American Journal of Pathology, Vol. 141, No. 4, October 1992

Role of β1-Integrins in Epidermotropism of Malignant T Cells

Wolfram Sterry,* Volker Mielke,* Ulrich Konter,† Imke Kellner,* and Wolf-Henning Boehncke*

From the Department of Dermatology, University of Ulm, Ulm, and Bundeswehrkrankenhaus,† Hamburg, Germany*

To better understand the molecular mechanisms of epidermotropism, we immunohistochemically analyzed the expression pattern of adhesion molecules belonging to the integrin and immunoglobulin superfamilies in cases of mycosis fungoides (MF) (n = 15), pleomorphic T cell lymphoma (n = 10), and high-grade T cell lymphoma (n = 7). The cutaneous T cell lymphomas (CTCLs) investigated were categorized into cases with or without epidermotropism. Focal neoexpression of ICAM-1 on keratinocytes was restricted to epidermotropic lymphomas. Both LFA-1 and LFA-3 were expressed on infiltrating cells in all cases investigated. In contrast, β1-integrins showed differential expression, most prominent in the case of VLA-1 and VLA-6. These molecules were present on infiltrating cells in most cases with epidermotropic MF and absent in most other CTCLs. We conclude that the phenomenon of epidermotropism might involve different sets of adhesion molecules in different entities of CTCL, with VLA-1 being the most influential β1-integrin in the case of MF. (Am J Pathol 1992, 141:855–860)

New perspectives in understanding tumor cell biology of cutaneous T cell lymphomas (CTCLs) emerged from the discovery of cell surface receptors, which play a central role in adhesive interactions of T cells with other cells as well as with the extracellular matrix.[1] These adhesion molecules regulate immune functions like adherence to vascular endothelial cells,[2,3] migration of lymphocytes into extravascular tissue,[4] T cell interaction with antigens and accessory cells,[5] as well as nonrandom recirculation.[6]

Integrins[7] are perhaps the most versatile of the adhesion molecule families. They are composed of heterodimers with a subfamily-specific unique β-chain and an individual α-chain. Up to now, five subfamilies have been distinguished by their β-subunits. Most important are the β1-, β2- and β3-integrins. The β1-integrin subfamily[8] includes cell receptors that bind to the extracellular matrix components fibronectin, collagen, and laminin. VLA-4 has a dual function as both matrix and cell receptor.[9] LFA-1, a member of the β2-integrins,[10] interacts with ICAM-1[11,12] and ICAM-2,[13] both belonging to the immunoglobulins. Two other members of the immunoglobulins form the receptor–ligand pair LFA-3/CD2.[14,15]

Cutaneous T cell lymphomas are lymphoproliferative malignancies mainly of $CD4^+$ T cells.[16] Most prominent in the histopathology of cutaneous lymphomas is the phenomenon of T cell epidermotropism. Lymphocytes aggregating within the epidermis, thus forming Pautrier's abscesses, are a characteristic finding in early mycosis fungoides (MF). Progression of the disease into tumor stage often results in a loss of epidermotropism and subsequent systemic dissemination of tumor cells.[17]

There is evidence that both the initial epidermotropism as well as the subsequent dissemination of T cells in CTCLs are caused by changes in the expression pattern of adhesion molecules: ICAM-1 can be expressed on a variety of cells, including keratinocytes. Its inducibility by inflammatory mediators is an important mechanism for the regulation of its interaction with LFA-1, resulting in a mononuclear cell infiltrate at the site of inflammation.[18] In a similar way, during early stages of CTCL, T cells are present in an epidermis, exhibiting keratinocytes that express high levels of ICAM-1.[19] In a case of Sézary's syndrome lacking epidermotropism, however, Nickoloff and co-workers found that ICAM-1 expression of keratinocytes was also missing.[20] The authors conclude that, because of this lack of ICAM-1 expression, malignant T cells are released from the epidermal compartment now causing systemic disease.

To further determine the role of adhesion molecules in the phenomenon of epidermotropism, we analyzed and compared the expression pattern of nine adhesion molecules on keratinocytes and the mononuclear infiltrate in cases of epidermotropic and nonepidermotropic CTCLs. We show that focal neoexpression of ICAM-1 is restricted to epidermotropic CTCLs. Infiltrating cells positive for

Accepted for publication April 14, 1992.

Address reprint requests to Dr. Wolfram Sterry, Department of Dermatology, University of Ulm, Oberer Eselsberg 40, 7900 Ulm, Germany.

VLA-1 and VLA-6 were a characteristic feature of epidermotropic MF.

Materials and Methods

Specimens

We investigated biopsy material from patients with MF (n = 15), pleomorphic T cell lymphoma (n = 10), and high-grade T cell lymphoma (n = 7) that were excised under local anesthesia before systemic or topical treatment. Informed consent was obtained. Biopsies were snap-frozen in 0,9% NaCl solution with liquid nitrogen and stored at −80°C in a freezer. Serial 6-μ thick frozen sections were cut from each block on a cryostat, air dried for 24 hours, and stored at −20°C until used.

Monoclonal Antibodies

The anti ICAM-1 monoclonal antibody (MAb) RR1/1,[21] anti LFA-3 MAb TS2/9,[22] and anti VLA-1 MAb TS2/7[23] were gifts from Dr. T. A. Springer (Boston). Anti VLA-β1 MAb A-1A5[24] and anti VLA-4 MAb B-5G10[25] were placed at our disposal by Dr. M. E. Hemler (Boston). R. Kantor (New York) provided us with the anti VLA-3 MAb J143.[26] 10G11[27] detecting VLA-2 and GoH3[28] directed against VLA-6 were gifts from Dr. von dem Borne (Amsterdam) and Dr. Sonnenberg (Amsterdam), respectively. Dr. Damsky (San Fancisco) provided us with the anti VLA-5 mAb BIIG2.[29] Horseradish peroxidase conjugated rabbit anti-mouse antibodies and goat anti-rabbit antibodies were purchased from Dakopatts (Denmark) and Medac (Germany).

Indirect Immunoperoxidase Procedure

Immunohistochemical stainings were performed using a standard three-step immunoperoxidase technique.

Results

Focal Neoexpression of ICAM-1 on Keratinocytes Is Restricted to Epidermotropic Lymphomas

On keratinocytes, LFA-1, VLA-1, VLA-4 and VLA-5 were not detectable in either MF, pleomorphic T cell lymphoma, or high-grade T cell lymphoma (Table 1); LFA-3 was found to be expressed by keratinocytes located basally and in the stratum spinosum, whereas VLA-2 was restricted to basal keratinocytes. Thus, these two markers show the same distribution in these dermatoses as in normal skin. Compared with normal skin, keratinocytes in CTCLs exhibit focal neoexpression of ICAM-1 (Figure 1, Table 1). This neoexpression was restricted to cases of CTCL with epidermotropism. Expression of VLA-3 was found both on basal keratinocytes as well as in suprabasal layers. VLA-6 is the only adhesion molecule included in this study showing differential expression: As in normal skin, basal keratinocytes in pleomorphic and high-grade T cell lymphoma stain positively for this marker, whereas in MF VLA-6 expression is also detectable suprabasally. In MF, keratinocytes expressing ICAM-1, VLA-3, or VLA-6 were localized close to Pautrier's microabscesses.

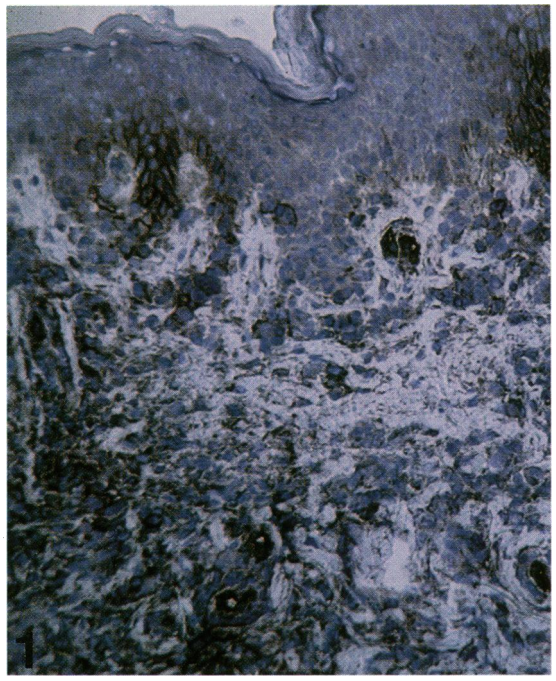
Epidermotropism Is Most Frequent in MF

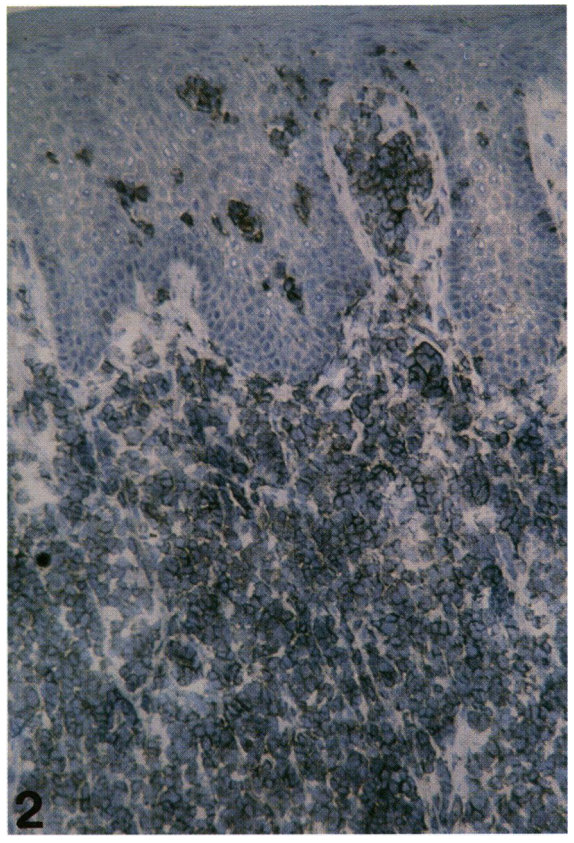
Analyzing the distribution pattern of the cellular infiltrate in the cases of CTCLs investigated, groups of cases with and without epidermotropism could be distinguished (Table 2). Epidermotropism was most frequent in MF, in which nine of 12 cases were classified as epidermotropic. In contrast, only two of 10 cases of pleomorphic T-cell lymphoma and two of seven cases of high-grade T-cell lymphoma showed pronounced epidermotropism.

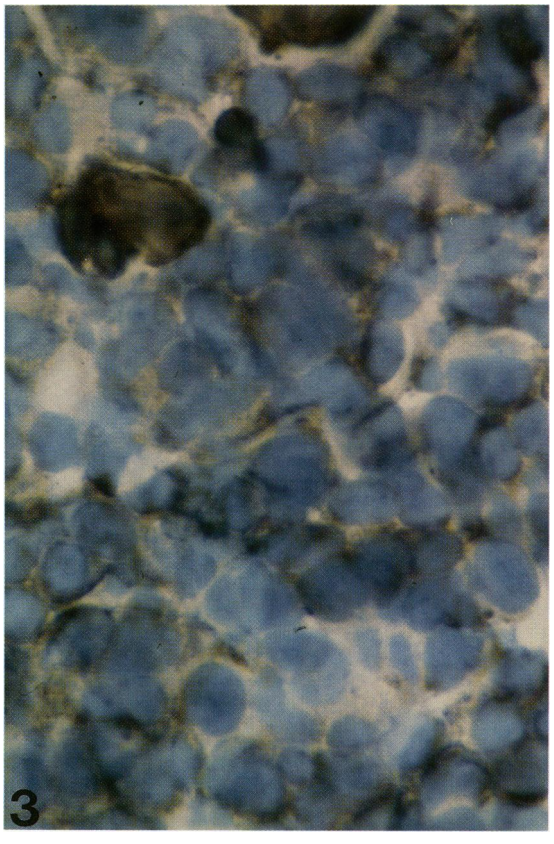
Table 1. *Expression of Adhesion Molecules on Keratinocytes in Mycosis Fungoides, Pleomorphic and High-grade T-cell Lymphoma in Comparison to Normal Human Skin*

	MF	Pleo. TCL	High-grade TCL	Normal skin
LFA-1	Neg	Neg	Neg	Neg
LFA-3	Basal/spin	Basal/spin	Basal/spin	Basal/spin
ICAM-1	Focal*†	Focal*	Focal*	Neg
VLA-1	Neg	Neg	Neg	Neg
VLA-2	Basal	Basal	Basal	Basal
VLA-3	Basal/sb.†	Basal/sb.	Basal/sb.	Basal
VLA-4	Neg	Neg	Neg	Neg
VLA-5	Neg	Neg	Neg	Neg
VLA-6	Basal/sb.†	Basal	Basal	Basal

* Expression restricted to cases with epidermotropism.
† Cells expressing this marker were localized close to Pautrier's microabscesses.
basal = basal layer; sb. = suprabasal layers; spin = stratum spinosum.







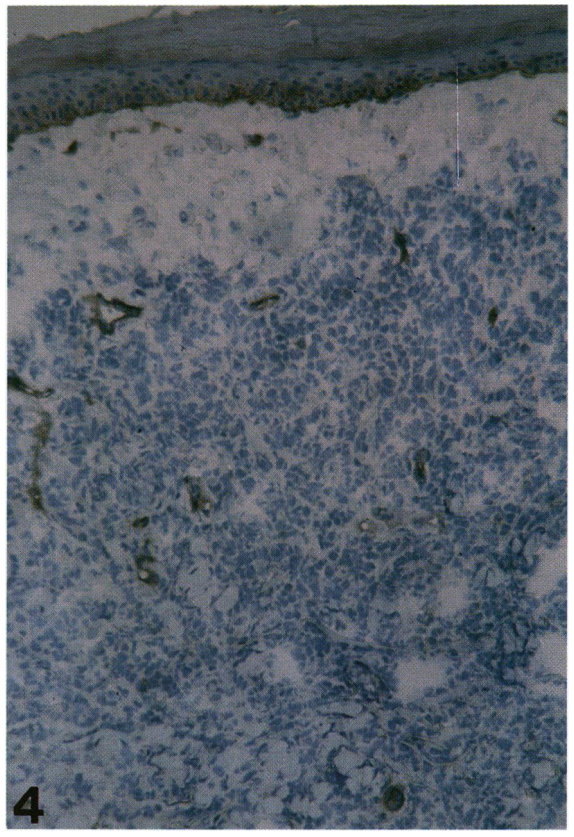


Figure 1. *Cryostat section of a case with pleomorphic T-cell lymphoma. Immunoperoxidase staining for ICAM-1. Note the focal expression on keratinocytes. Original magnification ×200.*
Figure 2. *Expression of LFA-1 in a case of high-grade T-cell lymphoma detected by immunoperoxidase staining. Original magnification ×200.*
Figure 3. *Immunoperoxidase staining of the dermal infiltrate in a case of mycosis fungoides for VLA-1. Note the high number of VLA-1+ cells compared to Figure 4. Original magnification ×500.*
Figure 4. *Cryostat section of a case with pleomorphic T-cell lymphoma. Immunoperoxidase staining for VLA-1. Original magnification ×200.*

Table 2. *Expression of Adhesion Molecules on Infiltrating Cells in Cutaneous T-cell Lymphomas*

		LFA-1	LFA-3	ICAM-1	VLA-1	VLA-2	VLA-3	VLA-4	VLA-5	VLA-6
Mycosis fungoides										
a)	e:	+ + + +	+ + + +	+ +	+ + +	−	−	+	+ +	+
	s:	+ + + +	+ + + +	+ + + +	+ +	−	−	+ + +	+ + +	+ +
b)	e:	0	0	0	0	0	0	0	0	0
	s:	+ + + +	+ + + +	+ + +	+	−	+	+ +	+ +	−
Pleomorphic T-cell lymphoma										
a)	e:	+ + +	+ + +	+ +	−	−	−	+ +	+ +	−
	s:	+ + +	+ + + +	+ + + +	−	−	−	+ +	+ +	−
b)	e:	0	0	0	0	0	0	0	0	0
	s:	+ + +	+ + +	+ + + +	−	−	+	+ +	+	−
High-grade T-cell lymphoma										
a)	e:	+ + + +	+ + + +	+ + + +	−	−	−	−	+	−
	s:	+ + + +	+ + + +	+ + + +	−	−	−	+ +	+ +	−
b)	e:	0	0	0	0	0	0	0	0	0
	s:	+ + + +	+ + +	+ + +	−	−	−	+ + +	+ + +	−

e = epidermal; s = subepidermal; 0 = no infiltrate; − = no cells express marker; + = 1–25% express marker; + + = 25–50% express marker; + + + = 50–75% express marker; + + + + = 75–100% express marker.
A representative case is listed for each of the entities investigated both with (a) and without epidermotropism (b).

The Cellular Infiltrate in CTCLs With and Without Epidermotropism Exhibits Similar Expression Patterns of Most Adhesion Molecules

No differences were observed for expression of most markers investigated in epidermotropic *versus* nonepidermotropic cases. Most infiltrating cells were positive for LFA-1 (Figure 2), LFA-3, and ICAM-1. VLA-2 was not detectable in any case. Expression of VLA-3 was restricted to the dermal infiltrate of few cases. VLA4$^+$ and VLA5$^+$ cells were found both in the dermal and epidermal infiltrate, but expression of these markers was less frequent compared with LFA-1, LFA-3, and ICAM-1. This pattern was similar in all three entities examined.

Intraepidermally Localized VLA-1$^+$ Cells Are a Characteristic Feature of MF

In contrast to the other markers investigated, VLA-1 and VLA-6 were found to exhibit different expression patterns of adhesion molecules in the different entities examined. With a single exception, VLA-1$^+$ cells were detected only in epidermotropic CTCLs. Expression was most frequent in MF (eight of nine cases) (Figure 3), the only entity exhibiting VLA-1$^+$ cells in epidermal localization (7/9). In contrast, only three of seven cases with epidermotropic pleomorphic T cell lymphoma showed the presence of VLA-1$^+$ cells; none of them were found within the epidermis (Figure 4). Expression of VLA-1 was absent in high-grade T cell lymphoma.

As for VLA-1, expression of VLA-6 was mostly restricted to epidermotropic CTCLs. Again, most of cases with MF were found to exhibit VLA-6$^+$ cells, whereas only two high-grade T cell lymphomas showed few cells expressing this marker.

Discussion

Adhesion molecules and their ligands with a multitude of interactions and various regulatory mechanisms provide an ideal means of organizing complex processes like differentiation of multicellular organisms[30] or coordination of activities of the immune system.[1] They are also known to be involved in cutaneous inflammation and malignancies.[18,31]

Malignant T cells in CTCLs predominantly belong to the helper/inducer subset,[32] also referred to as memory T cells.[33] Circulating memory T cells express increased levels LFA-1, LFA-3, VLA-4, VLA-5, and VLA-6.[5] Expression of these molecules on memory T cells correlates with increased binding capacity,[5] thus facilitating their binding to endothelium and emigration into the skin.[2,34] These findings are reflected by our observation that LFA-1, LFA-3, VLA-4, and VLA-5 were readily detectable on infiltrating cells in all cases of CTCLs investigated.

If adhesion molecules were important for epidermotropism of T cells, one would expect increased expression or avidity of these markers on cells infiltrating the epidermis and a less pronounced expression or lower avidity on dermally located cells and in cases without epidermotropism. In all cases investigated here, we could not identify any adhesion molecule included in this study that would be expressed in all epidermotropic CTCLs and not in cases lacking epidermotropism. From this we conclude that epidermotropism can not be explained by differential expression of a single adhesion molecule.

Regulation of cellular adhesion is also possible through regulating the avidity of adhesion molecules rather then their quantitative expression. This takes place, for example, in the case of LFA-1 interaction with its counter receptor ICAM-1 and in LFA-3/CD2 interactions.[1] Thus, the unchanged expression pattern of a given adhesion molecule does not necessarily exclude this marker as possible cause for epidermotropism. Therefore, we cannot rule out a possible contribution of LFA-1 and LFA-3 to the phenomenon of epidermotropism despite their expression on the cellular infiltrate in both epidermotropic and nonepidermotropic CTCLs.

Although we cannot exclude adhesion molecules with unchanged expression patterns in epidermotropic versus nonepidermotropic CTCLs from the list of candidates with epidermotropic effects, we can do so for those markers that are absent in the infiltrate of epidermotropic CTCLs. The finding of epidermotropic CTCLs that were negative for most β1-integrins studied suggests to us that these molecules are not essential for epidermotropism. It should, however, be noted that there are differences between MF, pleomorphic T cell lymphoma, and high-grade T cell lymphoma with regard to the percentage of epidermotropic cases staining negative for a given marker. This is particularly true for VLA-1, which is present in seven of nine cases with epidermotropic MF. One case of MF characterized by the presence of a $V\beta8^+$ epidermotropic T cell clone[35] showed a particularly strong preference of VLA-1 expression on T cells located in the epidermis. In contrast, only three of seven epidermotropic pleomorphic T cell lymphomas and no high-grade lymphomas were VLA-1^+. Therefore, it is possible that epidermotropism is regulated differently in different entities of CTCL.

Adhesion molecules are not necessarily the only factors contributing to the process of epidermotropism. In a mouse model, Shiohara and co-workers[36,37] demonstrated the positive effect of keratinocyte-derived cytokines on epidermotropism. Monoclonal antibodies to LFA-1 were able to inhibit this phenomenon. These results suggest that LFA-1 interaction with its ligand ICAM-1 alone might mediate epidermotropism in the presence of certain chemoattractants. Our data on the exclusive expression of ICAM-1 on keratinocytes in epidermotropic CTCLs as well as the LFA-1^+ phenotype on infiltrating cells are consistent with this hypothesis.

The postulated function of adhesion molecules in epidermotropism is a means of explaining generalization of a disease initially affecting only the skin. Loss of adhesion molecule expression could result in a release of malignant cells from the epidermal compartment. Medeiros and co-workers[38] observed that 90% of LFA-1–positive low-grade lymphomas turn LFA-1 negative during the course of disease. The authors were unable to correlate LFA-1 expression and clinical course, however. The same effect could be caused not by a loss of adhesion molecule expression on infiltrating cells, but by a lack of resident cells to further express their ligands. Nickoloff and colleagues[20] described a patient with erythrodermic CTCL in whom epidermotropism was absent and suggested that this could be due most likely to a lack of keratinocytes to express ICAM-1. Our results support this finding in as much as we observed upregulation of ICAM-1 on keratinocytes in epidermotropic CTCLs at sites neighboring infiltrating T cells.

One reason for a loss of ICAM-1 expression on keratinocytes might be the emergence of T cells that do not produce inducers of ICAM-1–like interferon gamma.[20] It is interesting to speculate whether this postulated loss of production of certain cytokines might be associated with a loss of capability to express LFA-1. In this case, both components of the receptor–ligand pair LFA-1/ICAM-1 would contribute to a generalization of the disease due to a loss of epidermotropism of the malignant T cells.

In conclusion, our data are consistent with the hypothesis that LFA-1/ICAM-1 interaction alone might mediate epidermotropism in the context of appropriate epidermal chemoattractants. Several other adhesion molecules, namely LFA-3, and in the case of MF also VLA-1, might contribute to this phenomenon. Also, different sets of adhesion molecules might be used in different entities of CTCL. Because several adhesion molecules were not expressed on epidermotropic T cells in individual cases, they can be ruled out as major contributors to the phenomenon of epidermotropism. This is true for all β1-integrins but VLA-1.

References

1. Springer TA: Adhesion receptors of the immune system. Nature 1990, 346:425–434
2. Picker LJ, Kishimoto TK, Smith CW, Warnock RA, Butcher EC: ELAM-1 is an adhesion molecule for skin-homing T cells. Nature 1991, 349:796–799
3. Kyan-Aung U, Haskard DO, Poston RN, Thornhill MH, Lee TH: Endothelial leukocyte adhesion molecule-1 and intercellular adhesion molecule-1 mediate the adhesion of eosinophils to endothelial cells in vitro and are expressed by endothelium in allergic cutaneous inflammation in vivo. J Immunol 1991, 146:521–528
4. Springer TA: The sensation and regulation of interactions with the extracellular environment: The cell biology of lymphocyte adhesion receptors. Annu Rev Cell Biol 1990, 6: 359–402
5. Shimizu Y, van Seventer GA, Horgan KJ, Shaw S: Roles of adhesion molecules in T-cell recognition: Fundamental similarities between four integrins on resting human T cells (LFA-1, VLA-4, VLA-5, VLA-6) in expression, binding, and costimulation. Immunol Rev 1990, 114:1–34

6. Mackay CR: Skin-seeking memory T cells. Nature 1991, 349:737–738
7. Hynes RO. Integrins: A family of cell surface receptors. Cell 1987, 48:549–554
8. Hemler ME, Huang C, Schwarz L: The VLA protein family: Characterization of five distinct cell surface heterodimers each with a common 130,000 molecular weight β subunit. J Biol Chem 1987, 262:3300–3309
9. Hemler ME: VLA proteins in the integrin family: structures, functions, and their role on leukocytes. Annu Rev Immunol 1990, 8:365–400
10. Kishimoto TK, O'Connor K, Lee A, Roberts TM, Springer TA: Cloning of the β subunit of the leucocyte adhesion proteins: Homology to an extracellular matrix receptor defines a novel supergene family. Cell 1987, 48:681–690
11. Dustin ML, Rothlein R, Bahn AK, Dinarello CA: Induction by IL-1 and interferon teta: Tissue distribution, biochemistry and function of a natural adherence molecule (ICAM-1). J Immunol 1986, 137:245–254
12. Marlin SD, Springer TA: Purified intercellular adhesion molecule-1 (ICAM-1) is a ligand for lymphocyte function-associated antigen 1 (LFA-1). Cell 1987, 51:813–819
13. Staunton DE, Dustin ML, Springer TA: Functional cloning of ICAM-2, a cell adhesion ligand for LFA-1 homologous to ICAM-1. Nature 1989, 339:61–64
14. Springer TA, Dustin ML, Kishimoto TK, Marlin SDA: The lymphocyte function-associated LFA-1, CD2 and LFA-3 molecules: Cell adhesion receptors of the immune system. Annu Rev Immunol 1987, 5:223–252
15. Wallner BP, Frey AZ, Tizard R, Mattaliano R, Hession C, Sanders ME, Dustin ML, Springer TA: Primary structure of lymphocyte function-associated antigen3 (LFA-3): The ligand of the lymphocyte CD2 glycoprotein. J Exp Med 1987, 166:923–932
16. Slater DN: Cutaneous lymphoproliferative disorders: An assessment of recent investigative techniques. Br J Dermatol 1991, 124:309–323
17. Sterry W: Mycosis fungoides. Curr Top Pathol 1985, 74:167–213
18. Nickoloff BJ, Griffith CEM, Barker JNWN: The role of adhesion molecules, chemotactic factors, and cytokines in inflammatory and neoplastic skin disease: 1990 update. J Invest Dermatol 1990, 94(S):151–157
19. Nickoloff BJ: The role of IFN gamma in cutaneous trafficking of lymphocytes with emphasis on molecular and cellular events. Arch Dermatol 1988, 124:1835–1843
20. Nickoloff BJ, Griffith CEM, Baadsgaard O, et al: Markedly diminished epidermal keratinocyte expression of ICAM-1 in Sezary syndrome. JAMA 1989, 261:2217–2221
21. Rothlein R, Dustin ML, Marlin SD, Springer TA: A human intercellular adhesion molecule (ICAM-1) distinct from LFA-1. J Immunol 1986, 137:1270–1274
22. Sanchez-Madrid F, Krenzky AM, Ware CF, Robbins E, Strominger JL, Burakoff SJ, Springer TA: Three distinct antigens associated with human T-lymphocyte-mediated killing: LFA-1, LFA-2, LFA-3. Proc Natl Acad Sci USA 1982, 79:7489
23. Hemler ME, Jacobson JG, Strominger JL: Biochemical characterization of VLA-1 and VLA-2: cell surface heterodimers on activated T cells. J Biol Chem 1985, 260: 15246
24. Hemler ME, Ware CF, Strominger JL: Characterization of a novel differentiation antigen complex recognized by a monoclonal antibody (A-1A5): Unique activation-specific molecular forms on stimulated T cells. J Immunol 1983, 131: 334–340
25. Hemler ME, Huang C, Takada Y, Schwarz L, Strominger JL, Clabby ML: Characterization of the cell surface heterodimer VLA-4 and related peptides. J Biol Chem 1987, 262:11478–11485
26. Kaufmann R, Frösch D, Westphal C, Weber L, Klein CE: Integrin VLA-3: Ultrastructural localization at cell-cell contact sites of human cell cultures. J Cell Biol 1989, 109:1807–1815
27. Hemler ME, Crouse C, Takada Y, Sonnenberg A: Multiple very late antigen (VLA) heterodimers on platelets. Evidence for distinct VLA-2, VLA-5 (fibronectin receptor) and VLA-6 structures. J Biol Chem 1988, 263:7660–7665
28. Sonnenberg A, Modderman PW, Hogervorst F: Laminin receptor on platelets is the integrin VLA-6. Nature 1989, 336: 487
29. Werb Z, Tremble PM, Behrendtsen O, Crowley E, Damsky CH: Signal transduction through the fibronectin receptor induces collagenase and stromelysin gene expression. J Cell Biol 1989, 109:877
30. Ruoslahti E, Pierschbacher MD: New perspectives in cell adhesion: RGD and integrins. Science 1987, 238:491–497
31. Kellner I, Konter U, Sterry W: Upregulation of adhesion molecules in inflammatory skin diseases. Arch Dermatol Res 1990, 281:550
32. Berger CL, Warburton D, Raafat J, Logerfo P, Edelson RL: Cutaneous T cell lymphoma: Neoplasm of T cells with helper activity. Blood 1979, 53:642–651
33. Sanders ME, Makgoba MW, Shaw S: Human naive and memory T cells: reinterpretation of helper-inducer and suppressor-inducer subsets. Immunol Today 1988, 9:195
34. Sterry W, Bruhn S, Künne N, Lichtenberg B, Weber-Matthiesen K, Brasch J, Mielke V: Dominance of memory over naive T cells in contact dermatitis is due to differential tissue immigration. Br J Dermatol 1990, 123:59–64
35. Boehncke WH, Krettek S, Sterry W: Demonstration of clonal disease in early mycosis fungoides. Am J Dermatopathol 1992, 14:95–99
36. Shiohara T, Moriya N, Mochizuki T, Nagashima M: Lichenoid tissue reaction (LTR) induced by local transfer of Ia-reactive T-cell clones: II. LTR by epidermal invasion of cytotoxic lymphokine-producing autoreactive T cells. J Invest Dermatol 1987, 89:8–14
37. Shiohara T, Nagashima M: Monoclonal antibody (MAb) to lymphocyte function-associated 1 (LFA-1) inhibits epidermotropic migration of T cells in vitro and in vivo. J Invest Dermatol 1988, 90:608
38. Medeiros LJ, Weiss LM, Picker LJ, Clayberger C, Horning SJ, Krensky AM, Warnke RA: Expression of LFA-1 in non-Hodgkin's lymphoma. Cancer 1989, 63:255–259