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REVIEW

Innate Immune Cell Functions Contribute to Spontaneous HIV Control

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Abstract

Purpose of Review To review the role of innate immune cells in shaping the viral reservoir and maintenance of long-term viral control of spontaneous Elite and Viremic HIV controllers.

Recent Findings HIV controllers exhibit a smaller and transcriptionally suppressed viral reservoir. Different studies report that early responses from innate cells play a pivotal role in this reservoir configuration. NK cells, particularly those with cytotoxic activity and polyfunctional monocytes, have been linked to viral control, and DCs may contribute through early viral sensing and activation of adaptive responses. In some cases, cytotoxic NK cells appeared before HIV-specific CD8 + T cells, underscoring their importance in early viral suppression.

Summary Innate immune cells, including NK cells, monocytes, DCs, and γδ T-cells, are crucial in shaping the viral reservoir in HIV controllers. Early, robust innate responses may help to maintain long-term viral suppression and offer insights into potential therapeutic approaches.

Keywords Innate immunity · HIV infection · HIV elite control · HIV reservoir · Trained immunity

Introduction

Infections caused by the human immunodeficiency virus 1 (HIV-1, hereafter HIV) remain without cure, and it is estimated that approximately 39 million people are currently living with HIV worldwide [1]. The standard suppressive treatment of HIV traditionally contains three antiretroviral drugs, but two drug combinations have recently been shown to be effective as well [2]. Antiretroviral treatment (ART) aims to suppress the viral replication so that the plasma viral load becomes undetectable, disease progression is stopped, and immune responses are normalized so life expectancy reaches those of the non-infected population [3, 4]. However, despite all these improvements, HIV provirus will remain incorporated into the host DNA, and this state of latency will be reversed once ART is discontinued [5]. HIV can enter cells by attachment of HIV glycoproteins to certain cell membrane receptors, more specifically and especially through the interaction between HIV envelop glycoprotein gp120 and the primary CD4 cell membrane receptor and its coreceptors CCR5 and CXCR4. This simultaneous binding results in conformation changes that allow the fusion fragments (gp41) to insert themselves into the cell and merge the membranes [6]). Since CD4 and these coreceptors are most abundantly expressed on CD4.$^+$ T-cells, those are the main targets for HIV infection. Other cell surface receptors, such as α4β7, an integrin involved in immune cell homing to the gut [7], and C-type lectin receptors, such as mannose receptor (MR), DC-SIGN, and langerin, can also bind HIV and facilitate the uptake of the virus into cells by increasing the proximity of the virus to its target receptors [8].

Once HIV has entered the cytoplasm of CD4$^+$ T-cells, HIV reverse transcriptase encodes DNA based on the viral RNA genome. This DNA is then integrated into the host DNA of the cell, after which the host cellular machinery transcribes and translates mRNA and produces either replication-competent or incompetent (pro)viruses. The proviral DNA remains incorporated in the host DNA, even during long-term ART exposure, and forms the so-called viral reservoir. The frequency of cells harboring HIV is relatively low, occurring in about 1 in 10,000 to 1 in 100,000 CD4$^+$ T-cells [9, 10]. The reservoir is seeded early during the HIV infection [11]. Therefore, the nature of immune responses

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during the early phases of the infection may play an important role in shaping the reservoir dynamics.

Nevertheless, not all people living with HIV (PLHIV) have a similar natural course of HIV infection. A small subset of PLHIV called HIV controllers, can spontaneously suppress HIV replication to undetectable, named Elite controllers (ECs) or very low plasma viral load levels for years or decades without ART, the latter being called the viremic controllers [12]. ECs are, therefore, a heterogenous group of PLHIV, and definitions can vary across different studies [13–16], but sustained HIV-RNA plasma viral load levels and stable $CD4^+$ T cell counts over a defined period are commonly used criteria. As no immune deficiency develops, ECs remain free of HIV-related clinical symptoms or progression to disease.

Host and viral factors may contribute to the mechanisms that underlie the spontaneous control of HIV infection, but few studies have demonstrated the contribution of both host and viral factors [17–19]. Considering the host factors, the adaptive immune system and especially the induction of specific-$CD8^+$ T-cell responses are considered major effector mechanisms for combating HIV infections [20–22]. HIV-specific $CD8^+$ T cells expand in the periphery and upregulate cytotoxic effector molecules only within two weeks of infection [23, 24]. However, before adaptive responses are generated, innate immune responses are already operational and being further developed, which determines HIV dynamics and long-term consequences, not only shaping the immune response in acute but also during chronic HIV infection[25–28]. Consequently, long-lasting responses of both adaptive and innate immune responses are considered important for HIV vaccines to be effective [29]. Therefore, in the current review, we aim to describe responses exerted by innate immune cells, exploring their contributions to spontaneous HIV control and HIV reservoir dynamics. Understanding the contributions of innate immunity in HIV control may offer opportunities to identify innate immune-based modulators and mechanisms that may impact the course of HIV infection by altering the viral reservoir dynamics.

Unveiling Innate Immune Responses to HIV Infection

Innate immunity is a crucial factor in the early phase of any infection, including HIV infections [30–32]. Innate immune cells are essential in orchestrating adaptive immune responses through the production of soluble molecules and mechanisms derived from cell–cell interactions [33]. Macrophages, monocytes, dendritic cells (DCs), and NK cells are among the most studied innate immune cells known to play a role in exerting anti-viral immunity and HIV recognition [34]. The innate immune response against HIV starts with the sensing of viral pathogen-associated molecular patterns (PAMPS) by pathogen-recognition receptors (PRRs) of DCs and monocytes and macrophages, who are one of the first to encounter HIV. Some extracellular PRRs, such as Toll-like receptor (TLR)−2 and TLR4, can recognize the viral peptide gp120, while intracellular receptors, TLR7, TLR8, TLR9, and cyclic GMP-AMP synthase (cGAS), recognize viral single-stranded (ss)-RNA, CpG-rich DNA, and double-stranded (ds)-DNA from the virus [35–38]. Activation of these receptors leads to translocation of transcription factors such as interferon regulatory factors (IRFs) and NFκB, resulting in the production of cytokines including type-I Interferons (IFN) and IL-6, IL-1β, and TNFα [39, 40]. Therefore, sensing viral-derived particles through PRRs is among the first responses that signal the presence of HIV in the body.

Besides monocytes, macrophages, and DCs, NK cells display an array of both inhibitory and activating receptors, which are important for identifying and eliminating HIV-infected cells through cytotoxic mechanisms [41]. While some of the effector functions of NK cells depend on receptor interactions with other immune cells, NK cells can be activated by cytokines primarily from DCs such as type-I IFNs, IL-2, IL-12, and IL-15[30]. NK cells expand rapidly during early HIV infection, and their activity directly correlates with the level of viral replication during acute HIV infection [31]. Interestingly, the activation of NK cells by HIV-derived PAMPs is shaped by the functions mediated by macrophages and DCs, including the production of cytokines and the expression of antigen-presenting molecules, indicating a strong interaction between these innate immune cells in early and chronic HIV infection to achieve maintenance of viral control [32].

The direct recognition of HIV and HIV-infected cells by DCs and macrophages shapes the nature of the adaptive immune responses. DCs, also known as professional antigen-presenting cells (APCs), uptake and process HIV-derived particles or apoptotic HIV-infected cells into smaller peptides that can be further loaded and presented on MHC molecules to $CD4^+$ and $CD8^+$ T-cells. While the presentation of foreign antigens on MHC class-II molecules activates antigen-specific $CD4^+$ T-helper cells, the presentation of antigens on MHC class-I molecules results in the activation and proliferation of antigen-specific cytotoxic $CD8^+$ T-cells [42]. The latter process is termed cross-presentation and plays a crucial role in the anti-HIV responses. During HIV infections, cytotoxic CD8 + T-cells are activated through cross-presentation of viral antigens by DCs on MHC class-I molecules, as well as through signals from pro-inflammatory cytokines released by innate immune cells. [23] In addition, innate-derived cytokines such as IL-12, IL-15, IL-18, and type-I IFNs can induce antigen-independent IFNγ release from $CD8^+$ T-cells [43]. IFNγ is a crucial cytokine in

anti-viral immunity, as it modulates local immune cells, like tissue-resident DCs, macrophages, and NK cells, for augmented antiviral functions [44, 45]. Development of HIV-specific CD8 + T-cells occurs only 1–2 weeks after infection [46], which makes understanding the initial and continuous response of innate immunity crucial for the development of spontaneous HIV control.

In the past decade, immunotherapies have become one of the primary focuses of research for developing new treatments for various diseases, including infections as well as cancer and autoimmune disorders. Research efforts focusing on spontaneous controllers and their unique ability to shape the viral reservoir and control HIV naturally are of relevance for finding the most effective immunotherapeutic against HIV. In the following sections, we will aim to describe some of the main innate immune-derided mechanisms described so far as associated with the spontaneous control of HIV infections.

The Relevance of DCs in Boosting Antiviral Responses

As described above, DCs are innate immune cells important for initiating and regulating adaptive immune responses, primarily through their unique ability to cross-present antigens and activate T-cells. This capability is critical for the activation of CD8 + cytotoxic T-cells, which are essential for targeting and eliminating virally infected cells [47]. Classically, DCs can be divided into conventional (formerly myeloid) DCs (cDCs) and plasmacytoid DCs (pDCs) [48, 49].

Hartana et al. have described the upregulation of a long noncoding RNA (lncRNA) in cDCs of spontaneous controllers. This lncRNA was associated with an altered metabolic and immune profile characterized by increased oxidative phosphorylation and glycolysis activities in response to TLR3 stimulation, indicating increased DCs responsiveness in controllers. This effect in HIV controllers was attributed to epigenetic changes in members of the mTOR pathway and hypothesized as a mechanism to sustain the enhanced responsiveness to viral-derived ligands [50]. Martin-Gayo et al. identified a subpopulation of ECs whose myeloid dendritic cells (cDC) displayed higher baseline abilities to respond to intracellular HIV dsDNA stimulation. cDCs from ECs expressed significantly higher levels of the microbial DNA sensors cGAS, IFI16, and AIM2, in addition to higher levels of the RNA sensors TLR8 and RIG-I (Fig. 1) [51]. The enhanced sensing of cytosolic HIV replication products through the accumulation of viral reverse transcripts serves as substrates for the cytosolic DNA sensor cGAS. This recognition leads to rapid and sustained secretion of type I IFNs, triggering effective HIV-specific $CD8^+$ T-cell and NK cell responses [52]. Consequently, higher expression of cGas is thought to be causal for increased secretion of type I IFNs, therefore enhancing immune activation of T-cells and NK cells.

The unique ability of DCs to cross-present antigens and subsequently activate NK cells and T-cells is successfully utilized in novel immunotherapies for conditions such as cancer, with the first FDA-approved DC-based therapeutic cancer vaccine, Provenge (NCT00065442) [41, 53, 54]. There has been increased interest in using this technique to explore novel DC-based vaccines for HIV (as extensively reviewed in [55]). Interestingly, Learemans et al. recently showed that vaccinating ART-treated PLHIV with DC-based vaccines results in alterations in the NK cell repertoire, including a significant increase in the frequency of cytotoxic NK (cNK) cells. Additionally, changes in the NK cell phenotype were associated with migration and exhaustion following immunization with the DC-based vaccine. Hartana et al. shed light on the significance of innate immune cross-talk, particularly between cDCs and NK cells in ECs. Their findings elucidated that cDCs serve as a source of IL-15 in ECs, thereby bolstering the survival and cytotoxicity of cNK cells, a pivotal aspect in HIV control [56]. These results underscore the significance of understanding and harnessing the interplay between DCs and NK cells in the context of therapeutic vaccination for HIV.

Despite being less abundant than cDCs, representing only 0.2–0.5% of the PBMC fraction, pDCs are highly specialized in sensing viral and bacterial pathogens and release high levels of type I IFNs in response to infection. In PLHIV, however, pDC function is diminished with reduced ability to produce type I IFNs, which does not fully recover under long-term ART [57, 58]. However, studies have shown that pDCs from ECs preserve their ability to produce IFNα compared to normal progressors, similar to healthy controls [59]. In efforts to improve HIV-specific T-cell responses through pDC activation in immunological non-responders (INRs), a group of PLHIV who poorly respond to therapy, Jimenez-Leon et al. recently showed that pDCs activation with TLR7 and TLR9 agonists increases HIV-specific T-cell responses of INR to comparable levels to those of ECs [60]. Thus, this suggests that activation of pDCs could serve as a promising treatment target, aiming not only at achieving control of HIV replication in normal progressors but also at improving outcomes in PLHIV that show poor immunological response to ART. Illustrating the contributions of pDCs in improving HIV outcomes, their use as targets in approaches employing latency-reversing agents (LRAs) is noteworthy. LRAs are being studied in the context of cure strategies for HIV, aiming to reduce latent reservoirs, which is necessary to stop the virus from re-emerging. The "Shock and Kill" strategy is a two-step strategy that involves using LRAs to awaken dormant T-cells, thereby activating the HIV reservoir, and then employing anti-viral mechanisms to kill the virion-producing cells [61, 62]. The engagement of TLR7 and its

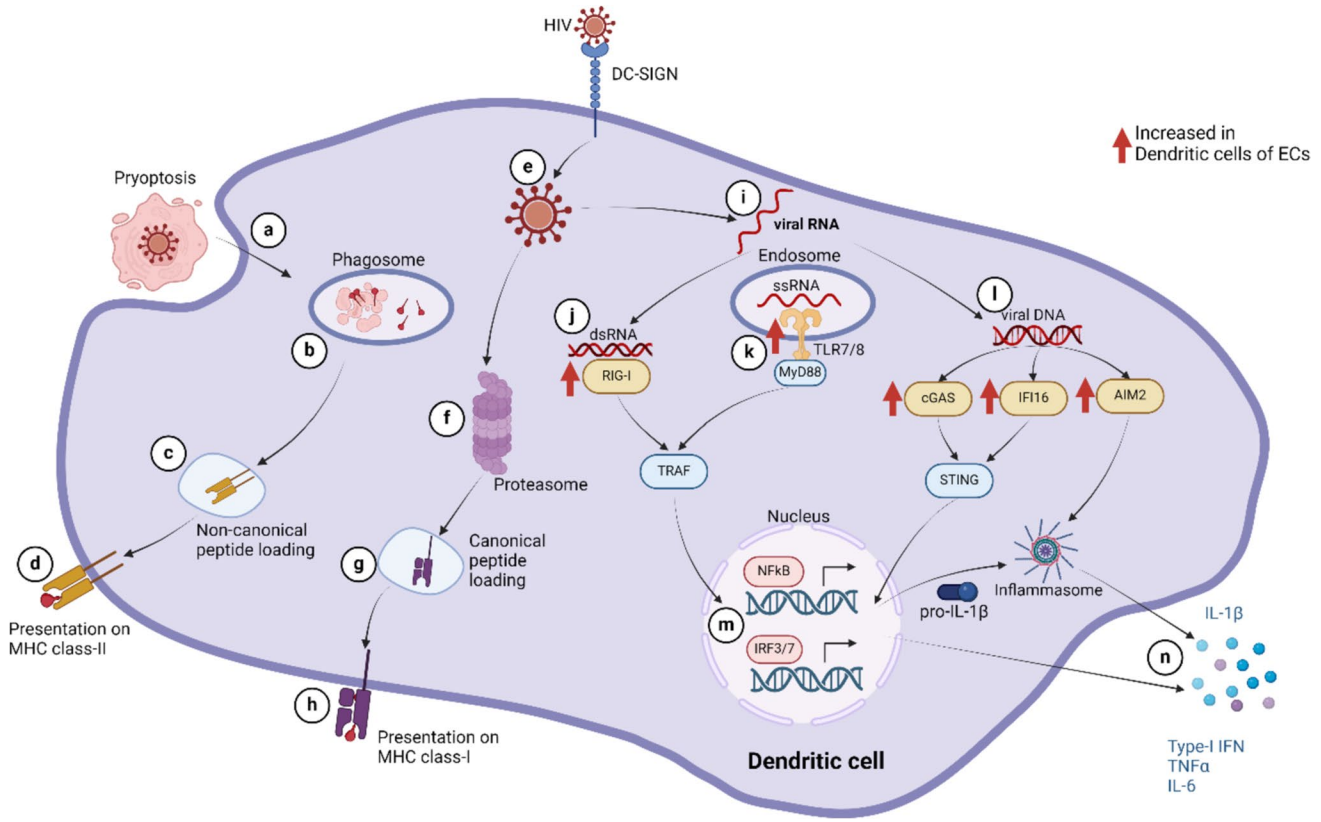

Fig. 1 Dendritic cells mount potent anti-viral responses in HIV elite controllers. (**a**) HIV-infected cells undergo pyroptosis, which induces its uptake by DCs into the phagosome. (**b**) The remaining cell particles and viral particles are broken down and (**c**) loaded onto MHC class-II molecules as non-canonical peptides. (**d**) viral antigens are then presented on MHC class-II molecules to be recognized by other immune cells such as $CD4^+$ T-cells. (**e**) HIV can also directly infect DCs via, e.g., DC-SIGN. (**f**) Internal HIV proteins are processed and broken down by the proteasome machinery, (**g**) and their peptides are loaded onto MHC class-I molecules as canonical peptides. (**h**) Viral peptides are then presented on the cell surface on MHC class-I molecules to be recognized by, e.g. $CD8^+$ T-cells. (**i**) Upon infection of DCs, viral nucleic acids are unpacked and recognized by a variety of intracellular PRRs. (**j**) While ds RNA can be recognized by RIG-I, (**k**) ssRNA is recognized by endosomal TLR7/8 and activate TRAF. (**l**) viral RNA is transcribed into DNA and can be recognized by cGAS, IFI6 or AIM2, either activating STING or the inflammasome, respectively. (**m**) Activation of Sting or TRAF activates downstream signalling pathways that result in activation of transcription factors such as NFκB and IRF3/7. (**n**) The activation of inflammatory genes results in release of pro-inflammatory cytokines such as IL-1β, TNFα and IL-6, as well as release of anti-viral type-I IFNs

downstream signaling pathway in pDCs have been explored and reported as a promising LRA in HIV cure strategies. The role of TLR7 agonists, particularly GS-9620 (Vesatolimod), was shown effective in inducing HIV-RNA in PBMCs from PLHIV on ART through the production of IFNα by pDCs. Depletion of pDCs in culture resulted in decreased IFNα levels and reduced activation of $CD4^+$ T-cells, underscoring the pivotal role of pDCs in this process. Additionally, GS-9620 was effective not only at triggering HIV expression but also at increasing activation of HIV-specific T cells and enhancing antibody-mediated clearance of HIV-infected cells [63].

Antiviral Mechanisms Mediated by NK Cells

NK cells are critical players of the innate immune system, directly recognizing viral proteins or virus-induced ligands, making infected cells more susceptible to NK cell-mediated lysis [64, 65]. The activation and inhibition of NK cells are tightly regulated by a repertoire of different receptors. For example, killer immunoglobulin-like receptors (KIRs) can be inhibitory or activating and interact with the MHC class-I molecules containing both self-and viral-derived peptides [66]. The binding of KIR to MHC class-I is modulated by the sequence of the peptide presented in the MHC class-I.

Genetic studies conducted in PLHIV, including both spontaneous controllers and non-controllers, identified the region encoding for the MHC genes on chromosome 6 are associated with spontaneous controller status [67–71]. The study identified the presence of single-nucleotide polymorphisms (SNPs) in this region as associated with slower disease progression and overall HIV control, particularly the HLA type B*57, a subtype of the *HLA-Bw4-I80* [72, 73]. Previous studies on spontaneous controllers carrying the *HLA-Bw4-I80* allele, describe the presence of NK

cells expressing the activating receptor KIR3DS1 (Fig. 2a) [74–77]. A combination of these specific MHC alleles and the activating KIR seems to be advantageous for HIV control since NK cells expressing the KIR3DS1 have a superior ability to eliminate HIV-infected $CD4^+$ T-cells [75]. These data provide evidence of the relevance of peptide sequences and MHC genetics as factors influencing the functional capabilities of NK cells in the context of HIV control. However, developing strategies to modulate the genetic background has proven challenging.

Among other mechanisms involving the role of NK cells in controlling HIV infections, Marras et al. [78] highlighted that NK cells from HIV controllers display a unique functional profile, characterized by enhanced IFNγ production and increased expression of activating receptors like NKp46, NKp30, NKG2D, and NKp80. These NK cells were inversely correlated with the HIV DNA reservoir size, indicating their potential role in limiting viral replication and integration in CD4 + T-cells. This work illustrates another scenario in which the immune pressure exerted by innate immunity could favor a decrease in HIV load during the early stages of HIV acquisition, thereby positively impacting the size of the reservoir in spontaneous controllers. The heightened activity of NK cells through ADCC assists in

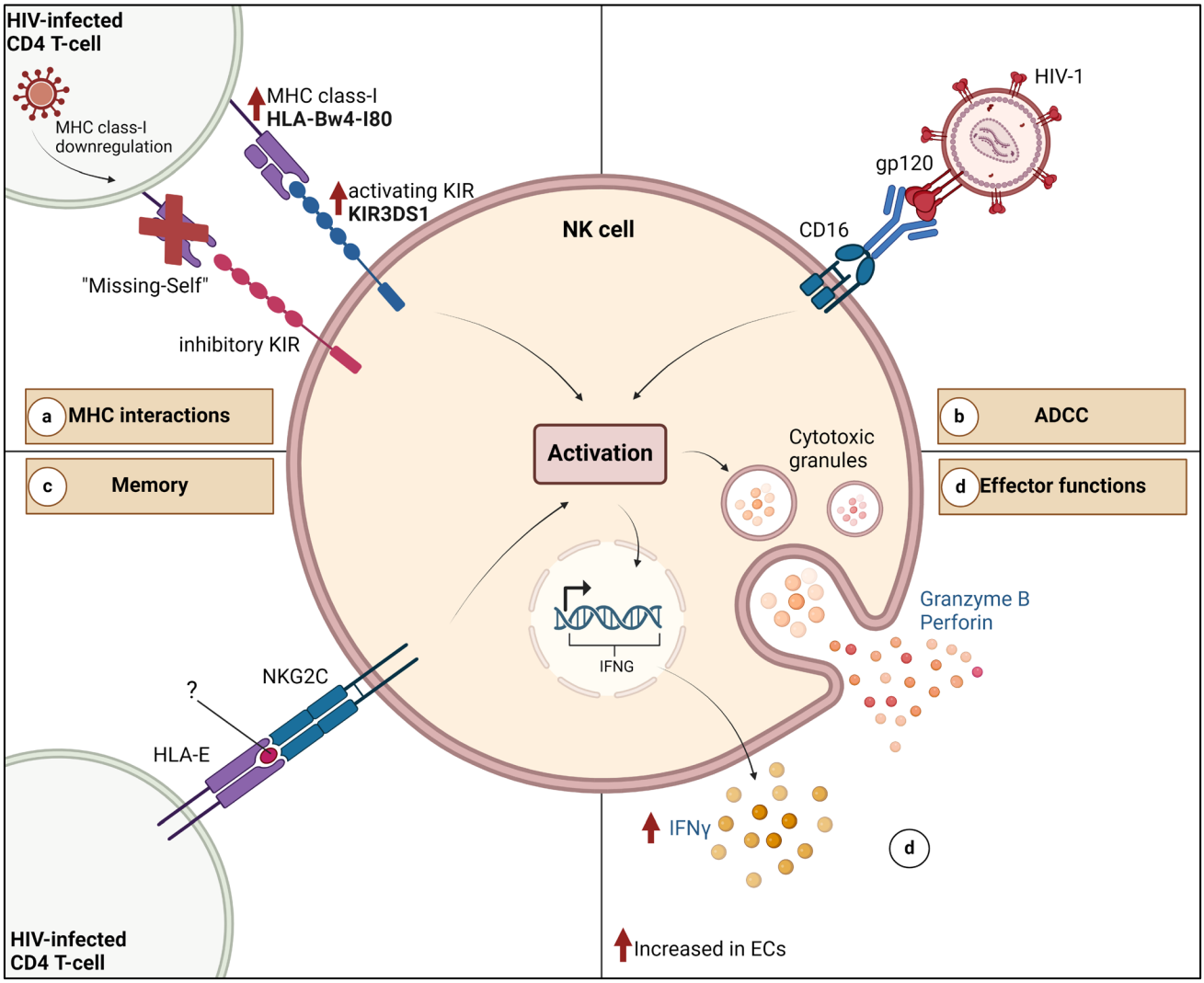

Fig. 2 NK cells possess several mechanisms to mount an anti-viral response in HIV elite controllers. MHC class-I molecules like HLA-Bw4-I80 are associated with HIV elite control and bind to their activating counterpart, KIR3DS1. HIV can also downregulate MHC class-I molecule expression, which induces a "Missing-Self" mechanism in NK cells by a lack of binding inhibitory KIRs (**a**). NK cells can mount anti-viral responses by activating ADCC. Anti-gp120-Ab bound to the pathogen can bind to CD16 with their respective Fc tail (**b**). The activating receptor NKG2C can bind to its ligand HLA-E in a memory-like response, but the exact mechanisms are unknown in HIV (**c**). These different mechanisms lead to the activation of NK cells, followed by the release of Granzyme B and Perforin from cytotoxic granules. Additionally, IFNγ is produced in large amounts to aid in anti-viral responses (**d**)

viral clearance in various viral infections [79, 80]. ADCC involves the interaction of the Fc region of antibodies with the CD16 receptor on NK cells, triggering the release of cytokines and chemokines, as well as cytotoxicity activities, to kill virally infected cells (Fig. 2b) [81]. Ackerman et al. and Lambotte et al. reported that despite lower titers of plasma anti-gp120 IgG NK cells of spontaneous controllers exhibited enhanced ADCC responses compared to normal progressors [82, 83]. Madhavi et al. identified higher levels of gp120-specific antibodies in controllers capable of stimulating NK cell responses in NK cell activation assays, including the induction of IFNγ secretion and CD107a externalization, compared to untreated normal progressors [84]. Studies have suggested that HIV-specific ADCC responses might influence the establishment of viral setpoints and correlate with slower rates of disease progression [85, 86].

In line with that, there have been efforts to enhance the NK cell-ADCC activity against HIV infection, specifically in combination with LRA, to pursue the "kill" aspect of the "Shock and Kill" strategy. Combining the TLR7 agonist GS-9620 with the broadly neutralizing antibody (bNAB) PGT121, recognizing HIV gp-120, has shown promise in reducing viral DNA levels in SIV-infected Macaques, notably through ADCC by NK cells [87]. Similarly, treatment with the TLR9 agonist MGN1703 has been shown to enhance innate immune responses by modulating pDCs, increasing plasma IFNα levels, and significantly activating of cytotoxic NK cells [88].

The Induction of Memory-Like NK Cells in Response to HIV Infection

Circulating NK cells have a short lifespan of approximately two weeks [89]. However, emerging research has spotlighted the expansion of memory-like NK cells in response to viral infections [90–92]. In cytomegalovirus (CMV) infections, $NKG2C^+$ NK cells exhibit heightened cytokine production and amplified release of cytotoxic granzyme B and perforin upon re-stimulation, elucidating their potent antiviral capabilities [92, 93]In the context of HIV infections, memory-like NK cells, reminiscent of those observed in CMV infections, underscore the importance of the activating NK cell receptor NKG2C and its interaction with HLA-E in shaping this NK cell subpopulation [94–96]. Notably, both the CMV peptide UL40 and HIV-Gag bind to HLA-E, suggesting a potential cross-protection between HIV and CMV infections via HLA-E/NKG2C interaction [97, 98]. Recent studies, particularly by Jost et al., have unveiled the development of memory NK cells following exposure to HIV peptides, largely reliant on NKG2C/CD94 interactions with HLA-E (Fig. 2c) [99]. While conflicting results regarding the prevalence of $NKG2C^+CD57^+$ NK cells in spontaneous controls compared to normal progressors persist, Ma et al. and Gondois-Rey et al. reported a negative correlation between the percentage of $NKG2C^+$ NK cells and concurrent viral load, indicative of a potential role in modulating viral set points [100, 101]. However, investigations by Alsulami et al. involving different NKG2C genotypes and HIV viral load set points yielded heterogeneous outcomes. This was potentially influenced by the impact of CMV-induced $NKG2C^+$ cells, given the prevalent CMV seropositivity among PLHIV in this study [94]. Very recently, however, Samchez-Gaona et al. showed that memory-like NK cells from ECs have a strong ability to kill HIV-infected cells through ADCC [102].

Given the possibility that memory-like NK cells can contribute to HIV control, the usage of CMV-based vaccines expressing SIV antigens holds promise as an alternative to trigger the expansion of these effector cells while also inducing anti-HIV immunity simultaneously. While efforts of CMV-based vaccines were made to elicit MHC-E restricted $CD8^+$ T-cell responses (extensively reviewed in [103]), NK cell responses have not been intensively evaluated due to the possibility of NK cell inhibition via the MHC-E/NKG2A-axis, the inhibitory counterpart of NKG2C. However, recent studies suggested that vaccination of healthy volunteers with the pandemic influenza vaccine Pandemrix® containing the adjuvant AS03 induced enhanced frequencies of NKG2C-expressing NK cells with cytotoxic properties 7- or 14 days post-vaccination. The authors suggested that the usage of AS03 as an adjuvant contributed to specific NK cell phenotype and functionality as a result of enhanced antigen-presentation and cytokine secretion induced by other innate immune cells, including DCs, macrophages, and monocytes [104]. Thus, the induction of virus-induced memory NK cells by vaccination is another example of therapeutic interventions, which may offer opportunities for long-term responses against HIV and holds promise for improving outcomes in HIV infections.

The Contributions of Soluble Mediators Produced by Monocytes

Monocytes play a pivotal role in driving inflammatory responses as a major source of inflammatory cytokines such as IL-6, TNFα, and IL-1β [105]. In HIV infection, excessive immune activation is often associated with poor disease prognosis, as it may facilitate HIV spread and favor reservoir seeding [106, 107]. In this context, increased NFκB translocation, a common regulator of the production of pro-inflammatory cytokines, also leads to heightened transcription of integrated HIV and subsequent virion production [108, 109]. Therefore, mechanisms that enhance cytokine production may simultaneously boost host responses against infectious agents but, if not well-balanced, may also contribute to detrimental effects due to excessive inflammation.

van der Heijden et al. reported increased IL-1β production capacity after stimulation with microbial-derived ligands of circulating monocytes from PLHIV in comparison to healthy individuals, and this ex vivo production capacity was sustained for at least a year [110]. Moreover, the authors demonstrated that the IL-1β production in PLHIV on ART correlated with increased plasma concentrations of high-sensitivity C-reactive protein and soluble CD14 hypothesized to contribute to the development of inflammatory comorbidities. The authors attributed these persistent increases in IL-1β to a concept called trained immunity, as it was demonstrated that PLHIV with high IL-1β levels had also increased circulating b-glucan [110]. b-Glucan is a component of the cell wall of Candida albicans, and it is known for its protective effects against both infection and cancer through trained immunity. The trained immunity concept was introduced by Netea et al. a decade ago and describes the presence of memory in innate immune cells through metabolic and epigenetic mechanisms [111, 112]. During a first encounter with a stimulus, specific acetylation and methylation marks are deposited on lysine residues of histones, leading to changes in chromatin accessibility, enabling increased functional responsiveness of innate immune cells upon subsequent encounters with a secondary stimulus [113].

Recently, Dubrovsky et al. showed that treatment of monocytes with HIV-Nef in extracellular vesicles (exNef) induces trained immunity in monocytes resulting in TNFα and IL-6 production upon LPS restimulation (Fig. 3) [114]. These findings were associated with changes in the chromatin of genes associated with inflammation and cholesterol metabolism, such as SMAD2, IL17RA, ABCB11, and SC5D. These results indicate a possible new role of virally induced long-lasting epigenetic modifications contributing to increased immune activation but also to chronic inflammation in PLHIV on ART. This observation was supported by the findings of Knoll et al. describing the alterations in the transcriptional landscape of immune cells, emphasizing the changes in proinflammatory gene programs of PBMCs from PLHIV compared to healthy controls. Specifically, monocytes from PLHIV showed enriched IFN-signaling, as evidenced by the upregulation of IFN-related genes, such as *CXCL10, STAT2, MX2,* and *XAF1* and attributed this to the chronic inflammation state in PLHIV [115].

In the context of spontaneous HIV control, in another study in which both PLHIV on ART and ECs as well as HIV-negative individuals were enrolled, the authors demonstrated that in comparison to PLHIV on ART, monocytes from ECs have an increased expression of the IFN–inducible genes IFIT1 and IFIT3. Furthermore, monocytes from ECs responded with increased production of IL-1β upon stimulation with the TLR4 ligand LPS compared to both HIV-negative controls and ART recipients [116]. Phenotypically, monocytes of both ECs and ART recipients had decreased CCR2 expression and increased CX3CR1 expression relative to HIV-negative controls, highlighting the impact of HIV on monocyte migration into tissues [116]. These findings suggest that while trained immunity in monocytes may contribute to enhanced immune responses in PLHIV, it may also play a role in sustaining chronic inflammation and immune dysregulation, even in those on ART.

Potential Contributions of Innate-Derived Responses in Shaping the Reservoir of HIV Controllers

The HIV reservoir consists of proviruses that are integrated into the host genome, bearing the potential to produce new, infectious HIV particles. Intact proviruses contain a complete and functional HIV genome, while defective proviruses contain genetic mutations, deletions, or other alterations that prevent them from producing functional HIV particles. The reservoir of spontaneous HIV controllers differs from that of normal progressors on ART in several ways. For instance, it has been shown that the reservoir size of spontaneous controllers is smaller, as measured by the amount of HIV DNA in $CD4^+$ T cells [117, 118]. Additionally, as the transcriptional activity of proviruses is under epigenetic influence, it is important where the proviral DNA is integrated into the host DNA. In controllers, intact HIV DNA is mostly located in regions accompanied by heterochromatin features that do not facilitate HIV replication, while defective proviruses are often found in permissive euchromatin regions ([119, 120]). $CD4^+$ T-cells containing replication-competent HIV proviral DNA in permissive euchromatin regions have been eliminated by the immune system so that only "blocked and locked" replication-competent proviral DNA remains in elite controllers, as well as defective provirus. The pressure imposed by the immune system aiming at eliminating HIV-infected cells is one of the mechanisms proposed to favor the virus to integrate into "gene deserts", which are centromeric satellite or microsatellite DNA of non-coding regions of the host genome that are far away from active transcription sites in heterochromatin regions (Fig. 4) [121–123], therefore mimicking the configuration reported in spontaneous controllers.

In ECs, the diversity of viral sequences within an individual is smaller than in non-controllers. This suggests that intact viral sequences in ECs were established early in the disease and stayed stable over time [124]. These findings point to a strong, early immune response as key to the unique way ECs control the virus. To maintain this control, it's important for the immune system to stay active and continue applying pressure on the virus.

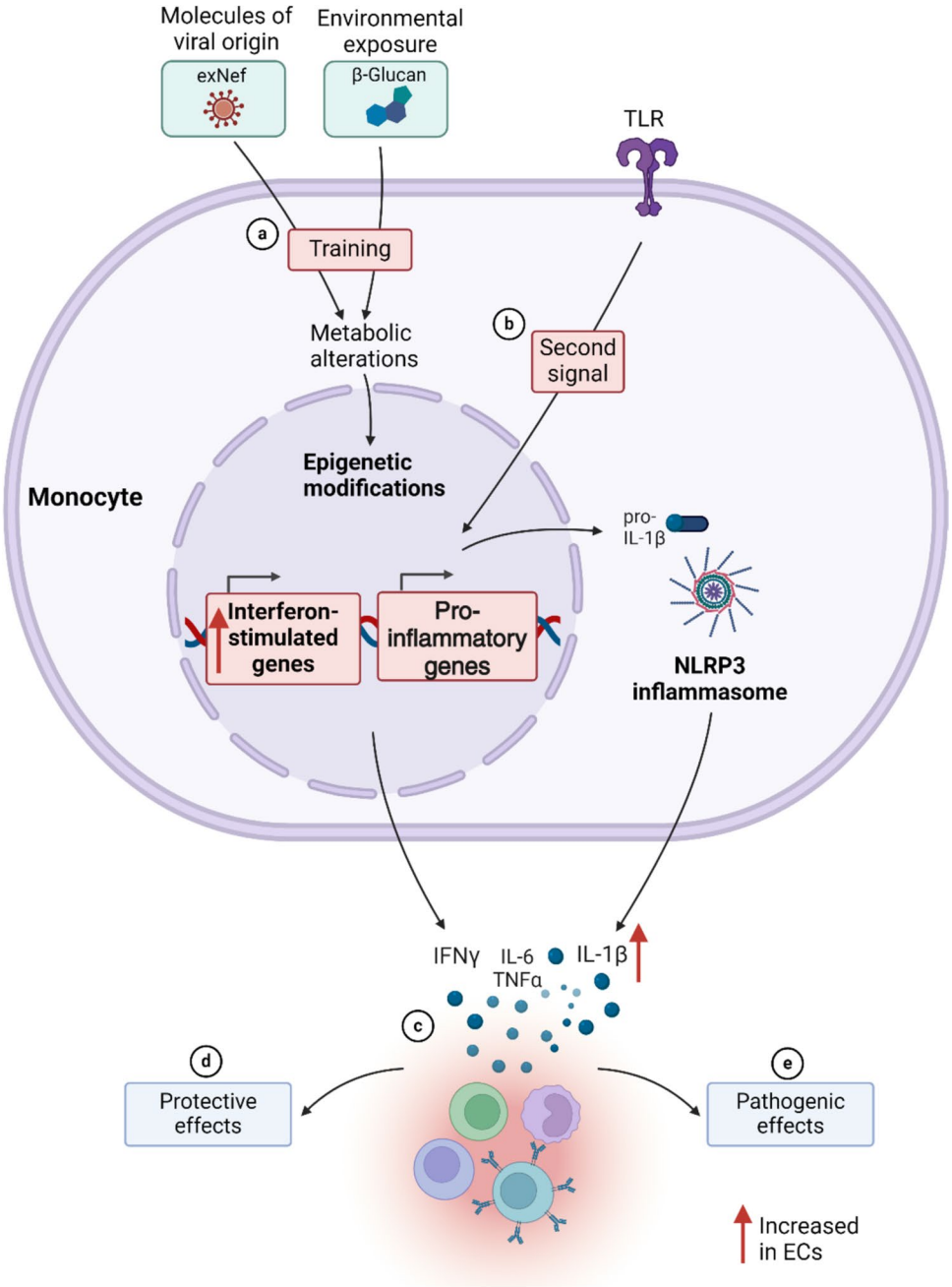

Fig. 3 Trained innate immune cells can contribute to increased immune activation or chronic inflammation in PLHIV. (**a**) Training through molecules of viral origin or environmental exposure to, e.g., exNef or β-Glucan induces epigenetic modifications through metabolic alterations in monocytes. (**b**) A second signal through, e.g., TLR activation activates inflammatory pathways that have been epigenetically modified, (**c**) which results in a potent release of inflammatory cytokines like IL-1β, IL-6, TNFα, and IFNγ, leading to immune-cell activation. (**d**) Immune activation can either lead to protective effects, e.g., against infections, or (**e**) pathogenic effects, like chronic inflammation

The mechanisms behind the atypical viral reservoir configuration in ECs are not completely understood. Research has shown that adaptive immune cells, specifically HIV-specific cytotoxic $CD8^+$ T cells, play a critical role in the elimination of the viral reservoir by triggering strong cytotoxic responses [20, 22, 125, 126]. As the innate immune system is the first line of defense and responds considerably faster to the initial HIV infection than the adaptive immune system, it can be hypothesized that an innate-driven effector mechanism would contribute to the elimination of virus-harboring cells during the early stages of the infection. Studies that investigate the role of the innate immune system influencing the reservoir composition in spontaneous controllers are scarce, but this interaction is becoming more relevant in recent studies. Studies that followed PLHIV immediately after HIV diagnosis highlighted the importance of NK cells, DCs, and monocytes during hyperacute HIV, further strengthening a potential role for innate immune responses against the virus, inducing EC-like status [127, 128]. Interestingly, treatment of active hepatitis-C-virus (HCV) infections in PLHIV with IFNα resulted in a significant reduction of HIV-DNA and $CD4^+$ T-cell-associated HIV-DNA copies, caused by the expansion of cytotoxic NK cells, while $CD8^+$ T-cells were not associated with the

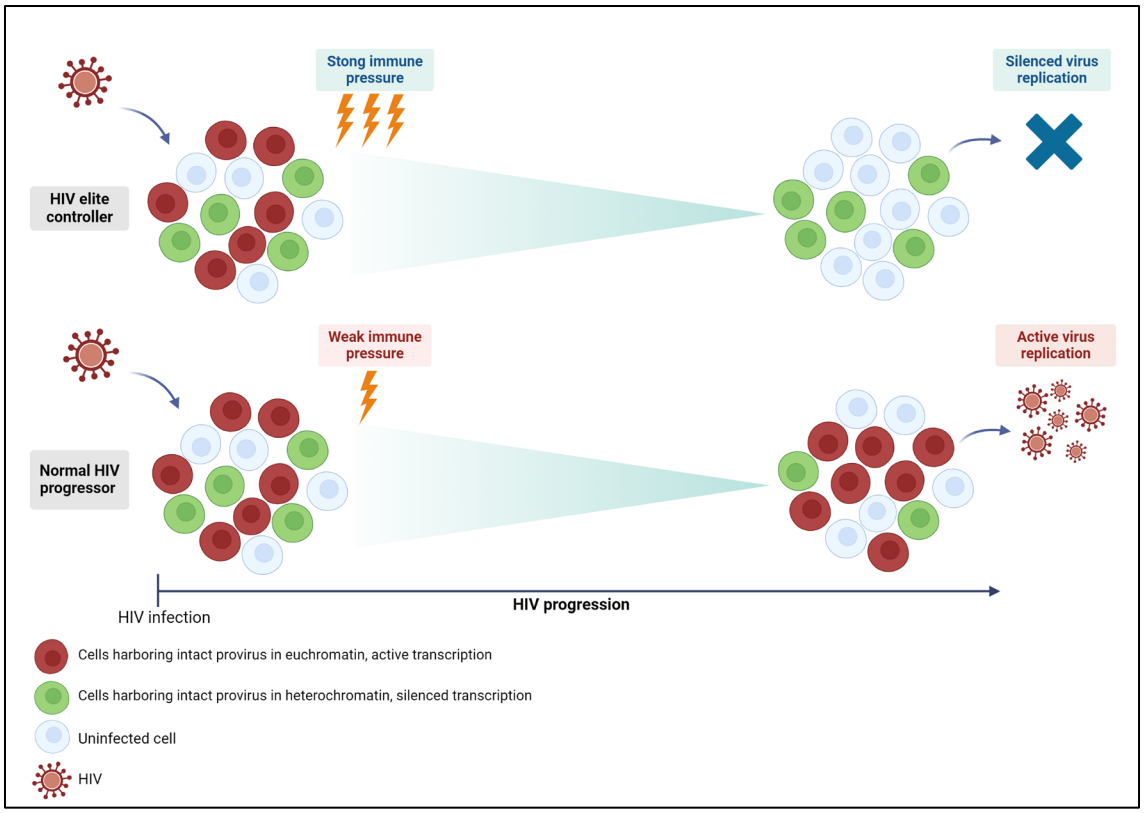

Fig. 4 Immune pressure shaping the unique viral reservoir in HIV elite controllers towards a 'locked and blocked' configuration. Upon HIV infection, the virus infects predominantly CD4 + T-cells and integrates its genome, preferably in euchromatin regions, for potent viral replication (red cells). In HIV elite controllers, this enables the immune system to recognize virally infected cells early on and eliminate infected cells. This creates an evolutionary pressure and infected cells with viruses integrated into heterochromatin regions with less active viral transcription survive this process (green cells), resulting in a small HIV reservoir with nearly silenced virus replication. In normal progressors, the immune pressure is not strong enough, and immune cells are not able to eliminate the cells harboring the viral genome in euchromatin, resulting in a viral reservoir with active viral transcription

observed reservoir-reduction [129, 130]. Kazer et al. found that some individuals (P3 and P4) that had EC-like features had proliferative, cytotoxic NK cells before HIV-specific CD8 + T cells emerged. This, along with the presence of polyfunctional monocytes, suggests that early innate immune responses are crucial for initiating viral control [127].

Other Innate Immune Cells in HIV Control

Natural Killer T-cells

Natural Killer T (NKT) cells are a unique T-cell population with innate and adaptive immune cell characteristics (reviewed in [131]). NKT cells produce both Th1 (IFNγ and TNFα) and Th2 cytokines (IL-21 and IL-22), which can modulate immune responses and contribute to immune regulation. Additionally, NKT cells can directly exert cytotoxic functions through the secretion of perforin, granzymes, and engagement of Fas on target cells via FasL, enabling them to eliminate infected cells, thereby contributing to the control of microbial and retroviral infections [132, 133]. The precise role of NKT cells in viral infections is not completely understood, but it is known that HIV infection causes significant depletion of NKT cells, with a rapid and selective reduction in NKT cell numbers during the course of infection [134]. Interestingly, HIV controllers have functional NKT cells similar to healthy controls, showing a similar pattern of cytokine secretion after stimulation with the potent NKT cell activator a-GalCer, predominantly Th1 type, with IFNγ and IL-2 secretion being the most frequent [135]. This suggests that the functionality of NKT cells is maintained in HIV controllers and may play a role in controlling HIV infection.

Gamma-*delta* T-cells

γδ T-cells are a subset of T-cells that express a unique T-cell receptor (TCR) composed of γ and δ chains, unlike the more common αβ T-cells that express TCRs composed of α and β chains. [136]. γδ T-cells play a significant role in the immune response to the virus, with the Vδ2 subset being

particularly important in early infection[137]. γδ T-cells have been found in various tissues where HIV reservoirs exist, such as the gut, spleen, bone marrow, and reproductive tracts, suggesting that γδ T-cells may have the potential to target and eliminate HIV-infected cells in these reservoir sites [138]. Riedel et al. showed that HIV controllers have significantly higher Vδ2 T-cells compared to normal progressors or HIV-negative individuals, suggesting that HIV controllers might be able to maintain this cell population, contributing to viral control [139].

Granulocytes

Among immune cells, neutrophils are the most prevalent in the blood, making up 50–80% of white blood cells [140]. However, very little is known about their role in HIV pathogenesis and potential contribution to HIV elite control. One study showed that neutrophils from ECs showed decreased HLA-DR expression after PBMC HIV infection, indicating lower HIV spread among mucosa or draining lymph nodes [141]. Another study suggests that granulocytes from ECs demonstrated elevated expression of antiviral factors upon stimulation with HIV [142]. Whether neutrophils, eosinophils, and basophils contribute to the HIV controller status and their unique HIV reservoir configuration remains to be studied further.

Conclusion

In this review, we summarize the findings regarding the contribution of innate immune cells to HIV control and reservoir dynamics. We highlighted the potential for innate-derived mechanisms in shaping the immune response, leading to elite control, which may subsequently impact the reservoir size in this group of PLHIV. Although our understanding of the involvement of the innate immune system in this process remains limited, a few studies have begun to demonstrate that spontaneous controllers possess enhanced innate immune functions. These functions could play a critical role during the early stages of infection by pushing the viral genome into a 'locked and blocked' state, transcriptionally silencing, and prohibiting the production of new virus particles by integration of the viral genome in transcriptionally inactive regions of the host genome. This state of viral dormancy is driven by mechanisms such as epigenetic modifications and the activity of certain immune effectors, which effectively "trap" the virus in a latent form. The collective action of non-genetic effector responses mediated by innate immune cells represents a coordinated front against HIV. Strategies that target multiple facets of innate immunity—such as enhancing antigen presentation, producing soluble mediators, regulating inflammation, and promoting viral clearance—may offer new opportunities for achieving elite control status and potentially eliminating the viral reservoir.

Key References

- Martin-Gayo E, Gao C, Calvet-Mirabent M, Ouyang Z, Lichterfeld M, Yu XG (2022) Cooperation between cGAS and RIG-I sensing pathways enables improved innate recognition of HIV-1 by myeloid dendritic cells in elite controllers. Front Immunol 13:1–12.
    - This study identifies that cDCs of ECs have increased detection mechanisms of viral genomic information.
- Hartana CA, Rassadkina Y, Gao C, Martin-Gayo E, Walker BD, Lichterfeld M, Yu XG (2021) Long noncoding RNA MIR4435-2HG enhances metabolic function of myeloid dendritic cells from HIV-1 elite controllers. J Clin Invest.
    - This work describes the regulation of cDCs in ECs via a lncRNA that impacts the immunometabolism and suggests a role for trained innate immunity in DCs.
- Hartana CA, Lancien M, Gao C, Rassadkina Y, Lichterfeld M, Yu XG (2023) IL-15-dependent immune crosstalk between natural killer cells and dendritic cells in HIV-1 elite controllers. Cell Rep.
    - This article describes mechanisms of crosstalk between cDCs and NK cells via IL-15 in ECs.
- Jost S, Lucar O, Lee E, et al. (2023) Antigen-specific memory NK cell responses against HIV and influenza use the NKG2/HLA-E axis. Sci Immunol 8:eadi3974.
    - This work elucidates the importance of the NKG2/HLA-E axis in memory responses of NK cells towards HIV-Env and HIV-Gag.
- Dubrovsky L, Brichacek B, Prashant NM, et al. (2022) Extracellular vesicles carrying HIV-1 Nef induce long-term hyperreactivity of myeloid cells. Cell Rep 41:111674.
    - This study elucidates molecular mechanisms behind exNef mediated trained immunity in monocytes.
- Jiang C, Lian X, Gao C, et al. (2020) Distinct viral reservoirs in individuals with spontaneous control of HIV-1. Nature 585:261–267
    - The study found that ECs have significantly lower levels of intact and defective proviral genomes compared to ART-treated individuals.

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Declarations

Competing Interests AH, AJAMvdV, and JCdS are part of the 2000HIV collaboration, which is supported by ViiV Healthcare. FSB declares no conflict of interest.

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