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Natural Killer cells in HIV-1 infection and therapy

Joanna Mikulak[1,2], **Ferdinando Oriolo**[1], **Elisa Zaghi**[1], **Clara Di Vito**[1], and **Domenico Mavilio**[1,3]

[1]Unit of Clinical and Experimental Immunology, Humanitas Clinical and Research Center, Rozzano, Milan, Italy

[2]Istituto di Ricerca Genetica e Biomedica, UOS di Milano, Consiglio Nazionale delle Ricerche (UOS/IRGB/CNR), Rozzano, Milan, Italy

[3]Department of Medical Biotechnologies and Translational Medicine (BioMeTra), University of Milan, Rozzano, Milan, Italy

Abstract

Natural killer (NK) cells are important effectors of innate immunity playing a key role in the eradication and clearance of viral infections. Over the recent years, several studies have shown that HIV-1 pathologically changes NK cell homeostasis and hampers their antiviral effector functions. Moreover, high levels of chronic HIV-1 viremia markedly impair those NK cell regulatory features that normally regulate the cross-talks between innate and adaptive immune responses. These pathogenic events take place early in the infection and are associated with a pathologic redistribution of NK cell subsets that includes the expansion of anergic CD56^{neg} NK cells with an aberrant repertoire of activating and inhibitory receptors. Nevertheless, the presence of specific haplotypes for NK cell receptors as well as the engagement of NK cell antibody dependent cell cytotocity (ADCC) have been reported to control HIV-1 infection. This dichotomy can be extremely useful to both predict the clinical outcome of the infection and to develop alternative anti-viral pharmacological approaches. Indeed, the administration of antiretroviral therapy (ART) in HIV-1 infected patients restores NK cell phenotype and functions to normal levels. Thus, ART can help to develop NK cell-directed therapeutic strategies that include the use of broadly neutralizing antibodies and toll like receptor agonists. The present review discusses how our current knowledge of NK cell pathophysiology in HIV-1 infection is being translated both in experimental and clinical trials aimed at controlling the infection and disease.

Keywords

HIV-1; NK cell; pathogenesis; anti-HIV-1 therapy

Corresponding author: Domenico Mavilio, M.D., Ph.D., Unit of Clinical and Experimental Immunology, Department of Medical Biotechnologies and Translational Medicine, University of Milan School of Medicine, Humanitas Clinical and Research Center, Via Alessandro Manzoni, 113, Rozzano (Milan), Italy., Phone: +39-02.8224.5157, FAX: +39-02.8224.5191, domenico.mavilio@unimi.it.

Conflict of Interest

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Introduction

Natural Killer (NK) cells are innate lymphoid cells that provide an extended surveillance against tumor-transformed or viral-infected cells in the absence of antigen specificity [1–4]. These cells are endowed with immune-modulatory functions that regulate and link innate and adaptive immune responses via the secretion of chemokines/cytokines and by undertaking synergic cross-talks affecting the maturation and function of antigen-presenting cells (APCs) [5–7]. Under homeostatic conditions, NK cells account for up to 5–15% of all circulating lymphocytes and are divided into two distinct populations on the basis of the surface expression of CD56 and CD16 [8]. The $CD56^{bright}/CD16^{neg}$ (termed $CD56^{bright}$ in this review) NK cell subset represent approximately 5–10 % of the whole population and mainly exerts important regulatory functions [i.e. production of soluble mediators such as interferon (IFN)-γ, tumor necrosis factor (TNF)-α and establishment of cellular interplays]. Conversely, $CD56^{dim}/CD16^{neg}$ ($CD56^{dim}$) NK cells (up to 90%) are primarily cytotoxic effectors eradicating tumor-transformed and viral-infected cell targets, but can also produce IFN-γ following activation [8, 9]. Moreover, unique subsets of human NK cells have been described in peripheral tissues where inflammation occurs and where the early innate immune responses pave the way for the subsequent priming of adaptive immunity. The tissue-specific human NK cell populations often carry phenotypic hallmarks that distinguish them from their circulating counterparts. These NK cells are present under homeostatic conditions in both secondary lymphoid organs [10, 11] and non-lymphoid organs such as healthy skin, gut, liver, lungs, and uterus [12, 13].

The effector functions of NK cells are controlled by a large family of NK cell receptors (NKRs), whose engagement is finely tuned by a dynamic balance between inhibitory and activating signals [14, 15]. Indeed, autologous cells are normally spared from NK cell killing via the engagement of inhibitory NKRs (iNKRs) [i.e. inhibitory Killer Ig-like receptors (iKIRs) and the C-type lectin receptors such as NKG2A] that recognize alleles of the major histocompatibility complex class I (MHC-I) (Table 1). The lack (i.e. allogeneic conditions or tumor transformation) or down-modulation (i.e. viral infections) of MHC-I expression lead to NK cell killing of cellular targets via the engagement of another family of activating NKRs (aNKRs) [i.e. Natural Cytotoxicity Receptors (NCRs) NKp30, NKp46 and NKp44, activating KIRs (aKIRs) and C-type lectin receptors such as NKG2D and NKG2C]. The latter bind to their putative ligands on stressed, viral-infected or cancer cells [16, 17]. This phenomenon is well known as the “missing self hypothesis” and explains the ability of NK cells to perform an optimal immune surveillance that malignant or virally transformed targets while sparing healthy cells [18, 19].

The dynamic balance between iNKRs and aNKRs regulate both NK cell effector functions that can employ different mechanisms for clearance of cellular targets: (i) exocytosis of cytotoxic granules containing perforin and granzymes that leads to cell lysis; (ii) signaling through TNF family death receptors such as FasL or TRAIL; (iii) production and secretion of pro-inflammatory cytokines with strong anti-viral and anti-tumor activities; and (iv) antibody-dependent cellular cytotoxicity (ADCC) occurring when the Fc portion of antibodies opsonizing target cells binds to the Fcγ receptor III on NK cells (FcγRIII or

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CD16). This binding then activates a downstream signal pathways ending with cytokine release, degranulation and cytotoxicity.

This review discusses the impact of HIV-1 replication on NK cell homeostasis and function as well as the clinical and therapeutic insights that these innate effector cells can exert on the natural history of HIV-associated disease.

NK cells and HIV-1 pathogenesis

Effects of HIV-1 viremia on NK cell homeostasis and phenotype

Frequencies, phenotypes and functions of NK cells are highly affected by HIV-1 viremia and undergo pathologic changes as disease progresses toward its chronic phases (Figure 1). Indeed, the absolute number of circulating NK cells first increases in the acute phase of HIV-1 infection due to the expansion of the $CD56^{dim}$ NK subset and the decreased frequency of the $CD56^{bright}$ NK cell population [20]. While the overall frequency of circulating NK cells appears to be restored as soon as HIV-1 infection enters in its chronic stage, the distribution of their different subsets undergo a pathological redistribution that deeply affects the overall NK cell anti-viral activity [21]. In particular, ongoing viral replication induces the expansion of a dysfunctional $CD56^{neg}/CD16^{pos}$ ($CD56^{neg}$) NK cell subset that counteracts the decrease of the cytotoxic $CD56^{dim}$ cells. Under homeostatic condition and in the absence of other viral infections, this population of $CD56^{neg}$ NK cells is either not detectable or present at very low frequency [21–29]. The distribution and activation of NK cell subsets is relevant also in the context of mother-to-child HIV-1 transmission as they influence the susceptibility to perinatal infection [30].

The down-modulation of CD56 is not the only NK surface marker altered by HIV-1 viremia. The expressions as well as the functional relevance of several aNKRs and iNKRs are pathologically modified by high levels of viral replication [22, 25, 31–38]. $CD56^{neg}$ NK cells expanded in HIV-1 infected patients express high levels of iNKRs and low levels of aNKRs, a condition that leads to a defective control of viral replication and to disease progression (Table 1) [4, 39]. The HIV-1-induced changes in the NK cell expression of CD56 and NKRs require a chronic exposure to the virus [25]. The only exception to this rule is represented by Siglec-7, a iNKRs constitutively expressed on the majority of NK cells. It is highly sensitive to HIV-1 viremia in the earliest phases of the infection and is down-modulated on the surface of NK cells in HIV-1 infected patients before CD56 [40–42]. This phenomenon makes it possible to identify two distinct subsets characterizing different stages of the disease: the $Siglec\text{-}7^{neg}/CD56^{dim}$ NK cells only present in the early stages of HIV-1 infection and the $Siglec\text{-}7^{neg}/CD56^{neg}$ NK cells that become detectable several months later in the chronic state of the disease.

All these HIV-1-induced phenotypic changes are reversible following the administration of a successful antiretroviral therapy (ART) under which the restoration of Siglec-7 expression on NK cells is much faster compared to that of CD56 and the NKRs. The impact of viral replication in inducing these phenotypic abnormalities has also been confirmed by experimental evidence. NK cells from those HIV-1 infected patients with a low/undetectable levels of viral replication that do not progress to AIDS (i.e. long-term non progressors or

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LTNP) are similar and undistinguishable from the ones from uninfected healthy individuals [40]. These NK cell features in response to viral exposure make it possible to easily monitor the clinical outcome and progression of the infection. Furthermore, they can also be used to assess the adherence and the efficacy of ART (Table 1).

Human cytomegalovirus (HCMV) is a major cause of co-morbidity in patients with HIV-1 infection and is associated with the expansion of NK cell subset expressing NKG2C [4, 43]. This phenotypic feature, together with the HIV-1-mediated down-modulation of NKG2A, pathologically reverses the ratio of NKG2A/NKG2C on NK cells in HIV-1 and co-infected with HCMV-infected patients [44]. Interestingly, HCMV infection is also associated with an epigenetic diversification of NK cells, thus demonstrating that these innate lymphocytes can be reprogrammed in response to this pathogen [45, 46]. An additional NK cell subset lacking the aNKR FcRy is expanded in chronically HIV-1 infected individuals. Similar to what it has been observed with HCMV-induced NK cells, this latter population expresses low levels of NKp30 and is endowed with remarkably high ADCC activity [47]. Taken together, these data indicate that NK cells from HIV and HCMV co-infected patients have unique immunologic features that can be potentially targeted for developing anti-viral therapeutic approaches.

Effects of HIV-1 viremia on NK cell effector-functions

The long exposure to HIV-1 viremia and the prolonged cellular activation represent the major factors likely driving the expansion of then “exhausted” and “functional compromised” $CD56^{neg}$ NK cell subset. However, a direct correlation between NK cell activation and disease progression remains controversial and depends on the patient’s disease state [48–51]. Different activation markers have been tested to monitor NK cells in HIV-1 infected patients and one study reported no correlation between NK cell activation and disease progression [49]. Yet, other groups have shown that levels of expression of CD38 and HLA-DR on $CD56^{dim}$ NK cells are associated with progression to AIDS, high plasma viral load and low $CD4^{+}$ T cell count [50, 52]. Moreover, CD38 and HLA-DR have been reported not to be increased in expression on NK cells from HIV-1 elite controllers (ECs), a rare group of healthy individuals who are able to naturally control viremia as well as to maintain low levels of innate immune activation similar to those of uninfected individuals [50].

Chronic HIV-1 infection also causes a defect in NKG2D-mediated NK cell killing due to the reduced expression on HIV-1 infected $CD4^{+}$ T cells of the NKG2D-ligand MIC-A. Instead, it is present at high level in the plasma of HIV-1 infected individuals [25, 53]. This finding explains, at least in part, the poor NK cell-mediated clearance of HIV-1 endogenously infected CD4+ T cells [39] and transformed cell targets [21]. Such aberrancies limit NK cell immune surveillance and allow the development of opportunistic infections and cancers. Another aNKR involved in the lysis of HIV-1-infected autologous $CD4^{+}$ T cells is the NCR NKp44 [54, 55]. Indeed, the surface expression of NKp44 ligand on HIV-1 infected $CD4^{+}$ T cells is induced by the viral protein gp41 and could theoretically induce NKp44-mediated killing. Hence, as suggested by some studies, this mechanism could be involved in the $CD4^{+}$ T cell depletion in HIV-1 infection and in the impaired immunologic recovery in ART

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treated patients [55–57]. However, this possibility does not represent the main pathogenic event associated with the drastic reduction of CD4+ T cell count in advanced HIV-1 infection: the expression levels of NKp44 on NK cells from viremic HIV-1 infected patients is very low, if not undetectable, even after *in vitro* stimulation [22, 25].

Pathologic CD56^{neg} NK cells are also defective in the production and secretion of important immune regulatory cytokines such as IFN-γ, TNF-α and Granulocyte-macrophage colony-stimulating factor (GM-CSF) [20, 25]. These latter NK cell dysfunctions have a strong negative impact on their interplay with autologous DCs. In fact, the expansion of CD56^{neg} NK cells in chronic HIV-1 infection is associated with: *i)* a reduced ability of NK cells to induce an optimal maturation of autologous DCs; *ii)* an impaired NK cell-mediated clearance of HIV-1 infected and immature DCs (iDCs); *iii)* the lack of T cell priming against HIV-1; and *iv)* the infection of CD4+ T cells through a mechanism associated with cellular interactions with HIV-1 infected and aberrant mature DCs (mDCs) [58, 59]. In turn, dysfunctional and HIV-1 infected mDCs fail to secrete adequate amounts of important regulatory factors such as IFN-α and interleukin (IL)-15. The lack of these important cytokines limits the priming of NK cells that then fail to kill HIV-1-infected CD4+ T cells through NKp46- and NKG2D-mediated signaling [60, 61]. However, it is not clear if these phenotypic and functional abnormalities of NK cells are due to the direct effect of HIV-1 on NK cells or are rather associated with the establishment of chronic inflammation affecting the homeostasis of the immune system. In this regard, NK cells express HIV-1 receptor and co-receptors such as CD4, CXCR4/CCR5 and Siglec-7 [42, 62–64], thus implying that a direct interaction between NK cells and HIV-1 occurs. However, controversial results were obtained regarding the susceptibility of NK cells to be targeted by HIV-1 since the existence of both viral latency and productive HIV-1 infection of human NK cells has never been demonstrated ex-vivo [22] but only in-vitro [62, 63].

Another strategy employed by HIV-1 to escape NK cell response is the Nef- and Vpu-induced down-modulation of poliovirus receptor (PVR or CD155) on infected CD4^{pos} cells. PVR is the cognate ligand of the DNAM-1 (CD226), an aNKR constitutively expressed on all NK cells and whose engagement to activate NK cell killing is impaired by the HIV-1 induced decreased binding with CD155 [65]. Vpu accessory protein can also down-modulate NTB-A co-activation receptor ligands, thus further contributing to hamper NK-cell-mediated clearance of HIV-1 infected targets [66, 67]. Finally, the expansion of highly defective CD56^{neg} NK cell has been also associated with the decreased expression of CD161, a aNKR receptor inducing proliferation and differentiation of NK cells [68].

NK cells also actively participate in the control of viral replication by releasing β-chemokines. In particular, they are an important source of the chemokines CCL3, CCL4 and CCL5 that represent the ligands for the co-receptor CCR5. Hence, the NK cell production of these β-chemokines could inhibit the entry of HIV-1 in the target cells by preventing the binding of CCR5 with viral envelope [21]. This effector function is highly impaired in active and chronic HIV-1 infection as NK cells from these viremic patients secrete low amount of these β-chemokines [69].

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An additional mechanism by which NK cells eliminate virus-infected cell targets is antibody (ab)-dependent cell cytotoxicity (ADCC) [70, 71]. High levels of anti-HIV-1 Abs inducing ADCC are associated with slower disease progression [72–74] and with the control of HIV-1 infection in ECs [75]. Nevertheless, the role of NK cell-mediated ADCC in the pathogenesis of HIV-1 remains controversial. A few studies have shown that NK cells in HIV-1-infected patients remain capable of mediating ADCC [76, 77], an activity that have been also reported to be specifically directed against Env, Pol, Vpu and Tat proteins [78, 79]. This NK cell recognition of HIV-1 via ADCC might also lead to viral escape in the presence of particular epitopes associated with protein variants [80]. Other reports demonstrated that "exhausted" NK cells in chronic HIV-1 infection express lower levels of CD16 together with an impaired downstream signal pathway of this FcγRIII[49, 81]. This down-regulation of CD16 occurs through a mechanism mediated by matrix metallo-proteinases (MMPs) in an anti-HIV-1 antibody-dependent manner [82, 83]. Notably, studies performed in ECs and LTNPs have shown a degree of NK cell-mediated ADCC similar to that of healthy individuals [56, 84].

NK cell-mediated control of HIV-1 infection

NK cell tolerance toward autologous cells expressing "self" MHC-I molecules is regulated by a mechanism known as NK cell "licensing". This process induces a proper terminal differentiation of NK cells from their precursor and requires the correct binding between iNKRs with specific self-HLA alleles representing their cognate ligands. The absence of these interactions affects the hypo-responsive state of NK cells and lead to the onset of auto-reactive clones [85–87]

Epidemiological studies showed that distinct genetic associations between KIRs expressed on NK cells and their specific HLA haplotypes on target cells influence the clinical outcomes of HIV-1 infection. More specifically, the presence of *KIR3DS1* combined with *HLA-Bw4-I80* allele in patients with chronic HIV-1 infection has a protective effect and is associated with lower viral load, slower decline of $CD4^{+}$ T cell count and delayed progression to AIDS [61, 88–90]. This epidemiological evidence has been also confirmed *in vitro* with *e*xperiments showing that $KIR3DS1^{pos}$ NK cells strongly inhibit HIV-1 replication in target cells expressing the HLA-Bw4-I80 allele [91]. This KIR3DS1 recognition of HLA-Bw4 is peptide-dependent, thus further demonstrating that changes in the peptide repertoire associated with viral infection provide a trigger for the engagement of this activating KIR and for the subsequent NK cell activation [92]. Also, the *KIR3DL1*h* allotype, the inhibitory counterpart of *KIR3DS1* characterized by an increased expression of this KIR, is associated with a reduced risk of HIV-1 infection in individuals expressing the *HLA-B*57* allele [93]. However, other studies suggest that differences in the KIR/HLA combination may play a dual role by being either a positive or a negative prognostic factor in the clinical outcome of HIV-1 infection [94–97]. In any case, the binding of KIRs with their cognate ligands certainly impact the natural history of HIV-1 disease as confirmed by the natural resistance to infection of those HIV-1 exposed but seronegative sex workers showing KIR2DL2/KIR2DL3 heterozygosity in the absence of HLA-C1 and KIR3DL1 homozygosity in the absence of HLA-Bw4 [98].

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MHC-I complex represents a natural target for HIV-1 proteins such as Nef, Vpu and Tat that induce the down-regulation of HLA-I molecules to avoid immune-surveillance [99–101]. On the other side, this mechanism of viral immune evasion might enhance the ability of NK cells to eliminate HIV-1 infected cells. In particular, the HIV-1-induced down-modulation of HLA-C, a MHC-I locus extensively interacting with the several inhibitory KIRs expressed by NK cells [102], can increase NK cell-mediated clearance of viral infected targets.

"Memory-like" NK cells in HIV-1 infection

A recent major advance in the field has been the identification of NK cells with adaptive immune traits. These long-living NK cells with specific "memory-like" features were first described in mice responding to a variety of antigens [103]. Only recently, a human $CD57^{pos}/KIRs^{pos}/NKG2C^{pos}$ "memory-like" NK cell subset showing increased effector functions when re-encountering viral antigens or following a proper activation with pro-inflammatory cytokines has been identified [44, 104–108]. The existence of antigen-specific NK cells has been recently reported also in rhesus macaques infected with simian or the simian/ human immunodeficiency virus (SIV/*SHIV*). These "memory-like" NK cells showed an antigen specificity towards Gag- and Env- viral proteins loaded on autologus DCs in an NKG2-dependent manner [109]. Notably, the recall of these adaptive traits of NK cells was associated with a high degree of cytotoxicity in animals vaccinated 5 years earlier with Ad26 (adenovirus 26 vectored SIV vaccine). Thus, this phenomenon likely lasts for quite a long time. Although very promising, this observation lacks direct evidence of NK cell memory responses in humans and, therefore, still remains an important and challenging aspect of NK cell biology in the context of viral infectioms.

NK cells and antiretroviral therapy

The main clinical milestone in the medical management of HIV-1 infection has been the introduction of therapeutic approaches using simultaneously different pharmaceutical compounds that dramatically suppress viral replication and reduce the plasma HIV-1 viral load to undetectable levels. Currently, even with salvage therapy, up to 90% of HIV-1-infected adults treated with these therapies become "aviremic", meaning that their viral RNA plasma levels is below the limits of detection with the most sensitive clinical assays (<50 RNA copies/mL) [110]. To date, the armamentarium available to physicians for the treatment of HIV-1 includes six different type of antiviral drugs: (1) nucleoside-analog reverse transcriptase inhibitors (NNRTIs), (2) non–nucleoside reverse transcriptase inhibitors (NNRTIs), (3) integrase inhibitors, (4) protease inhibitors (PIs), (5) fusion inhibitors, and (6) co-receptor antagonists [111]. Although requiring a patients' strong adherence to a life-long treatment with at least 3 of the above-mentioned anti-viral drugs. This anti-retroviral therapy (ART) is able to suppress viral replication for decades. It is also able to bring about the reconstitution of the immune system as measured by the increase in circulating $CD4^+$ T lymphocytes [112, 113].

The control of HIV-1 viremia by ART also leads to recovery of NK cells with cytotoxicity against tumor cell targets (Table 1) [21, 40, 114]. These studies have shown that both ART and the *in vivo* administration of IL-2 partially restore NK cell distribution and function [23,

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25, 40, 115, 116]. The positive effect of this therapy is also beneficial for DCs that acquire again the ability to undergo a proper maturation and to secrete those cytokines (i.e. IL-12, -15 and -18) required to prime NK cells and their production of IFN-γ [58]. In this regard, it has been reported that the "*recontitutio ad integrum*" of both NK cell phenotype and effector functions in HIV-1 infected patients requires not only viral suppression, but also the presence of properly functioning plasmacytoid DCs [117]. In addition, stimulation in vitro with IL-15 is able to rescue NK cells from apoptosis, enhanced proliferation and functional activity in HIV-1 patients not on ART [118, 119].

ART also targets the defective NK cell-mediated ADCC in HIV-1 infection. In fact, although the ability of plasma anti-HIV-1 Abs to mediate ADCC decreases under ART, probably due to the lack of antigen stimulation, NK cell-mediated ADCC improves soon after the administration of the therapy. Indeed, the earlier ART is administered to HIV-1-infected patients, the more pronounced is the recovery of NK cell-mediated ADCC. This immune response reaches its highest peak if the antiviral treatment starts prior to sero-conversion and/or when the $CD4^+$ T cell counts is above 350 cells/μl [120–122]. Importantly, the exposure of NK cells to IL-10 has been shown to reproduce an aberrant repertoire of NKRs that is similar to that observed during the course of HIV-1 infection. ART is able to lower the increased levels of IL-10 in active stages of HIV-1 infection and this response likely represents another mechanism of action by which this therapeutic approach normalizes NK cells in HIV-1 infected patients [123]. Other then recovering NK cell phenotypic and functional features, ART also enhances the terminal differentiation of $CD56^{dim}$ expressing CD57 [124]. The presence of this latter surface marker indicates the existence of a functionally stable and mature NK cell subset, whose frequency normally increases with age. High frequencies of circulating $CD57^{pos}/CD56^{pos}$ NK cells have been also associated with a better clinical outcome in cancer and autoimmune diseases [125]. Thus, this subset represents a good prognostic factor in several models of human diseases.

Residual degrees of NK cell activation have been shown to persist even after the administration ART and this finding does not correlate with T cell activation, HIV-1 viremia and CD4+ T cell count [49, 126]. The pathogenic and clinical relevance of this persistent NK cell activation during the course of active therapy is still unclear. In this regard, a recent study claimed that these higher levels of NK cell activation are detectable predominantly in $CD56^{dim}$ subset of immunologic non-responders HIV-1 infected patients and is inversely correlates with CD4+ T cell recovery and viral suppression [127].

While several studies have addressed the impact of ART on circulating NK cells in HIV-1 infection, only a few reports investigated their mucosal levels. Chronic HIV-1 infection reduces NK cell frequency both in the intraepithelial and lamina propria gut compartments. ART substantially expands intestinal NK cell populations despite the incomplete recovery of circulating CD4+ T cells [128, 129]. A similar impact of ART has been confirmed as well in SIV-infected Rhesus monkeys in which the initial drop of NK cells in the gut is reversed by the administration of antiviral treatment [130, 131].

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Targeting NK cells in HIV-1 therapy

The great advances in our understanding of NK cell physiology (i.e. ontogenesis, memory-like responses, editing of the adaptive immune system) and physiopathology (i.e. dysfunctions in immune-deficiency, autoimmune diseases, viral infections, etc.) gave us the opportunities to exploit novel therapeutic approaches that either manipulate or use NK cell antiviral immune-properties [4, 132]. Indeed, given the above-mentioned multifunctional effector-functions, NK cells can be efficiently employed to build protective vaccine responses and shape immune responses against HIV-1. Only recently, remarkable efforts targeting and optimizing NK cell functions in therapeutic and preventive interventions against HIV-1 have been put in place with encouraging results.

The natural development of therapeutically effective anti-HIV-1 broadly neutralizing Ab (bNAbs) is a rare observation even 2–4 years after the infection. Furthermore, those few patients able to produce bNAbs do not really benefit from their anti-viral activities because of low Ab titers in the plasma or the high variability and complexity of HIV-1 strains. Recently, a modern technology based on single cell cloning has made it possible to isolate, expand and characterize a 2nd generation of bNAbs [133–136]. These bNAbs show a wide range of affinities towards different sites on the HIV-1 envelope and are now being manufactured and tested in several clinical trials. In particular, we can now measure the ability of each of these monoclonal Abs (mAbs) obtained from millions of HIV-1-specific B cells purified from HIV-1 infected patients to inhibit viral replication. In regard to NK cell biology, bNAbs can be used to promote the killing of HIV-1 infected cells via ADCC [136–138] as the ability of these bNAbs to prevent HIV-1 infection has been extensively reported [139, 140]. Whether therapeutic approaches using ADCC will work in HIV-1 infection is still being debated and requires additional investigation and clinical trials. However, the protective effect of the RV144 human vaccine trial was associated, at least in part, with the increased ADCC activity [141–143].

Antibody Dependent Cell Cytotoxicity

The current working hypothesis postulates that ADCC employs two different mechanisms of action to boost the anti-viral potential of bNAbs: *i)* the direct clearance of free-cell HIV-1 via the binding of the viral envelope to the Fab fragment of these mAbs and *ii)* the lysis of HIV-1 infected targets via the recruitment of cellular effectors such as Fcγ$RIII^{pos}$ NK lymphocytes. Several *in vivo* studies have shown that HIV-1 viremia is remarkably higher when the engagement of Fcγ receptors is reduced. This finding demonstrates that the therapeutic efficacy of bNAbs requires both the involvement of immune cellular effectors and the activation of their downstream pathway triggered by the binding of the Fc fragments of bNAbs to Fcγ receptors [138, 144]. In line with this finding, the single infusion of 3BNC117 bNAb in HIV-1-infected patients showed that its neutralizing effect is not only due to the elimination of free circulating viruses or to the prevention of new cellular infections, but also to the clearance of HIV-1-infected cells [145]. This latter mechanism has been confirmed also in a humanized mouse model where the administration of bNAbs induced a direct lysis of HIV-1-infected CD4+ T cells via the engagement of Fcγ receptors [146]. These different features of ADCC, in the context of new therapeutic approaches with

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the 2nd generation of bNAbs, can really make the difference by having a strong clinical efficacy even when the Ab neutralizing potentials are compromised by the high heterogeneity of HIV-1 strains. In this regard, several *in vitro* and *in vivo* studies have demonstrated that the binding of bNAbs to FcγRIIIa induces NK cell-mediated ADCC [147–150]. Structural and functional analyses of bNAbs also revealed that mutations in the variable region of these mAbs are able to increase the affinity and specificity of bNAbs to different viral epitopes and, subsequently, to enhance their neutralizing activity again HIV-1 via ADCC mediated by NK cells [134, 151, 152]. Since it is unlikely that a vaccine trial may specifically induce such changes in the Fab fragments of Abs, the generation of engineered bNAbs carrying mutations in their variable regions is an alternative strategy that is currently under development. Another approach for increasing NK cell-mediated ADCC against HIV-1 infected targets is to improve the ability of the Fc fragment of bNAbs to bind CD16. This second strategy has been already developed in cancer therapy [153–155]. Indeed, the engineered Fc variant of the S239D-I332E bNAb exhibits a stronger ability to bind FcγRIIa, FcγRIIb and FcγRIIIa, a phenomenon enhancing the ADCC-mediated clearance of cancer cell targets expressing specific tumor antigens [153].

Another factor regulating the NK cell-mediated ADCC against HIV-1 infected targets is the glycosylation of the Fc domain of bNAbs. Specifically, the shift from a global antibody-glycosylation profile toward an agalactosylated glycoform improves Fc-mediated binding of NK cells and is associated with higher NK cell anti-viral activity [156]. Moreover, the presence of one or another of the 4 different isoforms of the IgG subclasses (IgG1-4) has a deep impact on the ability of bNAbs to bind Fcγ receptors. Indeed, the spontaneous suppression of HIV-1 replication and progression to AIDS in ECs in the absence of ART is associated with virus-specific isotype IgG3 and IgG1 responses [157]. Notably, IgG3 Abs from polyclonal HIV-1 immune globulins are more potent then other subclasses in neutralizing the virus [158]. Interestingly, the protection of the RV144 vaccine trial is also associated with the occurrence of an IgG3 response in subjects who are more resistant to HIV-1 infection [159, 160]. The Fc-regions of IgG1 and IgG3 antibodies represent human isotopes able to regulate both ADCC and antibody-mediated complement-mediated lysis (ADCML). Both bNAbs non-bNAbs can eliminate HIV-1 virions as well as infected cells via ADCC and ADCML [161]. In particular, the binding of C3 complement protein on target cells in HIV-1 infection in vitro has been show to increase NK cell-mediated ADCC cytotoxicity [162]. However, the mechanism(s) regulating the complement system in NK cell-mediated ADCC activity in HIV-1 therapy have been not yet disclosed and could represent an important therapeutic target. Indeed, the deposit of C3 complement protein on opsonized target cells in tumor therapy induced the reduction of FcγRIII binding by NK cells, a phenomenon that can be reversed by C3 depletion [163, 164]. Whether a similar phenomenon occurs also in ADCC based-therapies against HIV-1 infection is unknown.

Other compounds affecting NK cell-mediated ADCC activity are metalloproteinases such as the cytoplasmic metalloproteinase ADAM17 that can prevent the shedding of CD16 following NK cells activation [165]. In this regard, the administration of metalloproteinase inhibitors in trials of anti-tumor immunotherapy based on the infusion of mAbs improved NK cell-mediated ADCC [81, 166]. Finally NKRs such as NKG2D have been recently reported to act as co-receptors of Fcγ for NK cell ADCC during the course of HIV-1

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infection [167]. Moreover, both NKG2D and 2B4 synergize with Fcγ ligation to enhance NK cell calcium flux [168]. Yet, ligation of iKIRs with their specific alleles of MHC-I ligands can inhibit ADCC triggered by anti-HIV-1 and therapeutic monoclonal antibodies [169, 170].

TLR Ligands

The innate immune system, via TLR agonists, may enhance NK cell activity. TLRs belong to the family of pattern recognition receptors (PRR) and are able to activate an immune response against a given pathogen (eg. viral infections) following their direct interactions with different microbial compounds. TLRs are constitutively expressed on several immune cells from both innate and adaptive immune system, including NK cells [171]. Several studies have shown that TLRs agonists can directly activate NK cells and boost their anti-viral potentials [172–174]. One possible candidate is MGN1703, a novel TLR9 agonist currently under clinical testing for the treatment of metastatic colorectal cancer [175–178]. Indeed, MGN1703 is able to stimulate plasmacytoid DCs to produce IFN-α that, in turn, increase the expression of NKp46 on NK cells and induce the killing of HIV-1 infected T cell targets [22, 60, 174]. Recent clinical study confirmed that MGN1703 treatment in HIV-1 infected patients on ART has a dual potential by increasing HIV-1 transcription and enhancing cytotoxic NK cell activation [179]. Other agonists able to boost NK cell effector functions against cancer cells are the ones binding TLR7 [180, 181]. These latter compounds have also been reported to increase both CD8+ T cell- and NK cell-mediated lysis of HIV-1-infected cells [172].

Other Approaches

The currently available adoptive cell transfer therapies using NK cells to cure solid and hematologic cancers comprise several approaches that could be considered for HIV infection. These include the expansion *ex vivo* of autologous or allogeneic NK cells as well as the genetic engineering of NK cells to induce cytokine secretion, expression of Fc receptors and tumor-antigen receptors [182]. Recently NK cells obtained from human embryonic stem cells (hESCs), and induced pluripotent stem cells (iPSCs) are becoming an alternative promising source of NK cells for gene or immunotherapy. NK cells derived from hESCs and iPSCs have potent anti-HIV-1 activity against HIV-1 replication in $CD4^{pos}$ T cells both in vitro and in vivo [183]. Alternatively, a potent NK cell-mediates anti-HIV-1 activity can be achieve through recombinant chimeric antigen receptor (CAR) engineering. CAR T cells therapy are increasingly demonstrating success for the treatment of cancers and have been proposed for use in combating HIV-1 viral reservoirs [184, 185]. The efficacy of CAR-expressing NK cells in cancer treatment is currently being tested at the pre-clinical stage [186], In this regard, the possible use of CAR-NK cells to treat HIV-1 infection by implementing the technology of hESC- and/or iPSC-derided NK cells is currently being debated [183]. Hence, the development of the above-mentioned NK-cell immune therapeutic approaches will challenge the scientific community over the next decade.

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Future perspectives

Regardless of the negative impact of HIV-1 on NK cell activity, the remarkable advances in biomedical technology make it now possible to use or modify these innate lymphocytes for the development of innovative and potentially effective antiviral strategies. Indeed, a therapy based on the administration of 2nd generation anti-HIV-1 bNAbs is one of the possible options to design a therapeutic vaccine boosting NK cell effector functions. Moreover, the acquisition of the best technologies to engineer NK cells is another frontier that is being currently considered to generate potent anti-HIV NK cells in the context of a customized and personal medicine.

All these approaches targeting NK cells for the treatment of HIV-1 infection are either in preliminary experimental and clinical trials or are currently being discussed among the scientific community. ART can restore in HIV-1 infected patients the frequency, phenotype and function of NK cells. Thus, these cells can be made available for therapy by employing different strategies under development.

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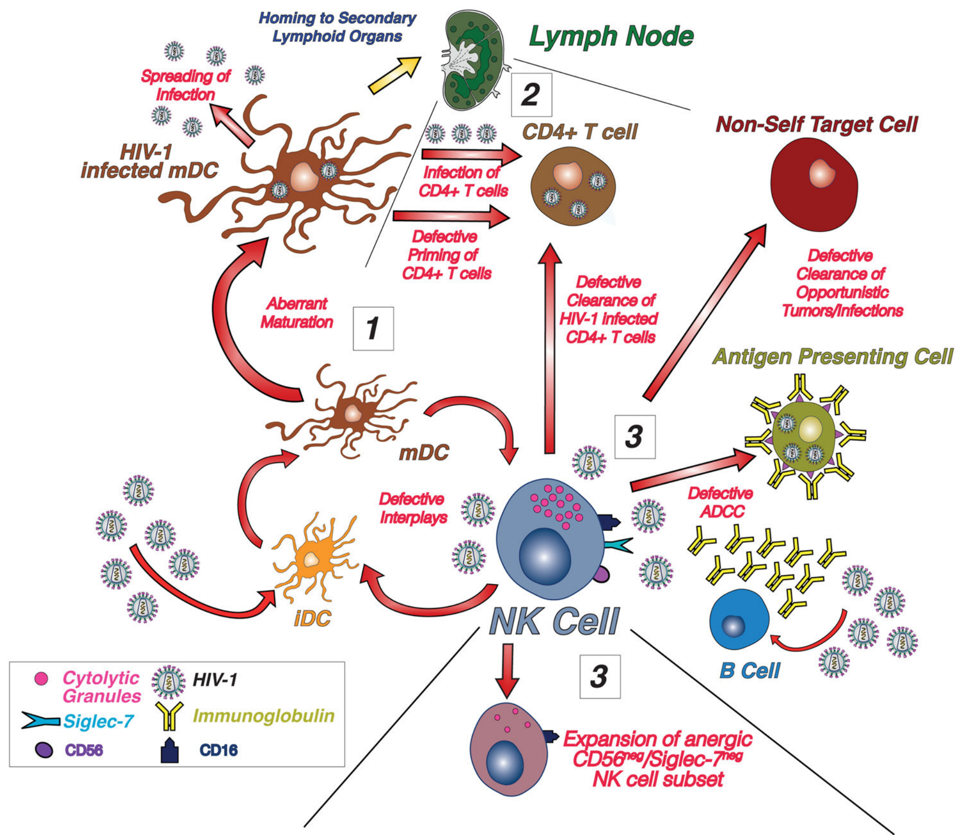

Figure 1. Impact of HIV-1 on NK cell homeostasis and functions

Since from the early stages of HIV-1 infection when tissue-resident antigen presenting cells (APCs) such as immature Dendritic Cells (iDCs) uptake the virus, the defective crosstalk between NK cells and DCs lead to an aberrant maturation and to the infection of these APCs (1). Once migrated to secondary lymphoid organs, these aberrant mature DCs (mDCs) contribute to infect autologous CD4+ T cells instead of ensuring an optimal activation and priming of adaptive immune responses (2). High levels of HIV-1 replication also markedly affects NK cell phenotype and function by inducing the expansion of an anergic subset that lack bot CD56 and Siglec-7 and that is highly impaired in killing autologous and viral infected CD4+ T cells, in the clearance of opportunistic infections and tumors and in performing antibody dependent cell cytotoxicity (ADCC) (3). This aberrant and highly pathogenic vicious loop is completely reversible following the administration of antiretroviral therapy that can restore NK cell homeostasis and anti-viral functions, thus making them an ideal cellular tool to follow-up disease progression and treatment efficacy as well as to develop alternative curative strategies to clear the infection.

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Table 1

Receptor	Function	Impact of HIV-Viremia	Impact of Antiretroviral Therapy	References
CD16 (FcγRIII)	ADCC	No change	No Change	8, 21, 22, 23, 24, 25, 26, 27, 28
CD56	Adhesion Molecules	Decrease	Restoration to normal levels	8, 21, 22, 23, 24, 25, 26, 27, 28
KIR2DL1 (CD158a)	Inhibitory	No change/Increase	Restoration to normal levels	6, 14, 15,18, 22, 25, 31, 32, 33, 35, 107
KIR2DL2 (CD158b)	Inhibitory	No change/Increase	Restoration to normal levels	6, 14, 15,18, 22, 25, 31, 32, 33, 36, 107
KIR3DL1 (CD158e1)	Inhibitory	No change/Increase	Restoration to normal levels	6, 14, 15,18, 22, 25, 33, 82, 107
KIR3DL2 (CD158k)	Inhibitory	No change	No change	6, 14,15,18, 22, 25
KIR2DL4 (CD158d)	Inhibitory	Unkown	Unkown	6, 14,15,18, 37
LIR1/ILT2 (CD85j)	Inhibitory	Increase	Restoration to normal levels	6, 14, 15, 18, 22, 25
Siglec-7	Inhibitory	Decrease	Restoration to normal levels	40, 41
KIR2DS1	Activating	Unkown	Unkown	6, 14,15,18, 76, 80
KIR2DS2	Activating	Unkown	Unkown	6, 14,15,18.
KIR3DS1	Activating	Increase	Unkown	6, 14,15,18, 33, 50, 68,71.
CD94 (KLRD1)	heterodimer coupled with NKG2 molecules	No change	No change	22, 25, 93.
NKG2A (CD159a)	Inhibitory	Decrease	Restoration to normal levels	6, 14, 15, 16, 18, 22, 25.
NKG2C (CD159c)	Activating	Increase (co-infection with HCMV)	No change	6, 14, 15, 16, 18, 89
NKG2D	Activating	No change	No change	6, 14, 15, 16, 17, 18, 22, 25, 54, 146
NKp46 (NCR1)	Activating (NCR)	Decrease	Restoration to normal levels	6, 14, 15, 16, 17, 18, 22, 25, 34, 54, 74
NKp30 (NCR2)	Activating (NCR)	Decrease	Restoration to normal levels	6, 14, 15, 16, 17, 18, 22, 25, 34
NKp44 (NCR3)	Activating (NCR)	Decrease	Restoration to normal levels	6, 14, 15, 16, 17, 18, 22, 25, 34
NKp80	Activating (co-receptor)	No change	No change	6, 14, 15, 16, 17, 18, 22, 25
NTB-A	Activating (co-receptor)	No change	No change	6, 14, 15, 16, 17, 18, 22, 25, 60, 61
2B4 (CD244)	Activating (co-receptor)	No change	No change	6, 14, 15, 16, 17, 18, 22, 25, 31
NKR-P1A (CD161)	Not classified	No change/Decrease	No change/Unkown	14, 29, 62, 107