EFFECTS OF IL-10 IN LIPOPOLYSACCHARIDE- AND SUPERANTIGEN-INDUCED LETHAL SHOCK IN VIVO

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INTRODUCTION

Interleukin-10 (IL-10) is a cytokine that has generated significant excitement since its discovery. This cytokine, as discussed elsewhere in this book, exhibits pleiotropic biological activities on various lineages of murine and human cells. These activities, summarized in Figure 13.1, include growth cofactor for some cells (mast cells, thymocytes, etc.) as well as, differentiation effects (Ia induction in B cells). However, the activity that has generated the most enthusiasm is its ability to downregulate macrophage function in a variety of ways. The latter effects of IL-10 strongly suggest that it has anti-inflammatory and/or immunomodulatory effects.

IL-10 PREVENTS THE TOXIC EFFECTS OF LPS IN VIVO

In macrophages, IL-10 downregulates the expression of several cytokines usually associated with inflammation (such as IL-1, IL-6 and TNF-α) (Fig. 13.2). This observation is especially important, since it suggested that IL-10 could have anti-inflammatory properties. The first formal demonstration of the anti-inflammatory effects of IL-10 in vivo came from its ability to prevent lipopolysaccharide (LPS)-induced toxic shock in mice. LPS is generally responsible for septic shock in humans and represents a significant public health problem. Accordingly, much
effort has been directed at controlling the inflammatory events that mediate this response. In this system, it had been shown that the main target for LPS is the macrophage, which is then activated to produce large amounts of some cytokines (IL-1, IL-6, TNF-α, as well as many chemokines). Experiments using neutralizing anti-cytokine antibodies have strongly suggested that TNF-α is the main mediator of toxic shock in this model. In fact, anti-TNF-α antibodies prevent, to a significant extent, the toxicity of LPS in vivo. Given the demonstrated in vitro ability of IL-10 to inhibit the activation of macrophages in response to LPS, it was a good candidate to inhibit the toxicity of LPS in vivo as well.

The results of such an experiment indicated that IL-10 was indeed capable of preventing the toxic effects of LPS in vivo. IL-10 could be administered up to 0.5 hours after LPS and still exhibit a protective effect in mice. Furthermore, measurements of TNF-α in the sera of these mice showed that the circulating levels of TNF-α in mice treated with IL-10 remained well below those of untreated mice challenged with LPS.

Two experimental protocols have been utilized to study LPS-induced toxicity. One relies on the administration of LPS alone, while the other includes pre-treatment of mice with D-galactosamine followed by LPS. The precise mechanism of action of D-galactosamine is not known, but it is believed to render the mice more susceptible to the toxic effects of LPS by neutralizing to a certain extent the ability of the liver to clear LPS from the circulation. IL-10 has been shown to be effective in preventing the toxic effects of LPS in either model (whether the protocol includes D-galactosamine or not).

**IL-10 INHIBITS T-CELL ACTIVATION IN VIVO**

The results discussed above suggest a potential use for IL-10 in septic shock. However, there are other possibilities for therapeutic use of IL-10 derived from its known in vitro activities. The most important focuses, again, on its effects on macrophages. As shown in Figure 13.1, another

*Fig. 13.1. Selected biological activities of IL-10.*