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Expression of Caveolin-1 in Pleomorphic Carcinoma of the Lung is Correlated with a Poor Prognosis

KYUNG CHUL MOON[1*], GEON KOOK LEE[2*], SEONG-HO YOO[1], YOON KYUNG JEON[1], JIN-HAENG CHUNG[1], JUNGHO HAN[3] and DOO HYUN CHUNG[1]

[1]*Department of Pathology, Seoul National University College of Medicine, Seoul;*
[2]*Department of Pathology, National Cancer Center, Goyang;*
[3]*Department of Pathology, Sungkyunkwan University School of Medicine, Seoul, Korea*

Abstract. *Background: Caveolin-1 is implicated in the oncogenic transformation of cells as a tumor suppressor. In several human carcinomas, the expression of caveolin-1 has been reported to be correlated with prognosis. The present study was designed to clarify the clinicopathological significance of caveolin-1 expression in pleomorphic carcinoma of the lung (PCL). Patients and Methods: Twenty-one cases of PCL were immunohistochemically evaluated for caveolin-1 expression. Results: Caveolin-1 was expressed in 18 out of 21 cases. Patients with high caveolin-1 expression in PCL showed lower disease-free and overall survival rates than those with low caveolin-1 expression. However, the expression level of caveolin-1 in PCL was not significantly correlated with age, stage, pT category, pN category, or tumor size. Conclusion: These results suggest that the overexpression of caveolin-1 is significantly correlated with a poor prognosis in patients with PCL and that it is a marker for predicting prognosis in PCL.*

The recent WHO classification of pulmonary neoplasms (1) describes a unique subgroup as "carcinomas having pleomorphic, sarcomatoid, or sarcomatous elements", which includes various entities such as pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma and pulmonary blastoma. Pleomorphic carcinoma of the lung (PCL) is defined as "a poorly-differentiated non-small cell carcinoma containing spindle cells and/or giant cells, or a carcinoma composed only of spindle cells and giant cells". PCL composes only 0.1 to 0.4% of all pulmonary malignant tumors and has a poor clinical outcome (1-3).

*K.C. Moon and G.K. Lee contributed equally to this work.

Correspondence to: Doo Hyun Chung, MD, Ph.D., Department of Pathology, Seoul National University College of Medicine, 28 Chongno-gu Yongon-dong Seoul 110-799, Korea. Tel: 822-760-2552, Fax: 822-743-5530, e-mail: doohyun@plaza.snu.ac.kr

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Caveolins, 21 to 25 kDa integral membrane proteins, are the principal structural proteins in caveolae. Caveolin-1 binds to signaling molecules, such as G-proteins, Src family tyrosine kinases, receptor tyrosine kinases (epidermal growth factor receptor), protein kinase C and eNOS, and can functionally inactivate the enzymatic activity of these molecules (4). Caveolin-1 has been found to possess paradoxical biological functions in malignant tumors. *In vitro* experiments demonstrated that the down-regulation of caveolin-1 induced oncogenic transformation in NIH3T3 cells (5), and that the overexpression of recombinant caveolin-1 inhibited tumor cell growth in breast cancer cell lines (6) and reduced sarcoma cell colony transformation (7). Moreover, reduced caveolin-1 expression has been reported in human ovarian carcinomas (8), human colon tumors (9), human soft tissue sarcomas (7), breast cancer cell lines (6), lung cancer cell lines (10) and colon carcinoma cell lines (9). Based on these results, it has been suggested that caveolin-1 may play a role as a tumor suppressor. Conversely, caveolin-1 overexpression has been observed in many human cancers, *e.g.*, breast carcinoma, prostate carcinoma, esophageal carcinoma and papillary carcinoma of the thyroid (11-14). In addition, caveolin-1 expression is also correlated with clinicopathological parameters in some human carcinomas (12, 15-17).

However, the expression pattern of caveolin-1 in PCL and its clinical significance have not been characterized. Therefore, the expression pattern of caveolin-1 in PCL was investigated by immunohistochemical analysis and its clinicopathological implications were examined.

Patients and Methods

Patients. A total of 21 PCL patients, who underwent surgical resection (6 pneumonectomies, 15 lobectomies) between January 1, 1991 and July 30, 2002 at the Department of Pathology, Seoul National University Hospital and Samsung Medical Center (Seoul, Korea), were included in this retrospective study. H&E-stained slides of each tumor were reviewed with regard to histological

Table I. *Clinical data of the 21 PCL patients.*

Case No.	Age/Sex	Site	Site of relapse	DFS (months)	OS (months)	Outcome	Stage
1	67/M	RUL	Axilla	2	2	AD, LOST	IIb
2	69/M	LUL	-	4	4	A, LOST	IIb
3	56/M	LUL	-	26	26	A	Ib
4	60/M	RUL	Thoracic wall, adrenal gland	3	15	AD	IIIa
5	67/M	RUL	-	70	70	A	IIIb
6	59/M	LUL	Lung	5	7	DOD	IIIa
7	56/M	RLL	Lung, kidney, adrenal gland	2	4	DOD	IIIa
8	65/M	LLL	Thoracic wall	7	9	DOD	Ib
9	46/M	LUL	-	61	61	A	Ib
10	51/M	RLL	Liver, stomach	2	3	DOD	IIIa
11	84/M	RUL	Lung	2	3	DOD	Ib
12	63/M	LUL	-	1	1	A, LOST	IIIb
13	66/F	LLL	Lung	2	4	DOD	Ib
14	51/M	RUL	-	88	88	A	Ib
15	47/M	RUL	Lung, kidney, bone, brain	22	26	AD, LOST	Ia
16	67/M	RML	-	19	19	A, LOST	Ia
17	71/M	RLL	-	31	31	A	Ib
18	71/M	LUL	-	21	21	A	IIb
19	63/M	LUL	-	2	2	A, LOST	IIIa
20	53/M	LLL	-	14	14	A	IIb
21	53/M	LUL	-	20	20	A	IIb

RUL, right upper lobe; LUL, left upper lobe; RLL, right lower lobe; LLL, left lower lobe; RML, right middle lobe; DFS, disease-free survival; OS, overall survival; AD, alive with disease; LOST, lost to follow-up; A, alive and well; DOD, died of disease.

classification and pathological staging. Tumors were classified using the current WHO classification (1) and staged according to the revised international system for the staging of lung cancer (18). Percentages and types of sarcomatous components (spindle or giant cells) and of the epithelial components (adeno-, squamous- or large cell carcinoma) were assessed for each tumor. Follow-up data were obtained from medical records.

Immunohistochemistry. All tumor tissues were processed using a heat-induced antigen retrieval procedure and immunostained using the conventional streptavidin-ABC technique. Mouse monoclonal anti-caveolin-1 antibody (clone 2297; Transduction Laboratories, Lexington, KY, USA) was incubated with sliced tissues for 1 h at a dilution of 1:250. Capillary endothelial cells and type I pneumocytes were used as caveolin-1-positive immunostaining controls, while the protocol described above without a primary antibody was used as a negative control.

Semi-quantitative estimation for caveolin-1 expression was used, as described previously (7). The staining intensity was graded from 0 to 3 (0, no staining; 1, weakly positive; 2, moderately positive; 3, intensely positive). The relative abundance of caveloin-1-positive cells was graded from 0 to 4 (0, <5% positive cells; 1, 5 to 25% positive cells; 2, 26 to 50% positive cells; 3, 51 to 75% positive cells; 4, 76 to 100% positive cells), and the composite score was obtained by multiplying the staining intensity score by the relative abundance. These scores were obtained separately in the epithelial and the sarcomatous components. The caveolin-1 score was determined as a mean value of composite scores of epithelial and sarcomatous components. To examine the clinical significance of the caveolin-1 expression level in PCL, we divided the cases into two groups of low (caveolin-1 score < mean) or high (caveolin-1 score > mean) caveolin-1 expression level.

Statistical analysis. Correlations between the caveolin-1 expression level and clinicopathological characteristics were analyzed using the Fisher's exact test. Continuous data were analyzed using the Mann-Whitney *U*-test. Overall survival was defined as the period between primary surgery and the last follow-up or carcinoma-related death. Disease-free survival was defined as the period between primary surgery and the last follow-up or evidence of progression of PCL. Survival curves were plotted using the Kaplan-Meier method, and statistical significance was assessed using the log-rank test. Univariate analysis of disease-free survival or overall survival was performed by the Kaplan-Meier method. The Cox proportional hazards model was used for the multivariate analysis. The caveolin-1 expression level, tumor stage, age and percentage of sarcomatous component were entered into a Cox regression. *P*-values of <0.05 were taken to be statistically significant.

Results

Clinical findings. The clinical data of the 21 patients are summarized in Table I. There were 20 men and one woman (male to female ratio 1:0.05), aged from 46 to 84 years (mean±SD: 61.2±9.1 years). The mean follow-up duration was 20.5±24.2 months (median 14 months; range 1-88 months). Recurrent disease at various sites was noted in 9

Table II. *Pathological features and caveoin-1 expression of 21 patients with PCL.*

Case No.	Size (cm)	%Sarc	Sarc	Epi	St Int* (Sarc)	Abund† (Sarc)	Score‡ (Sarc)	St Int (Epi)	Abund (Epi)	Score (Epi)	Cav-1 Score§
1	7.5	100	Mixed	Absent	3	4	12	-	-	-	12
2	11	100	Mixed	Absent	2	4	8	-	-	-	8
3	10	100	Mixed	Absent	2	4	8	-	-	-	8
4	11	100	Mixed	Absent	3	4	12	-	-	-	12
5	5	100	Mixed	Absent	2	4	8	-	-	-	8
6	5.5	100	Mixed	Absent	1	1	1	-	-	-	1
7	3.6	100	Mixed	Absent	3	4	12	-	-	-	12
8	11	95	Mixed	Large	3	4	12	3	4	12	12
9	7.5	95	Spindle	Large	0	0	0	0	0	0	0
10	7	80	Giant	Large	3	3	9	3	2	6	8.4
11	5	80	Spindle	Adeno	2	4	8	3	3	9	8.2
12	7	80	Giant	Large	3	2	6	1	3	3	5.4
13	4	70	Giant	Large	2	4	8	2	2	4	6.8
14	3.5	70	Mixed	Adeno	3	2	6	0	0	0	4.2
15	3	65	Spindle	Adeno	3	3	9	0	0	0	5.85
16	2.3	60	Spindle	Squamous	0	0	0	0	0	0	0
17	6.5	40	Spindle	Adeno	2	3	6	0	0	0	2.4
18	6	40	Spindle	Squamous	0	0	0	0	0	0	0
19	9	30	Spindle	Large	1	1	1	2	3	6	4.5
20	6.5	30	Mixed	Squamous	3	4	12	0	0	0	3.6
21	8.5	25	Spindle	Large	3	1	3	3	2	6	5.25
Mean	6.7	74.3			2.1	2.9	6.7	1.2	1.4	3.3	6.1

Sarc, sarcomatous component; Epi, epithelial component; Spindle, spindle cell component; Giant, giant cell component; Large, large cell carcinoma; Adeno, adenocarcinoma; Squamous, squamous cell carcinoma.
*The staining intensity was graded as 0 (no staining), 1 (weakly positive), 2 (moderately positive), or 3 (intensely positive). †The relative abundance of positive cells was scored as 0 (<5% of cells), 1 (5 to 25% of cells), 2 (26 to 50% of cells), 3 (51 to 75% of cells), or 4 (76 to 100% of cells). ‡The composite score was obtained by multiplying the staining intensity and the relative abundance. §The caveolin-1 score was obtained by [(Score(Sarc) x %Sarc + Score(Epi) x %Epi)/100].

patients and 6 died of recurrent disease. The mean disease-free survival duration was 19.2±24.7 months. According to the revised international system for the staging of lung cancer, there were 2 patients in stage Ia, 7 in stage Ib, 5 in stage IIb, 5 in stage IIIa and 2 in stage IIIb.

Pathological findings. Grossly, tumors ranged from 2.3 cm to 11 cm in greatest dimension (6.7±2.7 cm). Seven cases were composed of mixed spindle and giant cells without epithelial components. In the remaining 14 cases, which contained both epithelial and sarcomatous components, epithelial components ranged from 5% to 75%. Epithelial components were of large cell carcinoma in 7 cases, adenocarcinoma in 4 cases and squamous cell carcinoma in 3 cases. The sarcomatous components were spindle cells in 7 cases, giant cells in 4 cases and mixed in 10 cases (Table II).

Expression of caveolin-1 in PCL. Caveolin-1 showed membranous or cytoplasmic staining in 18 (85.7%) cases of PCL (Figure 1). The semi-quantitative results of caveolin-1 expression in PCL are summarized in Table II. Caveolin-1 was more frequently expressed in the sarcomatous component than in the epithelial component, but this was of borderline significance (85.7% *vs.* 50.0%, $p=0.053$). In addition, caveolin-1 immunoreactivity was more diffuse and intense in the sarcomatous component than in the epithelial component. The composite scores for caveolin-1 staining were significantly higher (6.7±4.3) in the sarcomatous component than in the epithelial component (3.3±4.0) ($p=0.018$). The clinicopathological variables of the low or high caveolin-1 expression level groups are listed in Table III. A significant correlation was found between the caveolin-1 expression level and the percentage of sarcomatous component. The caveolin-1 expression level in PCL was not found to be correlated with age, stage, pT category, pN category, or tumor size.

Prognostic significance of caveolin-1 expression. The high caveolin-1-expressing group showed poorer disease-free and

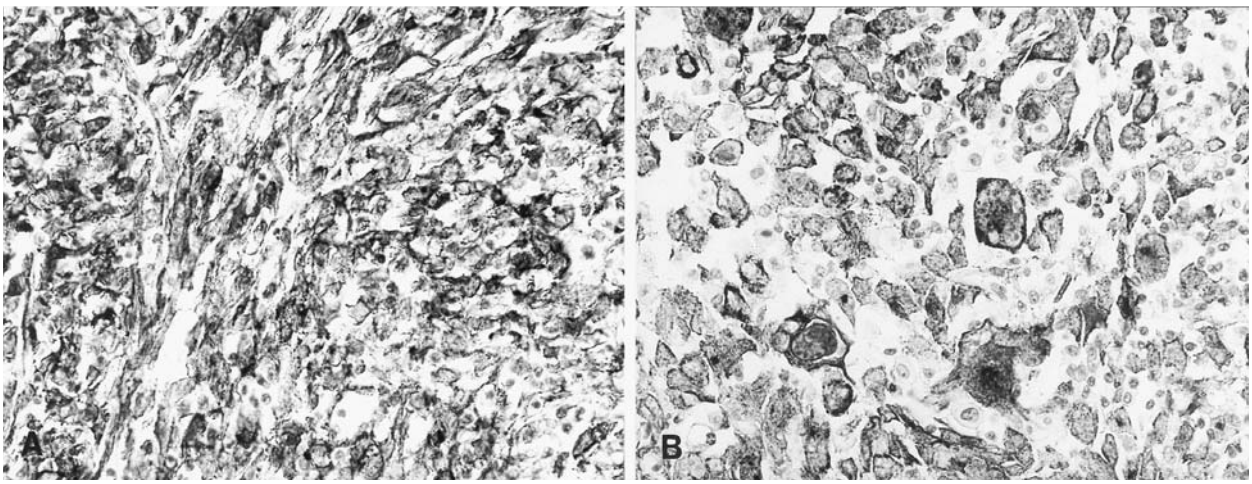

Figure 1. *Caveolin-1 immunoreactivity was observed in spindle cells (A) and giant cells (B) in PCL (anti-caveolin-1, x 200).*

overall survivals than the low caveolin-1-expressing group ($p=0.015$ and $p=0.034$, Figure 2). Other clinicopathological variables, *i.e.*, age, stage, pT category, pN category, tumor size and percentage of sarcomatous component, were not found to be correlated with PCL patient outcome in univariate analysis. In multivariate analysis, caveolin-1 expression level was identified as an independent prognostic factor for disease-free survival (Table IV).

Discussion

Caveolin-1 was first identified as a tyrosine phosphorylated protein in Rous sarcoma virus-transformed chick fibroblasts (19). The gene encoding human caveolin-1 is located in the chromosome 7q31.1 region, downstream of the D7S522 locus, in the fragile site FRA7G (20, 21). Deletions of this region are frequently noted in human cancers, including squamous cell carcinoma (22, 23), prostate carcinoma (24), renal cell carcinoma (25), ovarian carcinoma (26) and colorectal carcinoma (23). Furthermore, lower caveolin-1 expressions were reported in some human malignant tumors (7-9). These results suggested that caveolin-1 might be involved in oncogenesis as a tumor suppressor (21). In contrast, caveolin-1 overexpression has also been reported in some human carcinomas (11-14, 27). In addition, it has been reported that caveolin-1 expression in tumor cells affects the clinical outcome and prognosis of patients with prostate carcinoma (12), renal cell carcinoma (16), squamous cell carcinoma of the lung (15) and pancreatic ductal adenocarcinoma (28). Taken together, these results imply that, functionally, caveolin-1 acts to suppress tumorigenesis and plays a role in determining the biological aggressiveness of tumor cells.

Table III. *Clinicopathologic variables and caveolin-1 expression levels.*

Clinicopathological variables	No.	Cav-1 score		
		Low	High	*p*-value
Age				
≤60	10	6	4	0.670
>60	11	5	6	
Stage				
I, II	14	8	6	0.659
III	7	3	4	
pT				
T1, T2	13	7	6	>0.9999
T3, T4	8	4	4	
pN				
N0	15	8	7	>0.9999
N1, N2, N3	6	3	3	
Tumor size				
<7 cm	11	7	4	0.395
≥7 cm	10	4	6	
Sarc (%)				
<80%	9	8	1	0.008
≥80%	12	3	9	

Sarc, sarcomatous component.

Previously, we reported that pulmonary squamous cell carcinoma patients showing caveolin-1 up-regulation tend to have a poorer prognosis, which suggests that caveolin-1 expression is significantly correlated with an advanced pathological stage and a poor prognosis in non-small cell carcinomas of the lung (15). In the current study, statistical analysis revealed that PCL patients with a low caveolin-1 expression level in tumor cells showed a significantly better

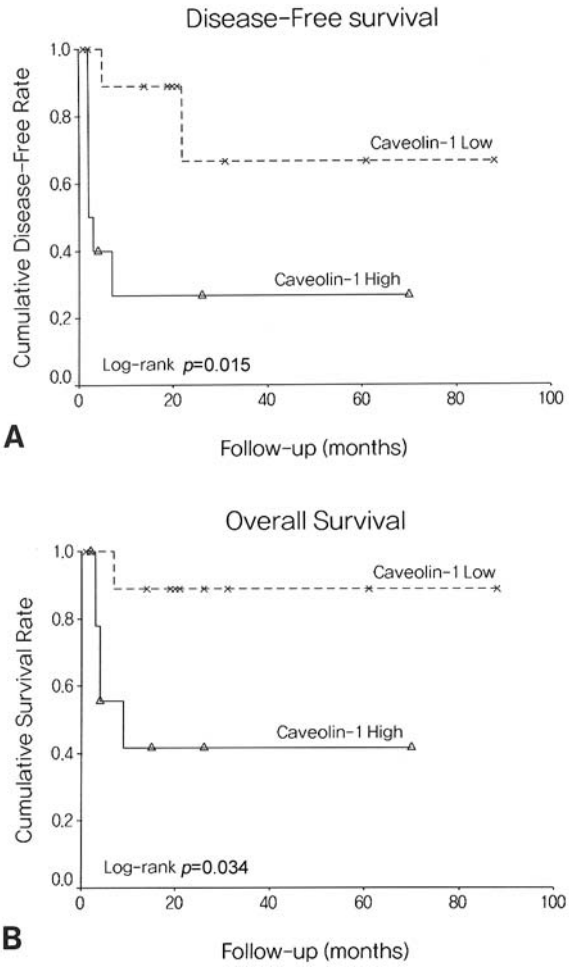

Figure 2. *Disease-free (A) and overall (B) survival curves of PCL patients with respect to caveolin-1 expression levels. Significant differences in the disease-free and overall survival were noted for the high and low caveolin-1 groups (p=0.015 and p=0.034).*

Table IV. *Univariate and multivariate analysis of disease-free survival or overall survival in patients with PCL.*

	P-value, DFS (Hazard ratio, 95% CI)	*P*-value, OS (Hazard ratio, 95% CI)
Univariate analysis		
Caveolin-1 high or low	0.015	0.034
Age >60 or ≤60	0.924	0.714
Stage I, II or III	0.110	0.130
T1, T2 or T3, T4	0.970	0.322
N0 or N1, N2, N3	0.066	0.130
Tumor size ≥7 cm or <7cm	0.833	0.778
Sarc <80% or ≥80%	0.077	0.092
Multivariate analysis		
Caveolin-1 high or low	0.040 (5.361, 1.082-26.558)	0.073 (7.221, 0.830-62.790)
Age >60 or ≤60	0.558 (0.659, 0.164-2.656)	0.867 (1.160, 0.204-6.595)
Stage I, II or III	0.497 (1.670, 0.380-7.338)	0.625 (1.584, 0.250-10.048)
Sarc <80% or ≥80%	0.764 (0.672, 0.050-9.035)	0.852 (1.345, 0.060-29.942)

Sarc, sarcomatoid component; DFS, disease free survival; OS, overall survival; CI, confidence interval.

prognosis than those with a high expression level. However, it should be mentioned that the number of PCL cases included in the present study was relatively small, and the clinical follow-up was rather short compared with other studies. Nevertheless, our results suggest that the enhanced expression of caveolin-1 in PCL is associated with a poor prognosis after surgery, and that caveolin-1 expression is a candidate indicator of prognosis in PCL patients. Several reports have also suggested that caveolin-1 expression is significantly correlated with prognosis in several other human cancers. In human prostate cancer, multivariate analysis for caveolin-1 and other prognostic markers revealed that the expression of caveolin-1 is an independent predictor of disease progression (12). Horiguchi *et al.* showed that the caveolin-1-positive group had significantly shorter progression-free survival in renal cell carcinoma patients without metastasis to the regional lymph nodes and in those with distant metastasis at initial presentation (16). In pancreatic ductal carcinomas, caveolin-1 expression was found to be correlated with tumor diameter, histopathological grade and a poor prognosis (28). Recently, Kato *et al.* reported that the overexpression of caveolin-1 in esophageal squamous cell carcinoma is correlated with lymph node metastasis, pathological stage and overall survival (13). These findings, in several types of malignant tumors, suggest that caveolin-1 expression alters the biological activity and morphological phenotypes of tumor cells, such as increased invasiveness and histological grade.

With respect to the relationship between the caveolin-1 expression and histological lung cancer grade, elevated histological grades in squamous cell carcinoma and adenocarcinoma of the lung were reported to be correlated with a low rate of caveolin-1 expression (15, 29). Moreover, caveolin-1 expression has been reported to be correlated with tumor grade in renal cell carcinoma (16), pancreatic ductal adenocarcinoma (28) and urothelial carcinoma of the urinary bladder (17, 30). Fong *et al.* reported that caveolin-1 expression was stronger in areas of squamous differentiation in urothelial carcinoma of the urinary bladder, thus suggesting that histological differentiation might also be

correlated with caveolin-1 expression in tumor cells (17). The present study also revealed higher caveolin-1 expression in sarcomatous components than in epithelial components. Thus, based on these previous results and present findings, we suggest that caveolin-1 participates in the differentiation of some carcinomas including lung cancer.

Caveolin-1 has been reported to be expressed in normal and neoplastic lung tissues. In the adult lung, caveolin-1 protein is detected on alveolar epithelial type I cells (31) and in non-small cell lung cancers such as adenocarcinoma and squamous cell carcinomas (15, 29). Caveolin-1 expression in non-small cell carcinoma of the lung has been reported to have a positivity rate that ranges from 31.7 to 72% (15, 29). This discrepancy between the positive rates of caveolin-1 expression in non-small cell carcinomas might be due to the different positivity cut-off values used. In the present study, we found that 85.7% of PCL cases expressed caveolin-1, which is higher than that found in other types of non-small cell carcinomas. In addition, the expression rate and level of caveolin-1 was higher in the sarcomatous component than in the epithelial component of PCL. In true sarcomas, caveolin-1 staining was reported to be weaker than in their benign counterparts (7), thus suggesting that caveolin-1 may act as a tumor suppressor in human sarcomas. In contrast, the present study found that caveolin-1 expression is elevated in the sarcomatous component rather than the epithelial component. The enhanced caveolin-1 expression of PCL is correlated with the poor prognosis of these tumors. Thus, it is feasible that caveolin-1 in PCL acts by increasing the biological aggressiveness of tumor cells rather than by functioning as a tumor suppressor, although its exact biological roles remain unclear.

It seems that caveolin-1 is more intensively expressed in sarcomatous components of PCL than in the tumor cells of true sarcomas, which reflects the origin of the sarcomatous component from carcinoma rather than true sarcoma. Although the oncogenesis of carcinomas composed of mixed epithelial and sarcomatous components remains unclear, previous studies support a divergence hypothesis whereby a single totipotential cell differentiates into separate epithelial and mesenchymal components, rather than the mix being caused by a true collision of tumors derived from two or more stem cells (32-36). According to the divergence hypothesis, it is more likely that the expression level of caveolin-1 in the sarcomatous component is enhanced during mesenchymal differentiation rather than during the clonal expansion of totipotential cells in early oncogenesis.

In summary, our immunohistochemical study showed that caveolin-1 is highly expressed in PCL, and that this elevated caveolin-1 expression is correlated with a poor prognosis. These results suggest that caveolin-1 plays a biological role in the regulation of tumor invasiveness in PCL, and that it should be regarded as a prognostic marker for these tumors.

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