Editorial

The Path Not Taken

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In the past few decades, our understanding of the immunologic basis of psoriasis has increased. This information was used in the development of the biologic therapies we employ today. For many years, psoriasis was viewed as a helper T (T_H) cell type 1–associated disease with a principal role for IFN-γ. In 1998, several years before the discovery of T_H17 cells, Teunissen et al[1] reported that the majority of the $CD4^+$ and $CD8^+$ T-cell clones derived from lesional psoriatic skin in humans expressed IL-17, irrespective of their IFN-γ or IL-4 production. They also showed that IL-17 expression was detectable in biopsies from lesional psoriatic skin but not in nonlesional control biopsies. They concluded that IL-17 is a proinflammatory cytokine that could amplify the development of cutaneous inflammation and may support the maintenance of chronic dermatoses through stimulation of keratinocytes to augment the secretion of proinflammatory cytokines.[1] A novel and unique subset of IL-17–producing $CD4^+$ T_H17 cells, distinct from T_H1 and T_H2 cells, was discovered.[2] T_H17 cells secrete many proinflammatory cytokines including IL-17A, IL-17F, IL-6, and tumor necrosis factor α that can trigger an inflammatory cascade. IL-17A is 1 of 6 members of the newly described family of proinflammatory IL-17 cytokines (IL-17A–F) and has been implicated in a variety of human autoimmune diseases including psoriasis.

The development and maintenance of T_H17 cells have been linked to IL-23, a key initiating cytokine in the development of autoimmunity.[3] Research has demonstrated elevated levels of IL-23 and T_H17-related cytokines in the skin lesions and the serum of patients with psoriasis, the association of IL-23R gene variants with psoriasis, and the evidence of a functional role of T_H17 cells in autoimmunity.[4] These observations have provided the impetus for an increasing interest in the IL-23/T_H17 axis in the pathogenesis of psoriasis. One of the major cytokines produced by T_H17 cells is IL-22. The role of IL-22 in the pathogenesis of psoriasis has been extensively examined because of its peculiar activities in immune innate response and functions on epithelial cells.[5]

From these studies, a concept emerges that IL-17A and IL-22 are key mediators of cutaneous inflammation, linking T_H17 activity with epithelial pathology and therefore contributing to the pathogenesis of psoriasis. The IL-23/T_H17 axis model for psoriasis integrates the well-defined type 1 inflammatory pathway model in which T_H1, cytotoxic T cell (T_C) type 1, and dendritic cells are the major initiators of the events leading to psoriasis.[6]

Specific inhibition of IL-17 represents a targeted approach to the management of psoriasis that may provide an alternative therapeutic approach for patients who have lost response, failed to respond, or are intolerant to currently available therapies. It also will be interesting to evaluate the safety profile of this approach compared with currently marketed therapies.

Selective inhibition of the proinflammatory cytokine IL-17A using a novel fully human monoclonal antibody showed considerable early promise for the treatment of psoriasis in a phase 2 double-blind randomized trial.[7] The study involved 36 participants with chronic plaque psoriasis who were randomized to a single intravenous infusion of the antibody (AIN 457) at 3 mg/kg or placebo and then followed for 12 weeks. The mean decrease in psoriasis area and severity index score 4 weeks following the infusion was 58% in the antibody-treated participants versus 4% with placebo. At 12 weeks, the mean reduction in psoriasis area and severity index was 63% in antibody-treated participants and 9% with placebo. The medication exhibited a favorable side effect profile in this small study. No serious adverse events were attributed to the study drug.[7]

Further investigation of this treatment and related biologic therapies will hopefully expand

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our options in the treatment of psoriasis. It is encouraging that in 2010 we are still gaining further insight into the pathogenesis of this condition.

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