

The Psoriatic Epidermal Lesion and Anagen Hair Growth May Share the Same "Switch-on" Mechanism

RALF PAUS, M.D., AND RICHARD E. LINK

*Dermatopathology Laboratory, Yale University School of Medicine,
New Haven, Connecticut*

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Based on striking parallels between the cell kinetics in the epidermal lesion of psoriasis and the proliferation of hair matrix keratinocytes during the anagen phase of the hair growth cycle, the hypothesis is proposed that both phenomena may share the same "switch-on" mechanism. Particular emphasis is placed on a comparison between the Koebner phenomenon in psoriasis and wounding-induced anagen hair growth. In discussing alternative theoretical models for the proposed common "switch-on" mechanism, some useful experimental tools are suggested. Research into the mechanisms which control epithelial proliferation in psoriasis and hair growth may provide new insights into other growth processes, such as embryonic organogenesis and neoplasia, in which similar epithelial-mesenchymal interactions play a pivotal role.

Psoriasis, one of the most common skin diseases of man, and the growing (anagen) hair follicle provide unique models for the study of epithelial-mesenchymal interactions. Both exhibit an intricate and still imperfectly understood interplay of epithelial and mesenchymal elements (epidermis/dermis and hair bulb/dermal papilla), which is characterized by a state of increased epithelial proliferation. This interplay results in the typical psoriatic plaque and the formation of a new hair from keratinized hair bulb cells, respectively.

On the surface, hair growth and psoriasis hardly seem interrelated since psoriasis does not usually interfere with hair growth [1]. On closer inspection, however, some interesting analogies between the initial epidermal lesion of psoriasis and the proliferation of hair matrix keratinocytes during the growth phase of the hair cycle are revealed. It is tempting to speculate that a common underlying "switch-on" mechanism may exist for both systems.

The hair follicle undergoes a cyclic pattern of growth, passing through a growth phase (anagen), a degeneration phase (catagen), a resting phase (telogen), and finally returning to the growth phase. The "developmental revolution" which leads from a small, apparently unorganized cell cluster of telogen germ into the well-organized early anagen follicle [2] exhibits both one of the fastest patterns of cell proliferation found in normal human tissues and a negligibly small G_0 population [3]. This proliferation pattern is in striking accordance with the cell kinetics of lesional psoriatic skin: greatly increased mitotic activity in two or three basal cell layers with a growth fraction of reportedly 100 percent [4] supports the pathognomonic epidermal hyper-

Abbreviations: CsA: cyclosporine A EGF: epidermal growth factor EPF: epidermal proliferation factor ETAF: epidermal thymocyte activating factor IL-1: interleukin 1 IL-2: interleukin 2 IL-3: interleukin 3 IFN- α : alpha interferon IFN- β : beta interferon IFN- γ : gamma interferon LTB4: leukotriene B4 ODC: ornithine decarboxylase PGE2: prostaglandin E2 PUVA: psoralen plus ultraviolet A light TGF- α : transforming growth factor alpha TGF- β : transforming growth factor beta UV: ultraviolet

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proliferation of psoriasis, a condition which combines both the growth characteristics of a benign tumor and a seemingly stable equilibrium of cell proliferation and loss [5].

The calculated cell cycle times of 36–38 hours for psoriasis [6] and 38.8 hours for human scalp hair matrix [3] only further emphasize the similarities between psoriasis and hair growth (although there is some disagreement on the actual cell cycle time in psoriasis [7]). One really wonders why neither the very rapidly dividing cells of the hair bulb nor the hyperproliferating epidermis in psoriasis show an increased incidence of malignancy. What is the regulatory system which turns on such a high rate of proliferation without losing control? Evidently, a better understanding of epithelial-mesenchymal interplay in psoriasis and hair growth, particularly its “switch-on” mechanism, would be of profound interest not only to dermatologists but also to developmental biologists and oncologists.

Apart from the correlation in cell kinetics, a number of clinical and experimental findings, as well as some theories concerning growth regulation, lend credence to the hypothesis that a common “switch-on” mechanism governs epithelial proliferation in both the anagen follicle and the psoriatic lesion.

The withdrawal of corticosteroid therapy is known to induce psoriatic efflorescences [8], and steroids can produce symptomatic hypertrichosis [9]. Steroids applied to psoriatic lesions also produce a fast remission [10] and may be applied in pathologic conditions involving hair loss, such as alopecia areata, for hair regrowth [9,11]. Other drugs affecting both psoriasis and hair growth include the psoralens, cyclosporin A (CsA), bromocriptine, and anthralin. Psoralens are among the standard repertoire in psoriasis treatment [e.g., as psoralen plus ultraviolet A light (PUVA) therapy] and can occasionally induce hypertrichosis [9]. One of CsA's most common side effects is a dose-dependent hypertrichosis [12], whereas at the same time its effectiveness in the treatment of psoriasis has increasingly become appreciated [13,14]. In addition, experimental hair growth induction by CsA administration in nude mice [15,16] and hair regrowth in one patient with alopecia areata by topical application of CsA [17] make this drug a fascinating tool for parallel research into psoriasis and hair biology. The dopaminergic agonist bromocriptine has been described as useful in the treatment of hirsutism due to hyperprolactinemia [9] as well as in the treatment of psoriasis [18]. Finally, anthralin (dithranol) is a highly effective agent for topical treatment of psoriatic lesions [10]. Recently, it has also been shown to induce terminal hair regrowth in some patients with alopecia areata [19].

Likewise, ultraviolet (UV) light affects both hair growth and psoriasis. Not only is UV light among the most widely applied therapeutic regimens for psoriasis (Goeckerman therapy, PUVA, and so on) [10], but it has also been successfully applied to induce hair regrowth in alopecia areata (PUVA) [11] and to induce anagen in marsupials [20]. Hypertrichosis is a documented side effect of PUVA treatment [21] and UV light can, on occasion, trigger psoriatic lesions, in the form of a Koebner phenomenon [22] (i.e., the development of isomorphic pathologic lesions in the traumatized uninvolved skin of patients with cutaneous disease [25]).

In summary, all these exogenous agents—whether they exert a positive or negative effect on psoriasis and hair growth—are likely to interfere with the regulatory pathway responsible for initiating or inhibiting epithelial proliferation. Reverse effects of a given agent on psoriatic epidermis and hair follicles could easily be explained by the respective differences in targets for this agent (receptors, cell population, cell metabo-

lism, and the like). The scalp—with about 85 percent of hair follicles in anagen—is the most frequently involved site of psoriasis [23], and the interfollicular epidermis in the scalp of psoriatics shows a threefold greater rate of proliferation than controls [24]. This fact could be indicative of a lowered threshold for development of the psoriatic epidermal hyperproliferation in the scalp, due to the presence of factors maintaining the high level of hair growth in this area.

KOEBNER PHENOMENON AND WOUNDING-INDUCED ANAGEN

Initiation and inhibition of epidermal proliferation can, in our context, most profitably be studied in the Koebner phenomenon, and plucking or stripping induced anagen hair growth in rodents. Especially in psoriasis, it has long been appreciated that mechanical traumatization of the skin can lead to the appearance of lesions in previously uninvolved skin [26]. On the other hand, resting hair follicles can almost invariably be induced to enter the growth phase by traumatizing them [27] (e.g., plucking of rat vibrissae follicles, stripping of telogen mice with wax/rosin).

If what we hypothesize holds true, then a traumatizing stimulus that induces one of these two phenomena should, in theory, also be capable of inducing the other. The fact that mechanical trauma, as well as UV light, is a potent inducer of both the Koebner phenomenon in psoriasis and hair growth [11,22] certainly supports our proposal for a common “switch-on” mechanism. Thus, the Koebner phenomenon and the wounding-induced anagen follicle could serve as clean and predictable vehicles for evaluating hypotheses concerned with characterizing the regulatory mechanism for growth induction and inhibition.

The most important conclusion arising from our postulate, however, is that a research approach should be pursued which integrates data from psoriasis research with that from investigation into hair biology. It may be highly rewarding to study carefully the effects of agents, which have been implicated with the initiation of the psoriatic epidermal lesion, on the induction/inhibition of hair growth. Likewise, drugs which have proven clinically useful or experimentally interesting in one of these two fields should systematically be assessed for their actions in the other. This integrated research approach may lead to new therapeutic strategies for the treatment of psoriasis, other skin diseases characterized by a disorder of epidermal proliferation, and hair disease.

STIMULATION VERSUS DISINHIBITION

In pursuing this approach we must keep in mind that, to date, not even the most fundamental aspects of the regulatory processes underlying epidermal/hair growth have been answered satisfactorily. Two contrasting hypotheses explain interference with the inherent control mechanisms of epidermal/hair matrix proliferation, which can be summarized under the heading “stimulatory signal versus disinhibition.” There is evidence for the presence of both types of control, whose relative effect in epithelial tissues yet awaits elucidation.

Chase [28] hypothesized that the stimulus for the initiation of follicle activity may be the loss of an inhibitor of proliferation, whose gradual build-up during anagen would lead to the resting stage of the growth cycle. Gradually being used up or dispersed during telogen or removed by wounding of the follicle (plucking/stripping), the now disinhibited epithelium would resume proliferation. Although it has been argued that repeated plucking—contrary to Chase’s disinhibition hypothesis—does not lead to

continuous growth activity of the hair follicle [29], other important findings support Chase's theory: Bullough et al. [30] have isolated an "epidermal chalone," which is thought to inhibit epidermal mitotic activity at the level of gene expression [31] and could be envisaged as a candidate for Chase's postulated inhibitor. More recently, Elgjo et al. have purified from mouse skin a pentapeptide that inhibits epidermal mitosis in mice [32], inhibits proliferation, and enhances terminal differentiation of cultured mouse epidermal cells [33], thus lending further credence to the pioneering concept of disinhibition.

A similar mechanism has been proposed for the initiation of the psoriatic lesion via a loss of normal epidermal proliferation control [34]. This hypothesis suggests a defective inhibitory system. The newer immunological concepts of the etiology of psoriasis are of particular interest in this context, since they also integrate the concept of a stimulatory signal which may override the prevailing suppressor influences for proliferation. One recent theory depicts psoriasis as a T-helper lymphocyte-mediated disease in which hyperproliferation of keratinocytes is mediated by a number of cytokines, released by interacting T-helper and Langerhans cells in response to a putative "psoriatic antigen," insufficiently controlled by the normally dominant suppressor mechanisms [35].

This theory, of course, immediately raises the fascinating possibility that similar immunological interactions may play a substantial role in the "switch-on" mechanism for anagen hair growth. Unfortunately, however, the immunology of the hair follicle is, at present, almost completely obscure, so that a more thorough understanding of hair follicle immunology is a prerequisite for this tempting speculation. The profound differences of "inflammatory" parameters (mast cells, histamine, serotonin) during the rat hair cycle [29] strongly point toward further investigation into the immunology of the hair follicle.

With respect to the induction of anagen, it has been suggested that a stimulatory signal rather than disinhibition causes increased mitotic activity, especially in wounding-induced anagen, where it has been proposed that some local product of injured cells ("wound hormone") may provide this signal for proliferation induction (e.g. [36]). Under physiologic conditions, this signal could be released from the dermal papilla (as Van Scott et al. have suggested [37]), whose presence has been demonstrated to be essential for anagen induction [38,39]. In further support of the stimulation hypothesis, the description of epidermal growth factor (EGF), an epidermal growth- and keratinization-promoting polypeptide [40], and EGF receptors in rat hair follicles [41] could be cited; however, the precise role of EGF in the regulation of epidermal proliferation and hair growth awaits clarification.

Correspondingly, a host of stimulatory signals has been implicated in the primary stage of the psoriatic epidermal hyperproliferation: cyclic nucleotides, prostaglandins, leukotrienes, polyamines, phospholipase A2, ornithine decarboxylase, the protease-antiprotease system, and various cytokines are all known to have an effect on the regulation of epidermal proliferation and have attracted particular attention in psoriasis [42]. It would now seem mandatory to analyze carefully the effects of these supposed regulatory agents on anagen induction.

Irrespective of the probably dominant intrinsic control apparatus of cell proliferation in hair growth and psoriatic epidermis, systemic factors are also operative which may potentially modify the proposed inhibition/disinhibition signal (e.g., influence of steroid and thyroid hormones on hair growth [43,44] and triggering or exacerbation of

psoriasis by infection and stress [10,22]). These influences, extrinsic to the skin, demand a clear-cut model to study their relative importance in comparison with any intrinsic regulatory mechanism of epithelial proliferation. In probing this relation, as well, the Koebner phenomenon and wounding-induced anagen seem to be the most promising areas for study and comparison.

A few practical approaches with which our hypothesis of a common "switch-on" mechanism in psoriasis and anagen hair growth could be tested are described below.

CYCLOSPORINE AND CYTOKINE PRODUCTION

Perhaps the most interesting experimental agent for a joint study of psoriasis pathogenesis and hair growth regulation is cyclosporine A (CsA), whose effectiveness in both suppressing the psoriatic epidermal lesion and inducing hair growth has previously been mentioned. Our growing insight into the still imperfectly understood action of this immunosuppressive drug may very well serve to reveal general regulatory principles governing the induction of epithelial proliferation.

Since we have come to understand the skin as an active immunomodulating organ [14,45,46], the notion that CsA inhibits the production of a variety of cytokines, including interleukin 1 (IL-1), interleukin 2 (IL-2), interleukin 3 (IL-3) and gamma interferon (IFN- γ) in mononuclear cells and macrophages [47,48], makes CsA an attractive experimental tool for interfering with the regulatory loops of the skin immune system. These regulatory loops have already been shown to exert considerable influence on keratinocyte proliferation (e.g., via IL-1, epidermal proliferation factor [EPF], and epidermal thymocyte activating factor [ETAF] [49]), particularly in psoriasis [14,35]. Do these CsA-inhibited cytokines also regulate anagen?

It is believed that CsA inhibits the synthesis of cytokine mRNA, particularly inhibiting IL-2 gene transcription [50]. Hess and Colombani have suggested that CsA, which is known to bind to the cytosol proteins calmodulin and cyclophilin [51,52], may block calmodulin-dependent mRNA transcription [53]. In addition to being useful in psoriasis research [54], calmodulin antagonists, such as anthralin and miconazole, should then be highly interesting experimental tools in the study of hair growth regulation: do they antagonize or enhance CsA-induced hair growth? Are these calmodulin inhibitors able to stimulate hair growth on their own? (In alopecia areata, topical anthralin seems to induce terminal hair regrowth in some patients [19].) If so, is CsA-induced anagen induction a calmodulin-mediated process?

Although, certainly, the whole repertoire of cytokines influenced by CsA (including IL-1, IL-2, IL-3, IFN- γ , transforming growth factor alpha [TGF- α]/EGF, transforming growth factor beta [TGF- β], and possibly others) deserves systematic study, IL-2 seems to be an especially rewarding candidate for further examination, since the effects of CsA on IL-2 production are already documented by a wealth of data [47,53]. In addition, recent reports suggest a strongly synergistic effect of CsA and anti-IL-2 receptor antibodies (e.g., [55]).

The demonstration of CsA-induced hair growth *in vivo* [12,15–17] leaves us with a number of alternative theories, whose verification would mean a decisive leap forward in our understanding of hair growth regulation.

CsA may inhibit the production of an anti-proliferation protein (possibly disinhibition of anagen by inhibition of IL-2, interferon alpha/beta [IFN- α/β], TGF- β).

CsA could simulate the effects of a stimulatory "switch-on" molecule for anagen growth (perhaps IL-1).

Hair growth induction by the immunosuppressant CsA indicates an important and so far unappreciated role for the hair follicle immune system in the regulation of hair growth.

CsA's mechanism of action on the cytosol and intranuclear level may be similar to that of the anticipated regulatory protein(s) of hair growth.

PHOSPHOLIPASE A2, PROSTAGLANDINS, AND LEUKOTRIENES

Phospholipase A2 is an important regulatory step in the production of prostaglandins and leukotrienes by its release of arachidonic acid from cell membranes [56]. Interestingly, CsA can inhibit phospholipase A2 [57] (via calmodulin perhaps). This enzyme is significantly increased in non-lesional psoriatic epidermis [58]—as is the phospholipase activator calmodulin [59]. Therefore, hyperactivity of the calmodulin-phospholipase A2 system is a strong candidate for explaining a primary metabolic defect as an essential component of the “switch-on” mechanism of epidermal hyperproliferation in psoriasis as well as for explaining hair growth induction. The abnormalities of leukotriene and prostaglandin concentration in psoriatic epidermis (especially of leukotriene B4 [LTB4] and prostaglandin E2 [PGE2] [42]), could then well be understood as the (secondary) mediating system which provides a strong stimulus for cell proliferation. Studies assessing the effect of different eicosanoids and inhibitors of cyclooxygenase and 5-lipoxygenase on hair growth should help to clarify this intriguing possibility.

PROLACTIN AND BROMOCRIPTINE

Hyperprolactinemia is one of the causes of hirsutism and has been treated successfully with bromocriptine [9]. At least in women, increased hair loss is a known side effect of bromocriptine therapy [60], which profoundly lowers prolactin levels via its dopaminergic agonism (dopamine inhibits the hypophyseal release of prolactin) [61]. Bromocriptine, in turn, has been reported to be an effective drug for the treatment of psoriatic lesions [18]. The authors thought this result to be due to an inhibitory effect of bromocriptine on growth hormone release. This hypothesis and the use of bromocriptine as a therapeutic regimen in psoriasis, however, have not been generally accepted [62,63,64]. In the light of CsA's effectiveness in psoriatic lesions [14], the finding that CsA and prolactin compete for binding to a common receptor and that CsA's mechanism of action may even be mediated via its antagonism of the prolactin receptor [65,66], it is reasonable to assume that the effects of bromocriptine on psoriasis are, in fact, due to this drug's potency for lowering serum prolactin levels.

This assumption makes prolactin and bromocriptine another interesting pair of research tools; is prolactin involved in the induction of epithelial proliferation in psoriasis and hair growth (where its effect, at least clinically, is manifested in hirsutism in patients with hyperprolactinemia), and can its effect be antagonized by bromocriptine?

It could well be possible that prolactin plays an important role in the extrinsic control of epithelial proliferation via the hypothalamic-hypophyseal axis. Such an assumption would, on the one hand, help to explain why stress—a well-documented stimulus for prolactin release [61]—can trigger or exacerbate psoriasis [22]. On the other, it would account for the finding that cooperation of hypophyseal hormones seems to be important for androgen effect on and responsiveness of hair follicles as peripheral targets of these hormones [43]. To carry this speculation even further, the

immunomodulatory properties of prolactin [65,67] may designate this hormone to be a crucial messenger on the neuroimmune axis for the achievement of central nervous system modulation of epithelial proliferation and skin immune parameters.

Polyamines (putrescine, spermidine, and the like) are closely associated with cell proliferation and have been found to be increased in lesional and non-lesional skin of psoriatics (with ornithine decarboxylase [ODC] as rate-limiting enzyme for the polyamine synthesis) [42]. Likewise, ODC shows significantly higher concentrations in anagen hair than in telogen hair [68], and plucking of rat hairs induces high levels of ODC [43]. In light of Larsson's hypothesis that prolactin and other peptide hormones exert their effect on DNA and protein synthesis via the induction of ODC and that CsA antagonizes this prolactin induction of ODC [65], a closer analysis of the polyamine biosynthetic pathway, with respect to the proposed "switch-on" mechanism, seems worthwhile.

Study of the protease-antiprotease system, which seems to be involved in growth regulation ([69], in psoriasis [42,70,71]), may be even more profitable in elucidating the proposed common "switch-on" mechanism. The increased activity of plasminogen activator in lesional and non-lesional psoriatic epidermis [70]—apparently correlated with the disease activity [72]—has prompted some researchers to propose that the protease-antiprotease equilibrium in the epidermis could well be a contributing component to Bullough's "epidermal chalone" and an abnormal proteolytic activity in the epidermis could account for the induction of the psoriatic epidermal hyperproliferation [71]. It would be most interesting to learn whether wounding-induced anagen hair growth is also associated with a higher activity of plasminogen activator, and whether this class of serine proteases can induce anagen on its own.

CONCLUSION

Based on striking parallels between the epithelial cell kinetics in the psoriatic epidermal lesion and anagen hair growth, we have proposed the hypothesis that both states of increased epithelial proliferation may share a common "switch-on" mechanism. This conclusion is supported by distinct clinical and experimental evidence. Therefore, the pathogenesis of psoriasis and the regulation of hair growth should no longer be approached isolated from each other. Instead, the systematic exchange of data and ideas between these two fields of dermatologic research is advocated. Specific pharmacological investigations may prove particularly valuable in the pursuit of this new integrated research approach with its interesting therapeutic implications. In addition, investigations into the regulatory mechanisms which govern epithelial proliferation in psoriasis and hair growth may aid in furthering our understanding of other growth phenomena, such as neoplasia and embryonic organogenesis, in which similar epithelial-mesenchymal interactions play important roles.

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