Virchows Archiv A Pathol Anat (1993) 422:203–210

Virchows Archiv A
Pathological Anatomy and Histopathology

Expression of β1 integrins in non-neoplastic mammary epithelium, fibroadenoma and carcinoma of the breast

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Received November 25, 1992 / Received after revision January 6, 1993 / Accepted January 11, 1993

Abstract. β1 Integrins were examined immunohistochemically in normal and mastopathic mammary glands, 12 benign tumours and 90 carcinomas of the breast using monoclonal antibodies against β1 and α1 to α6 subunits. When compared with epithelial cells of non-neoplastic mammary glands and of benign tumours, carcinoma cells showed considerable quantitative changes in the pattern of α2, α3 and α6 subunit expression. In contrast, the distribution pattern of β1, α1, α4 and α5 antigens corresponded to the situation observed in non-neoplastic mammary gland epithelium in most instances. An abnormal expression of α2 was found in 71.0% of the carcinomas ranging from a remarkably low number of α2-positive tumour cells in 27.5% of the cases to a complete absence of the α2 molecule in 43.5% of the carcinomas. Of the carcinomas 39.9% exhibited quantitative changes in α3 expression with an abnormally low content of α3-positive neoplastic cells in 15.4% and a complete absence of this molecule in 24.5% of the cases. Expression of α6 was abnormal in 73.2% of the carcinomas, consisting in a greater number of α6-negative tumour cells in 31.9% and in a complete absence of α6 in 41.3% of the tumours. The abnormally low expression/absence of α2 and α3 subunits correlated with oestrogen receptor negativity ($P < 0.033$ and $P < 0.04$, respectively). In addition, abnormally low expression/absence of α2 correlated with poor differentiation of the tumours ($P < 0.014$). The quantitative changes in the expression pattern of β1-associated α subunits in breast carcinomas may cause a disturbed cell-cell and/or cell-matrix interaction that increases the invasive and migratory property of the tumour cells.

Key words: β1 Integrins – Immunohistochemistry – Breast tissue – Prognostic parameters

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Introduction

Cell-cell and cell-matrix interactions play an important role in biological events such as tissue morphogenesis and cell differentiation, tissue repair, immune response and malignant transformation. They are mediated by a variety of cell surface receptors which includes the integrins, in addition to adhesion molecules of the immunoglobulin supergene family, cadherins, selectins, and lymphocyte homing receptors (Albeda and Buck 1990).

Integrins are a superfamily of non-covalently associated transmembrane αβ heterodimers. The large extracellular domains contain the ligand binding region; the small intracytoplasmic domains link the integrins to the actin cytoskeleton. Integrins recognize their ligands via specific amino acid sequences. A considerable number of integrins recognize peptides containing arginine-glycine-aspartic acid or closely related amino acid sequences in their corresponding ligands. However, other sequences are also important for recognition (Hynes 1992).

Based on different β subunits, the integrins are subdivided into protein subfamilies. Up to present, at least 8 different β and 14 different α subunits have been described which build up 20 αβ heterodimers (Hynes 1992).

The largest number of integrins are members of the β1 subfamily, also known as very late antigens since some of these molecules were first described on T cells at very late stages of activation (Hemler et al. 1984). The β1 subunit is usually associated with one of six well-defined α subunits, called α1 to α6 (Hemler 1990). Meanwhile, one or more ligands including extracellular matrix proteins and even cell adhesion molecules have been identified for all of these α subunits (Table 1). Thus, β1 integrins not only form a major set of extracellular matrix components but also are involved in cell-cell interactions. Recent work has shown that there are at least three additional α subunits which are capable of complexing with the β1 subunit in certain cell types (Hynes 1992).

Table 1. β1 Integrin subunits detected and monoclonal antibodies used in this study

Antigen	Mol.wt. (kDa)	Receptor for/function[a]	CD number	Clone	Authors
α1	210	Collagen/laminin	–	TS2/7	Hemler et al. (1985)
α2	170	Collagen/(laminin)	CDw49b	CLB-thromb/4	Giltay et al. (1989)
α3	130/25	Collagen/laminin/fibronectin/ epiligrin/entactin	–	J143	Fradet et al. (1984)
α4	150	Fibronectin/VCAM-1/ICAM-2	CDw49d	HP2/1	Sanchez-Madrid et al. (1986)
α5	135/25	Fibronectin	–	SAM1	te Velde et al. (1988)
α6	120/30	Laminin	CDw49f	GOH3	Sonnenberg et al. (1987)
β1	130	Common β chain of α1 to α6	CD29	K20	Amiot et al. (1986)

[a] Hynes (1992); Dedhar et al. (1992)

The expression of β1 integrins is not stable. Thus, different cytokines including transforming growth factor-β, interleukin-1β, tumour necrosis factor-α and some steroids have been shown to modulate the expression of β1 integrins on different human neoplastic cell lines (Lopes et al. 1991; Santala and Heino 1991). Furthermore, changes in β1 integrin expression have been observed during malignant transformation and metastasis of epithelial neoplasms like skin (Peltonen et al. 1989), breast (Zutter et al. 1990; Koukoulis et al. 1991), colon (Koretz et al. 1991), and lung carcinomas (Zylstra et al. 1986) and of malignant melanomas (Albeda et al. 1990; Klein et al. 1991). In colonic carcinomas and in malignant melanomas, these changes were found to correlate with prognostic parameters such as Dukes' stage (Koretz et al. 1991) and Breslow index (Albeda et al. 1990), respectively. In addition, a correlation between β1 integrin expression and oestrogen receptor status was assumed in breast carcinomas (Zutter et al. 1990).

This led us to study the detailed in situ distribution pattern of β1 integrins in a clinico-pathologically well-characterized series of breast carcinomas large enough to enable statistical analysis. For comparison, normal and mastopathic mammary glands as well as benign tumours of the breast were also examined.

Table 2. Clinico-pathological features of 90 breast carcinomas studied

Hormone receptor status:		
Progesterone receptors	Positive	50
	Negative	35
	No data	5
Oestrogen receptors	Positive	51
	Negative	34
	No data	5
Lymph node status:		
Lymph node metastases	Present	43
	Absent	28
	No data	19
Histopathological tumour type:		
Invasive ductal		65
Invasive lobular		19
Mucinous		4
Unclassified		2
Histological tumour grading:		
Grade I/II		1
Grade II		58
Grade II/III; III		18
Grade III/IV		13

Materials and methods

Tissue samples of at least 1 cm^2 and various thickness reached our laboratory within 1 h of surgical removal. They were snap-frozen in liquid nitrogen and stored at -70° C until sectioning. Serial sections of 4–6 μm thickness were cut, air-dried, fixed in acetone for 10 min at room temperature and stained immediately or stored at -20° C for 1–3 weeks.

The series of tumours comprised 10 fibroadenomas, 2 benign phyllodes tumours, and 90 unselected primary malignant breast tumours which were collected in the course of a clinico-pathological study on mammary carcinomas. In addition, representative tissue specimen of 5 normal non-lactating mammary glands and of 10 tissue samples exhibiting various aspects of fibrocystic disease were studied.

Clinico-pathological characteristics of the breast carcinomas are shown in Table 2. The oestrogen and progesterone receptor status was determined biochemically by the dextran-coated charcoal assay (Raam et al. 1982). The threshold for positivity was 20 fmol/mg protein. Histological tumour grading was carried out according to Bloom and Richardson (1957).

The primary monoclonal antibodies (mAb) to β1 integrin subunits used in this study are listed in Table 1. They were generous gifts from the producing laboratories (see Acknowledgements) except for mAb SAM1 which was supplied by Dianova (Hamburg, Germany). MAb HD77 directed against the pan-leuco/histiocytic CD53 antigen (Hadam 1989) was produced in our own laboratory in collaboration with B. Dörken and G. Moldenhauer. Except for mAb GOH3, which was of rat origin, the mAb were raised in mice. A polyclonal biotinylated sheep antibody to mouse immunoglobulin and, for detection of rat-derived mAb GOH3, a polyclonal biotinylated sheep antibody to rat immunoglobulin, and a streptavidin-biotinylated peroxidase complex, all obtained from Amersham (High Wycombe, UK), served as detection system for the primary mAb.

After rehydration with phosphate-buffered saline solution (PBS; pH 7.4), the frozen sections were incubated for 1 h with primary mAb. MAb in culture supernatant were applied undiluted, ascites preparations were diluted 1:2000 in PBS, purified reagents were used in a protein concentration of about 10 μg/ml PBS. All incubation steps were carried out in a humid chamber at room temperature and were followed by double rinsing with PBS. Using 3-amino-9-ethylcarbazole as the chromogen (0.4 mg/ml in 0.1 M acetate buffer, pH 5.0, with 5% dimethylformamide and 0.01% hydrogen peroxide for 10 min), the peroxidase reaction caused an intense red precipitate. The sections were rinsed in tap water, counterstained with Harris' haematoxylin, and mounted with glycerol gelatin.

Negative controls were in each case performed by omitting the primary mAb. No staining was observed except for scattered granulocytes. This staining was due to endogenous peroxidase which was not blocked for the benefit of optimal antigenicity. Carcinoma cells were discriminated from lymphohistiocytic stromal cells by incubating one of the serial sections of each case with CD53 (HD77).

The expression pattern of $\beta 1$ integrin subunits in normal and neoplastic myo-/epithelial cells was evaluated independently by three of the authors (G.M., M.M., P.M.) in a semi-quantitative fashion as follows: +, (almost) all cells positive; + > −, clearly more positive than negative cells; +/−, positive and negative cells in equal amounts; − > +, clearly more negative than positive cells; −, (almost) all cells negative. Discrepancies in evaluation were discussed at a triple microscope and a consensus assessment was obtained. Fisher's exact test was applied for statistical analysis. P values of <0.05 were considered significant.

Results

The expression patterns of $\beta 1$ integrin subunits in myoepithelial cells and in ductal/lobular epithelial cells of normal and mastopathic mammary glands and of benign tumours of the breast are summarized in Table 3.

Myoepithelial cells were consistently and strongly $\beta 1$-, $\alpha 2$-, $\alpha 3$- and $\alpha 6$-positive in all tissue samples studied (Fig. 1 b–d). In addition, the myoepithelial compartment showed a weak and inconsistent staining for $\alpha 1$ that was occasionally higher in mastopathic glands and in benign tumours of the breast (Fig. 1 a). $\alpha 4$ and $\alpha 5$ antigens were completely absent in all myoepithelial cells.

In normal mammary gland, the clear majority of ductal/lobular epithelial cells was also $\beta 1$-, $\alpha 2$- and $\alpha 6$-posi-

Table 3. Compiled expression pattern of $\beta 1$ integrins in normal and mastopathic mammary glands and in benign breast tumours

Antigen	Normal gland		Mastopathic gland		Benign tumours	
	ME[a]	DE/LE[a]	ME	DE/LE	ME	DE/LE
$\alpha 1$	◍	○	◍	○	◍	○
$\alpha 2$	●	●	●	◍	●	●
$\alpha 3$	●	◍	●	●	●	●
$\alpha 4$	○	○	○	○	○	○
$\alpha 5$	○	○	○	○	○	○
$\alpha 6$	●	●	●	◍	●	●
$\beta 1$	●	●	●	●	●	●

(Almost) all cells positive ● or negative ○; ◍ clearly more positive than negative cells; ◍ positive and negative cells in equal amounts; ○ clearly more negative than positive cells

[a] ME, myoepithelial cells; DE/LE, ductal/lobular epithelial cells

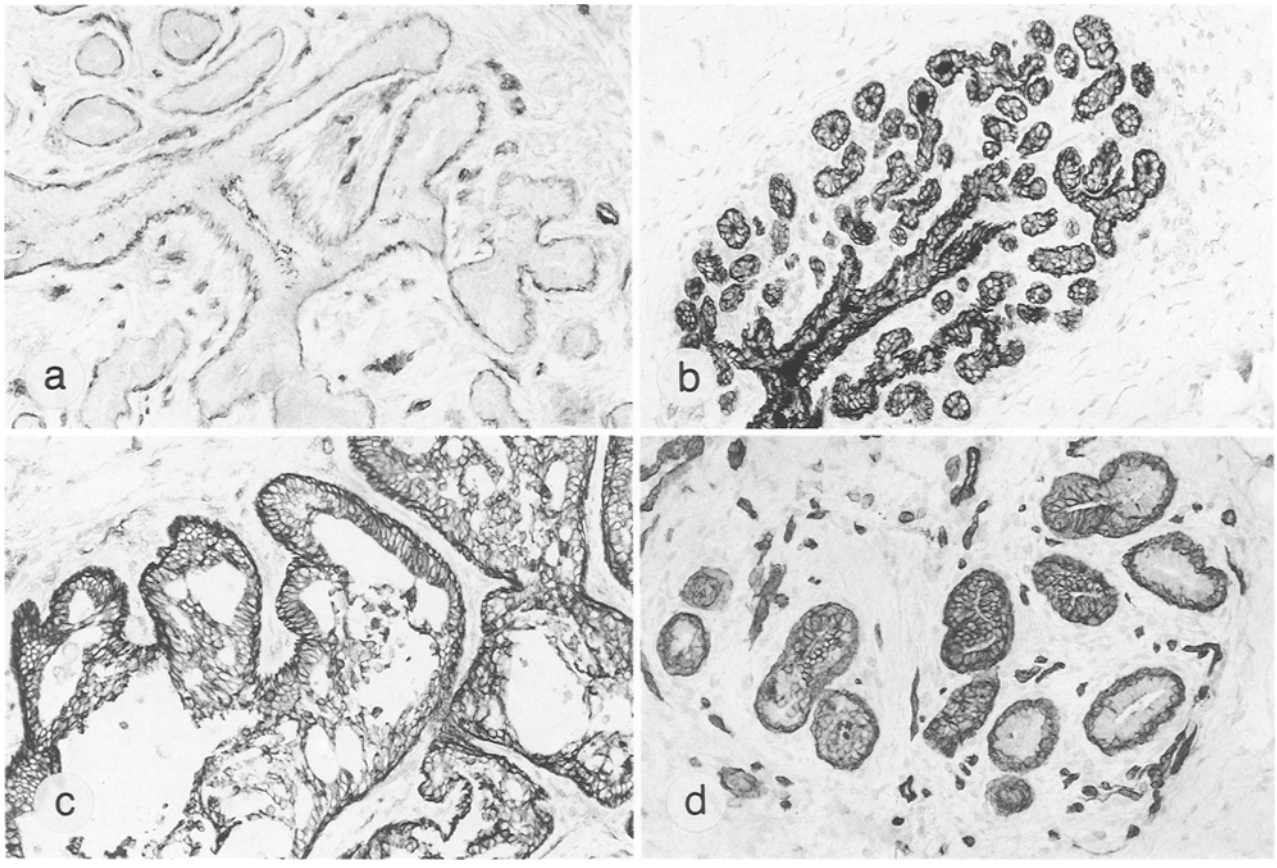

Fig. 1. a Fibroadenoma. Myoepithelial cells are $\alpha 1$-positive while absent in the ductal epithelium. ×150. **b** Normal mammary gland. $\alpha 2$ is expressed in the entire myoepithelial and ductal/lobular epithelial cell compartment. ×150. **c** Mastopathy with epitheliosis. Both myoepithelial and ductal epithelial cells are strongly and consistently $\alpha 3$-positive. ×150. **d** Mastopathy with adenosis. All myoepithelial cells are $\alpha 6$-positive; the ductal epithelium shows a mixed pattern of $\alpha 6$-positive and $\alpha 6$-negative cells. ×150

Table 4. Detailed expression pattern of the α2 subunit in breast carcinomas

Type	●		◉		◍		◌		○	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Ductal invasive	18	20.2	6	6.6	8	8.8	4	4.4	29	32.5
Lobular invasive	4	4.4	4	4.4	2	2.2	1	1.1	8	8.8
Mucinous	3	3.3	–	–	–	–	–	–	1	1.1
Unclassified	1	1.1	–	–	–	–	–	–	1	1.1
Total	26	29.0	10	11.0	10	11.0	5	5.5	39	43.5

(Almost) all cells positive ● or negative ○; ◉ clearly more positive than negative cells; ◍ positive and negative cells in equal amounts; ◌ clearly more negative than positive cells

tive (Fig. 1b, d). Furthermore, a major ductal/lobular epithelial cell population expressed the α3 molecule. Anti-α1, −α4, and -α5 mAb yielded no convincing staining in the ductal/lobular epithelium of normal glands and of most mastopathies and benign tumours. Only rarely was a faint and partly cytoplasmic staining for α1 and α5 observed in ductal/lobular epithelial cells of mastopathic glands and benign tumours. However, in areas showing adenosis the amount of α2- and α6-negative ductal epithelial cells was slightly higher than in normal mammary glands (Fig. 1d). Conversely, the amount of α3-positive ductal epithelial cells was higher in areas showing epitheliosis and in some fibroadenomas as compared to their normal counterparts (Fig. 1c).

In all but 4 carcinomas studied, the pattern of expression of the β1 subunit in tumour cells was similar to that found in the ductal/lobular epithelium of normal mammary glands. Only 2 cases showed a lower expression of the β1 molecule when compared with the normal state, and 2 further cases were completely β1-negative.

Corresponding with their non-neoplastic counterparts, nearly all breast carcinomas examined lacked any detectable α1 molecule in the neoplastic population. Expression of the α1 subunit was restricted to 3 carcinomas which showed a weakly α1-positive tumour cell subset.

In contrast, a considerable number of the carcinomas examined showed an abnormally low expression of the α2 molecule when compared with non-neoplastic ductal/lobular breast epithelium (Table 4). Thus, in 10 carcinomas the number of α2-negative tumour cells was slightly higher than that of normal mammary gland epithelium (Fig. 2a). A further 10 cases showed α2-positive and α2-negative tumour cells in about equal proportions. In 5 cases α2-negative clearly outnumbered α2-positive tumour cells. Moreover, in 39 carcinomas the entire neoplastic population was α2-negative (Fig. 2b). Altogether, 71.0% of the carcinomas had an abnormally low content of α2-positive neoplastic cells or even lacked this antigen completely.

An abnormally low expression of α3 was found in 39.9% of the carcinomas studied (Table 5). These included 6 cases showing α3-positive and α3-negative tumour cells in about equal amounts, 8 cases in which expression of α3 was restricted to a minor tumor cell subset (Fig. 2c), and 22 carcinomas with complete absence of α3 in the neoplastic population. In 54 cases the carcinoma cells showed a pattern of α3 antigen expression that was comparable to that found in non-neoplastic mammary gland epithelium (Fig. 2d).

Like the results for α1, the tumour cells of the great majority of breast carcinomas studied, in common with non-neoplastic mammary gland epithelium, showed a complete absence of any detectable α4 subunit. Focal and weak expression of α4 was restricted to a neoplastic subset of 2 carcinomas.

A weak but consistent expression of the α5 subunit was observed in only 3 carcinomas (Fig. 2e). Moreover, a minor tumour cell subset was α5-positive in 13 further cases but in all other carcinomas examined the tumour cells were α5-negative throughout.

Finally, the α6 subunit showed a remarkably low expression in breast carcinoma cells (Table 6). In 9 cases the number of α6-negative tumour cells was slightly higher when compared with non-neoplastic ductal epithelium. Thirteen carcinomas comprised α6-positive and α6-negative tumour cells in about equal proportions. In 7 cases expression of α6 was restricted to a minor neoplastic subset. In addition, in 37 cases the neoplastic population was α6-negative throughout (Fig. 2f). Thus, 73.2% of the carcinomas examined were characterized by an abnormally low content or even a complete absence of α6 within the tumour cell population.

With respect to tumour type, no obvious link to presence or absence of β1 integrin subunits emerged.

Statistical analysis of the mode of α2, α3 and α6 expression and (1) progesterone receptor status, (2) oestrogen receptor status, (3) histopathological tumour grading and (4) presence of lymph node metastases (Table 7) was carried out. Abnormally low expression/absence of α2 and α3 subunits was correlated with oestrogen receptor-negativity ($P<0.033$ and $P<0.04$, respectively). Furthermore, abnormally low expression/absence of the α2 antigen was correlated with poor differentiation of the carcinomas ($P<0.014$). In contrast, there was no correlation between the mode of α subunit expression and progesterone receptor status or presence of lymph node metastases.

In summary, the mode of β1, α1, α4 and α5 expression in carcinoma cells was in most instances comparable to that found in non-neoplastic ductal/lobular breast epithelium. In contrast, an abnormally low expression or even a complete absence of α2, α3 and α6 subunits was a frequent finding within the neoplastic population of our series of breast carcinomas. The low expression/absence of α2 and α3 molecules yielded a significant correlation with the oestrogen receptor status. Moreover, low expression/absence of α2 was significantly more frequent in poorly differentiated tumours.

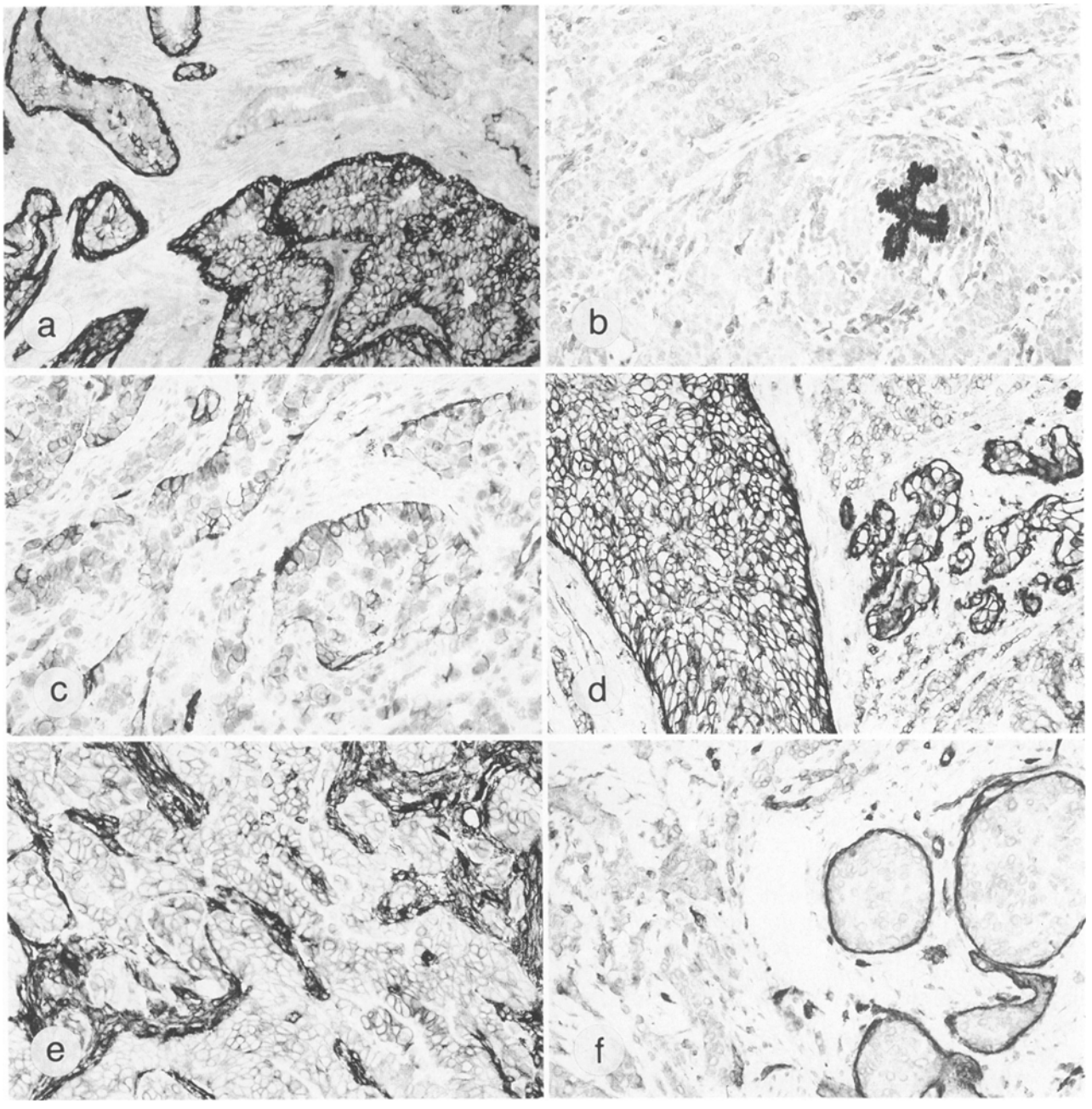

Fig. 2. **a** Invasive ductal carcinoma. Myoepithelial remnants and the majority of carcinoma cells are α2-positive; a minor neoplastic population is α2-negative. × 150. **b** Lobular invasive carcinoma. The carcinoma cells lack any detectable α2 molecule while a small ductal remnant is strongly α2-positive. × 150. **c** Invasive ductal carcinoma. Only a minor carcinoma cell subset shows a basolaterally accentuated expression of α3. × 150. **d** Invasive ductal carcinoma. The majority of tumour cells is strongly α3-positive; a minor carcinoma cell subset shows only a weak α3 expression. × 150. **e** Invasive ductal carcinoma. The carcinoma cells exhibit a weak staining for α5 as compared to strongly α5-positive stromal cells. × 150. **f** Invasive ductal carcinoma. Both intraductal and invasive tumour cells are devoid of any detectable α6 antigen while strongly expressed by myoepithelial remnants. × 150

Table 5. Detailed expression pattern of the α3 subunit in breast carcinomas

Type	●		◍		◍		○		○	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Ductal invasive	32	35.8	5	5.5	5	5.5	7	7.7	16	17.9
Lobular invasive	11	12.2	2	2.2	–	–	1	1.1	5	5.5
Mucinous	3	3.3	–	–	1	1.1	–	–	–	–
Unclassified	–	–	1	1.1	–	–	–	–	1	1.1
Total	46	51.3	8	8.8	6	6.6	8	8.8	22	24.5

(Almost) all cells positive ● or negative ○; ◍ clearly more positive than negative cells; ◍ positive and negative cells in equal amounts; ○ clearly more negative than positive cells

Table 6. Detailed expression pattern of the α6 subunit in breast carcinomas

Type	●		◍		◍		○		○	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Ductal invasive	16	18.0	6	6.6	9	9.9	7	7.7	27	30.3
Lobular invasive	6	6.6	2	2.2	4	4.4	–	–	7	7.7
Mucinous	1	1.1	1	1.1	–	–	–	–	2	2.2
Unclassified	1	1.1	–	–	–	–	–	–	1	1.1
Total	24	26.8	9	9.9	13	14.3	7	7.7	37	41.3

(Almost) all cells positive ● or negative ○; ◍ clearly more positive than negative cells; ◍ positive and negative cells in equal amounts; ○ clearly more negative than positive cells

Table 7. Correlation between α2, α3 and α6 subunit expression and prognostic parameters in mammary carcinomas

	α2	α3	α6
	P values		
Oestrogen receptors	0.0327	0.0399	n.s.
Progesterone receptors	n.s.	n.s.	n.s.
Lymph node metastases	n.s.	n.s.	n.s.
Histopathological grading	0.0134	n.s.	n.s.

n.s., Not significant

Discussion

In this study, we investigated the detailed in situ distribution pattern of β1 integrins in non-neoplastic and neoplastic human breast tissue. Carcinoma cells are frequently characterized by an abnormally low content of β1-associated α2, α3 and α6 subunits when compared with their cells of origin. The hypo-expression or lack of α2 and α3 subunits correlated with the prognostic variables, oestrogen receptor negativity and a low level of differention of the carcinomas. These data suggest that important changes in β1 integrin expression occur during malignant transformation of human breast epithelium.

In agreement with others (d'Ardenne et al. 1991; Koukoulis et al. 1991; Pignatelli et al. 1991), we found a strong expression of β1, α2, α3 and α6 molecules in the absence of α4 and α5 subunits in non-neoplastic myoepithelial cells. Unlike the results of d'Ardenne et al. (1991) and Koukoulis et al. (1991), however, expression of α1 in the myoepithelial compartment was inconsistent in our experience.

There is an agreement on the complete absence of α4 in normal ductal/lobular breast epithelium, but for the other α subunits, our results and those reported in the literature disagree. Like Koukoulis et al. (1991), we found the ductal/lobular epithelium of normal mammary glands to be α5-negative whereas others (Zutter et al. 1990; d'Ardenne et al. 1991) observed at least a weak α5 expression in this cellular compartment. Moreover, corresponding to the data by d'Ardenne et al. (1991) but unlike those of Koukoulis et al. (1991), we did not find any convincing staining for α1 in normal ductal/lobular epithelial cells. Furthermore, our findings that α2, α3 and α6 antigens are broadly distributed in non-neoplastic ductal/lobular breast epithelium agrees with the results of d'Ardenne et al. (1991). These data, however, are at variance with those of Koukoulis et al. (1991) and Pignatelli et al. (1991) who observed only a weak expression of these molecules at the basolateral surface membrane. We further confirm that mastopathic mammary glands and benign tumours of the breast exhibit a β1 integrin immunoprofile which, in most aspects, is comparable to that observed in normal mammary gland epithelium (d'Ardenne et al. 1991; Koukoulis et al. 1991).

In contrast, mammary carcinoma cells were frequently characterized by an abnormally low expression of α2, α3 and α6 subunits. Quantitative changes in β1, α1, α4 and α5 subunit expression, however, were an extremely rare phenomenon in our series of carcinomas.

With regard to the mode of expression of α1, α4 and α5 molecules, our results are in good correspondence with those present in the literature (d'Ardenne et al. 1991; Koukoulis et al. 1991). The data on the β1 subunit in breast carcinomas, though, are controversial. In contrast with our results which indicate that the expression of the β1 subunit is conserved in mammary carcinomas, Pignatelli et al. (1991) and Jones et al. (1992) found abnormally low levels or even a complete absence of the β1 molecule in a considerable number of their breast carcinomas. In this context it is worth mentioning that Jones et al. (1992) found differences in β1 subunit staining by application of two different anti-β1 antibodies. It is, therefore, possible that these discrepancies might be due to differences in affinity of the anti-β1 mAb.

Reduced expression of α2 in breast carcinomas was first described by Zutter et al. (1990) and was also frequently observed in the cohorts studied by Pignatelli et al. (1991) and by Jones et al. (1992). In contrast, others (d'Ardenne et al. 1991; Koukoulis et al. 1991) did not find such changes in α2 expression. Our series of breast carcinomas, however, clearly shows that expression of α2 is remarkably low or even completely absent in the majority of breast carcinomas. Moreover, the association between an abnormally low expression of the α2 molecule and oestrogen receptor negativity first suggested by Zutter et al. (1990) was substantiated by a statistically significant correlation of these variables in our series. In addition, like Pignatelli et al. (1991), we found a statistically significant correlation between abnormally low expression of α2 and poorly differentiated carcinomas. A correlation between α2 expression and prognostic variables has also been found in colonic carcinomas where an abnormal reduction/loss of α2 correlated with Dukes' stage C/D of the carcinomas (Koretz et al. 1991).

Conversely, in malignant melanomas and lung carcinomas, tumour progression was found to be associated with increased expression of α2 (Zylstra et al. 1986; Klein et al. 1991). These data lead to the presumption that abnormal levels of α2 in different types of neoplastic cells might have different consequences regarding the invasive and/or disseminative potential. It should be also mentioned that α2 has been found to serve as a collagen receptor on some types of cells and as a laminin receptor on others (for review see Hynes 1992).

Expression of the α3 molecule was abnormally low or completely absent in a considerable number of breast carcinomas. This confirms and extends observations reported by Pignatelli et al. (1991) but in addition, we find that the abnormally low expression/absence of α3 is correlated with oestrogen receptor-negativity. The preferential localization of α3 at cell-cell contact sites in various cell cultures suggested its involvement in intercellular interactions (Kaufmann et al. 1989). These data were substantiated by Carter et al. (1990) who demonstrated that α3 plays an important role in cell-cell and cell-substrate adhesion of human epidermal cells. Thus, the low expression/absence of α3 in breast carcinomas might facilitate cell dissociation and augment the migratory potential of the tumour cells.

In support of the data of d'Ardenne et al. (1991) and Jones et al. (1992), an abnormally low expression of the laminin receptor α6 was observed frequently in our series of breast carcinomas. In parallel with these findings, Natali et al. (1991) demonstrated that naevus cells express high levels of α6 whereas malignant melanomas often showed a reduction or loss of the α6 molecule. In breast carcinoma and melanoma cell lines an alternative non-integrin laminin receptor was found, the expression of which was associated with increased cell adhesiveness to laminin and a more invasive phenotype (Wewer et al. 1987; Albini et al. 1989). These findings seem to be contradictory. However, until the exact function of α6 in breast (carcinoma) cells is known, the net effect of abnormally low α6 expression on invasion and metastasis cannot be predicted.

In conclusion, malignant transformation of mammary ductal/lobular epithelial cells is accompanied by considerable quantitative changes in the pattern of β1 integrin expression. These alterations consist mainly of an abnormally low expression or complete absence of α2, α3 and α6 subunits, some of which changes were correlated with known prognostic variables. It is conceivable that alterations in the β1 integrin profile associated with malignant transformation of breast epithelium may cause a disturbed cell-cell and/or matrix interaction leading to increased invasive and migratory properties of tumour cells.

Acknowledgements. This study was supported by a grant form the Deutsche Krebshilfe/Dr. Mildred Scheel-Stiftung (W50/89Mö2). We would like to thank Dr. L. Boumsell (Institut de Recherche sur les Maladies du Sang, Université de Paris VIII, France) for antibody K20, Dr. M.E. Hemler (Division of Tumor Virology, Dana-Farber Cancer Institute, Boston, Mass., USA) for antibody TS2/7, Dr. W. Modderman (Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam, The Netherlands) for antibodies CLB-thromb/4 and GOH3, and Dr. L.J. Old (Memorial Sloan-Kettering Cancer Center, New York, USA) for antibody J143. We are indebted to A. Müller and S. Westenfelder for skillful technical assistance and to R. Lefaucheur for linguistic advice.

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