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RAPID CD4 T CELL DEPLETION IN HUMAN-PBL-SCID MICE BY NON-CYTOPATHIC MACROPHAGE-TROPIC ISOLATES OF HIV.
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Distinct isolates of human immunodeficiency virus (HIV) differ in their cell 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 transplanted with human peripheral blood leukocytes (hu-PBL-SCID mice). The macrophage-tropic strains HIV-1_{SF162} and HIV-2_{UC1}, which are non-cytopathic *in vitro*, induced the most rapid and extensive CD4 T cell depletion in the hu-PBL-SCID mice, whereas HIV-1_{SF33}, 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-1_{SF33} 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-tropism 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 the gp120 envelope protein. [supported by NIH grants AI29182, AI30238 (DEM), and AI29394 (JAL)]

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HIV-SPECIFIC T HELPER CELL ACTIVITY IN NEWBORNS OF HIV-INFECTED WOMEN. M. Clerici*, ^A. V. Sison, J. A. Berzofsky*, T. Rakusan#, C. Brandt#, D. J. Venzon*, J. L. Sever# and G. M. Shearer*. *Natl. Cancer Inst. Bethesda, MD 20892, ^ Georgetown Univ. Med. Sch., Washington, D.C. 20007, #Children's Natl. Med. Ctr., Washington, D.C. 20010.

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 10/23 (43%) newborn CBL samples responded to two or more of five synthetic gp160 envelope (*env*) peptides. Three of the 23 offspring were shown to be HIV-infected. All three of the infected newborns were unresponsive to *env*, and none of the 10 offspring who were responsive to *env* at birth were found to be infected. No correlation was detected between the mothers' *env*-specific TH response and vertical transmission of HIV, and TH reactivity of mother and newborn 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)

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REGULATION OF INTERFERON-γ PRODUCTION BY IL-12, TNF AND IL-10 IN SCID SPLENOCYTES. C.S. Tripp and E.R. 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. Anti-TNF antibodies also inhibit IFN-γ 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 SCID splenocytes. This data indicate that macrophages produce TNF, 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.

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TNF-α UPREGULATES IL-10 EXPRESSION IN HUMAN PERIPHERAL BLOOD MONOCYTES. Chingchai Wanidworanun and Warren Strober Mucosal Immunity Section, Laboratory of Clinical Investigation, NIAID, National Institutes of Health, Bethesda, MD 20692. 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 tested the hypothesis that one of the inflammatory monokines is responsible for IL-10 production in human monocytes. Accordingly, we co-cultured purified human peripheral blood monocytes with a panel of cytokines including TNF-α, IL-1α, IL-1ß, IL-6, GM-CSF, TGF-ß and IFN-α; 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 2-3-fold effect. In addition, we established that induction of IL-10 by LPS was in fact 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 antibody. The induction of IL-10 mRNA by TNF-α in monocytes is dose-dependent and begins between 8-24 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 bioassay dependent on the capacity to inhibit IFN-γ production (a "CSIF" assay), we showed that the culture medium 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 induce 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.

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IL-10 INHIBITS MACROPHAGE (Mϕ) CO-STIMULATORY ACTIVITY BY SELECTIVELY INHIBITING THE UPREGULATION OF B7 EXPRESSION. L. Ding, P. S. Linsley, L-Y Huang, R. N Germain, and E. M. Shevach. LI/NIAID, NIH, Bethesda, MD 20892 and Bristol-Myers Squibb, Seattle, WA 98121.

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 costimulatory activity, we have used a system in which Mϕ develop into effective costimulator cells and the effect of IL-10 on this process can be examined in the absence of T cells. After fixation, resting 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 IFNγ for 24h and then fixed, were effective AC, expressed B7, and their co-stimulatory activity 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 costimulatory 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 ICAM-1 and MHC class II antigens was not affected. Furthermore, the defective costimulatory ability of both resting and IL-10 treated Mϕ could be restored by the addition of fixed L cells which expressed high levels of B7 following transfection, but not by non-transfected L cells. As B7 plays a key role in the costimulation of IL-2 and IFNγ production, the regulation of B7 expression and Mϕ costimulatory activity by IL-10 may play an important role in the generation of Th2 cells or in the induction of T cell anergy.

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IL-13 AFFECTS HUMAN MONOCYTE MORPHOLOGY, PHENOTYPE AND FUNCTION. R. de Waal Malefyt, C. Figdor and J. E. de Vries. DNAX Research Institute, Palo Alto, CA 94304, NKI, Amsterdam, The Netherlands.

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.