected patients at different stages of disease recruited from clinics in the Gambia, there were similar frequencies of NK cells in both asymptomatic HIV-1- and HIV-2-infected individuals. However, in subjects with a CD4 count in the normal range, NK cell cytolytic activity was significantly higher in HIV-2-infected individuals, in whom it was comparable to that seen in seronegative controls (Nuvor et al. 2006). These differences between HIV-1 and HIV-2 infection were lost in the groups with disease progression as evidenced by lower CD4 counts: this suggests that preserved NK function may play a part in viral control in the long asymptomatic period of HIV-2 infection.

Further studies in these subjects demonstrated higher levels of expression of activating NKp44 and NKp46 receptors on NK cells from HIV-2- compared with HIV-1-infected individuals, while the expression of NKp30 was similar between the groups (V. Nuvor, personal communication). The levels of expression of the inhibitory receptor CD158a were similar between HIV-1- and HIV-2-infected subjects, but there was significantly higher expression of inhibitory receptors p70 and CD158b in HIV-1+ compared to HIV-2+ subjects. The expression levels of the NKG2D receptor and coreceptors, 2B4 and NTBA, were similar in both infections. The upregulation of activating receptors on the NK cells in HIV-2-infected subjects and the absence of the increased expression of some inhibitory receptors seen in HIV-1-infected subjects may explain our previous observations of enhanced NK-mediated cytotoxicity in HIV-2 asymptomatic infection compared to HIV-1-infected donors at the same stage of disease (Nuvor et al. 2006).

NKT Cells in HIV-2 Infection

Another lymphocyte subset, natural killer T (NKT) cells, which express invariant αβ T-cell receptors, may also play a role in HIV infection. These cells express NK cell receptors as well as the CD3 marker characteristic of T cells. Natural killer T cells form part of the early response to infection but can also enhance adaptive immunity by activating cytotoxic T lymphocytes through the secretion of Th1/2 cytokines such as IFN-γ, TNF-α, IL-4, IL-10, and IL-13 upon activation (Kotsianidis et al. 2006). These cytokines play a critical role in regulating the immune response: secretion of IL-4 in particular inhibits Th1 responses by inducing a Th2 response, whereas the production of IFN-γ enhances Th1 responses, resulting in an effective adaptive immune response. However, NKT cells are susceptible to HIV-1 infection and are significantly reduced in the peripheral blood of HIV-1-infected individuals with high levels of viremia (Mureithi et al. 2011). $CD4^+$ NKT cells appear to be even more susceptible to infection than conventional $CD4^+$ T cells. Thus, they are rapidly depleted during disease progression when the viral load is high, whereas $CD4^-$ NKT cells are much less affected by HIV-1 infection.

It was noted that a population of NKT cells that express CD4 but are impaired in IFN-γ production was expanded in asymptomatic HIV-1- compared to HIV-2-infected individuals (Nuvor et al. 2012). These cells may serve as target cells for virus infection and replication in HIV-1-infected individuals leading to their subsequent depletion during chronic infection.

HLA-KIR Genotypes in Resistance and Susceptibility to HIV-2 Infection and Disease Progression

The function of individual NK cells is tightly regulated by the combination of inhibitory and activating receptors expressed on their surfaces, which interact with specific MHC Class I molecules and other unidentified ligands. Among these receptors are the killer cell immunoglobulin-like receptor (KIR) groups, which are categorized according to the number of immunoglobulin-like domains they encode (Borrego et al. 2002; Moretta et al. 2001). The binding of these receptors usually transmits inhibitory signals to NK cells, preventing their activity. However, when there is downregulation of MHC or altered MHC Class I expression, as observed during HIV-1 infection (Hultstrom et al. 2004), the inhibitory receptors are not engaged by their MHC ligands, allowing the activation of NK cells and subsequent lysis of their target cells. Certain KIR gene products have been strongly implicated in the control of HIV-1 (Carrington et al. 2008), for example, KIR3DS1 in combination with ligands HLA-B Bw4-80 has been shown to confer protection against rapid progression to AIDS in HIV-1 infection (Martin et al. 2002). A recent report from Yindom et al. analyzed the relationship between KIR and HLA alleles with susceptibility and resistance to HIV-2 infection in a community cohort in Caio, Guinea Bissau (Yindom et al. 2010). This cohort was of Manjako ethnicity and was found to have more activating KIRs than seen in other W. African populations, particularly KIR3DS1. Although, in this cohort, there were no significant associations between KIR genotypes and HIV-2 disease progression, certain compound genotypes of KIR and HLA (KIR2DS2 and KIR2DL2 with at least one HLA C allele of the C1 group) were with resistance to HIV-2 infection, raising the possibility of a contribution of NK cell activity to preventing HIV-2 infection.

Conclusion

Taken together, the published data suggest that the early innate immune function of NK cells may contribute to both resistance to HIV-2 infection and long-term viral control. Adaptive cellular responses are much better preserved in asymptomatic HIV-2-infected compared to HIV-1-infected subjects, and it may be that the interactions between NK, NKT, and T cells make an important contribution to this phenomenon.

Although the NK cell function appears to be preserved in asymptomatic HIV-2-infected individuals, further studies to explore the contribution of NK cells to immune control and determine the underlying mechanisms. These efforts will complement the current search for effective vaccines and immunotherapy for HIV-1 infection.

References

- Abouya L, Coulibaly IM, Coulibaly D, Kassim S, Ackah A, Greenberg AE, Wiktor SZ, De Cock KM. Radiologic manifestations of pulmonary tuberculosis in HIV-1 and HIV-2-infected patients in Abidjan, Cote d'Ivoire. Tuber Lung Dis. 1995;76:436-40.
- Ahmad R, Sindhu ST, Tran P, Toma E, Morisset R, Menezes J, Ahmad A. Modulation of expression of the MHC

class I-binding natural killer cell receptors, and NK activity in relation to viral load in HIV-infected/AIDS patients. J Med Virol. 2001;65:431-40.

- Alter G, Altfeld M. NK cells in HIV-1 infection: evidence for their role in the control of HIV-1 infection. J Intern Med. 2009;265:29-42.
- Andre P, Spertini O, Guia S, Rihet P, Dignat-George F, Brailly H, Sampol J, Anderson PJ, Vivier E. Modification of P-selectin glycoprotein ligand-1 with a natural killer cell-restricted sulfated lactosamine creates an alternate ligand for L-selectin. Proc Natl Acad Sci U S A. 2000;97:3400-5.
- Andrews DM, Scalzo AA, Yokoyama WM, Smyth MJ, Degli-Esposti MA. Functional interactions between dendritic cells and NK cells during viral infection. Nat Immunol. 2003;4:175-81.
- Biassoni R, Cantoni C, Pende D, Sivori S, Parolini S, Vitale M, Bottino C, Moretta A. Human natural killer cell receptors and co-receptors. Immunol Rev. 2001;181:203-14.
- Biron CA, Brossay L. NK cells and NKT cells in innate defense against viral infections. Curr Opin Immunol. 2001;13:458-64.
- Borrego F, Kabat J, Kim DK, Lieto L, Maasho K, Pena J, Solana R, Coligan JE. Structure and function of major histocompatibility complex (MHC) class I specific receptors expressed on human natural killer (NK) cells. Mol Immunol. 2002;38:637-60.
- Bouckenooghe A, Shandera W. HIV trends in African blood donors. J Infect. 1999;39:122-8.
- Brun-Vezinet F, Rey MA, Katlama C, Girard PM, Roulot D, Yeni P, Lenoble L, Clavel F, Alizon M, Gadelle S, et al. Lymphadenopathy-associated virus type 2 in AIDS and AIDS-related complex. Clinical and virological features in four patients. Lancet. 1987;1:128-32.
- Campbell JJ, Qin S, Unutmaz D, Soler D, Murphy KE, Hodge MR, Wu L, Butcher EC. Unique subpopulations of CD56+ NK and NK-T peripheral blood lymphocytes identified by chemokine receptor expression repertoire. J Immunol. 2001;166:6477-82.
- Carrington M, Martin MP, van Bergen J. KIR-HLA intercourse in HIV disease. Trends Microbiol. 2008;16:620-7.
- Chen Z, Luckay A, Sodora DL, Telfer P, Reed P, Gettie A, Kanu JM, Sadek RF, Yee J, Ho DD, Zhang L, Marx PA. Human immunodeficiency virus type 2 (HIV-2) seroprevalence and characterization of a distinct HIV-2 genetic subtype from the natural range of simian immunodeficiency virus-infected sooty mangabeys. J Virol. 1997;71:3953-60.
- Cooper MA, Fehniger TA, Caligiuri MA. The biology of human natural killer-cell subsets. Trends Immunol. 2001;22:633-40.
- De Cock KM, Brun-Vezinet F. Epidemiology of HIV-2 infection. AIDS. 1989;3 Suppl 1:S89-95.
- De Maria A, Biassoni R, Fogli M, Rizzi M, Cantoni C, Costa P, Conte R, Mavilio D, Ensoli B, Cafaro A, Moretta A, Moretta L. Identification, molecular cloning and functional characterization of NKp46 and NKp30 natural cytotoxicity receptors in Macaca fascicularis NK cells. Eur J Immunol. 2001;31:3546-56.
- Duvall MG, Jaye A, Dong T, Brenchley JM, Alabi AS, Jeffries DJ, van der Sande M, Togun TO, McConkey SJ, Douek DC, McMichael AJ, Whittle HC, Koup RA, Rowland-Jones SL. Maintenance of HIV-specific CD4+ T cell help distinguishes HIV-2 from HIV-1 infection. J Immunol. 2006;176:6973-81.
- Eholie S, Anglaret X. Commentary: decline of HIV-2 prevalence in West Africa: good news or bad news? Int J Epidemiol. 2006;35:1329-30.
- Fehniger TA, Herbein G, Yu H, Para MI, Bernstein ZP, O'Brien WA, Caligiuri MA. Natural killer cells from HIV-1+ patients produce C-C chemokines and inhibit HIV-1 infection. J Immunol. 1998;161:6433-8.
- Ferlazzo G, Munz C. NK cell compartments and their activation by dendritic cells. J Immunol. 2004;172:1333-9.
- Ferlazzo G, Tsang ML, Moretta L, Melioli G, Steinman RM, Munz C. Human dendritic cells activate resting natural killer (NK) cells and are recognized via the NKp30 receptor by activated NK cells. J Exp Med. 2002;195:343-51.
- Guyader M, Emerman M, Sonigo P, Clavel F, Montagnier L, Alizon M. Genome organization and transactivation of the human immunodeficiency virus type 2. Nature. 1987;326:662-9.
- Hayakawa Y, Screpanti V, Yagita H, Grandien A, Ljunggren HG, Smyth MJ, Chambers BJ. NK cell TRAIL eliminates immature dendritic cells in vivo and limits dendritic cell vaccination efficacy. J Immunol. 2004;172:123-9.
- He XS, Draghi M, Mahmood K, Holmes TH, Kemble GW, Dekker CL, Arvin AM, Parham P, Greenberg HB. T cell-dependent production of IFN-gamma by NK cells in response to influenza A virus. J Clin Invest. 2004;114:1812-9.

- Hultstrom AL, Bratt G, Cosma A, Erfle V, Wahren B, Carbone E. Autologous cytotoxicity of natural killer cells derived from HIV-infected patients. Immunol Lett. 2004;91:155-8.
- Kiessling R, Hochman PS, Haller O, Shearer GM, Wigzell H, Cudkowicz G. Evidence for a similar or common mechanism for natural killer cell activity and resistance to hemopoietic grafts. Eur J Immunol. 1977;7:655-63.
- Kotsianidis I, Silk JD, Spanoudakis E, Patterson S, Almeida A, Schmidt RR, Tsatalas C, Bourikas G, Cerundolo V, Roberts IA, Karadimitris A. Regulation of hematopoiesis in vitro and in vivo by invariant NKT cells. Blood. 2006;107:3138-44.
- Kottilil S, Shin K, Jackson JO, Reitano KN, O'Shea MA, Yang J, Hallahan CW, Lempicki R, Arthos J, Fauci AS. Innate immune dysfunction in HIV infection: effect of HIV envelope-NK cell interactions. J Immunol. 2006;176:1107-14.
- LaBonte ML, McKay PF, Letvin NL. Evidence of NK cell dysfunction in SIV-infected rhesus monkeys: impairment of cytokine secretion and NKG2C/C2 expression. Eur J Immunol. 2006;36:2424-33.
- Martin MP, Gao X, Lee JH, Nelson GW, Detels R, Goedert JJ, Buchbinder S, Hoots K, Vlahov D, Trowsdale J, Wilson M, O'Brien SJ, Carrington M. Epistatic interaction between KIR3DS1 and HLA-B delays the progression to AIDS. Nat Genet. 2002;31:429-34.
- Martinez-Steele E, Awasana AA, Corrah T, Sabally S, van der Sande M, Jaye A, Togun T, Sarge-Njie R, McConkey SJ, Whittle H, Schim van der Loeff MF. Is HIV-2- induced AIDS different from HIV-1-associated AIDS? Data from a West African clinic. AIDS. 2007;21:317-24.
- Moretta A, Bottino C, Vitale M, Pende D, Cantoni C, Mingari MC, Biassoni R, Moretta L. Activating receptors and coreceptors involved in human natural killer cell-mediated cytolysis. Annu Rev Immunol. 2001;19:197-223.
- Mota-Miranda A, Gomes H, Lima-Alves C, Araujo F, Cunha-Ribeiro LM, Taveira N. Perinatally acquired HIV-2 infection diagnosed at 15 and 24 years of age. AIDS. 2001;15:2460-1.
- Mureithi MW, Cohen K, Moodley R, Poole D, Mncube Z, Kasmar A, Moody DB, Goulder PJ, Walker BD, Altfeld M, Ndung'u T. Impairment of CD1d-restricted natural killer T cells in chronic HIV type 1 clade C infection. AIDS Res Hum Retroviruses. 2011;27:501-9.
- Ndour M, Sow PS, Coll-Seck AM, Badiane S, Ndour CT, Diakhate N, Diop B, Faye M, Soumare M, Diouf G, Colebunders R. AIDS caused by HIV1 and HIV2 infection: are there clinical differences? Results of AIDS surveillance 1986-97 at Fann Hospital in Dakar, Senegal. Trop Med Int Health. 2000;5:687-91.
- Norris S, Doherty DG, Collins C, McEntee G, Traynor O, Hegarty JE, O'Farrelly C. Natural T cells in the human liver: cytotoxic lymphocytes with dual T cell and natural killer cell phenotype and function are phenotypically heterogenous and include Valpha24-JalphaQ and gammadelta T cell receptor bearing cells. Hum Immunol. 1999;60:20-31.
- Nuvor SV, van der Sande M, Rowland-Jones S, Whittle H, Jaye A. Natural killer cell function is well preserved in asymptomatic human immunodeficiency virus type 2 (HIV-2) infection but similar to that of HIV-1 infection when CD4 T-cell counts fall. J Virol. 2006;80:2529-38.
- Nuvor SV, Whittle H, Rowland-Jones S, Jaye A. Higher expansion of IFN-g - CD4+NKT cells in asymptomatic HIV-1 than in HIV-2 individuals. World J AIDS. 2012;2:103-8.
- Parato KG, Kumar A, Badley AD, Sanchez-Dardon JL, Chambers KA, Young CD, Lim WT, Kravcik S, Cameron DW, Angel JB. Normalization of natural killer cell function and phenotype with effective anti-HIV therapy and the role of IL-10. AIDS. 2002;16:1251-6.
- Parrish-Novak J, Dillon SR, Nelson A, Hammond A, Sprecher C, Gross JA, Johnston J, Madden K, Xu W, West J, Schrader S, Burkhead S, Heipel M, Brandt C, Kuijper JL, Kramer J, Conklin D, Presnell SR, Berry J, Shiota F, Bort S, Hambly K, Mudri S, Clegg C, Moore M, Grant FJ, Lofton-Day C, Gilbert T, Rayond F, Ching A, Yao L, Smith D, Webster P, Whitmore T, Maurer M, Kaushansky K, Holly RD, Foster D. Interleukin 21 and its receptor are involved in NK cell expansion and regulation of lymphocyte function. Nature. 2000;408:57-63.
- Pien GC, Satoskar AR, Takeda K, Akira S, Biron CA. Cutting edge: selective IL-18 requirements for induction of compartmental IFN-gamma responses during viral infection. J Immunol. 2000;165:4787-91.
- Portales P, Reynes J, Pinet V, Rouzier-Panis R, Baillat V, Clot J, Corbeau P. Interferon-alpha restores HIV-induced alteration of natural killer cell perforin expression in vivo. Aids. 2003;17:495-504.
- Rodriguez SK, Sarr AD, MacNeil A, Thakore-Meloni S, Gueye-Ndiaye A, Traore I, Dia MC, Mboup S, Kanki PJ. Comparison of heterologous neutralizing antibody responses of human immunodeficiency virus type 1 (HIV-1)-

and HIV-2-infected Senegalese patients: distinct patterns of breadth and magnitude distinguish HIV-1 and HIV-2 infections. J Virol. 2007;81:5331-8.

- Scott-Algara D, Paul P. NK cells and HIV infection: lessons from other viruses. Curr Mol Med. 2002;2:757-68.
- Seaman WE. Natural killer cells and natural killer T cells. Arthritis Rheum. 2000;43:1204-17.
- Smith PL, Lombardi G, Foster GR. Type I interferons and the innate immune response-more than just antiviral cytokines. Mol Immunol. 2005;42:869-77.
- Valentin A, Rosati M, Patenaude DJ, Hatzakis A, Kostrikis LG, Lazanas M, Wyvill KM, Yarchoan R, Pavlakis GN. Persistent HIV-1 infection of natural killer cells in patients receiving highly active antiretroviral therapy. Proc Natl Acad Sci U S A. 2002;99:7015-20.
- van der Loeff MF, Awasana AA, Sarge-Njie R, van der Sande M, Jaye A, Sabally S, Corrah T, McConkey SJ, Whittle HC. Sixteen years of HIV surveillance in a West African research clinic reveals divergent epidemic trends of HIV-1 and HIV-2. Int J Epidemiol. 2006;35:1322-8.
- Yindom LM, Leligdowicz A, Martin MP, Gao X, Qi Y, Zaman SM, van der Loeff MS, van Tienen C, Jaye A, Aveika A, Worwui A, Diatta M, Vincent T, Whittle HC, Rowland-Jones SL, Walton R, Carrington M. Influence of HLA class I and HLA-KIR compound genotypes on HIV-2 infection and markers of disease progression in a Manjako community in West Africa. J Virol. 2010;84:8202-8.
- Ylinen LM, Keckesova Z, Wilson SJ, Ranasinghe S, Towers GJ. Differential restriction of human immunodeficiency virus type 2 and simian immunodeficiency virus SIVmac by TRIM5alpha alleles. J Virol. 2005;79:11580-7.
- Yu H, Fehniger TA, Fuchshuber P, Thiel KS, Vivier E, Carson WE, Caligiuri MA. Flt3 ligand promotes the generation of a distinct CD34(+) human natural killer cell progenitor that responds to interleukin-15. Blood. 1998;92:3647-57.
- Zhang D, Shankar P, Xu Z, Harnisch B, Chen G, Lange C, Lee SJ, Valdez H, Lederman MM, Lieberman J. Most antiviral CD8 T cells during chronic viral infection do not express high levels of perforin and are not directly cytotoxic. Blood. 2003;101:226-35.

Natural Killer Cells and Innate Immunity in HIV-2 Infection

Dr. Samuel Victor Nuvor — School of Medical Sciences, University of Cape Coast, Cape Coast, West Africa

DOI: 10.1007/SpringerReference_384957

URL: http://www.springerreference.com/index/chapterdbid/384957

Part of: Encyclopedia of AIDS

Editors: Dr. Thomas Hope, Dr. Douglas D. Richman and Dr. Mario Stevenson

PDF created on: October, 17, 2014 04:16