Is Interleukin-18 a Proviral or Antiviral Cytokine in HIV-1 Infection?

To the Editor—Sailer et al. [1], in their recent study, have shown that, during the early stages of HIV-1 infection, interleukin (IL)—18 might suppress HIV-1 by increasing the Th1 immune response and reducing CXCR4 coreceptor expression. They also suggested an antiretroviral role for IL-18 and proposed that the administration of this cytokine might increase natural antiretroviral function.

Although the involvement of IL-18 in HIV-1 infection remains speculative, in my opinion the main and not yet solved issue is whether IL-18 might have proviral or antiviral activity during HIV-1 infection. IL-18, as a proinflammatory cytokine, acts on Th1 cells to produce interferon (IFN)–γ in the presence of IL-12, whereas, in the absence of IL-12, it actually promotes the differentiation of Th2 cells [2]. It has been demonstrated that there is a marked deficiency of IL-12 production in peripheral blood mononuclear cells of HIV-1–infected patients [3] and that the inhibition of IL-12 production by accessory cells after HIV-1 infection is a potential factor responsible for the impaired innate and Th1 immune response [4]. In our previous study [5], we demonstrated a marked increase in serum levels of IL-18 during the symptomatic and advanced stages of the disease, whereas IL-18 serum levels were not increased during the asymptomatic stage of the disease. By contrast, Sailer et al. [1] demonstrated increased serum levels of IL-18 during the early stages of HIV-1 infection.

However, decreased production of IL-12, IL-2, and IFN-γ rather than activated production of IL-18 during the asymptomatic stage of HIV-1 infection might lead to an inhibition of the Th1 immune response with unsuccessful long-term control of HIV-1 infection [6]. Nevertheless, during the advanced stage of the disease, especially when IFN-γ and IL-12 production is further decreased, persistent elevations in IL-18 levels might promote an ineffective Th2-related immune response and persistent viral replication [6].

In an experimental animal model (infection with simian immunodeficiency virus), Kaizu et al. [7] demonstrated high levels of plasma IL-18 during primary viremia, along with a rapid decline of CD4 T cells and high viral set points, suggesting that IL-18 does not cause effective protection from HIV-1 during the early stage of the disease. In addition, we have previously demonstrated that, in vitro, IL-18 stimulates the replication of HIV-1 in chronically infected promonocytic cells and that this provokes decreased cytotoxic responses and decreased Th1 immune responses [8].

Indeed, during the early stages of the disease, the combined activation of all proinflammatory cytokines, including IL-12, IL-2, IL-18, and IFN-γ, is crucial to mounting a strong and effective Th1 immune response against HIV-1. It should be noted that activation of single proinflammatory cytokines after therapeutic administration (e.g., IL-2 or IL-18, as postulated by Sailer et al. [1]) could not guarantee an effective and persistent Th1 immune response.

However, during the early stages of several viral infections, there is a viral strategy to escape the activation of the Th1 immune response. In addition, HIV-1 itself might inhibit the activation of proinflammatory cytokines, and this could allow for a persistence and worsening of HIV-1 infection [6]. In this scenario, IL-18, as a double-edged sword, has weak proinflammatory activity in attempting to counteract viral replication but is able to stimulate production of HIV-1.

In conclusion, contrasting activity of IL-18 during HIV-1 infection confirms that this cytokine during the different stages of the disease might have proviral activity in both maintaining and worsening HIV-1 infection.

Donato Torre
Section of Infectious Diseases, General Hospital, Cittiglio, Italy

References
7. Kaizu M, Ami Y, Nakasone T, et al. Higher levels of IL-18 circulate during primary infection of...
monkeys with a pathogenic SHIV than with a nonpathogenic SHIV. Virology 2003; 313:8–12.


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Reprints or correspondence: Donato Torre, Section of Infectious Diseases, General Hospital, Via Luvini 1, Cittiglio (Varese) 21033, Italy (donatotorre@libero.it).

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Reply to Torre

To the Editor—We appreciate the comments from Torre [1] in response to our report on the role of interleukin (IL)–18 in early HIV-1 infection [2]. Torre points out the interaction between IL-18 and IL-12, in which IL-12 induces the expression of IL-18 receptors and enhances IL-18 activity. Defective in vitro IL-12 production in peripheral blood mononuclear cells (PBMCs) of HIV-1–infected patients is mentioned as a possible mechanism of reduced HIV-1 immunity. We agree that interactions between IL-18 and IL-12 might be important contributors to HIV-1 control. However, there are situations in which IL-12 might not be required for IL-18 activity. For example, IL-18 increases HIV-1 production in chronically infected monocytic U1 cells and in lymphocytic ACH2 cells in vitro, with no demonstrated role played by IL-12 in these cells [3, 4]. Therefore, IL-18 might affect HIV-1–infected cells independently of IL-12.

Torre et al. [5] have shown elevations in IL-18 levels during symptomatic but not asymptomatic stages of HIV-1 infection. We demonstrated elevated IL-18 levels in persons with precisely defined acute or recent (very early) infection, at a time when the viral set point is being established [2]. We believe that it is important to study antiretroviral immunity soon after infection, when a robust host response can control viral replication [6]. Therefore, our results showing elevated IL-18 levels during early infection might indicate an antiretroviral role of IL-18 during a pivotal time in the host-pathogen interaction. Torre speculates that unsuccessful long-term HIV-1 control might be due to mechanisms other than the inability of IL-18 to enhance Th1-type immunity, such as reduced production of IL-12, IL-2, or interferon (IFN)–γ. We agree. Torre further speculates that elevations in IL-18 levels during the later stages of HIV-1 infection are associated with reductions in IL-12 and IFN-γ levels and that this might result in IL-18 enhancement of Th2-type immunity and increased HIV-1 replication. Contrary to this hypothesis, increased IL-18 levels during the later stages of the disease might represent a compensatory measure to drive a degraded immune system.

Torre notes that, in an animal model of simian immunodeficiency virus infection, increased viremia and declining CD4 cell counts were associated with elevated IL-18 levels, which suggests that IL-18 is not antiviral during early infection. We interpret these observations differently. IL-18 might in fact be antiviral, but suppression is incomplete and results in increases in both viral load and IL-18 levels. If the biological effect of IL-18 had been blocked in these animal studies, viremia might have increased and revealed an antiviral role for IL-18. Torre references a publication by his group showing IL-18–induced HIV-1 synthesis in promonocytic cells (actually a chronically infected T cell line) as a demonstration of IL-18 proviral effects. Our group was the first to demonstrate a proviral effect of IL-18 in a human monocytic cell line infected with HIV-1 [4]. However, the activity of IL-18 in chronically infected monocytic and lymphocytic cell lines might not reflect the effects of IL-18 in vivo. For example, we have shown that IL-18 inhibited HIV-1 production in primary human PBMCs infected with HIV-1 [7]. Primary human PBMCs infected with virus more closely reflect in vivo conditions, and these results support an antiviral role for IL-18. It appears that IL-18 possesses proviral or antiviral effects depending on cell type, cytokine microenvironment, or stage of disease.

Torre points out that HIV-1 replication results in a blunted cytokine response and reduced Th1-type immunity. HIV-1–induced damage to the immune system is uncontested, and we believe that escalating immune dysfunction might explain increases in IL-18 levels during disease progression. Because the failing immune system becomes less responsive to IL-18, IL-18 levels rise in an attempt to drive Th1-type immunity. Torre notes that proinflammatory cytokines are important for an effective antiretroviral host response and that there is no guarantee that administration of a single molecule (such as IL-18) will enhance immunity in patients. Although proof that IL-18 enhances Th1 immunity and is antiretroviral in infected patients must await clinical study, several observations suggest that this strategy has merit. First, IL-18 enhances both Th1 immunity and inflammation. Therefore, IL-18 can augment the antiretroviral host defense, increase IFN-γ (IL-18 is also known to be an IFN-γ-inducing factor), enhance IL-12 function (because IL-12 increases IL-18 receptor expression), and increase the production of proinflammatory cytokines that Torre notes might be important for HIV-1 suppression. Second, IL-18 has demonstrated antiviral activity in several animal models [8–10].

We agree with Torre that the precise role of IL-18 in HIV-1 infection is not settled and can only be determined by continued in vitro and in vivo study. An important step in determining a proviral or antiretroviral role of IL-18 will be taken by specifically blocking IL-18 in infected patients and observing the effect on viral loads.

Carrie A. Sailer1 and Leland Shapiro1,2
1Denver Veterans Affairs Medical Center and 2University of Colorado at Denver and Health Sciences Center, Denver