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Selenium and Interleukins in Persons Infected with Human Immunodeficiency Virus Type 1

M. K. Baum, M. J. Miguez-Burbano, A. Campa, and G. Shor-Posner

Division of Metabolism and Disease Prevention, Department of Psychiatry and Behavioral Sciences, University of Miami School of Medicine, Miami, Florida

An important role for selenium in human immunodeficiency virus (HIV) disease has been proposed. Decreased selenium levels, as found in persons with HIV infection or AIDS, are sensitive markers of disease progression. Selenium deficiency, an independent predictor of mortality in both HIV-1–infected adults and children, is an essential micronutrient that is associated with an improvement of T cell function and reduced apoptosis in animal models. In addition, adequate selenium may enhance resistance to infections through modulation of interleukin (IL) production and subsequently the Th1/Th2 response. Selenium supplementation up-regulates IL-2 and increases activation, proliferation, differentiation, and programmed cell death of T helper cells. Moreover, selenium supplementation may down-regulate the abnormally high levels of IL-8 and tumor necrosis factor-α observed in HIV disease, which has been associated with neurologic damage, Kaposi's sarcoma, wasting syndrome, and increased viral replication. Together, these findings suggest a new mechanism through which selenium may affect HIV-1 disease progression.

Selenium and Human Immunodeficiency Virus (HIV) Infection

The natural history of HIV-caused disease is best described as a continuous process in which immune dysfunction and loss of CD4 helper T cells occur at the time of infection and increase progressively, leading to opportunistic infections and oxidative stress [1]. Nutritional status is considered to be one of the determinants of host resistance to infections, and selenium has an important role in both immunologic function and antioxidant defense. As a biologic antioxidant, it is required for the activity of glutathione, a major protective enzyme against oxidative stress. In addition, selenium may have a critical role in viral emergence/evolution [2], thus affecting both resistance and susceptibility to infection. HIV can encode selenoproteins and use oxidative stress conditions to promote HIV gene activation and viral replication [3], which is additional evidence for the critical role of selenium during HIV infection. Although selenium has multiple ways in which to impact HIV disease, we will focus on its possible effect on cytokines, which may direct the intracellular signaling process toward proviral transcription and immune impairment, even in the era of highly active antiretroviral therapy (HAART) [1, 4].

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Reprints or correspondence: Dr. Marianna K. Baum, University of Miami School of Medicine, Dept. of Psychiatry and Behavioral Sciences, 1400 N.W. 10th Ave. (D21), Miami, FL 33136 (mbaum@med.miami.edu).

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Cytokine Imbalance and HIV Infection

Cytokines usually function as intracellular messenger molecules that evoke specific biologic activities after binding to a receptor on a responsive target cell. Although a variety of cells can secrete cytokines, T helper (Th) lymphocytes, one of the principal cytokine producers, are classified as two major effector subsets on the basis of the cytokines they produce [5, 6]. Interleukins (ILs) of the Th1 subset include IL-2 and interferon (IFN)-γ, while the signature cytokines of the Th2 subset are IL-4, -5, -6, and -10. Immunity to infectious agents depends on the activation of Th cells secreting an appropriate pattern of cytokines [5, 6]. Th1 cells are especially effective when cellular response is needed in response to antigens such as viruses, whereas Th2 cells are helpers for B cells and appear to be adapted to support antibody response and defense against parasites. Thus, during diseases that require cellular defense, the Th1 response is activated. A switch from Th1 to Th2, however, has been observed with diseases that include tuberculosis, leprosy, and HIV infection and is associated with disease progression [5–8].

As reported by Clerici and Sheaver [8], several studies have found that with HIV disease progression, IL-2 and IFN levels decline, whereas IL-4, -6, and -10 levels increase. These observations suggest that the activity of the Th1 subset decreases and that of the Th2 subset increases during HIV disease progression. Others have found that an imbalance in expression of cytokines may contribute to the pathogenesis of AIDS [5–8]. Moreover, in vitro studies demonstrate that elevated levels of some ILs may contribute to the progression of HIV from latency to lytic infection, especially those in the Th2 repertoire [9].

Because HIV utilizes normal intracellular signaling pathways

to regulate its expression, there has been considerable attention to the role of selected host transcriptional factors in its initial activation by interaction with the long terminal repeat (LTR) of the integrated provirus [10]. Transcriptional activation of the LTR depends largely on a major enhancer composed of two directly repeated sequences that respond to the transcription factor NF-κB. Related κB enhancers are present in the regulatory region of various ILs, including IL-6 and IL-8 and tumor necrosis factor (TNF)-α [9].

IL-2 and HIV infection/AIDS. One of the earliest observations of immune system impairment in HIV infection was a reduction in the number of T cells and subsequent susceptibility to opportunistic infections. Depletion of T cells normally induces T cell maturation within the thymus to restore the peripheral T cell numbers. The binding of soluble gp120 to CD4 cells and the reduced levels of IL-2 interfere with the maturation process in the thymus and lead to a lack of replacement by developing thymocytes [9].

Soon after a person is infected with HIV, there is a decreased ability of T lymphocytes to proliferate in vitro in response to mitogens or soluble antigens. A decline in the number of T cells is responsible for the reduced mitogen response; later phases of HIV disease are also associated with an inability of T cells to respond to mitogens, even after antiretroviral treatment or when T cell numbers are increased [9]. The absence of an antigen-specific T cell response suggests that T cells in AIDS patients receive an inappropriate activating signal from IL-1 and IL-2, inducing these cells to become anergic and/or to program the cells for apoptosis.

T cells generate a population of effector cells with lytic capabilities called cytotoxic T lymphocytes (CTL). These effector cells have an important role in the recognition and elimination of altered cells, including virus-infected cells. IL-2 is the principal cytokine required for differentiation and activation of these effector cells. In HIV infection, low levels of IL-2 do not permit cytotoxic cells to express IL-2 receptors and do not proliferate or display cytotoxic activity [9]. These findings are of special interest, as new quantitative techniques have demonstrated an association between CTL and virus load [11] and nonprogressive HIV infection [12, 13].

IL-2 also stimulates the activation and proliferation of natural killer (NK) cells, which are important in nonspecific killing tumor cells. Because of decreased IL-2 levels, persons with AIDS have diminished NK activity; not unexpectedly, they commonly develop various types of tumors [14]. The delayed type hypersensitivity (DTH) response, an important host defense mechanism against intracellular pathogens such as *Pneumocystis carinii,* mycobacteria, *Candida, Histoplasma,* and *Cryptococcus* organisms, is also primarily dependent on the Th1 subset. Given the limited circulating levels of IL-2, IFNs, and IL-8 receptors, it is not surprising that with a decrease in T_{DTH} cell function, there is a significant increase in susceptibility to intracellular pathogens [9].

IL-2 and HAART. A major advance in the treatment of HIV disease includes the administration of HAART, which is associated with a significant reduction in virus burden and an increase in CD4 cells [15]. The degree of immunosuppression and the extent of immune function recovery, however, may not be absolute [16, 17], and slower, incomplete immune recovery has been reported in severely immunocompromised patients [18]. Immunologic reconstitution with IL-2 has been tested in numerous trials. Long-term IL-2 supplementation improves CD4 cell counts, but the robust response is observed mainly in patients with baseline CD4 cell counts >300 [16, 18]. While extremely useful, IL-2 therapy is associated with severe secondary effects that frequently result in discontinuation of the therapy. The cost of this long-term therapy is high and requires parenteral administration. Therefore, there is a critical need for therapeutic factors that affect cytokine secretion without producing toxic side effects and that can be used in all HIV-infected persons.

Selenium, HIV Infection, IL-2, and HIV Replication

In parallel with the diminished production of Th1 ILs in HIV disease, there is a reduction in selenium levels with disease progression [4, 19–21]. Selenium deficiency occurs more frequently in HIV-seropositive persons with disease progression as documented by low plasma and red blood cell selenium levels [4, 19, 21]. Immune dysfunction has been found secondary to the selenium deficiency in HIV-infected patients and in persons with other diseases [19]. This dysfunction includes impaired T cell response, decreased lymphocytes, including T cells, impaired phagocytic function, and decreased immune cytotoxicity.

Selenium's immunologic properties include the selenium-dependent glutathione peroxidase system that protects against oxidative stress and is increased in HIV disease [1, 3, 4, 19–21]. The selenium–glutathione peroxidase system uses reducing equivalents from glutathione to catabolize hydrogen peroxide and protect cells from the oxidant molecules that are increased as a result of chronic immune activation. Studies from several laboratories indicate that HIV gene expression can be controlled by intracellular transduction pathways that are redox regulated, suggesting that HIV takes advantage of both immune activation and the pro-oxidative environment to replicate itself through the NF-κB pathway [1, 4]. Selenium deficiency results in a decrease in the activity of all glutathione peroxidases. Glutathione peroxidase activities in the plasma and liver are very sensitive to selenium supply. During HIV infection, adequate selenium levels are especially important, as unopposed oxidative stress programs a state of steady increase in virus load [4].

Selenium and IL-2. In in vitro models, selenium regulates levels of IL-2, the cytokine responsible for the earliest and most rapid expansion of T lymphocytes. The process appears to occur through the increased expression of a high-affinity receptor,

particularly the α and β subunits [22, 23]. In these in vitro studies, selenium enhanced IL-2 production in a dose-dependent manner. Roy et al. [22] demonstrated in vitro and in vivo that supplementation of selenium-deficient animals with low doses of selenium significantly enhanced the ability of activated lymphocytes to proliferate and differentiate in cytotoxic cells. This was related to the ability of selenium to induce an augmented expression of the high-affinity IL-2 receptor. Selenium supplementation significantly increased the expression of high-affinity receptors in 49% and low-affinity receptors in 55% of the IL-2 binding sites. These data indicate that selenium increases the expression of high-affinity receptors at ratios comparable to those in cells of selenium-adequate animals. Selenium also enhanced both the production and internalization of IL-2, indicating that IL-2 production after exogenous addition of selenium is functional [22], which may explain the broad effect of this trace element in the cellular immune system.

TNF-α and HIV Infection/AIDS. Chronic inflammation, which develops in a large percentage of HIV-infected patients, is due to prolonged persistence of HIV antigens and often induces significant tissue damage and wasting. Two cytokines in particular, IFN and TNF, play a central role in the development of chronic inflammation. William Colley first observed the activity of TNF around 1900 in cancer patients (reported in [9]). Decades later, in animal models, TNF secretion was related to tumor cells but not to normal cell destruction. In HIV-infected patients, TNF appears to play a major role in the pathogenesis of Kaposi's sarcoma. Several clinical studies have found a positive correlation between high levels of TNF and the presence of Kaposi's sarcoma [24, 25]. Recent studies suggest that the effect of TNF on Kaposi's disease is mediated through the TNF receptor [25]. The importance of this inflammatory cytokine is also indicated by clinical reports of the progression of Kaposi's sarcoma in patients treated with TNF [26].

TNF also seems to have a prominent role in the pathogenesis of anorexia and cachexia of chronic diseases, including cancer [27]. In HIV infection, the administration of thalidomide (a TNF inhibitor) to HIV-1–infected patients with weight loss has consistently resulted in weight gain [27]. In clinical studies, high serum levels of TNF-α were found in AIDS patients, suggesting the possible involvement of TNF in disease progression [4, 25]. TNF-α exhibits a strong activating effect on HIV replication in vitro through nuclear translocation of NF-κB, which then transactivates the HIV-1 long terminal repeat in both chronically and acutely infected cells [28]. TNF also increases HIV-induced syncytium formation in peripheral blood mononuclear and CD4 T cells [9].

Selenium and TNF-α. Infection with HIV is characterized by an initial acute viremic stage followed by months and sometimes years of clinical latency prior to disease escalation. The factors that stimulate replication of HIV determine the duration of clinical latency and the course of the disease. In vitro studies from several laboratories suggest that HIV gene expression can be controlled by intracellular signal transduction pathways modulated by the presence of antioxidants [1]. Selenium is an essential trace element involved in cellular antioxidant systems. Moreover, selenium supplementation suppresses TNF-α–induced HIV-1 replication. The mechanism by which selenium supplementation suppresses TNF-induced HIV replication is not fully understood but seems to involve its role in selenoprotein synthesis, especially glutathione and thioredoxin systems [29]. In addition, Look et al. [4] demonstrated in HIV-infected patients that plasma selenium levels are inversely correlated with levels of soluble TNF type II receptors. Selenium supplementation may therefore reduce TNF receptors and prevent some of the deleterious effects of high TNF circulating levels such as wasting and Kaposi's sarcoma.

IL-8 in HIV infection. Elevated levels of circulating IL-8, a potent chemotactic factor for granulocytes and T cells, are found in HIV-infected subjects [4]. The HIV-1 transactivator protein, tat, increases IL-8 secretion after antigen stimulation. The enhanced production of IL-8, while beneficial initially, results in a subsequent increase in oxidative stress resulting in severe secondary damage. In contrast to the high circulating levels, low levels of both IL-8 receptors (A and B) have been found in HIV-infected patients, resulting in defects of cell degranulation in subjects with high plasma levels [30].

IL-8 is involved in the migration of leukocytes and has been implicated in inflammatory diseases in the central nervous system of HIV-infected persons [31, 32]. IL-8 is also associated with a severe inflammatory response in HIV-infected persons with respiratory infections (bacterial infections, *P. carinii* pneumonia, and tuberculosis) [33]. IL-8, by binding to its receptors, induces a variety of cell type-specific responses, including the induction of a neutrophil respiratory burst and lysosomal enzyme release. In addition, high levels of IL-8 have been found in patients with tuberculosis who died in contrast to those who survived [34].

Increased production of IL-8 may have other consequences. Altered concentration gradients between the periphery and site of inflammation may disseminate the virus to other sites of the body. In addition, IL-8 in its unique role in the recruitment of target cells to the sites of viral replication may increase the migration of T cells to lymph nodes, providing target cells necessary for continuous HIV replication.

Selenium and IL-8. Recent studies in HIV-infected and -noninfected persons have shown that serum selenium levels are inversely correlated with serum concentrations of IL-8 [4]. Two possible explanations have been suggested: First, that the increased oxidative stress in HIV infection is caused by elevated IL-8 levels, which exhausts the available selenium that protects the cells exposed to inflammatory stress [4], and second, as shown by in vitro studies, selenium in the glutathione peroxidase system can inhibit IL-8 release by endothelial cells [35, 36].

Summary

There is substantial evidence of an important role for selenium in ameliorating the physiopathologic process of HIV-1 infection. As part of the antioxidant defense system, selenium decreases oxidative stress and inhibits viral cytotoxic effects. Through its regulation of cytokine levels (IL-2, TNF, IL-8), selenium impacts both T lymphocyte proliferation and differentiation and cytokine-induced HIV-1 replication. The importance of this essential micronutrient in HIV-1–related survival suggests that selenium supplementation may be immunorestorative and of therapeutic benefit in persons with HIV infection or AIDS, particularly when antiretroviral treatments are not readily available. High levels of antioxidants, however, may interfere with the host's oxidative processes [37] and must be carefully monitored. The long-term clinical and survival implications of selenium therapy are unknown. Clinical studies of selenium supplementation over time will be necessary to evaluate the long-term impact of selenium on the cytokine network and the ability of selenium to slow HIV disease progression.

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