13 Pro- and Anti-inflammatory Effects of IL-4: From Studies in Mice to Therapy of Autoimmune Diseases in Humans

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13.1 IL-4: A Pro- or Anti-Inflammatory Cytokine?

Interleukin (IL)-4 is largely known for its anti-inflammatory effects due to its capacity to suppress Th1 responses and protective immunity against intracellular pathogens. This was first demonstrated in 1990 in infections of mice with Leishmania major (Sadick et al. 1990). This report showed that early and complete neutralization of IL-4 for 6 weeks with anti-IL-4 mAb redirects Th2 into Th1 immunity and provides protective immunity against L. major. This conflicts with a 1989 study, where IL-4 transfection of tumor cells induced potent anti-tumor immunity (Tepper et al. 1989). Based on this first report with cytokine-transfected tumor cells, several clinical trials with IL-4 in humans were conducted in tumor patients but failed. The understanding of IL-4 was further complicated by data
showing that IL-4-producing Th2 cells directly mediate tissue destruction and lead to autoimmune diseases if transferred to immunodeficient hosts (Pakala et al. 1997; Lafaille et al. 1997). These data indicated that the anti-inflammatory role of IL-4 depends on several co-factors that influence the outcome of immune responses but remained to be identified.

13.2 Differential Role of IL-4 During the Initiation Versus Established Immune Response

In leishmaniasis, Th1 cells mediate delayed-type hypersensitivity reactions (DTHR), which provide protective immunity. In contrast, Th2 responses to *L. major* fail to establish protective DTHR and consequently, Th2-dominated immune reactions to *L. major* provide only insufficient protection. In the case of leishmaniasis, Th2 cells lead to fatal disease courses. DTHR are important for the integrity of the host organism in case of infection with intracellular pathogens, but Th1 cells can also mediate harmful DTHR that cause inflammatory autoimmune diseases. In cases of such harmful DTHR, antigen-specific deviation of Th1 immunity into Th2 immunity may be a new approach possibly devoid of the side effects associated with the current immunosuppressive treatment regimens. Whether it is possible to induce anti-inflammatory Th2 cells in order to protect against Th1-mediated, harmful autoimmune and inflammatory diseases was first tested in experimental allergic encephalomyelitis (EAE), an animal model for multiple sclerosis. The results showed that antigen-specific Th2 cells did not induce EAE and that a Th2-inducing regimen prevented the development of EAE (Racke et al. 1994; Nicholson et al. 1995; Falcone et al. 1998). These studies showed that deviation of a Th1 immune response by IL-4 into an IL-4-producing Th2 phenotype can attenuate DTHR. Based on these and other studies in mice, Th-cell differentiation in patients suffering from organ-specific autoimmune diseases such as multiple sclerosis, inflammatory bowel diseases, rheumatoid arthritis, and psoriasis were analyzed. The data showed that all these diseases were associated with Th1 responses. For human diseases, treatment of ongoing inflammatory processes as opposed to prevention is