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Overexpression of group II phospholipase A_2 in human breast cancer tissues is closely associated with their malignant potency

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Summary Membrane-associated phospholipase A_2 (M-PLA_2) is an enzyme that hydrolyses the *sn*-2 fatty acyl ester bond of phosphoglycerides. We measured M-PLA_2 concentration in tissue extracts from 325 human breast cancers using a specific radioimmunoassay recently developed. Correlation analyses between the tissue concentration of M-PLA_2 and clinicopathological factors showed that the enzyme level was significantly higher in patients with distant metastasis than in those without. In addition, M-PLA_2 concentration was significantly higher in scirrhous carcinoma than in other histological types. No significant association was found between M-PLA_2 concentration and age, menstrual status, tumour size, histological grade, vessel involvement or oestrogen receptor (ER) and progesterone receptor (PR) status. The expression of M-PLA_2 mRNA was examined in a fibroadenoma, a stage IV breast cancer and its metastatic site of skin. Northern blot analysis showed a clear hybridisation band corresponding to M-PLA_2 mRNA in both primary breast cancer and its metastatic site, while the fibroadenoma expressed a faint band corresponding to M-PLA_2 mRNA. Breast cancer patients with high M-PLA_2 concentrations exhibited significantly shorter disease-free and overall survival than those with low M-PLA_2 concentration at the cut-off point of 5 ng 100 mg^{-1} protein, which was determined in a separate study. In multivariate analysis, M-PLA_2 was found to be an independent prognostic factor for disease recurrence and death in human breast cancer. The possible significance of M-PLA_2 expression in human breast cancer tissue is discussed.

Phospholipase A_2 is a lipolytic enzyme that specifically hydrolyses the 2-acyl position of a glycerophospholipid (Vadas & Pruzanski, 1986). There are two structurally different forms of phospholipase A_2 (PLA_2): groups I and II (Heinrikson *et al.*, 1977; Kanda *et al.*, 1989). Group I PLA_2 is often characterised as the pancreatic type as it is abundant in pancreatic secretions. Group II PLA_2 was initially divided into two types – membrane-associated PLA_2 (M-PLA_2) and secretory PLA_2 – but later studies demonstrated that these two types are identical (Kanda *et al.*, 1989; Seilhamer *et al.*, 1989). Group I PLA_2 has been investigated by many researchers in relation to several diseases, such as acute pancreatitis, but little is known about the physiological role of group II PLA_2, despite the presence of this form in a variety of mammalian cells (van den Bosch, 1980).

Recently, we developed a specific radioimmunoassay for human M-PLA_2 (Matsuda *et al.*, 1991) and reported that the tissue concentration of M-PLA_2 in human breast cancer is likely to be a prognostic factor (S. Yamashita *et al.*, 1993). In the previous study including 78 patients (S. Yamashita *et al.*, 1993), we determined the optimal cut-off point of 50 ng 100 mg^{-1} protein according to the method of Tandon *et al.* (1990). However, creating a cut-off point for continuous variables and then using it on the same data set inevitably leads to optimistic results. Therefore, we have now extended this study and determined M-PLA_2 concentrations in tissue extracts from another group of 325 patients with breast cancer, and evaluated the prognostic significance of this enzyme in human breast cancer using the cut-off point determined previously (S. Yamashita *et al.*, 1993). In addition, we have investigated the expression of M-PLA_2 mRNA in both the primary site and metastatic site of human breast cancer. This study provides evidence for a possible significance of M-PLA_2 expression in the progression of human breast cancer.

Materials and methods

Patients

The 325 breast cancer patients analysed in this study are those who underwent curative or non-curative mastectomy in the Department of Surgery II, Kumamoto University Hospital, during the 8 year period from 1982 to 1987. The median follow-up period for patients was 8.2 years (range 5.5–10.7 years). The clinicopathological parameters reviewed in this study were age, menstrual status, tumour size, number of positive nodes, presence or absence of distant metastasis, histological type, histological grade, vessel involvement, oestrogen receptor (ER) and progesterone receptor (PR). When histological typing was performed according to the World Health Organization (WHO) classification (1981), all tumours were classified into the same category, i.e. invasive ductal carcinoma. Therefore, each tumour was further analysed according to the classification of the Japanese Breast Cancer Society (1988), and was graded in parallel according to the criteria described by Bloom and Richardson (1957), except for 12 comedocarcinomas. ER and PR were determined by the dextran-coated charcoal method as described previously (McGuire *et al.*, 1977). The results of ER and PR were summarised as negative (<10 fmol mg^{-1} protein) or positive (≥ 10 fmol mg^{-1} protein).

Assay for M-PLA_2

Tumour samples were drawn from a pool of frozen specimens (stored at −80°C) and each specimen was homogenised and extracted with 50 mM Tris–HCl buffer (pH 7.4) containing 0.25% Triton X-100 (Sigma, St Louis, MO, USA) as described previously (Yamashita *et al.*, 1986). M-PLA_2 concentration was measured by a radioimmunoassay using anti-M-PLA_2 monoclonal antibody as described by Matsuda *et al.* (1991). There is no cross-reactivity of this antibody with human P-PLA_2, pancreatic trypsin, chymotrypsin, elastase 1 and pancreatic secretory trypsin inhibitor (Matsuda *et al.*, 1991). The purified M-PLA_2 was iodinated with [^{125}I]sodium iodide (New England Nuclear, Boston, MA, USA) by the chloramine-T method (Hunter & Greenwood, 1962), and the ^{125}I-labelled M-PLA_2 was purified by gel filtration on a PD-10 column (Pharmacia Fine Chemicals, Sweden). Its specific activity was approximately 3.5 MBq μg^{-1}. The detection limit of M-PLA_2 is 7 ng 100 mg^{-1} protein. The intra-assay coefficient of variation (CV) was obtained by testing one sample on the same kit ten times. Those for the high, middle and low sample levels were 3.8, 5.6 and 5.7% respectively. The inter-assay CV was calculated from assays using the same sample during a period of 1 month, and those for the three sample levels were 4.4, 4.5 and 3.2% respectively.

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Northern blot analysis

Total RNA was extracted from a fibroadenoma, a primary breast cancer and its metastasis to skin by the guanidine thiocyanate–caesium chloride procedure (Sambrook *et al.*, 1989). Total RNA (5 μg per lane) was separated by 1% agarose–formaldehyde gels, and transferred to nylon membrane (Hybond N^+) by Northern blotting. The blots were hybridised with ^{32}P-labelled specific probes. The 336 bp *NcoI–ScaI* fragment of group II PLA_2 cDNA (Seilhamer *et al.*, 1989) was used for its mRNA detection. Filters were washed in 0.2 × SSC and 0.1% SDS at 65°C. As a control, filters were stripped and rehybridised with a radiolabelled G3PDH probe. The bands were quantitated by a BAS2000 image analyser.

Statistics

The Kruskal–Wallis test was used for the analysis of M-PLA_2 concentration in relation to clinicopathological factors. The Cox proportional hazards model (Cox, 1972) was used in multivariate analysis to assess the independent prognostic significance.

Table I Correlation between M-PLA_2 concentration and clinicopathological factors of human breast cancer

Factor	*M-PLA_2 concentration*[a]	P-*value*
Age (years)		
<50 (143)[b]	68 ± 21	
⩾50 (182)	54 ± 9	NS
Menstrual status		
Pre/perimenopause (168)	72 ± 18	
Post-menopause (157)	47 ± 10	NS
Tumour size (cm)		
>2 (67)	60 ± 10	
2–5 (203)	52 ± 14	NS
>5 (55)	89 ± 25	
Node involvement		
0 (184)	49 ± 7	
1–3 (68)	89 ± 21	NS
⩾4 (73)	61 ± 13	
Distant metastasis		
Absent (290)	34 ± 10	
Present (35)	273 ± 45	0.025
Histological type		
Papillotubular (75)	21 ± 6	
Solid tubular (120)	36 ± 12	
Scirrhous (114)	116 ± 24	0.016
Others (16)	24 ± 3	
Histological grade[c]		
Grade I (88)	46 ± 11	
Grade II (122)	68 ± 13	NS
Grade III (103)	69 ± 13	
Vessel involvement		
Absent (207)	55 ± 22	
Present (118)	69 ± 15	NS
ER		
Positive (163)	62 ± 12	
Negative (128)	50 ± 17	NS
Unknown (34)	88 ± 27	
PR		
Positive (99)	71 ± 30	
Negative (184)	49 ± 15	NS
Unknown (42)	83 ± 26	

[a]Mean ± s.e. [b]Numbers in parentheses are the number of patients. [c]Twelve comedocarcinomas were excluded from this analysis. NS, not significant.

Results

Relation between M-PLA_2 concentration and clinicopathological factors

M-PLA_2 was detected in tissue extracts from 311 of 325 specimens, the concentration ranging from 7.3 to 1,755 ng 100 mg^{-1} protein. The median value of M-PLA_2 concentration was 52 ng 100 mg^{-1} protein. Table I shows the correlation between M-PLA_2 concentration and the characteristics of the patients. When M-PLA_2 concentration was compared in terms of age, menstrual status, tumour size, nodal status, histological grade, vessel involvement, ER and PR, no significant association was found between M-PLA_2 concentration and any of these features. However, M-PLA_2 concentration was significantly higher in scirrhous carcinoma than in other histological types ($P = 0.016$). Similarly, M-PLA_2 concentration was significantly higher in distant metastatsis-positive than in -negative patients ($P = 0.025$).

Relation between M-PLA_2 concentration and survival

To evaluate the prognostic significance of M-PLA_2, we analysed disease-free survival and overall survival in 290 breast cancer patients. Thirty-five patients with distant metastases at the time of primary therapy were excluded from this analysis. The cut-off point of 50 ng 100 mg^{-1} protein was used because our previous study of another group of patients demonstrated that this cut-off point could give a statistically significant separation for risk of relapse according to the method of Tandon *et al.* (1990). This cut-off point is close to the median value (52 ng 100 mg^{-1} protein) of the present series. As shown in Figure 1, patients with breast

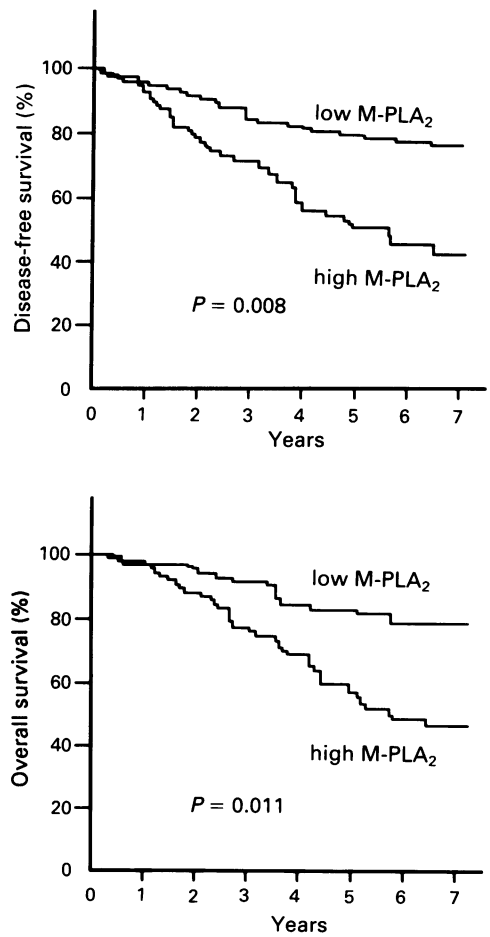

Figure 1 Disease-free and overall survival curves in 290 breast cancer patients having no distant metastasis according to M-PLA_2 concentration in tumour extracts. The cut-off point between high and low enzyme level was 50 ng 100 mg^{-1} protein. Number of paitents in each group: high M-PLA_2, 133; low M-PLA_2, 157.

cancer tissue containing a high concentration of M-PLA_2 had a significantly shorter disease-free survival ($P = 0.008$) and overall survival ($P = 0.011$) time than those with a low content of the enzyme. In multivariate analysis including all variables, M-PLA_2 was found to be an independent prognostic factor for recurrence and for death of about the same import as lymph node involvement (Tables II and III).

M-PLA_2 mRNA expression

Northern blot analysis of total RNA from one fibroadenoma, one stage IV breast carcinoma and its skin metastasis is shown in Figure 2. Using a radiolabelled M-PLA_2 cDNA probe (336 bp *NcoI–ScaI* fragment), M-PLA_2 mRNA was clearly demonstrated in total RNA preparations from breast carcinoma and its metastasis site, while fibroadenoma expressed only a faintly hybridising band of M-PLA_2 mRNA. Interestingly, the metastasis site expressed more M-PLA_2 mRNA than the primary tumour.

Discussion

We and other investigators have demonstrated that a transient increase in serum M-PLA_2 concentration is observed during surgery (Matsuda *et al.*, 1991) and in various clinical conditions such as endotoxic shock (Vadas & Hay, 1983) and multiple injuries (Uhl *et al.*, 1990), suggesting that this enzyme is one of the acute-phase reactants. We also showed that serum M-PLA_2 concentration was significantly elevated in patients with various malignant tumours (Matsuda *et al.*, 1991). Since the incidence and magnitude of the elevation were greater in patients with advanced breast cancers than in those with early stages, we speculated that this enzyme might be produced by breast cancer cells themselves.

Immunohistochemical study showed that M-PLA_2 was preferentially stained in breast cancer cells rather than breast stromal cells (Yamashita *et al.*, 1993), indicating that breast cancer cells produce a large amount of this enzyme.

In the present study, correlation analyses showed that tissue M-PLA_2 level was significantly higher in distant metastasis-positive than in -negative patients. Furthermore, of interest was the finding that the distant metastasis from a stage IV carcinoma showed even larger amounts of M-PLA_2 mRNA than the primary tumour. These results suggest that the expression of this enzyme may be related to the metastatic potency of human breast cancer.

Histologically scirrhous carcinoma, which is characterised by its prominent stromal cellularity, was also related to high M-PLA_2 concentrations in tissue extracts. In our previous report, the intensity of immunohistochemical staining was

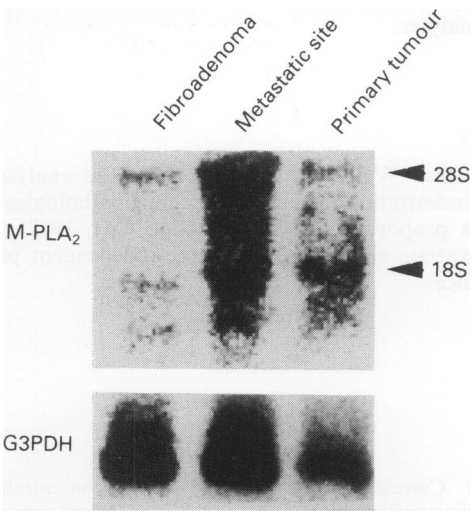

Figure 2 Northern blot analysis of total RNA from a fibroadenoma, a primary breast cancer and its metastasis to skin. Total RNA was hybridised with cDNA from human group II PLA_2 as probe. To assess equal load of mRNA per lane, the filter was subsequently hybridised to a G3PDH probe. 28S and 18S rRNA bands were used as molecular weight markers.

Table II M-PLA_2 and clinicopathological parameters as prognostic factors for relapse in 290 stage I–III breast cancer patients

	Univariate analyses		*Multivariate analyses*	
Parameters	*Relative risk*	P-*value*	*Relative risk*	P-*value*
Independently associated with relapse				
Nodal status				
0	1.0		1.0	
1–3	2.2	0.001	1.7	0.001
⩾4	4.1		2.9	
M-PLA_2 concentration				
<50	1.0		1.0	
⩾50	3.3	0.008	2.7	0.015
Associated with relapse only when evaluated alone				
Tumour size (cm)				
<2	1.0			
2–5	1.5			
>5	2.7	0.024		NS
Histological grade				
Grade I	1.0			
Grade II	1.7			
Grade III	3.0	0.015		NS
Vessel involvement				
Absent	1.0			
Present	2.0	0.050		NS
Not associated with relapse				
Age		NS		NS
Menstrual status		NS		NS
Histological type		NS		NS
ER		NS		NS
PR		NS		NS

NS, not significant.

Table III M-PLA_2 and clinicopathological parameters as prognostic factors for deeath in 290 stage I–III breast cancer patients

Parameters	*Univariate analyses* Relative risk	P-value	*Multivariate analyses* Relative risk	P-value
Independently associated with survival				
Nodal status				
0	1.0		1.0	
1–3	2.1	0.001	1.6	0.001
⩾4	3.6		2.5	
M-PLA_2 concentration				
<50	1.0		1.0	
⩾50	3.5	0.011	2.5	0.022
Associated with survival only when evaluated alone				
Tumour size (cm)				
<2	1.0			
2–5	1.1			
>5	1.9	0.034		NS
Histological grade				
Grade I	1.0			
Grade II	1.2			
Grade III	2.9	0.030		NS
Vessel involvement				
Absent	1.0			
Present	1.5	0.048		NS
PR				
Positive	1.0			
Negative	1.4	0.044		NS
Not associated with survival				
Age		NS		NS
Menstrual status		NS		NS
Histological type		NS		NS
ER		NS		NS

NS, not significant.

greater in scirrhous carcinoma than in other histological types (S. Yamashita *et al.*, 1993). Immunohistochemically M-PLA_2-positive cells were localised at the invading edge of the tumour where cancer cells were in contact with surrounding non-neoplastic tissues (S. Yamashita *et al.*, 1993). Recently, we found that human M-PLA_2 itself has a mitogenic effect on fibroblasts (Kurizaki *et al.*, 1992). In addition, M-PLA_2 augments the production of prostaglandin E_2 (PGE_2), which is known to stimulate mitogenesis in fibroblasts (Nolan *et al.*, 1988; Hara *et al.*, 1991). These findings suggest that M-PLA_2 may play an important role in stimulating the growth of stromal cells in breast cancer tissues in a paracrine fashion. Further, PGE_2 released at the tumour site inhibits the host immunological response and enhances tumour growth (Balch *et al.*, 1984; Okada *et al.*, 1990). The release of fatty acids is at least two orders of magnitude greater than eicosanoid production, and these fatty acids also have many direct biological effects on normal and malignant cells (Imagawa *et al.*, 1989; Clerc *et al.*, 1991).

Reliable predictors of survival or relapse in patients with breast cancer aid in determining the use of adjuvant chemotherapy or endocrine therapy. Established prognostic indicators, such as age, lymph node involvement, tumour grade and hormone receptor status, assist in predicting patient outcome or response to treatment, but are not entirely dependable. Several enzymes determined in the cytoplasm and organelles of tumour cells have been found to have prognostic value in human breast cancer. Most of these enzymes are proteinases, such as plasminogen activator (Janicke *et al.*, 1989; Duffy *et al.*, 1990; J. Yamashita *et al.*, 1993) and cathepsin D (Spyratos *et al.*, 1989; Tandon *et al.*, 1990), which have been implicated in tumour infiltration and metastasis. The present study offers statistical evidence that M-PLA_2 concentration in tissue extracts is an independent prognostic factor that clearly identifies high- and low-risk patients using a cut-off point determined previously. To our knowledge, this is the first lipolytic enzyme which can be added to the list of second-generation prognostic factors in human breast cancer.

In conclusion, the present study provides evidence that M-PLA_2 expression is closely associated with the malignant potential of human breast cancer and that this new biological factor can be an independent prognostic factor.

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