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Expression of leucocyte function-associated antigen-1 and 7F7-antigen, an adhesion molecule related to intercellular adhesion molecule-1 (ICAM-1) in non-Hodgkin lymphomas and leukaemias: possible influence on growth pattern and leukaemic behaviour

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SUMMARY

In 160 non-Hodgkin lymphomas (NHL) of B and T cell origin the expression of leucocyte function-associated antigen-1 (LFA-1) and one of its counter-structures named 7F7-antigen was studied. Functional and structural similarities and the 7F7-reactivity of pICAM-1 transfected COS-cells prove that 7F7-antigen is identical with ICAM-1. The expression of both adhesion structures occurred variably and clearly depended on the maturation stage and on the B and T cell origin of lymphomas but was not associated with the proliferative status of tumour cells. The concomitant expression of both adhesion molecules was a characteristic feature of germinal centre derived NHL, particularly of those with neoplastic follicular structures (corr. contingency coeff. = 0·506; $P < 0{\cdot}02$), whereas both adhesion structures were less often expressed on lymphomas with a more diffuse pattern of tumour infiltration. Most B-NHL of low-grade malignancy expressed LFA-1 while their counterparts of high-grade malignancy often tended to be LFA-1 negative. In B cell neoplasias of low-grade malignancy the lack of ICAM-1 and a leukaemic course of the disease were significantly correlated ($P < 0{\cdot}0005$). The results indicate that the differential expression of both adhesion molecules may account for distinct patterns of growth and spread in subtypes of lymphoid malignancies.

Keywords leucocyte function-associated antigen-1 intercellular adhesion molecule-1 7F7-antigen non-Hodgkin lymphomas

INTRODUCTION

Adhesion molecules play an essential role in the immunological network by mediating the contact between immunocompetent cells. Among these molecules there is the leucocyte function-associated antigen-1 (LFA-1) (Davignon *et al.*, 1981), a membrane structure that mediates the target cell killing by cytolytic T lymphocytes (Sanchez-Madrid *et al.*, 1982), the interaction between accessory cells and T lymphocytes (Dougherty, Murdoch & Hogg, 1988), the cooperation between helper T cells and B cells (Durandy & Fischer, 1987) and the homotypic aggregation of certain T, B, and myeloid cell lines (Rothlein *et al.*, 1986). An inherited LFA-1 deficiency results in an impaired leucocyte function and in disturbances of all aspects of immune reactions (Springer *et al.*, 1984). Recently, interest has focused on the expression of LFA-1 on non-Hodgkin lymphomas (NHL), since high-grade malignancy lymphomas lacking the expression of LFA-1 may be associated with a higher rate of tumour relapses (Clayberger *et al.*, 1987). An 85-kD membrane molecule, ICAM-1, has been identified as one ligand for LFA-1 (Rothlein *et al.*, 1986).

We have recently described a membrane adherence molecule of similar molecular weight, termed 7F7-antigen, which is predominantly expressed on activated cells (Schulz *et al.*, 1988a). Antibodies to the 7F7-antigen block the induction of T cell responses probably by interfering with the contact between T cells and monocytes (Schulz *et al.*, 1988b). A detailed analysis of the functional and structural features of the 7F7-antigen (Schulz *et al.*, 1988c) and the reactivity of pICAM-1 transfected COS cells with monoclonal antibody (MoAb) 7F7 (Vogetseder *et al.*, 1989) has revealed that 7F7-antigen is identical with ICAM-1. Furthermore, the specifity of 7F7-antibody for ICAM-1 (CD54) has been defined by the 4th Leucocyte Antigen Workshops (Vienna, 1989).

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Because of the possible role of adherence molecules for the growth and spread of NHL we examined the expression of ICAM-1 and of LFA-1 in a large panel of B and T cell lymphomas and leukaemias.

MATERIALS AND METHODS

Immunostaining

Immunostaining of all sections was performed by using a double-sandwich immunoperoxidase technique (Gattringer *et al.*, 1984). Bone marrow biopsies were prepared and immunostained as described recently (Thaler *et al.*, 1987); however, blocking endogenous peroxidase with sodium azide was not carried out, since the use of sodium azide reduced the sensitivity of the assay (results not shown).

MoAb

Supernatant of MoAb 7F7 (Schulz *et al.*, 1988a) which is specific for ICAM-1 (CD54) (4th Leucocyte Antigen Workshops, Vienna, 1989) was used in a 1:2 dilution. The expression, of LFA-1 was studied by using MoAb MHM 24 (Hildreth *et al.*, 1983) which is directed against the alpha-chain of LFA-1 (CD11a) (Cobbold, Hale & Waldmann, 1987). MoAb MHM 24 was kindly supplied by Professor A. J. McMichael, John Radcliffe Hospital, Oxford. Following other investigators (Greil *et al.*, 1986), lymphoma cells were termed ICAM-1- or LFA-1-positive when >20% of the tumour cells showed a positive staining for the relevant antibody. Follicular dendritic reticulum cells (FDRC) were detected by the specific MoAb KiM4 (Dakopatts, Weybridge, UK) as well as by the anti-CR1 (CD35) MoAb To5 (Dakopatts) and MoAb Tuel (CD23) (Biotest Diagnostics, Vienna, Austria).

Determination of the growth fraction

The growth fraction of lymphoma cells was evaluated by analysing the expression of the nuclear antigen Ki67 (Gerdes *et al.*, 1983). The results of this analysis and technical details have recently been described (Greil *et al.*, 1988). In 61 cases of B- and T-NHL, the proliferation rate was defined as the percentage of cells positive for this antigen within 20 fields of vision chosen at random and counted with a projection microscope (Reichart, Vienna).

Histopathological diagnosis and classification of malignant B cell differentiation

NHL were obtained from two centres (University of Innsbruck and Institute of Pathology, Vienna). The classification of NHL and the attribution to the two main groups of low- and high-grade malignancy were performed according to the criteria of the Kiel classification (Lennert *et al.*, 1975) by applying conventional histological and immunohistological criteria. B cell lymphomas were categorized in three different stages of B cell differentiation; the rationale for this maturation sequence has been discussed by Greil *et al.* (1986).

Definition of leukaemic growth pattern

A leukaemic course was defined by the presence of >4000 lymphocytes/μl, or >5% atypical lymphoid cells in peripheral blood as assessed by morphological or immunohistological means. Applying these criteria, 29 out of 33 cases of B chronic lymphocytic leukaemia (CLL); 11 out of 19 cases of immunocytic (IC) NHL; two out of 11 cases of centroblastic/centrocytic (CB/CC) NHL; five out of 13 cases of centrocytic (CC) NHL; one out of eight cases of centroblastic (CB) NHL; three out of 11 cases of B-immunoblastic (B-IB) NHL; one out of two cases of B-lymphoblastic (B-LB) NHL; one out of four cases of Burkitt NHL; and six out of eight cases of common acute lymphocytic leukaemia (cALL) were characterized by a leukaemic course of the disease.

Table 1. Comparison of presence of ICAM-1 and LFA-1 in B-NHL of low- and high-grade malignancy

		Cases expressing			
		ICAM-1		LFA-1	
Diagnosis	Cases (*n*)	*n*	%	*n*	%
Low-grade malignancy	82	36	44	60	73
High-grade malignancy	33	10	30	12	36

Statistical analysis

The correlation between the expression of ICAM-1 and LFA-1 was determined by using Pawlik's corrected contingency coefficient. Depending on the number of cases, the level of significance for this correlation was evaluated by Fisher's exact test or the χ^2 test.

The correlation between the proliferative potential of tumour cells and the expression of adhesion molecules was evaluated by using the two-sided Wilcoxon, Mann–Whitney *U*-test.

The significance of the correlation between clinical parameters and the ICAM-1/LFA-1 reactivity of tumour cells was determined by applying the χ^2 test or Fisher's exact test.

RESULTS

Expression of ICAM-1

On cryostat sections of reactive lymphatic tissue antibody 7F7 bound to germinal centre B cells and stained some B cells of the follicular mantle and marginal zone (data not shown). Within the T cell areas interdigitating reticulum cells strongly expressed this antigen, whereas T cells were ICAM-1-negative. The strong staining of FDRC, high endothelial venules (HEV) and macrophages was remarkable.

An almost equal level of ICAM-1 expression was observed in B-NHL of low-grade and high-grade malignancy (Table 1). In detail, the presence of ICAM-1 clearly depended on the maturation stage and the B or T cell origin of lymphomas (Table 2). Most cases with NHL of an immature B cell stage as defined above were negative for ICAM-1. ICAM-1 was found in 20% of CLL and 30% of IC on NHL of the mid-B cell stage of differentiation (Table 2). The highest percentage of ICAM-1-positive cases, however, was found in the germinal-centre derived group, i.e. CC, CB/CC and CB. There was a strong correlation between the presence of invariably ICAM-1-positive FDRC and ICAM-1 expression by lymphoma cells. This feature was most evident in CB/CC (10 out of 11 cases positive for FDRC and ICAM-1) and CC (eight out of 15 cases positive for

Table 2. Expression and co-expression of ICAM-1 and LFA-1 within subtypes of NHL

Histology (*n*)	ICAM-1-positive	%	LFA-1-positive	%	Corr. *cc*/*P*
NHL of early B-cell stage					
cALL (7)	1	14	4	57	
LB (2)	0	0	0	0	$P<0{\cdot}4$
Burkitt (4)	0	0	0	0	
NHL of mid B-cell stage					
CLL (35)	7	20	26	74	$P<0{\cdot}1$
IC (20)	6	30	11	55	
CC (15)	11	73	12	80	$cc=0{\cdot}506$
CB/CC (12)	12	100	11	92	$P<0{\cdot}02$
CB (8)	4	50	6	75	
NHL of late B-cell stage					
IB (12)	5	42	2	16	
HCL (17)	11	65	4	23	$P<0{\cdot}09$
Myeloma (9)	7	78	1	11	
T-cell lymphomas/ leukaemias (19)†	3	16	16	84	$P=1{\cdot}0$

* Corr. *cc*, Pawlik's corrected contingency coeff.; not determined where $P>0{\cdot}05$.

† T cell lymphomas included three cases of T-IB, four cases of T-LB, five cases of plemorph T cell- and two cases of Ki-1 lymphoma as well as one case of T-ALL, two cases of T-CLL and two cases of Sézary syndrome.

NHL, non-Hodgkin lymphoma; cALL, common acute lymphocytic leukaemia; LB, lymphoblastic; CLL, chronic lymphocytic leukaemia; IC, immunocytic; CC, centrocytic; CB, centroblastic; IB, immunoblastic; and HCL, hairy cell leukaemia.

FDRC and ICAM-1), whereas in CLL, IC and CB the simultaneous presence of FDRC and ICAM-1-positive lymphoma cells was occasionally detected. NHL belonging to the terminal stages of B cell differentiation were characterized by high levels of ICAM-1 expression (Table 2). In IB, which are often heavily infiltrated by numerous histiocytic cells, the majority of monocytes also expressed this antigen.

In contrast to B cell lymphomas, tumour cells of most T cell derived NHL were not identified by the anti-ICAM-1 antibody (Table 2).

Expression of LFA-1 on NHL and its correlation to the expression of ICAM-1

Most cells of both the B and T cell areas of reactive lymphatic tissue strongly stained with the monoclonal anti-LFA-1 antibody MHM 24 (data not shown). FDRC and HEV usually lacked LFA-1, and this was in clear contrast to the strong ICAM-1-reactivity of these accessory cells.

B-NHL of low-grade malignancy were characterized by a high percentage of LFA-1-positive cases, whereas B lymphomas of high-grade malignancy often lacked LFA-1 (Table 1). In detail, LFA-1 was detected in a substantial proportion of cALL (four out of seven cases LFA-1-positive) (Table 2). Two B-LB and four cases of Burkitt NHL were LFA-1-negative; only one case in this group showed a simultaneous expression of both adhesion molecules. An almost equal level of LFA-1 expression was seen in the histological entities of mid B cell stage. Most cases investigated were positive for the LFA-1 molecule. Therefore, in many cases of CLL and IC no concomitant expression of LFA-1 and ICAM-1 was observed, thus leading to some contrast in the presence of these two markers in these entities ($P<0{\cdot}1$) (Table 2). However, there was a highly significant co-expression in germinal-centre derived lymphomas (cc = 0·506; $P<0{\cdot}02$). Therefore, germinal-centre derived NHL were characterized by the simultaneous presence of ICAM-1-positive FDRC and lymphoma cells, which co-expressed both ICAM-1 and LFA-1. The majority of lymphomas of a stage of advanced B cell maturation lacked staining with the anti-LFA-1 antibody resulting in a heterogenous pattern of ICAM-1 and LFA-1 expression ($P<0{\cdot}09$).

LFA-1 expression was observed in the majority of T cell NHL (Table 2) even on entities assigned to an early stage of T cell development (one positive case of T acute lymphocytic leukaemia (T-ALL); three out of four cases of T-LB positive). All four cases of early T cell lymphomas could be assigned by means of the immunophenotype to a stage of neoplastic T cell development corresponding to the maturation step of common thymocytes as defined by Reinherz *et al.* (1980).

Correlation between proliferative activity of lymphoma cells and expression of ICAM-1 and LFA-1

The number of proliferating tumour cells was compared with the expression of adhesion molecules in B-NHL of low-grade ($P>0{\cdot}2$) and high-grade malignancy ($P>0{\cdot}2$) and in T-NHL ($P>0{\cdot}2$) (data not shown). Thus it was established that the expression of ICAM-1 and LFA-1 occurs independently of the proliferative status of malignant cells in NHL.

Comparison of leukaemic course of NHL and expression of adhesion molecules

In B-NHL of low-grade malignancy, the spread of lymphoma cells into the blood and a lack of ICAM-1 were significantly correlated ($P<0{\cdot}0005$) (Table 3). In detail, the germinal-centre derived entities (CC, CB/CC) showed ICAM-1 reactivity and an aleukaemic course of the disease, wheras in B-CLL and IC most cases were characterized by a lack of ICAM-1 and a leukaemic

Table 3. Comparison of leukaemic or aleukaemic growth pattern and expression of ICAM-1 and LFA-1 in B-NHL

	Aleukaemic growth pattern	Leukaemic growth pattern	*P*
B-NHL of low grade malignancy ($n=76$)			
ICAM-1 positive	20	9	<0·0005
ICAM-1 negative	9	38	
LFA-1 positive	20	33	<0·9
LFA-1 negative	9	14	
B-NHL of high grade malignancy ($n=33$)			
ICAM-1 positive	5	3	<0·4
ICAM-1 negative	16	9	
LFA-1 positive	6	5	<0·3
LFA-1 negative	15	7	

growth pattern. In B cell lymphomas of high-grade malignancy no correlation between ICAM-1 expression and the presence of tumour cells in peripheral blood was observed ($P<0{\cdot}4$). A correlation between the expression of LFA-1 and a leukaemic course of the disease could not be demonstrated in low-grade ($P<0{\cdot}9$) or in high-grade B-NHL ($P<0{\cdot}22$).

DISCUSSION

The data presented here demonstrate that (1) ICAM-1 and its ligand LFA-1 are variably expressed in NHL, clearly depending on the maturation stage and on the B or T cell origin of lymphomas; (2) the expression of both membrane structures occurs completely independent of the proliferative status of tumour cells; (3) the concomitant presence of both adhesion molecules is a characteristic feature of germinal-centre derived NHL, particularly of those with neoplastic follicular structures; both ICAM-1 and LFA-1 are less often expressed on NHL of a diffuse pattern of tumour infiltration; (4) B-NHL of low-grade malignancy are often LFA-1-positive while their counterparts of high-grade malignancy tend to lack LFA-1; and (5) in B cell NHL of low-grade malignancy ICAM-1 expression is associated with an aleukaemic course of the disease, whereas the lack of ICAM-1 is correlated with a spread of lymphomas cells into the blood.

LFA-1 mediates a variety of cell-to-cell adhesions. Specifically LFA-1 molecules on target as well as on effector cells play a role in cytolytic T cell–target cell conjunction (Krensky *et al.*, 1985). Therefore, it was postulated previously that the lack of LFA-1 from tumour cells might be crucial in their escape from the host's immunosurveillance mechanisms (Clayberger *et al.*, 1987). In support of this hypothesis, we found that LFA-1 expression clearly varied in B-NHL of low- and high-grade malignancy. In contrast to that, both aggressive and indolent B-NHL express ICAM-1. Presence of ICAM-1 is associated with tumour progression in malignant melanoma (Holzmann *et al.*, 1987) and the lysis of Burkitt cells by T cells *in vitro* (Gregory *et al.*, 1988), suggesting that ICAM-1 represents the signalling molecule on the tumour cells, whereas LFA-1 is the corresponding adhesion structure on effector cells. However, our results indicate that the expression of ICAM-1 seems to be of less importance than LFA-1 for the putative escape from immunosurveillance.

The homotypic adhesion of lymphocytes *in vitro* is mediated at least in part by the glycoproteins LFA-1 (Rothlein & Springer, 1986) and its ligand ICAM-1 (Schulz *et al.*, 1988d). In support of the hypothesis that such self-aggregation might regulate the migration and circulation of lymphocytes (Hamman *et al.*, 1988) we found that the concomitant expression of LFA-1 and ICAM-1 is associated with a nodular growth pattern, whereas most lymphomas with a diffuse pattern of infiltration lack both antigens. Recent studies have suggested that the presence of LFA-1 may account for the distinct growth pattern and clinical course in different lymphoproliferative disorders (Inghirami *et al.*, 1988). Our observations suggest that the membrane molecule LFA-1 exerts its influence on the growth behaviour of lymphomas by cell-to-cell adherence contacts that are mediated at least in part by an interaction of LFA-1 with ICAM-1.

Interactions of lymphocytes with many cell types are regulated by LFA-1 and ICAM-1 (Dougherty, Murdoch & Hogg, 1988; Dustin *et al.*, 1988; Schulz *et al.*, 1988b). The follicular growth in lymphomas is often characterized by the presence of ICAM-1-positive FDRC and tumour cells that co-express LFA-1 and ICAM-1. These results indicate that, like the interaction of carcinoma cells with fibroblasts (Vogetseder *et al.*, 1989), the cooperation between neoplastic lymphocytes and accessory cells is mediated by an LFA-1/ICAM-1 dependent adhesion process.

In the regulation of lymphocyte circulation, distinct homing receptors direct the organ-specific cell extravasation of reactive and neoplastic lymphocytes via an adhesion to HEV (Gallatin, Weissmann & Butcher, 1983; Picker *et al.*, 1988). Recently, LFA-1 has been demonstrated to play an accessory role in this cell trafficking (Hamann *et al.*, 1988). In view of these findings, the correlation between the deficiency of ICAM-1 and a leukaemic course in B-NHL of low-grade malignancy is particularly intriguing. Our conclusion that ICAM-1 is likely to play a role in the dissemination of NHL is corroborated by the characteristic dissemination and ICAM-1-expression patterns observed in NHL subgroups. For example, NHL categories with a weak ICAM-1-expression such as B-CLL and IC almost invariably present at a generalized clinical stage.

Both markers are useful tools in the immunophenotyping of lymphomas and, more importantly, may help to gain insight into mechanisms that determine the growth, spread and clinical behaviour of lymphoid malignancies.

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