IL-12 protects from psoriasiform skin inflammation

Abstract

Neutralization of the common p40-subunit of IL-12/23 in psoriasis patients has led to a breakthrough in the management of moderate to severe disease. Aside from neutralizing IL-23, which is thought to be responsible for the curative effect, anti-p40 therapy also interferes with IL-12 signalling and type 1 immunity. Here we dissect the individual contribution of these two cytokines to the formation of psoriatic lesions and understand the effect of therapeutic co-targeting of IL-12 and IL-23 in psoriasis. Using a preclinical model for psoriatic plaque formation we show that IL-12, in contrast to IL-23, has a regulatory function by restraining the invasion of an IL-17-committed gdT (gdT17) cell subset. We discover that IL-12 receptor signalling in keratinocytes initiates a protective transcriptional programme that limits skin inflammation, suggesting that collateral targeting of IL-12 by anti-p40 monoclonal antibodies is counterproductive in the therapy of psoriasis.