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The Loss of Expression of Caveolin-1 in Gastrointestinal Stromal Tumors

**Eo-Jin Kim · Jin Hee Sohn
Min-Kyung Kim · Seoung Wan Chae
Hye Seung Lee[1] · Eun Yoon Cho[2]
Woo Ho Kim[3]**

Department of Pathology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul; [1]Seoul National University Bundang Hospital, Seongnam; [2]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul; [3]Seoul National University College of Medicine, Seoul, Korea

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Corresponding Author
Woo Ho Kim, M.D.
Department of Pathology, Seoul National University College of Medicine, 28 Yongon-dong, Jongno-gu, Seoul 110-799, Korea
Tel: 02-740-8269
Fax: 02-765-5600
E-mail: woohokim@snu.ac.kr

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Background : The down-regulation of caveolin-1, a putative tumor suppressor gene, has been demonstrated in several types of sarcomas. However, it's not known whether or not the gastrointestinal stromal tumors (GISTs) express caveolin-1. We carried out this study to investigate the caveolin-1 expression in GISTs and to determine the correlation between the clinicopathologic profiles of GISTs and the expression of caveolin-1. **Methods :** One hundred eight cases of formalin-fixed and paraffin-embedded tissues of GISTs were immunohistochemically evaluated for the expression of caveolin-1 by using the tissue-array method. Survival data of 98 cases of primary GISTs was analysed according to the expression status of caveolin-1. **Results :** Ninety three cases (86.1%) of 108 GISTs did not express caveolin-1 protein. There was no correlation between the caveolin-1 expression status and any of the clinicopathologic variables, including mitosis (p=0.948) and tumor grade (p=0.334). The expression of caveolin-1 was not correlated with other immunohistochemical marker proteins including, c-kit (p=0.373), CD34 (p=0.437) and SMA (p=0.831). On the univariate analysis, the caveolin-1 expression status (p=0.635) was not a significant predictor of the disease-free survival for GIST patients. **Conclusions :** The results of this study suggest that caveolin-1 might act as a tumor suppressor gene in the GIST oncogenesis, but it has no function as a prognostic marker for disease free survival.

Key Words : Gastrointestinal stromal tumors; Immunohistochemistry; Caveolin-1; Disease-free survival

Gastrointestinal stromal tumors (GISTs) used to include a wide variety of spindle cell neoplasms such as leiomyomas, cellular leiomyomas, leiomyoblastomas, leiomyosarcomas, schwannomas and etc. However, recent studies have indicated that GISTs form a biologically distinctive group, and the current classification by the World Health Organization excludes leiomyomas, leiomyosarcomas and schwannomas from this category.[1] There has been a lot of controversy about the exact origin of GISTs, and it has been recently suggested that they originate from multipotent mesenchymal cells that can differentiate into Cajal cells and smooth muscle cells.[2]

The constitutive activation of the KIT receptor tyrosine kinase is a central pathogenetic event in most GISTs[3] and c-kit immunostaining is the gold standard for the diagnosis of GIST[4]. However, recent studies have reported the existence of c-kit-negative GISTs.[5,6] Some of these c-kit-negative GISTs have the platelet-derived growth factor-alpha (PDGFRA) mutation[5] and Blay *et al*.[6] have suggested that protein kinase C-θ (PKC-θ) might be a marker for c-kit-negative GISTs. Although *c-KIT* plays a pivotal role in the pathogenesis of GISTs, GISTs also have a number of cytogenetic anomalies that correlate with its disease progression.[7]

Caveolae are 50-100 nm ω-shaped invaginations of the plasma membrane, and these have been implicated in transcytosis, potocytosis and signal transduction.[8] Caveolae exist in two forms: (i) invaginations of the plasma membrane proper and (ii) the vesicles residing near the membrane (i.e. the plasmalemmal vesicles).[8] They are notably abundant in terminally differentiated mesenchymal cells such as fibroblasts, adipocytes, endothelial cells, smooth and striated muscle cells, type I pneumocytes, and epithelial cells.[8] Caveolins are a family of highly conserved 20-25 kd integral membrane proteins, and these are the principal protein components of caveolae.[8] The mammalian caveolin family consists of four proteins, caveolin-1α, -1β, -2 and -3, and these are encoded by three genes (*CAV-1*, *CAV-2*, and *CAV-3*, respec-

tively). *CAV-1* and *CAV-2* are co-localized to the D7S522 locus (7q31.1), which is known to be a fragile site (FRA7G) and this locus is frequently deleted in a variety of human cancers.[9]

Caveolin-1 and -2 are co-expressed, whereas the expression of caveolin-3 is muscle-specific.[8] In general, caveolins bind to and inactivate signaling molecules, including receptor tyrosine kinases, their downstream targets (e.g., H-RAS, MEK1, and ERK2), serpentine receptors, G-protein and eNOS.[8,10] It has been suggested that caveolin-1 may possess transformation suppressor activity.[10] In addition, caveolin-1 expression is lost or reduced during cell transformation via the activated oncogenes,[11] and so it is considered as a putative tumor suppressor gene.[8] The down-regulation of caveolin-1 has been demonstrated in several types of sarcomas.[12] However, it is not known whether or not the GISTs express caveolin-1.

In this study, we have investigated the immunohistochemical expression status of caveolin-1 in GISTs and we analyzed the relationship between the expression of caveolin-1 and the various clinicopathologic factors, including the tumor grade and the survival data.

METHODS

Materials

All the consecutive gastrointestinal mesenchymal tumors that were diagnosed from 1989 to 1999 as leiomyomas, leiomyosarcomas, leiomyoblastomas, schwannomas, smooth muscle tumors, spindle cell sarcomas or GISTs were retrieved from the files of the Seoul National University Hospital Surgical Pathology department. We reviewed the original hematoxylin & eosin (H&E) stained slides and the immunohistochemical results. We performed additional immunohistochemical staining for c-kit, CD34, SMA, S-100 and desmin in the cases in which this was necessary for the diagnosis. The cases of GIST were selected by 3 pathologists, based on the typical morphology and immunohistochemical findings proposed by Fletcher *et al*.[4] A total 108 GISTs were included in this study on the basis of the availability of the corresponding material and the clinical information. Among the total of 108 cases, 98 patients underwent complete resection of primary tumors, 6 underwent resection of recurred or metastatic tumors and 4 patients underwent palliative surgery due to unresectable tumors. The clinical data and follow-up information were obtained by reviewing the medical records of the patients. In each case, the age, gender, tumor size, tumor location, mitotic counts per 50 high power fields (HPFs) and tumor grade were evaluated. All of histopathological characteristics, excluding immunohistochemical results, were evaluated in the original H&E stained slides. The tumors were graded according to the risk groups proposed by Fletcher *et al*.[4]

Table 1. Primary antibodies used for immunohistochemical study

Antibody	Clone name	Dilution	Company	Method of antigen retrieval
c-kit	Polyclonal	1:250	DAKO	Microwave
CD34	QBEND10	1:400	Immunotech	Microwave
SMA	1A4	1:150	DAKO	Proteinase
S-100 protein	Polyclonal	1:500	DAKO	-
Desmin	D33	1:150	DAKO	Pressure cooker
Caveolin-1	2297	1:250	Transduction	Microwave

SMA, α-smooth muscle actin.

High-throughput tissue microarray

For conducting the immunohistochemical study, selected representative areas were identified on the H&E stained slides and these were marked for sampling to build a tissue microarray. Core tissues (2 mm in diameter) were taken from the individual paraffin-embedded tumors (the donor blocks) and these core tissues were arranged into 3 recipient paraffin blocks (the tissue array block) using a trephine apparatus (Superbiochips Laboratories, Seoul, Korea). Each tissue array block contained tissue samples from up to sixty cases. Each block contained an internal control that consisted of normal smooth muscle tissue, nerve tissue, vessels tissues and adipose tissue.

Immunohistochemistry

Studies were performed on the 4 μm thick sections that were obtained from the tissue array blocks with using the avidin-biotin-peroxidase complex detection system via a Vectastain ABC-kit (Vector Labs, Burlingame, CA) with diaminobenzidine as the chromogen. The primary antibodies, dilution, companies of source and epitope retrieval modalities are listed in Table 1. Normal saline was used instead of the primary antibody for the negative control. For assessment of the degree of immunoexpression status, we compared it with the internal control in the tissue array blocks and it was graded as nonexpression, mild, moderate and strong expression. The staining intensities were interpreted as strong expression when the tumor cells were intensely stained like the internal control. If the tumor cells were faintly stained

or weakly stained when they were compared with the internal control, then this was considered as a mild or moderate expression, respectively. We regarded those cases with moderate and strong expressions as weak positive and strong positive, respectively. Those cases with nonexpression and mild expression were regarded as negative.

Statistics and survival analysis

The caveolin-1 expression status in relation to the clinicopathologic variables was analyzed by using T-test, Mann-Whitney U test, Kruskal-Wallis test and Jonckheere-Terpstra test. The correlation between each immunohistochemical expression status was estimated by Spearman's rank correlation with using the SPSS version 11.0 software program. The clinical outcomes of the 98 GIST patients who underwent complete resection were followed up from the date of surgery to either the date of recurrence, metastasis, death or the last date of follow-up. The recurred and metastatic cases at the date of surgery or the patients who underwent palliative surgery due to the advanced stage of the disease were excluded from the survival study. Recurrence, metastasis and disease-related death were all defined as events during the analysis of the disease free survival rate. Those patients who died due to unrelated causes, those who were lost to follow-up or those who were alive at the time of the last follow-up were regarded as censored data. Actuarial survivals according to the caveolin-1 expression status were determined by Kaplan-Meier analysis, and the statistical significance was determined by the log-rank test. p values of less than 0.05 were considered statistically significant.

Table 2. Clinicopathologic characteristics and correlation with the expression of caveolin-1 in GISTs

	No. of case (%)	No. of caveolin-1 expression				p value
		None	Mild	Moderate	Strong	
Gender						
Female	49 (45.4)	31	8	7	3	
Male	59 (54.6)	42	12	2	3	0.273
Age						
mean; 54.9						
≤50	34 (31.5)	22	8	3	1	
>50	74 (68.5)	51	12	6	5	0.820
Size (cm)						
mean; 8.05						
≤2	11 (10.2)	6	2	2	1	
>2, ≤5	30 (27.8)	17	7	5	1	
> 5, ≤10	45 (41.7)	34	8	1	2	
>10	22 (20.4)	16	3	1	2	0.086
Mitosis (/50HPF)						
mean; 19.8						
≤5	47 (43.5)	32	9	4	2	
>5, ≤10	23 (21.3)	14	6	2	1	
>10	38 (35.2)	27	5	3	3	0.948
Grade (risk group)						
Very low	7 (6.5)	3	2	1	1	
Low	16 (14.8)	9	4	2	1	
Intermediate	27 (25.0)	21	3	3	0	
High	58 (53.7)	40	11	3	4	0.334
Site						
Stomach	57 (52.8)	33	13	8	3	
Small intestine	34 (31.5)	27	5	0	2	
Colorectum	9 (8.3)	6	1	1	1	
Ometum	5 (4.6)	4	1	0	0	
Others	3* (2.8)	3	0	0	0	0.164

GIST, gastrointestinal stromal tumor; *, metastatic hepatic lesion.

RESULTS

Clinicopathlogic findings

The 108 GISTs cases were made up of 59 (54.6%) men and 49 (45.4%) women. Age showed a unimodal distribution, with a mean age of 54.9 years (range: 23-78 years). GISTs occurred predominantly in the middle-aged or older-aged patients and their occurrence was rare in patients less than 40 years old. The GISTs were composed of relatively uniform, ovoid or short spindle cells arranged in short fascicles or whorls with pale eosinophilic cytoplasm and ovoid or short spindle nuclei. Some cases showed partly mixed rounded cells, but the pure epithelioid type was

Table 3. Correlation between the immunohistochemical expression status in GISTs

	No. of case (%)	No. of caveolin-1 expression				p value
		None	Mild	Moderate	Strong	
c-kit						
Negative	7 (6.5)	3	1	2	1	
Positive	101 (93.5)	70	19	7	5	0.373
CD34						
Negative	29 (26.9)	19	4	3	3	
Positive	79 (73.1)	54	16	6	3	0.437
SMA						
Negative	77 (71.3)	51	15	6	5	
Positive	31 (28.7)	22	5	3	1	0.831
S-100						
Negative	71 (65.7)	45	15	7	4	
Positive	37 (34.3)	28	5	2	2	0.396
desmin						
Negative	104 (97.2)	71	19	9	5	
Positive	3 (2.8)	2	1	0	0	0.659

SMA, α-smooth muscle actin.

not found. More than half of the tumors (56.5%) had a high mitotic count of more than 5 per 50 HPF (mean: 19.8, range: 0-253). Approximately two thirds of the patients (62.1%) had tumors larger than 5 cm (mean: 8.05 cm, range: 1-30 cm). For the tumor grade, there were seven (6.5%) very low risk, 16 (14.8 %) low risk, 27 (25.0%) intermediate risk and 58 (53.7%) high risk tumors. Regarding the presenting site, 57 (52.8%) were in the stomach, 34 (31.5%) were in the small intestine, nine (8.3%) were in the colorectum and five (4.6%) were in the omentum (Table 2). There were three (2.8%) primary extra-gastrointestinal (omental) stromal tumors and two recurred omental cases.

Correlation and the prognostic significance of the caveolin-1 expression

93 cases (86.1%) of the 108 GISTs did not express caveolin-1 protein. Among the 15 cases, that showed caveolin-1 positivity, six cases (5.6%) revealed a strong caveolin-1 expression and nine cases (8.3%) showed a moderate expression (Fig. 1). The clinicopathologic characteristics and their relationship with the expression of caveolin-1 are listed in Table 2. There was no correlation between the caveolin-1 expression status and any of the clinicopathologic variables, including mitosis (p=0.948) and tumor grade (p=0.334). The expression of caveolin-1 was not correlated with the other immunohistochemical marker proteins, including c-kit (p=0.373), CD34 (p=0.437) and SMA (p=0.831) (Table 3). All of the three (2.8%) desmin-positive GISTs showed c-kit positivity, but they did not express caveolin-1 protein.

The disease free survival of the patients who underwent complete resection of primary tumor was examined (Fig. 2). The mean disease-free survival was 76 months (range: 1-132 months), and the disease-free survival rates were 84% at 1 year, 67% at 3 years and 54% at 5 years. On the univariate analysis, the caveolin-1 expression status (p=0.635) was not a significant predictor of

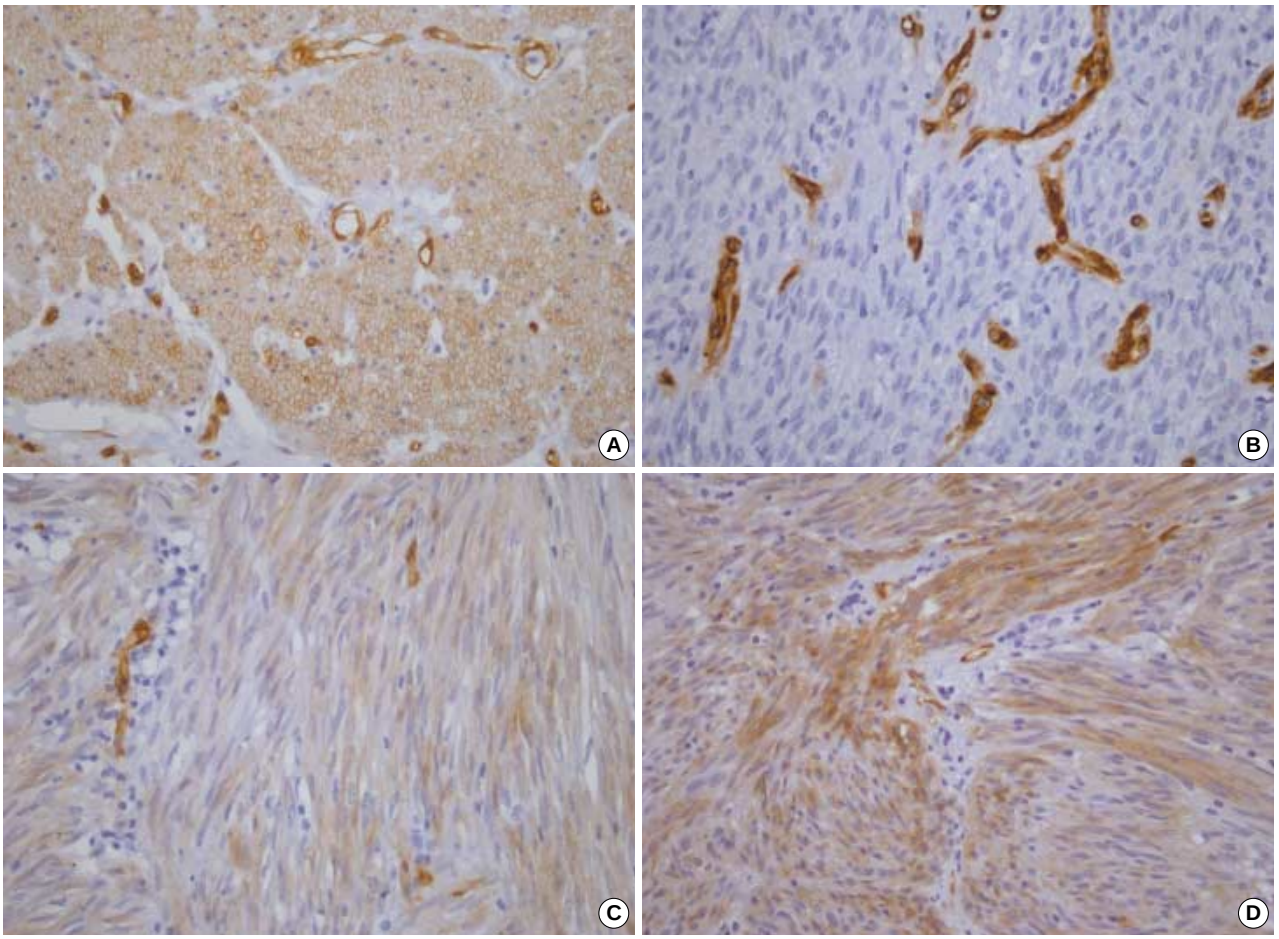

Fig. 1. Immunohistochemical staining for caveolin-1 in GISTs. (A) Internal control tissue core in tissue array block shows caveolin-1 immunoreactivity at the cell membrane of the cross-sectioned smooth muscle cells and at the cytoplasm of the vascular endothelial cells. (B) Tumor cells show no caveolin-1 immunoreactivity. (C) Tumor cells show slightly weak caveolin-1 immunoreactivity of cytoplasmic pattern, compared with the vascular endothelial cells. (D) Tumor cells show strong cytoplasmic and membranous caveolin-1 expression.

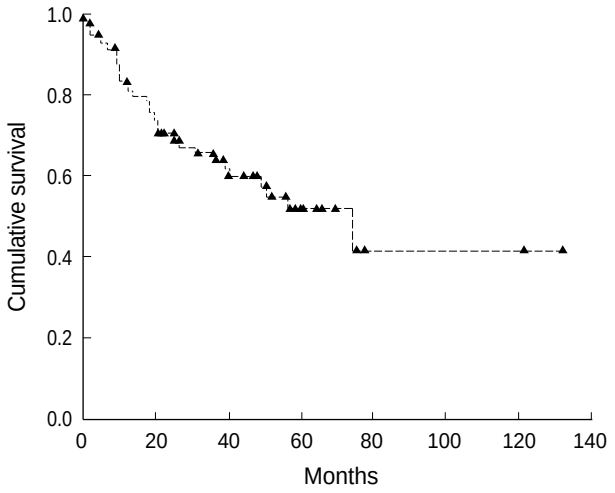

Fig. 2. Disease free survival after complete resection of primary GISTs (n=98).

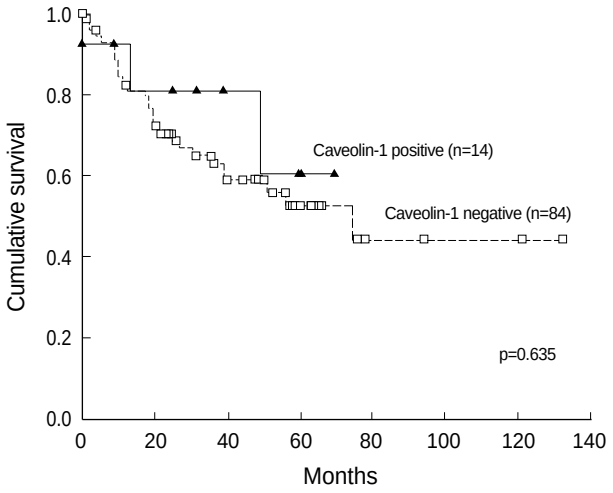

Fig. 3. Disease free survival after complete resection of primary GISTs, based on the expression of caveolin-1.

disease-free survival for GISTs (Fig. 3).

DISCUSSION

GIST is the designation that is used for a major subset of non-epithelial tumors that arise in the gastrointestinal tract. It also includes tumors that occur in intraabdominal locations outside of the gastrointestinal tract proper, and especially in the omentum and mesentery.[2] So, instead of the previous postulation that proposed the interstitial cell of Cajal (ICC) as the cellular origin of GIST,[13] it has been recently suggested that GIST originates from multipotent mesenchymal precursor cells that can differentiate into ICC and smooth muscle cells.[2] The inability to unambiguously distinguish a poorly differentiated leiomyosarcomas from GISTs would be consistent with the postulated common derivation of smooth muscle cells and ICCs and indeed, some leiomyosarcomas can exhibit c-kit staining.[14]

Caveolae are flask-shaped invaginations of the plasma membrane that play an important role in several cellular processes, including molecule transport, cell adhesion, and signal transduction.[8,15] Caveolin-1 is an essential structural component of the caveolae and this protein functionally regulates the activity of many signaling molecules such as G-proteins, Src family kinases, H-Ras, protein kinase C, epidermal growth factor receptor, endothelial nitric oxide synthase, and integrins, and all of these are potentially involved in the development of human cancer by generating preassembled signaling complexes.[8,16] There is accumulating evidence to suggest that caveolin-1 acts as a tumor suppressor gene. Oncogenic transformation of cells has been associated with the reduction of caveolin-1 expression,[17] and further, the antisense-mediated down-regulation of caveolin-1 expression was sufficient to drive oncogenic transformation in NIH 3T3 cells.[18] Decreased caveolin-1 expression was found in ovarian carcinomas[19] and in prostate carcinomas due to the hypermethylation of the promoter region of caveolin-1.[20] The down-regulation of caveolin-1 has also been demonstrated in several types of sarcomas[12] and mutation-positive cases have been found in invasive scirrhous ductal carcinomas.[21]

Conversely, the elevated expression of caveolin-1 has been found in carcinomas of the esophagus, colon, thyroid, breast and prostate.[22-25] Caveolin-1 expression in bladder carcinoma has been directly related to the tumor grade, and this suggests that the altered expression of the caveolin-1 protein is a component of tumor dedifferentiation in the high grade tumors.[26] Thus, caveolin-1 appears to play differential roles in its function depending on the types of tumors, and these findings have led some investigators to hypothesize that caveolin-1 may play a role in the various stages of carcinogenesis. However, the exact biological roles of caveolin-1 for the development and progression of malignant tumors remain unclear.

In this study, we showed that 86.1% of GISTs did not express caveolin-1 protein and this is the first time such a finding has been reported. We performed an extensive review of the literature for articles that investigated the ultrastructure of GIST, yet we could not find any description about the presence of caveolae in GISTs, except for one study. In that study, Park *et al.*[27] described that caveolae or pinocytotic vesicles were rarely seen in GISTs. Therefore, it is clear that GISTs rarely have the caveolae structure and this finding corresponds to our result that showed the

loss of expression of caveolin-1 in GISTs. Previous studies for the electron microscopic structure of normal ICC have revealed that they had conspicuous caveolae,[28] or modest amounts of plasmalemmal caveolae,[29] and Cho *et al*. have recently proved that caveolin-1 was present in all classes of ICC, the ICC-myenteric plexus, the ICC-deep muscle plexus, the ICC-serosa and the ICC-intramucosa by performing double-immunofluorescent labeling with the primary antibodies for c-kit and caveolin-1.[30] In addition, it is well known that caveolae are notably abundant in smooth muscle cells.[8]

According to the findings of ICCs and smooth muscle cells, it can be suggested that multipotent mesenchymal precursor cells, which can differentiate into ICCs and smooth muscle cells, also have the caveolae structures. In regard to the smooth muscle tumors, Eyden *et al*.[29] reported that leiomyoma and leiomyosarcoma showed maximum levels of smooth-membraned plasmalemmal caveolae in their ultrastructural study of gastrointestinal mesenchymal tumors. Our additional study revealed that 3 cases out of 4 gastrointestinal leiomyosarcomas and all of the 38 gastrointestinal leiomyomas showed strong caveolin-1 expression. The one remaining leiomyosarcoma showed caveolin-1 negativity and it also showed desmin negativity. So, it is possible that this case was a c-kit-negative GIST or a very poorly differentiated leiomyosarcoma close to GIST. Therefore, we suggest that caveolin-1 down-regulation may contribute to the pathogenesis of GISTs instead of the differentiation of normal ICC or smooth muscle cell, or the development of smooth muscle tumors from postulated common precursor cell of smooth-muscle cells and ICCs. However, we could not find any correlation between the loss of caveolin-1 expression and tumor aggressiveness, and so caveolin-1 down-regulation in GISTs may have a role in the early stage of oncogenesis rather than for tumor progression.

In the present study, the expression of caveolin-1 was not correlated with the expression of c-kit ($p=0.373$) and SMA ($p=0.831$). It means that caveolin-1 down-regulation and the constitutive activation of the KIT receptor tyrosine kinase are mutually independent pathogenetic processes and that the caveolin-1 expression status does not correlate with the smooth muscle differentiation of GISTs. In other words, although the tumor cells of GISTs differentiate to smooth muscle cells, the caveolae structures are not significantly increased. This cellular disposition can also be suggested from the result that all of the three desmin-positive GISTs, which also showed c-kit positivity, did not express caveolin-1 protein.

In conclusion, our results suggest that caveolin-1 might act as a tumor suppressor gene in the early stage of GIST oncogenesis, but it has no function as a prognostic marker for disease free survival. In addition, the absence of caveolae structure could be one of the characteristic features of GIST cells to distinguish them from smooth muscle tumor cells.

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