B cell-derived IL-10 suppresses inflammatory disease in Lyn-deficient mice

Patrizia Scapini,a,b,1 Chrystelle Lamagna,a Yongmei Hu,a Karim Lee,a Qizhi Tang, Anthony L. DeFranco,d and Clifford A. Lowell,a,1

Departments of aLaboratory Medicine and bMicrobiology/Immunology, University of California, San Francisco, CA 94143; cDepartment of Pathology and Diagnostics, Division of General Pathology, University of Verona, 37134 Verona, Italy; and dDiabetes Center and Departments of Medicine and Surgery, University of California, San Francisco, CA 94143

AUTHOR SUMMARY

IL-10 is an anti-inflammatory cytokine that reduces the activity of immune cells, limiting tissue damage during inflammatory responses. IL-10 exerts its immunosuppressive effects primarily on innate immune cells, such as macrophages, by reducing their production of proinflammatory cytokines. IL-10 also suppresses the activation of T cells (1). Disruption of IL-10 production leads to excessive tissue damage during host defense reactions to pathogen infections. IL-10 deficiency can also result in the development or exacerbation of inflammatory autoimmune diseases, such as colitis (2). However, the role of IL-10 in the pathogenesis of the autoimmune disease systemic lupus erythematosus (SLE) remains controversial (3). This controversy partly stems from the complex set of roles that IL-10 plays. In addition to suppressing innate immune cells and T cells, IL-10 strongly promotes the survival, proliferation, and antibody production of B cells (1). Most patients with SLE have significantly elevated serum IL-10 levels, which often correlate with disease severity. In this study, we used the Lyn-deficient mouse model of SLE to investigate the role of IL-10 and IL-10–producing B cells in disease pathogenesis. Our results show that IL-10–producing B regulatory cells (Bregs) play a dominant role in limiting disease progression in this model.

IL-10 is produced by B and T cells, myeloid cells, and a number of fibroblast-type cells (2). Which of these cells play the most important role in the IL-10–mediated suppression remains unclear. Several different types of immunosuppressive cells, including T regulatory cells (Tregs; a special type of T cell that expresses the IL-10 protein linked to GFP (referred to as IL-10−/−/GFP−/− mice). These animals showed markedly enlarged spleens and lymph nodes, dramatically increased myeloid and T-cell activation, and severe tissue inflammation, leading to premature mortality. The double-mutant mice had dramatically higher levels of a number of proinflammatory cytokines and reduced expression of the Foxp3 transcription factor in Tregs, which has been linked to the loss of immunosuppressive function in these cells. To directly examine the production of IL-10, lyn−/− mice were crossed with mice carrying a gene expressing the IL-10 protein linked to GFP (referred to as IL-10−/−/GFP−/− mice). Because GFP emits a green light signal under fluorescent light, it allowed us to follow the cell types producing IL-10. The lyn−/− mice showed a dramatic increase in IL-10−/−/GFP−/− cells. Among these, the frequency of IL-10–producing B cells (i.e., Bregs) was particularly increased, starting from very early

1To whom correspondence may be addressed. E-mail: clifford.lowell@ucsf.edu or patrizia.scapini@univr.it.
However, as the disease progressed, we also observed an increase in the number of IL-10–producing T cells and myeloid cells. To determine which of the cellular sources of IL-10 was the most effective in reducing disease development, we carried out a series of adoptive transfer experiments in lyn−/−IL-10−/− mice. When WT (or even Lyn-deficient) B cells were transferred into lyn−/−IL-10−/− mice, we observed a significant reduction in the proliferation of myeloid cells and T-cell activation. This protective function of B cells depended on IL-10, because adoptive transfers of IL-10-deficient B cells were unable to suppress myeloid and T-cell activation. In contrast, the transfer of WT T cells (including purified Tregs) or myeloid cells into lyn−/−IL-10−/− animals had no effect on the disease process (Fig. P1).

From these results, we conclude that IL-10 plays a major role in suppressing the lupus-like disease in the Lyn-deficient model of SLE, primarily by reducing myeloid and T-cell activation. Moreover, these data reveal that IL-10 derived from B cells, rather than from T cells or myeloid cells, has the greatest immunosuppressive effect, extending our current understanding of the role of IL-10 and Bregs in SLE. To our knowledge, no direct comparisons between different cellular sources of IL-10 have been made in a single-disease model to examine their relative efficiency in immune regulation. Our data also support the concept that elevated levels of IL-10 (including increased numbers of IL-10–producing B cells) observed in patients with SLE may reflect a compensatory response of the host immune system to limit disease activity and not an underlying cause of autoimmunity. Currently, a number of clinical trials are attempting to transfer Treg populations as therapy for autoimmune diseases. Our observations suggest that, at least in some autoimmune disease states with strong inflammatory components, cellular therapies that use IL-10–producing Bregs may serve as an alternative or additional therapeutic approach.