

Editorial: In this issue...*What Goes Wrong in the Keratinocyte in Psoriasis?*

The psoriasis lesion is the result of complex interactions between resident skin cells and invading immune and inflammatory cells. We consider psoriasis an immune disease, meaning that the immune system plays a central role in initiating the disease process. This is not to say, however, that treatment principles other than those primarily directed towards e.g. lymphocytes may not be effective either alone or in combination with immunomodulatory drugs. Calcipotriol, the primary effect of which may be to decrease keratinocyte proliferation in the psoriasis lesion, may serve as a good example.

Understanding keratinocyte biology under normal and pathological conditions is a major goal in psoriasis research. In this issue Björntorp *et al.* (p. 403) address a central question in this respect, namely the regulation (or the lack of regulation) at the gene level of keratinocyte differentiation in psoriasis.

The behaviour of a cell, be it proliferation, differentiation, interactions with other cells, responses to hormones, secretion, migration, etc. is largely determined by the extent to which its genes are activated. By gene activity we mean the

“transcription” of the information stored in the DNA to messenger RNA. Gene regulation is executed by a large number of proteins called transcription factors. These cellular proteins act by binding to specific regulatory parts of genomic DNA and can have stimulatory or inhibitory effects on gene activity. In addition to the large number of different transcription factors, many of which are tissue specific, functional multitude is derived from complex interactions between different transcription factors, and from the wide variation in content and distribution of regulatory elements (i.e. transcription factor binding segments of DNA) among individual genes.

Björntorp and her co-workers asked whether the disturbed keratinocyte differentiation in psoriasis might involve the transcription factor Id1. Id stands for “Inhibition of binding and differentiation”. The Id factors belong to a larger group of transcription factors with a common three-dimensional structure motif named “helix-loop-helix”. They inhibit differentiation by interfering with the binding to DNA of other helix-loop-helix transcription factors (see Fig. 1).

Using methods which allowed specific detection of Id1 messenger RNA as well as the Id1 protein, the authors first verified that cultured keratinocytes express Id1, and that this

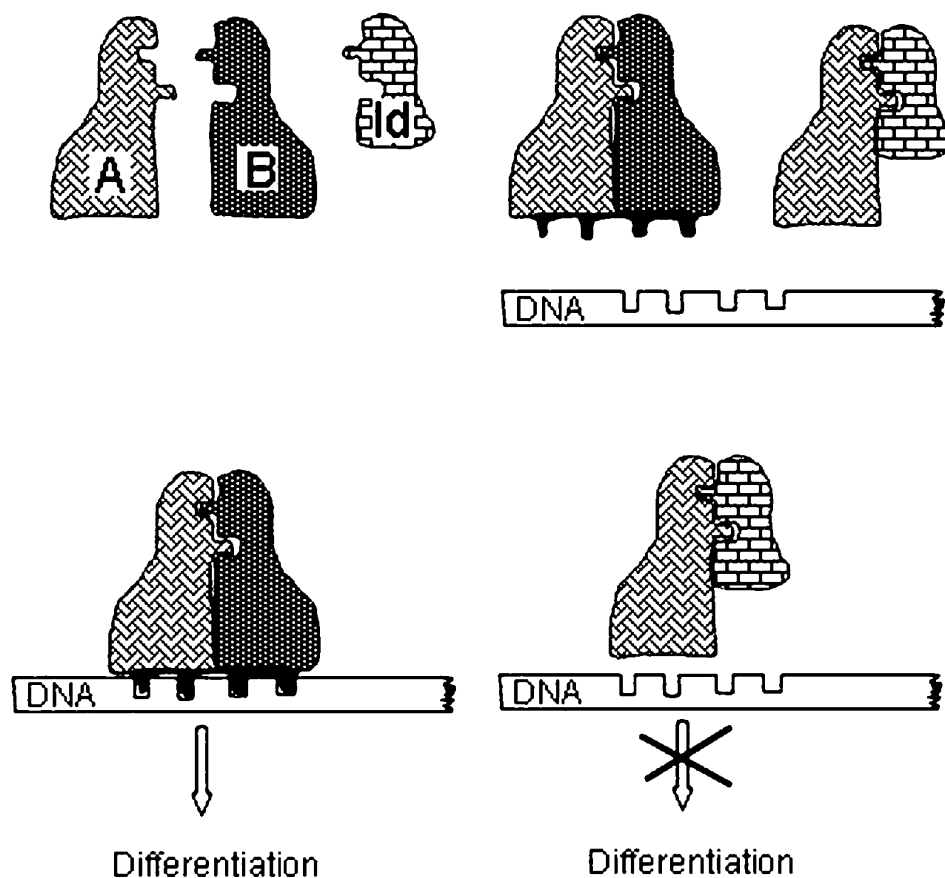


Fig. 1. Principles of Id1 action. A, B, and Id depict helix-loop-helix transcription factors. None of them can bind to DNA as single molecules. Whereas complexes formed by A and B can bind to specific regulatory parts of DNA, complexes with Id can not. Binding to DNA leads to activation of genes, which makes the cell differentiate. An increase in cellular content of Id will thus inhibit differentiation (Modified from Norton JD and Deed RW, Trends Cell Biol 8:58–65, 1998).

expression is highest in undifferentiated cells which can still proliferate. They then looked for Id1 expression in skin from psoriatics and normal controls. As compared to non-lesional psoriatic skin and normal skin, the expression of Id1 was almost four times as high in psoriasis lesions. Id1 could be detected in all cell layers except for the stratum corneum in psoriasis lesions. In non-lesional psoriatic skin and normal skin, Id1 could barely be detected and then only in epidermal basal cells.

The authors conclude that "Id1 may be involved in a regulatory pathway in the epidermis *in vivo*, and that this pathway may be activated in psoriasis". They also suggest means by which the possible relevance of the Id1 pathway in psoriasis can be investigated. A further goal would be to elucidate the genetic and other mechanisms involving Id1 in keratinocytes. Most likely such an achievement would take us closer to one of the ultimate goals of psoriasis research, i.e. understanding what goes wrong in keratinocytes in psoriasis. Why do they proliferate and why don't they differentiate properly?

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Immunoglobulin Therapy in Dermatology – Is it Worth its Price?

High-dose intravenous immunoglobulin therapy (HdIVIg) has recently entered dermatology and is used in selected cases, when the usual immunosuppressive therapy fails. Two reports describe the outcome of using HdIVIg in six patients with very severe atopic dermatitis (Jolles et al., p. 433) and in ten patients with toxic epidermal necrolysis (TEN) due to medication (Campione et al., p. 430). HdIVIg is a very expensive treatment and not without side effects. Therefore, it is fair to ask: Is its use justified? The two diseases described here are well known: Atopic dermatitis is a chronic disease, which in rare patients can be extremely severe leading to a very low quality of life. In contrast, TEN is very acute and short-lasting, but potentially life-threatening. Both groups of investigators conclude that HdIVIg is a valuable remedy. I agree with Campione et al. who conclude that it is very helpful for TEN, as only one patient died from an unrelated disease. Still, it should probably be reserved for severe cases of TEN and not milder forms due to its high costs. Most patients with TEN will survive, so the treatment is not mandatory. I am more sceptical if HdIVIg has a role in atopic dermatitis. Four of six patients saw improvement of their skin scores during a 3-month follow-up period. But – this is rather short within the time period of a lifelong disease. Markers of inflammation (IFN- α and TNF α) were not changed. Also, the patients needed six treatment cycles and although no side effects were observed, immunological side effects could be suspected from this treatment. Finally, Paul et al. (1) did not, in a randomized study following two HdIVIg treatments, see any improvement of atopic eczema.

REFERENCE

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immunoglobulin in adults with severe atopic dermatitis. *Br J Dermatol* 2002; 147: 518–522

Is Juvenile Mycosis Fungoides Really Mycosis Fungoides?

In this issue of *Acta Dermato-Venereologica*, Ben-Amitai and colleagues (p.451) present a detailed clinical and histological description of ten children with a diagnosis of mycosis fungoides (MF) (see Figs. b and d below). Juvenile MF is hardly seen in Scandinavia, so their findings are surprising. It is even more surprising that they are able to "cure" 9 of their children and that none of them had a relapse in the follow-up period, which was on average 3.4 years. This is not what we normally see in MF, where patients are elderly and cure is rare to non-existing. They also observe that there seems to be an over-representation of CD8+ T cells among juvenile patients with MF – at least this is the impression from studies in the literature as indeed their own experience. Recent Dutch investigations (1) and my own unpublished findings, indicate that the more CD8+ T cells in epidermis, the better the prognosis for the patient. This fits the observations by Ben-Amitai and others. Their study also underlines that our knowledge about the pathophysiology of MF and diagnostic improvement for this disease is scarce.

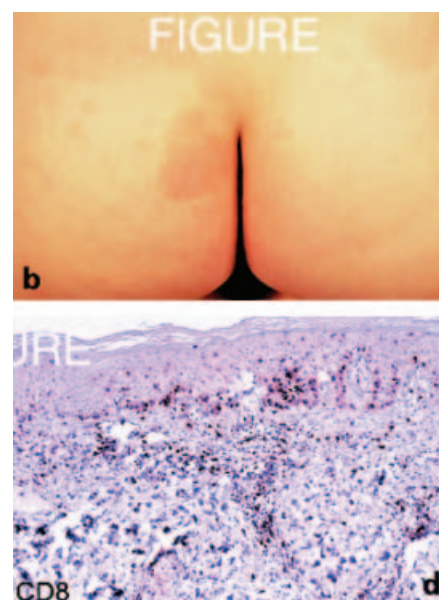


Fig. (b) MF patch on the buttocks of a 13-year-old girl. (d) Numerous CD8+ lymphocytes in the epidermis with junctional preferences. (Figures from the article.)

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1. Vermeer MH, van Doorn R, Dukers D, Bekkenk MW, Meijer CJ, Willemze R. CD8+ T cells in cutaneous T-cell lymphoma: expression of cytotoxic proteins, Fas Ligand, and killing inhibitory receptors and their relationship with clinical behavior. *J Clin Oncol* 2001; 19: 4322–4329.

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