T Lymphocytes in Psoriasis

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Tlymphocytes play an important role in the pathogenesis of psoriasis; however, the main topic of debate today is whether T lymphocytes may be considered as the initiators of psoriasis or as the maintainers of a "psoriatic milieu" responsible for the characteristic dermal and epidermal alterations in psoriasis. According to the latter point of view, T lymphocytes are recruited to the skin and activated nonspecifically via chemokines, followed by adherence to upregulated adhesion molecules on endothelial cells in lesional skin. We reviewed the literature on T lymphocytes in psoriasis and attempted to delineate their role in the pathogenesis of psoriasis.

T-Cell Infiltrates in Different Stages of the Disease

Uninvolved Psoriatic Skin

Some decades ago it was stated that "psoriasis exists as a basic aberration throughout the skin" and that "clinically uninvolved skin of psoriatic patients is not normal."[1] These statements are still valid today, even when immunophenotypic and polymerase chain reaction (PCR) studies on T-lymphocyte subsets in uninvolved psoriatic skin are considered.[2,3] Besides epidermal alterations such as enhanced proliferation and biochemical, enzymatic, and cytokine abnormalities, uninvolved psoriatic skin is further characterized by dilated capillaries and a variable degree of perivascular, perifollicular, and epidermal lymphocytic infiltration.[4,5] The different immunoregulatory T-lymphocyte subsets are equally represented, but the absolute numbers of CD4+ and CD8+ T lymphocytes are significantly increased.[4,5] Such alterations are generally not observed in the skin of healthy individuals. Histologically, with respect to the numbers and distribution of T lymphocytes, uninvolved psoriatic skin seems to form an intermediate between normal healthy skin and lesional psoriatic skin. Uninvolved skin of psoriatic patients also contains small numbers of the HLA-DR+/CD1a− sub-

class of antigen-presenting cells (APCs), which have an enhanced capacity to stimulate T cells.[6,7] Together with local T lymphocytes, these APCs may be involved in the initiation of psoriasis. All alterations in uninvolved skin mentioned above, referred to as *prepsoriasis*, make it understandable as to why the whole skin of genetically predisposed individuals can develop psoriasis.

Early Psoriatic Macule or Papule

Extravasation of CD4+ T lymphocytes and monocytes is the earliest immunohistologic alteration in newly arising psoriatic lesions.[5] Some studies indicate that degranulation of resident dermal mast cells may be a primary event. Mast cell products initially induce endothelial cell gaps and activation, perforation of the basement membrane, and the subsequent extravasation of mononuclear cells followed by epidermal changes.[8] T lymphocytes and monocytes are first seen perivascularly, mainly in the papillary tips.[9] Monocytes migrate toward the basement membrane and remain there lined up in close proximity to epidermal basal cells.[10] T lymphocytes migrate toward and invade the epidermis and induce discrete spongiosis (Plate 6). At this stage, dermal polymorphonuclear neutrophils are scarce.[11,12] The contributions of CD4+ and CD8+ T lymphocytes are equal, with a CD4/CD8 ratio of approximately 1.[4,5] A further increase in this ratio is observed in cases of rapid evolution into plaque lesions. Based on the observation that the extravasation and subsequent infiltration of CD4+/CD25+ T lymphocytes into the epidermis *precede* the epidermal changes, some authors suggest that T lymphocytes and monocytes play a key role in the induction of new psoriatic lesions.[13] Relevant to the early involvement of T lymphocytes is the marked increase in the number of HLA-DR+/CD1a− dendritic cells and the slight decrease in the number of HLA-DR+/CD1a+ Langerhans cells in the epidermis from early psoriatic skin lesions.[5,6] In addition, intraepidermal CD4+ T lymphocytes were observed in close apposition to HLA-DR+ dendritic cells, a picture normally seen in contact hypersensitivity skin reactions.[14]

Guttate Psoriatic Lesion

In the guttate lesion there are sufficient changes that make the histologic diagnosis of psoriasis possible. The infiltrate is more pronounced, there is still a predomi-

nance of T lymphocytes, and monocytes and neutrophils are now well represented in the infiltrate.[15] Neutrophils are also seen in the epidermis, especially at sites with evident parakeratosis.[16]

The association between guttate psoriasis and group A β-hemolytic streptococcal infection is well documented.[17] Generally, the course of events induced by triggering factors resulting in typical psoriatic lesions remains largely unclear. The poststreptococcal or guttate psoriasis model is an attractive one because of the involvement of a clear antigen. In the latter model, reactivity of antibodies or T-cell receptors (TcRs) to streptococcal antigens, especially M protein, which shares homology with human keratin, is considered to be a conceivable mechanism.[18,19] This cross-reactive immune response induces local activation of the skin immune system and, finally, psoriatic lesions in individuals with the "psoriatic genotype." A similar mechanism may also occur in acute rheumatic fever.[20] The following observations provide evidence for the induction of guttate psoriasis by group A β-hemolytical streptococci: (1) antibodies to streptococcal M proteins cross-reacted with normal and lesional psoriatic skin[21]; (2) streptococcal antigens induced enhanced proliferation of T lymphocytes from the peripheral blood and skin lesions of patients with guttate and plaque-type lesions[18,22]; (3) these T cells were of the CD4+, TcR α/β+, and memory phenotype and produced helper-T-cell type 1 cytokines such as interleukin-2 (IL2) and interferon γ (IFN-γ)[22,23]; (4) local administration of streptococcal antigen induced new psoriatic lesions[24]; and (5) there is a shift of peripheral T cells, similar to streptococcal antigen-specific T cells, expressing TcR β chain variable (V) gene segment 2 (Vβ2) to dermis and epidermis and, to a lesser extent, of Vβ5.1+ T cells to dermis in patients with guttate and plaque-type psoriasis.[23,25]

Pustular Lesion

Immunohistologic time course studies on pustular psoriasis are scarce, but some studies on palmoplantar pustulosis are available. Polymorphonuclear neutrophils are the most prominent cells in this form of psoriasis. In the earliest phases, however, neutrophil accumulation is preceded by T-cell infiltration into the epidermis.[26,27] As in early nonpustular psoriatic lesions, the epidermal T lymphocytes are CD4+/CD25+ and are seen in close apposition to epidermal dendrocytes.[14] Marked attraction of neutrophils forming Munro's microabscesses or spongiform pustules of Kogoj also occurs in plaque-type lesions and has been related to increased local production of IL-8.[28,29] The latter assumption is questionable because IL-8 is also overexpressed in other cutaneous disorders such as allergic contact dermatitis, lichen planus, and mycosis fungoides (own immunohistochemical observations) in which neutrophils are not prominent or even absent. In all likelihood, a combination of the altered interactions with the psoriatic endothelium and the epi-

dermis and the spectrum of locally produced chemoattractants underlies this specific pattern of neutrophil attraction. It may well be that in pustular psoriasis there is further aberration of the altered epidermal cytokine profile. To date, the exact basis for the specific attraction of neutrophils remains unclear.

Plaque-Type Lesion

In plaque-type lesions the dense inflammatory infiltrate in the dermis is composed of lymphocytes, monocytes, dendrocytes, and polymorphonuclear leukocytes. In the dermis, T lymphocytes are seen perivascularly and at the tips of the elongated papillae. Activated T lymphocytes are regularly observed in the epidermis. The number of intraepidermal T lymphocytes is highest in psoriasis when compared with other inflammatory skin diseases. Studies by different authors have demonstrated that the epidermal T lymphocytes are of the helper–inducer or memory type and express the following membrane markers: CD4, CD11a, CD25, CD45RO, CD49d, CD54, Cdw60, HLA-DR, CLA (Plate 7).[2,4,6,11,30–32]

Based on their cytokine production profile, human CD45RO+ helper T lymphocytes may be classified into helper T type 0, 1, and 2 lymphocytes (Mossman T. Oral communication, Third International Conference on Cytokines, March 28–30, 1994). It was unclear whether in psoriasis the infiltrating lymphocytes belonged to the helper T type 1 or helper T type 2 (IL-4 and IL-5 producers) subset because little was known about the profile of cytokines produced by T lymphocytes in situ in psoriatic lesions. Elevated levels of IL-2, soluble IL-2 receptor, IFN-γ, and IFN-γ-induced protein-10 (γ-IP-10) have been reported in psoriatic lesions, whereas IL-4 was never detected.[33–35] Thus, these data favor a role for helper T type 1 lymphocytes in the pathophysiology of psoriasis. This was recently corroborated by the results of PCR experiments by Uyemura and others for the detection of cytokine mRNA in skin extracts from lesional and nonlesional psoriatic skin and healthy control skin.[3]

Signs of T-Cell Activation in Psoriasis

Further indirect evidence for the involvement of the cellular immune system has been obtained from blood, serum, suction-blister fluid, and urine and skin tests of psoriatic patients. Peripheral blood of psoriatic patients displays signs of T-cell activation such as an increased number of activated (CD25+/HLA-DR+) T lymphocytes (Table 1)[6] and elevated levels of soluble IL-2 receptor, soluble CD8, and soluble intercellular adhesion molecule 1 (ICAM-1) and shows increased migratory activity in response to appropriate chemoattractants.[36–40] These findings merely represent markers for inflammation and are not specific for psoriasis, because elevated levels of serum IL-2 receptor are also observed in atopic dermatitis, rheumatoid arthritis, and other inflammatory diseases.[37] Suction-blister fluid from psoriatic plaques contains ele-

Table 1. Immunophenotyping of Peripheral Blood Mononuclear Cell Samples From Patients With Psoriasis, Control Subjects, and Patients With Allergic Contact Dermatitis (ACD)

Monoclonal Antibody	Patients With Psoriasis (n = 24)	Controls Subjects (n = 60)	Patients With ACD (n = 24)
CD20	6.1 ± 2.5	7.0 ± 3.7	6.2 ± 3.6
CD3	57.7 ± 8.2	59.1 ± 13.1	61.1 ± 9.6
CD4	38.2 ± 6.6	38.4 ± 10.9	38.1 ± 9.5
CD8	20.5 ± 6.3	20.8 ± 5.4	23.1 ± 5.4
CD4/CD8	2.0 ± 0.9	2.0 ± 0.8	1.7 ± 0.8
CD14	22.6 ± 8.6	18.9 ± 8.5	19.1 ± 7.7
HLA-DR	29.3 ± 8.3	27.5 ± 8.8	27.6 ± 8.1
CD25(IL-2 receptor)	4.4 ± 9.7*	0.2 ± 0.2	1.1 ± 0.6
CD71(TFR)†	4.3 ± 4.8*	0.5 ± 0.5	1.7 ± 1.2

Note. Results are expressed as the mean percentage ± SD of monocyte and lymphocyte subsets in PBMC samples from patients with psoriasis, healthy control subjects, and patients with ACD. Clusters of differentiation (CD) are shown.
* P < .001, WT, when compared with the results for healthy control subjects.
† TFR, transferrin receptor.

vated IL-6, IFN-γ, and IFN-α activity.[33,40,41] Psoriatic patients with increased IL-6 levels in blister fluid from plaque-type lesions displayed no increase in IL-6 levels in blister fluid from nonlesional skin and in serum.[41] This indicates that the IL-6 was locally produced in the psoriatic lesions; however, other studies of patients with severe psoriasis did show elevated serum levels of IL-6, possibly derived from activated peripheral blood mononuclear cells (PBMCs).[42,43] Levels of IFN-γ and IFN-α are also increased in the sera from psoriatic patients and correlate positively with disease activity.[44] Immunohistologically, the expression of IFN-α and IFN-γ was confined to basal keratinocytes and to stratum corneum and dermal mononuclear cells, respectively.[45] Lesional T lymphocytes are to be considered the most likely source of the elevated IFN-γ levels because keratinocytes do not produce bioactive IFN-γ.[46] Indeed, in vivo, psoriatic keratinocytes exhibit signs of exposure to IFN-γ such as expression of γ-IP-10 and ICAM-1, but in most cases not HLA-DR.[34,47] The expression of these molecules partially parallels the elevated levels of IFN-γ in psoriatic lesions. The sporadic expression of HLA-DR on psoriatic keratinocytes is remarkable and probably based on the differences in responsiveness to IFN-γ between normal and psoriatic keratinocytes.[48-50] Psoriatic keratinocytes show decreased upregulation of HLA-DR, less inhibition of cell growth, enhanced production of transforming growth factor (TGF-α), and no downmodulation of their epidermal growth factor (EGF)/TGF-α receptor on stimulation with IFN-γ.[49,50] In psoriatic skin the IFN-γ receptors are in fact confined to the basal epidermal layers, whereas the IFN-γ receptors are distributed throughout the epidermis of normal skin.[51] The reported induction or exacerbation of psoriasis by recombinant IFN-γ and IFN-α stresses their inductive role in this disease.[52,53]

The urine of psoriatic patients contains increased

levels of neopterin, a substance indirectly related to T-cell activation.[54,55] The concentration of neopterin in the urine seems to correlate positively with the disease activity in psoriasis, whereas different antipsoriatic treatments significantly reduce the level of neopterin in the urine.[54,55]

In vivo delayed hypersensitivity skin test reactions to dinitrochlorobenzene (DNCB), a potent sensitizer, seem to be impaired in psoriatic patients.[56] The impairment appears to be related to the disease activity, because patients free of lesions do not exhibit this impairment. Intradermal tests using purified mycobacterial protein derivative (PPD) and streptokinase/streptodornase partially confirmed the results obtained with DNCB, because 48 hours after skin testing, only the skin reactions to streptokinase/streptodornase differed significantly from those of the controls.[56] In the same study, it was noted that the reactions to PPD persisted longer in patients with psoriasis, which suggested an impaired ability to switch off cell-mediated immune reactions.

Evidence for Immunopathogenic Mechanisms in Psoriasis

The potential pathogenic role of bone marrow-derived cells in psoriasis is illustrated by the clearance of longstanding severe psoriasis after allogeneic bone marrow transplantation,[57] as well as induction of psoriasis in a recipient of HLA-matched bone marrow from an individual with psoriasis.[58] Moreover, manifestation of psoriasis in a patient without neutrophils and monocytes in the peripheral circulation again indicates a prominent role for T lymphocytes in the initiation of psoriasis.[59] This case also indicates that neutrophils are not a prerequisite for the initiation of psoriasis. Studies on intravenous administration of anti-CD3/CD4 monoclonal antibodies showed that depletion of circulating T lymphocytes resulted in the improvement of psoriasis.[60] Finally, the course of psoriasis is generally characterized by remissions and exacerbations of the disease. A similar course is also often observed in classic autoimmune (skin) diseases. In the latter case, the variation in disease activity is attributed to the imbalances between effector and suppressor mechanisms of the immune system.[61] Comparable mechanisms may regulate disease activity in psoriasis. In conclusion, these observations indicate that the abnormalities in psoriatic keratinocytes may be triggered by, or are highly dependent on, CD4+ T lymphocytes and their cytokines and emphasize the importance of immunopathogenic mechanisms in psoriasis.[62,63]

In Vitro Studies on the Function of T Lymphocytes in Psoriasis

Data on the in vivo situation showing that T lymphocytes are consistently involved in early psoriatic lesions were summarized in the previous paragraphs. These data support the hypothesis that psoriasis is a disease of keratino-

cyte proliferation induced by T lymphocytes and T cell-derived proinflammatory agents.[13] The most relevant data on in vitro T lymphocyte function in psoriasis are presented in the following paragraphs.

Cell-Mediated Immunity

The data on cell-mediated immunity in psoriasis are conflicting. Early studies reported a decreased proliferative response of PBMCs from psoriatic patients after stimulation with mitogens such as phytohemagglutinin (PHA) and concanavalin A (ConA),[64,65] however, normal responses to PHA and pokeweed mitogen have also been reported.[66] CD3-triggered peripheral T-cell proliferation is decreased, but is enhanced by extracellular matrix (ECM) components.[67] The autologous mixed-lymphocyte reaction (MLR) appears to be decreased in patients with psoriasis, with the proliferation inversely correlated with disease activity.[68] The decreased proliferation was attributed to the reduced production of IL-2 and IFN-γ by peripheral blood T lymphocytes[69]; however, this decreased response to stimuli of psoriatic T cells was not observed in vitro in our studies.[6] As mentioned, in other articles consistently increased levels of IFN-γ and IL-2 receptor in suction-blister fluids and sera from psoriatic patients were reported.[33,37,44] These inconsistent findings may be related to arbitrary conditions, such as timing of the in vitro testing in relation to disease activity. In vitro testing for drug allergy, for example, has shown that a severe drug eruption is followed by a period of "anergy" during which PBMCs show decreased or no antigen-specific proliferation. Restoration of antigen-specific proliferation in PBMCs depends on clearance of the drug eruption and is usually observed some weeks later.[70]

T cells from peripheral blood of psoriatic patients, in the absence of added antigen, show a clear proliferative response in vitro to autologous epidermal cells from lesional as well as uninvolved skin.[6,71,72] Such a reaction is called the autologous mixed epidermal cell–T lymphocyte reaction (MECLR). Increased autologous MECLR is also observed in cutaneous T-cell lymphoma and atopic dermatitis and after 4 MED UVB irradiation of normal skin.[73–75] In cutaneous T-cell lymphoma and atopic dermatitis, the autologous MECLR is increased only when epidermal cells from involved skin are used.[73,74]

Putative Psoriasis-Related Antigen

At present, it remains unclear whether the MECLR is antigen driven. Nevertheless, the epidermal HLA-DR+ APCs play a central role by presenting antigen (putative psoriasis-related) to autologous T lymphocytes.[6,76] Skin-infiltrating T cells in psoriasis may recognize MHC class II-associated molecules like superantigens or autopeptides present in the MHC groove.[77,78] As discussed earlier, M proteins of group A β-hemolytic streptococci or mycobacterial peptides may act as superantigens via molecular mimicry.[19] Other potential antigens may be persisting

viral or retroviral antigens, drugs themselves, or drug-induced MHC class II-associated neoepithelial antigens.[76,79,80] In fact, alterations in (the glycosylation of) plasma membrane proteins are primary features of the psoriatic keratinocyte.[81] Although clear evidence has to be provided, these neo-epithelial proteins may be recognized as nonself on recognition by immunoregulatory cells. Examples of these upregulated (keratinocyte-specific) proteins include calgranulins A and B, carcinoembryonic antigen, cystatin A, psoriasin, Pso 27, and psoriasis-associated fatty acid-binding protein (PA-FABP).[82–84] This altered protein expression seems to be related to the hyperproliferative state of these cells, inflammatory stimuli or both.[82] Other "aberrant" membrane markers expressed by psoriatic keratinocytes are squamous cell carcinoma-related antigen, CD13, CD14, CD36, and CD68.[85–87] Despite the data in favor of an epidermal psoriasis antigen, such an antigen may not be solely confined to the skin. This may explain the occurrence of arthritis in a proportion of the patients.

Accessory Cells

Analysis of the APC function in the MECLR shows that not the "classic" Langerhans cells (LCs) (HLA-DR+/CD1a+), but HLA-DR+/CD1a− APCs are the principal stimulators of T cells in this reaction (Fig 1).[6] Lesional keratinocytes do not stimulate T cells in the MECLR, probably as result of the limited number of HLA-DR+ keratinocytes in psoriatic lesions.[88] Our own findings indicate that, besides HLA-DR, adhesion molecules such as CD2, CD11a, CD18, CD54, CD58, and membrane-associated IL-1 on psoriatic epidermal cells also fulfill an accessory role in the autologous MECLR (Prens E. Submitted for publication). In normal skin, only one type of epidermal APC — the HLA-DR+, CD1a+, Fc-γ and C_3 receptor-bearing LC — predominates.[89,90] This means that epidermal cell suspensions depleted of HLA-DR+/CD1a+ LC are unable to present antigen to autologous T cells to stimulate allogeneic T cells.[91,92]

Several reports describe the predominance of HLA-DR+ cells over CD1a+ cells in epidermal cell suspensions from psoriatic lesions (Table 2).[6,93,94] It is known that cultured LCs lose their CD1a expression and cytoplasmic Birbeck granules, but the expression of HLA-DR is upregulated and their stimulatory capacity is increased.[95–97] Fresh LCs process and present native antigen more efficiently than cultured LCs, whereas cultured LCs are equally efficient at presenting preprocessed antigen, but superior at stimulating allogeneic T lymphocytes.[96,97] Cultured LCs exhibit a unique feature that is not shared by fresh LCs, namely, an extraordinary capacity to stimulate syngeneic T lymphocytes.[97] Thus, fresh and cultured LCs may be considered as the in vitro representatives of their in vivo counterparts, respectively: intraepidermal LCs and LCs that have migrated to the draining lymph nodes (nodal LCs).[97] Elevated levels of cytokines may
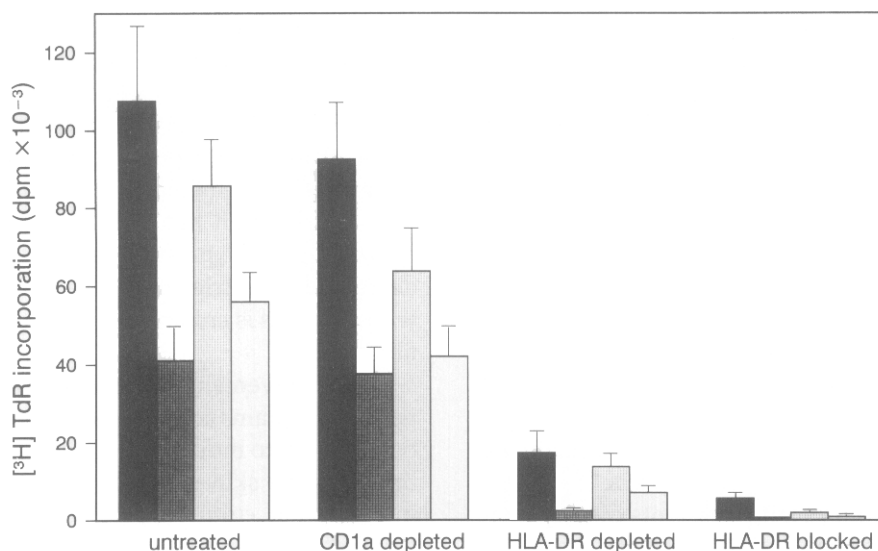
Figure 1.   The role of HLA-DR+ and HLA-DR/CD1a+ skin APC subsets in the autologous MECLR. Purified T lymphocytes were cocultured with autologous total epidermal cells (ECs), CD1a depleted ECs, or EC suspensions depleted of CD1a+ and HLA-DR+ cells, all at a concentration of 4 × 10⁴ ECs per well. The cultures were pulsed with tritiated thymidine and harvested 8 hours later. Blocking was performed by addition of dialyzed anti-HLA-DR mAb to the cultures. Filled, bold speckled, fine speckled, and blank bars represent the arithmetic mean ± SEM dpm of quadruplicate cultures on the day of maximum proliferation of an individual patient. Paired results of four representative patients are shown. Reprinted with permission from Prens et al.[6]

alter the microenvironment in psoriatic lesions in such a way that in vivo lymph node or in vitro culture conditions are stimulated. As the phenotype and some functional characteristics between "cultured" LCs and HLA-DR+/ CD1a− APCs occurring in psoriatic lesions are similar, the latter cell type may be considered as the in vivo equivalent of in vitro "cultured" LCs.[98] Thus, HLA-DR+/CD1a− APCs in psoriatic lesions probably represent cytokine-activated LCs.

Interference of T Lymphocytes With Stroma and Epidermal Cell Behavior

Extravasation, (epi)dermal recruitment, and recirculation of T lymphocytes are essential processes for immune surveillance of the skin. Lymphocyte trafficking comprises at

Table 2. Levels of Expression of Activation Markers on Epidermal Cells From Lesional Psoriatic (PP), Uninvolved Psoriatic (PN), and Healthy Control (NN) Skin

	Percentage Expression		
Marker	PP	PN	NN
CD36(OKM5)+	23 ± 12*	0.3 ± 0.1	0.5 ± 0.1
CD54(ICAM-1)+	31 ± 14*	0.6 ± 0.1	0.5 ± 0.1
mIL-1+	57 ± 21*	12 ± 3*	4 ± 0.5
HLA-DR+	5.1 ± 1.6*	1.9 ± 0.6	1.6 ± 0.4
CD1a+	1.8 ± 0.7	1.6 ± 0.4	1.5 ± 0.4

Note. Results are expressed as the mean percentage of positive cells ± SD.
* These figures are significantly higher than those for uninvolved psoriatic skin and/or control epidermal cells.

least two components: adhesion and migration. Cellular adhesion is controlled by interactions between lymphocytes and endothelial cells via adhesion molecules. Chemokines, chemoattractants for leukocytes, are responsible for the migration of lymphocytes to sites of inflammation. During cutaneous inflammation, adherence of T lymphocytes to the endothelium is followed by diapedesis and immigration into dermis and, finally, epidermis. The interactions of T lymphocytes with (eip)dermal cells and ECM components, the consequences of these interactions, and their role in the pathogenesis of psoriasis follow.

Interaction of T Lymphocytes With Endothelial Cells

Adhesion of T lymphocytes to vascular endothelium involves a multistep cascade: (1) initial "rolling" of T lymphocytes on the endothelium via selectin-mediated interactions; (2) activation of T-cell integrins by chemokines or divalent cations, resulting in high-affinity ligand binding; and (3) strong adhesion mediated by T-cell integrins.[99] Chemokines immobilized by endothelial proteoglycans may regulate the type of infiltrating T cells. A clear example of such a cytokine is macrophage inflammatory protein (MIP)1β. This protein preferentially attracts CD4+ T cells and potentiates the adhesion of CD8+ T cells to vascular cell adhesion molecule (VCAM) 1 on endothelial cells.[100] Selective recruitment of T-cell subpopulations into the skin is also evidenced by the interaction between cutaneous lymphocyte-associated antigen (CLA) and E-selectin on endothelial cells. This interaction induces di-

rectional migration of a unique subset of skin-associated memory T cells to sites of chronic cutaneous inflammation.[31,101] Once in the skin, the expression of CLA may be upregulated further by transforming growth factor β1 (TGF-β1) and, to a lesser extent, by IL-6, both of which are produced by activated keratinocytes.

Interferon γ derived from infiltrating T cells regulates the expression of E-selectin and production of IL-6 by endothelial cells.[102] Vice versa, endothelial cells treated with IFN-γ were able to induce antigen-dependent proliferation and cytokine production of helper T type 2 cells, but not helper T type 1 cells. This implies that endothelial cells, by virtue of their capacity to function as accessory and/or antigen-presenting cells, selectively stimulate the transmigration and function of T-cell subsets.[103]

Peripheral T cells from psoriatic patients display augmented binding to normal endothelium as compared with healthy controls and patients with atopic dermatitis and rheumatic arthritis.[32,104] This augmented lymphocyte binding is reversible with treatment and clinical improvement. The reverse is also true. Normal CD4+ T cells bind specifically to dermal capillary endothelia in psoriatic plaques, but not in uninvolved psoriatic or normal control skin.[32] Dermal capillaries in psoriatic skin express elevated levels of ICAM-1 and E-selectin, and preferentially allow the adherence of LFA-1+ and CLA+ memory T helper cells as compared with the vessels in normal skin.[32] Furthermore, in psoriasis, VCAM-1 and endoglin, a new 180-kDa dermal endothelial cell activation antigen, are variably upregulated on dermal endothelium.[105,106] The activated status of endothelium in psoriasis is further illustrated by the increased expression of (tumor necrosis factor α) TNF-α and TNF receptor on dermal blood vessels.[107] Cytokines such as IL-1, IL-6, TNF-α, and IFN-γ which predominate in the psoriatic (epi)dermal microenvironment are the potential candidates for the upregulation of adhesion molecules. These molecules on psoriatic endothelium have been shown to be less sensitive to the downregulatory effects of TGF-β1.[108] Psoriatic endothelial cells display structural abnormalities that together with an increased adhesiveness for T lymphocytes facilitate trafficking of these cells.

Interaction of T Lymphocytes With Fibroblasts and Extracellular Matrix Components

After extravasation, skin-infiltrating T cells encounter dermal constituents like fibroblasts and ECM components. T cell–fibroblast interaction results in a mutual activation and in an increased production of TNF-α, IFN-γ, and IL-6, with T cell-derived TNF-α being responsible for the upregulation of ICAM-1 on fibroblasts.[109] Thus, T cells initiate a cell contact-mediated mechanism for selection, accumulation, and retention of mononuclear cells via fibroblast ICAM-1 during cutaneous inflammation.[110]

Interaction of lymphocytes with ECM proteins may induce persistent cytokine or chemokine synthesis and

ECM components are able to maintain tissue inflammation in such a manner. For instance, thrombospondin, a protein that is highly upregulated in inflamed skin, preferentially binds to activated very late activation antigen 4 (VLA-4) and VLA-5 present on memory T cells.[111] The β1 integrin (CD29)-mediated interaction between primed T cells and laminin has been shown to induce persistent cytokine gene expression in mononuclear cells.[112] The decreased CD3-triggered T-cell proliferation in patients with psoriasis is enhanced by collagen types I and IV and fibronectin.[67]

The involvement of fibroblasts in the pathogenesis of psoriasis remains controversial. Psoriatic fibroblasts have been shown to induce hyperproliferation of normal keratinocytes in a skin-equivalent model.[113] Our own studies indicate that cultured psoriatic fibroblasts produce increased amounts of biologically active IL-6, a cytokine able to induce keratinocyte and lymphocyte proliferation (Debets R, et al. Manuscript in preparation). This altered IL-6 production by lesional psoriatic fibroblasts is associated with a decreased expression of TNF receptor and an altered expression of platelet-derived growth factor (PDGF) receptor B.[114] At present, it is not known whether these alterations are of a primary nature or are merely a consequence of cellular activation due to T cell–fibroblast interactions. Thus, ECM proteins may be involved in the maintenance of psoriatic lesions.

Interaction of T Lymphocytes With Keratinocytes

Different studies on the interaction between T cells and keratinocytes indicate that three interactive mechanisms are involved: (1) via soluble cell products (cytokines), (2) via cell–cell contact (direct activation), (3) a combination of both mechanisms. Interactive signaling, autocrine, paracrine, and pleiotropic effects are the hallmarks of these mechanisms. The interaction between T cells and keratinocytes can affect the phenotype and function(s) of both cell types. Illustrative are the observations that, on the one hand, T cells from lesional psoriatic skin release growth factors that induce activation, proliferation, and a "psoriatic phenotype" in cultured keratinocytes.[30,115] On the other hand, cytokines released by lesional psoriatic, but not normal, epidermal cells potentiate T-cell activation.[116]

T-cell cytokines have clear growth regulatory effects on keratinocytes. Supernatants from unstimulated PBMCs ConA-stimulated PBMCs, and allostimulated purified T cells are able to effectively induce or maintain keratinocyte proliferation in vitro.[117] The stronger the T cells were stimulated, the more their supernatants induced keratinocyte proliferation. Not only mixtures of cytokines released by stimulated T cells, but also single (recombinant) human cytokines may induce or maintain their proliferation.[118] Although IFN-γ has been shown to inhibit the proliferation of keratinocytes in vitro,[119] an increased keratinocyte proliferation was measured in

vivo following its local administration.[120] Other cytokines with keratinocyte growth-inducing capacities are IL-1 and IL-6.[42,121] Vice versa, keratinocyte-derived IL-6, IL-7, and TNF-α support T-cell growth.[122] T cell-derived IFN-γ induces MHC class II, ICAM-1, and γ-IP-10 expression on keratinocytes.[4,34,118] Gamma-IP-10, secreted by activated keratinocytes, is a chemoattractant for monocytes and activated CD4+ and CD29+ T cells and potentiates the adhesion of T cells to endothelial cells.[123] Phenotypically altered "activated" keratinocytes acquire the ability to serve as accessory cells for superantigen- or mitogen-induced T-cell proliferation.[124] Lymphocyte function-associated antigen 1/ICAM-1 interaction is crucial for this accessory function.[124] The exact role of the CD28 ligands in the accessory cell function of keratinocytes is still unclear.[124,125] T-cell epidermotropism depends on keratinocyte-derived chemotactic cytokines such as IL-1, IL-8, TGF-β, and the eicosanoid leukotriene B4 (LTB4) and keratinocyte adhesion molecules such as E-selectin and the B7/BB-1 molecules, which interact with the T-cell molecules CLA and CD28, respectively. VLA-3+ T cells are able to interact with and to penetrate the epidermal basement membrane via adhesion to epiligrin, a basement membrane component.[126]

Although the data are not always consistent, it is conceivable that T cell–keratinocyte interactions cause several alterations in the expression of cytokines and their receptors on psoriatic epidermal cells. The regulation of IL-1 is clearly abnormal in psoriatic skin; low levels of IL-1α, elevated levels of a nonfunctional IL-1β, and an elevated ratio of IL-1 receptor antagonist (IL-1α) to IL-1 prevail in extracts of lesional psoriatic skin.[127,128] Using freshly isolated viable cells, we were able to demonstrate that lesional psoriatic epidermal cells have an enhanced ability to secrete biologically active IL-1β[129] (Debets R. Submitted). Epidermal cells from lesion-free skin were shown to contain elevated levels of IL-1β mRNA.[3] These data indicate that keratinocyte-derived IL-1 may play a more important role in the pathogenesis of psoriasis than previously assumed.

Other cytokine abnormalities in psoriatic keratinocytes are increased expression of IL-6, IL-8, Gro-α, and TGF-α and overexpression of monocyte chemoattractant protein 1 (MCP-1) mRNA.[42,130–133] Cytokine/growth factor receptors overexpressed in psoriatic epidermis are EGF/TGF-α, insulin-like growth factor 1 (IGF-F) and IL-4 receptors[134,135] (Prens E. Submitted). Decreased expression of IL-1 receptor has been observed on psoriatic epidermal cells (Prens E. Submitted).

In summary, the data presented here clearly illustrate that T cell–keratinocyte interactions in psoriasis are responsible for enhanced bidirectional cellular activation. Minute quantities of cytokines released during these interactions may trigger a cascade of intercellular cytokine signals which induce or boost cutaneous inflammation, or both. Therefore, the identification of the primary signal

and its cellular source in psoriasis remains extremely difficult.

Effects of Antipsoriatic Therapies on T Cells

Potentially effective antipsoriatic drugs may improve psoriasis by influencing the steps that are important in T-cell activation and T-cell trafficking into inflamed tissue. These steps include mechanisms such as reducing chemokines, downmodulating adhesion molecules on endothelial cells and/or keratinocytes, influencing the epidermal cytokine milieu, and inhibiting APC function. If one or more of these steps are interfered with, it is conceivable that also the final goal of such a therapy, namely, the reduction of keratinocyte proliferation and normalization of epidermal architecture, will be achieved. It is now known that the most effective antipsoriatic treatment modalities have marked immunosuppressive or immunomodulatory effects. Especially the observations that cyclosporine A was effective in clearing psoriasis emphasized the role of T lymphocytes and cell-mediated immune mechanisms in psoriasis.[136–138]

Anthralin

Anthralin (Dithranol), a synthetic substitute for chrysarobin, acts primarily as an inhibitor of DNA synthesis and several cytosolic enzymes and by its clear effects on mitochondria and thus on the cellular respiratory system.[139] Besides the inhibitory effects on DNA synthesis and DNA repair in human lymphocytes, little else is known on the precise effects of anthralin on lymphocytes. Functional studies showed that neutrophil migration is inhibited by therapeutically relevant concentrations of anthralin and that the allogeneic MECLR is inhibited, probably via toxic effects on epidermal Langerhans cells.[140] Resolution of anthralin-treated psoriatic lesions is accompanied by a slight decrease in the number of epidermal T cells, but not by a decrease in the number of epidermal dendritic cells.[141]

Cyclosporine A

Cyclosporine A (Cy A), a cyclic polypeptide initially used to prevent renal allograft rejection, by coincidence also appeared to improve psoriasis.[142] In subsequent studies, CyA appeared to inhibit T-cell activation and the release of IL-2.[143,144] This property of CyA formed the basis for establishing its efficacy in psoriasis and other chronic inflammatory diseases in which cell-mediated immune reactions were suspected. Analysis of the literature allows the conclusion that CyA may improve psoriasis via two different pathways.[145] The first pathway comprises its inhibitory effects on cells of the inflammatory infiltrate and their soluble products. The second pathway comprises its direct antiproliferative effect on keratinocytes, which is not discussed further as it is beyond the scope of this review.
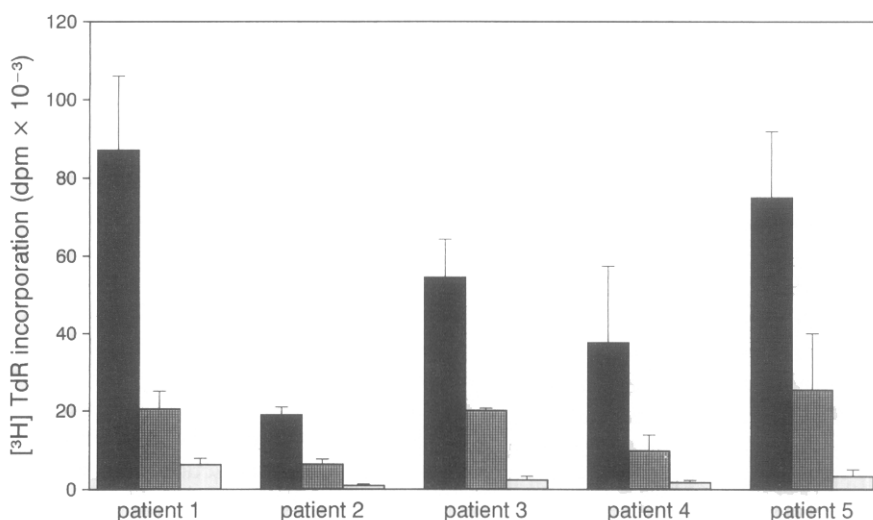
Figure 2. *Effect of in vitro preincubation of lesional epidermal cells (ECs) with cyclosporin A (CyA) on the autologous MECLR. Lesional ECs were incubated with 2.5 μg/mL CyA in RPMI containing 1% human AB serum for 1 hour at 37°C. The cells were washed five times with warm RPMI complete medium containing 15% human AB serum. The cultures were pulsed with tritiated thymidine and harvested 8 hours later. Bars represent the mean ± SEM dpm of quadruplicate cultures on the day of maximum proliferation. The difference between treated (speckled bars) and untreated (solid bars) ECs is statistically significant (P < .05, Wilcoxon signed rank sum test). Blank bars represent the autologous mixed-lymphocyte reaction of each patient. Reprinted with permission from Prens et al.[6]*

Besides inhibition of IL-2, CyA is now also known to inhibit transcription of IFN-γ, IL-3, IL-4, the IL-8/NAP-gene family, and TNF-α in T lymphocytes.[143-146] The downregulation of ICAM-1 on endothelial and epidermal cells and that of γ-IP-10 on keratinocytes following CyA treatment are probably secondary to the inhibition of T cell-derived cytokines.[147,148] The latter would imply that besides the phenotype of keratinocytes, their proliferation may also be inhibited via decreased release of "growth factors" by T cells. Not only the function, but also the number of T lymphocytes in psoriatic lesions is reduced by CyA.[149] Immunohistologic studies by different investigators have shown that clinical improvement of psoriasis is accompanied by marked reductions in the number of activated CD25+ and HLA-DR+ epidermal T cells.[149,150] The prevailing imbalance of epidermal dendritic cell subsets is restored by a significant increase in the number of HLA-DR+/CD1a+ cells after CyA therapy.[151] Although initially debated, there is now agreement that CyA inhibits the stimulatory capacity of epidermal APCs.[6,152-154] This inhibition is observed in the autologous and allogeneic MECLR following in vitro and in vivo CyA treatment, respectively.[6,7,154] In the autologous MECLR, under carefully defined in vitro conditions, preincubation of lesional epidermal cells with CyA significantly inhibited the T-cell response (Fig 2).[6] The synthesis of IL-1, a cytokine essential for the activation of T cells during the presentation of antigen, is inhibited in APCs by CyA treatment.[155]

Glucocorticosteroids

Glucocorticosteroids have well-known anti-anflammatory effects. Their mode of action, particularly their effects on T lymphocytes, is still incompletely understood. Glucocorticosteroids effectively inhibit DNA synthesis via interaction with the glucocorticoid-responsive element and by modulation of Ca^{2+} influx into the cell.[156] Synthesis of inflammatory mediators such as arachidonic acid metabolites is inhibited via upregulation of lipomodulin and phospholipase A_2.[157] Besides their antiproliferative effects on T cells, corticosteroids may also impair cytokine production by these cells.[158]

More detailed data are available on the effects of corticosteroids on APCs. Antigen-presenting capacity and also the production of IL-1 are clearly inhibited by corticosteroids.[159,160] In vivo treatment of human, mouse, and guinea pig skin resulted in "depletion" of epidermal APCs.[161-163] This "depletion" consisted in part of a decrease in the number of HLA-DR+ cells and in part of a downmodulation of surface membrane markers such as CD1a and ATPase. Epidermal cells from a normal skin area that was treated in vivo with a class IV corticosteroid did not induce antigen-specific T-cell proliferation, whereas epidermal cells from an untreated area did so effectively.[161,162] Treatment of normal skin also resulted in a marked decrease in the number of dermal mast cells.[164] This, together with the capacity of glucocorticosteroids to inhibit neutrophil accumulation,[165] may be

clinically relevant because mast cell degranulation is observed in emerging prepinpoint psoriatic lesions. Topical treatment of psoriatic lesions with a class IV corticosteroid resulted in a rapid decrease in the number of activated epidermal T cells.[141] The same treatment also resulted in a gradual decrease in the number of HLA-DR+ dendritic cells, such that even a lower level than in untreated normal skin was reached when the lesions resolved.[141]

Methotrexate

Methotrexate (MTX) is an antimetabolite that exerts its antipsoriatic effects via antagonism of folic acid and inhibition of thymidylic acid in DNA synthesis. Especially cells in S phase, such as the increased pool of epidermal cells in S phase in psoriatic lesions, are highly susceptible to the antimetabolic effect.[166,167] Again, not much is known about the mode of action of MTX on T lymphocytes. The effect of MTX on T lymphocytes in S phase will probably be similar, but particularly the weekly cyclic dose scheme makes it difficult to predict the in vivo effects on lymphocytes; however, a major part of epidermal and dermal T lymphocytes in psoriatic lesions are not in S phase. Methotrexate, furthermore, inhibits T-cell activation by APCs in part via inhibition of IL-1 bioactivity.[168,169] This indicates that probably interference with the epidermal compartment, which always contains some cycling cells, is a more likely target for MTX.

Retinoids

The well-known "normalizing" effects of synthetic retinoids such as etretinate and acitretin on epithelial differentiation and proliferation are not reviewed here. In this section, we discuss the immunomodulatory effects of retinoids on a variety of hematopoietic cells and nonepithelial tissues. Although the data on the effects of etretinate in humans are rather conflicting, an attempt has been made to summarize them. The inhibition of neutrophil migration was an early event during systemic treatment of psoriasis with etretinate.[170,171] Regression of psoriatic lesions after treatment with etretinate was accompanied by a distinct increase in the number of dermal and epidermal CD1a+ dendritic cells.[172] Inhibition of IFN synthesis by natural killer cells and blockage of IFN-induced upregulation of HLA-DR in monocytes and probably epithelial cells have also been observed.[173,174] Retinoic acid may enhance or inhibit T-cell proliferation depending on the nature of the stimulus.[175] Skin reactions to DNCB seemed to be enhanced in patients with psoriasis during oral therapy with retinoids.[176] Interestingly, retinoic acid enhanced epidermal IL-1 production in rats.[177]

Ultraviolet Therapy

Although ultraviolet radiation (UVR, UVB, as well as PUVA) has clear effects on the human immune system, these effects have been studied best in the animal model. The effects on the skin immune system include inhibition of keratinocyte proliferation, effects on epidermal Langerhans cell function, induction of suppressor cells, and modulation of epidermal cytokine production.[178-180] Epidermal Langerhans cells were significantly depleted in mouse and human skin exposed to UVR.[178,179] Langerhans cell depletion was accompanied by a decreased ability of mouse skin to become sensitized by contact allergens.[179,180] Similar results have been obtained in humans, in whom delayed-type hypersensitivity responses were also markedly inhibited by UVR. UVR causes an increase in the synthesis of IL-1 and an IL-1 antagonist by epidermal cells.[180-182] Cell-mediated reactions may thus be inhibited by antagonism of IL-1 bioactivity by IL-1ra and/ or via induction of prostaglandin E_2 synthesis in target cells by IL-1. Initial results of UV-photopheresis studies in psoriasis suggest that T-cell proliferation is directly inhibited by photochemotherapy.

Vitamin D_3 and Analogs

1,25-Dihydroxyvitamin D_3 (calcitriol) and its synthetic analog calcipotriol have significant immunomodulatory functions.[183] Vitamin D_3-deficient rats exhibit impaired immune responses, mainly because of an impaired APC function, that can be restored by supplementation of vitamin D_3.[184] The APC function of monocytes and dendritic cells may be inhibited or stimulated by calci(po)triol depending on their stage of differentiation.[185] The immunomodulatory effects are rather pleiotropic, as they are codependent on the cytokine and hormone milieu, the stage of differentiation of the cells involved, and the nature of eventual costimuli.[185] For example, the obvious "normalizing" effect of calci(po)triol on keratinocyte differentiation and proliferation is mediated in part by inhibition of the production of IL-1 and IL-6 in inflammatory cells and enhancement of the production of TGF-β1 and β2 by keratinocytes.[186-188] Besides IL-1 and IL-6, vitamin D_3 has also been shown to inhibit the production of lymphokines such as IL-2, TNF-α, and IFN-γ by human mononuclear cells.[187] The inhibition of IL-2 synthesis by T cells indicates that T cells may be a direct target of vitamin D_3.[187] CD45RO+ memory T cells seem more sensitive to the immunosuppressive effects of this drug than CD45RA+ T cells.[189] The inhibitory effects on T lymphocytes are further potentiated by simultaneously using 1,25-dihydroxyvitamin D_3 and CyA.[190]

Calcitriol inhibits IL-8 synthesis in human dermal fibroblasts, keratinocytes, and PBMCs, but not in endothelial cells.[191] In view of the potent chemotactic properties of IL-8 for T lymphocytes and neutrophils, this may prove to be an important mechanism of action of calci(po)triol in psoriasis.

Conclusions

Psoriasis may be considered the net outcome of a locally ongoing immune inflammation. The earliest signs in

emerging lesions are mast cell degranulation and extravasation of T lymphocytes and monocytes. A wide variety of etiologic stimuli such as superantigens, drugs, physical (Koebner), and autoimmune stimuli result in a final common pathway of inflammation. Proinflammatory mediators released by activated T cells, dendritic APCs, and keratinocytes may recruit leukocytes and initiate skin inflammation via interactive signaling between resident and nonresident skin cells and ECM components. The type and the mixture of chemotactic and cell-activating cytokines during the early phases of inflammation dictate the net migratory behavior of the inflammatory cells.

Selectin and integrin interactions in the dermis, the ECM, and the epidermis are crucial to the development and regulation of inflammation in psoriasis. The sequence of events discussed above represents a finely balanced functional network of interactions between cellular constituents of the skin immune system, their soluble products, and the ECM. Imbalances or genetically determined inabilities to produce or tendencies for overproduction of certain molecules of this interactive system form the basis of skin diseases such as psoriasis. One should, however, bear in mind that the cascade of T cell–ECM–keratinocyte interaction-derived proinflammatory cytokines operative in psoriasis under normal conditions (eg, would healing) has beneficial effects for the host.

The majority of the antipsoriatic therapies, apart from their effects on keratinocyte proliferation and differentiation, also interfere in crucial processes such as antigen presentation to T cells, T-cell activation/proliferation, and T-cell trafficking into inflamed tissue in psoriasis.

Acknowledgments

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