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RAPID CD4 T CELL DEPLETION IN HUMAN-PBL-SCID MICE BY NON-CYTOTOXIC MACROPHAGE-TROPHIC ISOLATES OF HIV. D. E. Mosier, R. J. Galizia, P. D. Masia, B. E. Torbett, and J. A. Levy. The Scripps Research Institute, La Jolla, CA 92037 and UCSD, San Francisco, CA 94143.

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 vitro by using them to infect SCID mice (transgenic mice lacking functional IL-2 receptor (p55) (hu-PBL-SCID mice)). The macrophage-trophic strains HIV-1sg2 and HIV-2ac1, which are non-cytotoxic in vitro, induced the most rapid and extensive CD4 T cell depletion in SCID mice. The human HIV-1 (HIV-1srm3s), which is highly cytopathic 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-1sg2 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-trophic thus correlate with enhanced capacity for CD4 T cell depletion in the hu-PBL-SCID model, but not for cytopathic 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 sequences in CD4 depletion. (Supported by NIH grants AI29182, AI30238, and AI29394 (JAL)).

IL-10 INHIBITS MACROPHAGE TROPISM FOR HUMAN IMMUNODEFICIENCY VIRUS. D. E. Mosier, R. J. Gulizia, P. D. Masia, B. E. Torbett, and J. A. Levy. The Scripps Research Institute, La Jolla, CA 92037 and UCSD, San Francisco, CA 94143.

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 using them to infect SCID mice with HIV-1 clonal isolates which differ in their biological properties. The HIV-1 clones that were tested were derived from two sources: 1) the laboratory of Dr. M. H. Rothbard (NIH) and 2) the Laboratory of Dr. M. H. Hawn (NCI). The rate of CD4 T cell depletion in hu-PBL-SCID mice was not correlated with viral burden, as HIV-1sg2 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-trophic thus correlate with enhanced capacity for CD4 T cell depletion in the hu-PBL-SCID model, but not for cytopathic 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 sequences in CD4 depletion. (Supported by NIH grants AI29182, AI30238, and AI29394 (JAL)).

TNF-α UPREGULATES IL-10 EXPRESSION IN HUMAN Peripheral BLOOD MONOCYTES. Chi-Cheng Wang and Warren G. Stobro. Macaulay Immunology Center, Laboratory of Clinical Investigation, NIAID, National Institutes of Health, Bethesda, MD 20892. In previous studies it has been shown that LPS induces an initial burst of inflammatory monokine production in human monocytes, which is followed by substantial IL-10 production; the IL-10 then down-regulates the monokine production as well as IL-10 production itself. In the present studies we assayed the hypothesis that one of the inflammatory monokines is responsible for IL-10 production in human monocytes. Accordingly, we cultured purified human peripheral blood monocytes with a panel of cytokines including TNF-α, IL-1α, IL-1β, IL-6, GM-CSF, TGF-β, and IFN-γ; and then measured IL-10 mRNA production using a semi-quantitative RT-PCR technique. We found that TNF-α had a major effect on IL-10 mRNA production, inducing a 20-120-fold increase over baseline; in contrast, none of the other cytokines had more than 2-fold effect. In addition, we established that induction of IL-10 by LPS was in part due to TNF-α by showing that LPS-induced IL-10 production by monocytes decreased when the cells were cultured in the presence of anti-TNF-α antibodies. The induction of IL-10 mRNA by TNF-α in monocytes is dose-dependent and begins between 3-24 hr following the addition of the TNF-α; this suggests that the increased IL-10 mRNA level is due to de novo mRNA synthesis rather than mRNA stabilization. Finally, using an IL-10 kinase dependent on the capacity to inhibit TNF-α production (a "CHIP assay"), we showed that cultured mononuclear cells obtained from TNF-α-treated monocytes contains an increased level of IL-10 protein, i.e., the TNF-α effect occurs at both the mRNA and protein level. Taken together, these results suggest that TNF-α plays a key role in the induction of IL-10 in human monocytes; as such, it may indicate a molecule that provides a negative feedback for its own production. In addition, these studies suggest that TNF-α, via its effect on IL-10, may affect TH1/TH2 differentiation in T cells.


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 (FcεRII). 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.

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

Regulation of interferon-γ production by IL-12, TNF, and IL-10 in SCID splenocytes. G. S. Triege and E. F. 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-12 production is necessary for heat killed Listeria monocytogenes (hk-LM) to stimulate IFN-γ production since neutralization of IL-12 abolishes IFN-γ production. A high number of cells fails to produce IL-10 production. Thus both IL-12 and TNF are co-stimulators for IFN-γ production. IL-10 inhibits hk-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 hk-LM contains IL-12, TNF, and IL-10 which regulate IFN-γ production by NK cells. This data indicate that macrophages produce IFN-γ, IL-12 and IL-10 in response to hk-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. (Supported by NIH grant AI06626 (G.S.T.)).

IL-10 inhibits macrophage (Mφ) co-stimulatory activity by selectively inhibiting the upregulation of B7 expression. L. D. Sieh, D. E. Mosier, and E. M. Sheets. U. of Minnesota, Minneapolis, MN 55455.

We have previously 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 (AC). 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-stimulator cells and the effect of IL-10 on this process can be examined in the absence of T cells. After PMA treatment, 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 24-48 hr then fixed were effective AC, expressing high levels of co-stimulatory activity that was related to their level of cell surface B7 expression. 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 IL-10 expression. The inhibitory effect of IL-10 on the upregulation of B7 was selective since the upregulation of both ICAM-1 and MHC class II antigens was not affected. Furthermore, the defective co-stimulatory activity of both resting and IL-10 treated Mφ could be restored to the Mφ 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 IFN-γ production, the regulation of B7 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.