Lymphocyte Trafficking in Psoriasis: A New Perspective Emphasizing the Dermal Dendrocyte with Active Dermal Recruitment Mediated Via Endothelial Cells Followed by Intra-Epidermal T-Cell Activation

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Prominent within the inflammatory infiltrate of psoriasis are HLA-DR positive T lymphocytes and factor XIIIa positive dermal dendrocytes. Many investigators studying psoriasis have assumed that the HLA-DR positive T cells are activated, and thereby capable of producing lymphokines such as gamma interferon. However, by immunohistochemical analysis, greater than 95% of the dermal T cells in psoriatic lesions are Ki-67 negative, which suggests that they are in a resting or non-cycling (Go) state. In contrast to the dermal T-cell population, the epidermal T-cell population contains a greater proportion of Ki-67 positive lymphocytes. The entry of the T cells into the epidermis is, therefore, apparently associated with an important activation event, which in all likelihood involves interaction with the keratinocyte. The presence of activated intraepidermal T cells has been substantiated by the ability to detect gamma interferon mRNA by polymerase chain reaction in epidermal sheets of psoriatic lesions. The pathophysiologic implication of psoriasis for these distinctions and compartmentalization involving dermal and epidermal T cells are placed into the context of a cascade of cellular trafficking events, which are further dissected into a specific network of molecular mediators of inflammation. This report suggests that more attention should be placed on the microenvironment of the skin, with specific emphasis on the mechanism by which T cells accumulate in the dermis and epidermis, and elucidation of the selective inductive and recruitment capabilities of endothelial cells, perivascular dermal dendrocytes, and keratinocytes. J Invest Dermatol 95:355–378, 1990

By virtue of their HLA-DR expression, it is commonly assumed that the infiltrating T lymphocytes in the skin of psoriatic lesions are in an activated state. Whereas it has been clearly demonstrated that when T cells are activated by a variety of stimuli in vitro (HLA-DR negative T cells became HLA-DR positive after several days [1]), it is less clear how many of the T cells within the skin of inflammatory dermatosis are in a continual or persistent state of activation. This problem has been investigated by the use of in situ immunoperoxidase staining of tissue sections using the anti-Ki-67 antibody, which identifies cycling cells (G1, S and G2/M phases) rather than resting or non-cycling (Go) cells [2]. Several previous investigators using the anti-Ki-67 antibody have observed that the T lymphocytes in psoriatic lesions are virtually devoid of cycling dermal T cells [3,4]. This finding has important and far reaching implications concerning the lack of cycling T cells in psoriatic dermal infiltrates.

First, this result implies that the T cells must be primarily proliferating elsewhere; i.e., in a non-cutaneous site, such as lymph nodes. Second, there must be a skin-specific recruitment process by which these extra-cutaneously proliferating and activated T cells preferentially accumulate in the skin compared to other organs in the body. Third, the microenvironment of the dermis must not be conducive to the continued stimulation necessary to maintain the T cells in their active phases of the cell cycle. Fourth, because it is well established that cytokine production by T cells, including gamma interferon (IFN-γ) and IL-2, is strictly correlated to early phases of the T-cell activation process [5], the Ki-67 negative cells would not be producing or secreting these types of molecules, many of which have pleiotropic immunomodulatory effects.

We have previously proposed a final common molecular pathway for intraepidermal trafficking of T cells in a wide variety of skin disease, including psoriasis [6,7]. This pathway emphasizes the binding of lymphocyte-function-associated antigen-1 (LFA-1) expressing T cells and monocyte/macrophages to intercellular adhesion molecule-1 (ICAM-1) positive keratinocytes. Whereas normal keratinocytes both in vitro and in vivo do not express ICAM-1, after exposure to either IFN-γ or tumor necrosis factor-alpha (TNF-α), there is rapid induction of keratinocyte ICAM-1 expression [8]. In order to better understand the possible immunologic consequences of LFA-1 expressing T cells binding to ICAM-1 positive keratinocytes and entering the epidermal compartment in psoriasis, we stained psoriatic lesions for Ki-67, because we have recently observed that in patch/plaque stage mycosis fungoides, only the intraepidermal, but not dermal T cells, were Ki-67 positive [9]. The Ki-67 pattern in psoriasis included prominent and near contiguous nuclear staining of the basal keratinocytes but no staining of the dermal mononuclear cells or endothelial cells, in good agreement with previous investigators [3,4]. However, as in mycosis fungoides, the intraepidermal T cells of the psoriatic lesion were found to be Ki-67 positive. The Ki-67 positive T cells were located primarily overlying the "squirting papillae," which is also where the greatest concentration of keratinocyte ICAM-1 has been detected.

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tected [8]. In contrast to mycosis fungoides in which > 80% of the intraepidermal T cells were Ki-67 positive, only approximately 20% of the psoriatic intraepidermal T cells were Ki-67 positive. It should also be noted that the superficial dermal post-capillary venules within the psoriatic lesion were intensely ICAM-1 positive.

These results strongly suggest that in psoriasis, as in mycosis fungoides, there is non-cycling dermal T cells stimulated to enter the cycle when they migrate into the epidermal compartment. As it has been previously demonstrated that anti-LFA-1 antibodies can trigger resting T-cell activation [10], it is possible that when LFA-1 positive T cells attach to ICAM-1 positive keratinocytes, they are triggered to enter the cell cycle via an LFA-1/ICAM-1 interaction. Because T-cell production of lymphokines is related to the cell cycle, the ability of T cells to reciprocally influence keratinocytes [11] is strongly related to their entry into the epidermal compartment. The intraepidermal mediated activation of T cells as evidenced by the Ki-67 staining reaction in mycosis fungoides and psoriasis, provides the first direct immunologically relevant documentation that something very special is occurring when T cells traffic from the dermis into the epidermis. This intraepidermal T-cell activation with IFN-γ production may locally augment the degree of keratinocyte ICAM-1 production and chemotactic factor production, generating an immunologic pro-inflammatory cycle at the top of the dermal papillae (Fig 1). Using the polymerase chain reaction, we have identified IFN-γ mRNA transcripts in psoriatic epidermal sheets in four of five patients. These current results clearly indicate the necessity for understanding the regulation of keratinocyte-derived chemotactic factor production and adhesion molecule expression. In this regard, we observed that indeed there is coordinate transcriptional regulation of cultured keratinocyte chemotactic factor production (interleukin-8, and monocyte chemotactic and activating factor) which is linked to ICAM-1 production [12].

Perhaps the most important implication of our current study is that the dermal T-cell infiltrate in psoriasis accumulates primarily from persistent recruitment of T cells from the blood, rather than local dermal proliferation. It is tempting to speculate that the dermal endothelial cells play a pivotal role in this active recruitment. We have observed that in both acute (allergic contact dermatitis) and chronic inflammation (psoriasis) the endothelial cells can express multiple leukocyte adhesion molecules such as ICAM-1, as well as endothelial leukocyte adhesion molecule-1 (ELAM-1) and vascular cell adhesion molecule-1 (VCAM-1). Given the close proximity of keratinocytes and endothelial cells, we have suggested that keratinocytes may actually be the "pre-eminent cell" of the skin [6], because of its ability to also influence the endothelial cells [13,14]. We can make the analogy that the keratinocyte could serve as the "maestro" of the skin, high up in its epidermal podium, where it may conduct/choreograph the orchestrated movement of dermal cells beneath it by activating the endothelium. We have suggested that the zone of skin between the rete pegs, at the tips of the dermal papillae, serves as a conduit for the transportation of important inflammatory signals via the multi-cellular contiguous network of Keratinocytes–Dermal Dendocytes–Endothelial Cells [13]. Whereas the enhanced ICAM-1 expression by the dermal endothelial cells could participate in the recruitment of LFA-1 expressing T cells [14], there is almost certainly a significant contribution being made by the interaction of a skin-specific vascular addressin, with a skin-specific T-cell homing receptor [15–18]. This hypothesis implies the existence of skin-specific T cells in the circulation, and we would predict that whereas no current evidence is available to support this hypothesis, monoclonal antibodies to skin specific surface molecules on T-cell subsets will eventually be discovered, thus allowing discrimination of such cells, both in the blood and in the peripheral lymph nodes. When this discovery occurs, it may be possible to effectively treat a wide variety of inflammatory skin diseases by focusing on the specific molecular interaction between skin-specific T cells and their respective cutaneous endothelial cell receptor/ligand. Also, it remains for the future to further understand why the dermal microenvironment is not conducive towards T-cell activation and cell cycling (possibly because of excessive transforming growth factor-beta [19]), and to determine exactly how the epidermal compartment switches on T-cell cycling and which lymphokines (besides IFN-γ) the T cells produce under such conditions.

These results also suggest that the location of the relevant etiologic agent stimulating the initial activation and proliferation of T cells in psoriasis may actually reside beyond the skin, and that closer examination of other extra-cutaneous organ systems such as lymph nodes, gastrointestinal tract, etc., for identification of the etiologic agent is indicated. The spatial microenvironmental relationship between T cells, keratinocytes, dermal dendocytes, and endothelial cells may help our understanding of the complex molecular interactions involving IFN-γ, transforming growth factor-α, and epidermal growth factor receptor expression, which we have recently studied in psoriasis [20]. Indeed, we continue to dissect the molecular constituents of the psoriatic lesions into both their dermal and epidermal cellular components [21]. Whereas therapy directed solely at the skin may temporarily improve the local inflammatory cutaneous reaction, a more permanent therapeutic outcome and actual cure cannot be envisaged until all of the skin [22] in addition, perhaps, to the entire systemic circulation, is taken into consideration.

Finally, our current working model regarding the importance of inflammatory cell trafficking to the pathophysiology of psoriasis is illustrated in Fig 1, with particular emphasis on the central role of the dermal dendocyte. The focus on the dermal dendocyte is justifiable, because these cells are dramatically increased in psoriasis [23,24] and in many psoriatic lesions the most prevalent dermal mononuclear cell is the dermal dendocyte (even outnumbering T cells). The dermal dendocytes contain TNF-α immunoreactivity [21], which could initiate the inflammatory cellular cascade pictured in Fig 1 in response to a variety of endogenous and exogenous
stimuli. Whether known triggering factors for the induction of psoriasis, including HIV-1, lithium, stress, etc, lead directly to dermal dendrocyte TNF-α release awaits further study.

REFERENCES