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Innate immunity in the control of HIV/AIDS: recent advances and open questions

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Part II	1 415 words
Part III	764 words
Conclusion	279 words
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1 **Abstract**

2

3 From the publication of the first *AIDS* issue onwards, major advances have been made
4 in the field of innate immunity during human immunodeficiency virus (HIV) infection. Innate
5 immunity can be defined as the first and unspecific lines of defense constitutively present and
6 ready to be mobilized upon infection. Although a large body of literature adamantly
7 highlights that innate immunity is a critical weapon of defense against HIV and its simian
8 parents (SIV), innate immunity is still underexplored. Focusing on innate immunity may open
9 new paths for the development of innovative therapeutics and vaccine strategies against HIV.
10 Understanding innate immunity may shed light on the natural protection occurring in rare
11 HIV-1 infected individuals who control their infection. Recent discoveries illustrate the
12 diversity of innate key mechanisms that individuals and non-human primates can mount
13 against HIV-1/SIV. Innate immune defenses are composed of a multitude of molecular and
14 cellular protagonists, including dendritic cells (DC), macrophages and natural killer cells
15 (NK), directed at halting viral intrusion. This objective is achieved with a variable degree of
16 success according to the genetic background of individuals. The responses can also have
17 detrimental effects such as amplification of inflammation and recruitment of HIV target cells.
18 This review focuses on innate mechanisms sensing HIV-1 entry, controlling HIV-1 infection,
19 promoting inflammation and innate mechanisms shaping adaptive immunity.

20

21 **Key words:** HIV, SIV, innate immunity, NK, DC, Interferon

1 **Introduction** (246 words)

2

3 Since the beginning of the HIV pandemic, scientific attention has effortlessly been
4 aiming at developing new affordable strategies to prevent HIV infection. Therefore the
5 identification of protective factors against HIV infection and/or disease is extremely
6 beneficial in deriving rational approaches for vaccines or therapeutics. However, the field is
7 still lacking knowledge regarding the immune correlates of protection, including the role of
8 innate immunity (Tab. 1). Rare individuals displaying spontaneous resistance to infection, i.e.
9 “exposed uninfected” (EU) [1] or to progression to AIDS, i.e. “long-term non-progressors”
10 (LTNP) and “elite controllers” (EC) [2, 3], can help identify and elucidate natural
11 mechanisms of protection. The majority of EC display robust anti-HIV-1-specific CD8+ T-
12 cell responses. However, a large proportion of EC lack efficient T-cell responses [4]
13 suggesting that innate responses might be involved in HIV control in EC. Furthermore, some
14 African non-human primates naturally infected with SIV lack signs of generalized immune
15 activation and are AIDS resistant despite viremia as high as those observed in viremic patients
16 [5, 6] or in SIV-infected macaques. These simian models can provide, respectively, crucial
17 clues to understand innate mechanisms associated with resistance or susceptibility to disease
18 progression [7, 8]. Therefore, studying all these individuals and non-human primate models
19 sheds light on the role of innate immune responses, their complexity and their influence on
20 the control of and the outcome of HIV/SIV infections. This review will emphasize in
21 particular the role of dendritic cells and NK cells as examples of innate immune responses to
22 HIV.

23

1 **Innate Immunity as a firewall sensing HIV-1 entry into host target cells** (648 words)

2

3 ***Recognition via TLR in plasmacytoid dendritic cells***

4 During mucosal infections, HIV must breach the robust physical barrier formed by
5 epithelial cells to infect the deeply embedded CD4⁺ T-cells [9, 10]. On its way to the basal
6 epithelium, resident innate target cells such as dendritic cells (DC) can capture HIV-1 upon
7 gp120-CD4 interactions. These cells express PRR acting as viral sensors, notably the Toll-like
8 receptors (TLR) that “recognize” viral intrusion (Fig. 1). HIV-1 recognition by plasmacytoid
9 DC (pDC) is mediated mostly by TLR7, but also by TLR9 [11-13]. This recognition is
10 intracellular and requires virion endocytosis followed by trafficking to early endosomes [14].
11 PDC can sense HIV-1-infected cells more efficiently than free virions [13, 15]. Increased
12 expression of TLR7/9 by pDC following pDC-epithelial cell interactions *in vitro* [16]
13 supports the concept that *in vivo* pDC may respond to infection to gain HIV-1 sensing
14 activity. Upon HIV-1-mediated TLR7 activation, pDC do not fully mature but upregulate
15 IRF7 expression and persistently become type I interferon (IFN-I)-producing cells [14]. IFN-I
16 is known to inhibit early stages of the HIV-1 replication cycle [17]. It seems counter intuitive
17 for HIV-1 to trigger a long-lasting IFN-I response as it could hinder its replication. However,
18 as we will discuss in further sections, HIV-1 tends to promote IFN-I and innate inflammatory
19 responses to recruit activated target cells leading to a local amplification of infection. HIV-1
20 is also capable of escaping IFN-I induced anti-viral activity.

21

1 *Alternative sensors of HIV-1*

2 Additional sensors of HIV may be in place and remain to be clearly identified. Notably
3 activation of unknown innate sensor(s) was proposed in myeloid DC (mDC) upon viral
4 capsid-cyclophilin A interactions [18, 19]. Other, but yet unidentified, innate nucleic acid
5 sensors act in T cells and TREX1 has been shown to counteract their effects in HIV-1
6 infection [20, 21]. *In vitro*, epithelial-like cells can sense HIV-1 in an IRF3 dependent manner
7 [15] and secrete chemokines in response to HIV to recruit DC [22]. At later stages of HIV/SIV
8 infections, pDC die by apoptosis [23] and seem to be no longer the major producers of IFN-I
9 [24]. Understanding HIV sensing mechanisms in DC is currently an important area of
10 research [19, 25].

11 Nod-like receptors (NLRs) have been proposed as an alternative to TLRs in other
12 infections [26, 27]. The NLR Family pyrin domain containing 3 (NALP3, also known as
13 NLRP3) has been recently proposed as a novel cytoplasmic sensor for cytidine-phosphate-
14 guanosine DNA motifs present in bacteria and viruses and for viral ssRNA and dsRNA [26].
15 NALP3 interacts with co-adaptor proteins to form molecular complexes known as
16 inflammasomes. The inflammasome triggering leads to the production of pro-inflammatory
17 interleukin (IL) such as IL-1 β and IL-18 [27]. The latter are released in substantial amounts
18 during HIV/SIVmac infections [28-30]. Although no data clearly show that HIV-1 genetic
19 material can activate the inflammasome, polymorphisms in NALP3 and in IL1B are
20 associated with a higher risk for HIV-1 infection [31, 32]. Inactivated HIV-1 also induces an
21 important *NALP3* RNA expression within 4h in monocyte-derived DC accompanied by
22 increased release of IL-1 β [33]. Notably DC from HIV-1⁺ individuals, independent of the
23 presence of ART, failed to increase *NALP3* expression due to already elevated basal
24 expression. This finding suggests a chronic state of activation of DC in HIV-1 infection [33].

25 HIV/SIV transmission occurs at higher rates during co-infection, i.e. with HSV-2 [34].

1 More studies [34, 35] are required on the impact of such co-infections on the innate immune
2 responses, i.e TLR, inflammasome triggering and consequences for adaptive responses
3 controlling the outcome of HIV/SIV infections.

4
5 In conclusion, DC are critical protagonists during the first steps of HIV-1 infection as
6 they detect viral intrusion. More investigations are needed regarding the mechanisms of
7 recognition, the role of sensors other than TLRs, and on the consequential processes
8 following the sensing of HIV. These responses are important either to confine infection at the
9 site of entry or to promote inflammation and viral dissemination.

10

11 **Innate immunity controlling HIV-1 infection and promoting viral dissemination** (1 415
12 words)

13

14 ***Intrinsic cellular hindrance of viral replication***

15 Innate restriction factors, i.e. TRIM5 α , APOBEC-3G or Tetherin, can inhibit HIV
16 replication at different stages of the replication cycle [36]. While not generally considered
17 part of the innate immune system, these intrinsic factors represent a natural activity against
18 HIV infection. Nonetheless, several of them are produced by cells of the innate immune
19 system and/or triggered by IFN-I which is released predominantly by pDC in the case of HIV,
20 as described above.

21 SAMHD1 is the most recently discovered restriction factor with its activity
22 specifically confined to differentiated uncycling cells like macrophages and mDC [37, 38].
23 Polymorphisms in genes encoding for restriction factors such as APOBEC3G and TRIM5 α
24 have been associated with the rate of disease progression [39]. In most cases, HIV-1 has
25 evolved to counteract these innate antiviral factors: the viral capsid for TRIM5 α ,

1 Vpu/Nef/Env for Tetherin, Vif for APOBEC3G and Vpx for SAMHD1 [25]. These instances
2 of viral escape demonstrate that such restriction factors potentially are important components
3 of defense.

4 More recently, evidence shows that EU have an unappreciated molecular mucosal
5 composition [40]. Characterization of cervical mucosa protein expression showed an over-
6 abundance (>40%) of protease inhibitors, including Serpins, Cystatins, and A2ML1, amongst
7 360 unique proteins identified as compared to HIV-1⁺ controls. It is not known, however, if
8 these factors are causal for HIV-1- resistance, or merely associated with this phenotype [40].
9 Previously described anti-HIV-1 factors, elevated in EU mucosal secretions, such as
10 RANTES [41], chemokines SLPI and MIP- α/β [42], and Elafin [43] have also been suggested
11 as correlates of resistance to HIV-1.

12 Additional intrinsic resistance of target cells, especially in macrophages, equally leads
13 to host hindrance of HIV-1 replication [44]. Macrophages are one of the HIV-1 cell targets
14 and may play a role in the reservoir and pathogenesis of HIV-1 infection. On one hand,
15 aggregation of activating immunoglobulin G Fc receptors by immune complexes inhibits
16 reverse transcript accumulation and integration of HIV-1 in macrophages *via* the induction of
17 the cyclin-dependent kinase inhibitor p21 (Cip1/WAF1) [45]. On the other hand, HIV-1 is
18 blocked in macrophages activated *via* TLR3, 4 or 8 ligands [46]. The TLR4-activated primary
19 macrophages were reported to down-regulate CCR5 expression and to acquire resistance to
20 R5 HIV-1 entry and replication [47]. This response might be important once the infection is
21 established and particularly during HIV-1-induced bacterial translocation. *In vitro*-derived
22 macrophages and CD4⁺ T-cells from EC individuals dramatically restrict HIV-1 replication
23 during reverse transcription in contrast to macrophages from HIV-1-seronegative donors [48].
24 This reduced susceptibility to infection is not due to increased expression of the known innate

1 restriction factors (TRIM5 α , APOBEC3G, Tetherin). Nevertheless, the degree of restriction
2 observed *in vitro* correlated with the size of the viral reservoir *in vivo* [48].

3

4 ***Control of HIV-1 infection by NK cells***

5 Exposure to IFN-I and contact with activated DC producing IL-12 and IL-15 enhance
6 proliferation, IFN- γ production, and cytotoxic activity of NK cells against infected cells [49-
7 52]. NK cells in mucosa [53, 54] are among the first lines of defense against HIV-1-infected
8 cells. NK cell subset distribution is tissue-specific [55]. NK cells represent up to 70% of
9 leukocytes in the decidua [56] and may participate [57] along with local decidual soluble
10 factors [58] in the innate control of HIV-1 infection at the materno-foetal interface. During
11 HIV-1 infection, NK cells may control the virus, especially at the early stages of HIV-1
12 infection before adaptive immunity is initiated [59]. A balance between activating and
13 inhibitory signals explains the fine-tuning of NK cell activation [60, 61]. The expression of
14 NK cell surface receptors can be modified by specific cellular ligands expressed on HIV-1-
15 infected cells. For instance, HIV-infected mDC lead to the down-regulation of CD85j
16 expression on NK cells whereas CD85j⁺ NK cells highly protect mDC from HIV-1 infection
17 [62]. Association of KIR polymorphism with different outcome of HIV-1 infection [39, 60,
18 63] emphasizes the fundamental role of NK cells [64, 65]. In line with this, EU exhibit higher
19 *ex vivo* NK cell cytotoxic activity and cytokine production (IFN γ) [66, 67]. This finding was
20 made in association with the expansion of particular NK cell subsets bearing a high
21 KIR3DS1/KIR3DL1 ratio, associated with down-regulated KIR3DL1 transcript levels, or an
22 enhanced NKG2C/NKG2A ratio.

23 HIV-1 seems to have the ability to escape from active NK cell immune surveillance by
24 adapting the Vpu-Env region to host KIR genotypes, especially *KIR2DL2* [68]. These “KIR

1 footprints” in Vpu-Env result in enhanced binding of inhibitory KIRs to HIV-1-infected CD4⁺
2 T-cells *in vitro*.

3 During acute HIV-1 infection, cytotoxic CD56^{dim} NK cells preferentially expand
4 concomitantly with decreased numbers of cytokine producing CD56^{bright} NK cells [69]. In
5 addition, an expression of inhibitory receptors begins during primary infection [69-71] and is
6 maintained during the chronic phase in association with viremia and immune activation [72].
7 Chronic HIV-1 infection is associated with an expansion of the anergic CD56^{neg} NK cell
8 subset at the expense of both the CD56^{bright} and CD56^{dim} NK cells [73]. During progressive
9 HIV-1 infection NK cell mucosal distribution is altered [54]. In lymph nodes [14], acute HIV-
10 1 infection does not change the numbers or distribution of NK cell subsets as compared to
11 healthy individuals [74], with KIR⁻ NK cells being the major NK cell subset. This finding is
12 explained by a decreased capacity of KIR⁺ and KIR⁻ NK cells for homing to LN.
13 Nevertheless, LN KIR⁻ NK cells are highly activated and express TRAIL [74]. The decreased
14 homing capacity of cytotoxic KIR⁺ NK cells offers an additional opportunity for HIV-1 to
15 escape a control of viral replication and to establish long-term infection in LN [74]. It has
16 been suggested that NK cells from EC or LTNP resist anergy [75]. However, EC NK cells are
17 less robust than CD8⁺ T-cell at killing autologous CD4⁺ T-cells and their role in regulating the
18 size of the reservoirs remains to be defined [76]. The existence of other innate cells with
19 increased cytotoxic activities such as DC in LTNP and EC is not excluded either [77, 78].

20

21 ***Inflammation and viral dissemination***

22 During viral infection, innate immunity is critical in limiting the size of the viral
23 reservoir. However, innate responses may also amplify the viral reservoir instead of limiting
24 viral spread by attracting new HIV target cells to the sites of infection. Upon HIV/SIV
25 mucosal infection, amplification of viral replication within the site of entry is necessary

1 before dissemination to the LN [79]. Local inflammatory innate responses triggered upon
2 sensing of HIV-1 may be a prerequisite for establishment of these foci [79]. Cytokines and
3 chemokines released by innate immune cells, i.e. pDC, macrophages and NK cells can
4 theoretically promote recruitment of other innate cells as well as activated CD4⁺ T cells [80].
5 Thus, more target cells become available for infection. Of note, chemokines such as
6 CXCL9/10 can also promote viral latency in resting CD4⁺ T-cells and thus enhance the
7 establishment of viral reservoirs capable to escape immunosurveillance [81]. The cytokine
8 storm is produced very early after HIV-1 infection [30, 82]. PDC may contribute to this early
9 cytokine storm [83]. As soon as a few hours post-infection they are attracted to the
10 submucosae and have been shown to be hyperfunctional during the early stages of primary
11 infection and to produce high levels of IFN-I and other cytokines [84, 85].

12 IFN-I priming leads to ISG (Interferon-stimulated gene) expression, including
13 chemokines, i.e. CXCL9/10/11, which could further amplify recruitment of cells to sites of
14 infection. Chronic responsiveness to IFN-I has also been suggested to account for the loss of
15 IL-17 immunity [86, 87]. To date, IFN-I and ISG expression is considered one of the best
16 inflammatory markers associated with HIV-1 pathogenesis [7, 88]. In line with this, natural
17 SIV infections lack chronic ISG expression in all compartments in contrast to SIVmac
18 infection [7, 89]. This characteristic may result from an efficient down-regulation of
19 inflammation by the end of the acute infection in the natural hosts [90]. It is unclear however
20 so far to what extent IFN-I and ISG expressions contribute directly to generalized immune
21 activation or only represent excellent surrogate markers of inflammation.

22 In the future, the earliest innate responses that result either in early containment of
23 viral replication or in harmful inflammation with viral dissemination and the mechanisms that
24 tip this balance have to be addressed (Fig. 2). Macrophages were extensively studied in the
25 early days of HIV research. Nevertheless, the role of HIV-macrophage in this balance should

1 be revisited in view of the latest findings on the early events of HIV infection. A major
2 contribution in inflammatory processes by other innate immune cells, i.e. neutrophils, is not
3 excluded and remains to be explored.

4

5 **Innate immunity and its modulatory role in shaping adaptive immunity** (764 words)

6

7 *HIV-1 infection modulates the NK/DC cross-talk*

8 In the majority of HIV-1+ individuals, the rate of disease progression depends on the
9 host capacity to mount efficient adaptive immune responses. This is well-achieved in the rare
10 EC who exhibit robust CD8+ T cell responses [2, 3, 91]. DC equipped with the full antigen
11 presentation machinery are necessary in shaping T-cell responses. MDC are not directly
12 activated by HIV, but the IFN-I and TNF- α released by pDC induce bystander maturation of
13 mDC [92, 93]. Circulating mDC from EC display increased antigen-presenting properties and
14 release less inflammatory cytokines with regard to HIV-1⁺ progressors [94]. The latter exhibit
15 numerical and functional DC deficiencies reviewed in [92, 95].

16 Activated NK cells may indirectly help to prime T cell responses by secreting
17 cytokines, such as interferon- γ (IFN- γ), which promote the differentiation of activated CD4⁺
18 T cells into Th1 effector cells [80]. DC and NK cells are both present in sites of infection and
19 inflammation [53, 54, 74]. NK/DC interactions were found to be a critical checkpoint in
20 shaping the adaptive immune response [92] that ensures an optimization of the DC
21 differentiation process. At high NK/DC ratios, interactions lead to the killing of immature DC
22 (iDC), through engagement of the activating receptor NKp30, so only the mature DC survive
23 and migrate to inductive sites to fully present HIV-1 antigens and license T-cells. Conversely,
24 at low NK/DC ratios, DC activate NK cells.

1 The NK/DC cross-talk during HIV-1 infection remains to be further explored. HIV-1
2 infection of DC may interfere with their ability to prime the appropriate NK cell response
3 [65]. HIV-1 Vpr hinders pDC production of IFN-I and IFN- γ production by NK cells upon
4 NK/pDC interaction [96]. Furthermore, NK cells from viremic patients show a decreased
5 ability to kill iDC [97, 98]. The defect is associated with an increase in the proportion of rare
6 CD56⁻ NK cells with impaired NKp30 function during acute HIV-1 infection, early depletion
7 of CD56^{bright} NK cells as discussed above and an upregulation of the high mobility group box
8 1 protein (HMGB1) [98, 99].

9 Interestingly, a recent report shows that the strength of the NK/DC cross-talk is greater
10 in EU [100]. Activated NK cells from these individuals exhibit a higher ability to eliminate
11 autologous iDCs. In turn, iDCs from these individuals produced more IL-12, which may
12 positively feedback the robust NK cell activity [101]. Also iDCs from EU enhance NK cell
13 activity (degranulation and IFN- γ production) in comparison to that observed with HIV-1⁻ or
14 other HIV-1⁺ individuals [100, 102]. This increased NK cell ability was not associated with
15 higher expression of NKp30 or other NK cell surface receptors, nor with a peculiar expression
16 of MHC class I molecules [100].

17

18 *Protective coordination of NK and CD8⁺ T-cell responses during HIV-1 infection?*

19 Dynamics of NK and HIV-1-specific CD8⁺ T-cells have previously been characterized
20 [59]. NK cell responses start very early during acute HIV-1 infection and are dramatically
21 elevated, when HIV-1-specific CD8⁺ T-cell responses are still absent or weak, and then
22 decline after the emergence of HIV-specific CD8⁺ T-cells. In contrast, both NK and CD8⁺ T-
23 cell populations are substantially expanded during rebound of viral replication after ART
24 interruption in chronic HIV-1 infection [59].

1 Growing evidence from studies in mice reveal an unappreciated role of NK cells as
2 rheostat [103-105] (or competitor) of T-cell responses. NK cell depletion improves memory
3 CD8⁺ T-cell formation [106]. Of note, NK cells negatively affect both CD4⁺ and CD8⁺ T-cell
4 expansion and effector functions during MCMV infection whose clearance depends mainly
5 on NK cells [104]. In contrast, during LCMV infection in which CD4⁺ and CD8⁺ T-cells are
6 required for immune control, the presence of NK cells inhibits virus-specific poly-functional
7 T-cells [103, 105]. They therefore negatively impact the efficiency of viral clearance by
8 directly suppressing activated CD4⁺ T-cells [105]. During the natural course of HIV-1
9 infection, to achieve a minimal size of viral reservoirs, NK and virus-specific CD8⁺ T-cells
10 must cooperate in a timely manner. This coordination between NK and T-cell responses might
11 be compromised during chronic HIV infection. Paradoxically and interestingly with respect to
12 HIV infection, NK cell-mediated killing of activated CD4⁺ T-cells prevents
13 immunopathology and mortality in the LCMV infection model [105].

14 Despite the lack of knowledge regarding ways to trigger a potential (and still
15 debatable) specific memory NK cell response [107, 108], it is time now for rational
16 approaches focusing on NK cells in HIV vaccine research. The observations from mice
17 studies raise exciting questions for the control of HIV-1 infection and disease progression.
18 The EU and the EC individuals could reflect the different strength in NK cell activity and
19 NK/DC cross-talk (see model Fig. 3).

20

21 **Concluding remarks** (279 words)

22

23 HIV is capable of breaching the first lines of mucosal defense to gain access to its
24 preferred targets: activated CD4⁺ T-cells. Innate immunity is an organized network of cells
25 and signals that HIV dismantles, progressively and thoroughly. Innate immune responses

1 triggered upon viral entry and sensing have a long-term impact for the outcome of HIV-1
2 infection. In some conditions, they promote adaptive immune responses and are associated
3 with efficient confinement of viral replication. In others, they can help establish viral
4 reservoirs and promote viral dissemination or chronic inflammation and thus progression to
5 AIDS. Therefore, innate inflammatory responses appear to be a two-edged sword in HIV
6 infection.

7 Understanding which early viral-host interactions lead to the establishment of chronic
8 HIV infection remains an indispensable enterprise. Amongst numerous compelling questions,
9 knowledge on the fate and location of the virus within these first days and subsequent
10 regulation of inflammation/dissemination is required. SIV⁺ macaque models and natural hosts
11 will provide further insights on the early protective mechanisms of control of inflammation in
12 mucosa and in lymphoid organs. Among the many actors of the innate immune system, we
13 focused here on the role of DC and NK cells. As we discussed, the critical impact of NK/DC
14 interactions on the adaptive immunity, their responsiveness to the cytokine milieu (IFN-I,
15 chemokines, other innate soluble factors) and to the mucosal environment (epithelial cells,
16 neutrophils, innate lymphocytes) is also a missing piece in the puzzle. Eventually, pursuing
17 the identification of specific viral determinants, which interact with these innate cell
18 participants and their specific signaling pathways, is a mandatory prerequisite. Understanding
19 these parameters and interactions can be selectively exploited in future rational approaches
20 for efficient vaccine designs and therapeutic interventions.

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2

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13 HIV-seronegative individuals. *J Virol* 2011,**85**:3507-3516.

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1 **Table 1. Components of the innate immune system**
 2
 3

<i>COMPONENTS OF THE INNATE IMMUNE SYSTEM</i>	<i>ROLE</i>
Cellular	
Mast cells	Release of chemokines / Cell recruitment
Phagocytic cells	
monocytes / macrophages	Microbial clearance / Antigen presentation / Cell recruitment
dendritic cells (including Langerhans cells, interstitial dendritic cells, myeloid and plasmacytoid dendritic cells)	Antigen presentation / Regulation of adaptive immunity
Granulocytes	
eosinophils	Killing of invading pathogens
basophils	Histamine release / Cell recruitment
neutrophils	Microbial clearance
NK cells	Elimination of infected cells
NKT cells	At the interface between innate and adaptive immunity / Cytokine production
$\gamma\delta$ T cells	
Soluble factors	
Antimicrobial peptides	
LL-37	Inactivation / Direct killing of microbes
defensins	
Lactoferrin	
Lysozyme	
Interferons	
Complement	Inactivation of microbes / Activation of adaptive immunity / Recruitment of phagocytic cells
Chemokines	Attraction of cells
Cytokines	Cell signaling

4

1 **Figure legends**

2

3 **Figure 1. Inflammatory innate responses are a two-edged sword.** Early innate events
4 either preventing viral replication (displayed in blue) or promoting viral amplification and
5 inflammation (displayed in red) are shown here. They may occur simultaneously *in vivo* and
6 the balance of these events may determine the efficiency of viral confinement at the site of
7 entry or viral spread to lymphoid organs. Upon viral entry, either as free virions or as
8 infected-carrier cells, HIV-1 has to breach the first lines of innate immunodefense to reach its
9 preferred target cells: activated CD4⁺ T-cells. Upon capture by plasmacytoid dendritic cells
10 (pDC), HIV-1 triggers inflammatory cytokines and chemokines and thereby the recruitment
11 of new target cells (activated CD4⁺ T-cells, DC) at the site of entry. Activated CD4⁺ T-cells
12 are the highest producers of HIV locally and lead to the emergence of *foci*. Among
13 inflammatory cytokines and chemokines released by DC, type I IFN (IFN-I) and TNF- α
14 enhance mDC maturation and increase their homing capacity to lymphoid organs. The latter
15 may thus promote HIV-1 dissemination to lymphoid organs. Additionally, strong and
16 harmful inflammation triggers anti-inflammatory cytokine production, i.e. IL-10, TGF- β in an
17 unsuccessful attempt to suppress inflammation. These detrimental side effects of the innate
18 response are counterbalanced by the capacity of innate immunity to confine HIV replication.
19 Indeed, activated DC can lead to NK cell activation to ensure killing of virus-infected cells.
20 The discovery of innate restriction factors, intrinsic hindrance of HIV-1 replication in target
21 cells in EC as well as the peculiar composition of mucosal secretions in EU individuals
22 emphasizes the protective role of innate immunity.

23

1 **Figure 2. Early innate events are determinant for the degree of viral dissemination.**

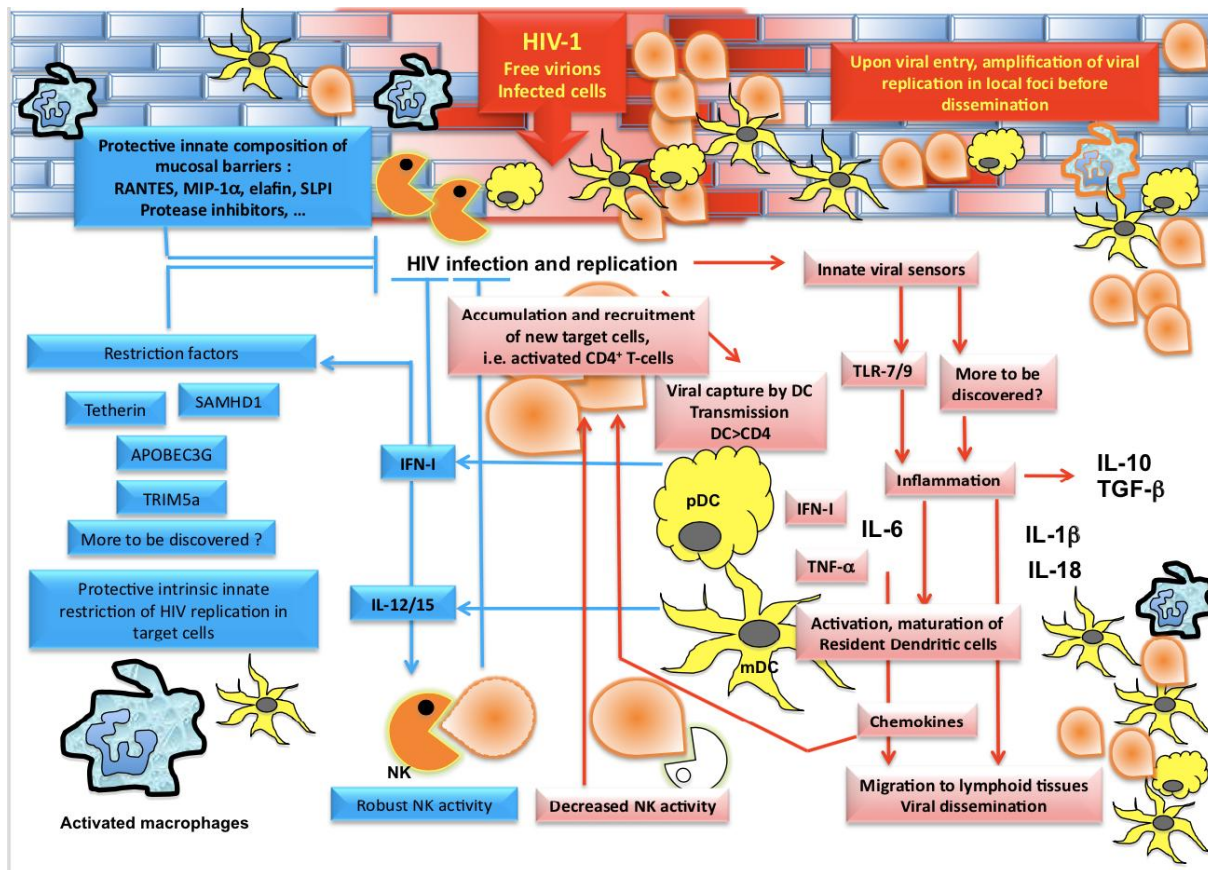
2 HIV-1 triggers innate inflammatory responses leading to confinement of infection at the site
3 of entry (in blue) *versus* deleterious inflammation promoting viral dissemination (in red).
4 Understanding the precise signals that tip this balance may help to control the size of viral
5 reservoirs.

6

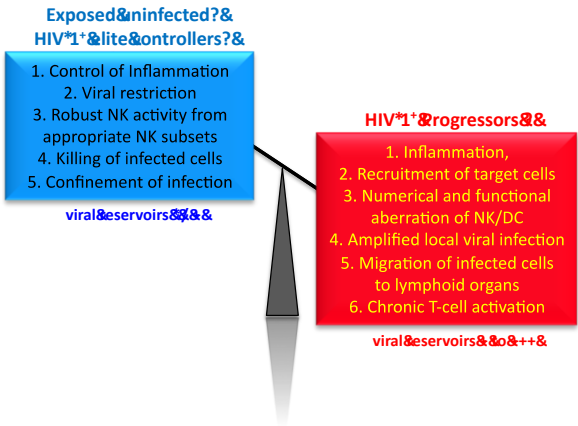
7 **Figure 3. Different strength in NK/DC cross-talk and shaping of T-cell responses:
8 possible consequences for the outcome of HIV-1 infection. A.** In our model, EU individuals

9 are characterized by the most intense NK/DC cross-talk: NK cells display *ex vivo* higher
10 cytotoxic capacity against infected cells and DC. In turn, DC enhance NK cell activation.
11 Hypothetically, this could result in robust confinement of HIV-1 infection at the site of
12 exposure and in the prevention of viral dissemination. Killing of DC may explain poor T-cell
13 responses [109, 110]. In EU, NK cells could be the genuine “viral controllers”. **B.** EC and
14 LTNP individuals exhibit anergy-resistant NK cells with milder cytotoxic activity than CD8⁺
15 T-cells. The latter are easily detected at least in blood and might be accountable for control of
16 viral reservoirs [4]. DC from EC have increased antigen-presenting properties and diminished
17 propensity to release pro-inflammatory cytokines [94]. Appropriate DC maturation and
18 migration to lymphoid organs trigger protective T-cell responses. Hypothetically, the NK/DC
19 cross-talk in those individuals is balanced and leads to a healthy and protective cooperation
20 between innate and adaptive immune responses. In addition, in EU and EC, appropriate NK
21 cell cytotoxic activity might prevent the accumulation of unwanted activated CD4⁺ T-cells. **C.**
22 A loss of appropriate NK/DC cross-talk might contribute to progressive HIV-1 infection.
23 Expansion of unwanted NK cell subsets may explain this different NK/DC crosstalk. This
24 would result in amplified inflammation at the site of entry as well as in lymphoid tissues and
25 to the lack of appropriate killing of DC. The latter disseminate HIV-1 and license T-cell

1 responses, which become exhausted as infection remains uncontrolled and chronic. This
2 exhausted T-cell responses might as well come from licensing DC with functional aberrations
3 due to inappropriate NK/DC cross-talk. Ultimately, these disorganized innate events
4 contribute to a deleterious state of generalized immune activation and to progression to AIDS.
5

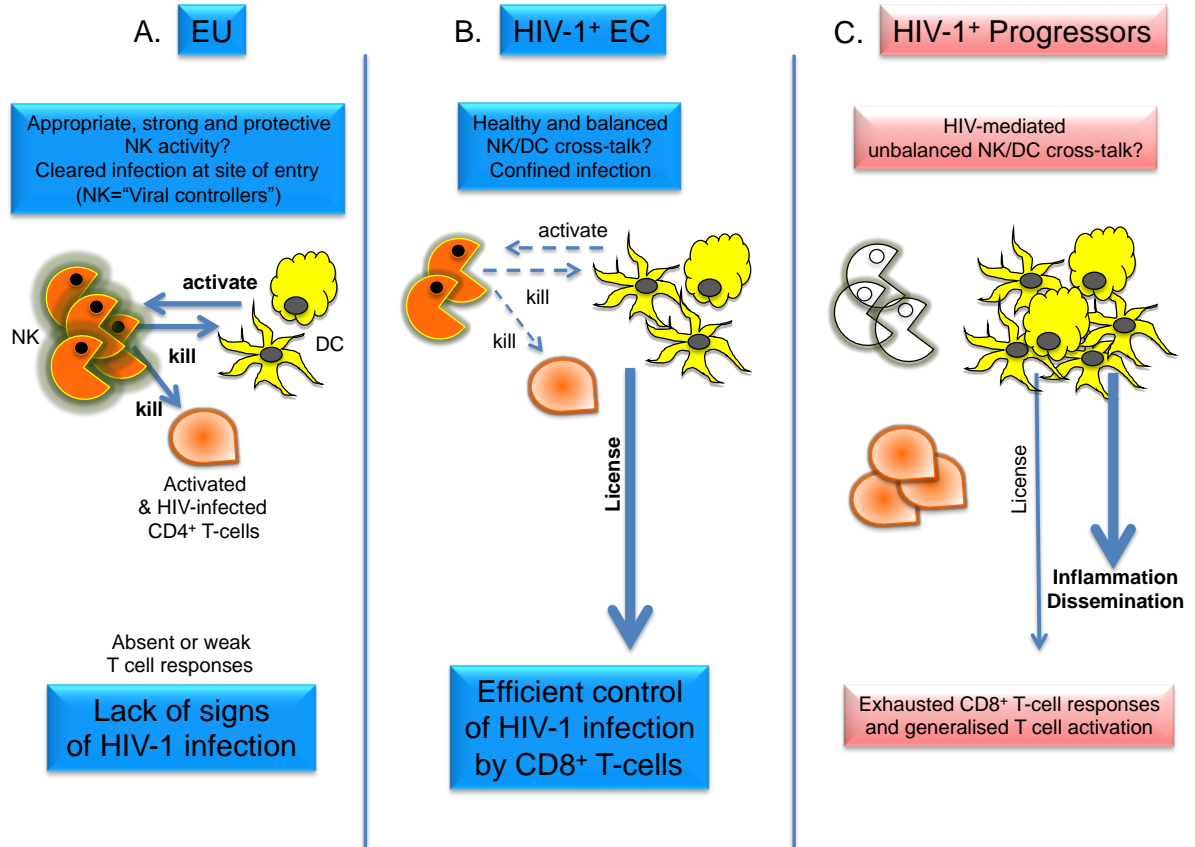


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