

Controversies in Experimental Dermatology

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Is psoriasis a T-cell disease?

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The etiology and pathogenesis of psoriasis – one of the most common chronic, inflammatory, hyperproliferative skin disorders of man – have long fascinated dermatologists, pathologists and biologists alike. Here, we have a model disease that offers to study neuroectodermal-mesenchymal interactions in the widest sense possible. Epithelial, endothelial, and hematopoietic cells as well as neurons projecting into the skin apparently all interact with each other to generate the characteristic psoriatic lesion. For decades, the ongoing controversy on the molecular nature, choreography and hierarchy of these complex interactions e.g. between epidermal keratinocytes, T cells, neurotrophils, endothelial cells and sensory nerves has served as a driving force propelling investigative dermatology to ever new horizons. This debate has not only been at the heart of our quest to develop more effective forms of therapy for this socially crippling disease, but it also has profoundly influenced how we view the skin as a whole: the numer-

ous competing theories on the pathogenesis of psoriasis published so far also are reflections on the evolution of mainstream thought in skin biology over the last decades. These days, conventional wisdom – infatuated with a T-cell-centered approach to inflammatory skin diseases – portrays psoriasis as an autoimmune disease, where misguided T lymphocyte activities cause secondary epithelial abnormalities. And yet, as this **CONTROVERSIES** feature reminds us, some authoritative “pockets of academic resistance” are still quite alive, and interpret psoriasis e.g. as a genetically determined, abnormal epithelial response pattern to infectious and/or physicochemical skin insults. Weighing the corresponding lines of argumentation is not only an intriguing, clinically relevant intellectual exercise, but also serves as a wonderful instrument for questioning our own views of the skin universe and its patterns of deviation from a state of homeostasis.

Viewpoint 1

Introduction – Statement of the Problem

Whether psoriasis represents a fundamental disease of skin, or the immune system, has been debated for several years (1). To a casual observer, the presence of psoriatic plaques that are clearly visible to the naked eye would point to a primary defect in skin. However, recent data from our laboratory demonstrates a critically important primary pathogenic role for bone-marrow derived im-

munocytes, rather than epidermal keratinocytes (2). From my perspective, until the gene(s) that determine the genetic basis for inheriting psoriasis are identified, a few experimental results are worth consideration.

Lessons From SCID Mouse Xenografts

Short of a definitive genetic solution to this conundrum in the field of psoriasis, a different ap-

proach can be taken from an immunobiological perspective (3). To try and establish cause-effect relationships, an animal model was created to facilitate progress on this difficult dilemma. Basically, either normal adult skin derived from an individual without any clinical evidence or family history of psoriasis (NN skin), as well as symptomless skin from a patient with psoriatic lesions elsewhere (PN skin), can be engrafted without subsequent rejection onto SCID mice (4). This surgical maneuver does not by itself trigger emergence of psoriatic plaques (PP skin) on engrafted NN or PN skin (*ibid*).

However, if peripheral blood-derived immunocytes from a psoriatic patient are activated using various stimuli such as bacterial superantigens, IL-2, neuropeptides, etc., the injection of activated lymphocytes into PN skin consistently induced a phenotypic conversion of PN to PP skin and/or maintenance of the psoriatic phenotype (2, 5–7). This ability to instigate psoriatic plaques was not possessed by all types of T cells. Rather, it appears that CD4+ T cells were imbued with a pre-psoriatic capacity, whereas CD8+ T cells lacked such activity (8). Moreover, only activated immunocytes from psoriatic patients could promote plaque formation, and not immunocytes from healthy individuals without psoriasis (2, 8).

Perhaps the most interesting question that was examined following these aforementioned studies, was whether even NN skin could be converted to PP skin. This question gets at the heart of the “controversy”. For example, if the keratinocyte was the key culprit in psoriasis, then one would predict that NN skin should not be able to be converted to PP skin (9). One obvious experimental dilemma that arises as one considers this line of inquiry is the possibility that injecting activated immunocytes from a psoriatic patient’s circulation into NN skin, or activated immunocytes from a healthy individual into PN skin, would provoke a cutaneous graft versus host reaction (GVHD).

Despite these reservations, such experiments have actually been performed, and led to the discovery of a novel type of immunocytes in psoriatic lesions (10). When activated immunocytes from a psoriatic patient were injected into NN skin (allogeneic mixture), rather than generating GVHD, plaques were generated with the identical clinical, histological and immunophenotypic characteristics as seen in patients; as well as in engrafted PN skin converted to PP skin by autologous immunocytes. This surprising result forced a re-thinking of conventional T-cell driven immune reactions and suggested the possibility that pathogenic T cells in psoriasis possessed surface receptors that could in-

hibit allogeneic type reactions (11). The presence of such inhibitory receptors was well known for natural killer cells (KIRs), and thus a search was initiated to determine if pathogenic T cells expressed KIRs.

Using well-characterized antibodies, it became clear that many T cells in acute and chronic psoriatic lesions contained a novel type of immunocyte – i.e. NK-T cells (T cells that bear NK receptors). This discovery led to a series of studies that uncovered several different NKRs on T cells in psoriasis, and a novel hypothesis that linked the immunological and genetic pathways in psoriasis (12, 13). Moreover, when it was observed that even murine skin adjacent to engrafted normal human skin was susceptible to phenotypic conversion to a state resembling psoriasis (10), this also led to the discovery of CD1d expression by epidermal keratinocytes. Since certain NK-T cells are triggered by interaction with CD1d, an important observation relevant to our murine studies was the documented ability of even murine CD1d to activate human NK-T cells (14). In addition, we have observed that a human NK-T cell line can trigger PN→PP conversion, and that human NK-T cell clones are activated by CD1d positive keratinocytes (15).

Besides observing that both allogeneic normal human skin (NN skin), and even adjacent murine skin (i.e. xenogenic skin) could be triggered to simulate psoriatic plaques following injection of pathogenic psoriatic blood derived immunocytes (10), several other grafts have been studied (10). To-date, in 3 of 6 different patient/skin combinations in which blood derived immunocytes were injected into engrafted NN skin, there was conversion to psoriatic plaques. The three different NN→PP phenotypic conversions are portrayed in Fig. 1 (panels A–C). For comparison, an example of NN skin that was not converted into PP skin following injection of psoriatic blood-derived immunocytes is provided in Fig. 2 (lower left panel). Finally, Fig. 2 demonstrates histological changes present when activated immunocytes from a healthy donor is injected into PN skin (lower right panel). Note the failure of activated T cells from a non-psoriatic individual to convert PN to PP skin argues against a non-specific Koebner-type response of engrafted PN skin.

While the ability of psoriatic immunocytes to trigger NN→PP conversion strongly supports an immunocyte-based rather than keratinocyte-based genetic abnormality, there is still one caveat that must be emphasized. Even though I was unable to find evidence of psoriasis for the 3 normal, healthy individuals that ended-up having their engrafted NN skin converted to PP skin, it is possible they

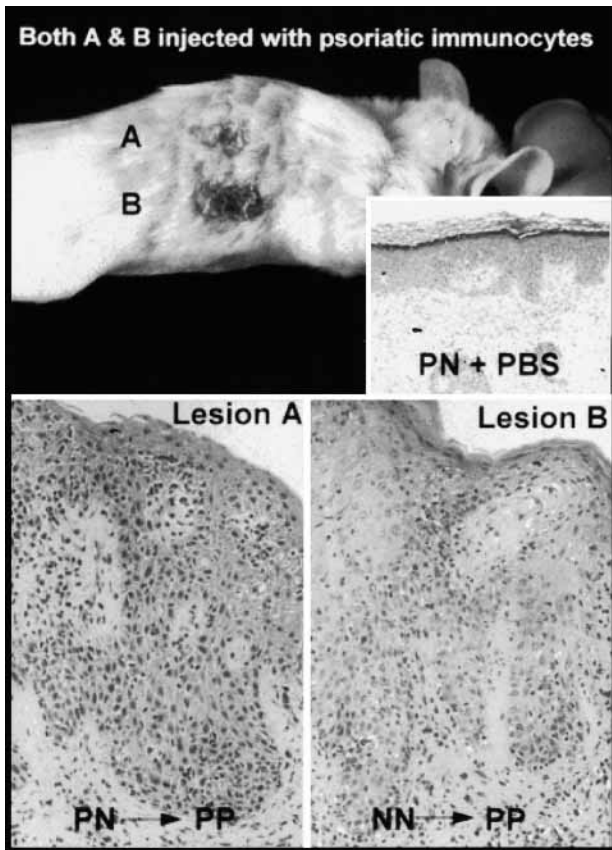


Figure 1. Clinical and histological appearance of either PN skin (lesion A) or NN skin (lesion B) engrafted onto a SCID mouse followed by injection with either phosphate-buffered saline, PBS (inset), or peripheral blood derived immunocytes (3×10^6 cells) from the psoriatic patient that donated PN skin. Note that injection of the superantigen (SEB/SEC2) plus IL-2 activated psoriatic immunocytes induced scale formation and skin thickening in the autologous PN graft (depicted as lesion A), but also created similar clinical changes in an allogeneic setting involving injection into the NN graft (depicted as lesion B). Compared to the engrafted PN skin injected with PBS in which there is orthokeratosis, intact granular cell layer and no acanthosis, the histological appearance of the graft injected with activated immunocytes reveals typical psoriatic changes for both PN and NN skin. For both grafts, there was parakeratosis, loss of granular cell layer, elongation of rete pegs and lymphocytes infiltrating the upper dermis and acanthotic epidermis. No evidence of GVHD was apparent in this allogeneic graft (lesion B; i.e. basal vacuolar degeneration or apoptotic keratinocytes).

inherited psoriasis-predisposing genes that we are unaware of at this moment. For one normal volunteer, an HLA-analysis was performed and she lacked the HLA-Cw6 allele, an important marker for psoriasis. Of course, since we do not precisely know the specific identity of the psoriasis gene(s), it is impossible to absolutely conclude that our normal volunteers did not carry any disease-susceptibility loci. In any event, to the best of our ability by clinical examination, and review of the fam-

ily histories, it appears that several normal healthy skin samples, upon engraftment onto SCID mice, can be converted to PP skin if injected by relevant pathogenic activated immunocytes derived from the circulation of a psoriatic patient. It should be noted additional clinical observations support the primary pathogenic role for bone-marrow derived immunocytes in that psoriasis was either created or cured by bone marrow transplants (16, 17).

Proposed Model Emphasizing Role of Immunocytes in Creation of Psoriasis

Based on the aforementioned experimental results, we can postulate several pathways by which immunocytes become activated and create a cytokine network that results in formation of psoriatic plaques. Fig. 3 (upper panel) portrays a central role for activated keratinocytes in which either T cells become activated by bacterial superantigen-derived peptides presented in the context of class II MHC (left side), or when NK-T cells become activated by glycolipids presented in the context of CD1d (13). In either case, IFN- γ is produced and a Th-1 type cytokine network established that results in conversion of symptomless skin into a psoriatic plaque. Besides keratinocytes, the professional antigen present cell (mature activated dendritic cell, DC), may also activate CD4+ T cells to produce a pathological cytokine network (Fig. 3; lower panel) (18). Potentially important costimulatory molecules involved in these T cell activating reactions include; LFA-1: ICAM-1; Natural killer receptors (NKRs): class I MHC; CD161: CD1d; and CD28: CD80.

Lessons From Transgenic Mice

Before closing, it is instructive to move from lessons learned from the SCID mouse – human skin xenograft model, to briefly review a few observations that may be instructive for psoriasis-related pathologies. Perhaps the most relevant studies to date, linking a systemic defect in the immune system with widespread dermatitis in mice, involves the transcription factor NF- κ B. When one of the five members of the NF- κ B family is genetically deleted by an integrated transgene, the *relB*^{-/-} mice develop multi-organ inflammatory infiltrates including skin (19). The RelB-deficient mice lack mature dendritic cells in the thymic medulla necessary for deletion of autoreactive thymocytes (20). The role of these autoreactive T cells in producing multi-organ inflammation was defined further, in which crossing RelB-deficient mice with

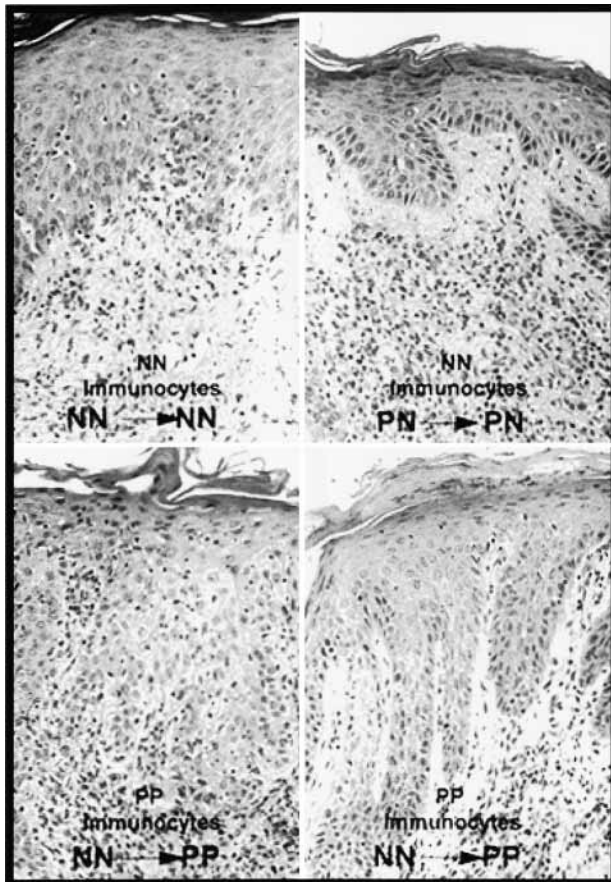


Figure 2. Histological appearance of two different sets of NN and PN grafts from separate individuals compared to Figure 1. Upper panels reveal that activated immunocytes from two different psoriatic patients, when injected into different NN skin grafts provoked psoriatic plaque formation. Note the parakeratosis, loss of granular cell layer, elongation of rete pegs and lymphocyte infiltration of the epidermis without evidence of GVHD. Lower left panel depicts the extent of histological changes when NN skin is injected with autologous activated immunocytes in which there is orthokeratosis, retention of granular cell layer and mild acanthosis, with lymphocytes in the upper dermis and lower-mid epidermis. Lower right panel portrays engrafted PN skin injected with allogeneic activated immunocytes from a healthy, non-psoriatic individual. Note the intact epidermal compartment without any change to suggest either psoriasis or GVHD, despite presence of lymphocytes in the upper dermis.

Nur77/N10 transgenic mice that lack T cells, blocked the development of the disease (21, 22). Of particular relevance to the current topic, it has also been recently shown that fibroblasts from *relB-/-* mice display markedly enhanced and persistent cytokine release after activation, because of decreased I κ B α stability (23). Thus, not only does RelB-deficiency facilitate development of autoreactive, pathogenic T cells in the circulation, but once these cells enter skin, the same genetic defect could promote an exaggerated and prolonged activation

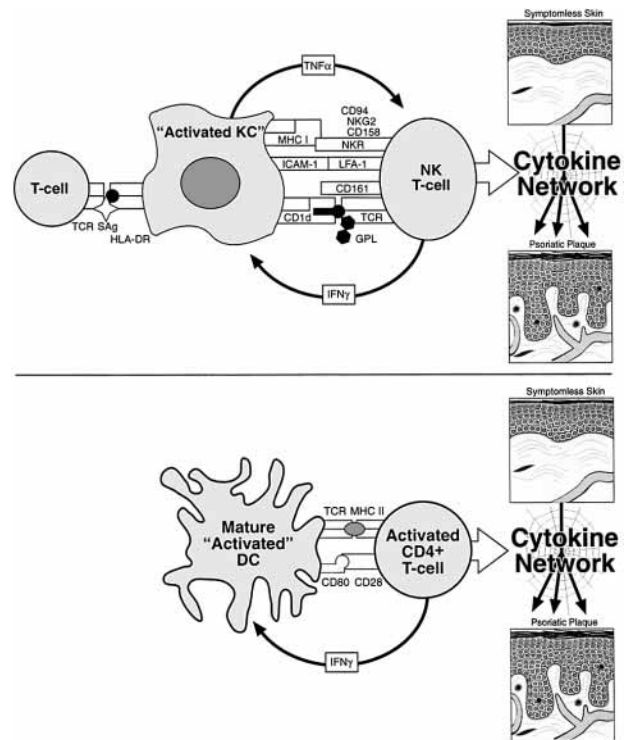


Figure 3. Proposed immunological models in which immunocytes become locally activated in skin and create a pathological cytokine network that converts symptomless skin (PN skin) into a psoriatic plaque (PP skin). Upper panel highlights the role of activated keratinocytes interacting with either conventional T cells (left side) or the novel NK-T cell subset (right side). The putative antigen for T-cells is a superantigen (SA) like peptide (black circle), whereas the NK-T cells respond to glycolipid-like molecules (GPL, black hexagon structures). Lower panel features role of activated DCs in which CD4+ T cells become stimulated to release key primary cytokines such as IFN- γ .

state by endogenous cells such as keratinocytes or fibroblasts; with the cytokine release leading to greater recruitment of additional T cells, and establishment of a vicious cycle. By analogy, it is possible to postulate a single genetic defect (i.e. producing NF- κ B dysfunction) that has a dual effect; on one hand leading to autoreactive T cells in the circulation, and on the other hand triggering a hyperresponsiveness on the part of the local cutaneous cell types (i.e. keratinocytes, fibroblasts, etc). As several groups are now focusing on the importance of NF- κ B-mediated signaling by keratinocytes *in-vitro* and *in-vivo*, rapid progress in this area is likely to be forthcoming, and of potential relevance to psoriasis (24–29).

Keratinocyte Response to Pathogenic Immunocytes

A final unresolved issue of fundamental importance in psoriasis involves defining the essential

cross-talk between immunocytes and keratinocytes that leads to rapid formation of a plaque. Even though current dogma indicates that psoriatic lesions represent hyperplasia of keratinocytes, I believe this is only part of the story. From on-going studies, it has become clear that there is a senescence-switch that is triggered in suprabasal layer keratinocytes within a psoriatic plaque (30). This switch involves induction of the cyclin dependent kinase inhibitor p16, which rather than facilitating cell progression and mitosis, actually inhibits further cell division. Thus, we postulate this senescent state is responsible for earlier observations that revealed that lesional keratinocytes were resistant to apoptosis (31). Moreover, we have postulated that the induction of p16 imbues the plaque with a strikingly effective resistance to transformation (12, 13). Work is in progress to define the relevant cytokines that contribute to this senescence switch, and the role of NF- κ B signaling in defining the tumor suppressor pathway within plaques.

Summary

In conclusion, based on the SCID-human skin xenograft animal model results, and the clinical bone marrow transplant cases, it appears that psoriasis is an immunocyte-mediated disease that manifests itself in the skin. Attention is now being directed at the NK-T cell subset of immunocytes with particular focus on the relevant receptor: ligand interaction that will explain the genetic basis and pathophysiology of this common and enigmatic inherited disorder. In addition, further studies are also indicated to elucidate the molecular basis by which immunocytes can trigger the creation of plaques that resist apoptosis and trans-

formation, and the signaling pathway involved in such a phenotypic conversion.

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Viewpoint 2

There is increasing evidence that bacterial infection initiates and/or propagates psoriasis. On the one hand, infection with Gram-positive bacteria such as *Staphylococcus aureus* or *Streptococcae* has been reported to exacerbate psoriasis (1). On the other hand, psoriatic lesions show far less infections than one would have expected in the light of an epidermal barrier defect and an increased surface due to excessive stratum corneum production (2).

Psoriasis histology also displays some characteristics that can also be found, at least in part, in microbial infection and/or wound healing: Apart from altered keratinocyte growth and differentiation, the active phase shows pronounced epidermal neutrophil accumulation, whereas T-lymphocytes predominate in chronic plaque psoriasis lesions, mainly within the dermal compartment (3).

In my opinion, the resistance to infections in the

fully developed plaque is difficult to explain by members of the cellular immune system, particularly T cells and its relation towards the presence of (super- or psoriasis-) antigens: If this were the case, one would expect that immune cells, once they had recognized the “psoriasis antigen” or “superantigens”, would recruit effector cells – here neutrophils – into the epidermis to eliminate the putative microorganisms. Interestingly, the *in vivo* application of superantigens to tape-stripped skin caused a mononuclear dermal and to a lesser extent also an epidermal cell infiltrate (4). More importantly, however, no neutrophil infiltrate – as it is known for active psoriasis and bacterial skin infection as well – was seen (4).

Therefore it is hard to believe that superantigen-dependent immune responses alone trigger the fully developed inflammatory tissue reaction seen in psoriasis.

I would like to suggest the following scenario: initiation of an antimicrobial defense program starts with recognition of microorganisms by keratinocytes, and not immune cells. This is followed by activation of keratinocytes (possibly by microbial compounds – not necessarily by antigens), primarily in order to produce antimicrobial peptides (in psoriasis scales tremendous amounts of the inducible peptide antibiotic human β -defensin-2, HBD-2 were found) (5). In parallel, recruitment of the major microorganism-eliminating professional leukocytes – neutrophils – is induced by production/liberation of IL-8 and Gro- α . Both are known to be the most abundant and neutrophil-selective chemoattractant in psoriasis (6) and stimulate the production of primary cytokines (which further would induce production of chemokines for neutrophil, and possibly mononuclear cell recruitment). Finally, this is followed by activation and recruitment of T cells.

Studies with organisms that do not have an adaptive immune system – such as invertebrates and plants – indicate that epithelial cells act as ancient defense cells that may play a more important, direct and epithelium-specific role in defense, especially prevention, against microbial infection of vertebrates, than commonly believed (7, 8). Therefore it is tempting to speculate that initiation of a psoriasis lesion is the consequence of alterations in the “epidermal innate defense system”, where the “alarm program” for “epithelial antimicrobial defense” is initiated by a mistaken signal or molecular “misunderstanding”.

The epithelial defense system consists of three major elements (Fig. 1): The first is the physical barrier, which includes the intact permeability barrier and the capability to produce stratum corneum or mucus in skin and mucosa, respectively, and

desquamation. In psoriasis, this barrier function is chronically altered in skin but not mucosa (9). The second, chemical barrier consists of constitutively secreted antimicrobial peptides and proteins, that seem to be important for defining and controlling the “physiologic” microflora (10). This chemical barrier also consists of inducible antimicrobial peptides that are produced only upon stimulation (7, 8). This may occur either with primary cytokines or – more importantly – upon contact with microbial components (not necessarily “antigens” or LPS) in the human system. Such a system represents an ancient epithelial defense principle that is well known for plants or insects (8).

In the fruit fly *Drosophila*, infection by various classes or microorganisms induces differential antimicrobial peptide genes (11). For example, the induction of the fungus-specific drosomycin (which is induced by fungi and not bacteria) occurs via so-called “Pathogen Pattern Recognition Receptors, PRRs” (12), which are topospecifically located at least in part on epithelial cells (13). Contact with Gram-positive bacteria leads to induction of Gram-positive bacteria-killing insect defensins (13). It is therefore tempting to speculate that human skin contains a similar epithelial defense system (13) (Fig. 1) which may be activated in psoriasis. This is likely because of the recent isolation of tremendous amounts of human β -defensin-2 (HBD-2) from lesional psoriatic scale extracts, the first inducible human peptide antibiotic which is active against Gram-negative bacteria and is selectively induced in keratinocytes by primary cytokines and Gram-negative bacteria (12). The third barrier is the immunological barrier, which includes the recruitment of immune cells as well as its effector cells into the affected skin.

As summarized in Fig. 1, there might be a cross-talk between all three barrier-systems upon disturbance of the physical barrier of living epidermal cells by microbial products. This might induce a number of responses in keratinocytes, including the production of HBD-2, which may then attract immature dendritic cells and memory T cells via the chemokine receptor CCR6 (14) into lesional skin. HBD-2 may also induce several primary cytokines as well as epidermal proliferation – as shown upon treatment of mouse skin with proteases (15).

Whereas defects in the local “epithelial defense program” would predict locally limited susceptibility towards recurrent infections with microorganisms, hyperreactivity (i.e. by a lowered threshold to initiate defense reactions) would predict premature initiation of local defense reactions and exacerbation. I consider it an attractive working hypothesis that such “hyperreactivity” occurs in psoriasis.

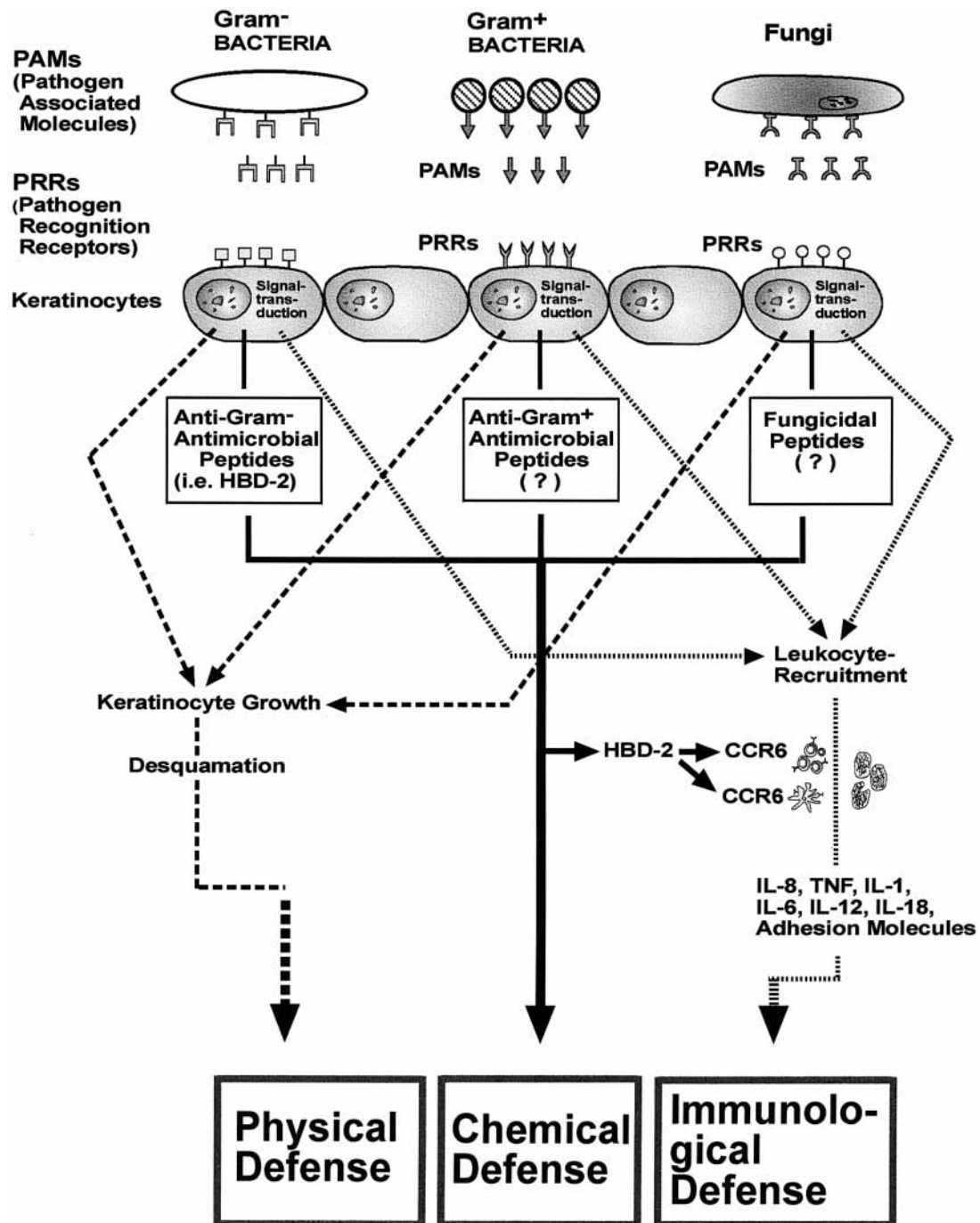


Figure 1. Hypothesis: The epidermis as initiator of defense reactions. Once Gram-negative bacteria, Gram-positive bacteria, fungi or their characteristic and distinct products ("Pathogen Associated Molecule Patterns, PAMs") come into contact with the living epidermis, they bind towards keratinocytes via PAM-selective receptors ("Pathogen Recognition Receptors, PRRs") (12). Depending upon the PRR and its signal-transduction cascade, pathogen-selective antimicrobial compounds are produced and released. (In the human system as yet only a single example is known: Gram-negative but not Gram-positive PAMs lead to the production of the Gram-negative bactericidal HBD-2) (5). In addition, other target-selective antimicrobial peptides are most likely produced by human keratinocytes. β -defensins may then recruit memory T cells and immature dendritic cells into tissue (14). Simultaneously, PAMs induce keratinocyte hyperproliferation (15) and influence desquamation. Furthermore, PAMs induce production and/or release of performed, bioactive IL-8 (18) and Gro- α , which results in immediate neutrophil recruitment. PAMs also induce in keratinocytes primary cytokines such as IL-1, IL-6, IL-12, IL-18 and TNF- α , chemokines, adhesion molecules, and the subsequent cytokine cascades. This will result in a coordinated recruitment of immune cells and their effector cells (here: neutrophils) into the affected skin. According to this hypothesis, it would be crucial to identify in psoriasis alteration(s) of an as yet unidentified PRR that recognizes Gram-positive-originating PAMs or related molecules, or alteration(s) in the corresponding signal transduction pathway(s), which would lead to an increased susceptibility towards PAMs, with the consequence of premature initiation of the whole epithelial defense cascade.

riasis. Furthermore, in psoriatics, a local defense reaction can be initiated by cutaneous injuries including local physical, chemical and microbiological “trauma” (Koebner phenomenon) (16). Thus, one may speculate that, in psoriasis, epithelial Pathogen Pattern Recognition Receptors, PRRs, such as Toll-like receptors (TLRs) and/or other, as yet not defined receptors for “Pathogen-Associated Molecule-Patterns”, PAMs (12) or their signal cascades are altered in a way that “physiologic” concentrations of PAMs or, alternatively, endogenous ligands – if they do exist – lead to exacerbated responses once they reach the living epidermis. Furthermore, threshold concentrations of microbial compounds may locally initiate a complete “defense response” in keratinocytes. This includes the induction of antimicrobial peptides, the production and/or release of proinflammatory cytokines, including chemokines, induction of epidermal proliferation and the recruitment of inflammatory cells (including T cell subsets) (Fig. 1).

A putative candidate PRR in psoriasis could be a receptor located on keratinocytes that recognizes streptococcal and staphylococcal PAMs and that may induce the production of antistreptococcal peptide antibiotics as well as primary cytokines, IL-8 and keratinocyte proliferation. Subsequently, this would induce immune cell activation and recruitment. A somewhat comparable example has been identified for atopic diseases, where a IL-4-receptor allele causes a change in the cytoplasmic domain of the IL-4-receptor, which results in enhanced signaling that leads to exacerbated IgE-synthesis (17).

In summary, the model of an erroneously activated epithelial defense system (which might be organ- and toposelective) in psoriasis, in my opinion, would unify the previously proposed T cell models, the “superantigen” model as well as the proinflammatory cytokine models. In addition, this scenario would integrate neutrophil and protease models, because alterations of all these systems

would be expected when the epithelial defense system is altered. Finally, this epithelial defense model would give us more convincing answers to key questions like:

1. Why do we see psoriasis in skin, but not in mucosa or other organs?
2. Why do we see psoriatic lesions often on the scalp?
3. Why is psoriatic skin so resistant towards infection?
4. Why does psoriasis histology resemble so much bacterial infection and wound healing?

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Viewpoint 3

Joining contemporary conferences on the pathogenesis of psoriasis could give the impression that this disease is a hypersensitivity reaction to whatever antigens in the skin, mediated by whatever T cells. This is mainly based on 1) their lesional presence, 2) experiments that transferred autologous immunocytes induced psoriasis-like lesions in skin of psoriasis patients transplanted onto SCID mice, 3) the fact that after transplantation of stem cells of a psoriatic donor psoriasis may occur in the recipient, 4) the response to drugs which are thought to be T-cell specific, 5) the association of psoriasis with HLA antigens such as Cw6, and 6) some data on aberrant clonal expansion of lesional T cells in the guttate subtype of the disease, which is suggested to be driven by superantigens (see viewpoint essays for citations).

A few critical comments on these arguments deserve to be considered:

1) Presence does not necessarily mean crucial participation in an inflammatory process.

2) In the transfer experiments, skin was obtained from psoriatic patients. No experiments have been carried out, in which skin of a healthy individual was forced to exhibit a psoriatic phenotype by transplantation of T cells only.

3) In bone marrow transplantation, stem cells recover **all** leukocyte lines thus not excluding the possibility that the primary defect is present in other lines. Furthermore, a "psoriatic diathesis" yet to be defined may be present in the recipient, normally a relative or HLA-antigen-matching individual as well and may lead to an outbreak of the disease in this peculiar post-transplantation scenario.

4) All the so-called T cell specific drugs may have an effect on other cells as well. Cyclosporin, for example, clearly has effects on neutrophils (1).

5) Psoriasis occurs in association with several HLA antigens. Is that really a clear hint to one or a few autoantigens in the epidermis? Furthermore, late onset psoriasis is much less strictly correlated with certain HLA antigens (2).

6) The guttata variant of psoriasis is relatively rare. Why should a superantigen-driven activation of whole T-cell receptor families not lead to disseminated psoriatic lesions in an individual with the "psoriatic diathesis" in a relatively unspecific manner? Is the fact that especially antigen-nonspecific, superantigen-induced T cell activation may lead to psoriasis lesions not the best argument *against* specific T cells reacting with specific antigens in psoriatic skin?

In summary, all these T cell data have to be taken seriously, but from my point of view presently fall short of demonstrating conclusively that the interaction between defined T cell clones and defined antigens in the epidermis is the only basic event in psoriasis.

What happens in normal psoriasis? Possibly induced by different local factors yet to be defined (for example, friction on the elbows and knees, or the local microbial colonization in the head, ear and perianal regions), a very unusual and possibly unique feature in the pathogenesis of psoriasis is sometimes not even mentioned any longer in present discussions. Numerous neutrophils enter the dermis and the epidermis at a very early timepoint, and form the well-known Munroe's microabscesses and Kogoi's pustules. This happens even though there are, to the best of our knowledge, no microbiological agents causing a classical infection.

This important phenomenon raises many open questions. Of course, we have known for many years that a number of certain chemotactic peptides and cytokines such as C5_{des arg}, LTB₄, IL-8, or Gro- α , mainly produced by the neutrophils or by activated keratinocytes, are present in psoriatic scales, and it has been suggested that these substances build up the necessary chemotactic gradient for neutrophil immigration (3). But what else do we know about the fascinating interaction between neutrophils and keratinocytes? It is my impression that our knowledge almost ends at the point where neutrophils leave the blood vessels in the upper dermis.

Interactions between neutrophils and dermal cells or the dermal matrix are almost completely uninvestigated in the skin (4), and the mechanisms of neutrophil transmigration through the basement membrane and the epidermis are almost completely unknown. What kind of adhesion interactions, for example, occur between the neutrophils and the keratinocytes? Using a simple adhesion assay we were able to identify CD11b/CD18, present on epidermotropic neutrophils (5), as a major ligand for keratinocyte binding on neutrophils (6). Similar results have been obtained in intestinal epithelial tissues (7). CD11b/CD18 can bind at least to ICAM-1, C3bi and fibrinogen. Terui et al. were successful to identify C3bi as a possible adhesion ligand (8), while a cell-cell adhesion to ICAM-1, for example, is not clearly established at the moment.

Leaving aside the problem of adhesion, what happens with epidermotropic neutrophils when

they transmigrate through the epidermis? To find hints to the answers it may be instructive to consider experiments from other epithelia. In chronic gingivitis, associated with intense transmigration of neutrophils, an amplifying loop of polymorphonuclear neutrophil activation by IL-8 was found (9). In airway epithelia, human neutrophil-epithelial cell interactions can increase LTB₄ formation through transcellular arachidonic acid metabolism (10). Furthermore, IL-8 release from neutrophils can be clearly increased when these cells adhere to lung epithelial keratinocytes (11). Given that IL-8 (12) and LTB₄ (13) are able to induce the keratinocyte hyperproliferation so characteristic of psoriatic lesions, this suggests that neutrophils may play an at least locally decisive boosting role.

What about other aspects of epithelial biology and neutrophils in psoriasis? It is well-known that the transepidermal water loss is dramatically increased in psoriasis (14) and that treatment with simple hydrocolloid dressings can suffice to reduce psoriatic lesions (15). Two recent papers (16, 17) support the concept that neutrophils are directly involved in the disturbances in epithelial differentiation and keratinization that form the basis of this increased transepidermal water loss, whose exact mechanisms remain unknown. Presently, I am aware of only one paper that tried to elucidate directly the role of neutrophils in psoriasis in an animal model. Using the "flaky skin" mouse model, Schön et al. found clearly reduced psoriasis-like lesions after experimental elimination of the neutrophils (18).

In summary, regarding the vicious circle in the pathogenesis of psoriasis, we still have not yet clearly enough defined the first and the major triggering players. There are some, in my view as yet

insufficient, data to claim that T cells are the first, or even the major relevant immune cells. For improving our understanding of what is really going on in psoriasis, it is clearly necessary to better understand the possible role of the perhaps locally decisive psoriasis-boosting neutrophils in this regard, and to answer the many open questions associated with their appearance on the "crime scene".

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Commentary 1

Designating psoriasis as a purely T cell disease is too simplistic. Psoriasis is a multifactorial skin disease with genetic and environmental interactions. Cytokines, chemokines, growth factors, adhesion molecules, neuropeptides and T cell receptors act in integrated ways to evolve unique inflammatory and proliferative reactions typical for psoriasis. Neuroimmunologic events as they relate to psoriasis are now a research focus. We will present how epidermal factors, NGF and its receptor sys-

tem (NGF-R), neuropeptides and the T lymphocytes interact in the pathogenesis of psoriasis.

Correlating clinical observations that stress exacerbates psoriasis and that psoriasis is symmetrically distributed, we have proposed a role for neuropeptides in the pathogenesis of psoriasis (1). Subsequently, many investigators have reported an upregulation of neuropeptides such as substance P (SP), VIP, and CGRP, along with marked proliferation of terminal cutaneous sensory nerves in

psoriatic lesions (2–4). Neuropeptides can play a significant role in the inflammatory and proliferative processes of psoriasis. SP activates T cells, upregulates adhesion molecules in endothelial cells, induces neutrophil chemotaxis, and releases IL-1 from keratinocytes. VIP is mitogenic to keratinocytes while CGRP act synergistically with SP to stimulate keratinocyte proliferation. Both VIP and CGRP are also potent mitogenes for endothelial cells.

There are several clinical reports that psoriasis does resolve at, or is excluded from sites of anesthesia or nerve damage (5, 6). As nerve growth factor (NGF) plays a role in regulating innervation and upregulating neuropeptides, we investigated the expression of NGF/NGF-R in the lesional and non-lesional psoriatic skin, normal skin and other inflammatory skin diseases. In immunohistochemical studies, we found that keratinocytes in lesional and non-lesional psoriatic tissue express elevated levels of NGF compared to the controls (7). Fantini et al. have reported similar results in tissue extracts, i.e. levels of NGF are higher in psoriatic lesions (8).

Several biological actions of NGF are particularly relevant to the inflammatory and proliferative processes of psoriasis (2). Nerve growth factor promotes keratinocyte proliferation and protects keratinocytes from apoptosis. NGF degranulates mast cells and induces migration of these cells; both are early events in a developing lesion of psoriasis. In addition, NGF activates T lymphocytes and recruits inflammatory cellular infiltrates. In a recent study, we have observed that NGF induces expression of the potent chemokine, RANTES, in keratinocytes (*Acta Derm Venereol*, 2000-in press), which is chemotactic for resting CD4+ memory T cells, and activated naive and memory T cells. It is plausible that in a developing psoriatic lesion upregulation of NGF induces an influx of mast cells and lymphocytes, which in turn initiates an inflammatory reaction contributing to the pathogenesis of psoriasis.

We have documented that there is a marked upregulation of NGF in the non-lesional psoriatic skin as well (7). However, in lichen planus, we found no upregulation of NGF in the keratinocytes and expression of NGF-R in the cutaneous nerves of lichen planus lesions was not increased (2, 7). A wound induces a reaction characterized by proliferation of keratinocytes, fibroblasts, vascular elements, nerves and an accumulation of inflammatory cells. In non-psoriatics, healing stops after a finite time depending on the nature of the wound. In psoriatics, a wound frequently results in papulosquamous lesions (Koebner phenomenon).

Given that NGF produced by keratinocytes may play a role in wound healing, (9) the increased expression of NGF in non-lesional skin may play a

key role in the development of a Koebner reaction in a psoriatic patient. Proliferation of keratinocytes induced by trauma will result in significantly higher levels of NGF in lesion-free skin, compared to control skin. Elevated levels of NGF would induce an inflammatory response, proliferation of nerves and upregulation of neuropeptides such as SP and CGRP (Fig. 1); Neuropeptides and NGF, in addition to their pro-inflammatory effects, promote keratinocyte proliferation. Mitogenesis of keratinocytes will result in increased levels of NGF. Thus a vicious cycle of proliferative and inflammatory loops will be established in an individual who is genetically psoriatic (Fig. 1). In contrast, in non-psoriatic individuals the expression of NGF per square mm of epidermis is 3–4 times lower than in non-lesional psoriatic skin (2, 7). We speculate that in non-psoriatic skin healing events after skin trauma, therefore, do not generate the critical levels of NGF and neuropeptides that we envisage to be required for initiating or maintaining cascades essential for a chronic inflammatory reaction.

Stress can alter the SP level in the CNS and in the periphery, stress can increase SP levels in the adrenal glands by activating the descending autonomic fibers. Some of the descending autonomic fibers innervate opioid interneurons in the dorsal horn, and interneurons exist in the spinal cord for SP containing nerves. Therefore, it is conceivable that descending autonomic paths can cause release of cutaneous neuropeptides (10). Stressful psychosocial events result in increased NGF blood levels and NGF mRNA synthesis in the hypothala-

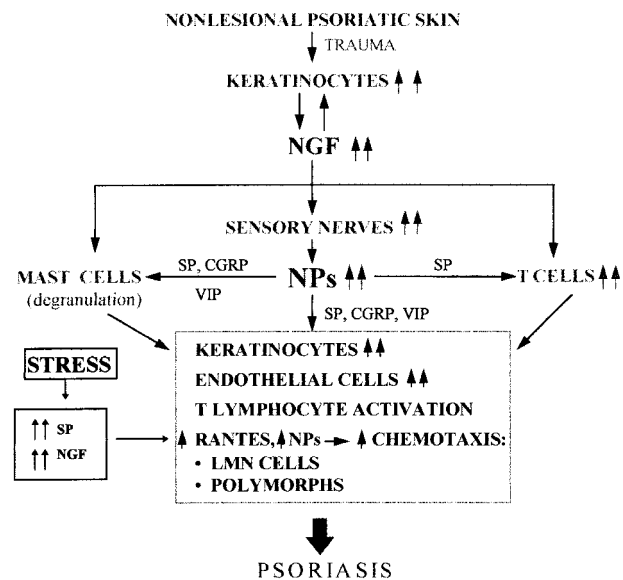


Figure 1.

mus (11, 12). Thus, a similar cascade of events as developed above may occur in "distressed" psoriatic patients.

Immunologic explanations alone fail to clarify various salient features of psoriasis. They do not explain the Koebner phenomenon, the resolution of psoriasis at sites of anesthesia (5–6), the symmetrical distribution of psoriasis lesions, or proliferation of cutaneous nerves and the upregulation of neuropeptides in psoriatic tissue (1–4).

Also, agents such as calcipotriol (Dovenox) and synthetic retinoids such as etritinate which affect the differentiation process of keratinocytes are very effective in psoriasis, while they are ineffective in other T-cell-mediated skin diseases such as atopic dermatitis or contact dermatitis.

Though psoriasis is considered by most authors to be an autoimmune disease, the antigen or specific endogenous factors responsible for activation of T cells have not yet been identified. Regarding the induction of psoriasis in transplanted non lesional skin to the SCID mouse by injecting autologous lymphomononuclear cells (15), it is important to note that activation of T cells not necessarily has to be induced by a superantigen or by an antigen cocktail. Nickoloff and his group reported that they could induce psoriasis by injecting lymphomononuclear cells activated with substance P (personal communication). We have observed that autologous immunocytes activated with NGF can convert non lesional skin to a psoriatic plaque in 3 weeks (unpublished date). As an artificial antigen

cocktail is not present in psoriatic skin, this suggests that local dermal and epidermal factors such as NGF, SP, RANTES involved in the neuroimmunologic cascades may play a role in activation (initiation/maintenance) of the lesional T-lymphocytes.

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Commentary 2

Your Honour,
Members of the Jury,
in the case of the scientific community against the T-cells in psoriasis the prosecution will highlight to you the overwhelming circumstantial evidence pointing towards these lymphocytes as the main suspects in the conspiracy against the epidermis that causes psoriasis. We will acknowledge some evidence that they are seduced to do so by a super stimulation, and are also victims of a specific milieu so that they are forced into action by fatal attraction, rather than committing the crime on purpose.

Why should T-cells be suspected at all?

Well, firstly they are there. The focus of the in-

filtrate is around the dilated capillaries in the dermal papillae from where they move on to invade the epidermis (Fig. 1). Here they create a milieu dominated by T helper type-1 cytokines (1). Secondly, if you get rid of them, you are a good doctor: Measures resulting in T-cell suppression, specifically removal of intraepidermal T-cells (2–4), or reversal of the T helper type-1 cytokine milieu (5), result in a favourable clinical response. Thirdly, psoriasis goes where they go: A young woman suffering from a non-Hodgkin's lymphoma encountered a complete remission following bone marrow transplantation from a brother who had psoriasis; 6 months later she, too, had psoriasis (6).

Just being at the site of a crime does not mean

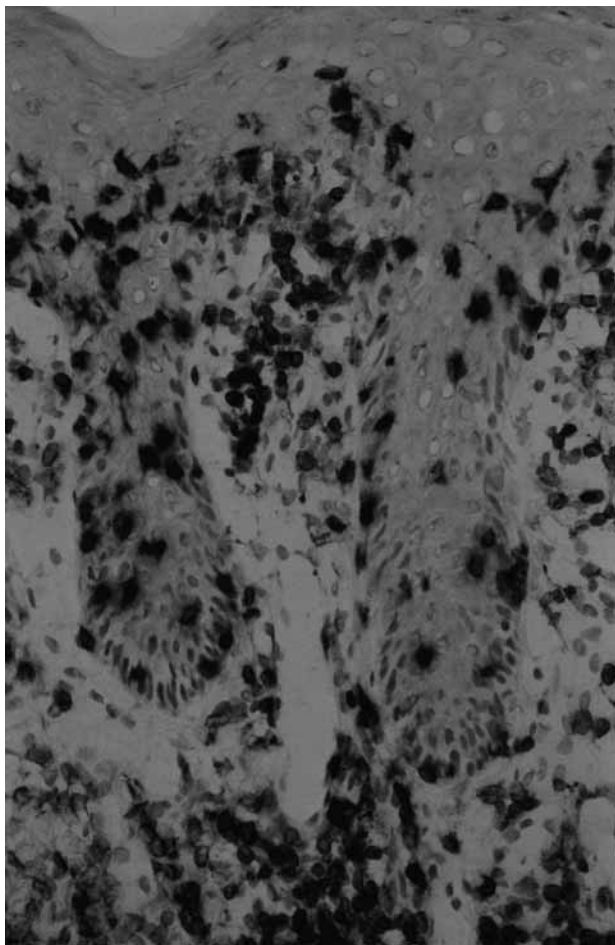


Figure 1. Psoriasis exhibits a dense infiltrate comprising exocytotic T-cells invading the epidermis and coming from the dermal papillae.

you are guilty. But if you actually *did* something you are in trouble. So, what do T-cells do up there in the epidermis?

T-cells are made to recognise specific peptides displayed in the context of antigen-presenting HLA-molecules utilising highly variable receptors. Let's have a look at their tools and see whether they have blood at their hands: If the T-cell response were driven by a specific antigen one would expect to find an (oligo-)clonal response, since only those T-cells would proliferate *in loco* which express a suitable receptor to recognise this antigen-HLA complex. In case of a reaction triggered by superantigens, an initial enrichment for T-cells expressing the corresponding T-cell receptor V β -chain would occur followed by the depletion of these cells. Another possibility is that they just enter the skin because everyone else goes there, too, thus being nothing but innocent bystanders in an ongoing inflammation. This would have no impact

on the T-cell receptor-repertoire of infiltrating vs. circulating cells.

To make a very long story very short, the T-cell receptor data suggest that psoriatic rashes can be triggered by bacterial superantigens; this is supported by clinical experience (7), along with direct experimental evidence (8). In fully developed plaques one can define clonal T-cell populations. Interestingly, looking at individuals characterised by similar HLA genotypes (e.g. concordantly affected monozygotic twins) one comes up with identical clonal motifs which point to the recognition of a similar antigen in these individuals (9). A case can be made for keratins cross-reactive with streptococcal proteins as potential autoantigens (10), although several other scenarios can be envisioned.

So there is blood on the T-cells' hands, but where is the victim?

The victim is the keratinocyte (see above). Now, if keratinocytes were the victims, why then are they so lively, and proliferate like mad, despite the bombardment of T-cell derived – and normally anti-proliferative – interferon-gamma? Well, psoriatic keratinocytes are a special breed; most noteworthy in this context is their reluctance to die, as reviewed by one of the contributors to this controversy (11).

Your Honour, Members of the Jury, I hope I could convince you that it is the T-cells that play the central role in the complex pathogenesis of psoriasis. They mount an autoimmune response, possibly directed against keratin-associated antigenic peptides. But they do so only after having been activated by bacterial superantigens. Their action results in massive epidermal thickening and scaling, but only because psoriatic keratinocytes are reluctant to undergo apoptosis. This particular milieu is a prerequisite for the onset of psoriasis. The judgement can therefore only be "guilty", but the sentence should be mild, given the additional factors contributing to the criminal action of the culprit.

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Commentary 3

Is Psoriasis a T-Cell Disease? The answer to that question depends on whether you think of Langerhans (LC) cells as T-cells or as macrophages or as none of the above!

That psoriasis is a disease caused by a cell of bone marrow origin is indisputably established (1). The only question that is arguable, in my opinion, is which lymphoid cell initiates the disease process. LC are lymphoid cells that express CD-4 antigen (2). Thus, when isolating CD-4⁺ cells from the peripheral blood one would potentially also be isolating LC or their precursors. Therefore, injection of CD-4⁺ LC as well as CD-4⁺ T_h cells into prepsoriatic skin should stimulate the expression of the psoriatic phenotype. This has been shown to occur (3). The subsequent appearance of CD-8 positive cells in the diseased skin may be an attempt to down regulate the hyperproliferation of keratinocytes that the CD-4⁺ cells have induced.

As every medical student knows, psoriasis is characterized by round, beefy-red plaques. The skin is bright red, not just a little pink. Thus, there must be a good deal of vasodilation in the superficial dermal vessels. The neuropeptide that is known to be responsible for vasodilation in blood vessels is nitric oxide (NO). The epidermal cells that contain inducible nitric oxide synthase (iNOS), the enzyme that generates NO, are the keratinocytes and LC (4). Indeed, it has demonstrated recently that psoriatic lesions produce high levels of nitric oxide (NO) (5). Thus, the only question remaining is the cellular source of the NO that causes the vasodilatation pathognomonic for psoriasis. Probably, in the fully developed plaque,

both the keratinocytes and LC contribute to the abundance of NO released by the epidermis, but I suggest that it is the CD-4⁺ LC that initiates these pathologic events (6).

The expression of antimicrobial peptides that is seen in the psoriatic plaques as well as, the expression of ICAMs, which has been documented in many inflammatory skin diseases probably is an epiphenomenon not the inducer of the disease itself (7).

We have recently demonstrated the co-localization of iNOS and 3-nitrotyrosine, the reaction product of NO cytotoxicity, in the epidermis but *not* the dermis of psoriatic plaques (8). This strongly suggests a pathogenic role for NO in this disease. Also, it rules out that fibroblasts instigate the psoriatic disease process.

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Commentary 4

No. That psoriasis is a T-cell disease is an assertion based on little evidence and is contrary to the everyday experience of those who see patients with psoriasis and who look at microscopic slides of skin disease.

Lichen planus and lupus look like T-cell diseases under the microscope; psoriasis doesn't. Two diseases that do resemble psoriasis both clinically and microscopically are seborrheic dermatitis and chronic mucocutaneous candidiasis. Both those involve an epidermal response to surface yeasts in which innate immunity via alternative complement pathway activation and not T-cell activity is responsible.

Vertebrate immune function, as Nossall once observed, is best comprehended as an attempt to cope with endotoxin. Psoriasis is an immunologically mediated response of the epidermis that makes most sense when viewed as being one of the ways by which the skin is used to help the body cope with microbial antigen of both external and circulating origin. Certainly T-cells are involved in this immune activity, but that does not make psoriasis a T-cell disease. Even the SCID mouse skin graft model of psoriasis works much better with added microbial antigen. And cyclosporin, a powerful immune suppressant, works on other cells of the immune system as well as on T-cells.

For an example of what removal of microbial stimuli can do in psoriasis, try to observe what

happens when a young person with terrible psoriasis, large tonsils, and an elevated DNase-B antibody titer undergoes tonsillectomy, a practice now apparently forgotten almost everywhere except in Japan. Or look for a patient who has thick, scaly, bright red, tender palms and soles (not pustular), and who wears a dental plate that is heavily colonized by *Candida albicans*: treat such a patient with fluconazole and an ultra-sonic cleaning machine for the dentures. The response of such patients to nothing but a reduction in microbial antigens is astonishing when seen for the first time.

Does any of this really matter? Unfortunately, it may do so, terribly. Fowler's solution (arsenic) was once used as an effective and easy treatment for psoriasis. Unhappily it later became apparent that such patients developed a predisposition to cancer some 20 years afterward. It used to be said that arsenic was an excellent treatment for psoriasis if either the patient or the doctor were over the age of 65. The widespread adoption of profoundly immunosuppressive treatment based on the unproven assumption that aberrant T-cells are the cause of psoriasis makes this symposium a most important forum.

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Commentary 5

While many factors leading to the generation of psoriatic lesions still remain obscure, compelling circumstantial evidence is accumulating that indicates a primary T lymphocyte-based immunopathogenesis (1).

This evidence is based upon the response of psoriasis to treatment with lymphocyte-specific compounds, such as cyclosporin A (2), the toxin DA-B₃₈₉IL-2 (3), and, in some cases, anti-CD4 monoclonal antibodies (4). In addition, there is a possible linkage of a psoriasis susceptibility gene with a gene involved in IL-2 regulation (5). Psoriasis does not recur after transplantation of bone marrow from healthy donors (6). Furthermore, the

association of psoriasis with certain HLA alleles, such as -B13, -B17, -Bw57, and -Cw6 (7) points to a pathogenic role of T cells. Eruption of psoriatic skin lesions coincides with epidermal infiltration and activation of T cells, resolution of the lesions is preceded by reduction or disappearance of those T cells (8), and lesional psoriatic T cells may alter keratinocyte differentiation and antigen expression (9, 10).

While this does not formally prove the primary role of T cells, they at least support this concept. Some investigators have reported a restricted T cell receptor variable gene usage of T cells within psoriatic lesions (11–14), a finding that strongly

suggests an antigen-specific response of T lymphocytes. The pathogenetic relevance of this oligoclonal T cell expansion is not entirely clear (15). However, it is possible that the failure to demonstrate oligoclonality in some cases of psoriasis is due, at least in part, to colonization of psoriatic lesions with superantigen-producing bacteria (16). Given the well-established role of bacterial superantigens in the pathogenesis of psoriasis (16, 17) and in view of recently identified sequence similarities between streptococcal M-peptides and human epidermal keratins, such as keratin 17, it is indeed possible that keratinocyte structural proteins function as autoantigens in the psoriatic disease process (8, 18).

Although there is no naturally occurring animal disease mirroring psoriasis, additional support for a primary role of T lymphocytes in the pathogenesis of psoriasis comes from animal studies. Indeed, in studies using a xenotransplantation model of psoriasis, injection of T lymphocytes from psoriasis patients into unaffected skin transplanted from the same patients onto severe combined immunodeficiency (*scid/scid*) mice resulted in the generation of psoriatic skin lesions (19), and bacterial superantigens apparently stimulate this pathogenic function of T cells (20). In another rodent model of psoriasis, transfer of minor histocompatibility-mismatched CD4⁺/CD45RB^{hi} T lymphocytes into *scid/scid* mice alone resulted in the generation of psoriasiform skin lesions in the absence of a primary epithelial abnormality (21). Bacterial superantigens enhance the disease severity in this model (22). In this model, co-injection of previously activated CD4⁺/CD45RB^{lo} T cells or transfer of unfractionated T lymphocytes suppressed the skin lesions indicating that psoriasiform lesions in this model are based upon T cell mediated immune dysregulation (21). Finally, in HLA-B27-transgenic

rats it has been demonstrated that the inflammatory disorder including psoriasiform skin lesions is initiated by T lymphocytes without pre-existing epithelial abnormalities (23).

Overall, I have little doubt that T cells are the primary pathogenic factor in the pathogenesis of psoriasis, and that this common disorder represents a T cell-mediated autoimmune disease.

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Commentary 6

There are innumerable studies and irrefutable evidence that activated T cell lymphocytes have an associated role in psoriasis (1–7). What is their role? Are they responsible for initiating psoriasis by invading the dermis and epidermis to unleash their armamentarium of cytokines and other substances to accelerate keratinocyte proliferation and alter differentiation, or are they simply performing their proscribed function by responding to some alteration that is inherent in keratinocytes that genetically have a propensity for developing psoriasis?

The biochemical fingerprints of T-cells have dammed them as the culprits for inducing psoriasis (1–7). The finding of CD4⁺ and CD8⁺ T lymphocytes at sites of psoriasis have led many investigators to hypothesize that psoriasis is a T lymphocyte-mediated disease directed against unknown autoantigens or superantigens (2–4). Since psoriasis may be triggered or exacerbated by infection of group A beta hemolytic streptococci, a role for bacterial super antigens and/or cross reactivity between bacterial antigens and a keratinocyte protein such as keratin has been proposed (3).

Compelling evidence suggests that suppression of CD4 positive +T lymphocytes, e.g. with cyclosporin, FK 506 (tacrolimus), anti-CD4 monoclonal antibody or DAB389 IL-2 is an effective treatment for psoriasis. Consequently, the treatment for this disease has been somewhat misguided in that a sledgehammer approach has been directed solely at the immune system. Not unexpectedly, most of the treatments have caused serious side effects.

An alternative view – that is a kinder and gentler approach to developing strategies to treat psoriasis – is controlling the principal instigator of psoriasis, the aberrant keratinocyte (psorinocyte), rather than by bludgeoning the immune system. There is a cumulative body of evidence that the psoriatic epidermis has both structural and functional abnormalities (8, 9). It is, therefore, plausible that psoriatic keratinocytes tease the immune system waking it from its slumber to secrete a barrage of cytokines and factors in a misguided attempt to restore keratinocytes to their normal proliferative state.

In the mid 1980s, a new approach for treating psoriasis was introduced. It was recognized that the basal cells of the epidermis have a vitamin D receptor and that 1,25-dihydroxyvitamin D₃ was a potent inhibitor of proliferation and stimulator of terminal differentiation (10). If, needed the signal for psoriasis is coming from the hyperproliferative keratinocyte either by the expression of a “psoriatic” antigen or production of a chemoimmune attractant, then a reasonable pharmacologic approach for treating this disorder is to restore psorinocytes to their normal proliferative state using non-cytotoxic agents. Based on a multitude of clinical trials, topical activated vitamin D compounds are both safe and effective for treating psoriasis (11–13). It is, however, true that vitamin D receptors exist in activated T and B lymphocytes as well as monocytes and can function as an immune modulator (14–15).

Another line of evidence that psoriasis is caused by an abnormal keratinocyte (psorinocyte) arises from the observation that parathyroid hormone related peptide (PTHrP), which is normally in maturing and differentiating keratinocytes (16), is absent in psoriatic keratinocytes (17). Furthermore, PTHrP is restored to its normal expression in psoriatic epidermis treated topically with 1,25(OH)₂D₃ (17). The PTHrP receptor agonist, PTH (1–34), inhibits the proliferation and induces terminal differentiation of keratinocytes (18). In a pilot study, topical PTH (1–34) was safe and effective in reversing the hyperproliferative and differ-

entiation abnormalities in psoriatic lesions (19). PTHrP does not have any significant immunomodulatory activity, suggesting that the clinical effectiveness of PTH (1–34) is due to its ability to normalize proliferation and differentiation of keratinocytes rather than alter the immune response. By normalizing keratinocyte proliferation and differentiation, the T cells no longer have a reason to be agitated and, once again, return to the quiescent state of activity.

Thus, if indeed, psoriasis is caused by the unwitting expression of an antigen on keratinocytes, or an enhanced production of a chemical stimulant, to initiate an onslaught by T cells, then the approach for treating psoriasis has been misguided. Instead of using the sledgehammer approach for demolishing the immune response, more effort should be directed towards treatments that encourage psorinocytes to return to their normal proliferative and differentiative states.

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