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Adhesion molecules on CD 34+ hematopoietic cells in normal human bone marrow and leukemia

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Summary. Expression of selected adhesion molecules of the integrin and immunoglobulin family was investigated on CD 34+ leukemic cells in 19 AML and 11 ALL cases to evaluate phenotypic differences in adhesive properties of malignant hematopoietic precursor cells in comparison to normal bone marrow CD 34+ cells. Of the β2-integrin family, CD 11 a was expressed on > 50% of CD 34+ cells in normal bone marrow and almost all leukemias, whereas CD 11 b and CD 11 c were not expressed on CD 34+ cells in normal bone marrow, but were found on CD 34+ blasts in some leukemias of a heterogeneous immunophenotype. Of the β 1-family, CDw 49 d (VLA-4) was strongly expressed on normal CD 34+ bone marrow cells and on the blasts of all 30 CD 34+ leukemic samples, whereas CDw 49 b (VLA-2) was absent on CD 34+ cells in normal bone marrow, but detected on CD 34+ cells in a few leukemias which did not constitute a clinical or phenotypic entity according to the FAB classification or immunocytological analysis. The lymphocyte-homing-associated adhesion molecule CD 44 (HCAM) and CD 58 (LFA-3) were expressed on CD 34+ cells in all investigated cases of normal and leukemic bone marrow. ICAM-1 (CD 54), the inducible receptor ligand for CD 11 a / CD 18, although present on CD 34+ cells in normal bone marrow, was lacking on blast cells of some ALL and AML cases. So far, the variable expression of β2-integrins as well as of VLA-2 and of ICAM-1 could indicate distinct differences in cell-cell or cell-matrix adhesion of leukemic cells in ALL and AML patients.

Key words: Adhesion molecules – Leukemia – CD 34 – Phenotype

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Introduction

Except for rare hematological diseases such as osteomyelosclerosis, hematopoiesis in man occurs exclusively in the bone marrow. Homing mechanisms of hematopoietic precursor cells to this preferred site for proliferation and differentiation are still not definitely understood, but they may involve adhesive capacities of immature cells to the bone marrow microenvironment. This view is supported by observations of variant expression patterns of adhesion molecules on hematopoietic cells during maturation which seem to indicate differentiation-dependent changes of adhesive properties of hematopoietic cells [4, 12, 18].

Generally, immature hematopoietic precursor cells, immunophenotypically characterized by their expression of the CD 34 antigen, are detected only in the bone marrow [1], while in leukemias they frequently occur in high percentages also in the peripheral blood. To obtain further insight into possible defective homing qualities of leukemic blasts, the expression of selected previously characterized adhesion molecules was investigated on CD 34+ peripheral and/or bone marrow-derived leukemic cells in comparison to their presence on normal CD 34+ hematopoietic precursor cells. For this purpose, among the integrins [2, 16], which as αβ-heterodimers are distinguished according to their β-chains, all members of the β 2-integrins that comprise CD 11 a, b, c, which are exclusively expressed on hematopoietic cells were analyzed. Of the β 1-integrins, also known as very late antigens CDw 49 b (VLA-2) participating only in cell-matrix interactions and CDw 49 d (VLA-4) [10] involved in cell-cell interactions in addition were investigated. Furthermore, the widely distributed CD 44 antigen, also referred to as the lymphocyte-homing-associated molecule (HCAM) [9, 13], with binding affinity to addressin of endothelial cells was studied. The intercellular adhesion molecule (ICAM-1) CD 54 [21], representing the inducible cell surface ligand for CD 11 a / CD 18, as well as CD 58 (LFA-3) [23], binding to the pan-T-cell antigen CD 2 [28], were analyzed as adhesion molecules of the immunoglobulin superfamily [29] that are possibly involved in immunoregulation of hematopoiesis.

Material and methods

Clinical samples

Heparinized bone marrow and/or peripheral blood samples were obtained from four healthy bone marrow donors and four patients without hematological disorders during thoracic or orthopedic surgery, as well as from 11 patients with acute lymphoblastic leukemia (ALL) and 19 patients with acute myeloid leukemia (AML). Diagnosis of leukemia was based on routine morphological evaluation and cytochemical staining of smears using the French-American-British classification (FAB) criteria as well as routine immunophenotyping. Immunophenotypical analysis of all leukemia cases was performed using a panel of monoclonal antibodies against various myeloid and lymphoid differentiation and activation antigens, as previously described [20]. To avoid extensive double labeling, only leukemias with more than 65% CD 34+ cells in peripheral blood and bone marrow were included in this study.

Monoclonal antibodies

Specificity, Ig subclasses, source, and references of the monoclonal antibodies (moabs) against the adhesion molecules investigated in this study are listed in Table 1. Most of them were available from the 4th International Workshop on Human Leukocyte Differentiation Antigens [14]. Different moabs against the same adhesion molecule available from the workshop were evaluated. For further differentiation of the CD 34+ blasts, c-kit [3] and CD 38 expression were studied.

Indirect immunofluorescence analysis

Mononuclear cells were obtained by Ficoll-hypaque density gradient centrifugation from heparinized peripheral blood and bone marrow aspirates. Single staining was performed using the indirect immunofluorescence technique, with moabs as first and $F(ab)_2$ fragments of fluorescein-isothiocyanate (FITC)-conjugated goat-anti-mouse immunoglobulins (Dianova, Hamburg, FRG) as second antibody layer.

Double-labeling experiments were carried out for each investigated adhesion molecule and CD 34 in normal bone marrow. The staining procedure was performed according to the following protocol: Cells were stained with the first monoclonal antibody and developed with goat anti-mouse-FITC; in the subsequent step the cells were incubated with excess mouse IgG to block free binding sites of the FITC conjugate. In the final step, cells were labeled with the CD 34-specific phycoerythrin (PE)-conjugated monoclonal antibody HPCA-2 (Becton Dickinson, San José, USA).

Fluorescence was evaluated on a FACS IV cell sorter (Becton Dickinson, San José, USA) as previously described [19]. Dual scatter gates (forward × 90° scatter) were set to electronically select mononuclear cells, of which the fluorescence distribution was analyzed. The green fluorescence of the FITC-labeled cells was measured through a 530-nm band pass filter and the yellow fluorescence of PE-stained compounds through a 570-nm band pass filter. After proper compensation with control beads the fluorescence intensities (log scale, 4 decades) and the scatter signals (linear scale) were analyzed by a data lister and evaluated on an IBM-AT using in-house programs.

Table 1. Characteristics of selected monoclonal antibodies

Antibody designation	CD Specificity	Ig Class	Reference / Source
ITM 3-2	CD 11 a	G 2 a	[14]
VIPIIIB 1	CD 11 a	G 2 a	[14]
11 C 2 E 2	CD 11 b	G 1	Own laboratory
S-HCL-3	CD 11 c	G 2 b	[15]
3.9.	CD 11 c	G ×	[11]
p 150,95	CD 11 c	G 1	Dianova
11 H 6	CD 18	G 2 a	[14]
F 10-44-2	CD 44	G 2 a	[5, 27]
HK 23	CD 44	G 1	[8]
7 F 7	CD 54	G 2 a	[14, 24]
RR 1/1	CD 54	G 1	[6, 14, 21]
LB-2	CD 54	G 2 a	[14]
ICAM-1	CD 54	G 1	Dianova
TS 2/9	CD 58	G 1	[23]
BRIC 5	CD 58	G 2 a	[13]
LFA-3	CD 58	G 2 a	Dianova
VLA-2	CDw 49 b	G 1	Dianova
VLA-4	CDw 49 d	G 1	Dianova
17 F 11	c-kit	M	[3]
Okt 10	CD 38	G 1	Ortho Diagnostics
HPCA-2	CD 34	G 1	Becton Dickinson

Results

Expression of adhesion molecules on CD 34+ cells in normal bone marrow

Using different moabs for the same investigated adhesion molecule, identical reactivity patterns of the moabs were observed for all adhesion molecules except for CD 54 (ICAM-1). In normal bone marrow > 50% of CD 34+ cells carried the CD 11 a antigen in all eight investigated individuals with concomitant expression of the CD 18 (β 2-chain) antigen (Table 2). The two other members of the β 2-integrin family, CD 11 b and CD 11 c, were not detected on CD 34+ cells. Among the members of the very late antigens, CD 34+ cells always expressed CDw 49 d (VLA-4), but only a very small minority of cells carried CDw 49 b (VLA-2). Normal CD 34+ bone marrow cells co-expressed CD 54, the intercellular adhesion molecule (ICAM-1), when stained with the CD 54 antibody from Dianova (Hamburg, FRG). However, no co-expression was documented using the workshop antibody LB-2 [14]. CD 58 (LFA-3), also a member of the immunoglobulin family, was found on most CD 34+ cells. Furthermore, the CD 34+ cells always carried the CD 44 antigen HCAM in normal bone marrow. In addition, CD 34+ cells expressed CD 38 and, in part, c-kit (Fig. 1).

Expression of adhesion molecules on CD 34+ leukemic blasts

Peripheral blood and/or bone marrow samples from 11 patients with ALL and 19 patients with AML were investigated for the expression of selected adhesion molecules. In two of the 30 patients expression of adhesion molecules on CD 34+ leukemic blasts was established by double-labeling experiments. Because of the high percentage of CD 34+ cells (> 65%) in all other bone marrow and blood samples, the presence or absence of adhesion molecules on CD 34+ blasts was deduced from single labelings.

Antigen distribution of CD 34+ blasts in correlation to the FAB subtypes are summarized in Tables 3 and 4.

Table 2. Expression of adhesion molecules on CD34+ normal bone marrow cells in double-labeling experiments

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
CD11a+/CD11a−	6/2[a]	11/ 5	7/ 4	4/2	9/ 1	4/3	8/0	4/0
CD11b+/CD11b−	< 1/6	1/12	0/ 9	0/6	1/13	0/7	0/7	0/4
CD11c+/CD11c−	< 1/5	0/11	2/ 9	0/6	2/13	0/6	0/8	0/4
CD18+/CD18−	4/3	10/ 2	6/ 6	2/4	8/ 2	4/3	7/2	4/1
CD54+/CD54−[b]	1/6	0/12	0/11	0/6	0/14	0/6	8/0	4/0
CD58+/CD58−	4/1	11/ 1	8/ 3	5/1	11/ 4	4/3	8/0	5/0
CD44+/CD44−	4/1	11/ 0	10/ 1	5/1	15/ 1	5/1	6/1	4/0
CDw49b+/CDw49b−	< 1/5	0/12	1/11	1/5	2/13	1/5	0/8	0/4
CDw49d+/CDw49d−	5/1	12/ 0	10/ 2	6/0	15/ 0	6/0	7/1	4/0

[a] Percent positive CD34+ cells/percent negative CD34+ cells.
[b] In patients 1–6 moab LB-2, in patients 7 and 8 moab from Dianova was used.

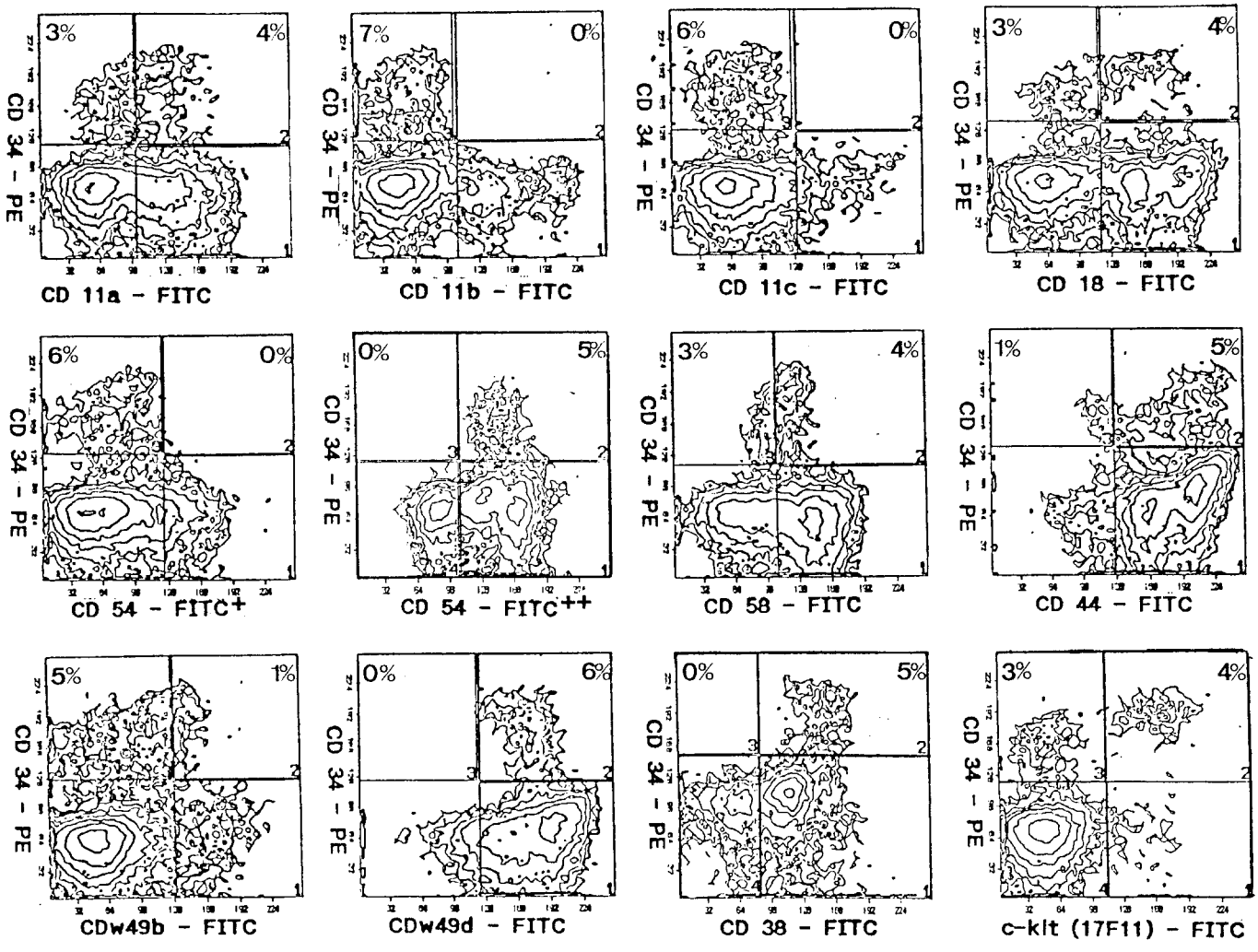

Fig. 1. Double-labeling contour display of bone marrow cells (pat. 6) shows expression of CD11a, CD11b, CD11c, CD18, CD54 (+, workshop moab LB-2; ++, moab from Dianova), CD58, CD44, CDw49b, CDw49d, CD38, and c-kit (numbers in the upper corners indicate percent positive or percent negative CD34+ cells)

CD38 was expressed on CD34+ cells in 12 of 15 investigated AML and nine of 11 ALL cases. C-kit was negative on CD34+ cells in all ALL cases, whereas in 14 of 15 AML cases a variable percentage of CD34+ cells carried the c-kit glycoprotein.

CD11a was expressed on CD34+ cells in 17 of 19 AML cases (Table 4) with concomitant expression of CD18. In one of the two CD11a− myeloid leukemias (no. 5) an unusual CD56+, CD19+ phenotype [20] of the CD13+, CD15+, CD34+ blasts was found. The

Table 3. Expression of adhesion molecules in acute lymphoblastic leukemias

Patient	Diagnosis	Material	Immunophenotype (Percent positive cells) CD34	CD38	17F11	CD11a	CD11b	CD11c	CD18	CD44	CD54	CD58	CDw49b	CDw49d
1	c-ALL	PB	65	84	2	96	16	5	92	98	54	84	6	96
2	c-ALL	BM	93	83	1	87	5	4	86	99	57	98	n.t.	n.t.
3	c-ALL	BM	97	6	0	70	n.t.	2	65	88	2	95	0	92
4	c-ALL	PB	85	88	n.t.	13	8	13	14	94	8	94	3	82
5	c-ALL	PB	67	11	3	78	7	0	50	95	89	96	0	98
6	c-ALL	PB	80	74	1	90	4	3	67	98	83	87	2	92
7	c-ALL	PB	94	60	n.t.	n.t.	1	1	94	98	1	99	87	98
		BM	93	30	n.t.	n.t.	0	1	92	98	0	98	72	97
8	0-ALL	PB	62	61	n.t.	34	1	32	33	99	68	91	n.t.	n.t.
9	t-ALL	PB	55	92	2	95	1	3	51	99	2	97	92	99
		BM	58	98	1	92	1	2	70	99	2	97	91	97
10	t-ALL	PB	89	93	n.t.	97	2	1	94	99	3	97	5	93
		BM	85	92	n.t.	98	2	2	95	97	4	96	2	96
11	t-ALL	BM	73	88	0	97	7	0	97	88	9	86	4	97

PB, Peripheral blood; BM, bone marrow; n.t., not tested

Table 4. Expression of adhesion molecules in acute myeloid leukemias

Patient	Diagnosis	Material	Immunophenotype (Percent positive cells) CD34	CD38	17F11	CD11a	CD11b	CD11c	CD18	CD44	CD54	CD58	CDw49b	CDw49d
1	AML-M0	PB	89	5	71	98	94	90	98	98	6	0	5	92
		BM	91	9	90	98	83	77	96	99	97	96	8	95
2	AML-M1	PB	93	93	40	97	51	3	97	99	4	98	3	95
3	AML-M1	PB	75	87	33	77	2	4	55	99	70	92	0	78
		BM	87	91	61	83	0	0	50	95	94	95	0	81
4	AML-M1	PB	78	n.t.	n.t.	87	3	5	85	97	67	93	4	93
5	AML-M2	PB	82	83	14	15	3	7	20	99	69	93	2	66
6	AML-M2	PB	70	86	62	90	15	20	88	98	62	92	81	n.t.
		BM	72	54	n.t.	74	10	5	58	96	65	82	0	82
7	AML-M2	BM	69	89	48	93	23	13	91	99	15	96	7	93
8	AML-M2	PB	60	18	n.t.	8	7	0	10	89	45	87	0	90
		BM	69	6	n.t.	87	15	0	70	87	88	95	0	91
9	AML-M2	PB	50	57	52	70	6	7	67	93	60	68	2	85
10	AML-M2	PB	55	63	53	59	14	39	57	94	63	91	0	88
		BM	60	65	n.t.	59	12	33	65	96	67	94	0	93
11	AML-M2	PB	66	70	55	95	28	28	88	99	88	88	7	93
		BM	90	70	55	97	8	93	91	99	93	93	1	95
12	AML-M2	PB	69	66	45	75	0	29	75	96	68	75	55	85
13	AML-M2	BM	75	n.t.	n.t.	80	21	16	78	95	59	87	75	98
14	AML-M4	PB	76	87	69	91	7	86	89	99	88	98	7	98
15	AML-M4	PB	88	14	85	75	12	4	94	99	86	92	6	93
16	AML-M4	BM	77	n.t.	58	94	14	29	94	96	52	74	0	76
17	AML-M5	BM	85	88	55	98	n.t.	60	98	99	87	99	84	99
18	AML-M5	PB	76	67	4	97	82	78	95	99	58	84	1	90
19	AML-M7	PB	69	n.t.	27	27	12	31	34	84	25	82	62	91

PB, Peripheral blood; BM, bone marrow; n.t., not tested

other case (no. 19) was classified by immunophenotyping and cytochemical analysis as M7-leukemia. In contrast to CD34+ cells in normal bone marrow, CD11b was expressed in one M0-leukemia with an unusual CD56+ phenotype (no. 1), in one M1-leukemia of a CD15+, CD33+ phenotype (no. 2), and in one M5-leukemia of monocyte lineage (no. 18). CD11c was found on CD34+ blasts in five cases of myeloid leukemia (nos. 1, 11, 14, 17, 18), which did not constitute a clinical or phenotypic entity also according to their expression of c-kit and CD38 on the leukemic blasts. In ALL (Table 3), CD11a and CD18 were not expressed on CD34+ cells in two of 11 leukemias classified as c-ALL and 0-ALL of the B-cell immunophenotype. CD11b and CD11c, however, were always negative on CD34+ blasts in ALL.

CDw49d (VLA-4), belonging to the β1-integrins, strongly stained all CD34+ cells derived from bone marrow and/or peripheral blood in all investigated cases of

ALL and AML, while CDw 49 b (VLA-2) was expressed in only a minority of leukemias. It was found on blasts of a CD 34+, CD 10+, CD 19+ c-ALL also carrying the myeloid differentiation antigen CD 33 (no. 7, Table 3), as well as on the leukemic cells of a CD 7+ t-ALL (no. 9), in which the CD 34+ cells co-expressed CD 10. Furthermore, CDw 49 b was expressed in only two CD 13+, CD 33+ myeloid leukemias of the M 2 subtype (no. 12, 13, Table 4), on monocytic blasts of one case of M 5-leukemia (no. 17) and in one CDw 41+, CD 33+, CD 34+, CD 11 a−, CD 18−, M 7-leukemia (no. 19). In one patient (no. 6) with a CD 13+, CD 33+ myeloid leukemia CDw 49 b was expressed only on the CD 34+ peripheral blood cells, but was negative on bone marrow cells.

In all investigated cases of ALL and AML, however, CD 34+ leukemic cells always carried CD 44 and CD 58. No difference in the expression of CD 44 on leukemic cells derived from bone marrow or peripheral blood was observed. Except for one case in which CD 58 expression was restricted to CD 34+ bone marrow cells, CD 58 was always found on CD 34+ cells derived from peripheral blood. In contrast to normal bone marrow, three AML (nos. 2, 7, 19) and six ALL cases (nos. 3, 4, 7, 9, 10, 11) lacked the expression of CD 54 on CD 34+ blasts according to stainings with the different moabs applied in this study.

Discussion

This study was designed to evaluate differences in the expression pattern of selected adhesion molecules on CD 34+ leukemic blasts in comparison to normal CD 34+ bone marrow cells as a possible phenotypic sign of differences in adhesive qualities of normal and pathological precursor cells.

Among the adhesion molecules analyzed, the β 2-integrins have been reported to be absent from early precursors and to be acquired during differentiation of hematopoietic cells [4, 18]. CD 11 a has been detected on μ-chain-positive pre-B cells and late myeloblasts. CD 11 b and CD 11 c were first observed on committed granulocyte and monocyte precursors in the bone marrow [18]. In this study, CD 11 a was expressed on $> 50\%$ of CD 34+ cells in normal bone marrow and on most CD 34+ blasts in almost all acute myeloid and lymphoblastic leukemias. All CD 11 a+ leukemias carried the common β 2-chain. In contrast to previous reports [4, 26], CD 11 a was also expressed in cases in which cytochemically and immunophenotypically very undifferentiated forms of myeloid leukemias were diagnosed, as well as in acute lymphoblastic leukemias of the c-ALL and t-ALL subtypes. Only in two cases of myeloid leukemia, one with an unusual CD 56+ phenotype, the other with an M 7-subtype, was CD 11 a absent on CD 34+ cells. CD 11 b – which is known to bind C 3 b, factor 10, fibrinogen, and ICAM-1 [6, 21] – and CD 11 c, which also reacts with C 3 b, were not expressed on CD 34+ normal hematopoietic precursor cells. In a few cases of myeloid leukemias representing the M 0–M 5 subtypes these adhesion molecules were found on the majortiy of CD 34+ cells. In ALL, CD 11 b and CD 11 c were not detected on CD 34+ cells.

The β 1-integrin CDw 49 b (VLA-2) was rarely detected on CD 34+ normal marrow cells, but it was found positive an most CD 34+ megakaryocytic blast cells of one analyzed M 7-leukemia, which is in agreement with a previous report [26]. In addition, CDw 49 b was detected on CD 34+ cells of some other AML and ALL cases which did not belong to a defined FAB subtype or represent immunophenotypically distinct leukemic blasts according to the expression of c-kit and CD 38. CDw 49 d (VLA-4), the other investigated β 1-integrin with a binding site for the recently characterized VCAM-1 on bone marrow stromal cells [7, 25] as well as for the matrix protein fibronectin was found on all CD 34+ cells of the normal bone marrow, but also on all blasts of all cases of acute leukemias analyzed, suggesting a broad distribution on malignant and normal hematopoietic precursor cells. CD 54 (ICAM-1), ligand for LFA-1, as well as CD 58 (LFA-3) binding to the T-cell surface molecule CD 2, were investigated as important accessory molecules for interaction with T cells possibly involved in immunoregulation of hematopoiesis. In normal bone marrow CD 54 was expressed on CD 34+ cells, which is in agreement with a recently published report [22]. Co-expression of CD 54 on CD 34+ cells, however, was not detected with the workshop antibody LB-2; this might be due to recognition of a different epitope. Irrespective of the antibody applied, CD 54 was absent in six of 11 ALL and in three of 19 AML cases. Leukemic blasts and CD 34+ cells in normal bone marrow did not differ in their expression of CD 58. In one case, however, CD 58 expression on CD 34+ malignant precursor cells was restricted to the bone marrow CD 34+ cells. Similarly, the lymphocyte-homing-associated adhesion molecule CD 44 was present on all normal bone marrow precursor cells, as described previously by Lewinsohn et al. [17], and also strongly expressed in all investigated leukemias. This could indicate that expression of these molecules is not relevant for the malignant phenotype of the leukemic cells.

So far, the adhesion molecules CD 11 b, CD 11 c, CD 54, and CDw 49 b (VLA-2) appeared to be altered in their expression on blasts of certain cases of ALL and AML which did not belong to a specific CD 34+ cell subset or comprise a distinct FAB subtype. In addition, in some leukemias loss or downregulation of the expression of CD 11 a, CD 18, CD 54 and CD 58 was observed on the CD 34+ blast cells when they were leaving the bone marrow. Thus, in our study variations in the expression of adhesion molecules were observed not only between normal and leukemic precursor cells, but also among immunophenotypically and clinically identical leukemic subtypes and even on the same leukemic blasts, depending on their localization in blood or bone marrow. Mere observations evoke the possibility that expression of adhesion molecules on leukemic and normal hematopoietic precursor cells could largely be regulated by their cellular and humoral environment. The physiological significance of this variable expression of adhesion molecules remains to be elucidated for differences in adhesive qualities between normal and certain leukemic hematopoietic precursor cells.

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