Mouse interleukin-12 (IL-12) p40 homodimer: a potent IL-12 antagonist

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Interleukin-12 (IL-12) is a cytokine that has regulatory effects on T and natural killer (NK) cells and is composed of two disulfide-bonded subunits, p40 and p35. It was recently reported that supernatants from cultures of mouse IL-12 (moIL-12) p40-transfected COS cells could inhibit IL-12-dependent responses in vitro (Mattner, F., et al., Eur. J. Immunol. 1993. 23: 2202). We have further characterized the nature of the inhibitory substance. Purified mouse p40 produced in a baculovirus expression system was found to consist of two species: the p40 monomer and a disulfide-linked p40 dimer [(p40)2]. The (p40)2 was 25- to 50-fold more active than the p40 monomer in causing specific, dose-dependent inhibition of IL-12-induced mouse concanavalin A (Con A) blast proliferation and could also inhibit IL-12-induced interferon-gamma (IFN-gamma) secretion by mouse splenocytes and IL-12-dependent activation of mouse NK cells. Competitive binding studies on mouse Con A blasts showed that (p40)2 was equally effective as moIL-12 in competing with 125I-labeled moIL-12 ([125I]moIL-12) for binding to mouse Con A blasts. However, in contrast to moIL-12, mouse (p40)2 displayed little ability to compete with 125I-labeled human IL-12 (huIL-12) for binding to high-affinity IL-12 receptors (IL-12R) on human phytohemagglutinin (PHA) blasts and caused little or no inhibition of huIL-12-induced human PHA blast proliferation. Nonetheless, mouse (p40)2 was equally effective as moIL-12 in competing with [125I] huIL-12 for binding to COS cells transfected with the human IL-12R beta subunit and expressing low-affinity IL-12 binding sites. These results suggest that (i) the majority of the structural determinants required for binding of IL-12 to its receptor are contained within the p40 subunit, but p35 is required for signaling, (ii) the p40 subunit of IL-12 interacts with the beta subunit of IL-12R, and (iii) (p40)2 may be a suitable IL-12 antagonist for studying the role of IL-12 in various immune responses in vivo as well as in vitro. Further studies are required to determine whether or not (p40)2 is produced by normal lymphoid cells and is a physiologic regulator of IL-12 activity.

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