MINIREVIEW

Lymphocyte-Homing Receptors and Preferential Migration Pathways (43201A)

YEE-HON CHIN,*,[1] ROBERT SACKSTEIN,*,† AND JIAN-PING CAI*

Departments of Microbiology and Immunology and Medicine,† University of Miami School of Medicine, Miami, Florida 33101 and the Miami VA Medical Center,† Miami, Florida 33125*

Lymphocytes recirculate continuously between blood and lymph. Through this process, T and B cells migrate to lymphoid organs such as peripheral lymph nodes (LN), intestinal lymphoid tissues (e.g., tonsils, Peyer's patches), and chronic inflammatory sites (reviewed in 1). The resultant redistribution and reassortment of lymphocytes facilitate antigenic recognition and promote cell-cell interactions central to the development of host immune defenses. Thus, knowledge of the molecular mechanisms controlling lymphocyte migration into tissues is of major importance to elucidating the pathophysiology of the immune response and may provide new strategies for regulating both normal and abnormal immune reactivity.

The first step in entry of blood lymphocytes into LN and intestinal lymphoid tissues is the binding of these cells to venules lined by high endothelium (HEV) (2). Recent studies have provided considerable insight into the lymphocyte and endothelial cell surface molecules that are involved in this interaction. In this review, we will describe the lymphocyte and endothelial surface membrane molecules involved in selective lymphocyte migration and the regulation of expression of these molecules with particular emphasis on the mediators and cytokines that potentially regulate the adhesive properties of high endothelial cells isolated from lymph nodes and Peyer's patches (PP).

Lymphocyte Migration Pathways and Homing Receptors

Lymphocyte migration through lymphoid tissues is nonrandom. Studies in rodents and sheep have demonstrated clearly that small lymphocytes and lymphoblasts exhibit preferential migration properties that are a function of lymphocyte class, stage of differentiation, and antigenic specificity (3). For example, lymphocytes from intestinal lymph tend to migrate through the gut-associated lymphoid tissue, while lymphocytes isolated from peripheral LN tend to recirculate through these organs (4). The differences in the migration patterns are even more prominent when lymphoblasts are studied (5). For lymphocytes to migrate selectively into peripheral or mucosal lymphoid organs, a mechanism must exist to permit these cells to leave the vasculature and emigrate into the parenchyma selectively. Over the past few years, it has become clear that the selective binding between circulating lymphocytes and HEV cells lining the postcapillary venules is an important factor controlling the nonrandom distribution of lymphocytes into different lymphoid organs. This adhesion process is mediated by lymphocyte glycoprotein molecules, functionally defined as homing receptors, which possess affinity for organ-specific endothelial ligands (vascular addressins) (6–8).

Monoclonal antibodies have been produced which identified homing receptors specific for HEV of LN in mouse (9), rat (10), and human (11) and specific for HEV of PP in rat (12) and mouse (13, 14). For example, in the rat, antibodies to lymphocyte surface molecules for LN HEV (A.11.5 antibody) block lymphocyte adhesion to HEV of LN, but not binding of these cells to HEV of PP, whereas antibodies to surface receptors for PP HEV (1B.2.6) block lymphocyte binding to HEV of PP but not to HEV of LN. In the mouse, the MEL-14 antibody blocks the adhesion of murine lymphocytes to HEV of LN but does not block lymphocyte binding to HEV of PP.

In addition to the tissue-specific homing receptor/ligand interaction, at least three other families of adhesion molecules appear to play an accessory role in lymphocyte-HEV binding. In humans, the Hermes an-

[1]To whom requests for reprints should be addressed.

Received 0037-9727/90/1964-0374$3.00/0

tigens were initially described as tissue-specific homing receptors on lymphocytes (15). The Hermes-3 monoclonal antibody specifically blocked the adhesion of human lymphocytes to mucosal HEV and immunoprecipitated a molecule with apparent molecular size of 90 kDa that was similar in size to the MEL-14 antigen (16). However, several lines of evidence now suggest that the epitopes identified by Hermes antibodies on human lymphocytes reside on a single molecule which may function in an accessory capacity for lymphocyte binding to vascular endothelial cells. Molecular cloning has revealed that the structure identified by the Hermes monoclonal antibodies is identical to CD44, the human homologue of the murine Pgp-1 molecule, and the extracellular matrix receptor type III (17, 18). These findings, coupled with the observation that the molecule is present on fibroblasts, monocytes, granulocytes, endothelial cells, keratinocytes, and lymphocytes, suggest that the Hermes molecule is a receptor for extracellular matrix proteins. Other studies have also suggested a relationship between receptors for extracellular matrix proteins and lymphocyte adhesion to PP high endothelium. The monoclonal antibody LPAM-1 blocks binding of murine lymphocytes to HEV of PP, but not to HEV of peripheral LN and immunoprecipitates a noncovalently associated heterodimer of 160- and 130-kDa subunits (14). A monospecific rabbit antiserum to human VLA-4a chain binds to the 160-kDa subunit. However, the expression of LPAM-1 molecules on transfected cells is not sufficient for HEV binding (19). Since VLA molecules are members of the integrin family and also function as receptors for extracellular proteins (e.g., fibronectin), the possibility therefore exists that lymphocytes may interact with extracellular matrix proteins that are present on the surface of HEV cells to strengthen the binding between the tissue-specific receptor/ligands. Interestingly, a very recent study using the *in vitro* lymphocyte-LN-frozen section binding assay reported that the VLA-4 molecules may also be involved in the adhesion of activated human B cells to germinal centers (20), thus providing additional support for the role of extracellular matrix in lymphocyte migration and segregation.

In addition to the VLA molecules, another member of the integrin family has also been shown to play a role in nonorgan-specific lymphocyte adhesion to HEV cells. Monoclonal antibodies to the LFA-1 molecule significantly, but incompletely, blocked the *in vitro* adhesion of murine and human lymphocytes to both HEV of LN and HEV of PP and also interfered partially with murine lymphocyte migration into LN and PP *in vivo* (21, 22). It is important to note that the integrin molecules LFA-1, Mac-1, and p150,95, which share a common β chain, have also been shown to be important in the adhesion of leukocytes to vascular endothelial cells as well as to other cell types, although the effects of anti-Mac-1 and anti-p150,95 on lymphocyte adhesion to HEV have not been tested. Interestingly, the migration of lymphocytes into the lungs of anti-LFA-1-treated animals was inhibited to an even greater extent than lymphoid tissues, thus suggesting that this molecule may play a pivotal role for lymphocyte localization into the lung (22).

Molecular Cloning of Genes Encoding Homing Receptors

In the past 2 years, cDNA clones encoding lymph node-homing receptors (LNHR) from several species have been isolated and sequenced. These studies have revealed that these proteins bear structural similarities to several other proteins that function in cell adhesion events, and thus may comprise a protein superfamily. In the mouse, LNHR clones were isolated from cDNA libraries by hybridization screening using oligonucleotides constructed using available sequences of the MEL-14 protein (23, 24). The deduced amino acid sequence of 372 residues shows interesting features: the N-terminal sequence of 118 amino acids exhibits high homology to C-type animal lectins, the next 37 amino acids consist of an epidermal growth factor-like domain (including the characteristic six consensus cysteine residues), and the remaining extracellular portion of the molecule includes two identical repeats of a 62-amino acid sequence homologous to complement regulating proteins which bind primarily to C3b or C4b. The DNA sequence suggests a hydrophobic transmembrane domain of 23 amino acids, followed by a cytoplasmic tail of 17 residues. The mature protein contains 10 potential *N*-glycosylation sites, consistent with previous reports that the MEL-14 antigen is heavily glycosylated. Interestingly, a similar domain structure has been found for the ELAM-1 molecule (25), a cell surface glycoprotein which appears to be an endothelial ligand for polymorphonuclear leukocytes but not lymphocytes. The mRNA for ELAM-1 is induced within 1–2 hr in cultures of umbilical vein endothelial cells by proinflammatory cytokines such as interleukin 1 (IL-1) and tumor necrosis factor (TNF) and then declines rapidly to basal levels within 24 hr. The rapid induction and decline of ELAM-1 *in vitro* is consistent with the idea that this molecule promotes polymorphonuclear leukocyte adhesion and emigration at sites of acute inflammation.

The human homologue of MEL-14 has been isolated from human lymphocyte cDNA libraries by differential hybridization (26), by immunoscreening of transfected cDNA clones (27), and by hybridization selection screening using MEL-14 cDNA probes (28, 29). The human homologue of MEL-14 appears to be the Leu-8 or LAM-1 molecule, and there is 77% amino acid sequence homology between these proteins with similar organization. We have isolated homologous rat

cDNA clones by immunoselection screening of a rat thoracic duct lymphocyte cDNA library using polyclonal antiserum directed against rat LNHR (A.11 protein). The organization of rat LNHR resembles that of mouse, with available sequence revealing −85% homology to mouse LNHR in the coding region. Using rat LNHR cDNA clones in transfection experiments, we have demonstrated that surface expression of the A.11 protein confers the functional capacity of cells to bind to LN HEV *in vitro*. Transfection of COS 7 cells or the mouse pre-B cell line 70Z/3 with a full-length rat LNHR cDNA clone inserted into the pCEXV vector leads to the expression of surface antigens recognized by the A.11.5 antibody and results in the capacity of these cells to specifically bind to HEV of LN but not to HEV of PP as assessed in the lymphocyte-frozen tissue adherence assay. Importantly, treatment of the transfected cells with A.11.5 antibody selectively blocks the adhesion. This finding provides strong evidence that expression of A.11 protein is a necessary feature for lymphocyte adhesion to HEV of LN in the rat.

As noted above, cDNA clones encoding the Hermes protein have been isolated and sequenced. The deduced amino acid sequence obtained from these studies reveals that Hermes protein is CD44 and there is no homology with MEL-14 or the integrin gene family. The N-terminal end of the Hermes molecule shares 30% homology with chicken and rat cartilage link proteins and part of the rat cartilage proteoglycan (17). This finding supports the idea that Hermes antigens may function in nonorgan-specific adhesion process and/or may facilitate the interactions between organ-specific homing receptor and endothelial ligands.

Regulation of Lymphocyte-Homing Receptor Expression. With the use of respective cDNA probes, Northern blot analysis of RNA from mouse and human demonstrates tissue-specific variation in LNHR levels. In both species, LNHR RNA abundance generally parallels cell surface expression of the homing receptor; LNHR RNA is highest in lymphoid cells capable of binding to LN HEV and is not seen in nonlymphoid cells. Of note, Northern blot analysis of mouse LNHR revealed transcripts of 1.5 kb, 2.5 kb, and 5.2 kb (23), whereas in the human either a single LNHR transcript of 2.5 kb is identified or two bands (at 1.7 kb and 2.6 kb) are observed (26, 27). In the rat, a single 2.2 kb LNHR transcript is detected in Northern blot analysis of RNA from lymphoid cells and tissues, and no signal is observed in nonlymphoid cells (liver and kidney). Of interest, in Northern blot analysis, rat thymocytes possess 5-fold higher LNHR levels than that observed from mature recirculating thoracic duct lymphocytes (TDL). However, sodium dodecyl sulfate-polyacrylamide gel electrophoresis analysis of immunoprecipitated radiolabeled surface protein reveals prominent LNHR expression on TDL cells but not on thymocytes. Moreover, metabolic radiolabeling studies using [^{35}S]methionine reveal *de novo* synthesis of LNHR in TDL but not in thymocytes. These data suggest a role for post-transcriptional regulation of LNHR expression in immature lymphocytes (30).

It has been known for some time that lymphocytes activated *in vitro* by exposure to exogenous antigens or cytokines failed to adhere to HEV and migrate into LN or PP *in vivo*. Recent studies have provided some insight into the mechanisms that may account for this phenomenon. Murine lymphocytes activated with phorbol ester shed a soluble LN-homing receptor that is 12 kDa smaller than the intact receptor (31). Similarly, the human MEL-14 homologue, LAM-1, is also released upon stimulation of human lymphocytes (32). In addition, we have also shown that expression of the rat PP-homing receptor is also modulated rapidly upon stimulation by phorbol ester but not by a biologically inert analog. Moreover, rat lymphocytes that are cultured in the presence of TNF-α also release the LN- and PP-homing receptor, albeit with different kinetics (33). This rapid shedding of the homing receptor may be a physiologic process which allows the lymphocyte to detach from the HEV cells after binding and migrate into the parenchyma.

The mechanism(s) responsible for the shedding of the homing receptors are unclear at present, although the possible involvement of a cell membrane protease has been proposed (31). This notion is supported partly by the observations that a trypsin-like serine protease is present in cloned murine lymphocytes and may facilitate lymphocyte extravasation through its ability to degrade extracellular matrix (34). It has also been reported that a serine endopeptidase is inducible in human T cell clones by lectin stimulation or by ligand binding to the CD3/T cell receptor complex (35). Alternatively, it is conceivable that endothelial-derived proteases may also be secreted by HEV cells after lymphocyte attachment. In this event, the synergistic action of the enzymes may lead to the rapid extravasation of lymphocytes *in vivo*. At present, the putative proteases have not been identified but it is known that a variety of protease inhibitors such as TPCK, leupeptin, pepstatin, aprotinin, and chymotrypsin have no effect on the modulation of murine lymphocyte MEL-14 antigen expression (36).

Cytokine Regulation of High Endothelial Cell Adhesiveness for Lymphocytes. Although considerable progress has been made in elucidating the molecular nature of the homing receptors, relatively little is known about the complementary adhesive ligands and the factors that regulate their expression. An elegant series of studies established that the endothelial component of HEV is capable of controlling the magnitude and specificity of lymphocyte adhesion: HEV in lymph nodes deprived of afferent lymphatic vessels rapidly lost

the characteristic columnar and cuboidal shape and became flat and migration of lymphocytes through these flattened vessels was severely impaired, even though the blood flow into these nodes was normal (37). Interestingly, kinetic studies demonstrated that the inability of lymphocytes to cross the HEV preceded the actual alteration in morphology of the high endothelia. Conversely, the tall, columnar characteristics of HEV could be restored by injection of macrophages into the affected LN or by antigenic stimulation, suggesting that the specialized phenotype can be induced locally (38). More recently, it has been reported that incubation of pulmonary endothelial cell lines with cytokines such as γ-interferon resulted in the induction of HEV-specific antigens detected by the MECA-325 antibody, which labels HEV of LN and HEV of PP specifically (39). These observations suggest that cytokines secreted by lymphocytes or monocytes/macrophages regulate the morphology and function of HEV cells and is consistent with the idea that cytokines can stimulate vascular endothelial cells to develop HEV-like properties and promote lymphocyte-endothelial cell adhesion in chronic inflammatory sites.

Recently, approaches have been developed to isolate and grow endothelial cells from postcapillary venules of rat LN (40, 41) and PP (42), and to study lymphocyte adhesion to monolayers of the cultured HEV cells. The identity of the HEV cells was verified by their capacity to incorporate radioactive sulfate, a property previously shown to be associated preferentially with cells lining the HEV. Interestingly, freshly isolated or cultured LN and PP HEV cells do not express either Factor VIII- or Factor XIIIa-related antigens, which are widely accepted markers for endothelial cells. The cultured HEV cells, however, incorporate high levels of acetylated low-density lipoprotein, thus distinguishing them from fibroblasts.

The cultured HEV cells provide a biologically relevant system to study the factors that regulate lymphocyte-HEV interactions *in vitro*. The results of these studies indicate that lymphocytes from thoracic duct lymph, spleen, and lymph nodes are capable of adhering to the HEV monolayers. In contrast, immature cells from the thymus and bone marrow are deficient in this capacity. This finding suggests that cultured HEV cells retain the function and specificity that characterized lymphoid HEV *in vivo*. In other experiments, it has been shown that lymphocytes from mucosal lymphoid tissues are heterogeneous in their capacity to bind to PP HEV cells, with gut intrapithelial lymphocytes (IEL) exhibiting an increased ability to bind to the HEV monolayers as compared with lymphocytes isolated from the Peyer's patch or the lamina propria of the small intestine (42). A number of studies have shown that murine IEL preferentially express the γ/δ chain of the TCR and may represent a unique population of cells with functional potentials differing from those lymphocytes in the periphery. Although the precise mechanisms that are responsible for the selective localization of IEL are not known, it is tempting to speculate that the preferential adhesion to PP HEV may play an important role in the assortment and distribution of IEL within the gut.

Cultured HEV cells have been employed by us to test the hypothesis that the functional properties of HEV are regulated by cytokines secreted within the lymphoid microenvironment. In the initial experiments, treatment of rat PP HEV cells with cytokines such as TNF-α, γ-interferon, or granulocyte-macrophage colony-stimulating factor resulted in the stimulation of endothelial adhesiveness for lymphocytes in a time- and dose-dependent manner. Thus, at a concentration as low as 0.5 units/ml and at an incubation time of 6 hr, TNF-α significantly increased the proportion of TDL binding to the PP HEV cell monolayers. Binding then declined over a period of 24–48 hr, regardless of the presence or absence of the cytokines in the culture medium.

Two lines of evidence suggest that the cytokines exert their effect by enhancing the expression of organ-specific endothelial ligands (vascular addressins) that PP HEV cells normally express *in vivo*. First, the cytokine-stimulated PP HEV cells promoted selectively the adherence of TDL, but not immature cells such as thymocytes which are deficient in homing receptor expression. Moreover, the cytokines do not stimulate the inherent low adhesiveness of rat dermal fibroblasts for mature lymphocytes. Second, the enhanced binding can be blocked specifically by pretreatment of lymphocytes with the PP-homing receptor-specific 1B.2.6 monoclonal antibody, but not by antibodies to the LN-homing receptor (A.11.5) or other lymphocyte surface molecules. Interestingly, recombinant murine IL-1β was relatively ineffective in stimulating the adhesiveness of PP HEV cells. This finding is intriguing, since it has previously been suggested that IL-1 and TNF stimulate a similar genetic program in large vessel endothelial cells, although the two cytokines bind to distinct receptors on the endothelial cell surface. This finding therefore suggests that HEV cells differ from large vessel endothelial cells in their response to certain cytokines. At present it is not known whether adhesion to HEV cells by neutrophils and monocytes are likewise promoted. Nevertheless, cytokine stimulation of HEV cells may be of physiologic significance. Secretion of TNF by macrophages or γ-interferon by activated T cells *in vivo* could result in increased lymphocyte traffic into PP. Conversely, activation of lymphocytes by the relevant cytokines could lead to the loss of homing receptor expression and sequestration of lymphocytes in the tissue. In conjunction with vasodilation of the PP vas-

culature, these processes would then result in increased delivery of lymphocytes into the tissue.

Additional studies have revealed that the regulation of HEV adhesiveness by cytokines likely involves a complex series of events. Transforming growth factor-β (TGF-β), an evolutionarily conserved family of polypeptide hormones that are bifunctional modulators of diverse biologic processes, may play a pivotal role in the modulation of HEV adhesiveness. At picomolar concentrations, TGF-β exhibits a potent antiproliferative effect on vascular endothelial cells. For example, TGF-β was shown to interfere with the adhesive interactions between human umbilical cord endothelial cells and neutrophils (43), and may play an anti-inflammatory role at sites of blood vessel injury. We have extended this analysis to investigate the effects of TGF-β on the adhesiveness of microvascular endothelial cells (44) and PP HEV cells for lymphocytes (45). Addition of TGF-β to the cultured HEV cells significantly decreases their ability to bind to circulating lymphocytes in a time- and dose-dependent manner. Furthermore, TGF-β blocks the effects of TNF-α and γ-interferon, two cytokines that normally enhance adhesiveness on HEV cells. In addition, TGF-β also abrogates the enhanced adhesiveness of HEV cells pretreated with TNF-α, γ-interferon, and granulocyte-macrophage colony-stimulating factor. In this context, the ability to the cytokine to decrease the adhesiveness of HEV cells for lymphocytes may be an important mechanism for the control of lymphocyte trafficking into lymphoid tissues.

Lymphocyte-HEV Interactions in Chronic Inflammatory Lesions. Although the phenotype and function of HEV plays an important role in lymphocyte migration into lymphoid tissues, it is important to recall that venules lined with plump, columnar, and cuboidal endothelial cells are not limited to lymphoid tissues. Morphologic and histochemical changes have been observed in venules associated with sites of chronic lymphocytic accumulation in diseased tissues such as synovium of rheumatoid arthritis, thyroid tissues in Graves disease, and the dermis of psoriatic lesions (reviewed in 46).

The obvious morphologic similarities between lymphoid HEV and the HEV-like vessels in chronically inflamed tissues suggest that they may share a similar function in promoting the prolonged and extensive emigration of lymphocytes from blood into such tissues. This possibility was investigated by examining the adhesive interaction between human lymphocytes and the postcapillary venules of psoriatic plaques through an *in vitro* lymphocyte-frozen tissue section adherence assay. The results demonstrated clearly that the specialized endothelial cells lining the postcapillary venules in psoriatic dermis are capable of promoting lymphocyte adherence (47). The adhesion process is energy and calcium dependent and involves surface molecules which are sensitive to trypsin and endoglycosidase treatment, requirements that are similar to lymphocyte binding to HEV of lymphoid tissues. However, the pretreatment of lymphocytes with antibodies against lymphocyte-homing receptors for LN and PP HEV had little effect on lymphocyte binding to the psoriatic postcapillary venules. Moreover, antibodies against CD11/CD18 molecules only decreased the binding partially. In other experiments, quantitative assessment of lymphocyte adhesion demonstrated that human CD4 T cells and the CD29 (memory) subset adhered preferentially as compared with the CD8 or CD45RA (naive) subset (48). Since an increase of memory T cells is a general feature of chronic inflammatory infiltrates in autoimmune diseases, the implication is that changes in the local vasculature to a lymphocyte-receptive phenotype may not be disease specific, but rather are a common feature in sites of lymphocyte infiltration. In support of this idea, other studies have found that B cell clones that bind LN and PP HEV failed to bind to HEV-like vessels in rheumatoid synovium, and that the MEL-14 antibody, which is specific for the LN-homing receptor, has no effect on lymphocyte binding to synovium (49). At the present time it is not clear whether the receptor/ligand interaction that mediates lymphocyte adhesion to psoriatic dermal endothelial cells is the same as that mediating adhesion to synovial vessels.

Most studies indicate that the development of HEV-like vessels within chronic inflammatory lesions is a rather late phenomenon. For example, it occurs many weeks after the appearance of anticolloid antibodies and initial immune reactivity in lymph nodes draining thyroid tissues in Graves' disease (50). Since activated T cells and antigen-presenting cells are known to secrete cytokines such as γ interferon, IL-1, and TNF, which can induce or stimulate adhesiveness of HEV cells and large vessel endothelial cells *in vitro*, exposure to these cytokines *in vivo* may induce the expression of novel endothelial ligands *in vivo* promoting endothelial adhesiveness.

Summary

Over the next few years, research can be expected to focus on the regulation of expression of the tissue-specific homing receptors, the molecular nature of the corresponding endothelial ligands, and the spectrum of factors regulating the adhesiveness of high endothelial venule cells *in vivo*. In addition, it would be important to elucidate whether other adhesion molecules also play a role in tissue-specific lymphocyte entry and localization into distinct regions of the lymphoid organ. The results of these studies should provide important insights into the mechanisms controlling lymphocyte trafficking into lymphoid tissues as well as chronic inflammatory sites.

This work was supported by grants from the National Institutes of Health, American Cancer Society, and American Heart Association. R. S. is a recipient of a VA Career Development Award. J-P. C. was partially supported by the CUPEP program, Atlanta, CA.

We thank Dr. Lourdes Rivera for critical review of the manuscropt. Due to space limitations, we apoligize for omissions in our citation of work in this active research area.

1. Butcher EC. The regulation of lymphocyte traffic. Curr Top Microbiol Immunol **128**:85–127, 1986.
2. Marchesi VT, Gowans JL. The migration of lymphocytes through the endothelium of venules in lymph nodes: an electron microscopic study. Proc R Soc Lond (Biol) **159**:283–303, 1964.
3. Ford WL. Lymphocyte migration and immune response. Proc Allergy **19**:1–112, 1975.
4. Cahill RNP, Poskitt DC, Frost H, Trnka Z. Two distinct pools of recirculating T lymphocytes: Migratory characteristics in intestinal T lymphocytes. J Exp Med **145**:420–433, 1977
5. Smith M, Martin E, Ford WL. Migration of lymphoblasts. Mongr Allergy **16**:203–232, 1983
6. Gallatin WM, St. John TP, Siegelman M, Reichert R, Butcher EC, Wissman IL. Lymphocyte homing receptors. Cell **44**:673–676, 1986.
7. Woodruff JJ, Clarke L, Chin YH. Specific cell-adhesion mechanisms determining the migration pathways of recirculatng lymphocytes. Annu Rev Immunol **5**:201–222, 1987.
8. Berg EL, Goldstein L, Jutila M, Nakache M, Picker L, Streeter P, Wu N, Zhou D, Butcher EC. Homing receptors and vascular addressins: cell adhesion molecules that direct lymphocyte traffic. Immunol Rev **108**:5–17, 1989.
9. Gallatin WM, Weissman IL, Butcher EC. A cell-surface molecule involved inorgan-specific homing of lymphocytes. Nature **303**:30–34, 1983.
10. Rasmussen R, Chin YH, Woodruff JJ, Easton TG. Lymphocyte recognition of lymph node high endothelium. VII. Cell surface proteins involved in adhesion defined by anti-HEBF$_{LN}$ (A.11) antibody. J Immunol **135**:19–24, 1985.
11. Kishimoto TK, Jutila MA, Butcher EC. Identification of a human peripheral lymph node homing receptor: A rapidly down-regulated adhesion molecule. Proc Natl Acad Sci USA **87**:2244–2248, 1990.
12. Chin YH, Rasmussen R, Woodruff JJ, Easton TG. Monoclonal anti-HEBF$_{PP}$ antibody with specificity for lymphocyte surface molecules mediating adhesion to Peyer's patch high endothelium of the rat. J Immunol **136**:2256–2560, 1986.
13. Holzmann B, McIntyre BW, Weissman IL. Identification of a murine Peyer's patch-specific lymphocyte homing receptor as an integrin molecule with an alpha chain homologous to human VLA-4a. Cell **56**:37–43, 1989.
14. Holzman B, Weissman IL. Integrin molecules involved in lymphocyte homing to Peyer's patches. Immunol Rev **108**:45–55, 1989.
15. Jalkanen S, Bargatze RF, Herron L, Butcher EC. A lymphoid cell surface glycoprotein involved in endothelial cell recognition and lymphocyte homing in man. Eur J Immunol **16**:1195–1202, 1986.
16. Jalkanen S, Bargatze RF, de los Toyos J, Butcher EC. Lymphocyte recognition of high endothelium: Antibodies to distinct epitopes of an 85–95 kD glycoprotein antigen differnetially inhibit lymphocyte binding to lymph node, mucosal, or synovial endothelial cells. J Cell Biol **105**:983–990, 1987.
17. Goldstein, L, Zhou D, Picker L, Minty C, Bargatze RF, Ding J, Butcher EC. A human lymphocyte homing receptor, the Hermes antigen, is related to cartilage proteoglycan core and link proteins. Cell **56**:1053–1072, 1989.
18. Idzerda RL, Carter WG, Wayner EA, Nottenburg C, Gallatin WM, St. John T. Structural homology between lymphocyte homing receptors and extracellular matrix receptor Type III. Proc Natl Acad Sci USA **56**:4659–4663, 1989.
19. Holzman B, Weissman IL. Peyer's patch-specific lymphocyte homing receptors consist of a VLA-4-like alpha chain associated with either of two integrin beta chains, one of which is novel. EMBO J **8**:1735–1742, 1989.
20. Freedman AS, Munro JM, Rice GE, Bevilaqua MP, Morimoto C, McIntyre BW, Rhynhart K, Pober JS, Nadler LM. Adhesion of human B cells to germinal centers in vitro involves VLA-4 and INCAM-110. Science **249**:1030–1033, 1990.
21. Hamann A, Jablonski-Westrich D, Duijvestijn A, Butcher EC, Baisch H, Harder R, Thiele R. Evidence for an accessory role of LFA-1 in lymphocyte-high endothelium interaction during homing. J Immunol **140**:663–670, 1988.
22. Pals ST, den Otter A, Miedema F, Kabel P, Keizer GD, Scheper R, Meijer CJL. Evidence that leukocyte function-associated antigen-1 is involved in recirculation and homing of human lymphocytes via high endothelial venules. J Immunol **140**:1851–1857, 1988.
23. Siegelman M, van de Rijn M, Weissman IL. Mouse lymph node homing receptor cDNA clone encodes a glycoprotein revealing tandem interaction repeats. Science **243**:1165–1172, 1989.
24. Lasky L, Yednock T, Singer M, Dowbenko D, Fennie C, Nguyen T, Rodriguez H, Stachel S, Rosen S. Cloning of a lymphocyte homing receptor reveals a lectin domain. Cell **56**:1045–1055, 1989.
25. Bevilaqua MP, Stengelin S, Gimbrone MA Jr., Seed B. Endothelial leukocyte adhesion molecule 1: An inducible receptor for neutrophils related to complement regulatory proteins and lectins. Science **243**:1160–1165, 1989.
26. Tedder TF, Issacs CM, Ernst TJ, Demetri GD, Adler DA, Disteche CM. Isolation and chromosomal localization of cDNAs encoding a novel human lymphocyte cell surface molecule, LAM-1: Homology with the mouse lymphocyte homing receptor and other human adhesion proteins. J Exp Med **170**:123–133, 1989.
27. Camerini D, James SP, Stamemkovic, Seed B. Leu-8/TQ 1 is the human equivalent of the MEL-14 lymph node homing receptor. Nature **342**:78–82, 1989.
28. Siegelman MH, Weissman IL. Human homologue of mouse lymph node homing receptor. Evolutionary conservation at tandem cell interaction domains. Proc Natl Acad Sci USA **86**:5562–5566, 1989.
29. Bowen BR, Nguyen T, Lasky LA. Characterization of a human homologue of the murine peripheral lymph node homing receptor. J Cell Biol **109**:421–427, 1989.
30. Sackstein R, Chin YH. Lymph node homing receptor gene expression in thymocytes is regulated at a post-transcriptional level. Blood **76**(supp 1):218A, 1990.
31. Jung TM, Dailey MO. Rapid modulation of homing receptors (gp90MEL-14) induced by activators of protein kinase C. Receptor shedding due to accelerated proteolytic cleavage at the cell surface. J Immunol **144**:3130–3136, 1990.
32. Tedder TF, Penta AC, Levine HB, Freedman AS. Expression of the human leukocyte adhesion molecule, LAM-1. Identity with the TQ1 and Leu-8 differentiation antigens. J Immunol **144**:532–540, 1990.
33. Chin YH, Cai JP. Regulation of lymphocyte adhesion to Peyer's patch high endothelial venule cells: role of tissue-specific homing receptors. Immunol Res (in press).
34. Simon MM, Simon HG, Fruth U, Epplen J, Muller-Hermelink HK, Kramer MD. Cloned cytotoxic T-effector cells and their malignant variants produce an extracellular matrix degrading trypsin-like serine protease. Immunology **60**:219–230, 1987.
35. Fruth U, Sinigaglia F, Schlesier M, Kilgus J, Kramer MD, Simon

MM. A novel serine protease (HuTSP) isolated from a cloned human CD8+ cytotoxic T cell line is expressed and secreted by activated CD4+ and CD8+ lymphocytes. Eur J Immunol **17**:1625–1633, 1987.
36. Huang K, Beigi M, Daynes RA. Peripheral lymph node-specific and Peyer's patch-specific homing receptors are differentially regulated following lymphocyte activation. Regional Immunol **3**:103–111, 1990.
37. Hendriks H, Eestermans IL, Hoefsmit EC. Depletion of macrophages and disappearance of postcapillary high endothelial venules in lymph nodes deprives of afferent lymphatic vessels. Cell Tissue Res **211**:375–388,1 980.
38. Hendriks H, Duijvestijn AM, Kraal G. Rapid decreae in lymphocyte adherence to high endothelial venules in lymph nodes deprived of afferent lymphatic vessels. Eur J Immunol **17**:1691–1699, 1987.
39. Nakache M, Berg EL, Streeter P, Butcher EC. The mucosal vascular addressin is a tissue-specific endothelial cell adhesion molecule for circulating lymphocytes. Nature **331**:41–47, 1988.
40. Ager A. Isolation and culture of high endothelial cells from rat lymph nodes. J Cell Sci **87**:133–148, 1987.
41. Ise Y, Yamaguchi K, Sato K, Yamamura Y, Kitamura F, Tamatani T, Miyasaka M. Molecular mechanisms underlying lymphocyte recirculation. I. Functional, phenotypical and morphological characterization of high endothelial cultures in vitro. Eur J Immunol **18**:1235–1243, 1988.
42. Chin YH, Cai JP, Johnson K. Lymphocyte adhesion to cultured Peyer's patch high endothelial venule cells is mediated by organ-specific homing receptors and can be regulated by cytokines. J Immunol **145**:3669–3677, 1990.
43. Gamble JR, Vadas MA. Endothelial adhesiveness for blood neutrophils is inhibited by transforming growth factor-beta. Science **242**:97–100, 1988.
44. Cai JP, Falanga V, Chin YH. Transforming growth factor beta-1 regulates the adhesive interactins between mononuclear cells and the microvascular endothelium. J Invest Dermatol (in press).
45. Chin YH, Cai JP. The effects of transforming growth factor beta-1 and IL-4 on the adhesiveness of Peyer's patch high endothelial venule cells. J Immunol (in press).
46. Chin YH, Falanga V, Streilein JW, Sackstein R. Lymphocyte recognition of psoriatic endothelium: evidence for a tissue-specific receptor/ligand interaction. J Invest Dermatol **93**:82S–87S, 1989.
47. Sackstein R, Falanga V, Streilein JW, Chin YH. Lymphocyte adhesion to psoriatic dermal endothelium is mediated by a tissue specific receptor/ligand interaction. J Invest Dermatol **91**:423–428, 1988.
48. Chin YH, Falanga V, Taylor JR, Cai JP, Bax J. Adherence of human helper/memory T-cell subsets to psoriatic dermal endothelium. J Invest Dermatol **94**:413–418, 1990.
49. Jalkanen S, Steere AC, Fox RI, Butcher EC. A distinct endothelial cell recognition system that controls lymphocyte traffic into inflamed synovium. Science **233**:556–559, 1986.
50. Freemont AJ. A possible route for lymphocyte migration into diseased tissues. J Clin Pathol **36**:161–166, 1983.