Human Immunodeficiency Virus in Bone Marrow: Still More Questions Than Answers

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The issue of human immunodeficiency virus type-1 (HIV-1) infection in bone marrow cells continues to loom as a controversial topic with important implications for patients with acquired immunodeficiency syndrome (AIDS), physicians, and researchers. Basic concepts of in vivo viral reservoirs, infected cell trafficking, and cytokine regulation of HIV expression and hematopoiesis directly affect practical and serious decisions on the use of hematopoietic growth factors as therapeutic regimens in the treatment of AIDS patients. In particular, two issues have received considerable attention: (1) direct infection of hematopoietic precursors (cells that possess morphologically recognizable lineage) by HIV-1, and (2) the adverse effects of cytokine therapy to enhance hematopoiesis in AIDS patients.

The article by Kitano et al in this issue of Blood addresses these issues. The authors report the effects of colony-stimulating and differentiating factors on the susceptibility of highly purified bone marrow precursor cells to HIV-1 infection. To achieve primary infection, the authors isolated CD34+CD4− bone marrow cells by flow cytometry and then added a relatively low multiplicity of infection of monocytotropic HIV-1. They showed a high correlation between the quantity of p24 antigen produced from infected cells and the number of monocyte-differentiated cells in culture. Differentiation of the CD34+/CD4− cells could be enhanced with granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-3 (IL-3). Concomitant with pretreatment of the precursor cells by use of these cytokines, rapid enhancement of HIV-1 production was observed. The authors concluded that cells contained in or derived from the stem cell compartment were susceptible to HIV-1 infection, but differentiation of precursor cells into macrophages was required before maximal production of HIV antigen.

What are the implications of such findings? Do they shed light on previous in vitro and in vivo data? Certainly, our own findings support the view that highly purified CD34+ bone marrow cells from healthy uninfected individuals are susceptible to HIV-1 at some point in the culture cycle. However, our studies were limited on the basis of determining whether (1) the CD34+ cell was infected at onset and expressed virus after long-term, culture-induced monocyte differentiation or (2) contaminating monocytes became infected initially and further infected long-term, culture-induced monocytes derived from CD34+ cells. While the work described by Kitano et al does not resolve this issue, it clearly indicates that monocyte differentiation is essential for virus production. Only by identifying both the CD34 marker and the HIV gene or gene products within the same cell using in situ dual labeling will this important question be answered.

Other investigators have attempted to characterize HIV-infected cells isolated from bone marrow. One recent study evaluated in vitro growth of myeloid and erythroid progenitor ( colony-forming) cells obtained from uninfected healthy individuals and AIDS patients. No statistical differences were observed in colony formation. Moreover, no HIV-1 DNA could be detected in the growing colonies. One might ask here, if a progenitor cell were infected would it even form a colony? Therefore, it was concluded that committed progenitor cells from persons with AIDS were negative for HIV-1 DNA and responsive to growth and differentiation by hematopoietic factors.

Since the earliest description of hematologic abnormalities and myelodysplasia associated with AIDS, many studies have been performed to determine how HIV affects, either directly or indirectly, the observed pathology. Discrepancies among reports concerning in vitro identification of HIV-infected precursor cells still hinder our understanding of the pathophysiology of HIV-associated bone marrow abnormalities. For example, investigators have reported in situ hybridization of bone marrow cells from AIDS patients that identifies virus-specific RNA in granulocyte and megakaryocyte precursors, but these results conflict with other reports. For instance, in one study only 1 in 14 patients had HIV DNA present in CD34+ cells. In addition, with regard to bone marrow colony growth, conflicts exist over information concerning the number of...
colony forming units from uninfected healthy individuals compared with those from AIDS patients. Further, disagreements over the purity of isolated precursor cells in some of these studies continue to plague interpretations. However, one indisputable result is that if progenitor cells are infected, they exist in very low frequencies, although the critical frequency at which a patient becomes at risk of enhanced viral replication during bone marrow regeneration is unknown.

Many potentially therapeutic cytokines act on hematopoietic cells. An important practical question arises over whether cytokines should be used as therapy for hematopoietic abnormalities in HIV-infected individuals. Great strides have been made in the use of growth factors, in particular GM-CSF, as a stimulator of both growth and differentiation of uninfected human progenitor cells in vivo. Encouraging results have been obtained in the treatment of AIDS patients with GM-CSF, G-CSF, and erythropoietin. In addition, progress has been made in reducing bone marrow toxicity with GM-CSF after 3'-Azido 2',3'-dideoxythymidine (AZT) treatment. Unfortunately, in this same study it was reported that enhanced circulating HIV p24 antigen occurred after administration of GM-CSF. Other in vitro studies have also reported beneficial effects of AZT from in vitro monocyte/macrophage infections with HIV when used in combination with GM-CSF. However, virus-enhancing effects were also observed when GM-CSF was used alone.

Theoretical use of cytokines such as GM-CSF and IL-3 in persons with AIDS can be argued pro and con. We anticipate that the balance will be shifted in favor of the myeloproliferative effects of growth and differentiation over the virus-enhancing effects. The long-term study of the effects of these cytokines on disease progression and survival will be the only true yardstick.

REFERENCES

1. Kitano K, Abboud CN, Ryan DH, Quan SG, Baldwin GC, Golde DW: Macrophage-active colony-stimulating factors enhance human immunodeficiency virus type 1 infection in bone marrow stem cells. Blood 77:1699, 1991
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