Lymphocyte Migration into the Skin: The Role of Lymphocyte Homing Receptor (CD44) and Endothelial Cell Antigen (HECA-452)

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Lymphocyte migration into the lymphoid organs and sites of inflammation is controlled by lymphocyte-endothelial cell interaction at sites where lymphocytes exit from the blood. Expression of Hermes-defined CD44 class of lymphocyte homing receptor and HECA-452 antigen specific for high-endothelium-mediating physiologic lymphocyte extravasation was studied in dermatitis herpetiformis, celiac disease, psoriasis, mycosis fungoides, lymphocytosis cutis, atopic dermatitis, and allergic contact dermatitis. Also, duodenal biopsies of patients suffering from dermatitis herpetiformis or celiac disease were studied for expression of these antigens.

Infiltrating lymphocytes in the skin and in the duodenal area expressed homing receptor molecules when studied with monoclonal antibodies, Hermes-1 and Hermes-3, that recognize the CD44 class of molecules involved in lymphocyte binding to high endothelial venules in peripheral lymph nodes, mucosa-associated lymphatic tissues, and inflamed synovium. However, the HECA-452 antigen was not detected on the venules, neither in the skin nor in the duodenum. Even the venules possessing high endothelial morphologically were HECA-452 negative. These findings suggest the CD44 class of lymphocyte homing receptor(s) is also involved in lymphocyte homing to inflamed skin and the duodenal area of the gut. However, on the basis of HECA-452 staining, high endothelial venules in inflamed skin and duodenum are not antigenically identical with high endothelial venules in organized lymphoid tissues. This finding indirectly supports the idea that molecules and/or mechanisms mediating lymphocyte extravasation might be distinct in these organs.

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ontinuous lymphocyte recirculation is an essential element of the immune system, allowing distinct cell populations to interact with antigens and with each other. It also allows antigen-specific cells to be selected out and to accumulate at sites of antigen deposits. Lymphocytes leave the blood by selectively binding to specialized high endothelial venules (HEV) in lymphoid organs and sites of chronic inflammation [1–3]. Lymphocyte binding to HEV is mediated by specific receptor-ligand molecule interactions [2,4]. In humans, the CD44 class of molecules on lymphocyte surfaces is involved in this process [5]. However, stable contacts between lymphocytes and HEV seem to be created by complex mechanisms also involving other molecules. Those molecules include at least lymphocyte-function-associated antigen-1 (LFA-1), very late activation antigen-4 (VLA-4), and a human equivalent of MEL-14 [6–9]. Ligand molecules on endothelial cells are largely unknown. LFA-1 uses intercellular adhesion molecules (ICAM-1 and ICAM-2) as its ligands in many adhesion events [10,11]. Even though endothelial ICAM-1 is involved as a ligand in part of LFA-1-mediated lymphoid cell binding to cultured endothelial cells, its role and also the role of ICAM-2 in lymphocyte binding to HEV is unknown [10,11]. HECA-452 is a marker of endothelium-mediating lymphocyte extravasation. However, the direct involvement as an endothelial cell ligand in lymphocyte homing has not yet been proved [12]. It is also expressed on a variety of cell types belonging to the myeloid and monocyte/macrophage lineage [12–15], but the biochemical structure of HECA-452 antigen on these different cell types is not known. Preliminary results suggest that the molecular weight of the HECA-452 antigen of cultured HEV cells is about 200 kDa under reducing conditions, shifting to 220–240 kDa under non-reducing condition [16].

Three functionally distinct lymphocyte-HEV interaction systems have been discovered: one mediates lymphocyte traffic to peripheral lymph nodes; another, to mucosa-associated lymphatic tissue; and a third, to inflamed joint tissue [17,18]. Recently, evidence for distinct homing specificities to the skin and lung-associated lymph nodes has been presented [19,20]. In vivo recirculation studies in sheep have shown that lymphocytes from intestinal lymph recirculate preferentially back into intestinal lymph, whereas lymphocytes from peripheral lymph nodes recirculate back into peripheral lymph node efferent lymph. A third population of lymphocytes has been shown to recirculate preferentially to lymph-draining sites of chronic inflammation [3,21]. However, even though lymphocyte traffic through HEV accounts for the majority of lymphocyte migration, there is a continuous low-grade migration of lympho-

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Abbreviations:
CD: celiac disease
DH: dermatitis herpetiformis
HEV: high endothelial venules

ICAM-1 is involved as a ligand in part of LFA-1-mediated lymphoid cell binding to cultured endothelial cells, its role and also the role of ICAM-2 in lymphocyte binding to HEV is unknown [10,11]. HECA-452 is a marker of endothelium-mediating lymphocyte extravasation. However, the direct involvement as an endothelial cell ligand in lymphocyte homing has not yet been proved [12]. It is also expressed on a variety of cell types belonging to the myeloid and monocyte/macrophage lineage [12–15], but the biochemical structure of HECA-452 antigen on these different cell types is not known. Preliminary results suggest that the molecular weight of the HECA-452 antigen of cultured HEV cells is about 200 kDa under reducing conditions, shifting to 220–240 kDa under non-reducing condition [16].

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* Duijvestijn (unpublished results).
cytes and monocytes from blood to afferent lymph at vascular beds. Besides lymphocytes, afferent lymph also transports antigens, macrophages, granulocytes, and Langerhans cells to lymph nodes, but only lymphocytes are seen in efferent lymph [22,23].

In certain dermatologic diseases, lymphocytes migrate to the skin. The flow of lymphocytes through inflammation areas of the skin may increase up to 20 times when compared to normal situations [3]. At sites of inflammation, simultaneously with lymphocyte infiltrations, venules resembling morphologically HEV in normal lymphoid organs appear [24]. In the present work, expression of an endothelial-cell antigen specific for venules mediating lymphocyte traffic, and expression of CD44 class homing-receptor molecules on the surface of infiltrating lymphocytes in the skin and duodenal area of the gut in different pathologic conditions were studied with Hermes-1/-3 and HECA-452 antibodies.

MATERIALS AND METHODS

Patients The skin disorders studied are presented in Table 1. The age range of the 60 patients was 19–66 years (mean, 38.2). Forty-two were female and 18 were male. Two 4-mm punch biopsies were taken from each patient after local anesthesia with lidocaine (20 mg/ml) without epinephrine. In case of mycosis fungoides (three patients), lymphocytosis cutis (one patient), and psoriasis (three patients), involved and uninvolved skin sites were biopsied. In atopic dermatitis (17 patients), skin testing was performed by application of 1,000,000 BU/ml of specific allergens (cat dander, house dust mite, birch, timothy and mugwort pollen, and cladosporium; Allergologisk Laboratorium, Hørsholm, Denmark) for 48 h on the backs of patients under Finn Chambers (Epikon, Helsinki, Finland). The positive test sites showing erythema and edema and normal appearing skin were biopsied after 72 h. In contact dermatitis (four patients), the patch testing was carried out with nickel, neomycin, methylmethacrylate, and DPPD (Chemothecnique, Malmo, Sweden) with 48 h of occlusion. Biopsies were taken from two patients with vesicular allergic reactions after 48 h, and from the other two patients demonstrating allergic patch test reactions after 96 h. Patients suffering from dermatitis herpetiformis (DH, 15 patients) or celiac disease (CD, 17 patients), skin lesions were induced on the upper arms by application of Trafuril ointment (tetrahydrofururyl-micotinate 10 mg/g) for 10 min [25]. The Trafuril-exposed and normal skin sites were biopsied after 24 h. Duodenal biopsy specimens from all patients suffering from DH and/or CD were taken from the descending duodenum with an Olympus GIF-XQ 10 endoscope and standard forceps (Olympus FB-24 K or FB-25 K). As control samples for staining, human tonsils (two patients), normal large bowel samples (six patients), and large bowel samples from patients suffering from ulcerative colitis (two patients) and Crohn's disease (two patients) were used.

Antibodies Production and specificity of Hermes-1 and -3 monoclonal antibodies that recognize distinct epitopes of CD44 molecule(s) mediating lymphocyte binding to peripheral lymph node, mucosal, and synovial HEV have been described earlier [5,26]. Hermes-1/-3 antibodies were used as the serum-free supernatants, and purified HECA-452 antibody was used at a concentration of 100 µg/ml [12]. Monoclonal antibody 9D8 was produced by immunizing mice with stromal elements of human inflamed synovium. This antibody was used to identify the vessels in the biopsies. 9D8 was used as a serum-free supernatant. Monoclonal antibody LB2 (generous gift from Dr. Clark) against ICAM-1 was used at a concentration of 20 µg/ml. Monoclonal antibodies against CD1 (6, Coulter) and HLA-DR (Coulter) were used at 1:100 dilutions, and polyclonal anti-Factor VIII antibody (Dako), at a 1:400 dilution. Monoclonal antibodies 281.2 against mouse heparan sulfate proteoglycan [27] and 3G6 against chicken T cells were used as negative control antibodies.

Immunohistologic Stainings All biopsy specimens were cut immediately into two pieces: one was frozen for immunohistochemical analyses and one was fixed in formalin and embedded in paraffin for histologic studies. All specimens (normal and inflamed) were stained with Hermes-1/-3, HECA-452, 9D8/anti-Factor VIII and negative control antibodies. In addition, all samples of patients suffering from atopic dermatitis were stained with antibodies to CD1 and HLA-DR. Furthermore, sections of biopsies from selected patients representing different disease groups with none, mild, or heavy lymphocyte infiltrations were stained with anti-ICAM-1 antibody. The extent of lymphocyte infiltrations in tissue samples was coded from - to ++++. Frozen sections were stained with the above-mentioned antibodies in the first step and with either peroxidase-conjugated rabbit anti-mouse Ig or anti-rat Ig in the second step (DAKO). In staining for Factor VIII, the second reagent was biotinylated goat antibodies to rabbit IgG (1:100, Vector Laboratories), and the third reagent was peroxidase-avidin (1:100, Vector). Second-stage antibodies were diluted in PBS containing 5% normal human serum. Diaminobenzidine was used as the chromagen, and the sections were counterstained with hematoxylin and eosin.

RESULTS

Lymphocyte Infiltrations In general, the inflammatory infiltrates in the skin of subjects with CD/DH, atopic dermatitis, and allergic contact dermatitis contained over 90% mononuclear cells and 1–10% eosinophils, but very few polymorphonuclear leukocytes. The only exceptions were two patients suffering from DH: one had 30% granulocytes and the other one had 50% granulocytes of total infiltrating leukocytes. Approximately 50% of the mononuclear cells consisted of small lymphocytes. Only six of 15 DH patients had macroscopically positive Trafuril reactions, and microscopically those patients also had lymphocyte infiltrations that varied from + to ++++. However, some patients who showed macroscopically negative Trafuril reactions microscopically had some infiltrating lymphocytes in their biopsy samples (one DH patient and six CD patients). All CD patients had negative Trafuril reactions. Mycosis fungoides patients, as well as the one patient with lymphocytosis cutis, had massive lymphocyte infiltrations coded as ++/+++ in psoriasis biopsies the extent of lymphocyte infiltrations varied from + (one patient) to ++++ (two patients). All patients with contact dermatitis had moderate (+, two patients) or higher (+++, two patients) infiltrations. In atopic patients, the intensity of lymphocyte infiltrations after application of specific antigens varied from + to ++++ (+, two patients; ++, eight patients; ++++, six patients). Some atopic patients had increased numbers of mononuclear cells in the biopsies taken from the skin areas looking macroscopically normal.

Eighteen patients (10 DH, eight CD) had diagnostic duodenal biopsies with villous atrophy. Sixteen of them (nine DH and seven CD) had highly or moderately increased numbers of plasma cells and other lymphocytes. The rest showed increased accumulation of lymphoid cells without atrophy of the villi.

Hermes-1/-3 Staining Only occasional leucocytes were seen in normal skin. Most of them were Hermes-1/-3 positive. Hermes-1 and Hermes-3 gave identical staining patterns as expected on the basis of earlier studies [5]. Practically all lymphocytes and other infiltrating leukocytes in inflamed skin and gut were Hermes-1/-3 positive, indicating the expression of the CD44 homing-receptor class of molecules on their surfaces (Table I, Figs 1B, 2B, 3A, and 4A).

HECA-452, 9D8/Factor VIII, and ICAM-1 Staining 9D8 antibody in conjunction with anti-Factor VIII antibody was used to identify vessels in both skin and gut specimens. Even though 9D8 is not entirely specific for endothelial cells, it served as a very useful antibody, because it recognizes endothelial cells in all types of vessels. Both normal and inflamed areas of the skin showed several vessels. In general, the number of the vessels in inflamed skin was increased compared to the noninflamed areas, and many of them had endothelial cells that were morphologically high. HECA-452 did not stain endothelial cells in any skin samples (Table I, Figs 1C and 2C) despite the fact that many patients, for example the mycosis fungoides patients, had massive lymphocytic infiltrations and venules morphologically resembling high endothelial venules, as
Table I. Reactivity of Hermes-1/-3 and HECA-452 in the Skin Specimens

<table>
<thead>
<tr>
<th>Skin Disorder</th>
<th>Number of Biopsies with Mononuclear Cell Infiltrates (Positive Cases/Tested Cases)</th>
<th>Hermes* Lymphocytes (Positive Cases/Tested Cases)</th>
<th>HECA-452* Monocytic/Dendritic (Positive Cases/Tested Cases)</th>
<th>HECA-452* Venules (Positive Cases/Tested Cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycosis fungoides</td>
<td>3/3</td>
<td>3/3</td>
<td>3/3</td>
<td>0/3</td>
</tr>
<tr>
<td>Lymphocytosis cutis NUD</td>
<td>1/1</td>
<td>1/1</td>
<td>1/1</td>
<td>0/1</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>3/3</td>
<td>3/3</td>
<td>3/3</td>
<td>0/3</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>16/17</td>
<td>16/17</td>
<td>16/17</td>
<td>0/17</td>
</tr>
<tr>
<td>Allergic contact dermatitis</td>
<td>4/4</td>
<td>4/4</td>
<td>4/4</td>
<td>0/4</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
<td>6(1)/15</td>
<td>7/15</td>
<td>7/15</td>
<td>0/15</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>0(6)/17</td>
<td>6/17</td>
<td>5/17</td>
<td>0/17</td>
</tr>
</tbody>
</table>

*Numbers in brackets indicate the number of patients with macroscopically negative Trafuriz reaction but with few infiltrating mononuclear cells in microscopical analyses.

shown in Figs 1A and 2A. However, in all infiltrates a population of cells was positive (Table I). On a morphologic basis, a majority of these cells belonged to the monocyte/macrophage lineage. Very few positive cells had the appearance of lymphocytes. This finding is in concordance with the findings of others who have reported that, besides high endothelial cells, HECA-452 also stains monocytes, macrophages, dendritic cells, plasmacytoid T cells (monocyte related), and cells at different stages during myelopoiesis [12–15]. Anti-HLA-DR antibody stained morphologically similar types of cells as HECA-452 suggesting (not formally proved) that HECA-452 positive cells also may bear MHC class II antigens (Fig 1C,D). In normal uninflamed skin there were occasional HECA-452-positive monocytes, but their absolute number significantly increased in inflamed skin. However, the relative ratio of HECA-452-positive and -negative cells stayed approximately the same in both inflamed and normal areas. The number of CD1 positive cells also increased at inflammatory sites, but the populations recognized by HECA-452 and anti-CD1 antibodies were not identical (data not shown).

In the normal gut, HECA-452-positive venules were found in large bowel as shown in Fig 3B. In the duodenal area the venules were HECA-452 negative despite accumulation of a large number of lymphoid cells in many patients (Fig 4B).

In contrast to HECA-452, expression of ICAM-1 was induced on the endothelium in the inflammatory areas in both the skin and gut. In the normal areas of the skin, venules were either totally negative or faintly positive with anti-ICAM-1 antibody. The number of positive vessels and intensity of staining was dependent on the extent of the mononuclear cell infiltration (Fig 5). In addition, practically all plasma cells in inflammatory gut lesions expressed ICAM-1. In the skin samples, the relative number of ICAM-1-positive mononuclear cells correlated to the extent of inflammation varying between 20% and 90%.

**DISCUSSION**

The Hermes-1/-3-defined 85–95-kD glycoprotein class of molecules is involved in lymphocyte homing [5,26]. Related molecules are expressed on a variety of other cell types, and recent studies suggest that Hermes-1/-3 define a widespread family of heterotypic cell adhesion molecules capable of binding also to extracellular matrix molecules such as fibronectin and collagen† [28,29]. However, on lymphocytes the gp90 Hermes (CD44) appears to specifically mediate interactions with lymph node and mucosal and synovial HEV [5]. On other leukocytes, for example on monocytes and neutrophils, this class of molecules may control the traffic of these cells to sites of inflammation.‡ Expression of Hermes-1/-3 antigen on infiltrating lymphocytes in the skin and duodenal area of the gut indicates that the lymphocytes in those tissues have receptors that

![Figure 1](image-url)  
**Figure 1.** Delayed hypersensitivity reaction caused by house-dust mite. The skin biopsy was taken 72 h after application of the antigen. A) 9DH staining; Several vessels are positive; arrows indicate the venules morphologically resembling HEV. B) Hermes-1 staining; practically all infiltrating leukocytes express variable amounts of Hermes antigen on their surfaces; arrowheads point to the positively stained surfaces of some cells. C) HECA-452 staining; HECA-452 does not stain the vessels, but several infiltrated cells (macrophage like) are strongly HECA-452 positive (arrowheads). D) HLA-DR staining; many infiltrating cells, several of which are morphologically similar to HECA-452 positive cells, bear HLA-DR antigen (arrowheads). (Hematoxylin-eosin counterstain, magnification X200). All figures are taken from the same area of the infiltration, but are not necessarily serial sections.  

belong to the same class of molecules as those mediating lymphocyte traffic to peripheral lymph node and mucosal and synovial HEV. Analogously, expression of the Hermes-1/3-antigen on other infiltrating leukocytes suggests that those cells might have used Hermes-defined molecules when entering the inflamed tissue. Because practically all recirculating lymphocytes bear Hermes-defined molecule(s), functional discrimination between distinct specificities of lymphocyte receptors cannot be done with the Hermes-1 antibody, which recognizes a common determinant of the CD44 class of molecules and not the domain for HEV recognition. That is also the case with Hermes-3 antibody, which inhibits lymphocyte binding to mucosal HEV. Binding of Hermes-3 antibody to one of the common determinants probably changes the conformation of the mucosal recognition domain, and thus causes inhibition of binding. Unfortunately, attempts to produce monoclonal antibodies that would bind to the organ-specific recognition domains on human lymphocytes have been unsuccessful. HECA-452 binds to endothelial cells of HEV in lymphoid organs and in sites of chronic inflammation with heavy lymphocyte infiltrations. In this work we could not find any HECA-452-positive vessels in the skin biopsies, even those with massive lymphocyte infiltrations and venules morphologically resembling HEV in organized lymphoid tissues. The first description of HECA-452 expression in different organs also included some dermatologic diseases. In that report the only skin disease found to contain HECA-452 positive vessels was benign pseudolymphoma. We do not know why the expression HECA-452 in those pseudolymphoma patients was different from that in all other patients with a wide variety of other dermatologic disease studied by us or Duijvestijn et al (lichen planus, acute, and chronic dermatitis) [12]. At the moment we can only speculate that pseudolymphoma is a very different entity, and that regulation mechanisms leading to expression of HECA-452 antigen are different than in other skin diseases. In general, the findings indicate that lymphocyte traffic to skin occurs independently of the expression of HECA-452, and HEV in the skin and organized lymphoid tissues are not antigenically identical. This also indirectly suggests that the lymphocyte-endothelial cell interaction might be functionally distinct from that in normal lymphoid tissues. This idea is also supported by recent results of Sackstein et al [19].

HECA-452 was found to be expressed on vessels in lamina propria of normal large bowel. However, duodenal areas of both heavily inflamed samples and samples that looked nearly normal in histopathologic examination were totally HECA-452 negative. Thus, HECA-452 is not normally expressed in this anatomical location, and it cannot be induced by inflammatory mediators active in DH or CD.

Inflammatory mediators interleukin-1 (IL-1), tumor necrosis factor (TNF), and lipopolysaccharide (LPS) have been shown to up-regulate leukocyte adhesion to cultured endothelial cells [30,31]. The target of this up-regulation is the endothelial cell. HECA-452 can be induced by interferon (IFN)-gamma in cultured umbilical cord endothelial cells; however, that expression is cytoplasmic, which may indicate that a second signal is needed for surface expression. IL-1, IL-2, and TNF do not have any effect on HECA-452 expression [32]. Besides HECA-452 up-regulation, IFN-gamma also increases lymphocyte binding to the endothelium [32,33]. Furthermore, an activation marker of human endothelial cells, H4/18, is expressed on the vessels of skin in delayed hypersensitivity reactions, but endothelial cells in non-inflamed areas are H4/18 negative [34]. In skin organ cultures, this marker can also be induced on the vessels mediating leukocyte and lymphocyte traffic with LPS, IL-1, and TNF [35]. In addition, ICAM-1 can be dramatically up-regulated by TNF-alpha, IFN-gamma, and IL-1. These mediators increase ICAM-1-dependent T-cell blast binding to human umbilical vein endothelium [36]. These examples indicate that the leukocyte traffic to sites of inflammation is probably regulated by several factors that act at the level of endothelial cells. In the inflamed skin, several of those factors may be working in complex interactions with each other and their down-regulators. However, the result of those interactions is not the expression of HECA-452.

Selective lymphocyte migration is an important factor in determining the in vivo distribution of functionally distinct lymphocyte subpopulations. Streilein [37] has proposed that, as in the gut, a specialized network of structures in the skin can be defined as the skin-associated lymphoid tissue. He also has suggested that there might exist a subpopulation of lymphocytes that recirculate predominantly from the blood to the skin, and to the lymph nodes draining the skin. His idea is supported by the recirculation studies in sheep: when lymphocytes collected from afferent lymph draining skin granulomas were injected back into animals they preferentially left the blood stream at the site of the granuloma rather than within regional lymph nodes. This preference was not granuloma.

† Jalkanen and Jalkanen (submitted for publication).
‡ Lewinson et al (unpublished data).
Figure 3. Biopsy of a normal large bowel. A) Hermes-1 staining: almost all lamina propria mononuclear cells express Hermes antigen on their surfaces, but the venule (arrow) is totally negative. B) HECA-452 staining: the endothelial cells of the venule show strongly positive staining with HECA-452 antibody (Hematoxylin-eosin counterstain, magnification ×200).

Figure 4. Duodenal biopsy of a DH patient with a large number of plasma cells. A) Hermes-1 staining: almost all mononuclear cells are Hermes-1 positive. The large venule does not stain with Hermes-1 (arrow). B) HECA-452 staining: in this area no HECA-452 positive cells are seen, and also the same venule as in A (dashed line) is totally negative with HECA-452 (Hematoxylin-eosin counterstain, magnification ×400).
Figure 5. ICAM-1 staining of a patient suffering from atopic dermatitis. A) Skin biopsy without application of specific allergens. Sill moderate mononuclear cell infiltration is present. Luminal surface of endothelial cells of the venule stain with anti-ICAM-1 (arrow), but most infiltrating mononuclear cells are ICAM-1 negative or very faintly positive. B) Biopsy from the same patient after application of house dust mite. The number of infiltrating cells has increased, and many of these bear variable amounts of ICAM-1 antigen on their surface (arrowheads). Intensity of ICAM-1 staining on endothelial cells has increased (arrow).

specific, because enhanced entry could be detected also into normal skin. The fact that staining results obtained with Hermes-1/-3 and HECA-452 were uniform in all dermatologic diseases supports the above idea of a skin-specific lymphocyte-endothelial cell interaction system. However, the staining results of inflamed duodenum in both DH and CD were identical with those obtained from inflamed skin. Because more specific markers are not presently available in human system, we cannot exclude the possibility that there is a common lymphocyte-endothelial cell interaction system for different sites of inflammation.

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REFERENCES