

## In This Issue—Full Court Press on Psoriasis

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In this issue, four articles relevant to psoriasis pathogenesis are published. In one, Kauffman *et al* (2004) describe initial favorable clinical responses in a phase 1 study using a human anti-interleukin (IL)-12 p40 antibody. IL-12 is a heterodimeric cytokine consisting of p35 and p40 subunit proteins. IL-23, a related heterodimeric protein, consists of p19 and p40 subunits. Thus, a human antibody directed against p40 (as used in the newly published study) effectively blocks the actions of both IL-12 and IL-23. Interestingly, IL-12 and IL-23 are both produced by activated (mature) dendritic cells and are critical in promoting differentiation and proliferation of type 1 cytokine-producing naïve and memory T cells, respectively. As elaborated further in the accompanying commentary (Nestle and Conrad, 2004), all of the following are found in excess in lesional psoriatic skin: (1) activated dendritic cells; (2) IL-23 and (less so) IL-12; and (3) type 1 cytokine-producing CD4+ and CD8+ memory T cells. Thus, the p40 subunit of IL-23/IL-12 is an attractive therapeutic target in psoriasis. Indeed, the paper by Kauffman and colleagues shows evidence that an anti-p40 antibody has concentration-dependent therapeutic activity in patients with psoriasis, although much additional work will be necessary to bring this new drug to the clinic. Importantly, the paper is noteworthy in the field of psoriasis pathogenesis in that it is the first to selectively target cytokines in humans that are produced almost exclusively by activated dendritic cells. With so much emphasis on the role of T cells and psoriasis, it is refreshing to see targeting of more "upstream" molecules, i.e., molecules that may initially be causing T cells to proliferate in the skin of patients with psoriasis. For additional reading on how dendritic cells and T cells may be interacting to result in the formation of psoriatic plaques, the reader is referred to an excellent recent review on the topic by Krueger and colleagues (Lew *et al*, 2004).

In a third paper on psoriasis pathogenesis published in this issue, Alessandrini *et al* describe abnormalities in enzymes involved in lipid formation in the stratum corneum of patients with psoriasis (Alessandrini *et al*, 2004). Lamellar sheets of lipids within the stratum corneum contain ceramides, cholesterol, and free fatty acids, which are essential in regulating epidermal permeability to water and water-soluble material. Ceramides are generated by degradation of glucosylceramides by glucosylceramide- $\beta$ -glucosidase and by hydrolysis of sphingomyelin by sphingomyelinase. Based upon previous work that showed increased trans-epidermal water loss and abnormal epidermal lipid lamellae in lesional psoriatic skin, Alessandrini and colleagues quan-

tified mRNA and protein levels of glucosylceramide- $\beta$ -glucosidase in lesional and non-lesional skin of patients with psoriasis. Somewhat surprisingly, they found that glucosylceramide- $\beta$ -glucosidase was decreased in non-lesional skin, whereas glucosylceramide- $\beta$ -glucosidase was increased in lesional skin. Interestingly, these results suggest that decreased ceramide formation (secondary to decreased glucosylceramide- $\beta$ -glucosidase) may contribute to subtle defects in epidermal barrier function in non-lesional skin of psoriatics. Theoretically, this may make non-lesional psoriatic skin more susceptible to a wide variety of epicutaneous antigens that may then trigger formation of psoriatic lesions. If disease occurs, Alessandrini *et al* assert that excess production of glucosylceramide- $\beta$ -glucosidase, as they document in lesional skin, occurs as a compensatory response in an attempt to repair damaged skin. Although more work is needed to understand the biochemistry of epidermal lipids in patients with psoriasis, this new manuscript offers potential clues as to how non-lesional skin of patients with psoriasis may be particularly susceptible to epicutaneous antigen exposure.

Ellis *et al* (2000) published a report showing that troglitazone improved psoriasis. Troglitazone belongs to a class of drugs called the thiazolidinediones that are selective ligand agonists of peroxisome proliferator-activated receptor-gamma (PPAR $\gamma$ ), a major transcription factor that belongs to the nuclear receptor superfamily. Although not explicitly a paper on psoriasis pathogenesis, He *et al* (2004) describe in this issue how troglitazone inhibits keratinocyte proliferation. Interestingly, they describe inhibition of cyclin D1 (a major cell cycle promoting protein) and subsequent inhibition of cell cycling in keratinocytes treated with troglitazone. Furthermore, in a somewhat surprising finding, troglitazone's effects on inhibiting the keratinocyte cell cycle are described as occurring independently of PPAR $\gamma$  signaling. Although the paper is presented with an eye toward how troglitazone could potentially be used to treat skin cancers, I viewed them as additional evidence on how troglitazone may be working when used to treat patients with psoriasis.

As this Issue of JID amply demonstrates, the molecular and cellular mechanisms underlying the pathogenesis of psoriasis continue to unfold. Undoubtedly, many additional clues regarding psoriasis pathogenesis will continue to be revealed by subsequent well-performed research. Hopefully, this body of work will someday lead to the discovery of the basic essential defect or defects that cause psoriasis.

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