Published in final edited form as:
Trends Immunol. 2011 May ; 32(5): 219–224. doi:10.1016/j.it.2011.02.003.

Mutiny or Scrutiny: NK cell modulation of DC function in HIV-1 infection

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Abstract

Accumulating data suggests that Natural Killer (NK) cells are not only involved in the innate [ET1]antiviral response following infection, but are also intimately involved in shaping the quality of the adaptive immune response by modulating the functional properties of myeloid Dendritic Cells (DC) during the acute immune response to infection. In this role, NK cells ensure that only fully maturated, immunogenic DCs gain access to inductive sites, where they might prime effective antiviral adaptive immune responses. However, increasing evidence now suggests that several aspects of this crosstalk between NK cells and DCs are compromised during HIV infection, potentially contributing to immune dysfunction.

NK-DC interactions during innate recognition of viruses

The innate immune response to infection serves as first line defense against incoming pathogens. Recent data suggests that innate immune responses might also play a vital role in shaping the quality of the ensuing adaptive immune response. This link between the innate and adaptive immune response is mediated by a unique subset of myeloid cells, dendritic cells (DC), that are innate immune sentinels centrally involved in the recognition of pathogens[1,2]. These include both myeloid DCs (mDCs) that act as potent antigen presenting cells and plasmacytoid DCs (DCs) that secrete copious amount of interferon-α (IFN-α) and initiate the antiviral immune response. In this capacity, tissue-resident DCs sense infection through pattern recognition receptors, rapidly take up foreign antigens, initiate the inflammatory cascade, and then traffic to inductive immune sites where they are able to present foreign antigens to cells of the adaptive immune system[3,4]. Mounting evidence now shows that these cells do not work in isolation, but instead interact with several other cells of the innate immune system. Among the innate immune cells involved in modulating DC activity, natural killer (NK) cells have received much attention over the past decade[5–8]. In addition to their role in eliminating foreign or infected cells from the body, NK cells are also involved in shaping DC function, and regulating the quality of DCs that gain access to inductive sites, thus ultimately influencing the quality of the adaptive immune response. This cross-talk is not unidirectional, and NK cells and DCs help each other acquire complete functionality to ultimately fine tune the ensuing adaptive immune response. This review will focus on the interplay between DCs and NK cells, and on how their interactions might be altered, resulting in poor antiviral control in the context of HIV infection. We suggest that

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the cross-talk between NK cells and DCs is impaired in HIV-1 infection, resulting in dysfunction of virus-specific adaptive immune responses.

Dendritic cells and induction immunity versus tolerance

DCs reside in tissues in an immature state, in which they are exquisitely poised to rapidly acquire and sample antigens from the extracellular milieu[3,4]. In this capacity, DCs persistently survey tissues for "danger signals" (Box 1), including pathogen specific antigens, through an array of germ-line encoded pattern recognition receptors, including the toll-like receptors (TLRs) that recognize conserved molecular microbial patterns[9]. In an immature state, DCs deliver abortive or tolerogenic signals to T cells, due to low level co-stimulatory antigen expression, resulting in suboptimal naïve T and B cell stimulation in inductive sites. Uptake of foreign/aberrant material coupled to "danger signals" (Box 1) results in the induction of a cascade of events whereupon DCs gain the capacity to present antigens due to the upregulation of major histocompatibility (MHC) class I and II molecules and a range of co-stimulatory molecules. In addition, DC motility increases during maturation allowing the cells to travel to inductive sites where they can prime adaptive immune responses. However, in the absence of "danger signals", DCs that take up antigens or apoptotic bodies may mature incompletely, leading to the delivery of tolerogenic signals. Thus immunogenic DC maturation hinges on the delivery of a tandem signal from a foreign antigen in the presence of a danger signal for optimal antigen presenting function and priming of adaptive immunity.

Box 1

Danger Signals
Pathogen associated signals *(ex. TLR ligands)*

Cytokines/Chemokines

Apoptotic Cells

Given the immune-stimulatory potency of DCs, and the fact that they heavily govern the direction of the immune response following infection, the immune system has evolved a number of checks and balances to ensure that DCs mediate their activity optimally. Among the cells that have been implicated in modulating DC function, NK cells have emerged over the past decade as key regulators of these potent antigen-presenting cells.

NK cells and immune surveillance

NK cells represent the body's first line defense against incoming pathogens and some tumors[10]. Through a complex array of germ-line encoded activating and inhibitory receptors[11,12], NK cells survey tissue and blood cells for normal expression of self-antigens, in particular major histocompatibility class (MHC) I. This provides recognition of tumor and infected cells, both of which are associated with a downregulation of MHC class I expression. NK cell recognition of aberrant cells that are "missing self", but which have also upregulated stress ligands for activating NK receptors, results in the rapid elimination of these cells[10,13]. This elimination is coupled to NK cell-mediated secretion of cytokines and chemokines aimed at creating an inflammatory environment that enhances clearance and control of the pathogen or tumor.

In humans, NK cells can be divided into at least two different subsets, with unique functional properties, based on their surface density of CD56[14]. The first subset, $CD3^{neg}CD56^{bright}$ NK cells, are poorly cytolytic, do not express killer immunoglobulin

receptors (KIR), Fcγ-receptors (FcγR), or perforin, but are able to secrete copious amounts of cytokines upon activation. In contrast the second subset, $CD3^{neg}CD56^{dim}$ NK cells, are highly cytolytic, express both KIRs involved in the recognition of MHC class I, and FcγR3a (CD16), required for antibody-mediated cellular cytotoxicity of antibody-opsonized material. Interestingly, the proportion of these two NK cell subsets diverges based on their localization within tissues and blood, where $CD56^{dim}$ NK cells circulate predominantly in blood (90% $CD56^{dim}$: 10% $CD56^{bright}$) and $CD56^{bright}$ NK cells form the primary resident subset in secondary lymphoid tissues such as lymph nodes (LN) (90% $CD56^{bright}$: 10% $CD56^{dim}$)[15]. This differential distribution might reflect distinct roles of these NK cell subsets in the direct antiviral response and in their unique roles in modulating DC functions during an acute immune response, as described further below.

NK/DC cross talk in tissues

NK cells play a central role in alerting DCs to an infection, and in promoting their functional maturation[6–8]. NK cell recognition of infected cells results in cytokine release, aimed at recruiting innate immune cells, including DCs, to the site of the antiviral response. Furthermore, these early cytokines, such as interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α) serve as potent signals by which NK cells ensure that DC maturation is skewed towards a Th1 response (Figure 1). NK/DC interactions seem to be most critical in the setting of improper or non-optimal DC maturation that might occur when DCs recognize a foreign/aberrant antigen in the absence of sufficient danger signals (Table 1) to undergo full maturation. In this setting of insufficient DC maturation, NK cells can play a central role in potentiating DC maturation[16,17] through the generation of apoptotic bodies containing antigens and the co-secretion of cytokines (Figure 1) that are required to fully activate DCs[18]. This NK cell-mediated maturation of DCs is cell-contact dependent, and might involve interaction between the natural cytotoxicity receptor (NCR) NKp30 on the surface of NK cells with its still undefined cellular ligand on the surface of the immature DCs[19].

NK/DC interactions are not unidirectional, and DCs can secrete a variety of cytokines that potentiate the proliferative and cytolytic capacity of NK cells (Figure 1). pDC production of type 1 IFNs represents one of the strongest early indirect activators of NK cells through mDCs[20]. In fact, IFN-α promotes IL-15-independent proliferation of $CD56^{bright}$ NK cells via DCs using a yet unknown, potentially contact dependent mechanism[21,22,23]. Similarly, IP-10, IL-8, , IFN-α and IL-18 augment NK cytolytic capacity and IFN-γ secretion[16,24,25], and receptor-bound IL-15 promotes proliferation of $CD56^{dim}$ NK cells[24] and NK cell priming and survival[26,27]. NK cell activation by DCs requires direct cell-to-cell contact, including NKG2D recognition of MHC class I –related (MIC) A and B stress ligands upregulated on IFN-α-stimulated mDCs[22]. This interaction results in the formation of a stimulatory synapse[28] allowing for the polarized secretion of IL-12 directly towards the NK cell. In response, NK cells secrete a number of cytokines that further promote DC activation. Taken together, NK/DC cross-talk is bidirectional and is critical for the optimal activation of NK cells and DCs.

Editing of DCs by NK cells

Given the potent immunomodulatory role of DCs, aberrant or improperly matured DCs could potentially induce autoimmunity or compromise the immune response to infection. Thus, in addition to their role played in DC-activation and maturation, NK cells also edit DC populations by eliminating inadequately matured DCs. This NK-mediated editing of DCs was first reported in mice, where NK cells were shown to inhibit myelopoesis in autologous hosts[29,30]. NK cell depletion resulted in increased numbers of myeloid precursors in the spleen, but not in the bone marrow, suggesting that NK cells eliminate DCs in the

periphery[31]. The DC-editing function of NK cells is regulated by the phenotypic differences in immature and mature DCs, mainly related to differential MHC expression (Figure 2). As mentioned above, DC maturation results in an upregulation of MHC and co-stimulatory molecules, and DCs gain migratory capacity. In contrast, immature DCs that aberrantly gain the capacity to traffic to secondary lymphoid sites can deliver tolerogenic signals due to incomplete upregulation of co-stimulatory molecules. To ensure that only fully mature DCs gain access to inductive sites, NK cells can eliminate immature DCs that gain aberrant access to the peripheral circulation (Figure 2). NK cell-mediated elimination of immature DCs[32], which is prompted by low levels of MHC class I and consequent low levels of HLA-E expression, is mediated by KIR-NKG2A+ NK cells[32] through the activating receptor NKp30[33].

How can NKp30+ NK cells promote both DC activation and elimination of immature DCs? After an inflammatory response, innate immune cells gradually accumulate in inflamed tissues, and the ratio of NK:DC appears to dictate whether an NK cell will activate or kill emigrating DCs. At low NK:DC ratios, NK cells secrete cytokines, and potently activate DCs, in an incompletely defined manner, although the receptors NKp30 and/or NKG2A may be involved[18]. At higher NK:DC ratios, however, NK cells eliminate DCs in an HLA-E-dependent manner[32]. This differential interaction between NK cells and DCs based on NK frequencies might represent an elegant mechanism aimed at limiting the window of opportunity in which DCs are able to leave tissues to prime adaptive immune responses, but the precise mechanisms underlying this differential effect need further investigation.

Dysregulation of NK/DC cross talk in HIV

Accumulating evidence suggests that the NK/DC axis is significantly impaired during HIV infection, related to significant alterations in phenotype and function of both NK cells and DCs. As early as the acute phase of infection, significant redistributions occur within the NK cell compartment, resulting in an early loss of $CD56^{bright}$ NK cells, followed by a loss of cytolytic $CD56^{dim}$ NK cells [34,35]. The loss of $CD56^{pos}$ NK cells occurs in concert with the accumulation of $CD56^{neg}$ NK cells that express a number of NK cell receptors, but fail respond upon stimulation [34,36]. Furthermore, progressive HIV infection results in an accumulation $NKp30^{low}$ expressing NK cells with aberrant TNF-related apoptosis-inducing ligand (TRAIL) activity, resulting in a reduced capacity to eliminate immature DCs [37,38]. Conversely, mDCs generated from untreated individuals with progressive HIV-1 infection exhibited an impaired capacity to secrete the cytokines needed to activate NK cells, resulting in insufficient levels of IFN-γ required to further mature the mDCs. Successful viral suppression under antiretroviral therapy can lead to the reconstitution of cytokine-secretion by mDCs, suggesting that active viral replication can reversibly impair myeloid cells and render them poor activators of NK cells[37]. Given that these impairments of NK/DC interactions occur early in HIV-1 infection, they can potentially contribute to poor initial viral control and compromised induction of protective adaptive immunity.

Recent data have highlighted novel mechanisms by which viruses may manipulate NK/DC cross-talk to evade protective immunity. Both chronic lymphocytic choriomeningitis virus and HIV infection are associated with high-level secretion of the anti-inflammatory cytokine interleukin (IL-10), which plays a central role in compromising the quality of the adaptive immune response in both infections[39,40]. Interestingly, IL-10 can profoundly modulate DC maturation, resulting in the differentiation of tolerogenic DCs that result in poor T cell induction[41–44]. Additionally, exposure of DCs to IL-10 can significantly change the expression of MHC class I and NKG2D-ligands on DCs, rendering mature DCs susceptible and immature DCs resistant to killing by NK cells[45]. Thus IL-10, which is normally secreted transiently following acute viral infections, might limit the window in which DCs traffic to

inductive sites rapidly through the generation of aberrant DC subsets that may be more vulnerable to NK-editing. However, in the setting of chronic persistent viral infections such as HIV-1, protracted IL-10 secretion can result in altered NK/DC editing, leading to an accumulation of tolerogenic DCs potentially responsible for the induction of dysfunctional adaptive immune responses. Immunotherapeutic modulation of the NK/DC crosstalk in chronic infection might therefore represent an attractive approach to enhance protective immunity to HIV-1.

Kinetics of DC-NK interactions modulate the quality of adaptive immunity

Recent data suggest that the duration and potency of the early NK-DC interaction can profoundly modulate the quality of the ensuing adaptive immune response. In the MCMV model, a single gene for an activating NK cell receptor (Ly49H) that recognizes a virally encoded MHC-class I homologue accounts for protection from MCMV infection[46,47]. Following MCMV infection, Ly49H+ NK cells expand specifically and contain infection[48]. Interestingly, recent studies suggest that qualitative rather than quantitative features of the acute NK cell response in Ly49H+ mice have a profound impact on the induction of more effective antiviral T cell responses[49,50]. These data from the MCMV model might provide some clues for the potential mechanisms that underlie the described epidemiologic associations between particular combined KIR and HLA class I genotypes and slower HIV disease progression, including the activating KIR3DS1 allele and particular KIR3DL1 alleles, when co-expressed with HLA class I Bw4 alleles[51,52].

Like the Ly49H+ NK cells in MCMV infection, KIR3DS1+ and KIR3DL1+ NK cell populations preferentially expand during acute HIV-1 infection in the blood of individuals also encoding for HLA-B Bw4 alleles[53]. This expansion of specific NK cell populations may have a direct impact on modulating the quality of the ensuing adaptive immune responses both through direct control of HIV viral replication, but also potentially by fine-tuning the DC populations that are able to gain access to inductive sites. While mounting evidence suggests that the KIR3DS1+ NK cells have a strong direct anti-HIV-1 activity in Bw4+ individuals[54], the mechanisms by which KIR3DL1+ NK cells might mediate their protective activity in HIV-1 infection is still unclear. The rules that determine the function of NK cells during development might provide some clues for the observed antiviral activity of NK cells from individuals encoding for KIR3DL1 and HLA-Bw4.

According to the “licensing” model of NK cell development, engagement of an inhibitory NK cell receptor to self MHC class I is required during NK cell development to render that particular NK cell fully competent[55,56]. In the absence of such an interaction between an inhibitory receptor and its MHC class I ligand that prevent auto-reactivity, NK cells remain unlicensed and are unable to respond to diverse stimuli[56]. Recent evidence furthermore suggests that licensing is a quantitative process, and that stronger inhibitory signals, conferred by higher frequency interactions between inhibitory KIRs and self-MHC, may lead to more functional NK cells that respond more strongly to MHC class I-deficient target cells [57]. Thus in addition to a potential direct antiviral role, KIR3DL1^{high} NK cells may also become better licensed in the presence of their HLA class I ligand HLA-B Bw4 during development[55,58], allowing them to more potently eliminate immature DCs that express lower levels of HLA class I, and limit production of excessive amounts of IFN-α[50]. Furthermore, KIR3DL1^{high} NK cells might be strongly inhibited by mature DCs expressing high levels of HLA class I. This capacity of licensed KIR3DL1^{high} NK cells to fine tune the balance between mature and immature DCs might have direct consequences for the quality of the antiviral T cell response, as suggested by recent data in the MCMC model[49,50], and its ability to effectively control viral replication.

Aberrant NK/DC interactions at the sites of HIV infection

The vast majority of HIV infections worldwide occur through mucosal tissues of the female genital tract[59], and following infection, the mucosal tissues of the gastrointestinal tract form the primary site of viral replication and dissemination[60]. However, these mucosal tissues harbor unique populations of NK cells that might modulate DCs in a disparate fashion to NK cells in the blood and LN. In fact, uterine and gut NK cells express high levels of CD56[61,62], but also express KIR, FcγRs, and perforin granules[63–65], more characteristic of $CD56^{dim}$ NK cells in the peripheral blood. Additionally, these mucosal NK cells secrete anti-inflammatory or regulatory cytokines such as IL-10[61,62], IL-22[66], and/or IL-17[67] rather than pro-inflammatory cytokines. The debate is still ongoing whether these IL-22-secreting cells are NK cells or lymphoid tissue inducer cells. Yet, it is clear that if mucosal NK cells secrete a remarkably different set of anti-inflammatory cytokines than the conventional/pro-inflammatory NK cells, they may have a profoundly different impact on DCs that encounter antigens within these sites. Thus DCs exposed to antigen at mucosal sites of initial HIV-1 transmission/replication in the presence of non-inflammatory NK cells may receive predominantly anti-inflammatory -less immunogenic signals, rendering them tolerogenic. Further studies of the NK/DC interactions at mucosal sites are required to gain a better understanding on how HIV may take advantage of the anti-inflammatory mucosal environment to compromise the induction of potent antiviral immunity.

Concluding remarks

NK cell-mediated activation and editing of DCs is now emerging as a novel axis that modulates the adaptive immune response to viral infection. Important questions that need to be addressed by future research are how HIV-1 precisely interferes with the cross-talk between NK cells and DCs, whether this cross-talk can be modulated, and whether the innate cross-talk between NK cells and DCs can be harnessed by vaccines and/or immunotherapeutic interventions to enhance the quality of adaptive immune responses. Novel approaches aimed at modulating the interactions between NK cells and DCs will provide exciting new avenues by which to potentiate the efficacy of vaccine approaches to fight various infections as well as other disease conditions.

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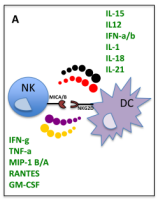

Figure 1.
Bi-directional interactions between NK cells and DCs. Secretion of cytokines and receptor–ligand (NKG2D–MIC-A or –B) interactions result in the potentiation of NK and DC responses in viral infections.

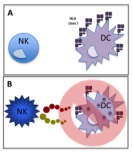

Figure 2.
NK cell-mediated editing of DC populations. a) NK cells perform quality control on all DCs in the circulatory system to ensure that only properly matured DCs, that express high levels of MHC class I are able to traffic to inductive sites. b) NK cells that come in contact with DCs that have been incompletely matured or infected (express low MHC class 1) are rapidly eliminated by NK cells.

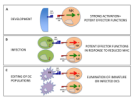

Figure 3.

Impact of NK cell licensing on the elimination of HIV-1-infected DCs. a) During NK cell development in the bone marrow, inhibitory KIRs expressed on NK cells that interact with a self-MHC class I ligand mediate a potent licensing signal that allows NK cells to emerge as cytolytic killers. b) Licensed NK cells expressing inhibitory KIRs might be more responsive to HIV-1-infected cells that have reduced expression of MHC class I. c) Similarly, licensed NK cells may be more easily inhibited by mature DCs expressing high levels of MHC class I, while licensed NK cells can effectively eliminate immature or infected DCs that have reduced MHC class I expression. (Red arrows indicate an inhibitory signal. Green arrows indicate an activating signal.)