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.

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monkeys with a pathogenic HIV than with a nonpathogenic HIV. Virology 2003; 313:8–12.

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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 mononcytic 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 mononcytic cell line infected with HIV-1 [4]. However, the activity of IL-18 in chronically infected mononcytic 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.

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