The Molecular Basis of Lymphocyte Recruitment to the Skin: Clues for Pathogenesis and Selective Therapies of Inflammatory Disorders

Michael P. Schön,* Thomas M. Zollner,† and W. -Henning Boehncke‡

*Department of Dermatology, Otto-von-Guericke-University, Magdeburg, Rudolf-Virchow Center for Experimental Biomedicine and Department of Dermatology, Julius-Maximilians University, Würtzburg, Germany; †Schering AG, CRBA Dermatology, Berlin, Germany; ‡Department of Dermatology, Johann-Wolfgang-Goethe-University, Frankfurt, Germany

Spatial compartmentalization and tissue-selective localization of T lymphocytes to the skin are crucial for immune surveillance and the pathogenesis of various disorders including common inflammatory diseases such as atopic dermatitis or psoriasis, but also malignancies such as cutaneous T cell lymphomas. Cutaneous recruitment of lymphocytes is a highly complex process that involves extravasation, migration through the dermal connective tissue, and eventually, localization to the epidermis. An intertwined network of cytokines and chemokines provides the road signs for leukocyte migration, while various adhesion receptors orchestrate the dynamic events of cell-cell and cell-substrate interactions resulting in cutaneous localization of T cells. Selectively targeting the functions of molecules involved in this interplay promises exciting new therapeutic options for treating inflammatory skin disorders. ***J Invest Dermatol 121:951–962, 2003***

Tissue-specific localization of T lymphocytes is a requirement for immune surveillance in the skin and plays a key role in the pathogenesis of various diseases. T cells have been implicated in the pathogenesis of benign inflammatory skin conditions, such as psoriasis, various forms of eczema, vitiligo, alopecia areata, drug-induced eruptions, or lichen planus (Groves and Kupper, 1996; Robert and Kupper, 1999), but are also pivotally involved in cutaneous malignancies, such as T cell lymphomas (Knowles and Halper, 1982). Insight into mechanisms of T cell recruitment to the skin is therefore essential for an understanding of the pathophysiology and potential therapies of these and other skin disorders. Given that tissue-selective trafficking of T lymphocytes is mediated by a multitude of complex and intricate interactions of cytokines and chemokines with adhesion receptors (Kunkel and Butcher, 2002), described here according to their molecular nature and function, these molecules are crucial for the site-specific recruitment and functions of T cells.

ADHESION MOLECULES: MOLECULAR LADDERS FOR CUTANEOUS LYMPHOCYTE RECRUITMENT

Rolling as the initial step of lymphocyte localization: the first contact The first steps of T cell localization to all tissues include leukocyte tethering and rolling on the vessel wall (schematically depicted in **Fig 1**), transient adhesive interactions that are mediated primarily by selectins (Groves *et al*, 1991; Shimizu *et al*, 1991; von Andrian *et al*, 1991; Smith *et al*, 1993; Springer, 1994; Butcher and Picker, 1996). Selectins are single-chain transmembrane adhesion molecules characterized by a lectin-like domain that binds to carbohydrate ligands displayed on glycoprotein scaffolds (Feizi, 2001; Varki, 1994; Ley, 2001). Activated endothelial cells, on the one hand, rapidly mobilize P-selectin (CD62P) to the cell surface (Bonfanti and Furie, 1989; McEver and Beckstead, 1989), while expression of E-selectin (CD62E) is transcriptionally regulated (Cotran and Gimbrone, 1986; Bevilacqua and Stengelin, 1989). Chemokine interactions with their receptors can modulate the functions of selectins very rapidly (Grabovsky *et al*, 2002). The pivotal role of P- and E-selectin for leukocyte rolling has been confirmed by a large variety of experimental approaches interfering with adhesive interactions of selectins and their carbohydrate ligands (Carlos and Harlan, 1994; Todderud *et al*, 1997). A number of studies have demonstrated overlapping and mutually compensating functions of selectins (Labow *et al*, 1994; Jung and Ley, 1999; Collins *et al*, 2001). Consistent with these studies, a function-blocking antibody specifically directed against E-selectin did not alleviate psoriasis in a recent clinical trial (Bhushan *et al*, 2002). This clinical observation suggested that some selectin-mediated functions may be redundant and that interfering with a single selectin alone is not sufficient to interrupt the inflammatory chain in certain diseases. This notion is further supported by efomycines, recently discovered specific small-molecule inhibitors of both E- and P-selectin functions. Blocking both E- and P-selectin by efomycine M significantly inhibited rolling of T lymphocytes on cutaneous microvessels and markedly alleviated chronic inflammatory skin conditions in a T cell-mediated murine model of psoriasis as well as in human psoriatic skin transplanted onto *scid/scid* mice (Schön *et al*, 2002).

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Reprint requests to: Michael P. Schön, MD, Rudolf-Virchow Center for Experimental Biomedicine and Department of Dermatology, Julius-Maximilians University, Versbacher Str. 9, 97078 Würzburg, Germany. Email: Michael.Schoen@virchow.uni-wuerzburg.de

Abbreviations: CLA, cutaneous lymphocyte-associated antigen; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; LEEP-CAM, lymphocyte endothelial-epithelial cell adhesion molecule; Th_1, T-helper-1 (cells); TSLP, thymic stromal lymphopoietin; VCAM-1, vascular cell adhesion molecule-1; VLA-4, very late antigen-4.

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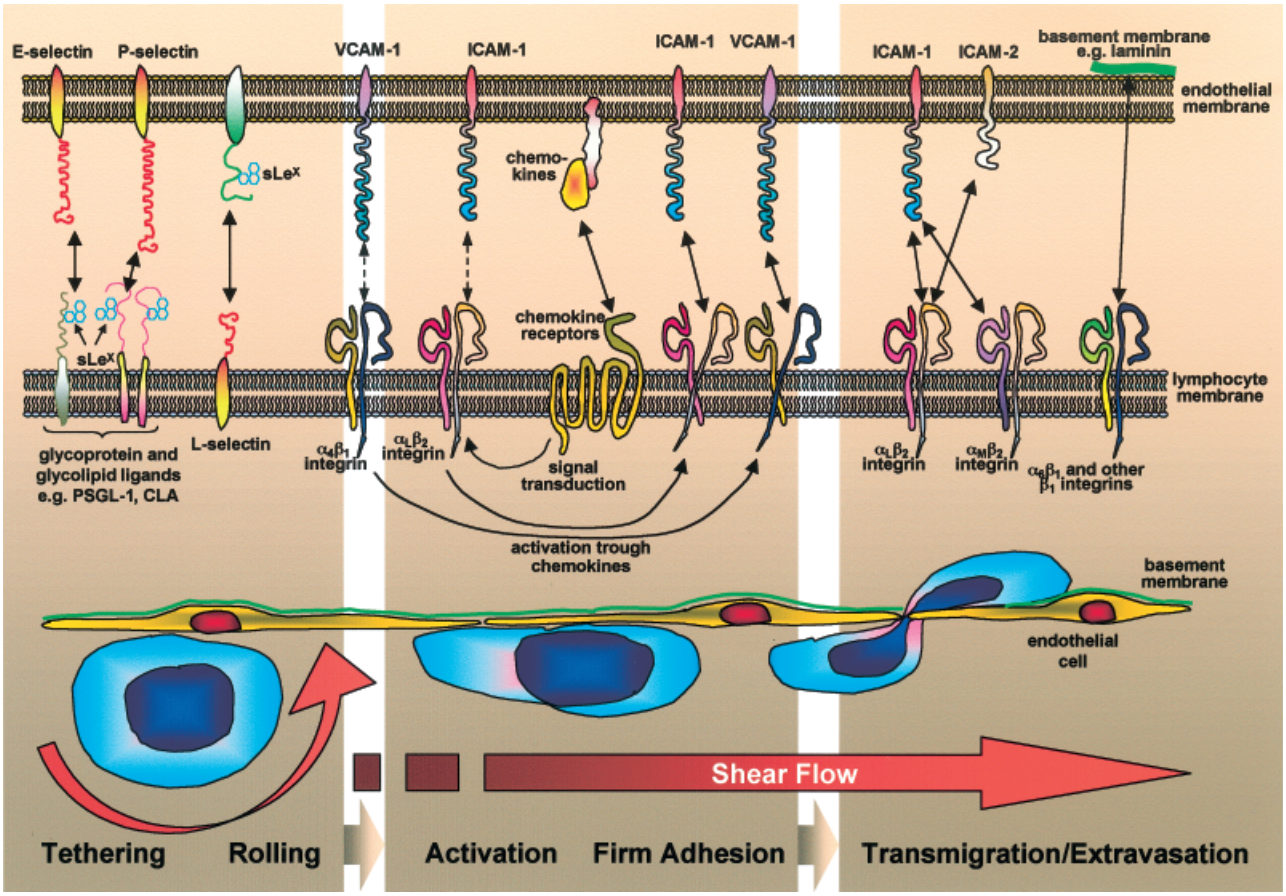

Figure 1. Adhesive interactions and chemokine-driven activation involved in lymphocyte extravasation in the skin. (*Bottom*) Key steps of interactions with the endothelial lining resulting in extravasation of lymphocytes. (*Top*) Selected adhesion molecules which mediate these events.

On the other hand, naive and central memory T cells express L-selectin (CD62L) that binds to endothelial cell selectin ligands (**Fig 1**). L-selectin ligands such as PNAd may be induced on dermal endothelial cells in chronic inflammatory skin disorders (Lechleitner *et al*, 1999; Hwang and Fitzhugh, 2001). The topographic distribution of L-selectin on the tips of microvilli of rolling leukocytes appears to be important for contact formation with endothelial ligands (Fors *et al*, 2001). It is thought that shedding of L-selectin, a proteolytic process mediated by metalloproteases (Condon *et al*, 2001; Zhao *et al*, 2001), also plays a role for proper lymphocyte rolling (Hafezi-Moghadam and Ley, 1999). Inhibition of L-selectin shedding results in increased LFA-1/intercellular adhesion molecule-1 (ICAM-1)-mediated firm adhesion and, consecutively, transmigration of lymphocytes (Hafezi-Moghadam *et al*, 2001), suggesting a regulatory function of the shedding process.

In addition, T cells express transmembrane glycoproteins bearing sialyl-Lewis^X (sLe^X) moieties, which function as E- and P-selectin ligands (Varki, 1994). T lymphocytes localizing to the skin express the sLe^X-bearing cutaneous lymphocyte-associated antigen (CLA), arising from specialized glycosylation of P-selectin glycoprotein ligand-1 (CD162) (Fuhlbrigge *et al*, 1997), which is thought to be involved in tissue-specific localization of cutaneous T cells (Picker *et al*, 1990, 1991). CLA-bearing T lymphocytes appear to extravasate preferentially through the endothelium of the superficial dermal plexus (Kunstfeld *et al*, 1997) suggesting topographic specialization of microvascular endothelial cells within the skin.

In addition to selectin-mediated rolling, very late antigen-4 (VLA-4, $\alpha_4\beta_1$-integrin, CD49d/CD29), a heterodimeric adhesion receptor of the integrin family that binds to the Ig-superfamily adhesion molecules vascular cell adhesion molecule-1 (VCAM-1) and mucosal addressin cell adhesion molecule-1 (**Fig 1**), has also been found to mediate rolling of certain leukocyte subsets (Berlin *et al*, 1995; Reinhardt *et al*, 1997; Singbartl *et al*, 2001). This involvement in leukocyte rolling is exerted in addition to its known function for firm adhesion (below) and is due, at least in part, to the topographic presentation of VLA-4 on microvilli of rolling cells, thus enabling the first contact to endothelial-bound counterreceptors (Berlin *et al*, 1995). VLA-4 affinity is thought to be rapidly upregulated upon T cell stimulation via signaling through the p56^{lck} Src kinase pathway (Feigelson *et al*, 2001), a process that may be important for the transition from rolling to firm adhesion. Although some aspects of the interplay of VLA-4- and selectin-mediated adhesive interactions involved in leukocyte rolling still remain to be unraveled, it appears that their relative contributions are influenced by tissue- and (micro)environment-specific factors and that there is some redundancy in their functions. In cutaneous inflammation in rats, all three receptors, E-selectin, P-selectin, and VLA-4, were required for rolling of memory T lymphocytes (Issekutz and Issekutz, 2002).

Firm adhesion and extravasation: commitment to leave the circulation Stimulatory effects exerted by a growing number of chemokines and other mediators initiate the subsequent adhesive steps of cutaneous lymphocyte localization (Schön and Ruzicka, 2001; Homey *et al*, 2002). After transient, selectin- and VLA-4-mediated rolling, leukocytes become activated (as outlined below) and firmly attach to the endothelium through adhesion of β_2-integrins, including LFA-1 (CD11a/CD18, $\alpha_L\beta_2$) or Mac-1 (CD11b/CD18, $\alpha_M\beta_2$), to immunoglobulin superfamily members, such as ICAM-1 (CD54) (Dustin *et al*, 1986; Griffiths

et al, 1989) (**Fig 1**). This mechanism appears to be of prime importance in various inflammatory skin conditions (Grabbe *et al*, 2002). In addition, β_1-integrins and their ligands, such as the $\alpha_4\beta_1$/VCAM-1 pair, are involved in leukocyte-endothelial cell binding (Groves *et al*, 1993). Proinflammatory cytokines, including interferon-γ, tumor necrosis factor-α, and interleukin (IL)-1 can increase T cell localization to inflammatory sites through induction of ICAM-1 and VCAM-1 (Griffiths *et al*, 1989; Barker *et al*, 1990; Groves *et al*, 1993; Petzelbauer *et al*, 1994). It is possible that additional mechanisms contribute to firm adhesion and endothelial transmigration of lymphocytes, similar to a novel mechanism proposed for the $\alpha_E\beta_7$-integrin within the intestinal lamina propria (Strauch *et al*, 2001), but such mechanisms in the skin remain to be unraveled.

Dermal localization: final destination for most cutaneous lymphocytes Once extravasated at cutaneous sites, lymphocytes utilize β_1-integrins to bind to and transmigrate through the dermal extracellular matrix (schematically depicted in **Fig 2**). These extracellular matrix receptors include the $\alpha_1\beta_1$-, $\alpha_2\beta_1$-, and $\alpha_5\beta_1$-integrins that bind to various extracellular matrix components such as collagen type I, fibronectin, chondroitin sulfate, laminin, or hyaluronans (Konter *et al*, 1989; Hemler, 1990; Hynes, 1992). In many inflammatory or malignant skin disorders dermal lymphocytes outnumber epidermal lymphocytes, suggesting that only a minority of infiltrating T cells have acquired the molecular armory to migrate into the cutaneous epithelium. Given that composition, fibril diameter, and three-dimensional arrangement of extracellular matrix molecules show site-specific variation (e.g., papillary dermis, reticular dermis, perivascular, or periadnexal areas may provide specific microenvironments) and may be altered profoundly in inflammatory states (Berthod *et al*, 2001), it appears likely that tissue-specific leukocyte localization and the distribution pattern characteristic for certain inflammatory skin disorders is modulated, at least in part, by such factors. Nevertheless, there is no direct evidence thus far to corroborate these hypotheses.

In addition to β_1-integrins, CD44, a hyaluronate receptor (Camp *et al*, 1993), and LFA-1, which may interact with an "adhesive path" formed by interstitial ICAM-1 (Nickoloff, 1988), appear to facilitate dermal localization of T cells. Binding to components of the epidermal basement membrane, such as collagen type IV and laminin, again appears to be mediated by β_1-integrins, including $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_3\beta_1$, and $\alpha_6\beta_1$ (Hynes, 1992). This adhesive interaction may be enhanced by keratinocyte-derived mediators, such as IL-7 (Wagner *et al*, 1999). In addition, T cells may utilize the $\alpha_3\beta_1$-integrin to bind to epiligrin within the basement membrane (Wayner *et al*, 1993).

EPIDERMAL T cell localization: destination for selected few In contrast to endothelial transmigration and dermal localization, we know relatively little about epidermal localization of T cells (schematically depicted in **Fig 2**). The epidermis of the skin is a multilayered, stratified, and polarized epithelium, whose different layers show distinct stages of differentiation and surface antigen expression. Another level of complexity is added by profound changes of the epidermal differentiation pattern under inflammatory conditions impacting on the ability of lymphocytes to localize to the epidermis. As a consequence, epidermal localization of lymphocytes appears to be a rather

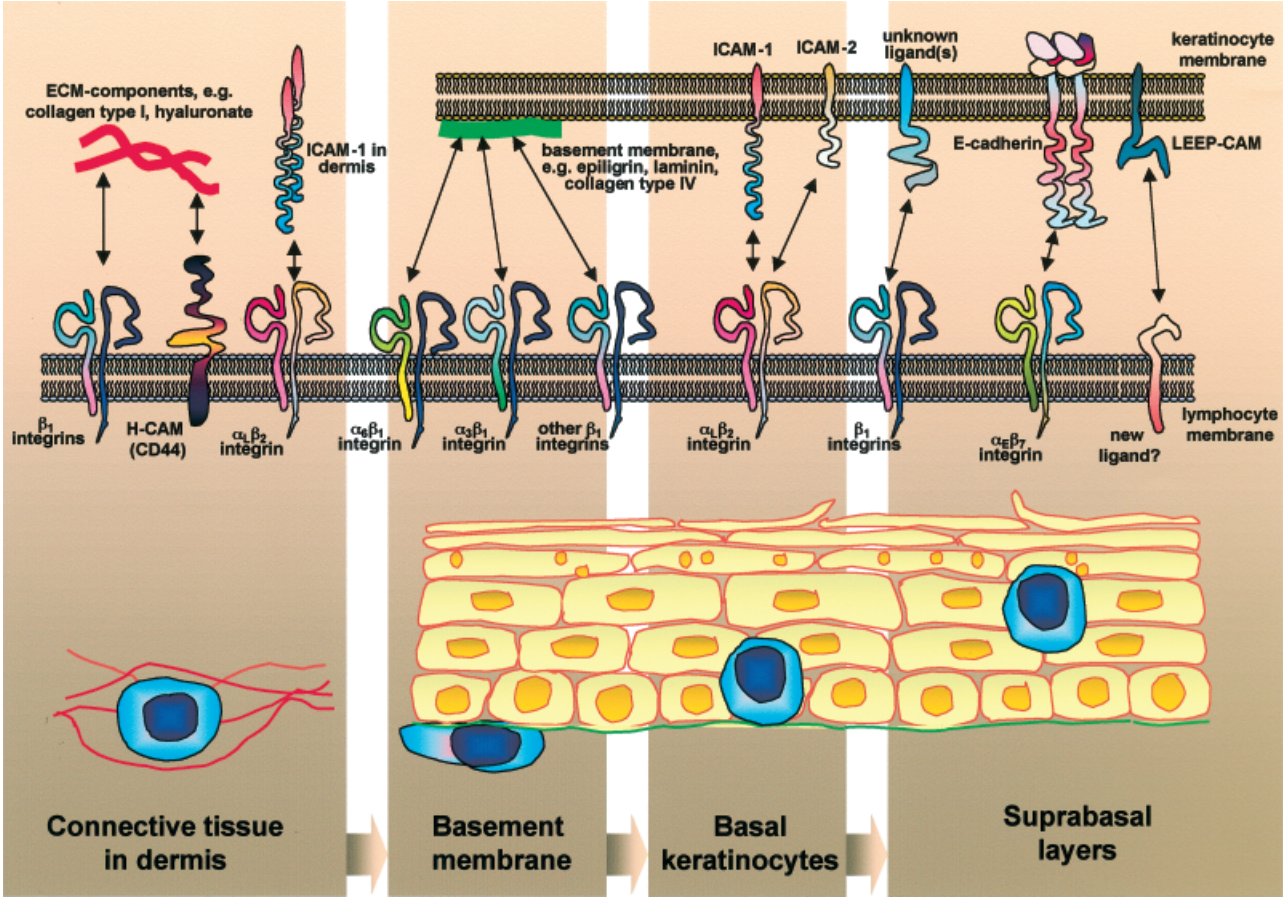

Figure 2. Overview of cellular events involved in dermal and epidermal localization of cutaneous lymphocytes. Similar to **Fig 1**, the *bottom* shows cellular interactions of infiltrating lymphocytes with resident extracellular matrix components and cells, whereas the *top* represents adhesion molecules involved in these interactions.

complex process in itself, and certain lymphocyte subsets may specifically localize only to particular layers of the epidermis. This is, at least to some extent, reflected by the expression pattern and spatial distribution of adhesion molecules involved in interactions with lymphocytes.

Although many extracellular ligands for β_1-integrins are not expressed beyond the epidermal basement membrane (Konter *et al*, 1989), β_1-integrins have been implicated in T cell epidermotropism based upon expression by intraepidermal T lymphocytes (Sterry *et al*, 1992). An example is the $\alpha_1\beta_1$-integrin, whose expression by lymphocytes appears to be associated with epidermotropic forms of cutaneous T cell lymphoma, but whose functional contribution to the process of epidermotropism remains unclear (Bank *et al*, 1999).

Induced by proinflammatory cytokines, there is epidermal *de novo* expression of ICAM-1 in inflammatory skin disorders, such as psoriasis (Dustin *et al*, 1988; Griffiths *et al*, 1989). Indeed, *in vitro* studies suggested that ICAM-1/LFA-1 interactions mediate binding of activated T cells to inflamed epidermis (Kashihara-Sawami and Norris, 1992). Given that ICAM-1 is induced primarily in basal keratinocytes upon inflammatory stimuli, it appears to be involved in the initial steps of epidermal T cell localization just beyond the epidermal basement membrane. Nevertheless, this may not be the only mechanism, because constitutive epidermal expression of ICAM-1 in transgenic mice did not result in spontaneous epidermal T cell infiltration (Williams and Kupper, 1994), and expression and spatial distribution of ICAM-1 and LFA-1 do not correlate in many cases of epidermotropic lymphocyte infiltration (Griffiths *et al*, 1989; Olivry *et al*, 1995). In addition, the interaction of LFA-1 expressed by lymphocytes with ICAM-3, which is constitutively expressed by epidermal keratinocytes, may be involved in epidermal T cell localization (Griffiths *et al*, 1995).

The recently identified glycoprotein lymphocyte endothelial-epithelial cell adhesion molecule (LEEP-CAM), whose ligand on T lymphocytes has not been identified yet, may also be involved in epidermal T cell localization (Shieh *et al*, 1999). The LEEP-CAM molecule, a 90- to 115-kDa cell surface glycoprotein, is a novel receptor mediating T cell adhesion to epithelial cells in static cell-to-cell adhesion assays *in vitro* (Shieh *et al*, 1999). It is expressed constitutively in the suprabasal epidermal layers, but is not expressed on T cells. Both its expression pattern and its adhesive functions *in vitro* make LEEP-CAM an interesting candidate molecule for mediating epidermal T cell localization. Because LEEP-CAM is expressed exclusively within suprabasal epidermal layers both in normal and in inflamed skin (Shieh *et al*, 1999), it appears to be the first adhesion receptor known thus far to preferentially mediate suprabasal localization of T cells.

Another player contributing to epidermal localization of certain T cell subsets is the α_E(CD103)β_7-integrin, which is expressed by the vast majority of intestinal intraepithelial T lymphocytes (Parker *et al*, 1992) and is thought to contribute to localization of diffusely distributed T cell subsets to the mucosal epithelium through binding to E-cadherin (Cepek *et al*, 1994; Karecla *et al*, 1995). Indeed, when integrin α_E(CD103)-deficient mice were studied, they exhibited a reduced number of mucosal intraepithelial T cells (Schön *et al*, 1999). Nevertheless, there is growing evidence that α_E(CD103)β_7 functions are not restricted to T cells within the intestinal mucosa, but extend to intraepithelial T lymphocytes in other tissues, whose epithelia express E-cadherin, the ligand for α_E(CD103)β_7 (Agace *et al*, 2000). Putative alternative ligand(s) for $\alpha_E\beta_7$ on epithelial (Brown *et al*, 1999) and endothelial cells (Strauch *et al*, 2001) have been proposed but not positively identified yet. In the skin, expression of α_E(CD103)β_7 has been demonstrated on epidermal T lymphocytes in some forms of inflammatory disorders (de Vries *et al*, 1997; Walton *et al*, 1997) and cutaneous T cell lymphomas (Simonitsch *et al*, 1994; Schechner *et al*, 1999). In a recent study, preferential expression of α_E(CD103)β_7 was demonstrated on basal and suprabasal epidermal CD8+ T cells within psoriatic lesions, consistent with the expression of its ligand, E-cadherin (Pauls *et al*, 2001), and there is no association of $\alpha_E\beta_7$ expression with expression of the chemokine receptor CCR4, which is expressed preferentially on dermal but not epidermal T cells (Rottman *et al*, 2001). Expression of α_E(CD103)β_7 was detected on very few dermal T cells in psoriatic lesions as well as in the peripheral blood. Thus, α_E(CD103)β_7 appears to be induced on CD8+ T cells *in situ* upon entering the epidermis, consistent with the focal expression of transforming growth factor-β_1 directly underneath the epidermis. In further support of an involvement in T cell epidermotropism, α_E(CD103)β_7 could be specifically upregulated by transforming growth factor-β_1 on $CD8^+$ T cells where it mediated adhesion to psoriatic epidermis as well as to cultured keratinocytes (Pauls *et al*, 2001).

CYTOKINES AND CHEMOKINES: THE ROAD SIGNS FOR T CELL TRAFFICKING

T cell trafficking does not only involve membrane-bound adhesion molecules but also a variety of soluble or membrane-borne chemotactic factors. A tissue-specific close functional interaction between such factors and adhesion molecules is a prerequisite for localization of lymphocytes to inflamed tissues. These factors include chemokines, small polypeptides whose biologic role in various tissues and disorders is a hot area of actively ongoing research. Presumably emerging during phylogenesis as a system to mediate innate immune cell trafficking and cell movement during morphogenesis, repeated gene duplication, and modification established a rich repertoire of chemokines and their respective receptors in more advanced vertebrate phyla. Selective pressure imposed on host defense by unique pathogen-commensal microbe relationships created a robust system of overlapping ligands and receptors that protects the host (Gerard and Rollins, 2001). This system is particularly well suited to complement the molecular ladder in the process of lymphocyte recruitment provided by adhesion molecules for at least three reasons: First, chemokines exist as a large multigene family, and the use of distinct chemokines at specific anatomic sites contributes to specificity of leukocyte recruitment. Second, they act via G-protein-coupled receptors that are known to mediate rapid cellular responses. Third, their association with glycosaminoglycans allows efficient presentation at the luminal surface of the endothelium (Ebnet and Vestweber, 1999).

The known chemokine system in humans currently comprises some 50 ligands and 20 G-protein-coupled receptors. Structurally, the ligands can be divided into two major subfamilies on the basis of the arrangement of the two N-terminal cysteine residues, depending on whether they have an amino acid between them (CXC) or are adjacent (CC). Two other classes of chemokines comprise lymphotactin (C), lacking cysteines one and three of the typical chemokine structure, and fraktalkine (CX3C) with three amino acids between the first two cysteines (Zlotnik and Yoshie, 2000). Constitutive and inducible chemokines have been described: The former are involved in basal leukocyte trafficking and forming the architecture of secondary lymphoid organs, whereas the latter recruit leukocytes in response to physiologic stress. Expression of inducible chemokines can be elicited by almost any stimulus that alters cellular homeostasis, and mRNA-encoding-induced chemokines can increase over 300-fold within a few hours of activation. Thus, inducible chemokines can be regarded as a vertebrate cellular "SOS response" that recruits leukocytes to areas of tissue injury (Gerard and Rollins, 2001).

Expression of chemokines and their receptors can easily be documented in disorders associated with leukocyte infiltration. Nevertheless, to date the only human disease for which there is a clear-cut evidence for an association with the chemokine system is HIV infection. In all other cases, definitive roles for chemokines in human pathology either are indirect or have been inferred from animal models. With this notion in mind, data on the

involvement of the chemokine system in lymphocyte recruitment to the skin are now discussed.

Chemokines mediate transition of T cells from rolling to firm adhesion As described above, the first step of T cell recruitment to the skin is the transition into a rolling motion along the vessel wall, mediated by short-lived interactions between selectins and their ligands. Subsequently, T cells must rapidly arrest on the vessel wall after a short period of rolling and resist detachment by disruptive shear flow, a task exclusively mediated by integrins. A unique feature of integrins is that their activity is dynamically regulated independent of their level of surface expression (Hynes, 1992). Immune cells are therefore capable of constantly adapting their adhesive behavior toward ligands on matrix surfaces (Shimizu *et al*, 1999). To avoid nonspecific sticking to blood vessels, circulating leukocytes maintain their integrins in largely nonadhesive states. Once captured by selectins, rolling leukocytes come in close contact with a relatively wide area of endothelium, which can be sampled for activation signals. *In situ* activation of integrins by endothelium-displayed signals results in increased integrin avidity and serves as a reversible checkpoint for tethered leukocytes to successfully arrest on target endothelial sites before initiating diapedesis. Activation of integrin avidity can take place within fractions of seconds (Campbell *et al*, 1998; Grabovsky *et al*, 2000) and is triggered by endothelium-displayed chemokines (Mackay, 2001). The rapid nature of chemokine stimulation of integrin-mediated adhesion under shear flow is ideally suited to bridge selectin-mediated rolling to firm integrin-mediated adhesion in various multistep adhesive cascades (Bargatze *et al*, 1995; Johnston *et al*, 1996).

It is overall well accepted that chemokines can contribute to leukocyte capture on the endothelial cell wall through triggering the avidity of leukocyte integrins. In apparent contrast to this function, a novel, antiadhesive, G-protein-independent, downregulatory activity of chemokines has been described recently that results in destabilizing L-selectin-mediated leukocyte rolling (Grabovsky *et al*, 2002). Whether or not chemokines may also have antiadhesive properties mediated via E- or P-selectin is currently not known.

Although chemokines released into the circulation are expected to activate leukocyte integrins systemically and transiently (Constantin *et al*, 2000; Chan *et al*, 2001), integrin activation by serum chemokines at locations remote from the target is unlikely to control leukocyte trafficking to specific sites. Instead, this process is determined by chemokines displayed *in situ*. Retention of soluble chemokines at the endothelial surface and presentation to leukocytes can be achieved by the thick endothelial glycocalyx which is rich in proteoglycans. These could serve as anchoring structures for chemokines, because the latter contain binding sites for heparin/heparan sulfate glycosaminoglycans (Anderson and Shaw, 1993; Proudfoot *et al*, 2001). The chemokines displayed are transported to the respective sites by means of transcytosis; this has been demonstrated for chemokines at intestinal and cutaneous sites alike (Middleton *et al*, 1997; Baekkevold *et al*, 2001; Homey *et al*, 2002).

The establishment of integrin-mediated firm adhesion of leukocytes to endothelial cells results from a rapid series of sequential and partially overlapping steps, only some of which require active participation of chemokines. The first step in avidity generation involves preformed integrin clustering on the leukocyte surface (Lub *et al*, 1997), preformed conformational states conferring variable affinity to ligands (Feigelson *et al*, 2001), or ligand-driven integrin clustering events (Yauch *et al*, 1997). Subsequently, upon encounter of the proper chemokine at the integrin-mediated contact, conformational changes in integrin ligand-binding domains can be induced. The molecular basis of integrin affinity regulation is still somewhat obscure. It is currently thought that disruption of key ionic interactions between membrane proximal cytoplasmic sequences on integrin subunits are involved (Takagi *et al*, 2001). Concomitant with chemokine-induced conformational alterations, integrin microclustering can be triggered by chemokines through effectors acting via G-protein-coupled receptors (Constantin *et al*, 2000; Grabovsky *et al*, 2000). In addition to chemokines, endothelial ligands to integrin-associated receptors may further enhance integrin avidity at dynamic contacts. An example for this effect is the enhancement of VLA-4-dependent lymphocyte adhesiveness to VCAM-1 under shear flow by rapid interactions between CD47 (a β_3-integrin-binding pentaspan) and endothelium-associated CD47 ligands like thrombospondin and signal regulatory protein 1α (SIRP1α) (Ticchioni *et al*, 2001). Next, integrins distal to the original endothelial adhesive zone established by the arrested leukocyte undergo patching in response to chemokine-triggered signals, again mediated via G-protein-coupled receptors (Constantin *et al*, 2000). Finally, integrin outside-in signaling is promoted at the leukocyte contact with the endothelial integrin ligands through anchorage to the actin cytoskeleton and a build-up of integrin complexes. These "adhesiosomes" link integrin occupancy to actin remodeling and microtubule reorganization, which in turn are key regulatory systems in cell spreading and contractility on endothelial surfaces (Sanchez-Madrid and del Pozo, 1999).

The general mechanisms mediating the transition from rolling to firm adhesion appears to be remarkably well preserved among different leukocyte types. It is the expression pattern of chemokines and their receptors which determines the type of cell that is attracted. This pattern is regulated under the influence of the local cytokine milieu: interferon-γ induces a number of chemokines that act to recruit monocytes, neutrophils, and T-helper-1 (Th_1) lymphocytes, whereas IL-4 and IL-13 induce CCL2, CCL11, CCL17, and CCL22, which leads to a Th_2-dominated pattern of cell recruitment (see **Table I**), with IL-4 and interferon-γ capable of antagonizing each other's chemokine induction (Bonecchi *et al*, 1998). Under most circumstances, only activated effector lymphocytes respond to inflammatory chemokines, because naive cells typically do not express the respective receptors (Syrbe *et al*, 1999). Similar to the chemokines, chemokine receptors, too, are regulated by a variety of inflammatory cytokines. Examples comprise the induction and maintenance of T cell expression of CCR1, CCR2, and CXCR3 by IL-2 or suppression of CCR5 expression by IL-10.

Given the redundancy within the chemokine system, it is not surprising that numerous chemokines exhibit roles in leukocyte trafficking which overlap at least in part (see **Table I**). With regard to T cell trafficking to inflamed skin, recent studies have highlighted the key role of two particular pathways, namely, the interactions between the chemokines CCL17 and CCL27 with their respective receptors, CCR4 and CCR10 (**Table I**). Increased expression of CCR4 was demonstrated in some forms of cutaneous T cell lymphoma and may play a role in localization through interaction with its ligands, TARC/CCL17 and MDC/CCL22 (Ferenczi *et al*, 2002). In a mouse model for delayed-type hypersensitivity, a supportive role of both CCR4 and CCL27 for T cell homing to the skin was demonstrated (Reiss *et al*, 2001). CCL27 is a skin-associated CC chemokine primarily expressed by basal keratinocytes in normal epidermis and throughout the epidermis in skin lesions from patients with atopic eczema as well as psoriasis (Kakinuma *et al*, 2003), from where it is released into the dermis; it is also seen on both the abluminal as well as the luminal sides of endothelial cells of the superficial dermal plexus (Homey *et al*, 2002). Skin-infiltrating lymphocytes are characterized by the expression of CCR10, the receptor for CCL27. Utilizing mouse models, it has recently been demonstrated that lymphocytes can be attracted by intracutaneous injection of CCL27 and that lymphocyte recruitment to the skin is impaired following neutralization of CCL27-CCR10 interactions (Homey *et al*, 2002). The role of CCR4 in T cell homing to the skin is supported by studies investigating normal and inflamed human tissues, including samples from atopic dermatitis (Kakinuma *et al*, 2001; Rottman *et al*,

Table I. Chemokines and their receptors involved in lymphocyte recruitment

Ligand(s)	Receptor(s)	Cellular distribution	Role in T cell trafficking
CXCL9, 10, 11	CXCR3	T cells ($Th_1 > Th_2$), B cells, NK cells	Recruitment of lymphocytes to Th_1-type inflammatory sites including CNS and intestine
CXCL12	CXCR4	Progenitor cells, lymphocytes, monocytes, macrophages, DCs	Thymocyte homing, early recruitment of T cells to inflamed lung
CXCL13	CXCR5	B cells, memory T cells	Lymphocyte migration to B cell follicles
CXCL16	CXCR6	Memory T cells	Recruitment of Th_1 cells to inflamed sites
CCL1, 4	CCR8	Th_2 cells	T cell recruitment to Th_2-type inflammatory sites
CCL3, 4, 5	CCR5	Progenitors, Th_1 cells, monocytes, macrophages, DCs	Recruitment to Th_1-type inflammatory sites
CCL3, 5, 7, 14, 15, 16, 23	CCR1	Memory T cells	Recruitment to most types of inflammation
CCL5, 7, 8, 13, 15, 24, 26	CCR3	Eosinophils, basophils, mast cells, T cells	Recruitment to Th_2-type inflammatory sites including lung and skin
CCL17, CCL22	**CCR4**	**T cells**	**Recruitment of T cells ($Th_2 > Th_1$) to inflammatory sites including lung and skin, cutaneous T cell lymphoma**
CCL20	CCR6	T cells, macrophages	Endothelial arrest of some memory T cells
CCL19, 21	CCR7	T cells, B cells, DCs	Homing to secondary lymphoid organs
CCL25	CCR9	$\alpha_4\beta_7+$ T cells, DCs, macrophages, thymocytes	T cell homing to small intestine, thymocyte selection
CCL27	**CCR10**	**CLA + T cells**	**T cell homing to skin**

Note. Boldface denotes that these chemokines and chemokine receptors seem to be most relevant with regard to T cell recruitment to cutaneous inflammation.

2001; Kunkel *et al*, 2002). In addition, the pair CCL20/CCR6 appear to be relevant for endothelial arrest of some memory T cells in the cutaneous microvasculature (Homey *et al*, 2000a; Fitzhugh *et al*, 2000).

Skin-homing T cells in humans are currently best identified by the skin-homing receptor CLA (see above), but a monoclonal antibody to CCR10 (Homey *et al*, 2002) labels only one third of these cells, suggesting the existence of additional chemokine receptors for skin homing. Based on recent data one can assume that at least one of the CCR4- or CCR10-mediated pathways must be functional to effectively recruit T cells to inflamed skin, but their involvement is overlapping inasmuch that either one is permissive (Reiss *et al*, 2001; Mackay, 2002).

A role for chemokines in lymphocyte transendothelial migration and migration into the skin In contrast to adhesion molecules, whose functions can be assigned to the different phases of lymphocyte recruitment to the skin, the exact role of chemokines throughout this process is rather difficult to define. This is, at least in part, due to the fact that chemokines tend to form gradients: Being highly basic proteins, secreted chemokines are immobilized on cells or extracellular matrix surfaces by interacting with negatively charged glycosaminoglycans. Of note, chemokines show differences regarding affinities to different types of glycosaminoglycans (Kuschert *et al*, 1999). The latter can vary depending on cell type, location, and inflammatory status. Selective immobilization at a given site may therefore be a regulatory step determining chemokine function in certain tissues or inflammatory states. In addition, oligomerization of chemokines occurs on glycosaminoglycans and may provide a mechanism for gradient formation (Hoogewerf *et al*, 1997). Chemokines near their sites of production may form oligomers of higher order on endothelial or extracellular matrix glycosaminoglycans, thereby creating and preserving higher chemokine concentrations near the initiating inflammatory or trafficking stimulus. This causes the leukocyte to move up the chemokine gradient and toward the relevant site (Olsen and Ley, 2002). In confirmation of this concept, it has indeed be demonstrated that leukocytes are capable to sense several distinct chemokine gradients and can navigate accordingly (Foxman *et al*, 1999).

The process of transendothelial migration is still poorly understood. Transendothelial migration comprises the crossing of adherent blood-borne cells in a nonproteolytic manner at or near their original contact site with the endothelium. Using cytokine-activated endothelial monolayers reconstituted with chemokines it has been demonstrated that endothelial-bound chemokines promote massive lymphocyte transendothelial migration (Cinamon *et al*, 2001). This process requires continuous exposure of lymphocytes to fluid shear. Thus, apical endothelial chemokines, besides triggering lymphocyte capture to the endothelial surface, are also relevant regarding postarrest events that promote lymphocyte transendothelial migration (Cinamon *et al*, 2001).

Once they have reached the skin, infiltrating lymphocytes can navigate along established chemokine gradients as outlined above. These gradients may vary among chemokines depending on their respective sources. With regard to the two apparently most important chemokine pathways for T cell homing to the skin, namely the CCL17–CCR4 (which also binds to CCL22) and the CCL27–CCR10 pathways, these sources differ: On the one hand, CCL17 is constitutively expressed and hyperinducible on cutaneous venules (and some other systemic venules), and upregulation of constitutive expression is also observed in some human fibroblast and keratinocyte cell lines (Yu *et al*, 2002). On the other hand, CCL27 is produced by keratinocytes but neither fibroblasts nor dermal microvascular endothelial cells (Homey *et al*, 2000b, 2002). CCL27 is therefore most likely secreted into the papillary dermis, immobilized on the extracellular matrix, and displayed on the surface of endothelial cells following transcytosis (Homey *et al*, 2002). Thus, it might be hypothesized that the CCL17–CCR4 pathway recruits lymphocytes as far as into the dermis, whereas the CCL27–CCR10 pathway may guide them all the way up into the epidermis. In line with this hypothesis are the observations that CCR4 + T cells preferentially populate the dermal compartment and not the epidermis (Rottman *et al*, 2001), while CCR10 + lymphocytes were detected within both dermis and epidermis (Homey *et al*, 2002). Nevertheless, there is experimental evidence that blockade of CCL27 alone is sufficient to block cutaneous inflammation (Homey *et al*, 2002), suggesting a complex interaction of different chemokines.

EMERGING MOLECULAR TARGETS: BRINGING UNDERSTANDING OF CUTANEOUS T CELL RECRUITMENT TO PATIENTS

The concept that T cells play a pivotal role in many inflammatory disorders, such as psoriasis, contact dermatitis, or atopic dermatitis, has been corroborated in human diseases as well as in

numerous animal models (Herz *et al*, 1998; Schön, 1999; Girolomoni *et al*, 2001; Asadullah *et al*, 2002a). Indeed, the number of T cells infiltrating the skin may be correlated with disease activity which has been demonstrated most elegantly for psoriasis (Krueger *et al*, 1995). Therefore, interfering with the multistep process directing T cells into the cutaneous compartments appears to be an attractive target to treat inflammatory skin diseases, an approach that is pursued by several pharmaceutical companies. However, there are several *challenges* that may make this approach very complex and unpredictable, and this is mirrored by the fact that most of the previous approaches were not satisfying in clinical trials such as trials using the sialyl Lewis^X-mimetic cylexin or an anti E-selectin monoclonal antibody (Bhushan *et al*, 2002). Some examples of these challenges are:

1. Redundancy Although it was initially believed that CLA expressed by skin-homing T cells is predominantly an E-selectin ligand (Berg *et al*, 1991; Rossiter *et al*, 1994), it is now clear that the carbohydrate moiety responsible for tethering and rolling of T cells along the skin microvasculature also binds to P- (Labow *et al*, 1994) and L-selectin (Jung and Ley, 1999; Collins *et al*, 2001). In fact, the overlap of the selectin functions is considerable (Jung and Ley, 1999; Labow *et al*, 1994). Although L-selectin is not expressed by endothelial cells, endothelial cells of chronically inflamed skin can express PNAd, which serves as a ligand for L-selectin expressed by either naive or central memory T cells. This may allow rolling of E-selectin ligand/CLA-negative T cells along the skin microvasculature. Furthermore, L-selectin-mediated rolling appears to be increasingly important in situations in which functional E- and P-selectin ligand expression is reduced or blocked by small molecules (Alon and Feigelson, 2002; Dwir *et al*, 2002). Another possibility for E-selectin ligand-negative T cells to roll along the endothelial lining is the formation of clusters with activated platelets. This has been demonstrated initially for lymph nodes (Diacovo *et al*, 1996, 1998) but holds also true for the skin (Ludwig *et al*, 2001). Even in the complete absence of selectins or selectin ligands residual rolling can be mediated via the interaction of T cell-expressed VLA-4 with endothelial VCAM-1 in the cremaster model (Jung and Ley, 1999). *In vitro*, however, it was found that CLA engagement is required for using the VLA-4/VCAM-1 pathway because the CLA/E-selectin and the VLA-4/VCAM-1 pathways were involved sequentially (Santamaria Babi *et al*, 1995). Redundancy may also be a major problem at the level of chemokine–chemokine receptor interaction (Zlotnik and Yoshie, 2000; Onuffer and Horuk, 2002).

2. Specificity Although it has been known for a long time that the E- and P-selectin ligand CLA is responsible for T cell trafficking into skin, interactions of E- and P-selectin with their T cell-expressed ligands are not specific for the skin. Therefore, interfering with E- and P-selectin-mediated interactions may result in immunosuppression in organs other than the targeted skin such as the intestine or the lymph nodes (Lowe, 1997; Smithson *et al*, 2001; Schön *et al*, 2002). The same holds true for chemokines, because CCR4 is also involved in leukocyte trafficking to the lung, and CCR10 binds not only CCL27

Table II. Inhibitors of selectin-function targeting lymphocyte rolling along the endothelial lining

Compound	Company	Status	Targeted indication/comment	Reference(s)
Small molecules				
CY-1503	Cytel Corp.	Inactive	Reperfusion injury of lung and heart, ischemic liver injury, sepsis-induced lung injury; carbohydrate sialyl Lewis^X analog; $t_{1/2}$ 10–30 min; ineffective in several clinical studies	Kerr *et al* (2000)
BMS-190394	BMS	Inactive	Delayed-type hypersensitivity, immune-complex arthus reaction; structural sulfatide analog, inhibitor of E-, P-, and L-selectin; no development has been reported since 1997	Birnbaum *et al* (1997)
Not known	Aventis	Inactive	Program stopped	Marinier et al (2001)
OC-229648	Ontogen Kanebo	Inactive	Atopic dermatitis; carbohydrate E-, P-, and L-selectin inhibitor	
Efomycine M	None	Preclinical	Psoriasis, inflammatory bowel disease; E- and P-selectin antagonist, efficacious in animal models	Schön *et al* (2002)
ESA-2	Novartis	Inactive?	Leukocyte rolling in TNFα-stimulated mouse cremaster; E-selectin inhibitor suppresses CCL22-mediated Th2 skin homing IC50 (E-sel) 36 μM	Biedermann *et al* (2002); Bantely and Ernst (2001); Thomson *et al* (1993); Thoma *et al* (2001)
OJ- R9188	Nippon Organon	Phase I/II	Psoriasis, delayed-type hypersensitivity, ovalbumin-induced skin inflammation, thioglycolate-induced peritonitis; Pan selectin inhibitor (IC_{50} in low μM range) with insufficient response in Phase I/II study for psoriasis	Ikegami-Kuzuhara *et al* (2001)
TBC-1269	Texas Biotechnology	Phase I/II	Psoriasis, ischemic renal failure, reperfusion heart injury, antigen-induced airway hyperresponsiveness; efficacious in open-label study in psoriasis	Abraham *et al* (1999); Anaya-Prado *et al* (2002)
Antibodies				
EP-5C7 HuDREG-55	Protein Design Labs	Phase I	Bispecific monoclonal antibody against E- and P-selectin	Berg *et al* (1995); He *et al* (1998)
HuDREG-200	Protein Design Labs	Phase Ib	Psoriasis; no results reported	
EL-246	LygoCyte	Preclinical	E- and L selectin antibody	Carraway *et al* (1998)
CDP-850	Celltech	Phase II	Psoriasis; E-selectin mAb, not effective in phase II trial	Bhushan *et al* (2002)
Others				
rhPSGL-1 Ig	Genetics Institute	Phase II	Acute myocardial infarction; stopped owing to disappointing results from phase II study	Khor *et al* (2000)
LD201t1	Wyeth NeXStar	Preclinical	Oligonucleotide inhibitor of L-selectin binding effective in SCID human model (nM IC_{50})	Hicke *et al* (1996)

Abbreviations: rhPSGL-1 Ig, recombinant human P-selectin glycoprotein ligand-1 immunoglobulin; TNFα, tumor necrosis factor-α.

produced by keratinocytes but also CCL28 produced by intestinal epithelial cells.

3. Unexpected effects Although a prominent role of the fucosyltransferase FucT-VII for homing and immune functions of T cells in the skin has been demonstrated in mice, the role of FucT-VII has been challenged in humans recently as a nonfunctional missense mutation had no effect on leukocyte rolling along E- and P-selectin (Bengtson *et al*, 2002). Another unexpected effect may relate to a recently identified regulatory activity of chemokines that results in antiadhesive, G-protein-independent destabilization of L-selectin-mediated leukocyte rolling (Grabovsky *et al*, 2002). One can hypothesize that this novel function could result in paradoxically enhanced inflammation when chemokines are targeted. Nevertheless, no experimental data have been published thus far that conclusively demonstrate whether or not chemokines may have antiadhesive properties under certain conditions.

As outlined above, T cell trafficking during an inflammatory response begins with lymphocyte rolling along the vessel wall involving predominantly E- and P-selectin expressed by the endothelium with carbohydrate moieties such as sLe^x and CLA. Therefore, various approaches have been taken to interfere with this crucial initial step. As summarized in **Table II**, many of the programs searching for small-molecule inhibitors of the selectin family have been stopped, a fact that may reflect inherent difficulties in targeting this very initial step. There are several reasons, which are not mutually exclusive, why some compounds generated so far have not entered the clinic or failed in clinical trials: (1) low IC_{50} values (e.g., for cylexin); (2) unfavorable pharmacokinetic properties such as short $t_{1/2}$ (e.g., cylexin); (3) specificity for only one selectin (e.g., CDP-850) or a suboptimal combination of selectin specificities (e.g., EL-246); and (4) lability of selectin–selectin ligand interaction which is essential for allowing short-lived lymphocyte–endothelial interactions mediating T cell rolling (**Table II**).

Another approach aimed at targeting T cell rolling along the skin microvasculature is interfering with fucosyltransferase-VII and -IV, key enzymes in the generation of selectin–ligand carbohydrate moieties. The rationale behind this approach comes from the observation that selectin ligand activity is absent or reduced dramatically in FucT-VII single or FucT-IV and–VII double-knockout mice. *In vivo* relevance of this impaired function was implicated by markedly reduced cutaneous inflammatory responses in several models using animals deficient for one or both enzymes (Maly *et al*, 1996; Weninger *et al*, 2000; Homeister *et al*, 2001; Asadullah *et al*, 2002b). One such approach is interfering with expression of FucT-VII via inhibiting its transcription using NF-κB inhibitors such as the proteasome inhibitor PS-519 or antioxidants such as *N*-acetylcysteine (Zollner *et al*, 2002). A potential disadvantage of this approach is its low specificity, because interfering with the pleiotropic effects of NF-κB may have many other effects on the immune system. Another potential approach might be inhibition of FucT activity by small-molecule compounds. Because post-translational glycosylation of proteins by FucTs occurs in the Golgi apparatus, it might, however, be challenging to find small molecules penetrating both the cell and the Golgi membrane. At least two different companies (Glaxo SmithKline, Kyowa Hakko Kogyo) have reported recombinant expression of FucT-VII protein (Shinkai *et al*, 1997; Smithers *et al*, 1997), suggesting that this latter approach is currently used as recombinant FucT-VII protein is necessary for performing high-throughput screening. In addition, panosialins A and B have been isolated as inhibitors of FucT-VII from the culture broth of *Streptomyces* sp., which inhibit FucT-VII activity and cell binding to immobilized selectin ligands *in vitro* (Shinoda *et al*, 1998).

Targeting the second step in the cascade of lymphocyte extravasation also appears very attractive because it has been reported recently that skin homing of lymphocytes is regulated by either two (CCR4 and CCR10) or only one chemokine receptor (CCR10) (Reiss *et al*, 2001; Homey *et al*, 2002). Given that many pharmaceutical companies have a long-standing experience with the generation of small-molecule inhibitors of chemokine receptor antagonists, and some of these compounds are in late preclinical or even early clinical stages (Onuffer and Horuk, 2002), inhibition of CCR4 and CCR10 appears attractive and feasible. Indeed, at least three companies (Millennium, Novartis, and Serono) report activity in the CCR4 field (Owen, 2001; Rottman *et al*, 2001; Soler *et al*, 2002). Expression of CCR4 is found on almost all CLA + T cells and is predominantly, albeit not exclusively, expressed on human and murine Th_2 cells. Almost all T cell clones generated from atopy patch tests express CCR4 when expanded in the presence of antigen plus IL-4 (Biedermann *et al*, 2002). This observation suggests that interfering with CCR4 using small molecules is attractive especially in Th_2-dominated skin diseases, such as atopic dermatitis. Whether or not inhibition of CCR10 will be beneficial is currently unclear; an antibody against CCR10 was ineffective in one murine model of contact hypersensitivity, but effective in another when using higher

Table III. Emerging drugs targeting integrin: immunoglobulin superfamily interactions

Target	Compound	Company	Status	Targeted indication/comment	References
CD11a	Efalizumab	Genentech/Serono	Phase III	Moderate to severe psoriasis; humanized monoclonal antibody against CD11a subunit of LFA-1	Gottlieb *et al* (2002); Papp *et al* (2001); Aruffo and Hollenbaugh (2001); Gniadecki and Calverley (2002)
	IC-747	ICOS	Phase II	Psoriasis; orally active synthetic compound able to block LFA-1 and ICAM-1	
ICAM-1	Alicaforsen ISIS-2302	ISIS	Phase II	Crohn's disease, rheumatoid arthritis, psoriasis; antisense phosphothioate oligonucleotide for topical application in Crohn's disease, rheumatoid arthritis, and psoriasis	Yacyshyn *et al* (2002); Maksymowych *et al* (2002); Robertson (1997)
VLA-4	Bio1211	Biogen	Phase I	Small molecule	Gniadecki and Calverley (2002); Aruffo and Hollenbaugh (2001); Shand and Forbes (2003)
	Antegren/ natalizumab	Biogen/Elan	Phase III	Multiple sclerosis, Crohn's disease; humanized monoclonal antibody against VLA-4 tested for multiple sclerosis and Crohn's disease	
LFA-3	Alefacept	Biogen	Phase III	Psoriasis; human recombinant LFA-3/IgG1 fusion protein interfering	Krueger *et al* (2002); da Silva et al (2002); Ellis *et al* (2001)

concentrations (Reiss *et al*, 2001; Homey *et al*, 2002). In addition, CCR10 is expressed only by a subset of CLA+ cells that are double negative for CCR7 and CD27 suggesting that they belong to the "effector" subpopulation (Soler *et al*, 2002).

Besides CCR4 and CCR10, thymic stromal lymphopoietin (TSLP) may be an attractive new target in Th_2-dominated skin inflammation for several reasons: First, TSLP-activated CD11c+ dendritic cells prime naive T cells to produce proallergic cytokines such as IL-4, IL-5, and IL-13. Second, TSLP induces the production of CCL22 (TARC), which may then chemoattract CCR4-expressing T cells into the skin. Finally, TSLP is expressed preferentially by lesional keratinocytes from patients with atopic dermatitis, but not by nonlesional keratinocytes (Leonard, 2002; Soumelis *et al*, 2002). Whether blockade of TSLP is of any biologic relevance in Th_2-dominated skin diseases remains to be unraveled.

The third step in the adhesion cascade involves the interaction of β_2-integrins such as LFA-1 (CD11a/CD18) or Mac-1 (CD11b/CD18) with immunoglobulin superfamily members such as ICAM-1 or VCAM-1. The first compounds targeting these molecules are already in clinical trials or entering the clinic such as the CD11a antagonist efalizumab from Genentech (Gottlieb *et al*, 2002), IC-747 from ICOS and other compounds summarized in **Table III**. In addition to inhibiting T cell recruitment into the skin, some of these compounds are also inducing apoptosis of activated T cells (da Silva *et al*, 2002) or inhibit T cell costimulation (Aruffo and Hollenbaugh, 2001), which may add to their clinical effectiveness.

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REFERENCES

Abraham WM, Ahmed A, Sabater JR, *et al*: Selectin blockade prevents antigen-induced late bronchial responses and airway hyperresponsiveness in allergic sheep. *Am J Respir Crit Care Med* 159:1205–1214, 1999

Agace WW, Higgins JM, Sadasivan B, Brenner MB, Parker CM: T-lymphocyte-epithelial-cell interactions: Integrin alpha (E) (CD103) beta (7), LEEP-CAM and chemokines. *Curr Opin Cell Biol* 12:563–568, 2000

Alon R, Feigelson S: From rolling to arrest on blood vessels: Leukocyte tap dancing on endothelial integrin ligands and chemokines at sub-second contacts. *Semin Immunol* 14:93–104, 2002

Anaya-Prado R, Ramos-Kelly JR, Toledo-Pereyra LH, Walsh J, Ward PA: Multiple selectin blockade with a small-molecule selectin inhibitor does not affect survival after a second inflammatory challenge with nonlethal LPS. *J Invest Surg* 15:171–180, 2002

Anderson AO, Shaw ST: T cell adhesion to endothelium: The FRC conduit system and other anatomic and molecular features which facilitate the adhesion cascade in lymph node. *Semin Immunol* 5:271–282, 1993

Aruffo A, Hollenbaugh D: Therapeutic intervention with inhibitors of co-stimulatory pathways in autoimmune disease. *Curr Opin Immunol* 13:683–686, 2001

Asadullah K, Lowe JB, Schottelius A: Differential influences on skin inflammation models in mice deficient of alpha (1, 3)fucosyltransferase VII. *Arch Dermatol Res* 294:43, 2002a

Asadullah K, Volk HD, Sterry W: Novel immunotherapies for psoriasis. *Trends Immunol* 23:47–53, 2002b

Baekkevold ES, Yamanaka T, Palframan RT, *et al*: The CCR7 ligand elc (CCL19) is transcytosed in high endothelial venules and mediates T cell recruitment. *J Exp Med* 193:1105–1112, 2001

Bank I, Rapman E, Shapiro R, *et al*: The epidermotropic mycosis fungoides associated alpha1beta1 integrin (VLA-1, CD49a/CD29) is primarily a collagen IV receptor on malignant T cells. *J Cutan Pathol* 26:65–71, 1999

Bantely R, Ernst B: Synthesis of sialyl Lewis X mimetics: Modifications of the 6-position of galactose. *Bioorg Med Chem Lett* 11:459–462, 2001

Bargatze RF, Jutila MA, Butcher EC: Distinct roles of L-selectin and integrins alpha4beta7 and LFA-1 in lymphocyte homing to Peyer's patch-HEV in situ: The multistep model confirmed and refined. *Immunity* 3:99–108, 1995

Barker JNWN, Sarma V, Mitra RS, Dixit VM, Nickoloff BJ: Marked synergism between tumor necrosis factor-alpha and interferon-gamma in regulation of keratinocyte-derived adhesion molecules and chemotactic factors. *J Clin Invest* 85:605–608, 1990

Bengtson P, Lundblad A, Larson G, Pahlsson P: Polymorphonuclear leukocytes from individuals carrying the G329A mutation in the (alpha) 1,3-fucosyltransferase-VII gene (FUT7) roll on E-and P-selectins. *J Immunol* 169:3940–3946, 2002

Berg EL, Fromm C, Melrose J, Tsurushita N: Antibodies cross-reactive with E- and P-selectin block both E- and P-selectin functions. *Blood* 85:31–37, 1995

Berg EL, Yoshino T, Rott LS, *et al*: The cutaneous lymphocyte antigen is a skin lymphocyte homing receptor for the vascular lectin endothelial cell-leukocyte adhesion molecule-1. *J Exp Med* 174:1461–1466, 1991

Berlin C, Bargatze RF, Campbell JJ, *et al*: Alpha 4 integrins mediate lymphocyte attachment and rolling under physiologic flow. *Cell* 80:413–422, 1995

Berthod F, Germain L, Li H, Xu W, Damour O, Auger FA: Collagen fibril network and elastic system remodeling in a reconstructed skin transplanted on nude mice. *Matrix Biol* 20:463–473, 2001

Bevilacqua MP, Stengelin S: Endothelial leukocyte adhesion molecule-1: An inducible receptor for neutrophils related to complement regulatory proteins and lectins. *Science* 243:1160–1163, 1989

Bhushan M, Bleiker TO, Ballsdon AE, *et al*: Anti-E-selectin is ineffective in the treatment of psoriasis: A randomized trial. *Br J Dermatol* 146:824–831, 2002

Biedermann T, Schwärzler C, Lametschwandtner G, *et al*: Targeting CLA/E-selectin interactions prevents CCR4-mediated recruitment of human Th2 memory cells to human skin in vivo. *Eur J Immunol* 32:3171–3180, 2002

Birnbaum Y, Patterson M, Kloner RA: The effect of CY-1503, a sialyl LewisX analog blocker of the selectin adhesion molecules, on infarct size and 'no reflow' in the rabbit model of acute infarction/reperfusion. *J Mol Cell Cardiol* 29:2013–2025, 1997

Bonecchi R, Sozzani S, Stine JT, *et al*: Divergent effects of interleukin-4 and interferon-gamma on macrophage-derived chemokine production: An amplification circuit of T helper 2 responses. *Blood* 92:2668–2671, 1998

Bonfanti R, Furie BC: PADGEM (GMP140) is a component of Waibel-Palade bodies of human endothelial cells. *Blood* 73:1109–1112, 1989

Brown DW, Furness J, Speight PM, *et al*: Mechanisms of binding of cutaneous lymphocyte-associated antigen-positive and alphaEbeta7-positive lymphocytes to oral and skin keratinocytes. *Immunology* 98:9–18, 1999

Butcher EC, Picker LJ: Lymphocyte homing and homeostasis. *Science* 272:60–66, 1996

Camp RL, Scheynius A, Johansson C, Pure E: CD44 is necessary for optimal contact allergic responses but is not required for normal leukocyte extravasation. *J Exp Med* 178:497–507, 1993

Campbell JJ, Hedrick J, Zlotnik A, Siani MA, Thompson DA: Chemokines and the arrest of lymphocytes rolling under shear flow conditions. *Science* 279:381–384, 1998

Carlos TM, Harlan JM: Leukocyte-endothelial adhesion molecules. *Blood* 84: 2068–2101, 1994

Carraway MS, Welty-Wolf KE, Kantrow SP, *et al*: Antibody to E- and L-selectin does not prevent lung injury or mortality in septic baboons. *Am J Respir Crit Care Med* 157:938–949, 1998

Cepek KL, Shaw SK, Parker CM, Russell GJ, Morrow JS, Rimm DL, Brenner MB: Adhesion between epithelial cells and T lymphocytes mediated by E-cadherin and the alphaEbeta7 integrin. *Nature* 372:190–193, 1994

Chan JR, Hyduk SJ, Cybulsi MI: Chemoattractants induce a rapid and transient upregulation of monocyte alpha4 integrin affinity for vascular cell adhesion molecule-1 which mediates arrest: An early step in the process of emigration. *J Exp Med* 193:1149–1158, 2001

Cinamon G, Grabovsky V, Winter E, *et al*: Novel chemokine functions in lymphocyte migration through vascular endothelium under shear flow. *J Leukoc Biol* 69:860–866, 2001

Collins RG, Jung U, Ramirez M, *et al*: Dermal and pulmonary inflammatory disease in E-selectin and P-selectin double-null mice is reduced in triple-selectin-null mice. *Blood* 98:727–735, 2001

Condon TP, Flournoy S, Sawyer GJ, Baker BF, Kishimoto TK, Bennett CF: ADAM17 but not ADAM10 mediates tumor necrosis factor-alpha and L-selectin shedding from leukocyte membranes. *Antisense Nucl Acid Drug Dev* 11: 107–116, 2001

Constantin G, Majeed M, Giagulli C, Piccio L, Kim JY, Butcher EC, Laudanna C: Chemokines trigger immediate beta2 integrin affinity and mobility changes: Differential regulation and roles in lymphocyte arrest under flow. *Immunity* 13:759–769, 2000

Cotran RS, Gimbrone MAJ: Induction and detection of a human endothelial activation antigen in vivo. *J Exp Med* 164:661–666, 1986

da Silva AJ, Brickelmaier M, Majeau GR, Li Z, Su L, Hsu YM, Hochman PS: Alefacept, an immunomodulatory recombinant LFA-3/IgG1 fusion protein, induces CD16 signaling and CD2/CD16-dependent apoptosis of CD2+ cells. *J Immunol* 168:4462–4471, 2002

de Vries IJM, Langeveld-Wildschut EG, van Reijsen FC, Bihari IC, Bruijnzeel-Koomen CAFM, Thepen T: Nonspecific T-cell homing during inflammation in atopic dermatitis: Expression of cutaneous lymphocyte-associated antigen and integrin $\alpha E\beta 7$ on skin-infiltrating T cells. *J Allergy Clin Immunol* 100:694–701, 1997

Diacovo TG, Catalina MD, Siegelman MH, von Andrian UH: Circulating activated platelets reconstitute lymphocyte homing and immunity in L-selectin-deficient mice. *J Exp Med* 187:197–204, 1998

Diacovo TG, Puri KD, Warnock RA, Springer TA, von Andrian UH: Platelet-mediated lymphocyte delivery to high endothelial venules. *Science* 273: 252–255, 1996

Dustin ML, Rothlein R, Springer T: Induction by IL-1 and interferon gamma: Tissue distribution, biochemistry, and function of a natural adherence molecule (ICAM-1). *J Immunol* 137:245–250, 1986

Dustin ML, Singer KH, Springer T: Adhesion of T lymphoblasts to epidermal keratinocytes is regulated by interferon gamma and is mediated by intercellular adhesion molecule-1. *J Exp Med* 167:1323–1340, 1988

Dwir O, Steeber DA, Schwarz US, Camphausen RT, Kansas GS, Tedder TF, Alon R: L-selectin dimerization enhances tether formation to properly spaced ligand. *J Biol Chem* 277:21130–21139, 2002

Ebnet K, Vestweber D: Molecular mechanisms that control leukocyte extravasation: The selectins and the chemokines. *Histochem Cell Biol* 112:1–23, 1999

Ellis CN, Krueger GG: Alefacept Clinical Study Group: Treatment of chronic plaque psoriasis by selective targeting of memory effector T lymphocytes. *N Engl J Med* 345:248–255, 2001

Feigelson SW, Grabovsky V, Winter E, *et al*: The Src kinase p56 (lck) up-regulates VLA-4 integrin affinity. Implications for rapid spontaneous and chemokine-triggered T cell adhesion to VCAM-1 and fibronectin. *J Biol Chem* 276: 13891–13901, 2001

Feizi T: Carbohydrate ligands for the leukocyte-endothelium adhesion molecules, selectins. *Results Probl Cell Differ* 33:201–223, 2001

Ferenczi K, Fuhlbrigge RC, Pinkus J, Pinkus GS, Kupper TS: Increased CCR4 expression in cutaneous T cell lymphoma. *J Invest Dermatol* 119:1405–1410, 2002

Fitzhugh DJ, Naik S, Caughman SW, Hwang ST: Cutting edge: C-C chemokine receptor 6 is essential for arrest of a subset of memory T cells on activated dermal microvascular endothelial cells under physiologic flow conditions in vitro. *J Immunol* 165:6677–6681, 2000

Fors BP, Goodarzi K, von Andrian UH: L-selectin shedding is independent of its subsurface structures and topographic distribution. *J Immunol* 167:3642–3651, 2001

Foxman EF, Campbell J, Butcher EC: Multistep navigation and the combinatorial control of leukocyte chemotaxis. *J Cell Biol* 139:1349–1360, 1999

Fuhlbrigge RC, Kieffer JD, Armerding D, Kupper TS: Cutaneous lymphocyte antigen is a specialized form of PSGL-1 expressed on skin-homing T cells. *Nature* 389:978–981, 1997

Gerard C, Rollins BJ: Chemokines and disease. *Nat Immunol* 2:108–115, 2001

Girolomoni G, Sebastiani S, Albanesi C, Cavani A: T-cell subpopulations in the development of atopic and contact allergy. *Curr Opin Immunol* 13:733–737, 2001

Gniadecki R, Calverley MJ: Emerging drugs in psoriasis. *Expert Opin Emerg Drugs* 7:69–90, 2002

Gottlieb AB, Krueger JG, Wittkowski K, Dedrick R, Walicke PA, Garovoy M: Psoriasis as a model for T-cell-mediated disease: Immunobiologic and clinical effects of treatment with multiple doses of efalizumab, an anti-CD11a antibody. *Arch Dermatol* 138:591–600, 2002

Grabbe S, Varga G, Beissert S, *et al*: β2 integrins are required for skin homing of primed T cells but not for priming naive T cells. *J Clin Invest* 109:183–192, 2002

Grabovsky V, Dwir O, Alon R: Endothelial chemokines destabilize L-selectin-mediated lymphocyte rolling without inducing selectin shedding. *J Biol Chem* 277:20640–20650, 2002

Grabovsky V, Feigelson S, Chen C, *et al*: Subsecond induction of alpha4 integrin clustering by immobilized chemokines stimulates leukocyte tethering and rolling on endothelial vascular cell adhesion molecule 1 under flow conditions. *J Exp Med* 192:495–506, 2000

Griffiths CE, Railan D, Gallatin WM, Cooper KD: The ICAM-3/LFA-1 interaction is critical for epidermal Langerhans cell alloantigen presentation to CD4+ T cells. *Br J Dermatol* 133:823–829, 1995

Griffiths CEM, Voorhees JJ, Nickoloff BJ: Characterization of intercellular adhesion molecule-1 and HLA-DR expression in normal and inflamed skin: Modulation by recombinant gamma interferon and tumor necrosis factor. *J Am Acad Dermatol* 20:617–629, 1989

Groves RW, Allen MH, Barker JN, Haskard DD, MacDonald DM: Endothelial leukocyte adhesion molecule-1 (ELAM-1) expression in cutaneous inflammation. *Br J Dermatol* 124:117–123, 1991

Groves RW, Kupper TS: Leukocyte recruitment in cutaneous inflammation. In Peltz G (ed). *Leukocyte Recruitment in Inflammatory Disease*. New York: Springer Verlag, 1996; p 71–84

Groves RW, Ross EL, Barker JN, MacDonald DM: Vascular cell adhesion molecule-1 (VCAM-1). Expression in normal and diseased skin and regulation in vivo by interferon gamma. *J Am Acad Dermatol* 29:67–72, 1993

Hafezi-Moghadam A, Ley K: Relevance of L-selectin shedding for leukocyte rolling in vivo. *J Exp Med* 189:939–948, 1999

Hafezi-Moghadam A, Thomas KL, Prorock AJ, Huo Y, Ley K: L-selectin shedding regulates leukocyte recruitment. *J Exp Med* 193:863–872, 2001

He XY, Xu Z, Melrose J, *et al*: Humanization and pharmacokinetics of a monoclonal antibody with specificity for both E- and P-selectin. *J Immunol* 160:1029–1035, 1998

Hemler ME: VLA proteins in the integrin family: Structures, functions, and their role on leukocytes. *Annu Rev Immunol* 8:365–400, 1990

Herz U, Bunikowski R, Renz H: Role of T cells in atopic dermatitis. *Int Arch Allerg Immunol* 115:179–190, 1998

Hicke BJ, Watson SR, Koenig A, *et al*: DNA aptamers block L-selectin function in vivo. 98:2688–2692, 1996

Homeister JW, Thall AD, Petryniak B, *et al*: The alpha (1,3)fucosyltransferases FucTIV and Fuc-TVII exert collaborative control over selectin-dependent leukocyte recruitment and lymphocyte homing. *Immunity* 15:115–126, 2001

Homey B, Alenius H, Müller A, *et al*: CCL27–CCR10 interactions regulate T cell-mediated skin inflammation. *Nat Med* 8:157–165, 2002

Homey B, Dieu-Nosjean M, Wiesenborn A, *et al*: Up-regulation of macrophage inflammatory protein-3α/CCL20 and CC chemokine receptor 6 in psoriasis. *J Immunol* 164:6621–6632, 2000a

Homey B, Wang W, Soto H, *et al*: The orphan chemokine receptor G protein-coupled receptor-2 (GPR-2, CCR10) binds the skin-associated chemokine CCL27 (CTACK/ALP/ILC). *J Immunol* 164:3465–3470, 2000b

Hoogewerf AJ, Kuschert GS, Proudfoot AE, Borlat F, Clark-Lewis I, Power CA, Wells TN: Glycosyminoglycans mediate cell surface oligomerization of chemokines. *Biochemistry* 36:13570–13578, 1997

Hwang ST, Fitzhugh DJ: Aberrant expression of adhesion molecules by Sezary cells: Functional consequences under physiologic shear stress conditions. *J Invest Dermatol* 116:466–470, 2001

Hynes RO: Integrins: Versatility, modulation, and signaling in cell adhesion. *Cell* 69:11–25, 1992

Ikegami-Kuzuhara A, Yoshinaka T, Ohmoto H, Inoue Y, Saito T: Therapeutic potential of a novel synthetic selectin blocker, OJ-R9188, in allergic dermatitis. *Br J Pharmacol* 134:1498–1504, 2001

Issekutz AC, Issekutz TB: The role of E-selectin, P-selectin, and very late activation antigen-4 in T lymphocyte migration to dermal inflammation. *J Immunol* 168:1934–1939, 2002

Johnston B, Issekutz TB, Kubes P: The alpha4 integrin supports leukocyte rolling and adhesion in chronically inflamed postcapillary venules in vivo. *J Exp Med* 183:1995–2006, 1996

Jung U, Ley K: Mice lacking two or all three selectins demonstrate overlapping and distinct functions for each selectin. *J Immunol* 162:6755–6762, 1999

Kakinuma T, Nakamura K, Wakugawa M, *et al*: Thymus and activation-regulated chemokine in atopic dermatitis: Serum thymus and activation-regulated chemokine level is closely related with disease activity. *J Allergy Clin Immunol* 107:535–541, 2001

Kakinuma T, Saeki H, Tsunemi Y, *et al*: Increased serum cutaneous T cell-attracting chemokine (CCL27) levels in patients with atopic dermatitis and psoriasis vulgaris. *J Allergy Clin Immunol* 111:592–597, 2003

Karecla PI, Bowden SJ, Green SJ, Kilshaw PJ: Recognition of E-cadherin on epithelial cells by the mucosal T cell integrin alphaM290beta7 (alphaEbeta7). *Eur J Immunol* 25:852–856, 1995

Kashihara-Sawami M, Norris DA: The state of differentiation of cultured human keratinocytes determines the level of intercellular adhesion molecule-1 (ICAM-1) expression induced by gamma interferon. *J Invest Dermatol* 98:852–856, 1992

Kerr KM, Auger WR, Marsh JJ, *et al*: The use of cylexin (CY-1503) in prevention of reperfusion lung injury in patients undergoing pulmonary thromboendarterectomy. *Am J Respir Crit Care Med* 162:14–20, 2000

Khor SP, McCarthy K, DuPont M, Murray K, Timony G: Pharmacokinetics, pharmacodynamics, allometry, and dose selection of rPSGL-Ig for phase I trial. *J Pharmacol Exp Ther* 293:618–624, 2000

Knowles DM, Halper JP: Human T-cell malignancies: Correlative clinical, histopathologic, immunologic, and cytochemical analysis of 23 cases. *Am J Pathol* 106:187–196, 1982

Konter U, Kellner I, Sterry W: Adhesion molecule mapping in normal human skin. *Arch Dermatol Res* 281:454–462, 1989

Krueger GG, Papp KA, Stough DB, Loven KH, Gulliver WP, Ellis CN: Alefacept Clinical Study Group: A randomized, double-blind, placebo-controlled phase III study evaluating efficacy and tolerability of 2 courses of alefacept in patients with chronic plaque psoriasis. *J Am Acad Dermatol* 47:821–833, 2002

Krueger JG, Wolfe JT, Nabeya RT, *et al*: Successful ultraviolet B treatment of psoriasis is accompanied by a reversal of keratinocyte pathology and by selective depletion of intraepidermal T cells. *J Exp Med* 182:2057–2068, 1995

Kunkel EJ, Boisvert J, Murphy K, *et al*: Expression of the chemokine receptors CCR4, CCR5, and CXCR3 by human tissue-infiltrating lymphocytes. *Am J Pathol* 160:347–355, 2002

Kunkel EJ, Butcher EC: Chemokines and the tissue-specific migration of lymphocytes. *Immunity* 16:1–4, 2002

Kunstfeld R, Lechleitner S, Groger M, Wolff K, Petzelbauer P: HECA-452+ T cells migrate through superficial vascular plexus but not through deep vascular plexus endothelium. *J Invest Dermatol* 108:343–348, 1997

Kuschert GS, Coulin F, Power CA, Proudfoot AE, Hubbard RE, Hoogwerf AJ, Wells TN: Glycosaminoglycans interact selectively with chemokines and modulate receptor binding and cellular responses. *Biochemistry* 38:12959–12968, 1999

Labow MA, Norton CR, Rumberger JM, *et al*: Characterization of E-selectin-deficient mice: Demonstration of overlapping function of the endothelial selectins. *Immunity* 1:709–720, 1994

Lechleitner S, Kunstfeld R, Messeritsch-Fanta C, Wolff K, Petzelbauer P: Peripheral lymph node addressins are expressed on skin endothelial cells. *J Invest Dermatol* 113:410–414, 1999

Leonard WJ: TSLP: Finally in the limelight. *Nat Immunol* 3:605–607, 2002
Ley K: Functions of selectins. *Results Probl Cell Differ* 33:177–200, 2001
Lowe JB: Selectin ligands, leukocyte trafficking, and fucosyltransferase genes. *Kidney Int* 51:1418–1426, 1997
Lub M, van Kooyk Y, van Vliet SJ, Figdor CG: Dual role of the actin cytoskeleton in regulating cell adhesion mediated by the integrin lymphocyte function-associated molecule-1. *Mol Biol Cell* 8:341–351, 1997
Ludwig RJ, Schultz JE, Weber C, Kaufmann R, Podda M, Zollner TM: Platelet activation in psoriasis: A possible link to inflammation? *J Invest Dermatol* 117:766, 2001
Mackay CR: Chemokines: Immunology's high impact factors. *Nat Immunol* 2:95–101, 2001
Mackay CR: New avenues for anti-inflamatory therapy. *Nat Med* 8:117–118, 2002
Maksymowych WP, Blackburn WDJ, Tami JA, Shanahan WRJ: A randomized, placebo-controlled trial of an antisense oligodeoxynucleotide to intercellular adhesion molecule-1 in the treatment of severe rheumatoid arthritis. *J Rheumatol* 29:447–453, 2002
Maly P, Thall A, Petryniak B, *et al*: The alpha (1, 3)fucosyltransferase Fuc-TVII controls leukocyte trafficking through an essential role in L-, E-, and P-selectin biosynthesis. *Cell* 86:643–653, 1996
Marinier A, Martel A, Bachand C, *et al*: Novel mimics of sialyl Lewis X: Design, synthesis and biological activity in a series of 2- and 3-malonate substituted galactoconjugates. *Bioorg Med Chem* 9:1395–1427, 2001
McEver RP, Beckstead JH: GMP-140, a platelet alpha granule membrane protein, is also synthesized by vascular endothelial cells and is localized in Waibel-Palade bodies. *J Clin Invest* 84:92–99, 1989
Middleton J, Neil S, Wintle J, *et al*: Transcytosis and surface presentation of IL-8 by venular endothelial cells. *Cell* 91:385–395, 1997
Nickoloff BJ: Role of interferon-gamma in cutaneous trafficking of lymphocytes with emphasis on molecular and cellular adhesion events. *Arch Dermatol* 124:1835–1845, 1988
Olivry T, Moore PF, Naydan DK, Danilenko DM, Affolter VK: Investigation of epidermotropism in canine mycosis fungoides: Expression of intercellular adhesion molecule-1 (ICAM-1) and beta-2 integrins. *Arch Dermatol Res* 287:186–192, 1995
Olsen TS, Ley K: Chemokines and chemokine receptors in leukocyte trafficking. *Am J Physiol Reg Integrative Comp Physiol* 283:7–28, 2002
Onuffer JJ, Horuk R: Chemokines, chemokine receptors and small-molecule antagonists: Recent developments. *Trends Pharmacol Sci* 23:459–467, 2002
Owen C: Chemokine receptors in airway disease: Which receptors to target? *Pulm Pharmacol Ther* 14:193–202, 2001
Papp K, Bissonnette R, Krueger JG, *et al*: The treatment of moderate to severe psoriasis with a new anti-CD11a monoclonal antibody. *J Am Acad Dermatol* 45: 665–674, 2001
Parker CM, Cepek KL, Russell GJ, Shaw SK, Posnett DN, Schwarting R, Brenner MB: A family of beta 7 integrins on human mucosal lymphocytes. *Proc Natl Acad Sci USA* 89:1924–1929, 1992
Pauls K, Schön M, Kubitza RC, *et al*: Role of integrin αE (CD103) β7 for tissue-specific epidermal localization of CD8+ T lymphocytes. *J Invest Dermatol* 117:569–575, 2001
Petzelbauer P, Pober JS, Keh A, Braverman IM: Inducibility and expression of microvascular endothelial adhesion molecules in lesional, perilesional, and uninvolved skin of psoriatic patients. *J Invest Dermatol* 103:300–305, 1994
Picker LJ, Kishimoto TK, Smith CW, Warnock RA, Butcher EC: ELAM-1 is an adhesion molecule for skin-homing T-cells. *Nature* 349:796–799, 1991
Picker LJ, Michie SA, Rott LS, Butcher EC: A unique phenotype of skin-associated lymphocytes in humans: Preferential expression of the HECA-425 epitope by benign and malignant T cells at cutaneous sites. *Am J Pathol* 136:1053–1068, 1990
Proudfoot AE, Fritchley S, Borlat F, *et al*: The BBXB motif of RANTES is the principal site for heparin binding and controls receptor selectivity. *J Biol Chem* 276:10620–10626, 2001
Reinhardt PH, Elliott JF, Kubes P: Neutrophils can adhere via alpha4beta1-integrin under flow conditions. *Blood* 89:3837–3846, 1997
Reiss Y, Proudfoot AE, Power CA, Campbell JJ, Butcher EC: CC chemokine receptor (CCR) 4 and the CCR10 ligand cutaneous T cell-attracting chemokine (CTACK) in lymphocyte trafficking to inflamed skin. *J Exp Med* 194: 1541–1547, 2001
Robert C, Kupper TS: Inflammatory skin diseases, T cells, and immune surveillance. *N Engl J Med* 341:1817–1828, 1999
Robertson D: Crohn's trial shows the pros of antisense. *Nat Biotechnol* 15:209, 1997
Rossiter H, van Reijsen F, Mudde GC, Kalthoff F, Bruijnzeel-Koomen CAFM, Picker LJ, Kupper TS: Skin disease-related T cells bind to endothelial selectins: Expression of cutaneous lymphocyte antigen (CLA) predicts E-selectin but not P-selectin binding. *Eur J Immunol* 24:205–210, 1994
Rottman JB, Smith TL, Ganley KG, Kikuchi T, Krueger JG: Potential role of the chemokine receptors CXCR3, CCR4, and the integrin aEb7 in the pathogenesis of psoriasis vulgaris. *Lab Invest* 81:335–347, 2001
Sanchez-Madrid F, del Pozo MA: Leukocyte polarization in cell migration and immune interaction. *EMBO J* 18:501–511, 1999
Santamaria Babi LF, Moser R, Perez Soler MT, Picker LJ, Blaser K, Hauser C: Migration of skin-homing T cells across cytokine-activated human endothelial cell layers involves interaction of the cutaneous lymphocyte-associated antigen (CLA), the very late antigen-4 (VLA-4), and the lymphocyte function-associated antigen-1 (LFA-1). *J Immunol* 154:1543–1550, 1995
Schechner JS, Edelson RL, McNiff JM, Heald PW, Pober JS: Integrins alpha4beta7 and alphaEbeta7 are expressed on epidermotropic T cells in cutaneous T cell lymphoma and spongiotic dermatitis. *Lab Invest* 79:601–607, 1999
Schön MP: Animal models of psoriasis—what can we learn from them? *J Invest Dermatol* 112:405–410, 1999
Schön MP, Arya A, Murphy EA, *et al*: Mucosal T lymphocyte numbers are selectively reduced in integrin α_E (CD103) deficient mice. *J Immunol* 162: 6641–6649, 1999
Schön MP, Krahn T, Schön M, *et al*: Efomycine M, a new specific inhibitor of selectin, impairs leukocyte adhesion and alleviates cutaneous inflammation. *Nat Med* 8:366–372, 2002
Schön MP, Ruzicka T: Psoriasis: The plot thickens.... *Nat Immunol* 2:91, 2001
Shand A, Forbes A: Potential therapeutic role for cytokine or adhesion molecule manipulation in Crohn's disease. in the shadow of infliximab? *Int J Colorectal Dis* 18:1–11, 2003
Shieh CC, Sadasivan BK, Russell GJ, Schön MP, Parker CM, Brenner MB: Lymphocyte adhesion to epithelia and endothelia mediated by the LEEP-CAM glycoprotein. *J Immunol* 163:1592–1601, 1999
Shimizu Y, Newman W, Gopal TV, *et al*: Four molecular pathways of T cell adhesion to endothelial cells: Roles of LFA-1, VCAM-1, and ELAM-1 and changes in pathway hierarchy under different activation conditions. *J Cell Biol* 113: 1203–1212, 1991
Shimizu Y, Rose DM, Ginsberg MH: Integrins in the immune system. *Adv Immunol* 72:325–380, 1999
Shinkai A, Shinoda K, Sasaki K, *et al*: High-level expression and purification of a recombinant human alpha (1,3)fucosyltransferase in baculovirus-infected insect cells. *Protein Expr Purif* 10:379–385, 1997
Shinoda K, Shitara K, Yoshihara Y, *et al*: Panosialins, inhibitors of an alpha 1,3 fucosyltransferase Fuc-VII, suppress the expression of selectin ligands on U937 cells. *Glycoconj J* 15:1079–1083, 1998
Simonitsch I, Volc-Platzer B, Mosberger I, Radaszkiewicz T: Expression of monoclonal antibody defined αEβ7 integrin in cutaneous T cell lymphoma. *Am J Pathol* 145:1148–1158, 1994
Singbartl K, Thatte J, Smith ML, Wethmar K, Day K, Ley K: A CD2-green fluorescence protein-transgenic mouse reveals very late antigen-4-dependent CD8+ lymphocyte rolling in inflamed venules. *J Immunol* 166:7520–7526, 2001
Smith CH, Barker JNWN, Morris RW, MacDonald DM, Lee TH: Neuropeptides induce rapid expression of endothelial cell adhesion molecules and elicit granulocytic infiltration in human skin. *J Immunol* 151:3274–3282, 1993
Smithers N, Kelly VA, Witham SJ, Edbrooke MR, Britten CJ: Expression of a secreted form of human alpha (1,3)fucosyltransferase VII from insect cells. *Biochem Soc Trans* 25:426, 1997
Smithson G, Rogers CE, Smith PL, *et al*: Fuc-TVII is required for T helper 1 and T cytotoxic 1 lymphocyte selectin ligand expression and recruitment in inflammation, and together with Fuc-TIV regulates naive T cell trafficking to lymph nodes. *J Exp Med* 194:601–614, 2001
Soler D, Humphreys TL, Spinola SM, Campbell JJ: CCR4 versus CCR10 in human cutaneous TH lymphocyte trafficking. *Blood* 101:1677–82, 2002
Soumelis V, Reche PA, Kanzler H, *et al*: Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP. *Nat Immunol* 3:673–680, 2002
Springer TA: Traffic signals for lymphocyte recirculation and leukocyte emigration: The multistep paradigm. *Cell* 76:301–314, 1994
Sterry W, Mielke V, Konter U, Kellner I, Boehncke WH: Role of β1 integrins in epidermotropism of malignant T cells. *Am J Pathol* 141:855–860, 1992
Strauch UG, Mueller RC, Li XY, Cernadas M, Higgins JMC, Binion DG, Parker CM: Integrin αE (CD103) β7 mediates adhesion to intestinal microvascular endothelial cell lines via an E-cadherin-independent interaction. *J Immunol* 166:3506–3514, 2001
Syrbe U, Siveke J, Hamann A: Th1/Th2 subset: Distinct differences in homing and chemokine expression? *Springer Semin Immunopathol* 21:263–285, 1999
Takagi J, Erickson HP, Springer TA: C-terminal opening mimicks 'inside-out' activation of integrin alpha5beta1. *Nat Struct Biol* 8:412–416, 2001
Thoma G, Magnani JL, Patton JT: Synthesis and biological evaluation of a sialyl LewisX mimic with significantly improved E-selectin inhibition. *Bioorg Med Chem Lett* 11:923–925, 2001
Thomson AW, Nalesnik MA, Rilo HR, Woo J, Carroll PB, van Thiel DH: ICAM-1 and E-selectin expression in lesional biopsies of psoriasis patients responding to systemic FK 506 therapy. *Autoimmunity* 15:215–223, 1993
Ticchioni M, Raimondi V, Lamy L, Wijdens J, Lindberg FP, Brown EJ, Bernard A: Integrin-associated protein (CD47/IAP) contributes to T cell arrest in inflammatory vascular endothelium under shear flow. *FASEB J* 15:341–350, 2001
Todderud G, Nair X, Lee D, *et al*: BMS-190394, a selectin inhibitor, prevents rat cutaneous inflammatory reactions. *J Pharmacol Exp Ther* 282:1298–1304, 1997
Varki A: Selectin ligands. *Proc Natl Acad Sci USA* 91:7390–7397, 1994
von Andrian UH, Chambers JD, McEvoy LM, Bargatze RF, Arfors KE, Butcher EC: Two-step model of leukocyte–endothelial cell interaction in inflammation:

Distinct roles for LECAM-1 and the leukocyte beta-2 integrins in vivo. *Proc Natl Acad Sci U S A* 88:7538–7542, 1991

Wagner LA, Brown T, Gil S, Frank I, Carter W, Tamura R, Wayner EA: The keratinocyte-derived cytokine IL-7 increases adhesion of the epidermal T cell subset to the skin basement membrane protein laminin-5. *Eur J Immunol* 29: 2530–2538, 1999

Walton LJ, Thornhill MH, Macey MG, Farthing PM: Cutaneous lymphocyte associated antigen (CLA) and αEβ7 integrins are expressed by mononuclear cells in skin and oral lichen planus. *J Oral Pathol Med* 26:402–407, 1997

Wayner EA, Gil SG, Murphy GF, Wilke MS, Carter WG: Epiligrin, a component of epithelial basement membranes, is an adhesive ligand for α3β1 positive T lymphocytes. *J Cell Biol* 121:1141–1152, 1993

Weninger W, Ulfman LH, Cheng G, Souchkova N, Quackenbush EJ, Lowe JB, von Andrian UH: Specialized contributions by alpha (1,3)fucosyltransferase-IV and Fuc-TVII during leukocyte rolling in dermal microvessels. *Immunity* 12: 665–676, 2000

Williams IR, Kupper TS: Epidermal expression of intercellular adhesion molecule-1 is not a primary inducer of cutaneous inflammation in transgenic mice. *Proc Natl Acad Sci USA* 91:9710–9714, 1994

Yacyshyn BR, Chey WY, Goff J, *et al*: Double-blind, placebo-controlled trial of the remission inducing and steroid sparing properties of an ICAM-1 antisense oligodeoxynucleotide, alicaforsen (ISIS 2302), in active steroid dependent Crohn's disease. *Gut* 51:30–36, 2002

Yauch RL, Felsenfeld DP, Kraeft SK, Chen LB, Sheetz MP, Hemler ME: Mutational evidence for control of cell adhesion through integrin recruitment, independent of ligand binding. *J Exp Med* 186:1–9, 1997

Yu B, Koga T, Urabe K, Moroi Y, Maeda S, Yanagihara Y, Furue M: Differential regulation of thymus- and activation-regulated chemokine induced by IL-4, IL-13, TNF-alpha and IFN-gamma in human keratinocytes and fibroblasts. *J Dermatol Sci* 30:29–35, 2002

Zhao LC, Edgar JB, Dailey MO: Characterization of the rapid proteolytic shedding of murine L-selectin. *Dev Immunol* 8:267–277, 2001

Zlotnik A, Yoshie O: Chemokines. A new classification system and their role in immunity. *Immunity* 12:121–127, 2000

Zollner TM, Podda M, Pien C, Elliott PJ, Kaufmann R, Boehncke WH: Proteasome inhibition reduces superantigen-mediated T cell activation and the severity of psoriasis in a SCID-hu model. *J Clin Invest* 109:671–679, 2002