Abstract

Mycobacterium tuberculosis is associated with the activation of cytokine circuits both at sites of active tuberculosis in vivo and in cultures of mononuclear cells stimulated by M. tuberculosis or its components in vitro. Interactive stimulatory and/or inhibitory pathways are established between cytokines, which may result in potentiation or attenuation of the effects of each molecule on T-cell responses. Here we examined the interaction of transforming growth factor beta1 (TGF-beta1) and interleukin-10 (IL-10) in purified protein derivative (PPD)-stimulated human mononuclear cell cultures in vitro. TGF-beta1 induced monocyte IL-10 (but not tumor necrosis factor alpha) production (by 70-fold, $P < 0.02$) and mRNA expression in the absence but not in the presence of PPD. Both exogenous recombinant (r) IL-10 and rTGF-beta1 independently suppressed the production of PPD-induced gamma interferon (IFN-gamma) in mononuclear cells from PPD skin test-positive individuals. Synergistic suppression of IFN-gamma in cultures containing both rTGF-beta1 and rIL-10 was only seen when the responder cell population were peripheral blood mononuclear cells (PBMC) and not monocyte-depleted mononuclear cells and when PBMC were pretreated with rTGF-beta1 but not with rIL-10. Suppression of PPD-induced IFN-gamma in PBMC containing both rTGF-beta1 (1 ng/ml) and rIL-10 (100 pg/ml) was 1.5-fold higher ($P < 0.05$) than cultures containing TGF-beta1 alone and 5.7-fold higher ($P < 0.004$) than cultures containing IL-10 alone. Also, neutralization of endogenous TGF-beta1 and IL-10 together enhanced PPD-induced IFN-gamma in PBMC in a synergistic manner. Thus, TGF-beta1 and IL-10 together potentiate the downmodulatory effect on M. tuberculosis-induced T-cell production of IFN-gamma, and TGF-beta1 alone enhances IL-10 production. At sites of active M. tuberculosis infection, these interactions may be conducive to the suppression of mononuclear cell functions.