Keratinocytes regain momentum as instigators of cutaneous inflammation

Brian J. Nickoloff

Skin Cancer Research Program, Loyola University of Chicago Medical Center, Cardinal Bernardin Cancer Center, 2160 South First Avenue, Building 112, Room 301, Maywood, IL 60153, USA

The primary role of skin is to serve as a protective coat and epidermal keratinocytes are responsible for this barrier function. Besides providing structural support, keratinocytes can initiate inflammatory reactions, thereby enhancing healing of skin that follows barrier perturbation. In complex diseases such as psoriasis, in which both barrier function and cutaneous inflammation are dysregulated, it is unclear whether the primary pathogenic disturbance resides in keratinocytes or in immunocytes, which are commingled in psoriatic plaques. Researchers have turned to animal models of cutaneous inflammation to gain insights into the pathogenesis of psoriasis. A recent report in which the inducible epidermal deletion of Jun proteins in adult mice triggered inflammatory skin lesions and destructive arthritis has shifted momentum towards the keratinocyte as a key instigator of cutaneous inflammation. However, because this transgenic mouse model mimics only some features of psoriasis, further studies are required before the prevailing view of psoriasis as a fundamentally immunocyte-driven disease can be replaced by the notion that keratinocytes are the primary pathogenic cells in psoriasis.

Do keratinocytes drive psoriasis?

Psoriasis is a common and chronic inflammatory skin disease that is accompanied by a progressive arthritis in one-third of affected individuals. Although it is not considered strictly an inherited disease, the predisposition to develop psoriasis has a genetic basis. The ultimate underlying cause (e.g. an autoantigen or a specific genetic abnormality) remains to be discovered. One of the liveliest debates in investigative dermatology (Figure 1) focuses on whether psoriatic skin lesions arise from primary abnormalities in epidermal keratinocytes or from primary abnormalities in immunocytes that secondarily activate otherwise normal keratinocytes [1]. This debate has become more intense after a recent high-profile report [2] featured on the cover of *Nature*. On this cover, the question 'What causes psoriasis?' is posed, with a subheading of: 'This new mouse model could solve the mystery'.

The new mouse model that generated excitement was created by Zenz *et al.* [2], and featured inducible and conditional double-knockout adult mice in which basal-layer keratinocytes were targeted for deletion of the genes encoding the activator protein-1 (AP-1) components Junb and Jun. Remarkably, these mice developed not only inflammatory skin lesions, but also a form of arthritis including bone destruction with 100% penetrance. This disease resembles psoriatic arthritis in that interphalangeal joints were affected. A key finding of this report [2] is the rapid upregulation of genes encoding the Ca^{2+}-binding proteins S100A8 and S100A9 in epidermal keratinocytes following knockdown of the Jun family members. The human *JUNB* gene (19p13.2) is localized in the psoriasis *PSORS6* susceptibility locus. The S100-related genes are also strongly overexpressed in psoriasis and are rapidly upregulated following epidermal injury; indeed, many molecular events in psoriasis also occur during cutaneous wound healing [3]. In addition to the chemotactic S100 proteins, which were rapidly overexpressed in keratinocytes following *Jun* deletion, many other pro-inflammatory cytokines were produced by the epidermal keratinocytes in this mouse model. These *in vivo* findings confirmed and extended *in vitro* studies highlighting the remarkable potential of keratinocytes to produce pro-inflammatory cytokines, adhesion molecules, growth factors and chemotactic polypeptides [4]. From a clinical perspective, agents that modify keratinocyte differentiation such as vitamin-D analogs and retinoids can produce remission of psoriatic plaques.

The novel findings in mice lacking *Junb* and *Jun* led Zenz *et al.* [2] to suggest that alterations in epidermal keratinocyte-based signaling pathways were sufficient to initiate the pathological changes in the skin and joints of these transgenic mice. As described in the following sections, at least two crucial questions concerning this animal model remain to be answered before psoriasis can be viewed as arising not from a primary abnormality in the immune system but from a primary abnormality in keratinocytes. The first question to be addressed is: what is the actual role for immunocytes in this mouse model? The second question is: what is the pathophysiological relevance of this mouse model to human psoriatic disease?

Probing below the surface of psoriatic plaques

Another intriguing aspect of the report of Zenz *et al.* [2] are the phenotypes of the *Junb;Jun* double-mutant mice and of *Rag2*-deficient mice that lack T cells. Although joint involvement was reduced by absence of T cells, skin lesions were still apparent, with epidermal thickening,

Corresponding author: Nickoloff, B.J. (bnickol@lumc.edu).
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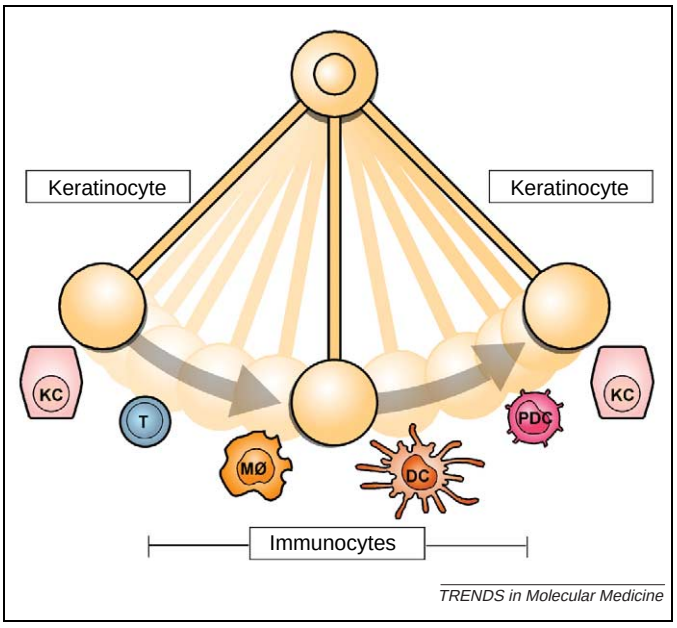

Figure 1. Different views of the primary pathogenic cell involved in psoriatic plaques. Note that the pendulum of opinion initially favored a primary role for epidermal keratinocytes (KCs) because in the late 1960s it was documented that the epidermis was characterized by abnormal proliferation of KCs; so, early treatments included the use of anti-proliferative agents (e.g. methotrexate), topical anthralin and crude coal tar designed to halt KC proliferation and restore normal epidermopoiesis. Then, in the late 1970s and early 1980s a major paradigm shift occurred, due to serendipitous clinical observation that the anti-rejection drug cyclosporine cleared psoriatic lesions. Because clinical trials confirmed the efficacy of this immunosuppressant agent, an immunological basis for psoriasis emerged. Following the cyclosporine-related events, the use of T-cell targeted therapy and SCID-Hu animal models highlighted a role for lymphocytes. The primary immunological theory of psoriasis was challenged by more recent animal models, including the *IKK2*$^{-/-}$ and *Junb*;*Jun* transgenic mice. These two models have suggested revisiting the primary pathogenic role for epidermal keratinocytes. Despite the uncertainty regarding the primary pathogenic cell type in the skin, all models and clinical experience point to an important role for TNF-α-producing macrophages (Mϕ) and dendritic cells (DCs) [5]. In regards to macrophages, both classical and alternatively active subsets are present in plaques [8]. Abbreviations: PDC, plasmacytoid dendritic cell; T, T cell.

altered keratinocyte differentiation and vascular dilation. The authors concluded that T cells have a minor role in the pathophysiology of psoriasis, favoring the view that psoriasis is a primary skin disease rather than a disorder of the immune system. However, immunocytes might be involved in the amplification of psoriatic skin lesions and in the emergence of extra cutaneous lesions. It will be interesting to look more deeply into immunocyte subsets other than T cells to explore further the role of mononuclear cells (macrophages and dendritic cells) that might contribute to the production of tumor necrosis factor-α (TNF-α). Because the keratinocytes in the *Jun* knockout mice [2] overexpressed TNF-α, it is possible that in this model system these cells bypass the requirement for T cells as direct or indirect (via activation of macrophages and/or dendritic cells) sources of TNF-α. A search for the cellular source of TNF-α is essential because development of the arthritis (but not the skin disease) was apparent in *Junb*;*Jun* knockout mice crossed with mice lacking TNF receptor 1 (TNFR1) [2]. Until recently, joint disease in psoriatic patients was believed to result from spillover of cytokines generated in the skin into the adjacent synovial tissue, but some of these patients taking TNF-α inhibitors have experienced greater relief of the pain caused by arthritis without similar clearing of skin lesions. Thus, additional studies are clearly indicated in both mice and humans to delineate the relative contributions of cytokines such as TNF-α and immunocyte subsets responsible for the production of type-1 cytokines and inflammation in the skin versus joints.

Do *Jun* knockout mice model human psoriasis?

To put the mouse-based report of Zenz *et al.* into perspective, a few additional important points regarding the etiology and pathophysiology of psoriasis need to be highlighted. First, in terms of what causes psoriasis (as asked on the cover of *Nature*) it should be stated that the cause of psoriasis is no mystery, although the etiology of the underlying pathogenesis is far from certain. We know that many diverse stimuli trigger psoriatic skin and joint lesions to become clinically apparent in previously healthy individuals; these include minor skin trauma, streptococcal pharyngitis, HIV-1 and medications (e.g. β blockers and lithium chloride) [5]. However, it is not clear why in these individuals genetically predisposed to develop psoriasis, these stimuli produce chronic inflammation in the skin and joints, whereas in non-psoriatic individuals stimuli such as mild trauma are transient and self-limiting. The interplay between environmentally derived precipitating factors and genetic make-up of the psoriatic patient has challenged clinicians for several decades [6].

The second point regarding the etiology and pathophysiology of psoriasis is that this condition is not defined exclusively by the presence of chronic inflammation [7]. Rather, well-defined erythematous lesions of classical plaques contain many cellular abnormalities involving groups of different cell types including: (i) keratinocytes displaying parakeratotic scale, altered differentiation (i.e. loss of the granular-cell layer) and elongation of rete ridges (i.e. downward thin finger-like extensions of thickened epidermis piercing into dermis); (ii) dilated and tortuous upper dermal blood vessels; (iii) influx of mononuclear inflammatory cells including T cells, dendritic cells and macrophages, together with neutrophils; and (iv) increased numbers of mast cells [8]. The third point is that these complex skin lesions can completely resolve, either spontaneously (rarely) or more often by administration of anti-inflammatory agents, such as systemic delivery of anti-TNF-α reagents. The treated lesions usually leave no trace of pre-existing plaque formation (i.e. no scar formation) and these plaques do not progress into skin cancer. Thus, should the recently reported animal model be considered a good model for human psoriasis? To answer this question, the criteria used to evaluate an animal model for psoriasis need to be clarified [9]. Such criteria might themselves generate debate but they should include:

(i) clinical criteria (are skin lesions well-demarcated from non-lesional skin and are lesions provoked by mild trauma?);
(ii) histological criteria (is there thickening of the interfollicular epidermis, parakeratotic scale, loss of granular-cell layer, prominent upper dermal