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Inhibitory effect of IL-10 on T cells by altering the CD28 signaling pathway

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Context

IL-10 is a pleiotropic Th2 cytokine that inhibits Th1 cytokine production by T cells and induces T cell anergy in various mouse models. Recently, a T cell subset has been described, designated as T regulatory 1 cells, which produce high levels of IL-10 but little or no IL-2 and IL-4. These cells are able to inhibit antigen-specific T cell responses in both mice and human antigen presenting cell (APC)-dependent culture systems. IL-10 diminishes the antigen presenting capacity of APCs by downregulating MHC class II expression. CD28 is an important costimulatory molecule for T cell proliferation and cytokine production. It has been shown that CD28-mediated signaling in murine T cell clones can block induction of anergy. However, little is known about the effect of IL-10 on T cells, particularly its involvement in the regulation CD28. To investigate the role of IL-10 in the induction of T cell unresponsiveness.

Significant findings

IL-10 inhibited anti-CD28 mediated-T cell proliferation but did not induce cell death. Although T cells stimulated with anti-CD28 mAb in the presence of IL-10 did not proliferate, they did show long-term survival. IL-10 induced unresponsiveness in T cells could also be reversed by certain stimuli such as IL-2 and anti-CD3, but not anti-CD28, indicating that these cells are probably anergic. The action of IL-10 was more precisely defined by the demonstration that IL-10 inhibited tyrosine phosphorylation of the CD28 molecule and the PI3-K p85 binding to CD28. Finally, production of various cytokines (both Th1 and Th2) was inhibited by IL-10, and neutralization of endogenous IL-10 in an antigen-specific stimulation by anti-IL-10 mAb enhanced both proliferation and cytokine production.

Comments

This paper describes the direct effect of interleukin (IL)-10 on T cells, and especially on its ability to alter the CD28 signaling pathway. This study provides new insights into the control of peripheral T cell responses, and particularly into the mechanism of anergy induction. The knowledge that IL-10 is increased in patients with systemic lupus erythematosus (Llorente *et al*, see Additional information) poses the question as to whether this cytokine is not able to induce anergy of autoreactive T cells. Previous studies have demonstrated that blockade of the B7/CD28 costimulation pathway induced long-term inhibition of murine lupus (Daikh *et al*, see Additional information). Thus, it would be interesting to examine if, in autoreactive T cells, IL-10 can reverse T cell unresponsiveness by altering the CD28 tyrosine phosphorylation and by blocking the binding of phosphatidylinositol 3-kinase (PI3-K) p85 to CD28.

Methods

Peripheral blood mononuclear cells (PBMC), monocyte-depleted PBMC and purified CD45RO+ T cells were stimulated with either plate-bound anti-CD28 or plate-bound anti-CD3 mAb and cultured in the presence of IL-10. Proliferation and cytokine secretion were determined by thymidine incorporation and ELISA, respectively. CD28 signaling events were determined by stimulation of PBMC in polystyrene tubes with anti-CD28 mAb in either the presence or the absence of IL-10. The reaction was stopped by adding lysis buffer, and the cell lysate was then immunoprecipitated with anti-CD28 mAb, immunoblotted and detected with an anti-PI3-K-p85 mAb.

Additional information

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