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Myelomonocytic Cell Lines in Modeling HIV-1 Infection of the Bone Marrow

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Additional information is available at the end of the chapter

Abstract

Human immunodeficiency virus type 1 (HIV-1), the etiologic agent of acquired immunodeficiency syndrome (AIDS), primarily infects T cells and cells of the monocyte-macrophage lineage. This is due to the presence of the cell surface receptor CD4 and the coreceptors, CXCR4, and CCR5. While the T-cell has classically been the cell type associated with HIV-1 disease progression, cells of the monocyte-macrophage lineage have also been shown to play a major role in this viral pathologic process. Classically, this has involved monocytic cells in the peripheral blood and tissue macrophages, however, over the course of HIV disease, the promyelomonocytic cells of the bone marrow (BM) have also been shown to play a role in pathogenesis retroviral disease in that they play an integral role in the reseeding of the periphery and end-organ tissues. This has involved an initial infection of the bone marrow hematopoietic progenitor cells. Given this observation, over the years there have been a number of cell lines that have been developed and provided valuable insights into research questions surrounding HIV-1 infection of the monocyte-macrophage cell lineage. In this regard, we will examine the biological and immunological properties of these BM-derived cell lines with respect to their utility in exploring the pathogenesis of HIV-1 in humans.

Keywords: HIV-1, HL-60, TF-1, myelomonocytic cells, latency

1. Introduction

Human immunodeficiency virus type 1 (HIV-1) has been shown to primarily infect cells of the lymphoid and myeloid lineages in the peripheral blood and bone marrow (BM). One of

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the roles of the bone marrow serves to repopulate the peripheral blood with fresh circulating cells in response to stimuli. During HIV-1 disease, the BM has been shown to be dysfunctional leading to the pathology commonly observed in the acquired immunodeficiency syndrome (AIDS), with thrombocytopenia, anemia, monocytopenia, and neutrocytopenia [1, 2]. HIV-1 infection of bone marrow stromal cells, changes in the cytokine milieu of the bone marrow, and cytotoxic effects of HIV-1 proteins are pathogenic mechanisms involved in the impairment of the differentiation and growth of hematopoietic progenitor cells (HPCs), ultimately leading to hematopoietic defects [3–5] during the course of HIV disease. Interestingly, HIV-1 DNA was not detected in bone marrow–derived CD34+ HPCs in HIV-1–infected patients on combination antiretroviral [6]. However, other investigators have detected HIV-1 DNA in CD34+ HPCs in patients who are on antiretroviral therapy [7]. Numerous coinfections, as well as some lymphomas commonly observed in AIDS patients [8], have been shown to further impact hematopoiesis in HIV-1–infected individuals. Direct HIV-1 infection of hematopoietic progenitor cells may contribute to hematopoietic abnormalities; however, the extent of infection in the bone marrow compartment remains controversial [9]. Numerous studies have demonstrated the susceptibility of CD34+ bone marrow–derived cell populations to HIV-1 both *in vivo* and *in vitro* [10–13]. In general, the permittivity of CD34+ HPCs has been shown to depend on the state of differentiation, with the committed progenitor cells being the most susceptible and the quiescent stem cells being the most refractile to HIV-1 infection [14, 15]. In this regard, it has been shown that macrophage colony stimulating factor (M-CSF) [11] induces HIV-1 infection of HPCs and subsequent virus production involving increased CD4 expression and enhanced viral replicative processes, respectively, emphasizing the crucial role that physiological changes in the bone marrow environment have on the HIV-1 susceptibility replicative capabilities of this cellular compartment.

During the course of chronic HIV-1 infection, there is a characteristic loss of CD4+ T cells over time in the absence of effective therapy. However, with the era of highly active antiretroviral therapy (HAART), this trend has been reversed. Interestingly, over the course of this time, cells of the myeloid lineage, even though CD4+, have been shown to less susceptible to virus-induced cytopathic effect and cell death with a drop in cell numbers much less evident during disease progression [16]. In addition, this cell lineage has been shown to be able to traverse various endothelial cell barriers, including the blood-brain barrier, allowing the infected circulating cell of the monocytic lineage to transport HIV into tissues as perivascular macrophages [17, 18]. Once in tissues, the emerging infectious HIV-1 particle can then go on to infect other resident cells of that tissue. As these cells migrate to other tissues and as the immune response causes a general state of inflammation, the bone marrow is involving in replacing cells lost to infection and to facilitate the immunologic response to HIV infection. Given that there are reports of HPCs becoming infected in the bone marrow, one intriguing possibility is that mature progenitor cells or cells that are committed to the monocyte lineage but still capable of a limited number of cell divisions, may be infected by HIV-1 while still in the bone marrow and subsequently migrate to the blood and subsequently into peripheral tissues thereby contributing to the continued viral dissemination [19].

Given these observations, we will briefly review hematopoiesis to define how myeloid cells differentiate from hematopoietic stem cells (HSCs). We will then review the literature that

demonstrates the bone marrow as a site of HIV-1 infection. This approach will provide a framework to review and assess the literature concerning a number of cell lines that are currently available to be used to model virus-host interactions, as well as experimental paradigms that have utilized these cell lines to understand basic virologic and immunologic concepts relevant to HIV infection. Finally, it will conclude by discussing the next most important pressing experiments to be performed and what questions these experiments will answer to understand HIV-1 infection of the bone marrow compartment and myeloid lineage of cells.

2. CD34+ hematopoietic stem and progenitor cells

All cells of the hematopoietic system are derived from a common precursor cell, the hematopoietic stem cell (**Figure 1**) [20]. Stem cells are defined as single cells that are clonal precursors of more stem cells of the same type, as well as a defined set of differentiated progeny cells [20, 21]. Stem cells normally represent only about 0.05% of cells in the bone marrow, and their population is maintained at a constant level through self-renewal [22]. CD34+ progenitor cell populations, which are heterogeneous cell population containing true pluripotent stem cells and other more mature cells, are often used for hematopoietic stem cell transplantation [23]. The ability of the hematopoietic stem cells to home to the bone marrow following intravenous injection is mediated by the interactions of selectins on bone marrow endothelial cells with integrins on the
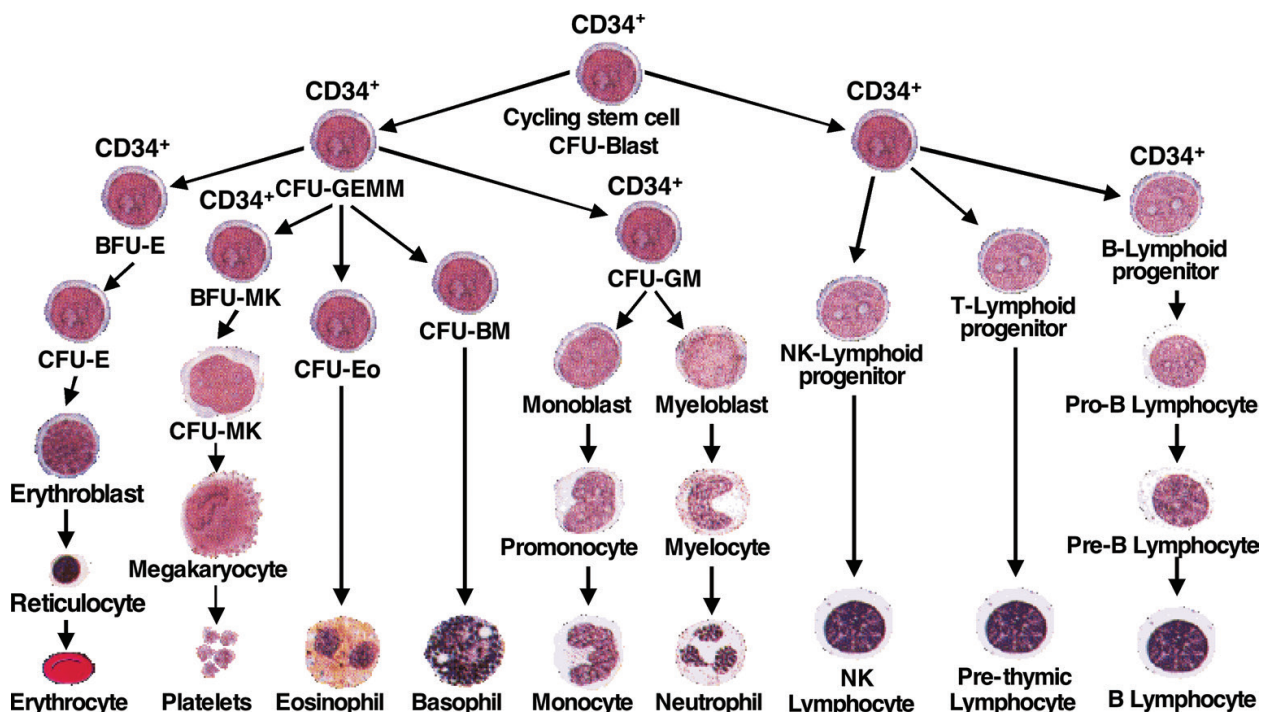
Figure 1. Differentiation of CD34+ stem cells. CD34+ stem cells can be differentiated into all of the cell types that are found in the blood. Cells have to go through a number of differentiated stages of progenitor and immature cells to finally become a mature blood cell. As a cell differentiates it commits to numerous cell lineages. Adapted from Ref. [31].

hematopoietic cells [24]. The CD34 sialomucin receptor is one of the several adhesions involved in the intra and extramedullary homing of progenitor cells into distinct microenvironments [25, 26]. The CD34 antigen is expressed on primitive human hematopoietic cells capable of both self-renewal and differentiation into diverse blood cell lineages [27]. HPCs normally reside in the bone marrow in close contact with the cells of stroma that provide cytokines, extracellular matrix proteins, and adhesion molecules [28]. Progenitor cells are compartmentalized in different areas of the bone marrow based on their degree of commitment and lineage differentiation [29]. Bone marrow–derived CD34+ cells isolated from HIV-1–infected individuals have a diminished colony potential [30]. Studying infection of CD34+ progenitor cells is important in understanding the cytopenias and impaired colony growth in advanced stage HIV-1–infected patients [8].

CD34+ cells are a heterogeneous population of multipotent hematopoietic progenitors at different stages of differentiation, residing in the adult bone marrow [32]. The CD34+CD38− immunophenotype defines a rare, quiescent (when a cell is neither dividing nor preparing to divide, remaining in the G_0 cell phase) subpopulation of primitive progenitor cells than can be functionally distinguished from committed CD34+/CD38+ progenitor cells by sustained clonogenicity in a long-term culture [33]. The more primitive CD34+CD38− cells are resistant to infection while the more committed CD34+CD38+ cells are more susceptible to HIV-1 infection [14]. Primitive hematopoietic cells are not directly infected though their function is markedly disturbed by the presence of virus [34]. HIV-1–infected individuals have been shown to have a decrease in the fraction of CD34+/CD38− stem cells in the bone marrow, compared to the healthy individuals [35]. No CD4 expression was detectable on the more primitive CD34+CD38− cells and no evidence for infection of these cells was demonstrated [14].

Hematopoietic stem cells are characterized by an extensive capacity for proliferation and differentiation, as well as the ability to self-renew. Stem cells give rise to daughter cells, which undergo irreversible differentiation along a number of different hematopoietic cell lineages [36]. Hematopoiesis consists of a cascade of finely regulated events by which totipotent stem cells differentiate to all cells present in the blood [37]. Lineage commitment, differentiation, maturation, and release of cells into the blood are under the control of a number of hematopoietic growth factors. Differentiation of hematopoietic stem and progenitor cells involves a series of molecular changes that result in progressive loss of self-renewal ability and pluripotency, and in parallel acquisition of specialized functions characteristic of mature blood cells [38]. Stem cells undergo two sequential differentiating processes; the first is commitment, by which stem cells lose their self-renewing capability and differentiate to other cells with a more limited differentiating potential. The second process is maturation, which allows the terminal differentiation of those cells committed to a specific terminal lineage [39]. Both the commitment and the maturation of hematopoietic cells arise from the gradual expression of lineage-specific genes. Commitment is defined as the decision a cell makes to enter, or generate progeny that enters, a particular maturation lineage at some future time [36]. This decision does not necessarily have to be accompanied by any immediate change in morphology or expression of novel membrane proteins or regulator receptors. Hematopoietic commitment is likely to be extrinsically regulated, but there is only limited evidence, and probably only a limited opportunity, for hematopoietic regulators to be involved in the commitment events [36]. Once established, maturation

programs do not seem to be qualitatively altered by the particular growth factors that activate mature cell production [36]. Most of the cell differentiation pathway takes place in the bone marrow. As CD34$^+$ cells differentiate, they can commit to a specific lineage at specifically defined branch points (**Figure 1**). A number of cytokines influence and promote the cell differentiation process. Once the cells have differentiated to monocytes, they can travel through the blood and migrate into tissues where they can become tissue macrophages or dendritic cells (**Figure 2**).

3. Cells of the monocyte-macrophage lineage

Monocytes belong to the mononuclear phagocytic system and constitute 3–8% of the peripheral blood leukocytes. Monocytic nuclei are eccentric, either oval or kidney shaped and contain small vacuoles in the cytoplasm that are lysosomes filled with degradative enzymes. Monocytes originate from promonocytes, which are rapidly dividing precursors in the bone marrow. When the mature cells enter the peripheral blood, they are termed monocytes (**Figure 2**). The monocytes often leave the blood and infiltrate tissues, undergoing additional changes and are then referred to as macrophages [40]. Macrophages act as effector cells, attacking microorganisms and neoplastic cells and removing foreign material, as well as presenting antigen
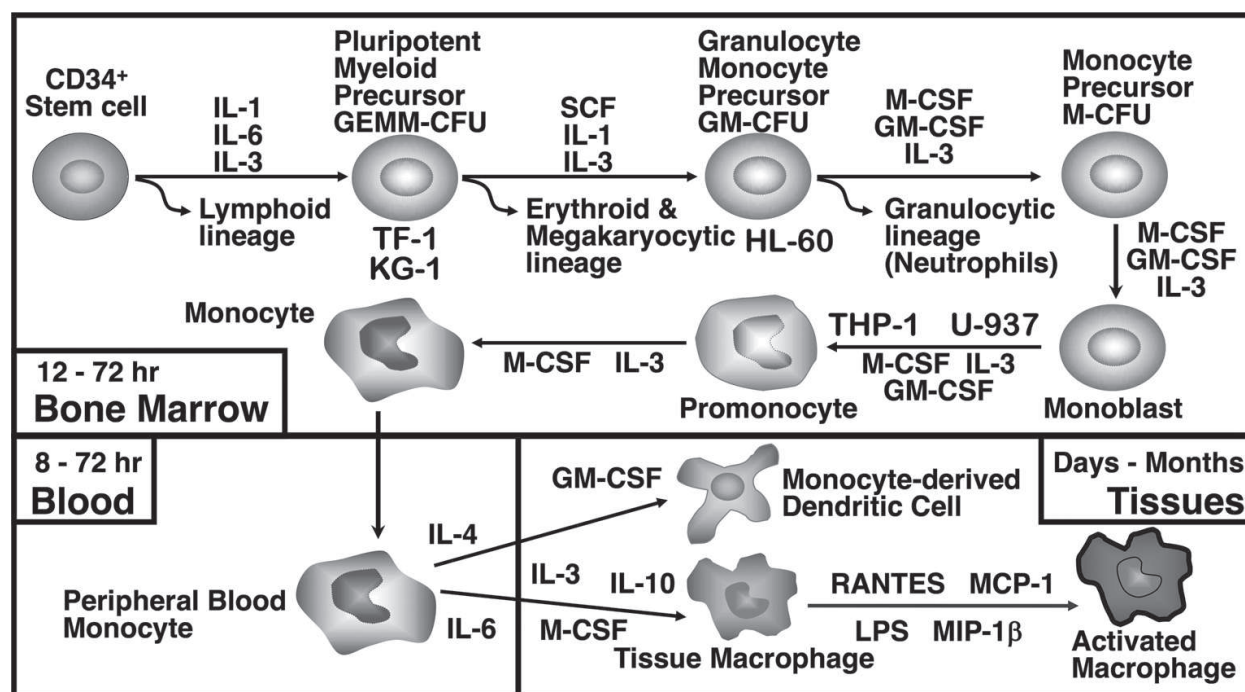
Figure 2. Differentiation of monocytes-macrophages from CD34$^+$ stem cells. The monocytic differentiation pathway and growth factors are involved, as well as the sites where the differentiation takes place is depicted. The majority of the cell differentiation stages occur within the bone marrow. As the CD34+ cell differentiates, it commits to the myeloid lineage at various branch points for other lineages, such as the lymphoid, erythroid, and granulocytic lineages. A number of cytokines that influence and promote cell differentiation are also shown. Certain cell lines and the point at which they are located in the cell differentiation pathway are also indicated. Once the cells have differentiated into monocytes, they can travel through the blood and migrate into tissues where they can become tissue macrophages or dendritic cells and also be activated.

to lymphocytes [41]. Macrophages contain receptors for antibody and complement, which enhance their ability to phagocytose organisms. Macrophages produce an enormous number of soluble factors that are important in the immune response and in the process of inflammation.

Monocytic cells are generated in the bone marrow from pluripotent stem cells that can differentiate into multiple hematologic cell types. Within the bone marrow, cytokines induce stem cells to divide and to produce lineages committed to differentiating into monocytic, granulocytic, erythroid, or megakaryocytic cell types (**Figure 2**) [42, 43]. The pluripotent progenitor cell, called the granulocyte-erythroid-megakaryocyte-macrophage colony forming unit (GEMM-CFU), becomes further committed toward either the granulocytic or monocytic phenotype in the presence of IL-1 and/or IL-3, becoming the granulocyte-macrophage colony forming unit (GM-CFU) (**Figure 2**) [39, 42, 43]. The granulocytic and monocytic lineages are closely bound together throughout hematopoiesis and are commonly referred to as the myelomonocytic lineage [42, 43]. Repopulation of the myelomonocytic GM-CFU occurs in the presence of IL-3 or granulocyte-macrophage colony stimulating factor (GM-CSF) [37]. Commitment toward the macrophage lineage requires the presence of macrophage colony stimulating factor (M-CSF), along with IL-3 or GM-CSF [44, 45]. The committed promonocytic cells mature into smaller monocytic cells that can enter the blood. Monocytes circulate within the blood for 8–72 hours before migrating into a number of different tissues where they complete their development, becoming mature tissue macrophages (**Figure 2**) [46–48]. Macrophages are larger in diameter than monocytes and possess increased lysosomal content and hydrolytic enzymes [49]. Macrophages are capable of division and can be a self-sustaining population.

The phenotype and function of the macrophage is dependent on the tissue in which it resides. Therefore, resident macrophages are often defined by the tissue-specific environment in which they ultimately reside. Specific types of macrophages include: the microglial cells of the brain, the Kupffer cells in the liver, the Langerhans cells of the skin, the alveolar macrophages of the lung, the mesangial cells of the kidney, and the sinus macrophages of the spleen [50–52].

4. Bone marrow hematopoiesis disorders associated with HIV-1 infection

Hematologic abnormalities are very common in HIV-1–infected individuals and they occur at all stages of disease, but the mechanisms by which HIV-1 contributes to these abnormalities are poorly understood [53, 54]. HIV-1 affects the hematopoietic system, causing a number of peripheral blood cytopenias [55, 56]. HIV-1–infected patients suffer from many hematologic disorders and exhibit uni or multilineage suppression of bone marrow hematopoiesis including anemia, lymphocytopenia, thrombocytopenia, granulocytopenia, monocytopenia, and neutropenia that can be attributed to malfunction or premature death of the specific hematopoietic cells [8, 57–59]. The hematopoietic disorders are frequently associated with impaired HPC growth, BM dysplasia, plasmacytosis, and lymphoid infiltrates [57, 60], and they suggest virus-induced abnormalities in the bone marrow microenvironment [61–63]. T cell depletion in AIDS is thought to be, at least in part, due to the failure of T cell development from lymphohematopoietic stem cells [14].

A large number of studies have been conducted to identify and characterize the pathophysi‐
ologic mechanisms leading to bone marrow dysfunction in patients with AIDS. HIV-1 may
affect hematopoietic stem cells (HSCs) by both direct and indirect mechanisms leading to
defects in maturation of CD34^{+} cells and the numerous cytopenias. A number of indirect
mechanisms for HIV-1–induced suppression of hematopoiesis have been proposed, such as:
the stimulation of abnormal cytokine production by HIV-1 infection [30, 64], the suppressive
effects of viral gene products [65, 66], and the activation of apoptosis by gp120-mediated
cross-linking of CD4 [67]. Hematologic abnormalities in the majority of infected individuals
could result from indirect effects of HIV-1, such as cytokine dysregulation, rather than HIV-1
expression in the bone marrow itself [53]. HIV-1 Tat has been shown to decrease differen‐
tiation in an HPC line [68]. In addition, the viral accessory protein Nef has been shown to
decrease hematopoiesis *in vitro* [69]. Studies have also demonstrated that HIV-1 may induce
apoptosis in hematopoietic cell lines [70, 71]. Modification of the behavior of hematopoi‐
etic accessory cells by HIV-1 infection may indirectly alter the growth and differentiation of
adjacent uninfected lymphoid, myeloid, and primitive hematopoietic cell populations and
account for HIV-1–mediated suppression of hematopoiesis [72]. Infection of auxiliary cells,
particular macrophages, and microvascular endothelial cells, induces a substantial alteration
in the supportive function of the hematopoietic stromal tissues, indirectly influencing the
survival and growth of hematopoietic progenitors [8].

5. Role of growth factors, cytokines, and cellular activation in HIV-1 pathogenesis in the bone marrow

Stem cells, progenitor populations, and their progeny are largely defined by their cytokine
responsiveness and cytokine receptor phenotype. Cytokines are soluble glycoproteins that act
through cell surface receptors at very low concentrations and control the production of stem
cells. The most prominent cytokines are erythropoietin for the production of red blood cells,
GM-CSF for granulocytes and macrophages, G-CSF for granulocytes, thrombopoietin for
platelets, and M-CSF or CSF-1 for monocyte-macrophage production and function. Cytokines
may be stimulatory or inhibitory and may show additive or synergistic effects on the renewal,
proliferation, survival, and differentiation of cells. They can also modulate cell migration and
adherence. Cytokines are important components of the immunoregulatory network and have
been demonstrated to play a major role in the regulation of HIV-1 expression *in vitro*. Potent
modulation of HIV-1 expression has been demonstrated either by manipulating endogenous
cytokines or by adding exogenous cytokines to culture. The net level of virus replication in
an HIV-1–infected individual reflects, in part, the balance between inductive and suppressive
host factors that are mediated mainly by cytokines. Reverse transcription, integration, and
virus spread are much more efficient in cells that have been activated by cytokines.

Cytokines and growth factors function by activating a number of different transcription
factors. Sequentially ordered activation of transcription factors controls lineage commitment.
Once a particular set of transcription factors has been induced, reversibility is limited. In

the early phases of differentiation, the regulatory roles of the growth factors overlap [36]. Later in development, some growth factors are lineage-specific, and govern the maturation of single lineages. Hematopoietic cells have distinctive patterns of growth factor receptor expression that evolve as the cells differentiate [36]. Binding of the growth factors to their receptors leads to activation of intracellular kinases and triggers cell proliferation [73, 74]. Hematopoietic growth factors not only stimulate cell proliferation, but also prolong cell survival by exhibiting antiapoptotic effects. Growth factors, such as G-CSF and GM-CSF, can stimulate early hematopoietic cell proliferation, increase the number of cells produced by the bone marrow, prolong the life span of cells, and augment cell function [75]. In the marrow, blood cells develop in two phases: the proliferative and the maturational phases. During cell proliferation, the precursors of blood cells normally undergo cell division at intervals of about 18–24 hours. In the maturational phase, cell division ceases, but additional modifications occur before the cell enters the blood. Progenitor cells exhibit a higher proliferative rate and more lineage restriction than stem cells. They are also responsive to a smaller subset of cytokines. The production of all cell types is controlled by a negative feedback mechanism. When demand for specific cell types increases, or peripheral levels of the cells fall, then stimulatory cytokines are released to generate new cells within a few days.

6. Organization of bone marrow and its role as a viral reservoir

Hematopoietic cells develop within the medullary space, which has a rich vascular supply and is populated by many cell types including: adipocytes, vascular endothelial cells, fibroblasts, and stromal cells (**Figure 3**). The frequency of HSCs in the bone marrow is relatively constant [76, 77]. Vascular endothelial cells, marrow fibroblasts, and stromal cells produce hematopoietic growth factors and chemokines that regulate blood cell production [78]. Vascular endothelial cells form a barrier that keeps immature cells in the marrow and permits mature cells to enter the blood. Macrophages in the bone marrow remove dead or apoptotic cells and clear the blood of foreign materials that enter the marrow (**Figure 3**). Stem cells and primitive cells bind tightly to the stroma, while maturing precursors and terminally differentiated cells are nonadherent.

The bone marrow may serve as an important reservoir of HIV-1 in the body. Previous results have suggested that the bone marrow macrophages may act as a reservoir for HIV, and infection of this cell population may affect hematopoiesis, either by transmission of HIV infection to developing progenitor cells or by altering the ability of the stroma to support normal development [80]. The circulating CD34+ progenitor cell population may be infected *in vivo* and may serve as a reservoir for HIV-1 that is capable of trafficking the virus to diverse anatomic compartments [13]. Peripheral blood–derived CD34+ progenitor cells may also be infected and disseminate HIV-1 to sites throughout the body. Integration of proviral DNA into stem cell genomes could lead to the spread of HIV-1 infection through the expansion of infected clones or interference with normal stem cell maturation and proliferation, resulting in the interruption of normal hematopoiesis [14]. Studies have shown that primary CD34+ progenitor cells are susceptible to infection by diverse strains of HIV-1, particularly as they begin to differentiate, and infection can be sustained for prolonged periods *in vitro* [13, 32]. This may contribute to a chronically infected pool of functionally altered cells containing viruses of different tropism across different cell lineages [32].
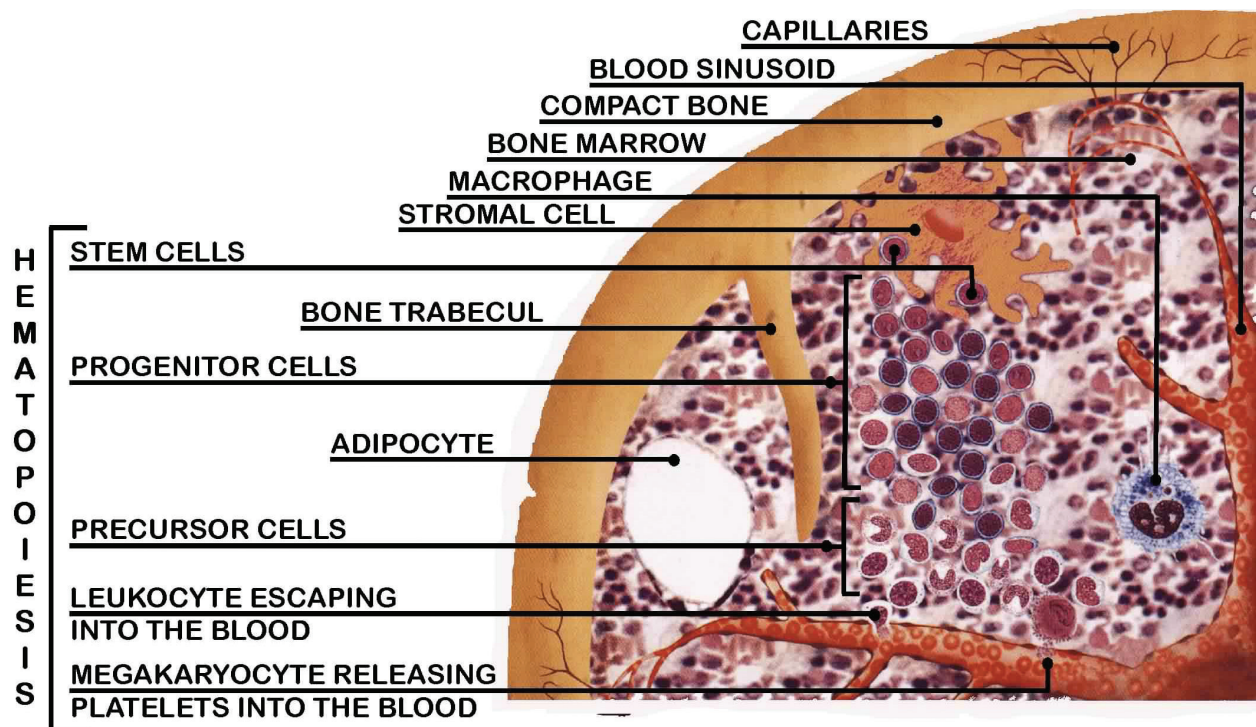
Figure 3. Hematopoiesis within the bone marrow. Hematopoiesis occurs within the bone marrow and begins with stem cells associated with stromal cells that nourish them and supply growth factors. Stem cells differentiate through various stages of progenitor cells and commit to various cell lineages eventually entering the blood circulation. Adapted from Ref. [79].

7. Direct infection of CD34+ hematopoietic progenitor cells by HIV-1

Direct involvement of HIV-1 infection may be important in leading to HSC failure and bone marrow dysfunction [59]. Direct infection and destruction of hematopoietic stem or progenitor cells may explain the defective hematopoiesis in HIV-1–infected individuals [81]. Attempts to understand HIV-1–mediated bone marrow dysfunction have yielded inconsistent results regarding the susceptibility of bone marrow progenitors to viral infection [14]. Conflicting studies have been reported regarding the susceptibility of human CD34+ cells to HIV-1 infection both *in vivo* and *in vitro*, and there has been a significant controversy regarding whether HIV-1 can infect HSCs directly, leading to bone marrow dysfunction and the cytopenias. A number of studies of HIV-1–infected individuals have failed to detect productively infected CD34+ progenitor cells from the bone marrow [54, 82, 83], while other studies have shown that rare infection of CD34+ progenitor cells can occur [84, 85] and may be more prevalent in patients with advanced disease [86].

Direct infection of the primitive progenitor cells, which represent 0.01% of bone marrow cells, is difficult to detect [13]. Several reports have described that bone marrow CD34+ stem and/or progenitor cells are infected with HIV-1 at low frequencies in some patients [84]. Purified CD34+ HPCs from adult peripheral blood were reported to be susceptible to HIV-1 infection, as shown by PCR analysis for the presence of proviral sequences in the ensuing myeloid and erythroid colonies or by virus production in culture [13, 81, 87]. Several studies have shown successful *in vitro* infection of the CD34+ population [11, 88], although studies in this area

have focused on hematological consequences of HIV-1 infection and its effects on progenitor cells [10, 81, 88]. HIV-1 infection *in vitro* has been reported in highly purified bone marrow–derived CD34+ cells [89] and in CD34+ progenitor cells that coexpress CD4 [70]. Based on a number of reports, it was found that a low fraction of progenitor cells is able to be infected *ex vivo* by HIV-1 under certain conditions, the growth of the few cells infected by HIV-1 may not be impaired as a result of the infection, while *in vivo* infection of progenitor cells occurs rarely, if ever [8].

The number of HIV-positive HPCs may sharply increase in advanced AIDS because of widespread HIV-1 infection, thus explaining the reports on *in vivo* HIV-positive CD34+ cells in the advanced disease [85, 86]. Studies suggest that HIV-1-expressing cells are present in the bone marrow during late stages of disease [53]. In individuals with advanced HIV-1 infection, about 1 in 500 CD34+ cells were shown to be infected with HIV-1 [86]. The CFU capacity of the bone marrow stem cells was impaired especially in patients with advanced disease, even if HIV-1 does not directly infect these cells [90]. Depletion of primitive progenitors observed in later stages of HIV-1 disease may represent a virus-induced alteration in progenitor cell differentiation [91–93].

Multiple and potentially synergistic mechanisms may be responsible for the resistance of CD34+ cells to HIV-1 infection [28]. Most studies indicate that bone marrow–derived HSCs cannot be infected by HIV-1 until they undergo modest differentiation in order to express the appropriate receptors to enable virus entry and subsequent replication [59]. Studies have demonstrated the presence of both CD4 [94] and the chemokine receptors CXCR4 and CCR5 [95] on CD34+ cells. The most primitive bone marrow HPCs lack the surface molecules CD4, CXCR4, and CCR5, which are required for HIV-1 infection, so they cannot be infected with HIV-1 [14]. CD4+ cells were found only within the more mature CD34+CD38+ cell population, explaining their susceptibility to infection [14]. Cell surface expression of CXCR4 and CCR5 has been found on peripheral blood–derived CD34+ progenitor cells [13]. When CD4 expression is low, infection becomes dependent on coreceptor expression levels. High chemokine receptor levels can compensate for low surface expression of CD4 in mediating HIV-1 infection [13]. T-tropic strains of HIV-1 have been shown to infect cultures of purified CD34+ progenitor cells *in vitro*, suggesting the presence of the CXCR4 coreceptor on the cells [62, 81]. The natural chemokine ligands for the major HIV-1 coreceptors are able to readily block entry of HIV-1 [96]. The CC-chemokines RANTES, MIP-1α, and MIP-1β are the natural ligands for CCR5 and block the entry of R5 viruses, whereas SDF-1, the natural ligand for CXCR4, blocks the entry of X4 viruses, thus inhibiting the infection and spread of the virus. The mechanisms relevant to inhibition of HIV-1 infection involve the blocking of binding of the virus to its coreceptor, thus blocking viral entry.

8. Specific viral populations within the CNS suggest bone marrow origination

Because the CNS has been shown to be more "immunologically privileged" than many other organs, it has been suggested that virus enters the CNS early after primary infection and then replicates there beyond the control of the peripheral immune system to a great degree.

In addition, some antiretroviral drugs such as protease inhibitors have trouble crossing the blood-brain barrier [97, 98]. Inefficient drug delivery combined with an "immunologically privileged" site leads to viral reservoirs remaining in the CNS throughout the duration of infection. Viral genome sequence analysis supports the notion that CNS-specific or neurotropic forms of virus exist [99–103]. Recent studies demonstrate that viral sequences within specific CNS regions match, phylogenetically, with sequences found in the bone marrow [104, 105]. This supports the hypothesis that virus could be transported into the CNS in hematogenous-derived cells.

HIV-1 gp160 sequences from postmortem tissues collected from a patient with HIV-1 dementia were isolated and analyzed for sequence similarity [105]. Gartner and colleagues found that the gp160 sequences from patients with dementia demonstrate remarkable sequence similarity between isolates from subcortical regions of the brain (particularly in deep white matter (DWM)) and those of the bone marrow [104]. Phylogenetic analysis showed that the sequences from DWM were more closely related to those from bone marrow and peripheral blood monocytes. Sequences from DWM and monocytes clustered together, indicating greater homology between the HIV-1 species in these groups, as well as a more recent evolutionary divergence between them, relative to the species in other tissues. The phylogenetic tree showed that the bone marrow sequences were clustered with the DWM and monocyte group, although the bone marrow species diverged at an earlier time. Viral species from the DWM were more closely related to those in bone marrow than those in other tissues, with the DWM, monocyte, and bone marrow sequences clustering together as a group. These observations suggest that of bone marrow–derived monocytes traffic into the DWM of the brain during late stage infection. Bone marrow–derived monocytes within the circulation may enter the DWM and become perivascular macrophages, potentially transmitting HIV-1 to neighboring cells [106]. A critical step toward the development of HIV-associate dementia may be an increase in monocyte trafficking into the brain [107]. This process may be either initiated and/or accelerated during late-stage infection, which could explain why dementia occurs at this time. These observations point to the bone marrow as the likely source of virus entering the CNS in terminal stages. The frequency and extent of infection and the kinetics of virus replication in bone marrow are not well classified.

9. Cell lines to model HIV infection of bone marrow

A number of different monocytic progenitor cell lines have been derived that can be used as experimental tools (**Figure 2**). These cell lines will be discussed from the least differentiated to the most differentiated cellular phenotype.

9.1. KG-1

The KG-1 cell line is a CD34$^+$/CD38$^+$ myelomonocytic progenitor cell line that was derived from the bone marrow of a patient with acute myelogenous leukemia [108]. A variant CD34$^+$/CD38$^-$ cell line, called the KG-1a subline, morphologically and histochemically resembles undifferentiated blast cells. The KG-1 cell line is composed predominantly of myeloblasts and

promyelocytes [109]. KG-1 cells can be induced to differentiate into dendritic-like cells by the addition of GM-CSF and TNF-α, or phorbol 12-myristate 13-acetate (PMA) with ionomycin or TNF-α [110]. KG-1 cells can be induced to differentiate into macrophage-like cells in response to phorbol esters such as 12-O-tetradecanoylphorbol-13-acetate (TPA), while the KG-1a cells are resistant to the effects of TPA [111, 112]. With respect to studies of HIV-1 pathogenesis and disease, this cell line has not been as widely used as you will see for HL-60 and TF-1 cell lines due to a very low to no expression of CD4 on the cell surface [113, 114]. However, many researchers who examine regulation of CD4, CCR5, and CXCR4 on the myeloid cell lineage use this cell line in combination with HL-60, TF-1, and others. Interestingly, a number of studies have examined coinfection of human herpesvirus type 6 (HHV6) and HIV-1 and demonstrated that if KG-1 cells were first infected with HHV6, this would induce CD4 expression thereby facilitating subsequent HIV-1 infection by viruses that use either CCR5 or CXCR4 as the coreceptor [113–115]. They have also been used for studies surrounding toxicity of drugs [116] or for alteration of normal cell function [117] for bone marrow myeloid lineage of cells potentially to be used for HIV treatments.

9.2. TF-1

The TF-1 cell line was established by Kitamura and colleagues in 1987 from a bone marrow aspiration sample of a 35 year old Japanese male with erythroleukemia and severe pancytopenia [118]. TF-1 cells, which have been shown to express several erythroid and myeloid markers, are CD34+/CD38+ erythro-myeloid HPCs blocked at an early stage of hematopoietic differentiation [118, 119]. The cells have also been shown to be completely dependent on IL-3 or GM-CSF for long-term growth [118]. Erythropoietin (EPO) also sustains the short-term growth of TF-1 cells but does not induce erythroid differentiation [119]. TF-1 cells can be induced to differentiate into two different pathways, and, depending on the type of inducer, are capable of differentiating into either mature erythroid cells or macrophage-like cells [118]. Hemin and δ-aminolevulinic acid can induce erythroid differentiation with hemoglobin synthesis in TF-1 cells, while PMA induces dramatic differentiation into macrophage-like cells [118]. TF-1 cells consist of a relatively homogenous population of medium-sized cells with the appearance of blasts [120]. They contain moderate amounts of dark basophilic, agranular cytoplasm with frequent small cytoplasmic vacuoles, and have a smooth cytoplasmic border. The nuclei are oval with fine chromatin and 1–3 macronucleoli. Many binucleated and occasional multinucleated forms are present [120].

The TF-1 cell line has provided a useful tool and *in vitro* model system to examine HIV-1 infection of a progenitor cell population during differentiation into monocytic cells. Previous studies have demonstrated that TF-1 cells can be productively infected by the R5-dependent BAL and YU-2 strains of HIV-1, but not by the X4-dependent LAI HIV-1 strain [121]. Differentiation of TF-1 cells down the myeloid pathway or the presence of higher levels of the CCR5 coreceptor as compared to the CXCR4 coreceptor could explain why a productive HIV-1 infection only occurred in cells infected with HIV-1 R5-dependent strains. PMA-induced macrophage-like differentiation of TF-1 cells, characterized by a decrease in nuclear size, an increase in the amount of nuclear chromatin condensation, absence of nucleoli, and

increased cytoplasm [120]. The majority of the cells have moderately abundant light basophilic, agranular to finely granular cytoplasm with irregular cytoplasmic borders [120].

TF-1 cells have been used extensively to understand host pathogen interactions between the HIV-1 protein Nef and numerous cellular pathways [122, 123]. These studies have led to a further understanding of how replication is differed between cell types. Specifically, these studies helped identify factors such as STAT3 that are affected by Nef and allow for the survival of TF-1 cells [124]. Like with KG-1 cells, TF-1 cells were also used to confirm that human herpesvirus 6 coinfection with HIV can lead to susceptibility of TF-1 cells to HIV-1 infection [113, 114]. In addition, it was shown in TF-1 cells that lymphocyte function-associated antigen 1 (LFA-1) was needed to confer susceptibility to HIV-1 infection [125]. TF-1 cells have also been used to assess transcriptional activation of the HIV-1 LTR in a number of activation and differentiation states of these cells. This demonstrated the importance of the C/EBP transcription factor in CD34+ progenitor cells for driving LTR activation [126]. In addition, the transcription factors NF-κB and Sp were shown to be important when TF-1 cells were activated by phorbol 12-myristate 13-acetate (PMA), conditioned medium from PMA-treated TF-1 cells, or IL-1² [127, 128].

9.3. HL-60

The HL-60 cell line, obtained by leukapheresis from the peripheral blood of a patient with acute promyelocytic leukemia, is a promyelocytic cell line [129]. In culture, the cells can be stained as promyelocytes or myeloblasts, although only about 10% of the cell population can progress to more mature cells [130]. Differentiation can be induced by a number of agents such as dimethyl sulfoxide (DMSO), butyrate, hypoxanthine, PMA, actinomycin D, and retinoic acid. The cells have the ability to differentiate into either granulocytic or monocytic cells, depending on whether they are treated with either DMSO or PMA, respectively [131–133]. Monocytic differentiation can also be induced by treatment with 1-25 dihydroxyvitamin D_3 or lymphokine [134, 135]. HL-60 cells exhibit increased adherence following differentiation toward either the monocytic or granulocytic pathways [131]. When HL-60 cells have been treated with PMA, they have been shown to exhibit morphologic changes that are characteristic of monocytic cells, including the appearance of pseudopodia, cerebriform nuclei, and the disappearance of azurophilic granules. However, they fail to produce secondary granules that are typical of mature cells indicating incomplete maturation [136]. Following chemically induced monocytic differentiation, increased production of acid phosphatase, β-glucuronidase, and myeloperoxidase has been observed [137]. Thus, the HL-60 cell line exhibits characteristics of an undifferentiated myeloid progenitor. Because of its ability to differentiate toward both granulocytic and monocytic cell types, HL-60 cells are considered a model for cells of the myelomonocytic lineage.

These cells have been widely used in studies on HIV-1 infection. This is because of their ability to be infected in an unactivated state as well as because of the development of the OM-10.1 cell, a clonally derived cell line from HIV-1–infected HL-60 promyelocytes which harbor a single integrated provirus that is silent until activated [138]. In the beginning of the epidemic, a number of studies were conducted with the HL-60 and OM-10.1 cells to

determine and characterize the viral infection and replication dynamics within cells of this lineage [138–143]. These cells have been shown to retain CD4, CXCR4, and CCR5 expression and retain CD4 expression unless viral replication is active [138]. Given this observation, the HL-60 and OM-10.1 cell lines have been used in several studies that simply aim at examining the levels of CD4, CXCR4, and CCR5 or other surface markers under various cellular physiological conditions and drug treatments [138, 144–159]. These cells have also been used to screen methodologies or drugs that may inhibit HIV-1 infection or reduce transcriptional activation of the virus [117, 160–173]. These cell lines have also been used in studies of drug toxicity, permeability, and/or effects on cellular activation and differentiation to gain an understanding of what specific drugs might do to cells in the bone marrow [144, 154, 174–183], as well as determining what signaling pathways may play a role or become dysregulated [184–189]. Additionally, other studies have been completed that utilize these cells to examine the role that distinct viral determinants as well as specific host factors have on cellular tropism, cellular differentiation, and cytopathology [190–193]. They have also been used in examining the role of CDK9 and characterizing its function based on known interactions with Tat [166] as well as how Nef manipulates intracellular Ca(2+) stores through SH3-mediated interactions in myelomonocytic cells [194].

Because of the more recent interest in HIV-1 latency, the OM-10.1 cell line has been used to understand drugs that may activate latent viral reservoirs for shock and kill or kick and kill type therapeutics. Some specific examples include a small molecule activator of protein phosphatase-1 (SMAPP-1) [195], NCH-51 [196], hybrid liposomes (HL) composed of dimyristoylphosphatidylcholine (DMPC) and polyoxyethylene alkyl [197], or contact with T cells [198]. Additionally, these cells have been used to characterize the mechanisms involved in maintaining HIV-1 latency [199]. The integrated provirus in these cells seems to be latent due to a transcriptional control mechanism and can be induced by TNF-α, suggesting a potential NF-κB-mediated control [200].

9.4. U-937 and THP-1

U-937 cells are an immature monocytic cell line derived from the pleural effusion of a patient with histiocytic lymphoma [201]. U-937 cells exhibit the morphologic and histochemical characteristics of monoblastic cells, including the expression of 2-glucuronidase and the release of lysozyme into the culture [201, 202]. Only a small percentage of undifferentiated U-937 cells are phagocytic. Furthermore, U-937 cells lack the ability to kill cells expressing foreign antigen presented by MHC class I [203, 204]. U-937 cell lines exhibit characteristics of monoblastic cells in their undifferentiated state, and can be induced to differentiate toward a more mature macrophagic cellular phenotype by a number of chemical agents. PMA can induce differentiation of U-937 cells toward a more mature monocytic phenotype [205, 206]. Differentiated U-937 cells have increased adherence and ramification, along with greater phagocytic activity and the induction of lysozyme and nonspecific esterase activity [206, 207]. Other chemical agents can also be used to induce macrophage differentiation of U-937 cells. Treatment with retinoic acid or 1-25 dihydroxyvitamin D_3 can induce the differentiation of U-937 cells. Like the HL-60 cell line, a U-937 cell line carrying integrated HIV-1 proviral DNA has been constructed with the integrated viral genome in a quiescent configuration that has been shown

to be capable of being activated into a transcriptionally active state capable of driving the production of infectious virus. This cell line was termed U1 [208]. Like with HL-60, the U-937 cell line has been used in several types of experiments including experiments to examine what is needed to reactivate the integrated virus [209–214] and most recently in using CRISPR/cas9 technology to excise HIV out of cells as a potential "cure" strategy [215].

THP-1 cells are a monocytic cell line derived from the peripheral blood of a 1-year old male patient who had acute monocytic leukemia [216]. The difference between THP-1 cells and U-937 cells is the origin and maturation stage of both cell lines. U-937 cells are of tissue origin and are therefore at a more mature stage. THP-1 cells are derived from a blood leukemia which represents a less mature stage. There is extensive literature describing the use of vitamin D3 or PMA to differentiate THP-1 cells into macrophages [216]. Recent literature has determined a protocol for PMA that seems to be the most effective to allow differentiation of THP-1 monocytes into macrophages [217]. Interestingly, comparing peripheral blood mononuclear cells (PBMC) monocytes and THP-1 cells has uncovered slight variations in their response to various stimuli. Upon stimulation with Lipopolysaccharide (LPS), PBMC monocytes produce a greater amount of proinflammatory cytokines such as, TNF-α, IL-6, and IL-8 compared to THP-1 cells [218]. These variations in response become much more similar when PBMC and THP-1 monocytes are differentiated into macrophages [219]. Interestingand important for several lines of experimentation, THP-1 cells can be polarized to the M1 or M2 phenotype depending on the stimuli provided.

Due to the differentiation state of U-937 and THP-1 cells, they have been used very widely to mimic HIV-1 infection of peripheral blood monocytes. Due to this, we will not review their use in HIV-1 research in depth as this review focused on promyelomonocytic cell systems. However, there have been some recent reviews that have focused more specifically on the peripheral blood monocytes as well as their utility in studies of HIV-1 latency [220–223].

10. Conclusion

Although HIV-1 may not be able to infect CD34+ stem cells, the research described above shows that they are able to infect the more differentiated progenitor cells. As the cells differentiate from the CD34+ stem cell, the HIV-1 receptor and coreceptor profiles become altered and enhance HIV-1 infection. Thus, the virus infects progenitor cells as they differentiate down the myeloid lineage in the BM and in the blood. Research surrounding this line of investigation has come from examining cells from patients as well as through development of derivative cell lines. As described here the KG-1, TF-1, and HL-60 cell lines have all been used to understand at which stage of the myeloid cell lineage HIV-1 may be able to infect. This has resulted in understanding this is restricted primarily by the levels of CD4 and CXCR4 or CCR5 on the cells. Given this it appears that HIV-1 can infect cells as early as the pluripotent myeloid precursor (**Figure 2**). Because of these models there has been extensive work to examine drug toxicities, regulation of HIV-1 infection, and understanding of how HIV-1 may affect hematopoiesis. However, due to ART making HIV-1 infection a more chronic

condition and the theory that one of the main reservoirs may involve the myeloid lineage of cells, including the promyelomonocytic cells of the bone marrow. Hence, this cellular compartment has now taken on a renewed interest. This is evident in the use of the OM-10.1 cell line model for mechanistic studies concerning HIV-1 latency as well as testing of latency reactivators on the various cell lines derived from this lineage of cells. It is the role of the myeloid precursor cells during the course of chronic infection that will be one of the major focal points of future research studies. The use of the TF-1 and HL-60 cells especially, will be very useful with respect to answering questions focused on determining when do these cells transverse the vascular endothelium at an increased rate. Do these infected bone marrow–derived cells traffic to end organs? Do they contribute to the increase in activated monocytes observed in the blood that link to HIV-1-associated neurocognitive impairment? Are these promyelomonocytic cells in the bone marrow infected by cell-free HIV-1 or through cell-to-cell contact with other cells? Are the viruses that infect these cells more dependent on CXCR4 or CCR5 and is there genetic variability more related to a reservoir virus that was generated early in infection and has remained or has continually developed over time in infected patients? These are a few questions that these cell lines will help to answer as research in this field advances.

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