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The role of cytokines in the acquired immunodeficiency syndrome

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Summary. HIV replication in vitro is regulated by many factors, including various exogeneous stimuli and proteins encoded by either virus or cellular genomes. During the asymptomatic period, cells latently or chronically infected with HIV gradually express virus, leading to immunosuppression and opportunistic infection. These conditions would result in the increased secretion of cytokines, especially TNF, from infected and uninfected cells, which can induce HIV and killing of infected cells. A vicious circle is then set in motion in which heterologous microbial infections directly or indirectly activate HIV and the production of cytokines, thereby accelerating lymphocyte depletion and immunodeficiency. AIDS is a disorder of the immune network caused by a unique retrovirus HIV. However, if the whole story described above is true, this disease can also be termed a "cytokine disease". Immunity resembles a "double-edged sword", with aspects not only protective, but also deleterious to the host. Therefore, it is essential to more extensively investigate the mechanism of cytokine regulation of HIV expression in vivo, not only to understand the complex patohophysiology of AIDS, but also to design a therapeutic strategy to halt this deadly disease.

Key words: Cytokines – TNF – AIDS – HIV

Introduction

There is little doubt that the human retrovirus human immunodeficiency virus-1 (HIV-1) is the primary causative agent of the acquired immunodeficiency syndrom (AIDS). However, infection with HIV does not usually result in immediate progression of the disease, and a rather long incubation period is needed for the development of full-blown AIDS [1]. It is, therefore, speculated that either physiological or non-physiological factors promote HIV replication and the killing of infected cells. In 1987 we reported that the phorbol ester 12-O-tetradecanoylphorbol-13-acetate (TPA) efficiently activated HIV replication in chronically infected MOLT-4 cells [2] and selectively killed HIV-infected cells. Several other factors, including those contributing to cell activation, such as phytohemagglutinin (PHA), bacterial toxoid and antigens, heterologous viruses, bacteria, and mycoplasma, can also stimulate HIV gene expression [3, 4]. This prompted us to investigate physiological factors, including cytokines, as possible "cofactors" for AIDS development.

Cytokines exert their biological effects on a wide variety of cell types and interact with each other to regulate the host immune system [5]. Several cytokines have been reported to activate HIV gene expression [3, 4, 6]. Among these, tumor necrosis factor (TNF)-α and -β, which are cytokines released by activated macrophages or activated T cells, augmented HIV growth efficiently and killed HIV-infected cells specifically [7–9]. Since TNFs have diverse biological activities, we regarded TNF as most likely to be involved in the progression of AIDS [4, 10].

Infection, latency, and activation of HIV

The typical clinical course of HIV infection and its progression to AIDS is well documented [11, 12]. A burst of antigenemia and a fall in the number of CD4(+) lymphocytes, which regulate the immune response, occur at the time of initial infection. This is followed by recovery of the CD4 count to the normal level and entry into the so-called latent period which lasts for several years. During this time, there is a gradual decline in circulating CD4(+) lymphocytes, although infected individuals are generally asymptomatic. Continuing loss of CD4 lymphocytes for approximately 7–10 years following initial infection renders the body highly susceptible to opportunistic infections and neoplasms. Although recent studies have shown that the virus grows actively in lymph nodes [13, 14], it is also clear that HIV gene expression is largely dormant and that HIV is suppressed by an active immune response. Latent infection of HIV-1 may be very important for maintenance of the infected state in the

host, since non-producing infected cells can escape from the host immune attack [15]. HIV latency appears to result from either integration blockade or post-integration blockade. The former seems to occur in non-dividing white blood cells that permit the infection but not the integration of HIV. The latter may result from the lack or low level of transcription factor, mainly NF-κB.

Although the immune system is apparently suppressed in AIDS patients, it is notable that HIV-infected individuals display "autoimmune" manifestations which are thought to be related to the hyperimmune state at the early stage of infection [16]. Activation of the immune system involves production of autoantibodies, including anti-cytokine antibodies, polyclonal B cell activation, increased immune complexes, increased interleukin-2 (IL-2) receptor (IL-2R) expression, and increased IL-1 secretion. Activation of cells results in stimulation of HIV expression, either directly through the induction of cellular transcriptional factors or indirectly through induction of various HIV-inducing cytokines. Thus, a hyperimmune state during the early course of HIV infection may account for the subsequent immune defect seen in AIDS patients.

Role of cytokines in the regulation of HIV expression

The effect of various cytokines on the replication of HIV-1 has been investigated in a variety of cell culture systems, including T cell lines, macrophage/monocyte cell lines, peripheral blood mononuclear cells (PBMC), and primary macrophages [4, 6]. The discovery of the upregulation of HIV-1 expression by TNF was fortuitous. In 1985 we reported that HTLV-I-infected MT-2 and MT-4 cells were highly susceptible to infection by HIV [17]. Upon infection these cells allowed the extremely rapid replication of virus and showed strong cytopathic effects. Subsequent studies showed that TNF, which is released by MT-2 cells, was responsible for this effect [7, 8]. TNF-α and -β showed essentially the same effect in terms of activation of HIV-1. Using various cell lines from T cell and macrophage/monocyte lineages and PBMC, the viral growth-promoting activity of TNF in either a recent or chronic infection was further demonstrated [18–21]. Anti-TNF-α antibody substantially suppressed HIV expression in TPA-treated ACH-2 and U1 cells, both dormantly infected with HIV-1, suggesting that TPA acts via the induction of TNF secretion [22]. TNFs also enhanced the formation of a syncytium between HIV-infected and uninfected T cells, and led to fusion-associated enhancement of HIV replication [23]. TNF-α accelerates the transcription of HIV, but does not increase the total amount of virus produced [18].

Upon stimulation with TNF, NF-κB is induced strongly. NF-κB was initially discovered as a nuclear transcription factor for the κ chain of immunoglobulin in B cells [24], and later was also found in various genes, including IL-2, IL-2R, IL-6, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage-CSF (GM-CSF), interferon (IFN)-γ, MHC class I T cell receptor (TCR), and β_2-microglobulin [4, 10, 25]. The HIV long terminal repeat (LTR) sequences also include these tandemly repeated elements and many other *cis* elements. We and others have found that the NF-κB enhancer element of the LTR is essential for the TNF-α-mediated activation of HIV gene expression [26, 27]. Osborn et al. [28] provided more direct evidence that the action of TNF on HIV-1 expression involved the induction of cellular factors that bind to the NF-κB site using the gel retardation assay; this mechanism being similar to that of mitogen activation of HIV. Further studies also suggested that G proteins were involved in the TPA and TNF-α induction of HIV-1 [29].

Other examples of multifunctional cytokines are IL-6 and IL-1. The functions of these cytokines overlap, although each possesses its own properties [30]. IL-6 is a monokine, originally characterized as the factor responsible for antibody production. IL-6 markedly stimulated HIV gene expression in U1 but not in ACH-2 cells [31]. The enhancing activity of IL-6 was also shown by infection of primary macrophages with HIV-1. This cytokine was reported to activate HIV-1 gene expression post-transcriptionally, since it did not increase the amount of HIV mRNA [31]. Interestingly, it suppressed HIV expression after infection of the U937 monocyte, a parental line of U1 cells [32].

Osborn et al. [28] showed that IL-1-stimulated HIV LTR in mouse cells but not in human T cells. However, our chloramphenycol acetyl transferase (CAT) assay with MOLT-4 cells chronically infected with HIV showed that IL-1 activated HIV expression [33]. However, the activation was rather weak compared with TNF. Very recently, Poli et al. [34] showed that both IL-1-α and -β induced HIV in latently infected U1 cells. They also showed that IL-1 synergized with IL-6, but not TNF, in enhancing HIV expression. Although most stimuli require NF-κB as an effector molecule for HIV-1 induction, they are categorized further into two groups based on whether they are dependent on protein kinase C (PKC). The antigen-induced stimulation pathway is PKC dependent, while stimulation by TNFs and IL-1 appears to be independent of PKC [4].

GM-CSF was first reported to have anti-HIV activity in recently infected U937 cells [35]. Folks et al. [36] then reported that this cytokine weakly stimulated expression of HIV, and this induction was further augmented by TNF-α in U1 cells. Using primary macrophages freshly infected with macrophage-tropic HIV-1 (JR-FL), Koyanagi et al. [31] clearly showed that GM-CSF enhanced HIV replication.

IFN-α, -β, and -γ are well known to induce an antiviral state in cells [38]. Pre-treatment of normal macrophages with IFN-γ resulted in apparent upregulation of viral expression after infection with the JR-FL strain of HIV-1 [37]. In contrast, this cytokine inhibited HIV expression when applied after infection. This suggests that the IFN effect may be determined by the status of the cells, especially their differentiation state.

Other cytokines, such as IL-3 and IL-4, also stimulate HIV gene expression rather strongly in infected primary macrophages [37]. IL-2 has been used to isolate HIV in vitro since early in the AIDS epidemic, in addition to

PHA. It is noteworthy that transforming growth factor-β significantly inhibits HIV expression in TPA-stimulated U1 and infected primary macrophages [39]. However, this cytokine appeared to upregulate the activation of HIV-1 in the acute infection of U937 cells [40]. In summary, the effects of cytokines on HIV replication are variable, depending on the experimental systems used, especially cell types and viral states.

Induction of cytokines by HIV-1

Several reports have described the induction of cytokines, especially TNF-α and -β, by different classes of viruses [41]. TNF-α and IL-1 induction was observed within a few hours of exposure to HIV virions in vitro [42]. Heat-inactivated virus also produced the same effect which was apparently blocked by soluble CD4. Similarly, HIV induced IL-6 mRNA and its secretion from monocyte/macrophage in vitro [43]. Wahl et al. [44] showed that IL-1 and prostaglandin E_2 production by human monocytes was stimulating by the addition of purified gp120. All these data suggest that a positive signal is transduced to produce and release cytokines once CD4 molecules bind gp120. However, Munis et al. [45] showed that productive infection of primary macrophages by macrophage-tropic HIV did not alter TNF-α secretion. Molina et al. [46] also showed that no increase of IL-1, IL-6, or TNF-α mRNA or protein was detected in fresh PBMC exposed to HIV or gp120. There are also several other conflicting studies on the role of HIV in the induction of various cytokines in vivo. Increased [47, 48], equal to control [49], or decreased [50] levels of TNF-α and -β were observed using PBMC of AIDS or AIDS-related complex (ARC) patients, although these investigators did not necessarily employ the same experimental systems.

Soluble cytokine receptors and immunoregulatory molecules

In HIV-1 infection and that of an other retrovirus, HTLV-I, increases in the serum levels of cytokine receptors, including IL-2R, IL-6R, and a possible signal transducer of IL-6, gp130, appear to be associated with disease progression [51, 52]. These soluble receptors have a lower molecular weight than their parental molecules. Our subsequent studies showed that soluble forms of these molecules were generated through an alternative splicing mechanism, although the possibility of proteolytic cleavage was not necessarily ruled out ([53]; Yamamoto et al., unpublished data).

Although s-IL-2R was not detectable in HIV-seronegative donors or in patients in the early stage of infection, it increased with disease progression [52]. Moreover, the s-IL-2R level was significantly correlated with serum IL-6. The s-IL-6R has been detected at a level as high as 50–100 ng/ml, even in normal sera, and was increased in HIV-infected individuals, thus suggesting a physiological as well as pathological role for the soluble form of this cytokine receptor. Upon infection of the monocyte-lineage cell line U937 with HIV-1, release of s-IL-6R was shown to be increased directly. It is important that the soluble forms of IL-6R and IL-2R are functional, i.e., they have the ability to bind their respective cytokines [52]. These results strongly indicate that s-IL-6R, s-IL-2R, and s-gp130 are involved in controlling the immune response and disease manifestation.

Some immunoregulatory molecules other than cytokine receptors, such as MHC-I, have also been shown to be released in the blood (Yamamoto et al., unpublished data). We have also demonstrated the presence of mRNA for MHC-I lacking the transmembrane domain, by reverse transcription/polymerase chain reaction and subsequent nucleotide sequencing of amplified DNA bands. The level of serum MHC-I also appeared to increase with disease progression. Because MHC-I is a prerequisite for cytotoxicity of CD8(+) T cells towards virus-infected cells, the presence of soluble MHC-I will probably disturb the host defense system. Further studies are certainly necessary to determine the role of soluble MHC-I. Although we also showed the presence of an alternatively spliced form of mRNA for TCR using the same technique, we failed to show that it was translated into a protein. Thus, the physiological role of this molecule remains to be determined.

Clinical significance of the increase in cytokines

Although a large body of evidence obtained from in vitro studies suggests a significant role for cytokines in HIV infection, definitive proof has not been obtained. For this we must await the results from an experimental animal model, such as a simian immunodeficiency virus system. Nevertheless, we can assume a role for cytokines in human HIV infection. Various cytokines upregulate HIV expression in infected T cells and macrophages, mainly by activating the specific nuclear factor, NF-κB. HIV can also augment its own expression by inducing the secretion of other cytokines (which lead to the unnecessary activation of cells by stimulating HIV replication) and disturbance of the immune network. Selective killing of HIV-infected cells by some cytokines may strengthen the effects.

It is thus important to investigate whether HIV-infected individuals have abnormal serum cytokine levels, and whether this abnormality is linked with disease status. Lahdevirta et al. [54] reported that serum TNF levels of asymptomatic HIV carriers and patients with lymphadenopathy were within the normal range, while all patients with AIDS and some ARC patients had elevated levels of TNF. The level of ARC patients frequently exceeded that capable of inducing HIV in vitro, again suggesting an active role for this cytokine. Essentially the same results were reported by several other investigators [55, 56]. Similarly, a number of reports have documented increases in IL-1, IL-6, TGF, and IFNs in the plasma of HIV-infected individuals [6].

Because TNFs have diverse biological effects, such as the induction of septic shock, cachexia, inflammation, and other systemic phenomena, we tried to correlate a variety of symptoms seen in AIDS patients with the activ-

ities of TNFs and other cytokines. We especially believe that the cachectin activity, the ability to promote endothelial cell growth, and the IL-6-inducing ability of TNF may explain the severe weight loss (cachexia), fever, frequent development of Kaposi's sarcoma, hypergammaglobulinemia, and central nervous system disorders [4]. It is also important to note that several of the secondary infections and neoplasms commonly seen in AIDS patients can induce the secretion of TNF-α and other cytokines.

Therapeutic aspects

If the above scenario in which endogenous cytokines play a role in the regulation of HIV expression is plausible, future treatment of HIV infection might include suppression of the immune system. The rationale for immune suppression is to avoid harmful activation of the immune system in the latent phase of the infection, which can lead to the enhancement of viral production and cell killing and progression of the disease. Indeed, a recent retrospective statistical study reported that cyclosporin A (CSA) significantly delayed the development of AIDS in patients infected with HIV during transplantation [57]. Furthermore, CSA and a similar but more potent immunosuppressive agent FK506 delayed syncytia formation and the growth of HIV-infected cells in vitro [58]. Banda et al. [59] reported that crosslinking of bound gp120 on human CD4(+) T cells, followed by signalling through the TCR for the antigen, resulted in activation-dependent cell death by a form of apoptosis. Groux et al. [60] described activation-induced apoptosis of CD4(+) T cells from HIV-infected asymptomatic individuals. This apoptosis mediated by signalling through the TCR can be blocked by CSA and FK506 ([60]; Yamamoto et al. unpublished data). These data suggest that CSA and FK506 exert their effects through blocking of the T cell activation responsible for cytokine production and apoptosis.

In the mouse, helper T cells are functionally divided into two subgroups: Th1 and Th2 [61]. Th1 cells are associated with cell-mediated immunity (CMI), including killer T cells and delayed-type hyper-sensitivity reactions, through the production of IFN-γ and IL-2, while Th2 cells promote humoral immunity, such as IgE production, leading to allergic reactions, through IL-4, IL-5, and IL-10. These two types of helper T cells are thought to function antagonistically; IFN-γ suppresses Th2 cell function while IL-4 and IL-10 inhibit Th1 cells. When the body is invaded by pathogens, "initiation cytokine" IL-12 is produced by macrophages, and this cytokine pushes uncommitted T cells towards becoming Th1 cells. From studies with HIV-infected individuals who do not show any evidence of disease for years (long-term survivors) or those who show a shift in status from asymptomatic to symptomatic, it seems that Th1-like function is important as a predictor of the onset of AIDS symptoms and death, even at a very early stage of HIV infection. Thinking along the same lines, Salk et al. [61] proposed designing a type of vaccine that can induce predominantly CMI. It will therefore be interesting to observe whether administration of cytokines (such as IL-12, IL-2, and IFN-γ) to HIV-infected individuals can shift them towards a protective CMI response and prevent the development of symptoms.

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