In this Issue

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What do those Epidermal T Cells do in Psoriasis?

Psoriasis is a complex inflammatory disease associated with polygenic inheritance and characterized by a unique clustering of activated T cells in the skin lesions. The presence of the activated T cells, however, is the controlling feature of psoriasis because treatments that specifically target activated T cells cause lesions to resolve. T lymphocytes are activated through the specificity of their T cell receptors (TCR), and can show clonal activation in response to defined classical antigens or restricted polyclonal activation (Vb subsets) to superantigens or unrestricted polyclonal activation to mitogens. Lymphocytes can also be defined by the cytokines that they produce. The type I (T1) cytokine pattern of activated T cells (IFN-γ, TNF-α, ±IL-2, and little IL-4) is associated with effector Type 1 cells such as in delayed type hypersensitivity (DTH) responses. The type II (T2) pattern (IL-4, IL-10, and little IFN-γ) influences antibody response and can down-regulate some Type I responses. Multiple approaches to elucidating the cause of psoriasis have suggested that lesions are associated with a Type I cytokine expression pattern, and that activated skin lymphocytes are oligoclonal or restricted polyclonal even early in the development of lesions. The intraepidermal T cells in psoriasis lesions, however, are largely activated CD8 T cells with a rather restricted TCR repertoire (Vb expression) suggesting clonal T cells, and are believed to be important in the maintenance of psoriatic plaques. What activates these cells and what is the function of these intraepidermal T cells?

A paper in this issue by Austin *et al* (p. 752) demonstrates that the epidermalal T cells in psoriasis have the ability to produce the T1 cytokines IFN-γ, TNF-α, and IL-2. Previous studies using immuno-histochemistry of psoriasis lesions, isolating T cell clones for psoriatic skin, and analysing cytokine message in biopsies, have previously suggested a TH1 (CD4) cytokine profile. Austin *et al* have directly isolated T cells from psoriasis epidermis and demonstrated that the majority of both CD8 and CD4 intraepidermal T cells can produce a general T1 cytokine pattern within the lesional epidermis. Because IFN-γ has been shown to be key in inducing and maintaining the epidermal proliferation and differentiation phenotype in psoriasis, this is strong evidence that these lymphocyte populations are critical in maintaining the psoriatic phenotype.

This evidence argues against speculation that these cells are immune suppressors, and it is also unlikely that these cells act as cytotoxic effectors in the traditional sense, because there is little evidence of overt keratinocyte apoptosis in psoriatic lesions. A recent study, however, shows that cytotoxic effectors can mediate their antiviral effects with cytokines alone and it looks like this is true for psoriasis.

The relative scarcity of T cells that produce T2 cytokines in the epidermis when compared with T1 cytokines or overall in the blood T cells, points to the potential for a general deficiency in T2 cytokine production in the lesion. This last speculation is supported by the intriguing observation that not only is there a strong T1 environment in the epidermis, but there is also a systemic shift towards T1 cytokine production in circulating T cells. Psoriasis may no longer be a disease just of the skin, but may be the result of a centralized immunologic imbalance.

This paper also provides additional support to the concept that psoriasis is a lymphocyte-driven disease in which the overall Type I cytokine pattern in the skin directly induces the "regenerative epidermal phenotype" characteristic of psoriasis.

How Do Melanocytes Die?

Phenolic agents are a major cause of occupational vitiligo, or more properly, occupational leukoderma. It has been proposed that pigment cells can develop "autocytotoxicty" when exposed to toxic chemicals, and the biochemistry of these events has been studied, especially with regard to effects on melanization. There is not clear evidence, however, on how toxic phenolic compounds induce cell death in human melanocytes.

In this issue, Le Poole *et al* (p. 725) report utilization of a very different approach to directly compare genes that are differentially activated or suppressed in melanocytes when the cells are exposed to a phenolic cytotoxic agent. They have used differential mRNA display to directly identify changes in mRNA expression in normal human melanocytes exposed to 4-tertiary butyl phenol (4-TBP) compared with untreated controls. They identified transcriptional activation of the L30 ribosomal protein, possible reflecting altered levels of protein synthesis in general in response to stress. They also identified the A2b receptor (a P1 receptor for adenosine). Differential expression of this gene was confirmed in an Rnase protection assay, by RT-PCR and by flow cytometry.

Interestingly, in some cell types this receptor has been associated with apoptosis induction, and the authors speculate that this may be the mechanism of 4-TBP cytotoxicity, which they feel is consistent with the morphologic changes seen.

If 4-TBP does induce melanocyte apoptosis, the lack of induction of transcription of key apoptosis inducers and control proteins suggests that in these cells, all of the proteins necessary for the apoptosis cascade are preformed and ready to be activated. Alternatively, the lack of induction of specific proteins may indicate that 4-TBP produces such a profound toxic stress that these cells are unable to mount a robust repair or stress response. Further studies will clarify this point.

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Control of Angiogenesis in the Skin Angiogenesis

Control of angiogenesis in the skin angiogenesis is the process of new blood vessel formation in an already established vascular network. It is a key component in critical biologic functions such as wound healing and coronary artery revascularization following infarction, and promotes disease in tumor survival, vascular neogenesis of the cornea, and diabetic neovasculaization. Angiogenesis is promoted by the interaction of multiple growth factors such as the multiple forms and isoform of VEGF, bFGF, PDGF, PKGF, angiopoietin 1, and matrix metalloproteinases, and is opposed by a growing list of inhibitors such as thrombospondin 1 and 2, angiostatin, and angiopoietin 2. Promotion of wound healing and promotion of tumor survival are two important areas of cutaneous biology considered in two papers in this issue.

Kyriakides *et al* (p. 782) have examined the role of angiogenesis in wound healing by measuring skin wound healing in a thrombospondin-2 (Tsp-2) null mouse. Wounds in the TSP-2 null mice healed more rapidly and with less scarring than in the parent line. The granulation tissue appeared to be more cellular and better vascularized in the tsp-2 null mice, but epithelialization did not appear to be affected. It appears that TSP-2 may play an important role in controlling granulation tissue formation during healing, perhaps by controlling fibroblast–matrix interactions.

Arbiser *et al* (p. 838) report a new angiogenic factor with rather selective pattern of function. Corticotropin releasing hormone (CRH) is the major hypothalamic regulator of the endocrine pituitary-adrenal axis. CRH is also released peripherally, is a mediator of inflammation, and is released by some tumors. Arbiser *et al* report that CRH acts as a chemotactic factor for endothelial cells, acting through the CRH receptor. In addition, a human epithelial tumor engineered to over-express CRH showed greatly enhanced angiogenesis and tumor growth when injected subcutaneously in a mouse animal model. Interestingly, CRH does not induce corneal neovascularization, suggesting a more selective angiogenic effect. Just as other neurohormones such as the proopopiomelanocortins have important biologic effects in the skin, CRH may be one of a group of neurohormones that regulate important systemic functions. The finding of CRH as an angiogenesis stimulator suggests that ectopic hormones secreted by cancers may serve to enhance tumor angiogenesis.

Regulation of angiogenesis and associated key biologic functions in animal models provides clues for future therapeutic directions to enhance wound healing and reduce scarring, to reverse tumor growth, and to eliminate neovascularization, which interferes with function.