Rapid CD4 T cell depletion in human-PBL-SCID mice by non-cytotoxic macrophage-tropic isolates of HIV.

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Distinct isolates of human immunodeficiency virus (HIV) differ in their tropism, rate of replication, pathogenicity, and ability to induce syncytial formation in vitro. We have compared a panel of molecularly cloned HIV-1 or HIV-2 isolates which differ in these biologic properties for their ability to deplete CD4 T cells in vivo by using them to infect SCID mice treated with a delayed but effective anti-CD4 monoclonal antibody (mAb) (GUI-PBL-SCID mice). The macrophage-tropic strains HIV-1sgm and HIV-2gvc, which are non-cytotoxic in vitro, induced the most rapid and extensive CD4 T cell depletion in hu-PBL-SCID mice. Why HIV-1sgm, which is highly cytotoxic for T cells in vitro, caused the slowest and least extensive CD4 T cell depletion in vivo. The rate of CD4 T cell depletion in hu-PBL-SCID mice was not correlated with viral burden, as HIV-1sgm showed higher replication capacity than other strains in vivo as well as in vitro. The HIV sequences in the env gene that are associated with macrophage-tropic virus thus correlate with increased capacity for CD4 T cell depletion in the hu-PBL-SCID model, but not for cytotoxic effects in tissue culture. The rate of CD4 depletion is more dependent on the particular viral strain than the extent of viral replication, implying a role for pathogenic sequence elements in this process.Supported by NIH grants AI29182, AI30238 (DEM), and AI29394 (JAL).

Peripheral blood leukocytes (PBL) from HIV-seropositive pregnant women and cord blood leukocytes (CBL) from their offspring were studied for in vitro T helper cell (TH) function by interleukin 2 (IL-2) production in response to HIV and non-HIV antigens to determine whether HIV-specific TH function of mother and/or infant correlated with absence of mother-to-infant transmission of HIV. Polymerase chain reaction and viral culture assays were performed to determine HIV infection of the infants. PBL from 10/23 (43%) mothers tested and from 9/23 (39%) newborn CBL samples responded to two or more of five synthetic gag/pol/env (em) peptides. These of the 23 offspring were shown to be HIV-infected. All three of the infected newborns were unresponsive to one, and none of the 10 offspring who were responsive to one or more at birth were found to be infected. No correlation was detected between the mothers' em-specific TH response and vertical transmission of HIV. Thus, maternal seropositivity or newborn seronegativity were not correlated. These results demonstrate that exposure to HIV antigens can occur in utero, and that such exposure can result in priming of the fetal T helper cell compartment. These results also raise the possibility that HIV-specific TH immunity may be protective in utero or in neonates.

Cytokines as regulators of myeloid cell biology (1024-1027)

Regulation of interleukin-6 production by IL-12, TNF and IL-10 in SCID splenocytes. C.S. Triece and E.S. Unanue. Washington Univ. Sch. of Med., St. Louis, MO 63110

Listeriosis in SCID mice is an established model of IFN-γ-dependent macrophage activation by NK cells in vitro and in vivo. Through a T-cell independent pathway, infection with Listeria results in the activation of macrophages with high expression of class II MHC molecules. Macrophages that take up Listeria release cytokines that induce NK cells to produce IFN-γ. In this study we demonstrate that IFN-γ production from SCID splenocytes is stimulated by IL-12 and TNF but inhibited by IL-10. IL-10 production is necessary for heat killed Listeria monocytogenes (hh-LM) to stimulate IFN-γ production since neutralization of IL-12 abolishes IFN-γ production. Addition of IL-10 inhibits IFN-γ production. Thus both IL-12 and TNF are co-stimulators for IFN-γ production. IL-10 inhibits hh-LM stimulated IFN-γ production by inhibiting TNF and IL-12 production by SCID splenocytes as well as by inhibiting these cells' ability to respond to IL-12 and TNF. Conditioned media from peritoneal macrophages stimulated with hh-LM contains IL-12, TNF and IL-10 which regulate IFN-γ production in vitro. This data indicate that macrophages produce TNF, IL-12 and IL-10 in response to hh-LM; IL-12 and TNF stimulates IFN-γ production by NK cells whereas IL-10 inhibits it at both the level of the macrophage and the NK cell.

IL-10 inhibits macrophage (Mφ) co-stimulatory activity by selectively inhibiting the upregulation of B7. Expression. L.J. de Vries, D. E. Mosier, R. J. Galizia, P. D. Mashhac, and E. M. Shevach. NIAID, NIH, Bethesda, MD 20892 and Bristol-Myers Squibb, Seattle, WA 98121.

Recently, we have demonstrated that the inhibitory effects of IL-10 on Con A induced T cell proliferation or IL-2 production by resting murine T cells were only observed when Mφ, but not when activated B cells, dendritic cells or L cells, were used as accessory cells (ACC). To further elucidate the mechanism of action of IL-10 on the inhibition of Mφ co-stimulatory activity, we have used a system in which Mφ develop into effective co-stimulatory cells and the effect of IL-10 on this process can be examined in the absence of T cells. After Con A, Mφ have no co-stimulatory activity for soluble anti-CD3 induced T cell proliferation nor do they express B7. In contrast, Mφ activated by culture, LPS, or IFN-γ for 24 hr and then fixed were effective ACs, expressing B7. Fixed and co-stimulatory activity was related to their level of cell surface B7 expression. In addition of IL-10 during the process of Mφ activation resulted in both a marked reduction in co-stimulatory activity and in the upregulation of B7 expression. The inhibitory effect of IL-10 on the upregulation of B7 was selective since the upregulation of both IAcM-1 and MHCI class II antigens was not affected. Furthermore, the defective co-stimulatory ability of both resting and IL-10 treated Mφ could be restored to these cells which expressed high levels of B7 following transfection, but not by non-transfected L cells. As B7 plays a key role in the co-stimulation of IL-2 and IFNγ production, the regulation of B7 expression and Mφ co-stimulatory activity by IL-10 may play an important role in the generation of Th2 cells or in the induction of T cell energy.


Recently, we cloned the human cDNA homologue of P600, a mRNA which is transcribed by activated mouse Th2 clones. Both human and mouse P600 proteins were biologically active on human monocytes and B cells. Therefore, we proposed that this novel cytokine be designated Interleukin-13 (IL-13). Human IL-13 is a non-glycosylated protein of 132 aa with a molecular mass (Mr) of 10 KD. IL-13 induced changes in the morphology of human monocytes. These cells formed long cellular processes and adhered strongly to the substrate when cultured in the presence of IL-13. In addition, IL-13 strongly enhanced the expression of class II MHC antigens on monocytes and induced expression of CD23 (FoxR II). Furthermore, IL-13 inhibited the LPS-induced production of monokines including IL-1, IL-6 and IL-8. Taken together, these data indicate that IL-13 has important immunoregulatory activities on human monocytes.