INTRODUCTION

Interleukin 10 (IL-10) was discovered in 1989 by Mosmann and colleagues as an activity produced by murine type 2 helper T cells which suppressed cytokine production by type 1 helper T cells (1). This activity, initially designated cytokine synthesis inhibitory factor (CSIF), was isolated by expression cloning by Moore and colleagues (2), who subsequently identified and isolated a human analogue of CSIF by cross hybridization (3), using as their source a human helper T-cell clone produced by Roncarolo et al. (M.-G. Roncarolo and H. Spits, unpublished). While a search of the available sequence data banks indicated that CSIF represented a novel cytokine, this search also revealed a remarkable homology between CSIF and a previously uncharacterized open reading frame, termed BCRF1, in the Epstein-Barr virus (EBV) genome (2–4). After further analysis of CSIF genomic structure, Moore and colleagues proposed the intriguing possibility that at some stage, EBV may have captured this mammalian gene, presumably to confer some survival advantage on itself.

The availability of recombinant CSIF, and neutralizing monoclonal antibodies that recognized it specifically (5), rapidly led to the discovery that this new cytokine accounted for two other novel activities under investigation at DNAX: (i) B-TCGF, a B cell-derived growth costimulator for thymocytes (6, 7); and (ii) MCGFIII, a B cell-derived growth costimulator for mast cells that could be distinguished from IL-3 and IL-4, the first two cytokines known to exhibit mast-cell stimulating function (8, 9). The realization that CSIF was a pleiotropic cytokine exerting effects on a diversity of cell types led to its renaming as interleukin 10 and initiated studies which demonstrated that a number of immunostimulatory and immunosuppressive properties could be attributed to this cytokine (6, 7, 9–16). In addition to a diversity of cell types that respond to IL-10, it is now apparent that interleukin 10 can be produced by B cells (8, 17) and monocyte/macrophages (12, 14) in addition to the TH0 and TH2 subsets (reviewed in Ref. 18) of helper T cells. In this review, we attempt to summarize what is currently known of the biological properties of IL-10 and speculate on its clinical potential and usefulness.

IMMUNOSUPPRESSIVE PROPERTIES OF IL-10 IN VITRO (TABLE I)

As indicated above, IL-10 was originally identified as a product of murine T helper 2 (Th2) clones that inhibited the production of IL-2, IL-3, tumor necrosis factor beta (TNFβ), granulocyte-macrophage colony-stimulating factor (GM-CSF), and interferon gamma (IFNγ) by Th1 clones following antigen presenting cell (APC)-dependent stimulation with antigen or soluble anti-CD3 monoclonal antibodies (1). The inhibitory effects of IL-10 on Th1 cytokine synthesis were especially pronounced
Table I. Immunosuppressive Properties of IL-10 in Vitro

- Inhibits monocyte/macrophage-dependent cytokine synthesis by PBMC, NK cells, and Th1 clones
- Inhibits monocyte/macrophage-dependent Th0, Th1, and Th2* proliferation
- Inhibits cytokine synthesis by activated macrophages/monocytes
- Inhibits monocyte class II MHC expression
- Inhibits macrophage production of reactive nitrogen oxides
- Inhibits macrophage intracellular and extracellular killing of parasites

*aSo far shown only in human system.

on the production of IFNγ and IL-3, both of which are normally synthesized late following activation of these clones. While murine-IL-10 is species specific, human- and EBV-derived viral IL-10 (vIL-10) inhibit cytokine synthesis by both mouse Th1 clones and human peripheral blood mononuclear cells (PBMCN) (3, 19). Human IL-10 inhibited strongly the production of IFNγ, GM-CSF, TNFα, and TNFβ by PBMCN following activation with phytohemagglutinin (PHA), anti-CD3 monoclonal antibodies, or IL-2. This inhibition of cytokine synthesis by murine Th1 clones and human PBMCN has been shown to occur at both the protein and the mRNA level (1, 3).

The mechanism by which IL-10 inhibits cytokine synthesis by helper T-cell clones or PBMCN has not been completely elucidated. Mosmann and colleagues initially showed that m-IL-10 does not act directly on murine Th1 clones, since IFNγ synthesis was unaffected when the T-cell clones were stimulated by immobilized anti-CD3 monoclonal antibodies or concanavalin A (Con A) in the absence of accessory cells (1). It was subsequently shown by O’Garra and Fiorentino, using purified populations of splenic or peritoneal APC, that IL-10 inhibited IFNγ synthesis by antigen-stimulated Th1 clones only when purified macrophages were used as APC, and had no effect on Th1 activation when antigen was presented by either conventional or Ly1+ B cells (13). Additional studies to elucidate this inhibition of macrophage APC function showed that IL-10 affected the antigen presenting capacity of metabolically active macrophages only. Furthermore, since macrophage-dependent Th1 stimulation by superantigens was also inhibited by IL-10, it appeared that the mechanism of IL-10-mediated suppression was not only at the level of antigen uptake or processing (13). The direct effect of IL-10 on processing has not been addressed as yet. Experiments to date make it unlikely that IL-10 acts by inhibiting the production of a soluble costimulatory activity or by inducing a suppressor activity by macrophages. Some effort has been focused on the possibility that IL-10 suppresses APC function of macrophages by down-regulation of class II major histocompatibility complex (MHC) expression on these cells. Indeed, Stein et al. (M. Stein and S. Gordon, personal communication) have demonstrated that IL-10 inhibits IFNγ-induced class II expression on polyacrylamide bead-elicited peritoneal macrophages. It remains to be determined whether this effect is also observed on resident macrophages which are inhibited by IL-10 from stimulating TH1 clones. Regardless of this outcome, several observations indicate that IL-10-mediated suppression of macrophage APC function involves additional factors other than class II MHC expression. First, IL-10 inhibited the antigen presenting capacity of an activated murine macrophage line without apparently decreasing its expression of class II antigens, although this could be due to slow turnover of class II (13). Second, IL-10 inhibited the IL-2-induced production of IFNγ by Th1 cells (13), a mode of stimulation which is dependent on a Mac 1+ accessory cell but not on antigen or class II MHC molecules (20). Finally, increases in either APC or antigen dose did not affect IL-10 action (13), again implicating suppression of an activation pathway other than T-cell receptor [TCR]–MHC class II interactions.

In a concurrent investigation of the mechanism of IL-10-mediated immunosuppression, de Waal-Malefyt and colleagues have analyzed the ability of human IL-10 to inhibit the production of IFNγ by PHA- or IL-2-activated human PBMCN (3, 19). Consistent with the above murine experiments, the inhibition of cytokine production by PHA-activated peripheral blood T cells is indirectly mediated via inhibitory effects of IL-10 on the antigen presenting or accessory function of human monocytes (R. de Waal-Malefyt, in preparation). Similar results were obtained to explain IL-10-mediated inhibition of IFNγ production by human natural killer (NK) cells stimulated with accessory cells plus IL-2 (19). In this system, IL-10 did not affect the small amounts of IFNγ produced by highly purified human NK cells stimulated with IL-2 in the absence of accessory cells. However, IL-10 caused profound suppression of the enhanced production of IFNγ by TNFα that occurs when purified monocytes are added to IL-2-stimulated NK cells. IL-10-mediated inhibition of NK cell derived-IFNγ has also been