Published in final edited form as:
Curr Opin HIV AIDS. 2011 January ; 6(1): 43–48. doi:10.1097/COH.0b013e32834086b3.

Hematopoietic stem/precursor cells as HIV reservoirs

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Abstract

Purpose of Review—Although latent HIV-1 infection in CD4+ T cells contributes to HIV persistence, there is mounting evidence that other viral reservoirs exist. Here, we review recent data suggesting that the infection of hematopoietic progenitor cells creates additional reservoirs for HIV in vivo.

Recent Findings—New studies suggest that some types of hematopoietic progenitor cells have the potential to generate reservoirs for HIV. This review focuses on two types that can be infected by HIV in vitro and in vivo: multipotent hematopoietic progenitor cells in the bone marrow and circulating mast cell progenitors. Of these two types, only CD34+ bone marrow cells have been shown to harbor latent provirus in HIV+ individuals with undetectable viral loads on HAART. Latent infection of these long-lived cell types may create a significant barrier to HIV eradication; indeed the potential infection of hematopoietic stem cells in particular could lead to an HIV reservoir that does not appreciably decay over the lifespan of the host.

Summary—To eradicate HIV infection, it will be necessary to purge all viral reservoirs in the host. The findings highlighted here suggest that multipotent hematopoietic progenitor cells and possibly tissue mast cells may constitute significant reservoirs for HIV that must be addressed in order to eliminate HIV infection. Future studies are needed to determine which types of CD34+ cells are infected in vivo and whether infected CD34+ cells contribute to residual viremia in people with undetectable viral loads on HAART.

Keywords

Hematopoietic progenitor cells; mast cells; HIV reservoirs; latent infection

Introduction

Reservoirs of latent HIV-1 infection represent a barrier to the eradication of the disease. Although latently infected resting CD4+ T cells are clearly an important viral reservoir,

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there is increasing evidence that resting T cells are not the only reservoir of HIV [1,2*,3*]. Recently, several studies have demonstrated that three subsets of hematopoietic precursor cells can become infected with HIV: multipotent hematopoietic progenitor cells (HPCs) [4**], mast cell progenitors [5], and monocytes (reviewed in [6]). As the infection of monocytes is important in the spread of HIV to the central nervous system, a topic addressed later this issue, these cells will not be discussed here. Instead, this review will focus on the infection of multipotent HPCs and progenitor mast cells, each of which has a unique potential to generate a long-lived reservoir of HIV. We will discuss the evidence for infection of multipotent HPCs and progenitor mast cells as well as the role that infection of these cells may play in HIV persistence.

HIV infection of multipotent HPCs

Studies of HIV infection in HPCs have focused on several cell populations. Many studies have examined infection in cells expressing CD34, a cell-surface marker found on many types of HPCs ranging from hematopoietic stem cells (HSCs) with extensive self-renewal capacity to progenitor cells committed to differentiation [7]. Other studies have examined the CD34+, CD133+ population, which is enriched for multipotent progenitor cells [7,8]. Finally, some studies have used in vitro colony-forming assays to focus on multipotent cells. Only multipotent cells – HSCs, multipotent progenitor cells (MPPs), and common myeloid progenitor cells (CMPs) – are capable of forming colonies with representatives from all myeloid lineages; thus colony-forming assays allow multipotent cells to be functionally defined [7]. Colony-forming assays do not allow lymphoid cells to grow, however, and thus HSCs and MPPs cannot be distinguished from CMPs with this assay. The surface markers and self-renewal capacity of CD34+ HPCs at different stages of differentiation are summarized in Figure 1.

Several studies have reported that a proportion of CD34+ cells express the HIV receptors CD4, CXCR4, and CCR5, making these cells potentially susceptible to HIV-1 infection (reviewed in [6]). Beginning more than twenty years ago, multiple studies suggested that infection in CD34+ cells was possible, though rare, both in vitro and in vivo [9-15]; however, these studies could not rule out contamination by other cell types. Furthermore, studies assessing HIV-1 infection of multipotent colony-forming or CD133+ HPCs failed to detect either HIV-1 infection or expression of any of the three main HIV receptors in these cells [16-19].

Based on these reports, the consensus has been that CD34+ cells are not an important target of HIV-1 infection and that HIV cannot infect multipotent HPCs at all. Recently, however, improved techniques have permitted reexamination of this topic, and this reexamination has unambiguously shown that a percentage of immature, multipotent HPCs are susceptible to HIV infection. First, a 2007 study investigated the ability of HIV-1 subtype C to infect multipotent CD34+ HPCs in vitro and in vivo [20**]. While the authors could not detect HIV-1 subtype B infection in HPCs capable of forming multilineage colonies, they found that several isolates of HIV-1C could infect multipotent cells. Furthermore, the authors were able to detect HIV proviruses in CD34+ cells from the peripheral blood of 12 out of 19 donors infected with HIV-1C; importantly, the level of HIV detected in 11/12 of these CD34+ samples was greater than the level observed in total peripheral blood mononuclear cells from the same patient, eliminating the potential for contamination that plagued earlier studies [20**]. The authors thus suggest that although HIV-1B may be unable to infect multipotent HPCs, HIV-1C faces no such barrier to infection.

While this study showed that HIV-1C infects multipotent HPCs, the ability of HIV-1B to infect multipotent HPCs remained ambiguous. The authors concluded that HIV-1B could

not infect multipotent HPCs because they could not detect HIV DNA in multilineage colonies generated from HPCs exposed to HIV-1B isolates. However, the absence of HIV+ colonies could instead indicate that although HIV-1B can infect multipotent cells, the infection is cytotoxic either immediately or upon proliferation and differentiation of the cells, leading to cell death rather than infected colony formation.

We undertook a study to definitively assess whether HIV-1B could infect multipotent HPCs [4**]. Using a flow cytometric assay to detect the expression of HIV proteins in individual CD34+ cells after very short incubation periods (three days), we found that a variety of human immunodeficiency viruses, including several HIV-1B isolates, could infect CD34+ cells derived from bone marrow or umbilical cord blood [4**]. Because HIV-1B was cytopathic for the cells, however, the number of infected cells declined dramatically over time. We furthermore showed that exposure of CD34+ cells to a non-cytotoxic, GFP-expressing HIV-1B viral construct permitted the formation of multilineage colonies that were uniformly GFP+, demonstrating that HIV-1B envelopes can target multipotent HPCs in vitro [4**].

We next examined whether CD34+ HPCs could harbor latent as well as active HIV-1, a distinction that had not previously been assessed. As noted above, the initially robust infection in CD34+ HPCs declined over time until active infection could no longer be observed [4**]. If these cells were exposed to agents that stimulated myeloid differentiation, however, we observed a resurgence of viral gene expression [4**]. This observation was most notable with a dual-tropic virus that could efficiently spread the resurging infection to the differentiating myeloid cells [4**]. We also created a novel HIV latency probe that, in addition to expressing HIV proteins under the control of the viral LTR, expresses GFP under the control of the constitutively active spleen focus-forming virus (SFFV) promoter. When this construct was used to infect HPCs, we could visualize a population of GFP+, HIV Gag-, latently infected cells that was stable for at least 20 days in culture [4**]. Together, these data demonstrate that latent HIV-1 infection of HPCs is possible in vitro.

Finally, our study assessed the infection of CD34+ bone marrow HPCs in HIV-infected patients. In a sample of HIV+ individuals with high viral loads (>50,000 copies HIV-1 RNA/mL), we could directly detect HIV Gag expression in CD34+, CD133+ cells from a subset of donors [4**]. In the remaining donors in this high viral load cohort, we observed HIV Gag expression when we stimulated the CD34+ cells with cytokines to induce myeloid differentiation, thus providing evidence that latent HIV infection occurs in CD34+ cells in vivo [4**]. As expected, some CD34-depleted bone marrow cells also expressed Gag initially. However, these cells rapidly died under our culture conditions, which were optimized for differentiating CD34+ cells. The ability to specifically propagate cells derived from CD34+ cells substantially reduced the possibility that contaminating cell types were confounding our results[4**].

We also looked for HIV-1 proviral DNA in CD34+ cells from a group of HIV-positive individuals on HARRT with clinically undetectable (<50 copies/mL) viral loads. As expected, these individuals had no evidence of active infection in their CD34+ cells [4**]. However, we detected HIV-1 DNA in CD34+ cells from more than 40% of these donors; in all cases, we could not detect comparable amounts of HIV DNA from bone marrow depleted for CD34, indicating that infected CD34- bone marrow cells do not persist at similar levels in people on HAART [4**]. The sensitivity of this assay was low – we could detect HIV genomes in CD34+ cells only if at least 1 in 10,000 cells harbored an HIV genome. This limit of detection is higher than the frequency of integrated genomes that have been observed in the resting CD4+ T cell reservoir in some patients [21]; thus, it is possible that other patients in our cohort harbor HIV-infected CD34+ cells at a lower frequency. The

ability of CD34+ cells to harbor latent HIV in vivo, even in patients undergoing successful HAART treatment, demonstrates that CD34+ cells can act as a long-lived reservoir of HIV. Additional studies are now needed to determine which type of CD34+ cells harbor HIV genomes in vivo and whether latently infected CD34+ cells contribute to residual viremia in patients on HAART.

HIV infection and hematologic abnormalities

In addition to creating a latent viral reservoir, HIV infection of CD34+ cells might lead to HPC death and hematopoietic abnormalities. Consistent with this possibility, many studies have reported hematopoietic defects associated with HIV [22-30], including the depletion of CD34+ bone marrow cells [31,32]. The existence of HIV-associated hematologic abnormalities is well known and has been attributed to a variety of factors, including altered stromal cytokine production [32] and use of specific antiretrovirals [33]. Recently, however, Redd and colleagues were able to show a direct association between infection of CD34+ cells and anemia in their cohort [20**]. This evidence suggests that in addition to creating a latent reservoir of virus, HIV-1 infection of HPCs can cause HPC death and hematopoietic defects.

A model for infection of multipotent HPCs

Although HIV-1 infection of hematopoietic stem cells has not been directly assessed, the presence of infected CD34+ cells even in individuals on successful HAART treatment suggests that at least some infected CD34+ cells are sufficiently long-lived to create a significant barrier to HIV eradication. Based on this finding and the studies described above, we have developed the following model describing HIV infection of HPCs in vivo (Figure 2). When multipotent HPCs become infected with HIV, there are two possible outcomes: either an active infection leads to HPC death, contributing to the HIV-associated hematologic abnormalities described above, or a latent infection occurs. If latent infection occurs in a cell with self-renewal capacity, continued self-renewal can generate a long-lived reservoir of latent HIV. If a latently infected daughter cell is stimulated to differentiate, however, the latent virus reactivates, leading to the death of the cell and further contributing to hematologic dysfunction. In this model, viral reactivation also results in virion release, contributing to the low-level viremia observed even in HAART-treated patients.

This model would seem to suggest that defective HIV-1 proviruses incapable of reactivation should be detectable in multiple hematopoietic lineages that cannot be infected by HIV-1. The presence of such defective proviruses in CD8+ T lymphocytes and granulocytes has been observed in one patient [34]; however, a second study detected only minimal integration of HIV genomes in naïve CD8+ cells from patients and could not rule out contamination by other cell types [35]. Additional studies are required to determine whether defective HIV-1 genomes can be observed in CD8+ T cells and other hematopoietic lineages in multiple patients.

Mast cell progenitor infection

In addition to multipotent HPCs, committed mast cell progenitors (prMCs) are also susceptible to HIV infection [5]. Mast cells are tissue-resident immune cells important in allergy, inflammation, and helminthic infection [36,37]. Although HIV-1 cannot infect mature mast cells [38*], HIV-1 can infect prMCs in peripheral blood [5]. As prMCs eventually migrate to tissues, where they survive for at least ten months [39,40], infection of prMCs could create a relatively short-term reservoir of HIV-1 infection (Figure 3).

Recently, placental tissue mast cells were shown to harbor latent HIV in vivo in pregnant, HAART-treated women with detectable viral loads [38*], suggesting that infection of

prMCs creates a reservoir in mast cells of patients with ongoing viral replication. However, a recent study could not detect active HIV-1 replication in tissue mast cells from ten donors [41*], suggesting that actively infected mast cells are rapidly cleared in successfully treated patients even though HIV-1 is not rapidly cytopathic in these cells [38*]. At present, long-term significance of the possible mast cell reservoir is unclear, and it is not known whether a mast cell reservoir exists in HAART-treated patients with undetectable viral loads. Additional studies of mast cell infection to determine whether there is a reservoir of latently infected mast cells in patients with undetectable viral loads would clarify the role of these cells in HIV persistence.

While prMCs were originally thought to be susceptible only to CCR5-tropic HIV-1, a recent report demonstrated that prMCs are also susceptible to CXCR4-tropic HIV infection in the presence of IgE [42**]. Interactions between IgE and FcεRI on the mast cell progenitor surface lead to a dramatic increase in CXCR4 expression and susceptibility to CXCR4-tropic HIV infection [42**]. Thus, if mast cells do constitute a reservoir of HIV in HAART-treated patients, they could harbor both CCR5- and CXCR4-tropic HIV-1. The putative role of mast cells in HIV persistence is shown in Figure 3.

Do multipotent HPC or mast cell reservoirs contribute to HIV persistence?

Although the role of HPCs in HIV persistence has not yet been directly evaluated, recent data on the structure of the residual viral population is consistent with the possibility that infection of HPCs generates a long-lived viral reservoir in many patients. A substantial body of evidence indicates that not all of the residual viremia in many HIV-infected individuals on successful HAART therapy originates from the resting CD4+ T cell reservoir [1,3*] or indeed from any peripheral blood cells [2*], though there is evidence that plasma viral sequences are more closely related to sequences in peripheral blood monocytes than to sequences in CD4+ T cells [43*]. In addition, residual virus does not undergo significant evolution during effective treatment, thus suggesting that continuing active replication is not a major source of residual viremia [44]. Together, these data suggest that a major source of residual viremia in treated patients may be neither latently infected CD4+ T cells nor continued active replication, but instead a heretofore uncharacterized reservoir of latent HIV.

There is also evidence that residual plasma viremia is largely homogenous, with just one or two viral clones accounting for most residual viremia in most patients on HAART [1] or most rebounding virus during treatment interruptions [45]. These data suggest that the major source of persistent HIV production is either a single cell, such as an actively infected mast cell that resists HIV-induced cell death, or a clonal population of cells originating from a single infected cell, such as a group of HPCs derived from the infection of a self-renewing HSC. Studies comparing proviral sequences in CD34+ cells and mast cells to residual plasma sequences would reveal whether either of these explanations is accurate.

Finally, a recent analysis of the decay kinetics of HIV reservoirs in HAART-treated patients suggests the existence of two long-term viral reservoirs: one with a half-life of 9-15 months, approximately consistent with the previously reported half-life of the resting T cell reservoir (6-44 months [46-49]), and a second reservoir with no appreciable decay over at least seven years [50*]. The indefinite half-life of this latter reservoir is consistent with the exceedingly long lifespan of a long lived precursor cell, potentially even HSCs. More research will be needed to determine which type of CD34+ cells harbor latent forms of HIV in vivo and what the half-life of this reservoir is.

Conclusion

Although for many years it was unclear whether multipotent HPCs could become infected with HIV-1, recent studies show that CD34+ cells support both active and latent infection in vitro and in vivo. Infection of these cells likely contributes to the anemia and hematopoietic dysfunction associated with HIV and furthermore creates a long-lived, stable viral reservoir that may contribute to residual plasma viremia in HAART-treated patients. This reservoir may seriously impede disease eradication, and thus an effort to better understand this viral reservoir is required.

Infection of progenitor mast cells may also generate an HIV reservoir in tissue mast cells; however, the longevity of this reservoir and its importance in HAART-treated patients remains to be investigated. A study of viral sanctuaries during HAART in a rhesus macaque model for HIV has revealed the presence of HIV DNA in both the bone marrow and the gastrointestinal tract, a region in which mast cells (as well as a variety of lymphoid cells) are abundant [38,51*]. Further study of this model to determine the particular cell types harboring HIV DNA in each anatomical location, as well as the contribution that each cell type makes to residual plasma viremia during HAART, could enhance our understanding of these potentially important viral reservoirs. As evidence mounts that the CD4+ T cell reservoir is not the sole source of persistent viremia during therapy, the role of additional reservoirs in HIV persistence must be thoroughly evaluated.

Acknowledgments

Lucy McNamara is a recipient of an NSF pre-doctoral fellowship and a Bernard Maas Fellowship. We thank Adewunmi Onafuwa-Nuga for critical reading of the manuscript.

Funding for this work was received from the National Institutes of Health and the Burroughs Wellcome Fund.

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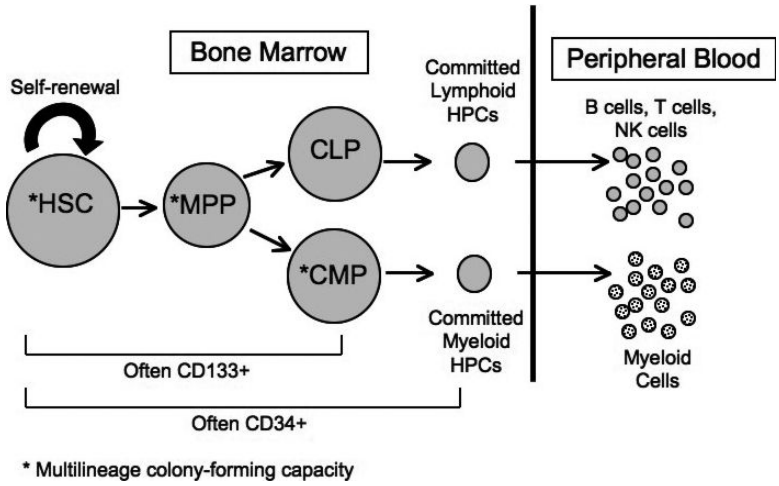

Figure 1. Hematopoiesis

Hematopoietic stem cells (HSCs) with extensive self-renewal capacity give rise to multipotent progenitor cells (MPPs), which can in turn differentiate into committed lymphoid progenitors (CLPs) or committed myeloid progenitors (CMPs). These cells further differentiate into committed progenitors and eventually mature blood cells. *Indicates cells capable of forming multilineage colonies in methylcellulose media (methylcellulose does not support the growth of lymphoid cells).

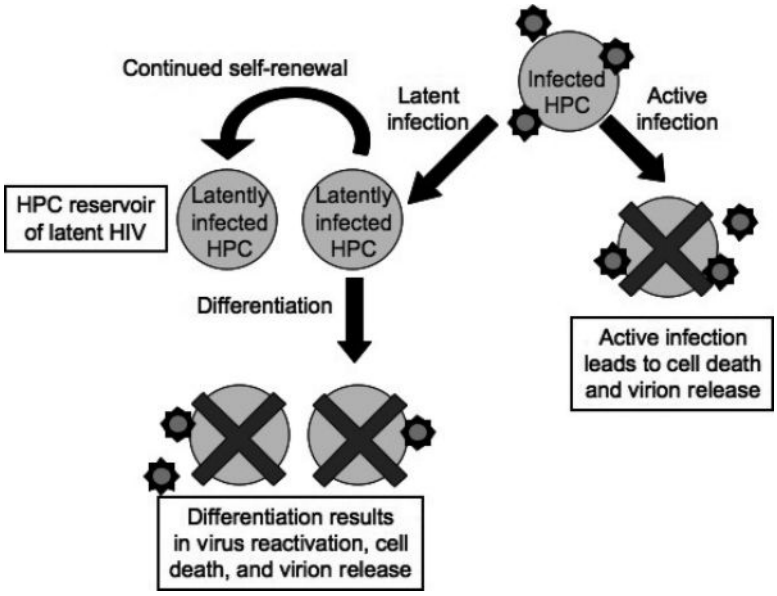

Figure 2. Model of HIV-1 infection in HPCs

Multipotent HPCs can become infected with HIV-1, leading either to active infection, cell death, and virion release, or to latent infection. Latently infected HPCs with self-renewal capacity will then continue to self-renew, generating an expanded reservoir of latent HIV-1 in these cells. If the host cell is stimulated to differentiate, the latent virus reactivates, leading to cell death and virion release.

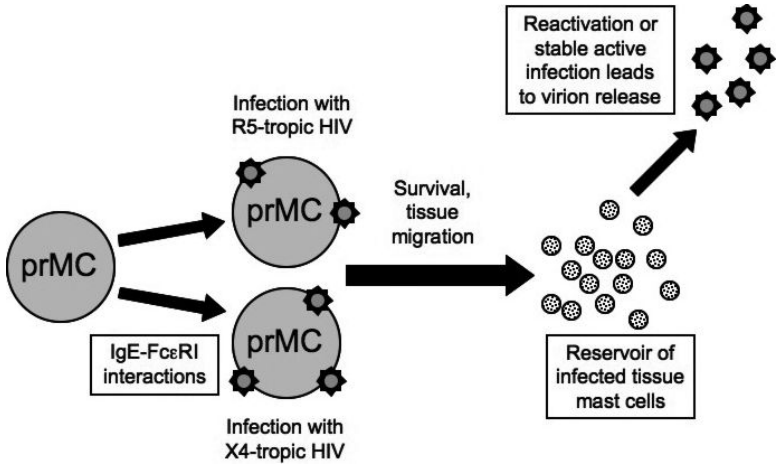

Figure 3. Current model of HIV-1 infection in mast cell progenitors (prMC) and the creation of a stable reservoir of infected tissue mast cells

Circulating mast cell progenitors can become infected with CCR5-tropic HIV-1 or, following interactions with IgE, CXCR4-tropic HIV-1 as well. The progenitor mast cells then mature into tissue mast cells that are resistant to new HIV-1 infection. These mast cells may harbor latent HIV-1 that can later be reactivated, or they may be able to continuously produce HIV-1 due to the virus's reduced cytotoxicity in this cell type. In either case, a viral reservoir in tissue mast cells is created and can contribute to viral persistence.