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Natural Killer Cells in HIV-1 Infection: A Double-Edged Sword

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Abstract

In order to propagate and persist within the host, HIV-1 subverts a variety of checkpoints of innate and adaptive viral immunosurveillance. Many of these are related to natural killer cells, which bridge innate and adaptive immunity and play a major role in defeating virus infections. HIV-1 affects cytotoxicity of natural killer cells towards infected cells and natural killer cell-mediated priming of effector cells of the adaptive immune system. Moreover, a subpopulation of natural killer cells was found sensitive to infection by HIV-1. Consequently, an efficient immune response against HIV-1 cannot be mounted in most patients. The current review highlights the molecular interplay between HIV-1 and effector cells of the host immune system with a focus on natural killer cells, and summarizes strategies of HIV-1 to escape from natural killer cell immunosurveillance. A detailed knowledge of these immune escape strategies might lead to the identification of access points for intervention in order to block infection and progression to AIDS. **(AIDS Rev. 2011;13:67-76)**

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Key words

NK cell. Innate immune system. Immune escape. CD4 cell depletion. gp41 3S motif. NKp44 ligand.

Introduction

HIV-1 infects mainly $CD4^+$ T-cells, leading to their quantitative depletion and concomitant immunodeficiency, which may finally result in opportunistic infections and AIDS. The large extent of $CD4^+$ T-cell depletion was puzzling for a long time since only a small fraction of these cells are infected by HIV-1. Further studies demonstrated that HIV-1 also affects uninfected effector cells of the immune system by induction of apoptosis, modulation of cytokine/chemokine levels and related impairment of differentiation, migration, and functionality of immune cells[1]. Furthermore, cells of the innate immune system can be directly infected. Cells of the innate immune system include dendritic cells (DC), monocytes, macrophages, and neutrophils, which originate from the myeloid lineage, and natural killer (NK) cells, which originate from the lymphoid lineage. Whereas macrophages are directly infected by HIV-1, DC capture the virus at mucosal surfaces and transmit it to T-cells in the lymph nodes. Although DC are not productively infected themselves, the virus influences essential functions of these cells concerning antigen presentation and immune activation that have fundamental consequences on the subsequent priming of the adaptive immune response. Natural killer cells play a major role to confine and defeat virus infections and bridge innate and adaptive immune responses; however, their role in HIV-1 infection is less clear. Interestingly, in order to weaken the host immune response, HIV-1 has evolved sophisticated mechanisms to inhibit NK cell cytotoxicity towards infected cells and to reroute NK cell killing to uninfected $CD4^+$ cells[2,3]. Since NK cells are the major effector cells of the early immune response to HIV-1 infection, we will first introduce these cells and summarize their functions at the molecular level.

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Effector functions of natural killer cells

Natural killer cells were first described in the 1970s for their ability to spontaneously kill tumor cells, which was the origin of their name, "natural killer" cells[4-9]. NK cells are large granular lymphocytes, which mainly develop and differentiate in the bone marrow and then enter into circulation[10,11]. Significant numbers of NK cells also develop and differentiate in thymus, spleen, tonsils, and lymph nodes[12,13]. These cells constitute around 15% of peripheral blood lymphocytes and migrate to various tissues and organs of the body in response to proinflammatory stimuli[10,14]. Due to their different sites and pathways of development, NK cells are a heterogeneous cell population, defined by the absence of CD3 and the variable expression of CD56 (neural cell adhesion molecule) and CD16 (FcγRIIIA) surface markers in humans. Based on the expression level of these two markers, NK cells can be subdivided into a $CD56^{bright}/CD16^{dim}$ and a $CD56^{dim}/CD16^{bright}$ subset[10], differing in their body distribution and function. The $CD56^{bright}/CD16^{dim}$ NK cells secrete large quantities of cytokines and play an important role as immune regulatory cells with limited cytotoxicity[15], whereas $CD56^{dim}/CD16^{bright}$ NK cells are highly cytotoxic[10]. The $CD56^{bright}CD16^{dim}$ NK cells are the predominant species (> 90%) in secondary lymphoid tissues[16], whereas the majority of cytotoxic $CD56^{dim}CD16^{bright}$ NK cells (> 90%) are present in the peripheral blood.

Natural killer cells are known to fight viruses like members of the family of human herpes virus, human cytomegalovirus, and HIV[17-20]. Their impact on viral immune surveillance is underscored by the fact that patients with NK cell deficiencies[21] and patients with low or dysfunctional NK cell activity[22] suffer from recurrent, life-threatening herpes virus infections.

Upon encountering malignant or virus-infected cells, cytotoxic NK cells can mediate cytolysis by (i) release of cytoplasmic granules containing perforin and granzymes[23], representing the dominant killing mechanism of NK cells, (ii) induction of apoptosis via Fas ligand or TRAIL signaling[24-26], or (iii) antibody dependent cellular cytotoxicity (ADCC)[27]. NK cell killing is regulated by a balance of downstream signals from agonistic and antagonistic cell surface receptors: (i) inhibitory receptors, which specifically recognize major histocompatibility complex class I (MHC-I) molecules and thus allow for the discrimination between normal cells and cells, which have lost their surface MHC-I molecules as a result of malignant transformation or viral infection, and (ii) activating receptors, which trigger the cytolytic activity against such cells[28-30] (Fig. 1).

Natural killer cell receptors

The pool of inhibitory receptors of human NK cells is comprised of (i) the promiscuous ILT2 receptor, (ii) the killer immunoglobulin-like receptors (KIR), which recognize different allelic groups of human leukocyte antigen (HLA) -A, -B or -C molecules, and (iii) the CD94/NKG2A receptor, which recognizes HLA-E[31]. Each type of KIR is expressed only by a subset of NK cells, and most NK cells express only one type of MHC-I-specific receptor. Therefore, in contrast to the entire NK cell pool, an individual NK cell might not be able to detect the absence of an HLA allelic variant on the surface of a target cell, as is the case in many cancer cells[32].

The major activating NK cell receptors are NKG2D and the non-homologous natural cytotoxicity receptors NKp30, NKp44, and NKp46[33,34]. The importance of natural cytotoxicity receptors for NK cell activity is underscored by the fact that expression of an insufficient amount of these receptors results in resistance of leukemia cells to NK cell cytotoxicity in patients with acute myeloid leukemia[35]. Receptor NKG2D binds to the stress-inducible cellular ligands MICA and MICB (MHC class I chain-related gene A/B), and to the unique long (UL) 16-binding proteins (ULBP) on target cells[36]. In contrast, the corresponding cellular ligands of natural cytotoxicity receptors are mostly unknown and poorly characterized at the molecular level. There is evidence that NKp44 and NKp46 bind to viral hemagglutinins[37,38], while NKp30 binds to pp65 of human cytomegalovirus, the HLA-B-associated transcript 3 (BAT3) and to the recently discovered B7-H6 ligand on target cells[39-41]. Besides these inhibitory and activating receptors, it is assumed that NK cells express a number of functional Toll-like receptors, allowing NK cells to respond rapidly to invading pathogens[42].

Natural killer cells contribute to adaptive immunity

The activation level of NK cells can be increased by cytokines, which are secreted by other immune cells upon infection[10]. As a consequence, the expression level of activating NK cell receptors is increased, thus lowering the threshold for a cytotoxic response[43]. Additionally, viral replication is suppressed by several chemokines and cytokines which are secreted from activated regulatory $CD56^{bright}/CD16^{dim}$ NK cells[16].

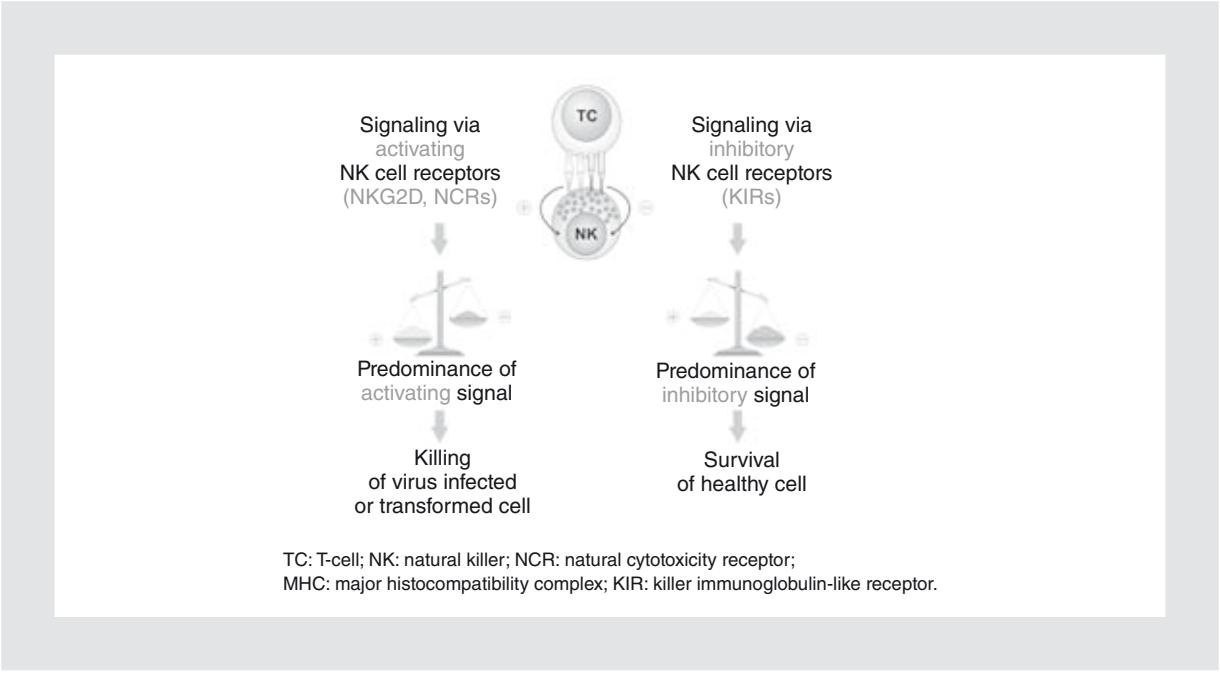

Figure 1. *Regulation of natural killer cell cytotoxicity by antagonistic and agonistic activating and inhibitory receptors. Natural killer cell recognition of target cells is regulated by the balance of activating and inhibitory signals delivered by activating and inhibitory receptors on the NK cell surface. MHC class I molecules on the target cell trigger inhibitory NK cell receptor signaling, blocking target cell lysis. In the case of tumor cells or virus-infected cells, the cell-surface expression of MHC class I molecules is downregulated and signaling via inhibitory receptors is reduced. Instead, triggering through activating receptors dominates, resulting in target cell lysis.*

Natural killer cells can promote the development of adaptive immunity via a bidirectional cross-talk with DC[44]. Upon encountering pathogen products, DC produce IL-12 and IL-15 to prime NK cells, which in turn secret cytokines (TNF-α, IFN-γ) to induce maturation of antigen-loaded DC. These mature DC can then migrate to sites where they activate effector cells of the adaptive immune system. Interestingly, the lack of MHC-I expression on immature DC leads to their clearance by NK cells. Thus, NK cells contribute to DC maturation and at the same time to removal of immature tolerogenic DC. This quality control over DC by NK cells is mediated through the interaction of inhibitory (CD94/NKG2A) and activating (NKp30) NK cell receptors with their corresponding cellular ligands on DC.

Immune evasion of HIV from immuno-surveillance by natural killer cells

In co-evolution with the immune system, viruses have developed diverse mechanisms to evade immunosurveillance in order to propagate and disseminate within the population. Among others, escape from NK cell immunosurveillance is a common strategy of persistent viruses, such as human cytomegalovirus, herpes simplex virus type 1 and 2, varicella zoster virus, hepatitis C virus, and HIV-1[45,46]. The strategies to modulate the activity of NK cells and to evade detection by NK cells fall into five categories: (i) selective down- or upregulation of HLA class I alleles from the host cell surface, (ii) expression of MHC-I homologs, (iii) expression of cytokine-binding proteins or cytokine receptor antagonists, (iv) inhibition of NK cell activating receptors, and (v) infection of NK cells[47,48]. In the following we will focus on the manifold inventions of HIV to compromise immunosurveillance by NK cells (Fig. 2, Table 1).

Downregulation of cellular ligands of natural killer cell receptors

Since cytotoxic T-lymphocytes (CTL) can recognize viral peptides presented on HLA class I molecules on the surface of infected cells, a common strategy used by a variety of viruses is to interfere with the process of antigen presentation[46,49,50]. However, global inhibition of MHC class I antigen presentation bears the risk of NK cell-mediated killing due to a lack of signals from inhibitory receptors[29]. In order to circumvent this problem, the HIV-1 protein Nef downregulates HLA-A and HLA-B molecules, which are the major mediators

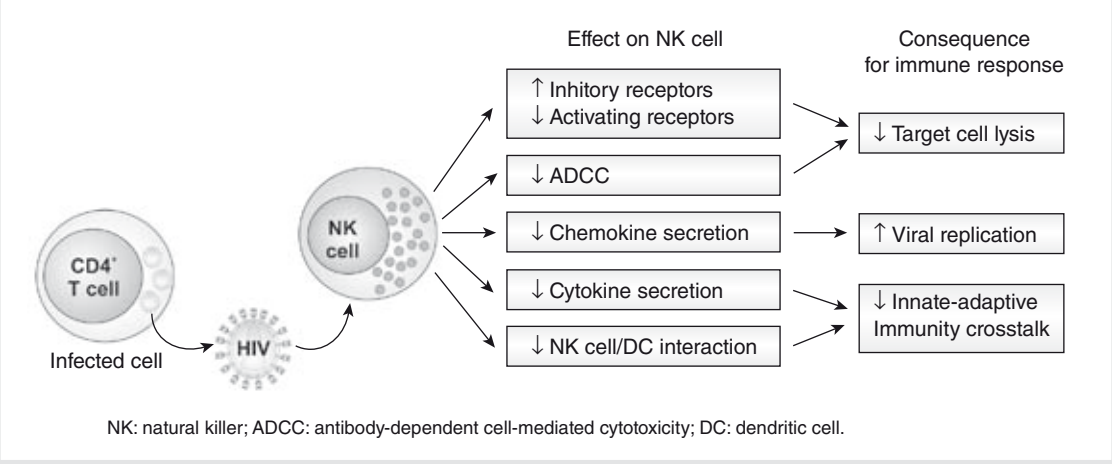

Figure 2. *Effects of HIV viremia on natural killer cell function. HIV viremia results in reduced ability of NK cells to lyse virus-infected target cells via reduction of activating and increase of inhibitory NK cell surface receptors. This effect is further promoted by the impairment of HIV envelope-specific antibody-dependent cell-mediated cytotoxicity. HIV viremia also inhibits the secretion of CC-chemokines by NK cells, which enhances their susceptibility to infection by HIV-1 through unblocked CC-chemokine receptors. The reduction of cytokine secretion as well as an impaired interaction of NK cells with dendritic cells leads to defective crosstalk between the innate and the adaptive immunity.*

of CTL killing, from the cell surface of HIV-infected cells by redirecting them to the endo-lysosomal pathway[51-53], while the HLA-C and HLA-E alleles are not affected and can still be recognized by the inhibitory KIR or CD94/NKG2A receptors of NK cells[51]. As a result, HIV achieves inhibition of both CTL-mediated as well as NK cell-mediated killing of the host cell[51,54].

Virus infection and cellular stress might lead to up-regulation of cellular ligands of NKG2D and render the infected cells sensitive to NKG2D-dependent killing by

Table 1. HIV proteins affecting natural killer cell-mediated immunity

Immune evasion	Mode of action	References
Nef	Downregulation of HLA-A and HLA-B, but not HLA-C or HLA-E	51,54
	Degradation of NKG2D ligands	56
	Retention of NKp44 ligands	112
	Modulation of cytokine milieu	113,114
Tat	Blocking *de novo* synthesis of HLA class I molecules	115
	Modulation of cytokine milieu	116-120
Vpu, Vpr	Blocking *de novo* synthesis of HLA class I molecules	121
	Regulation of NK cell degranulation	122,123
p24	Stabilization of HLA-E on the cell surface	124,125
gp120	Epitope masking and mutation	59
	Modulation of cytokine milieu	126
gp41	Epitope masking and mutation	59

HLA: human leukocyte antigen; NK: natural killer.

NK cells and CTL[28,55]. In order to escape from elimination, HIV-Nef mediates downregulation of MICA, ULBP-1, and ULPB-2, thus limiting the number of activating contacts and the degree of cytotoxicity[56].

Escape from antibody-dependent cellular cytotoxicity

HIV envelope proteins (gp120, gp41) are found on the surface of infected cells. Moreover, shed soluble variants can decorate uninfected cells after binding to CD4 and/or corresponding coreceptors. Consequently, these gp120 and gp41 bearing cells are a prime target for binding of neutralizing antibodies, which in turn trigger NK cell cytotoxicity via CD16 signaling[57,58]. This process is referred to as antibody-dependent cellular cytotoxicity (ADCC). In order to circumvent antibody binding to infected cells, the virus employs several strategies: (i) mutation of epitopes for these antibodies, (ii) masking of epitopes by glycosylation and trimerization of gp120/gp41 spikes or (iii) shedding of the envelope proteins[59]. Moreover, HIV-1 can induce shedding of CD16 from the surface of cells other than NK cells and thus produce soluble CD16 molecules, which act as competitors of ADCC[60].

Modulation of expression levels of natural killer cell receptors

Another clue for HIV-1 to subvert the immune response is to shift receptor pools of NK cells. Previous studies showed a significant increase in inhibitory KIR levels on NK and T-cells[61-63] and decreased levels of the natural cytotoxicity receptors[63,64], leading to compensation of predominant signaling of activating NK cell receptors, reduced cytotoxicity, and promotion of viral replication[65]. Interestingly, modulation of receptor expression levels was mainly observed in viremic patients and correlated with viral load[66,67]. Notably, the expression and function of NKG2D and several activating co-receptors, including 2B4, NKp80, and NTBA, are not affected by HIV-1[63,68].

Impaired interactions between natural killer and dendritic cells

Besides reduction of NK cell cytotoxicity, HIV-1-induced downregulation of activating NK cell receptors affects the crosstalk of NK cells and DC during establishment of an adaptive immune response. In this context, the maturation of DC is tightly controlled by NKp30-dependent killing of immature DC by NK cells. A decreased expression of natural cytotoxicity receptors mediated by HIV-1 leads to impaired clearance and thus accumulation of immature DC[69,70]. As a consequence, cytokine secretion is limited leading to impaired activation of NK cells[63,64].

HIV-1-induced killing of uninfected CD4$^+$ T-cells by natural killer cells

Interestingly, HIV-1 infections can result in increased sensitivity of uninfected cells to NK cell-mediated killing[71]. This phenomenon was first described by Debré, et al. who showed that NK cells actively contribute to CD4$^+$ T-cell depletion in HIV-1-infected patients, a major cause of the progression to AIDS[71]. Natural killer cell cytotoxicity is mediated by recognition of an HIV-1-induced cellular ligand of NKp44 (NKp44L) on CD4$^+$ T-cells. Surprisingly, mainly uninfected CD4$^+$ T-cells are sensitive to killing by NK cells (see below). The induction of NKp44L was HIV-1-dependent and was observed on 20% (*in vivo*) and 40% (*in vitro*) of the CD4$^+$ T-cells, respectively. The expression level of NKp44L correlated with viral load, and HAART diminished the proportion of CD4$^+$ T-cells that expressed NKp44L.

Surprisingly, in a SHIV/macaque model, Vieillard, et al.[72] could show *in vivo* that CCR5-dependent (R5) virus strains induced NKp44L and mediated killing of CD4$^+$ T-cells by NK cells, whereas dual tropic (facultative use of CCR5 and CXCR4, R5X4) virus strains failed to mediate NK cell killing. This observation might be explained by the fact that R5X4 virus strains lead to a much faster lysis of the host cell than R5 virus strains and might therefore not benefit from NK cell-mediated CD4$^+$ cell killing[73].

The expression of NKp44L on CD4$^+$ T-cells is induced by the highly conserved 3S motif (S^{102}WSNKS^{107}, numbers refer to gp41 of the HXB2 HIV-1 strain) within the HIV1 gp41 envelope protein[71]. Interestingly, the 3S motif is absent in HIV-2 or SIV strains, which may partially explain their lower pathogenicity. The 3S motif of HIV-1 is located in the extracellular part of gp41 between the N-terminal and the C-terminal heptad repeats and plays an important role in six helix bundle formation and fusion (Fig. 3 A). It is supposed that the 3S motif becomes accessible during conformational changes induced by docking of HIV-1 Env to cellular receptors[74,75].

Interestingly, NKp44L induction occurs only on uninfected CD4$^+$ T-cells, which recognize receptor-activated Env molecules on virions or cells after an aborted fusion process called hemifusion or "kiss of death"[76,77].

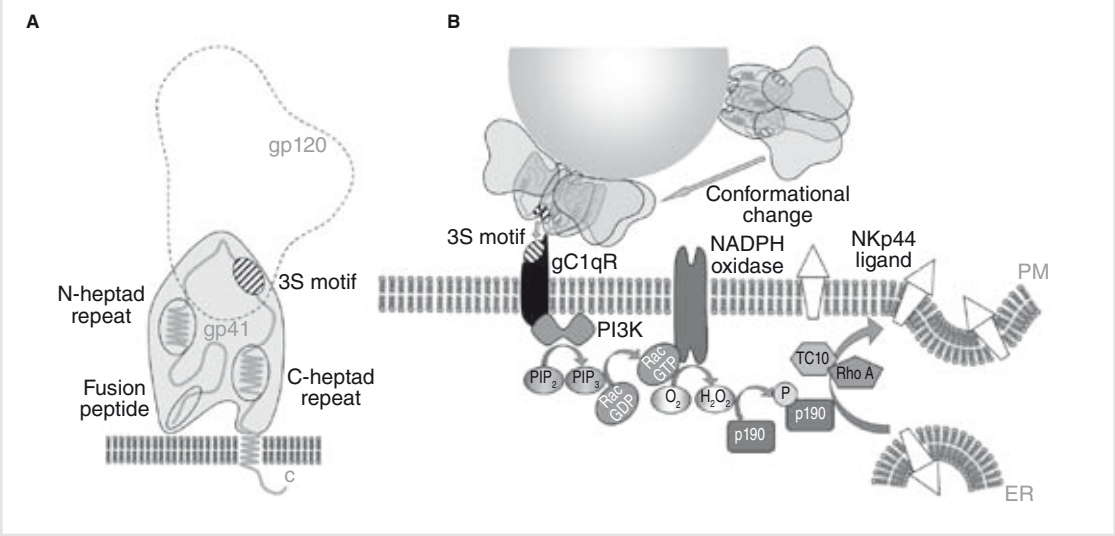

Figure 3. ***A:*** *NKp44 ligand (NKp44L) induction by the 3S motif of HIV-1 gp41. The 3S motif (SWSNKS), responsible for NKp44L ligand induction in noninfected CD4+ T-cells, is located between the N- and the C-heptad repeat within the extracellular part of gp41.* ***B:*** *Upon binding of HIV-1 Env to its cellular receptors, conformational changes render the 3S motif accessible for interaction with the complement receptor gC1qR. Activated PI3K leads to elevated PIP_3 and GTP-activated Rac levels that account for the production of reactive oxygen species (H_2O_2). Phosphorylated p190 RhoGAP-A, RhoA and TC10 finally mediate the translocation of NKp44L from intracellular vesicular bodies to the cell membrane.*

The identity of NKp44L is unclear; however, the signal transduction pathway that finally leads to the presentation of NKp44L was recently deciphered[78]. The authors could prove that the 3S motif binds to the complement receptor gC1qR on the surface of CD4+ cells, known to mediate entry of several pathogens[79-84]. Subsequently, the 3S motif triggers a signaling cascade, which leads to production of H_2O_2 and exocytosis of intracellular NKp44L (Fig. 3 B). Interestingly, about 30% of HIV-1-infected patients possess protective anti-3S antibodies, which lead to preservation of CD4+ cell counts and suppress NKp44L expression and related NK cell lysis[85]. These protective anti-3S antibodies arise early after infection; however, they disappear during the course of the disease. This fatal effect is due to the dependency of antibody production on anti-3S-specific CD4+ T-cells, which express high amounts of NKp44L and are therefore very sensitive to killing by NK cells.

These observations are in accordance with results from a 3S peptide vaccination study in macaques[86]. Here, the raised anti-3S antibodies inhibited NKp44L presentation on CD4+ cells and promoted stable CD4+ cell counts due to prevention of NK cell cytotoxicity. In humans, the NKp44L expression levels correlated with the virus load, as progressors showed a high level of NKp44L, long-term nonprogressors an intermediate level, and elite controllers a very low level (comparable to healthy individuals). Interestingly, anti-3S antibodies inhibited CD4+ T-cell lysis in progressors and long-term nonprogressors, preserving CD4+ T-cell counts close to those of uninfected individuals or controllers. Based on these results, NKp44L seems to be the major determinant for NK sensitization by HIV-1 and represents a promising therapeutic target.

Effects of HIV-1 on natural killer cell phenotype and function

Changes in the cytokine/chemokine milieu during HIV infection

HIV-1 affects the ability of NK cells to secrete cytokines and chemokines, which are essential for an effective NK cell responses in the host[87]. Whereas NK cells secrete more IL-10, IL-18, and transforming growth factor-beta upon infection, decreased levels of IL-2, IL-12, and IL-15 lead to an impaired crosstalk between NK cells and DC and concomitant malfunctions. In addition, HIV-1 reduces the ability of NK cells to secrete chemokines,

such as CCL3, CCL4, and CCL5, and leads to reduced NK cell-mediated inflammation and a higher number of surface-exposed, non-chemokine-engaged receptors for docking and entry of HIV[88-90].

Changing natural killer cell subsets

Although the overall NK cell number remains constant during the chronic phase of HIV infection, a significant change in the composition of the NK cell pool occurs during the course of the disease[91-93]. Progressive HIV-1 infection results in reduction of cytotoxic $CD56^{dim}CD16^{bright}$ NK cells and a simultaneous accumulation of anergic $CD56^{neg}CD16^{pos}$ NK cells[94-96]. This $CD56^{neg}CD16^{pos}$ NK cell subset is rare in healthy individuals and is characterized by impaired cytokine secretion and higher levels of inhibitory and lower levels of activating NK cell receptors[94,95].

Direct infection of natural killer cells by HIV-1

HIV-1 infects predominantly $CD4^+$ T cells, but other $CD4^+$ cell types of the brain, bowel, heart, kidney, liver, and other organs are infected as well[97]. Although NK cells express CCR5 and/or CXCR4[63,98-101], NK cells in the peripheral blood of infected and healthy individuals were reported to lack CD4 expression, and consequently no proviral DNA could be detected[63]. In contrast, other studies showed CD4-independent and nonproductive infection of NK cells *in vitro*[102,103]. Studies of Valentin, et al.[99] and Bernstein, et al.[104] identified a novel cytotoxic NK cell subpopulation, which expresses CD4, CCR5, and/or CXCR4 at the same time and can thus be productively infected by HIV-1[99,100]. Therefore, these NK cells could serve as an important viral reservoir *in vivo*. Although $CD4^+$ NK cells are rare in the peripheral blood (< 7% of NK cells), they comprise 14% of the NK cell pool in human tonsils and 60-80% in the thymus[104,105]. The $CD4^+$ NK cells display some unique features as (i) they are highly activated and express the activation markers HLA-DR and CD25[105,106], (ii) they express increased levels of IFNγ and TNFα, and (iii) they are capable of migrating towards the proinflammatory cytokine IL16[104]. Interestingly, high $CD4^+$ NK cell counts were found in the peripheral blood of HIV-1-infected individuals as a result of NK cell activation[99,100,104,105]. This phenomenon is reminiscent of the known CD4 induction on activated $CD8^+$ T-cells in the peripheral blood, which renders them susceptible to HIV-1 infection[107-109]. In contrast, HIV-1 infection of $CD4^+$ T-cells results in downregulation of CD4 expression and reduced migration to sites of acute inflammation[100,110]. This reflects another mechanism of HIV-1 to avoid NK cell killing at primary sites of virus replication (see above)[100].

Controversial data exist on the susceptibility of NK cells to HIV-1 infection. Several *in vitro* studies showed that stimulated NK cells expressing both CD4 as well as the chemokine co-receptors were infected by HIV-1[99,100,105]. Moreover, Valentin, et al.[99] and Bernstein, et al.[100] confirmed the infection of $CD4^+$ NK cells with X4-tropic HIV strains by entry inhibitors, specifically blocking CXCR4-mediated entry. However, as R5-tropic HIV-1 strains are responsible for most primary infections, several studies analyzed the infectivity of $CD4^+$ NK cells by these strains. While Valentin, et al.[99] reported that NK cells could be infected by R5-tropic HIV-1 strains in the absence of any other cell type, Harada, et al. could not detect infection of NK cells with R5 viruses[105]. However, upon co-culture of stimulated $CD4^+$ NK cells with $CD4^+$ T-cells, proviral DNA was detected in both cell types[105].

Future perspectives

As discussed in this review, HIV-1 affects NK cell activity in multiple ways in order to overcome both NK cell-mediated killing of infected cells and NK cell-mediated triggering of adaptive immune responses. Some open questions still remain, especially with regard to the sensitivity of NK cells to HIV-1 infection. A more detailed understanding of the early effects of HIV-1 infection on NK cell activity may help to develop therapeutic strategies to maintain or restore the crucial antiviral NK cell functions. Due to the central role of NK cells in orchestrating innate and adaptive immune responses, such strategies would enable a much more efficient antiviral immune response and might prevent viral spread and progression to AIDS. However, clearance of infected NK cells might be complicated by the fact that NK cells express a higher level of P-glycoprotein compared with other lymphocytes and are therefore more resistant to antiretroviral drugs, such as protease and reverse transcriptase inhibitors[99,111].

In summary, NK cells act as a double-edged sword: on the one hand NK cells directly mediate killing of HIV-1-infected cells, and on the other hand they contribute to killing of noninfected $CD4^+$ T-cells. Moreover, NK cells can be infected by HIV-1 and thus provide a reservoir for viral replication on their own. Therefore, NK cells represent a challenging but promising target for future antiviral therapies.

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References

1. Chang J, Altfeld M. Innate immune activation in primary HIV-1 infection. J Infect Dis. 2010;202(Suppl 2):S297-301.
2. Brunetta E, Hudspeth K, Mavilio D. Pathologic natural killer cell subset redistribution in HIV-1 infection: new insights in pathophysiology and clinical outcomes. J Leukoc Biol. 2010;88:1119-30.
3. Mavilio D, Hosmalin A, Scott-Algara D. Natural killer cells and human immunodeficiency virus. Academic Press. 2010:481-97.
4. Rosenberg E, McCoy J, Green S, et al. Destruction of human lymphoid tissue-culture cell lines by human peripheral lymphocytes in 51Cr-release cellular cytotoxicity assays. J Natl Cancer Inst. 1974; 52:345-52.
5. Jondal M, Pross H. Surface markers on human b and t lymphocytes. VI. Cytotoxicity against cell lines as a functional marker for lymphocyte subpopulations. Int J Cancer. 1975;15:596-605.
6. Ono A, Amos D, Koren H. Selective cellular natural killing against human leukaemic T cells and thymus. Nature. 1977;266:546-8.
7. Kiessling R, Klein E, Wigzell H. „Natural" killer cells in the mouse. I. Cytotoxic cells with specificity for mouse Moloney leukemia cells. Specificity and distribution according to genotype. Eur J Immunol. 1975;5:112-7.
8. Kiessling R, Petranyi G, Klein G, Wigzel H. Genetic variation of in vitro cytolytic activity and in vivo rejection potential of non-immunized semisyngeneic mice against a mouse lymphoma line. Int J Cancer. 1975;15:933-40.
9. Herberman R, Nunn M, Lavrin D. Natural cytotoxic reactivity of mouse lymphoid cells against syngeneic acid allogeneic tumors. I. Distribution of reactivity and specificity. Int J Cancer. 1975;16:216-29.
10. Cooper M, Fehniger T, Caligiuri M. The biology of human natural killer-cell subsets. Trends Immunol. 2001;22:633-40.
11. Moretta A, Bottino C, Mingari M, Biassoni R, Moretta L. What is a natural killer cell? Nat Immunol. 2002;3:6-8.
12. Di Santo J, Vosshenrich C. Bone marrow versus thymic pathways of natural killer cell development. Immunol Rev. 2006;214:35-46.
13. Freud A, Caligiuri M. Human natural killer cell development. Immunol Rev. 2006;214:56-72.
14. Maghazachi A. Compartmentalization of human natural killer cells. Mol Immunol. 2005;42:523-9.
15. Cooper M, Fehniger T, Turner SC, et al. Human natural killer cells: a unique innate immunoregulatory role for the CD56(bright) subset. Blood. 2001;97:3146-51.
16. Caligiuri M. Human natural killer cells. Blood. 2008;112:461-9.
17. 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.
18. Kuijpers T, Baars P, Dantin C, et al. Human NK cells can control CMV infection in the absence of T cells. Blood. 2008;112:914-5.
19. Sirianni M, Vincenzi L, Topino S, et al. NK cell activity controls human herpesvirus 8 latent infection and is restored upon highly active antiretroviral therapy in AIDS patients with regressing Kaposi's sarcoma. Eur J Immunol. 2002;32:2711-20.
20. Verhoeven D, de Hooge A, Mooiman E, et al. NK cells recognize and lyse Ewing sarcoma cells through NKG2D and DNAM-1 receptor dependent pathways. Mol Immunol. 2008;45:3917-25.
21. Biron C, Byron K, Sullivan J. Severe herpesvirus infections in an adolescent without natural killer cells. N Engl J Med. 1989;320:1731-5.
22. Lopez C, Kirkpatrick D, Read S, et al. Correlation between low natural killing of fibroblasts infected with herpes simplex virus type 1 and susceptibility to herpesvirus infections. J Infect Dis. 1983;147:1030-5.
23. Topham N, Hewitt E. Natural killer cell cytotoxicity: how do they pull the trigger? Immunology. 2009;128:7-15.
24. Zamai L, Ahmad M, Bennett I, et al. Natural killer (NK) cell-mediated cytotoxicity: differential use of TRAIL and Fas ligand by immature and mature primary human NK cells. J Exp Med. 1998;188:2375-80.
25. Montel A, Bochan M, Goebel W, Brahmi Z. Fas-mediated cytotoxicity remains intact in perforin and granzyme B antisense transfectants of a human NK-like cell line. Cell Immunol. 1995;165:312-7.
26. Lee R, Spielman J, Zhao D, Olsen K, Podack E. Perforin, Fas ligand, and tumor necrosis factor are the major cytotoxic molecules used by lymphokine-activated killer cells. J Immunol. 1996;157:1919-25.
27. Leibson P. Signal transduction during natural killer cell activation: inside the mind of a killer. Immunity. 1997;6:655-61.
28. Biassoni R. Human natural killer receptors, co-receptors, and their ligands. Curr Protoc Immunol. 2009;Chapter 14:Unit 14.10.
29. Moretta L, Bottino C, Pende D, Vitale M, Mingari MC, Moretta A. Human natural killer cells: Molecular mechanisms controlling NK cell activation and tumor cell lysis. Immunol Lett. 2005;100:7-13.
30. Gasser S, Raulet D. Activation and self-tolerance of natural killer cells. Immunol Rev. 2006;214:130-42.
31. Moretta L, Moretta A. Killer immunoglobulin-like receptors. Curr Opin Immunol. 2004;16:626-33.
32. Garrido F, Ruiz-Cabello F, Cabrera T, et al. Implications for immunosurveillance of altered HLA class I phenotypes in human tumours. Immunol Today. 1997;18:89-95.
33. Moretta L, Moretta A. Unravelling natural killer cell function: triggering and inhibitory human NK receptors. EMBO J. 2004;23:255-9.
34. Lanier L. NK cell recognition. Annu Rev Immunol. 2005;23:225-74.
35. Arnon T, Achdout H, Lieberman N, et al. The mechanisms controlling the recognition of tumor- and virus-infected cells by NKp46. Blood. 2004;103:664-72.
36. Obeidy P, Sharland A. NKG2D and its ligands. Int J Biochem Cell Biol. 2009;41:2364-7.
37. Arnon T, Lev M, Katz G, et al. Recognition of viral hemagglutinins by NKp44 but not by NKp30. Eur J Immunol. 2001;31:2680-9.
38. Mandelboim O, Lieberman N, Lev M, et al. Recognition of haemagglutinins on virus-infected cells by NKp46 activates lysis by human NK cells. Nature. 2001;409:1055-60.
39. Arnon T, Achdout H, Levi O, et al. Inhibition of the NKp30 activating receptor by pp65 of human cytomegalovirus. Nat Immunol. 2005;6: 515-23.
40. Brandt CS, Baratin M, Yi E, et al. The B7 family member B7-H6 is a tumor cell ligand for the activating natural killer cell receptor NKp30 in humans. J Exp Med. 2009;206:1495-503.
41. Pogge von Strandmann E, Simhadri VR, von Tresckow B, et al. Human leukocyte antigen-B-associated transcript 3 is released from tumor cells and engages the NKp30 receptor on natural killer cells. Immunity. 2007;27:965-74.
42. Lauzon N, Mian F, Ashkar A. Toll-like receptors, natural killer cells and innate immunity. Adv Exp Med Biol. 2007;598:1-11.
43. Lanier L. On guard--activating NK cell receptors. Nat Immunol. 2001; 2:23-7.
44. Walzer T, Dalod M, Robbins S, Zitvogel L, Vivier E. Natural-killer cells and dendritic cells: „l'union fait la force". Blood. 2005;106:2252-8.
45. Jonjic S, Babic M, Polic B, Krmpotic A. Immune evasion of natural killer cells by viruses. Curr Opin Immunol. 2008;20:30-8.
46. Loch S, Tampe R. Viral evasion of the MHC class I antigen-processing machinery. Pflugers Arch. 2005;451:409-17.
47. Lodoen M, Lanier L. Viral modulation of NK cell immunity. Nat Rev Microbiol. 2005;3:59-69.
48. Orange J, Fassett M, Koopman L, Boyson J, Strominger J. Viral evasion of natural killer cells. Nat Immunol. 2002;3:1006-12.
49. Koch J, Tampe R. The macromolecular peptide-loading complex in MHC class I-dependent antigen presentation. Cell Mol Life Sci. 2006;63:653-62.
50. Loch S, Klauschies F, Schölz C, et al. Signaling of a varicelloviral factor across the endoplasmic reticulum membrane induces destruction of the peptide-loading complex and immune evasion. J Biol Chem. 2008;283: 13428-36.
51. Cohen G, Gandhi R, Davis D, et al. The selective downregulation of class I major histocompatibility complex proteins by HIV-1 protects HIV-infected cells from NK cells. Immunity. 1999;10:661-71.
52. Schwartz O, Marechal V, Le Gall S, Lemonnier F, Heard J. Endocytosis of major histocompatibility complex class I molecules is induced by the HIV-1 Nef protein. Nat Med. 1996;2:338-42.
53. Le Gall S, Buseyne F, Trocha A, et al. Distinct trafficking pathways mediate Nef-induced and clathrin-dependent major histocompatibility complex class I down-regulation. J Virol. 2000;74:9256-66.
54. Bonaparte M, Barker E. Killing of human immunodeficiency virus-infected primary T-cell blasts by autologous natural killer cells is dependent on the ability of the virus to alter the expression of major histocompatibility complex class I molecules. Blood. 2004;104:2087-94.
55. Kloess S, Huenecke S, Piechulek D, et al. IL-2-activated haploidentical NK cells restore NKG2D-mediated NK-cell cytotoxicity in neuroblastoma patients by scavenging of plasma MICA. Eur J Immunol. 2010;40: 3255-67.

56. Cerboni C, Neri F, Casartelli N, et al. Human immunodeficiency virus 1 Nef protein downmodulates the ligands of the activating receptor NKG2D and inhibits natural killer cell-mediated cytotoxicity. J Gen Virol. 2007;88:242-50.
57. Wyatt R, Sodroski J. The HIV-1 envelope glycoproteins: fusogens, antigens, and immunogens. Science. 1998;280:1884-8.
58. Vivier E, Tomasello E, Baratin M, Walzer T, Ugolini S. Functions of natural killer cells. Nat Immunol. 2008;9:503-10.
59. Huber M, Trkola A. Humoral immunity to HIV-1: neutralization and beyond. J Intern Med. 2007;262:5-25.
60. Khayat D, Soubrane C, Andrieu J, et al. Changes of soluble CD16 levels in serum of HIV-infected patients: correlation with clinical and biologic prognostic factors. J Infect Dis. 1990;161:430-5.
61. Andre P, Brunet C, Guia S, et al. Differential regulation of killer cell Ig-like receptors and CD94 lectin-like dimers on NK and T lymphocytes from HIV-1-infected individuals. Eur J Immunol. 1999;29:1076-85.
62. Galiani M, Aguado E, Tarazona R, et al. Expression of killer inhibitory receptors on cytotoxic cells from HIV-1-infected individuals. Clin Exp Immunol. 1999;115:472-6.
63. Mavilio D, Benjamin J, Daucher M, et al. Natural killer cells in HIV-1 infection: dichotomous effects of viremia on inhibitory and activating receptors and their functional correlates. Proc Natl Acad Sci USA. 2003; 100:15011-6.
64. De Maria A, Fogli M, Costa P, et al. The impaired NK cell cytolytic function in viremic HIV-1 infection is associated with a reduced surface expression of natural cytotoxicity receptors (NKp46, NKp30 and NKp44). Eur J Immunol. 2003;33:2410-8.
65. Kottilil S, Shin K, Planta M, et al. Expression of chemokine and inhibitory receptors on natural killer cells: effect of immune activation and HIV viremia. J Infect Dis. 2004;189:1193-8.
66. Alter G, Malenfant J, Delabre R, et al. Increased natural killer cell activity in viremic HIV-1 infection. J Immunol. 2004;173:5305-11.
67. Ahmad R, Sindhu ST, Tran P, et al. 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.
68. Sirianni MC, Ensoli F, Alario C, et al. Distribution of the natural killer-related receptor for HLA-C during highly active antiretroviral therapy for human immunodeficiency virus infection. Hum Immunol. 2001;62: 1328-34.
69. Mavilio D, Lombardo G, Kinter A, et al. Characterization of the defective interaction between a subset of natural killer cells and dendritic cells in HIV-1 infection. J Exp Med. 2006;203:2339-50.
70. Tasca S, Tambussi G, Nozza S, et al. Escape of monocyte-derived dendritic cells of HIV-1 infected individuals from natural killer cell-mediated lysis. AIDS. 2003;17:2291-8.
71. Vieillard V, Strominger J, Debre P. NK cytotoxicity against CD4+ T cells during HIV-1 infection: a gp41 peptide induces the expression of an NKp44 ligand. Proc Natl Acad Sci USA. 2005;102:10981-6.
72. Vieillard V, Habib RE, Brochard P, et al. CCR5 or CXCR4 use influences the relationship between CD4 cell depletion, NKp44L expression and NK cytotoxicity in SHIV-infected macaques. AIDS. 2008; 22:185-92.
73. Schuitemaker H, Koot M, Kootstra N, et al. Biological phenotype of human immunodeficiency virus type 1 clones at different stages of infection: progression of disease is associated with a shift from monocytotropic to T-cell-tropic virus population. J Virol. 1992;66:1354-60.
74. Sattentau Q, Moore J. Conformational changes induced in the human immunodeficiency virus envelope glycoprotein by soluble CD4 binding. J Exp Med. 1991;174:407-15.
75. Weissenhorn W, Dessen A, Harrison S, Skehel J, Wiley D. Atomic structure of the ectodomain from HIV-1 gp41. Nature. 1997;387:426-30.
76. Garg H, Blumenthal R. Role of HIV Gp41 mediated fusion/hemifusion in bystander apoptosis. Cell Mol Life Sci. 2008;65:3134-44.
77. Perfettini JL, Castedo M, Roumier T, et al. Mechanisms of apoptosis induction by the HIV-1 envelope. Cell Death Differ. 2005;12(Suppl 1):916-23.
78. Fausther-Bovendo H, Vieillard V, Sagan S, Bismuth G, Debre P. HIV gp41 engages gC1qR on CD4+ T cells to induce the expression of an NK ligand through the PIP3/H2O2 pathway. PLoS Pathog. 2010; 6:e1000975.
79. Biswas AK, Hafiz A, Banerjee B, et al. Plasmodium falciparum uses gC1qR/HABP1/p32 as a receptor to bind to vascular endothelium and for platelet-mediated clumping. PLoS Pathog. 2007;3:1271-80.
80. Braun L, Ghebrehiwet B, Cossart P. gC1q-R/p32, a C1q-binding protein, is a receptor for the InlB invasion protein of Listeria monocytogenes. Embo J. 2000;19:1458-66.
81. Choi Y, Kwon Y, Kim S, et al. A hantavirus causing hemorrhagic fever with renal syndrome requires gC1qR/p32 for efficient cell binding and infection. Virology. 2008;381:178-83.
82. Ghebrehiwet B, Peerschke E. cC1q-R (calreticulin) and gC1q-R/p33: ubiquitously expressed multi-ligand binding cellular proteins involved in inflammation and infection. Mol Immunol. 2004;41:173-83.
83. Kittlesen D, Chianese-Bullock K, Yao Z, Braciale T, Hahn Y. Interaction between complement receptor gC1qR and hepatitis C virus core protein inhibits T-lymphocyte proliferation. J Clin Invest. 2000;106:1239-49.
84. Nguyen T, Ghebrehiwet B, Peerschke E. Staphylococcus aureus protein A recognizes platelet gC1qR/p33: a novel mechanism for staphylococcal interactions with platelets. Infect Immun. 2000;68:2061-8.
85. Vieillard V, Costagliola D, Simon A, Debre P. Specific adaptive humoral response against a gp41 motif inhibits CD4 T-cell sensitivity to NK lysis during HIV-1 infection. AIDS. 2006;20:1795-804.
86. Vieillard V, Le Grand R, Dausset J, Debre P. A vaccine strategy against AIDS: an HIV gp41 peptide immunization prevents NKp44L expression and CD4+ T cell depletion in SHIV-infected macaques. Proc Natl Acad Sci USA. 2008;105:2100-4.
87. Dorner B, Smith H, French A, et al. Coordinate expression of cytokines and chemokines by NK cells during murine cytomegalovirus infection. J Immunol. 2004;172:3119-31.
88. Fehniger T, Herbein G, Yu H, et al. Natural killer cells from HIV-1+ patients produce C-C chemokines and inhibit HIV-1 infection. J Immunol. 1998;161:6433-8.
89. Oliva A, Kinter A, Vaccarezza M, et al. Natural killer cells from human immunodeficiency virus (HIV)-infected individuals are an important source of CC-chemokines and suppress HIV-1 entry and replication in vitro. J Clin Invest. 1998;102:223-31.
90. Kottilil S, Chun T, Moir S, et al. Innate immunity in human immunodeficiency virus infection: effect of viremia on natural killer cell function. J Infect Dis. 2003;187:1038-45.
91. Azzoni L, Papasavvas E, Chehimi J, et al. Sustained impairment of IFN-gamma secretion in suppressed HIV-infected patients despite mature NK cell recovery: evidence for a defective reconstitution of innate immunity. J Immunol. 2002;168:5764-70.
92. Goodier M, Imami N, Moyle G, Gazzard B, Gotch F. Loss of the CD56hiCD16- NK cell subset and NK cell interferon-gamma production during antiretroviral therapy for HIV-1: partial recovery by human growth hormone. Clin Exp Immunol. 2003;134:470-6.
93. Lucia MB, Froio N, Tacconelli E, et al. CD16+CD56+CD8+ natural killer (NK) cells are decreased during HIV infection. Eur J Histochem. 1997;41(Suppl 2:197-8.
94. Alter G, Teigen N, Davis B, et al. Sequential deregulation of NK cell subset distribution and function starting in acute HIV-1 infection. Blood. 2005;106:3366-9.
95. Mavilio D, Lombardo G, Benjamin J, et al. Characterization of CD56-/CD16+ natural killer (NK) cells: a highly dysfunctional NK subset expanded in HIV-infected viremic individuals. Proc Natl Acad Sci USA. 2005;102:2886-91.
96. Hu P, Hultin L, Hultin P, et al. Natural killer cell immunodeficiency in HIV disease is manifest by profoundly decreased numbers of CD16+CD56+ cells and expansion of a population of CD16dimCD56- cells with low lytic activity. J Acquir Immune Defic Syndr Hum Retrovirol. 1995;10:331-40.
97. Levy J. HIV pathogenesis: knowledge gained after two decades of research. Adv Dent Res. 2006;19:10-6.
98. Shalekoff S, Pendle S, Johnson D, Martin D, Tiemessen C. Distribution of the human immunodeficiency virus coreceptors CXCR4 and CCR5 on leukocytes of persons with human immunodeficiency virus type 1 infection and pulmonary tuberculosis: implications for pathogenesis. J Clin Immunol. 2001;21:390-401.
99. Valentin A, Rosati M, Patenaude D, et al. Persistent HIV-1 infection of natural killer cells in patients receiving highly active antiretroviral therapy. Proc Natl Acad Sci USA. 2002;99:7015-20.
100. Bernstein H, Wang G, Plasterer M, et al. CD4+ NK cells can be productively infected with HIV, leading to downregulation of CD4 expression and changes in function. Virology. 2009;387:59-66.
101. Robertson M. Role of chemokines in the biology of natural killer cells. J Leukoc Biol. 2002;71:173-83.
102. Chehimi J, Bandyopadhyay S, Prakash K, et al. In vitro infection of natural killer cells with different human immunodeficiency virus type 1 isolates. J Virol. 1991;65:1812-22.
103. Scott-Algara D, Vuillier F, Cayota A, et al. In vitro non-productive infection of purified natural killer cells by the BRU isolate of the human immunodeficiency virus type 1. J Gen Virol. 1993;74 (Pt 4):725-31.
104. Bernstein HB, Plasterer MC, Schiff S, et al. CD4 expression on activated NK cells: ligation of CD4 induces cytokine expression and cell migration. J Immunol. 2006;177:3669-76.
105. Harada H, Goto Y, Ohno T, Suzu S, Okada S. Proliferative activation up-regulates expression of CD4 and HIV-1 co-receptors on NK cells and induces their infection with HIV-1. Eur J Immunol. 2007;37:2148-55.
106. Fogli M, Costa P, Murdaca G, et al. Significant NK cell activation associated with decreased cytolytic function in peripheral blood of HIV-1-infected patients. Eur J Immunol. 2004;34:2313-21.
107. Flamand L, Crowley RW, Lusso P, et al. Activation of CD8+ T lymphocytes through the T cell receptor turns on CD4 gene expression: implications for HIV pathogenesis. Proc Natl Acad Sci USA. 1998;95:3111-6.
108. Kitchen S, Korin Y, Roth M, Landay A, Zack J. Costimulation of naive CD8(+) lymphocytes induces CD4 expression and allows human immunodeficiency virus type 1 infection. J Virol. 1998;72:9054-60.

109. Yang LP, Riley JL, Carroll R, et al. Productive infection of neonatal CD8+ T lymphocytes by HIV-1. J Exp Med. 1998;187:1139-44.
110. Chen B, Gandhi R, Baltimore D. CD4 down-modulation during infection of human T cells with human immunodeficiency virus type 1 involves independent activities of vpu, env, and nef. J Virol. 1996; 70:6044-53.
111. Chaudhary P, Mechetner E, Roninson I. Expression and activity of the multidrug resistance P-glycoprotein in human peripheral blood lymphocytes. Blood. 1992;80:2735-9.
112. Fausther-Bovendo H, Sol-Foulon N, Candotti D, et al. HIV escape from natural killer cytotoxicity: nef inhibits NKp44L expression on CD4+ T cells. AIDS. 2009;23:1077-87.
113. Quaranta M, Camponeschi B, Straface E, Malorni W, Viora M. Induction of interleukin-15 production by HIV-1 nef protein: a role in the proliferation of uninfected cells. Exp Cell Res. 1999;250:112-21.
114. Pugliese A, Vidotto V, Beltramo T, Torre D. Regulation of interleukin-18 by THP-1 monocytoid cells stimulated with HIV-1 and Nef viral protein. Eur Cytokine Netw. 2005;16:186-90.
115. Carroll I, Wang J, Howcroft T, Singer D. HIV Tat represses transcription of the beta 2-microglobulin promoter. Mol Immunol. 1998;35:1171-8.
116. Ito M, Ishida T, He L, et al. HIV type 1 Tat protein inhibits interleukin 12 production by human peripheral blood mononuclear cells. AIDS Res Hum Retroviruses. 1998;14:845-9.
117. Ambrosino C, Ruocco M, Chen X, et al. HIV-1 Tat induces the expression of the interleukin-6 (IL6) gene by binding to the IL6 leader RNA and by interacting with CAAT enhancer-binding protein beta (NF-IL6) transcription factors. J Biol Chem. 1997;272:14883-92.
118. Poggi A, Zocchi M. HIV-1 Tat triggers TGF-beta production and NK cell apoptosis that is prevented by pertussis toxin B. Clin Dev Immunol. 2006;13:369-72.
119. Reinhold D, Wrenger S, Kahne T, Ansorge S. HIV-1 Tat: immunosuppression via TGF-beta1 induction. Immunol Today. 1999;20:384-5.
120. Zauli G, Furlini G, Re M, et al. Human immunodeficiency virus type 1 (HIV-1) tat-protein stimulates the production of interleukin-6 (IL-6) by peripheral blood monocytes. New Microbiol. 1993;16:115-20.
121. Kerkau T, Bacik I, Bennink J, et al. The human immunodeficiency virus type 1 (HIV-1) Vpu protein interferes with an early step in the biosynthesis of major histocompatibility complex (MHC) class I molecules. J Exp Med. 1997;185:1295-305.
122. Ward J, Davis Z, DeHart J, et al. HIV-1 Vpr triggers natural killer cell-mediated lysis of infected cells through activation of the ATR-mediated DNA damage response. PLoS Pathog. 2009;5:e1000613.
123. Shah A, Sowrirajan B, Davis Z, et al. Degranulation of natural killer cells following interaction with HIV-1-infected cells is hindered by downmodulation of NTB-A by Vpu. Cell Host Microbe. 2010;8:397-409.
124. Martini F, Agrati C, D'Offizi G, Poccia F. HLA-E up-regulation induced by HIV infection may directly contribute to CD94-mediated impairment of NK cells. Int J Immunopathol Pharmacol. 2005;18:269-76.
125. Nattermann J, Nischalke H, Hofmeister V, et al. HIV-1 infection leads to increased HLA-E expression resulting in impaired function of natural killer cells. Antivir Ther. 2005;10:95-107.
126. Borghi P, Fantuzzi L, Varano B, et al. Induction of interleukin-10 by human immunodeficiency virus type 1 and its gp120 protein in human monocytes/macrophages. J Virol. 1995;69:1284-7.