Significance of Cytokine Patterns in Alopecia Areata Before and After Therapeutic Allergic Contact Dermatitis

To the Editor:

The article by Hoffmann *et al* [1] describes changes in cytokine mRNA patterns associated with treatment of alopecia areata (AA) using diphenylcyclopropenone (DCP). The authors conclude that a Th1 reaction is involved in the pathogenesis of AA, and that this reaction is downregulated by DCP. In reaching this conclusion, which contradicts the results with other contact allergens [2,3], the authors illustrate the pitfalls of interpreting cytokine responses in human disease.

The study conclusion is based primarily on the fact that interleukin-10 (IL-10) mRNA is significantly increased in scalp biopsies from patients treated with DCP. This increase overshadows smaller rises in IL-2 and tumor necrosis factor–α (TNF-α) mRNA, which represent typical Th1-related cytokines. It is now known that IL-10 may be produced by both Th1 and Th2 cell clones in humans [4]. Therefore, citing this cytokine as a marker of Th2 activity is inaccurate. Furthermore, it appears that the balance of cytokine production is the ultimate determinant of a Th1 or a Th2 response [5]. On balance, DCP elicits an increase in IL-2, TNF-α, and IL-10 (proven or possible Th1 markers), while IL-4 and IL-6 (proven Th2 markers) remain suppressed. Thus, in contrast to what the authors claim, one could conclude that DCP therapy produces a Th1 response that controls AA.

The complexity of the cytokine network must be cautiously considered in evaluating the therapeutic effects of DCP and other contact sensitizers in human disease states [6].

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Reply

In alopecia areata (AA), the cascade of immunological events is not lethal for crucial elements of the hair follicle, which is why AA is usually reversible and the induction and periodic elicitation of an allergic contact dermatitis (ACD) is at present the most effective mode of treatment [1]. Because of the latter, AA and ACD have to share pathological mechanisms, but at what junction the pathways resulting in AA and those giving rise to ACD converge is unknown.

Our hypothesis is that a contrasting cytokine profile of ACD nonspecifically mediates the beneficial effect on AA. This hypothesis may oversimplify essential immunological mechanisms, but the effectiveness of ACD in the treatment of AA would be compatible with this concept. In untreated AA we have described aberrant *in situ* expression of interferon-γ (IFN-γ), interleukin-2 (IL-2), and IL-1β [2]. These results have been confirmed by other groups [3,4], and from the literature no evidence emerges that cytokines such as IL-4, IL-5, or IL-6 may be involved in the pathogenesis of AA. After therapy we found in scalp biopsies, 36 h after application of the contact sensitizer, increased mRNA-levels of IL-2, IL-8, IL-10, and tumor necrosis factor–α (TNF-α) [2]. Our results are in line (and do not contradict, as stated by Stricker and Goldberg) with several reports concerning cytokine profiles in ACD [5,6].

A considerable body of evidence indicates that during the pathogenesis of ACD a Th1 T-cell reaction is involved [6]. Once induced, ACD does not procede endlessly, but is rather self-limiting. During the last years various factors have been identified during the late phase of ACD, having the capacity to inhibit the primary immune response. In this regard, IL-10 has been shown to downregulate ACD [7,8] (a Th1 reaction). It seems reasonable to assume that factors involved in late stages of ACD modulate AA (also a Th1 reaction) and IL-10 might be one of those. We certainly agree with Drs. Stricker and Goldberg that it would be an oversimplification to believe that a single factor such as IL-10 is responsible for hair regrowth in AA after recurrent elicitation of an ACD. Because of the proven immunomodulating properties of IL-10 [9–11], we have discussed IL-10 as a possible piece in the puzzle of an immunological cascade.

According to recent publications [12–16], it seems still justified to catagorize IL-10 as a marker of Th2 activity. Whether IL-10 may be produced by Th1 or Th2 cell clones or both [17] is in the case of ACD not of decisive importance, because during ACD keratinocytes may also be a source of IL-10 [18]. We have not stated that ACD evokes a Th2 response. In sum, in consideration of the complexity of the cytokine network, we hope that Drs. Stricker and Goldberg will agree that factors inherent to the late phase of ACD likely modulate the T cell response present in AA, thus inducing hair regrowth.

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