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High chondroitin sulfate proteoglycan 4 expression correlates with poor outcome in patients with breast cancer

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ABSTRACT

Chondroitin sulfate proteoglycan 4 (CSPG4), a transmembrane proteoglycan originally identified in melanoma cells, has been reported to be expressed in breast cancer cells. This study was performed to examine the expression and significance of CSPG4 in a cohort of breast cancer patients. Immunohistochemical analysis of CSPG4 was performed on tissue microarrays constructed from tissue specimens from 240 breast cancer patients. CSPG4 staining was correlated with clinical and pathological characteristics, overall survival (OS), and disease recurrence. Contradicting to a previous report, our results showed that high CSPG4 expression was not related to triple-negative status of breast cancer patients. The Kaplan–Meier method showed that high CSPG4 expression was significantly associated with shorter time to recurrence (TTR). Patients with high CSPG4 expression had poorer OS and shorter TTR in a multivariate survival analysis after adjustment for stage, tumor grade, expression of estrogen receptor and progesterone receptor, and HER2 overexpression. This study showed that high CSPG4 expression correlates with disease recurrence and OS in breast cancers.

1. Introduction

Breast cancer is a highly heterogeneous disease in terms of morphology, molecular characteristics, and response to treatment. Molecular profiling studies have provided a glimpse of the complexity and underlying genetic signature of breast cancer [1–3]. Several molecular subgroups have been proposed with the aid of DNA microarray: luminal A, luminal B, human epidermal growth factor receptor 2 (HER2), normal, and basal-like [1–3]. Immunohistochemical profiling based on expression of estrogen receptor (ER), progesterone receptor (PR), and HER2 approximate the molecular taxonomy of breast cancer patients and provided prognostic information and basis for treatment options [4–8].

Chondroitin sulfate proteoglycan 4 (CSPG4), also known as NG2, is a transmembrane proteoglycan highly expressed in human melanoma cells [9]. CSPG4 plays an important role in growth, motility, and survival of melanoma cells [10–12]. In breast cancer, CSPG4 has been found to be highly expressed on aggressive breast cancer cell lines and contributed to the P-selectin binding that potentiates the metastatic spread of breast cancer [13]. CSPG4 has also been reported to be expressed in primary triple-negative breast cancer (TNBC), the subset of breast cancer that lacks the immunohistochemical expression of ER, PR, and HER2, lesions and TNBC cell lines, and may be a therapeutic target for mAb-based immunotherapy in breast tumors with TNBC phenotype [14]. However, the frequency and clinical significance of CSPG4 in breast cancer has yet to be determined. The objectives of the present study included identification of breast tumors exhibiting the CSPG4 phenotype, as well as assessment of CSPG4 expression in relation to prognosis and various clinical and pathological features.

2. Materials and methods

2.1. Breast tissue microarray

Our study cohort was composed of 240 tumor specimens from breast cancer excisions collected at the time of surgery between January 2000 and December 2006 at the Department of Surgery,

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Kaohsiung Medical University Hospital, Taiwan. All patients were newly diagnosed at the time of specimen collection and have not yet begun radiotherapy, chemotherapy, or hormonal treatment. Samples were fixed in 10% neutral buffered formalin and embedded in paraffin. Areas of invasive carcinoma were selected and marked on the hematoxylin and eosin stained slides. The corresponding tissue blocks were sampled for tissue microarray (TMA). Follow-up information, histopathological and clinical data including age, sex, tumor size, ER, PR, HER2 overexpression, tumor grade, stage, recurrence, and survival were obtained from the cancer registry and medical charts. The length of follow-up ranged from 1 to 131 months, with a mean of 84 months. This protocol was approved by the Institutional Review Board of Kaohsiung Medical University Hospital.

2.2. Immunohistochemistry

The breast TMA was evaluated for CSPG4 expression using immunohistochemical staining. Briefly, 4-μm-thick sections were deparaffinized in xylene, dehydrated through three alcohol changes. Endogenous peroxidase activity was quenched with 3% hydrogen peroxide in methanol. Antigen retrieval was performed in 96 °C solution of 0.01 mol/L sodium citrate buffer (pH 6.0) for 30 min. Slides were then incubated with anti-NG2 mouse monoclonal antibody (1:50 dilution, ab83508, Abcam, Cambridge, MA) for 30 min at room temperature. Human melanoma samples and an isotype- and concentration-matched nonimmune IgG (Abcam) were used as positive and negative controls, respectively. Staining was detected using the EnVision Detection Systems Peroxidase/DAB, Rabbit/Mouse kit (Dako, Glostrup, Denmark). After visualization, the TMA sections were then counterstained with hematoxylin (MERCK, Darmstadt, Germany). The expression of CSPG4 was evaluated for intensity of reactivity and percentage of positive cells. The intensity was evaluated as 0, 1, 2, and 3 for negative, weak, moderate, and strong staining, respectively. The percentage of tumor cells showing positive staining was recorded as follows: 0, staining in <1%; 1, staining in 1–10%; 2, staining in 11–50%; and 3, staining in >50% of tumor cells. The total score, ranged from 0 to 9, was calculated by multiplying the intensity and percentage scores. The CSPG4 immunoreactivity was assessed independently by two pathologists scoring coded sections and conflicting scores were resolved at a discussion microscope.

2.3. Statistical analysis

Receiver operating characteristics (ROC) curve analysis was applied to calculate the expression cut-off value predicting survival for CSPG4. Expression level of CSPG4 was analyzed with clinical data to assess for correlation with clinical outcome by Pearson's chi-square test. Overall survival (OS) and time to recurrence (TTR) were estimated by the Kaplan–Meier method and compared by the log-rank test. OS was defined as the time from diagnosis until the time of death. TTR was defined as the time between date of diagnosis and date of local recurrence/distant metastasis. Patients still alive/without evidence of recurrence were censored at last follow-up. The Cox proportional hazards regression model was used to test the statistical independence and significance of CSPG4 in predicting the risk of death and recurrence. Variables in the model included tumor grade, stage, ER, PR, and HER2 overexpression. A $p < 0.05$ was considered to indicate statistical significance.

3. Results

Table 1 depicts distribution of the intensity and percentage scores of CSPG4 immunohistochemical staining of the 240 breast tumor samples examined. A total score was obtained by multiplying the percentage and intensity scores for each sample. A cut-off value of 6 was established by ROC curve analysis and was used as the uniform cut-off point for subsequent analyses. High CSPG4 expression, as defined by a score of 6 or greater, was observed in 66 of the 240 (27.5%) breast tumors examined. Fig. 1 shows examples of cases with high and low CSPG4 expression. Clinical and pathological characteristics of patients, including triple-negative status, stratified by CSPG4 expression level showed that there was no apparent difference between the two groups (Table 2).

Table 1
Distribution of the intensity and percentage scores of CSPG4 immunohistochemical staining of the 240 breast tumors.

		Percentage score				*N*
		0	1	2	3	
Intensity score	0	40	0	0	0	40
	1	0	12	60	51	123
	2	0	0	11	46	57
	3	0	0	2	18	20
N		40	12	73	115	240

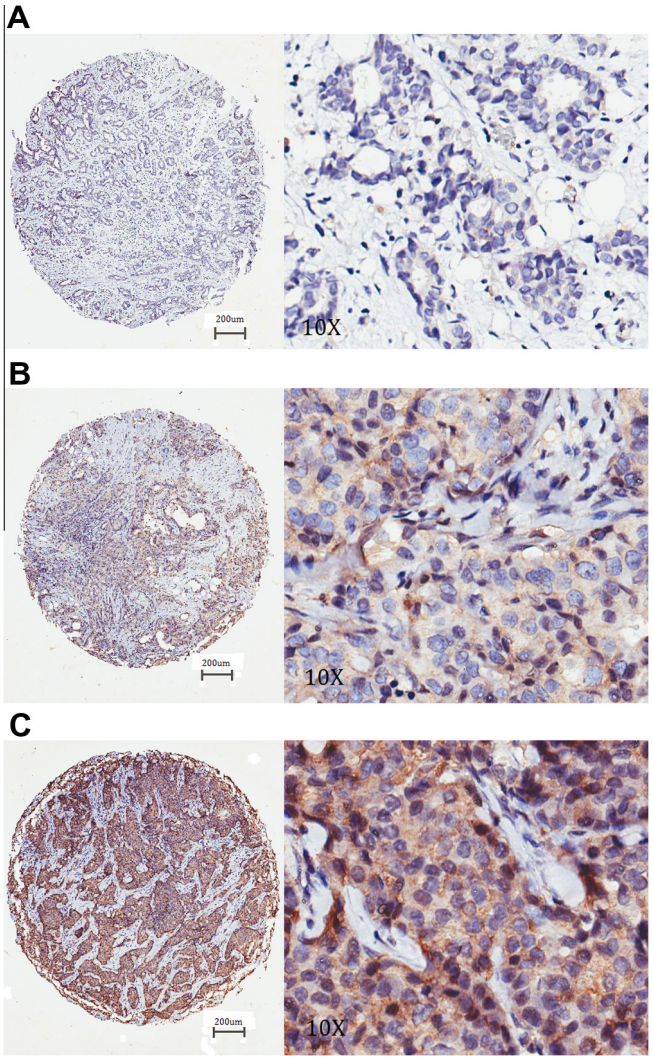

Fig. 1. Representative immunohistochemistry analysis of CSPG4 protein expression on TMA of breast cancer samples. The breast TMA was stained and scored as described in materials and methods. (A) Negative CSPG4 expression (score = 0). (B) Low CSPG4 expression (score = 4). (C) High CSPG4 expression (score = 6).

Table 2
Patient clinicopathological characteristics and CSPG4 expression in breast cancer patients.

	CSPG4 expression				N	p
	Low (N = 174)		High (N = 66)			
	N	%	N	%		
Age, years, mean (SD)	49.6 (11.4)		48.0 (11.1)		240	0.321
ER						
Negative	61	37.0	22	33.8	83	0.657
Positive	104	63.0	43	66.2	147	
PR						
Negative	78	47.9	27	42.9	105	0.500
Positive	85	52.1	36	57.1	121	
HER2 overexpression						
Negative	107	66.9	38	62.3	145	0.522
Positive	53	33.1	23	37.7	76	
Triple negative						
No	129	79.6	53	85.5	182	0.315
Yes	33	20.4	9	14.5	42	
Lymph node metastasis						
No	94	56.3	34	52.3	128	0.584
Yes	73	43.7	31	47.7	104	
Grade						
I	38	32.2	12	23.1	50	0.480
II	53	44.9	26	50.0	79	
III	27	22.9	14	26.9	41	
Stage						
0	23	13.7	10	15.6	33	0.621
I	33	19.6	9	14.1	42	
II	81	48.2	30	46.9	111	
III	29	17.3	15	23.44	44	
IV	2	1.2	0	0.0	2	

Table 3
Multivariate analysis for overall survival and time to recurrence of breast cancer patients.

Variable	OS			TTR		
	HR	95% CI	p	HR	95% CI	p
High CSPG4 expression	2.43	1.17–5.06	0.018	2.69	1.46–4.94	0.001
ER	0.33	0.11–0.96	0.042	0.33	0.14–0.78	0.011
PR	2.04	0.73–5.73	0.174	1.31	0.58–2.93	0.513
HER2 overexpression	1.01	0.47–2.17	0.988	0.88	0.46–1.66	0.684
Stage III, IV	3.89	1.80–8.40	0.001	2.98	1.57–5.64	0.001
Grade III	0.92	0.38–2.24	0.856	0.49	0.22–1.09	0.081

CSPG4 expression was analyzed for association with OS and TTR. The multivariate Cox model which isolated the effect of CSPG4 expression on OS from other variables (tumor grade, stage, ER, PR, and HER2 overexpression) indicated that high CSPG4 expression was an independent prognostic factor [hazard ratio (HR) = 2.43 (1.17–5.06), $p = 0.018$]. ER expression [HR = 0.33 (0.11–0.96), $p = 0.042$] and stage [HR = 3.89 (1.80–8.40), $p = 0.001$] were also independent factors influencing OS (Table 3). Multivariate analysis for TTR adjusted for the same variables revealed that high CSPG4 expression [HR = 2.69 (1.46–4.94), $p = 0.001$] was also significant with regard to disease recurrence. Similarly, ER positivity [HR = 0.33 (0.14–0.78), $p = 0.011$] and stage [HR = 2.98 (1.57–5.64), $p = 0.001$] also showed a statistically significant association

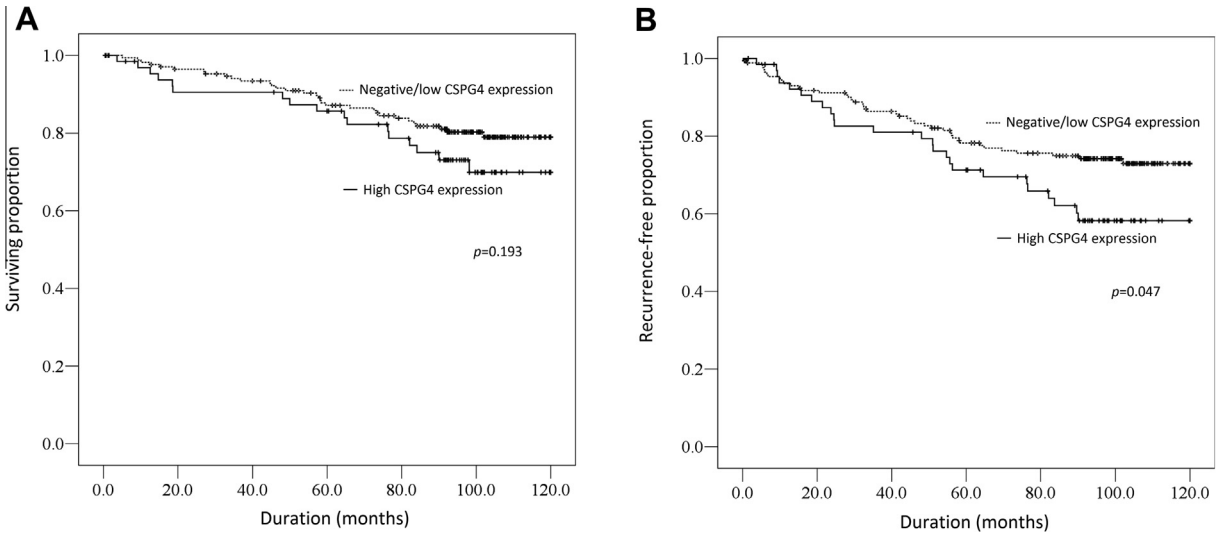

Fig. 2. Kaplan–Meier plots for (A) overall survival and (B) time to recurrence for patients according to CSPG4 expression.

with TTR. Kaplan–Meier analysis was used to estimate OS and TTR. The difference in OS between patients with high CSPG4 expression and those with negative/low CSPG4 expression was not significant ($p = 0.193$) (Fig. 2A). However, assessment of recurrence in these patients revealed that high CSPG4 expression was correlated with a shorter TTR ($p = 0.047$) (Fig. 2B).

4. Discussion

In breast cancer, CSPG4 has previously been suggested to be preferentially expressed in primary TNBC lesions in a study involving immunohistochemical analysis performed on a small set of samples and without performing statistical analysis [14]. In this study, we incorporated staining intensity and percentage of immunopositive tumor cells for the scoring of CSPG4 expression and examined a more diverse set of breast tumors. The results indicated that high CSPG4 expression was not statistically associated with triple-negative status of breast cancer patients. In the same study, Wang et al. also reported that CSPG4 is expressed in TNBC cell lines and used the spontaneous metastatic MDA-MB-435 cells line as a model of TNBC, and concluded that CSPG4 is a possible target for immunotherapy of TNBC [14]. The MDA-MB-435 cells were originally thought to be derived from a breast carcinoma as part of the MD Anderson series [15]. However, gene expression microarray profiling and immunohistochemistry studies have revealed that these cells originated from melanoma [16–19]. The MDA-MB-435 cells were found to be identical to the M14 human melanoma cell line [20] and the American Type Culture Collection has officially declared the MDA-MB-435 cells as melanoma cells. Thus, the MDA-MB-435 cells are not an acceptable model for TNBC [21].

Despite a statistically significant correlation could not be established between high CSPG4 expression and TNBC, the current study showed that high CSPG4 expression may correlate with disease recurrence and/or survival in patients with breast cancer. Kaplan–Meier analysis indicated that patients with high CSPG4 expression exhibited significant shorter TTR than those with negative/lower CSPG4 expression ($p = 0.047$). High CSPG4 expression was identified as an independent predictive factor for poor OS ($p = 0.018$) and shorter TTR ($p = 0.001$) when adjusting for various clinical and pathological parameters of breast cancer in the Cox regression models. The multivariate analysis also revealed that ER-positive women were associated with longer OS and TTR. This finding is in agreement with the reports that ER-positive tumors progress more slowly than ER-negative cells and women with ER-positive cancer currently have more treatment options [22,23].

Various mechanisms of how CSPG4 promotes tumor migration, metastasis, and chemoresistance have been proposed [12,13,24–29]. CSPG4-specific monoclonal antibody has been shown to produce anti-tumor effects likely via blocking of important migratory, mitogenic, and survival signaling pathways in tumor cells [30]. The present study supports an oncogenic role of CSPG4 in breast cancer [13] and with further validation, CSPG4 may be a promising new target to implement antibody-based immunotherapy in a subset of aggressive breast cancers.

The limitation of this study is that it suffered from a limited sample size. Given the heterogeneity of human breast cancer, a large sample size can more accurately identify molecular aberration that could be most associated with clinical features and outcomes. In conclusion, the present study suggests that high CSPG4 expression is not related to triple-negative status of breast cancer patients. In agreement with its oncogenic properties, high CSPG4 expression correlates with disease recurrence and OS, and may serve as a marker for poor outcome and possibly a target for treatment in aggressive breast cancers.

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