HIV-associated hematological abnormalities involve all lineages of blood cells, thus implying that the virus impairs the function of early HSCs. However, the underlying mechanisms of this defect are unknown, particularly since HSCs are largely resistant to HIV-1 infection. In this issue of the JCI, Prost and colleagues show that the viral accessory protein Negative factor (Nef) plays a potentially critical role in the pathogenesis of HIV/SIV-associated hematopoietic dysfunction by affecting the clonal genetic potential of HSCs (see the related article beginning on page 1765). Soluble Nef induces PPARγ in uninfected HSCs, thereby suppressing the expression of STAT5A and STAT5B, two factors necessary for proper HSC function. The identification of this novel activity of extracellular Nef defines a new mechanism of HIV/SIV pathogenesis and suggests that approaches aimed at increasing STAT5A and STAT5B expression may be considered in HIV-infected individuals with prominent hematological abnormalities. The results also raise the question of whether dysregulation of hematopoiesis by extracellular Nef plays a role in the development of T cell immunodeficiency and the high levels of chronic immune activation associated with AIDS.

HIV-1 infection causes immunodeficiency by inducing a progressive decline in number of CD4+ helper T cells. However, the mechanisms of HIV/AIDS pathogenesis are complex, as it is still unclear to what extent this progressive CD4+ T cell depletion is caused by direct killing of infected cells or rather by the indirect effects of chronic, generalized immune activation (1). Importantly, HIV infection is also associated with hematopoietic abnormalities characterized by impaired generation and function of cells of all blood lineages (i.e., red blood cells, platelets, and white blood cells). These hematopoietic dysfunctions may cause various levels of cytopenias and also contribute to the development of T cell immunodeficiency (Figure 1) (2). Since all blood cell lineages may be affected, HIV-1 infection apparently deregulates the function of early hematopoietic progenitor cells. This assumption was confirmed by studies showing that CD34+ progenitor cells from HIV-infected patients show reduced growth and differentiation in vitro (3, 4). HIV-associated hematological abnormalities seem to be dependent on the level of virus replication, as these abnormalities are severe in late-stage AIDS patients with high viremia but can be corrected by highly active antiretroviral therapy (HAART) (5, 6).

The mechanisms underlying these hematological abnormalities are still obscure. While HSCs express low levels of CD4 and CCR5,
several studies indicate that they are not susceptible to HIV-1 infection (7–9). Alternative mechanisms that were proposed — although without definitive experimental evidence — include an effect of HIV-1 proteins on uninfected HSCs as well as the hematosuppressive potential of certain proinflammatory cytokines that are produced at high levels during HIV infection (10–13).

**Impaired STAT5 and HSC function in SIV-infected macaques**

The study from Prost and colleagues in this issue of the *JCI* (14) describes a series of experiments aimed at elucidating the mechanisms causing the hematopoietic abnormalities associated with HIV infection and AIDS. The main conclusion is that the extracellular viral accessory protein Nef may affect the ability of HSCs to maintain normal levels of peripheral blood cells, based on the new findings of Prost and coworkers reported in this issue of the *JCI* (14). In addition, Nef may decrease the production of T cell precursors, thus contributing to the peripheral CD4+ T cell depletion observed in HIV-infected individuals that is caused by both the direct effects of HIV on infected cells and the indirect effects of chronic immune activation.

**A role for Nef in impaired hematopoiesis**

Surprisingly, the Prost study (14) shows that extracellular, soluble forms of the HIV and SIVmac Nef proteins may downmodulate STAT5 expression by activating the transcriptional suppressor PPARγ, thus providing a new mechanism to explain the HIV-associated HSC defects (Figure 2B). Of note, this inhibitory effect of soluble Nef on the clonogenic potential of progenitor cells (which the authors elegantly map to a central region of HIV-1 Nef between amino acids 66 and 97) might explain why the hematological abnormalities of HIV-infected patients are correlated with disease progression even though HSCs are not directly infected by the virus. Nef is an early accessory protein of immunodeficiency viruses that is required for efficient viral persistence and strongly accelerates disease progression in HIV-1–infected humans and in experimentally SIV-infected rhesus macaques (18). Nef performs a striking variety of activities that allow the virus to spread effi-
Nef-mediated suppression of hematopoiesis: viral immune evasion strategy or suboptimal virus-host adaptation?

As mentioned above, the current study (14) might explain why the severity of the hematologic abnormalities correlates with the levels of virus replication and why functional hematopoiesis is restored by HAART. The observation that extracellular Nef impairs the function of CD34+ progenitor cells in trans also clarifies why HIV-1 does not need to directly infect HSCs to cause hematological abnormalities. However, new interesting questions are raised by the observed results. For example, Prost et al. show that peptides corresponding to residues 66–97 of the central core region of HIV-1 Nef are sufficient to reproduce the defect of HSC function. Although this region is relatively well conserved, the HIV-1 and SIVmac251 Nef sequences differ in 9 of the 31 amino acid residues. Those of other SIVs are frequently even more divergent and — in contrast to HIV-1 Nef proteins — often do not contain an intact Src homology 3-binding (SH3-binding) domain in this region, raising the question of whether this Nef activity is conserved among the different groups of primate lentiviruses. This question is crucial as SIV infection of natural hosts such as the Sooty mangabeys or African green monkeys is not associated with immunodeficiency or impaired bone marrow function despite chronically high levels of virus replication (26). From this perspective, it will be interesting to elucidate whether this effect of Nef is mainly an indicator of suboptimal virus-host adaptation in the evolutionarily recent human and experimental rhesus macaque hosts or indeed a conserved strategy of primate lentiviruses to evade the host immune system by suppressing the clonogenic potential of HSCs.

**Perspectives**

While the current study by Prost and colleagues (14) is of great interest, much work will be required to define the mechanism by which extracellular Nef induces PPARγ and to determine whether the levels of Nef in blood and bone marrow are sufficient to impair HSC function during HIV infection. It will also be important to better understand (a) to what extent this impaired hematopoiesis contributes to the T cell immunodeficiency associated with progression to AIDS, and (b) how these hematological defects relate to the state of chronic hyperimmune activation that seems to drive the loss of CD4+ T cells and progression to immunodeficiency in HIV-infected individuals. As STAT5 signaling plays a critical role in T cell development and function (27), an additional question is whether Nef also affects T cell homeostasis by suppressing STAT5A/B function in other, more mature T cell subsets (28). From a clinical point of view, the results of Prost and colleagues may potentially identify Nef and/or PPARγ as target for new therapeutic approaches aimed at preventing or correcting the hematologic abnormalities associated with HIV-1 infection. On the other hand, the identification of PPARγ as a suppressor of HSC function might have implications for the use of PPARγ agonists, such as glitazones, in the treatment of diabetes.
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