Exp Oncol 2018
40, 4, 323–327

Experimental ONCOLOGY

CLINICAL SIGNIFICANCE OF SERUM CAVEOLIN-1 LEVELS IN GASTRIC CANCER PATIENTS

F. Tas, S. Karabulut, K. Erturk, D. Duranyildiz*
Institute of Oncology, University of Istanbul, Istanbul 34390, Turkey

***Aim*: Caveolin-1 plays a significant role in the pathogenesis of various carcinomas and its expression affects the survival of cancer patients. However, the molecular function of caveolin-1 and its possible clinical importance has remained uncertain in gastric cancer. No clinical trial has examined serum caveolin-1 levels in gastric cancer patients so far, instead all available results were provided from studies conducted on tissue samples. In the current study, we analyzed the soluble serum caveolin-1 levels in gastric cancer patients, and specified its associations with the clinical factors and prognosis. *Material and Methods*: Sixty-three patients with pathologically confirmed gastric cancer were enrolled into the trial. Serum caveolin-1 concentrations were detected by ELISA method. Thirty healthy subjects were also included in the study. *Results*: The median age of patients was 62 years, ranging from 28 to 82 years. The serum caveolin-1 levels in gastric cancer patients were significantly higher than those in control group ($p < 0.001$). The common clinical parameters including patient age, sex, lesion localization, histopathology, histological grade, disease stage, and various serum tumor markers (e.g. LDH, CEA, and CA 19.9) were not found to be associated with serum caveolin-1 levels ($p > 0.05$). Similarly, no correlation existed between serum caveolin-1 concentration and chemotherapy responsiveness ($p = 0.93$). Furthermore, serum caveolin-1 level was not found to have a prognostic role ($p = 0.16$). *Conclusion*: Even though it is neither predictive nor prognostic, serum caveolin-1 level may be a valuable diagnostic indicator in patients with gastric cancer.**
***Key Words*: serum, caveolin-1, gastric cancer, diagnostic.**

Multifactorial etiology plays a role in gastric cancer development whose genetic and immunological grounds have not been fully explained yet. *In vitro* trials determined that cultured gastric cancer cell lines generate extreme concentrations of growth factors and cytokines with pleiotropic biological actions. Furthermore, caveolins function as an autocrine and paracrine factor that motivates many cellular procedures including angiogenesis, invasion, tumor growth, and metastasis [1–3].

Caveolins are the main protein constituent of caveolae, characterized invaginations of the plasma membrane and join in vesicular trafficking incidents and signal transduction procedures [1–16]. The behaviour of caveolin-1 in tumorigenesis seems to shift with respect to the tumor type, e.g. while its expression is associated with cancer suppression in hepatocellular and ovarian carcinoma, it is associated with cancer progression in esophageal, renal cell and prostate cancers. Enhanced caveolin-1 expression in tumor cells has been associated with aggressiveness and, in some cases, a worse clinical survival [1–8]. Additionally, caveolin-1 loss contributes to the distinct activation of fibroblasts in gastric cancer microenvironment and gastritis mucosa, and its expression in both gastric cancer-associated fibroblasts and gastric inflammation-associated fibroblasts may serve as a potential biomarker for gastric cancer progression [9, 11].

Until recently, there have been several trials published that specifically are addressing the clinical importance of caveolin-1 expression in gastric cancer [4–16]. Increased caveolin-1 expression was also determined in gastric cancer cell lines with increased proliferation of gastric cancer cell and metastatic potential [4–16]. However, the molecular function of caveolin-1 and its possible clinical importance has remained uncertain in gastric cancer.

To the best of our knowledge, no clinical trial has examined serum caveolin-1 levels in gastric cancer patients so far, instead all available results were provided from studies conducted on tissue samples. Therefore, the importance of the circulating concentrations of caveolin-1in gastric cancer patients is not known yet. In the current study, we analyzed the soluble serum caveolin-1 levels in gastric cancer patients, and specified its associations with the prognosis, clinical factors, and responsiveness of chemotherapy.

MATERIAL AND METHODS

Patients and therapy. This study comprised sixty-three gastric cancer patients that were treated in the Institute of Oncology, Istanbul University. None of the patients had received any type of treatment, e.g. chemotherapy or radiotherapy, within six months prior to the study. The disease was staged based on the American Joint Committee on Cancer and the Union for International Cancer Control staging systems. The comprehensive history and physical examinations and blood tests, such as complete blood count and biochemistry analyses, were carried out for each patient. Patients were treated and followed-up according to standard international guidelines including National Comprehensive Cancer Network guidelines. Patients with ECOG performance status equal or less than 2, and appropriate blood tests received combination chemotherapy regimens consisting of various chemotherapeutics, such as 5-FU, leucovorin, cisplatin, epirubicine, capecitabine, and docetaxel. Response to the treatment was assessed with the revised RECIST criteria version 1.1.

Age (median age was 59 years; range, 25 to 78) and sex (female were predominant in number; n = 17,

Submitted: August 19, 2018.
*Correspondence: E-mail: faruktas2002@yahoo.com

57.0%) matched thirty healthy subjects with gastritis, ulcers and other benign lesions as control group were included in the analysis. Informed consents were provided from the patients. The Regional Ethic Committee (Institute of Oncology, Istanbul University) reviewed and confirmed the trial.

Measurement of serum caveolin-1 concentrations. Blood specimens of the patients were drawn on initial admission by venipuncture and clotted at room temperature. The sera were collected after centrifugation and frozen at –20 °C until analysis. The Human Caveolin 1 (CAV 1) ELISA (MyBioSource, Inc., USA) uses a double-antibody sandwich enzyme-linked immunosorbent assay to detect the concentration of Human Caveolin 1 in specimens. Serum specimens, standards and Biotin Conjugate were added to the wells and incubated for 1 h at 37 °C. Unbound material was washed away. Chromogen solution was added and incubated for 15 min (protected from light) at 37 °C for the conversion of the colorless solution to a blue solution, the intensity of which is proportional to the amount of CAV 1 in the sample. As the effect of the acidic stop solution, the color has become yellow. The colored reaction product was measured using an automated ELISA reader (Rayto, RT-1904C Chemistry Analyzer, Atlanta GA, USA) at 450 nm. The results were expressed as ng/ml.

Statistical analysis. Parameters were classified as median values as cut-off point. Relationships between clinical/laboratory parameters and serum caveolin-1 assay concentrations were done using Mann — Whitney U test. Survival was detected by Kaplan — Meier method and survival differences were performed by the log-rank statistics. A p value $\leqslant 0.05$ was considered as significant. The SPSS 16.0 software (SPSS Inc., Chicago, Illinois, USA) was used for statistical analyses.

RESULTS

Sixty-three gastric cancer patients were enrolled into this study. The demographic and histopathological characteristics of the patients are shown in Table 1. The median age of patients was 62 years, ranging from 28 to 82 years.

The serum caveolin-1 levels in gastric cancer patients were significantly higher than those in control group (median values 3.82 *vs* 0.25 ng/ml, respectively, $p < 0.001$) (Table 2). The common clinical parameters including patient age, sex, lesion localization, histopathology, histological grade, disease stage, and various serum tumor markers (e.g. LDH, CEA, and CA 19.9) were not found to be associated with serum caveolin-1 levels ($p > 0.05$) (Table 3). Similarly, no correlation existed between serum caveolin-1 concentration and chemotherapy responsiveness ($p = 0.93$).

The median survival was 42.0 ± 4.2 weeks. The 1-year survival rates were 42.2%. The presence of metastasis ($p = 0.03$), the antral tumor location ($p = 0.04$), the higher erythrocyte sedimentation rate ($p = 0.02$), the elevated serum CEA concentration ($p = 0.01$), the higher serum CA 19.9 levels ($p = 0.04$), and the unresponsiveness to chemotherapy ($p = 0.05$) were found to be statistically significant parameters of poor survival (Table 4). Furthermore, serum caveolin-1 concentration was not found to have a prognostic role on survival ($p = 0.16$) (Table 4, Figure).

Table 1. Patient and disease characteristics

Parameter	n (%)
No. of patients	63 (100)
Patient age	
⩾ 60 years	35 (56)
< 60 years	28 (44)
Sex	
Male	25 (40)
Female	38 (60)
Tumor localization	
Cardia	21 (33)
Antrum	27 (43)
Unknown	15 (24)
Histopathology	
Adenocarcinoma	42 (67)
Signet-ring cell	21 (33)
Histological grade	
I–II	10 (16)
III	44 (70)
Unknown	9 (14)
Tumor (T) stage	
1–3	14 (22)
4	22 (35)
Unknown	27 (43)
Number of lymph node involvement	
0–2	12 (19)
⩾ 3	13 (21)
Unknown	38 (60)
Disease stage	
Nonmetastatic	32 (51)
Metastatic	31 (49)
Liver metastasis*	
Yes	14 (45)
No	17 (55)
Curative surgery**	
Yes	17 (53)
No	9 (28)
Unknown	6 (19)
Serum hemoglobin level	
Low (< 12 g/dl)	35 (56)
Normal (⩾ 12 g/dl)	28 (44)
Serum white blood cell count	
Normal (< 10,000)	52 (83)
High (⩾ 10,000)	11 (17)
Serum platelet count	
Normal (⩽ 350,000)	54 (86)
High (> 350,000)	9 (14)
Serum LDH level	
Normal (< 450 U/l)	43 (68)
High (⩾ 450 U/l)	10 (16)
Unknown	10 (16)
Erythrocyte sedimentation rate	
High (⩾ 50/h)	16 (25)
Normal (< 50/h)	10 (16)
Unknown	37 (59)
Serum CEA level	
Normal (< 10 ng/ml)	44 (70)
High (⩾ 10 ng/ml)	13 (21)
Unknown	6 (9)
Serum CA 19.9 level	
Normal (< 40 IU/ml)	32 (51)
High (⩾ 40 IU/ml)	25 (40)
Unknown	6 (9)
Chemotherapy responsiveness	
Yes	13 (43)
No	17 (57)

Note: *In metastatic patients; **in nonmetastatic patients.

Table 2. The values of serum caveolin-1 levels in gastric cancer patients and healthy controls

Marker	Patients (n = 63)		Controls (n = 30)		
	Median	Range	Median	Range	p
Caveolin-1, ng/ml	3.82	2.38–15.98	0.25	0.02–0.97	< 0.001

Table 3. Comparisons between serum caveolin-1 levels and various clinical parameters in patients with gastric cancer

Parameters	Caveolin-1, ng/ml median (range)	*p*
Age of patients		
< 60 years	3.82 (2.58–15.74)	0.97
⩾ 60 years	3.82 (2.38–15.98)	
Sex		
Male	3.91 (2.38–8.58)	0.36
Female	3.48 (2.38–15.98)	
Localization		
Cardia	3.57 (2.58–15.98)	0.49
Antrum	3.74 (2.58–15.74)	
Histology		
Adenocarcinoma	3.87 (2.38–15.74)	0.56
Signet ring	3.82 (2.72–15.98)	
Grade of histology		
I–II	3.70 (2.58–4.81)	0.71
III	3.65 (2.38–15.98)	
Tumor (T) stage		
1–3	3.49 (2.58–8.46)	0.69
4	3.48 (2.58–15.98)	
No. of lymph node involvement		
0–2	3.87 (2.58–10.37)	0.77
⩾ 3	3.23 (2.72–15.98)	
Curative surgery		
Yes	3.82 (2.69–15.98)	0.99
No	3.48 (2.58–8.46)	
Stage of disease		
Metastatic	4.25 (2.38–15.74)	0.09
Nonmetastatic	3.48 (2.58–15.98)	
Liver metastasis		
Yes	4.12 (2.84–15.74)	0.77
No	4.25 (2.38–8.58)	
Serum hemoglobin level		
Low (< 12 g/dl)	3.91 (2.58–15.98)	0.42
Normal (⩾ 12 g/dl)	3.65 (2.38–15.74)	
Serum white blood cell count		
High (⩾ 10,000)	4.42 (2.38–7.73)	0.19
Normal (< 10,000)	3.74 (2.38–15.98)	
Serum platelet count		
High (> 350,000)	4.59 (2.72–7.73)	0.33
Normal (⩽ 350,000)	3.82 (2.38–15.98)	
Erythrocyte sedimentation rate		
High (⩾ 50/h)	4.38 (2.58–15.74)	0.15
Normal (< 50/h)	3.40 (3.06–4.84)	
Serum LDH level		
High (⩾ 450 U/l)	4.08 (2.58–8.58)	0.89
Normal (< 450 U/l)	3.74 (2.38–15.98)	
Serum CEA level		
High (⩾ 10 ng/ml)	4.33 (2.38–8.58)	0.96
Normal (< 10 ng/ml)	3.48 (2.38–15.98)	
Serum CA 19.9 level		
High (⩾ 40 IU/ml)	4.25 (2.38–15.74)	0.33
Normal (< 40 IU/ml)	3.48 (2.38–15.98)	
Response to chemotherapy		
Yes	4.33 (2.38–15.98)	0.93
No	3.74 (2.58–15.74)	

DISCUSSION

In this study, we found that the serum caveolin-1 levels in gastric cancer patients were significantly higher than those in non-cancer subjects. The common clinical parameters, such as patient age, sex, lesion localization, histopathology, histological grade, disease stage, and various serum tumor markers, e.g. LDH, CEA, and CA 19.9, were not found to be associated with circulating caveolin-1 levels. Similarly, serum caveolin-1 level was not correlated with outcome. The results of the present study suggest that even though it is neither predictive nor prognostic, serum caveolin-1 level may be a valuable diagnostic indicator in patients with gastric cancer.

Table 4. Univariate analysis of the patients' parameters

Parameters	Survival median, weeks (± SD)	1-year, % (± SD)	*p*
Age of patients			
< 60 years	44.0 (8.4)	43.0 (10.5)	0.61
⩾ 60 years	42.0 (9.3)	41.1 (9.8)	
Sex			
Male	44.0 (19.8)	47.3 (9.2)	0.56
Female	42.0 (7.6)	35.0 (10.9)	
Localization			
Cardia	NR	65.1 (11.9)	0.04
Antrum	37.0 (8.2)	31.9 (9.7)	
Histology			
Adenocarcinoma	44.0 (18.6)	48.5 (8.9)	0.22
Signet ring	42.0 (11.0)	31.3 (11.2)	
Grade of histology			
I–II	NR	75.0 (15.8)	0.10
III	37.0 (9.7)	36.2 (8.5)	
Tumor (T) stage			
1–3	NR	85.7 (9.4)	0.06
4	37.0 (16.8)	41.5 (11.2)	
No. of lymph node involvement			
0–2	NR	65.5 (16.7)	0.21
⩾ 3	68.0 (24.8)	60.6 (13.8)	
Curative surgery			
Yes	NR	64.8 (16.5)	0.36
No	68.0 (28.9)	57.6 (13.6)	
Stage of disease			
Metastatic	30.0 (11.0)	21.1 (8.9)	0.03
Nonmetastatic	82.0 (13.5)	61.3 (9.5)	
Liver metastasis			
Yes	42.0 (13.7)	35.7 (14.0)	0.11
No	23.0 (3.3)	NR	
Serum hemoglobin level			
Low (< 12 g/dl)	42.0 (12.4)	33.8 (9.5)	0.34
Normal (⩾ 12 g/dl)	82.0 (40.2)	51.7 (10.4)	
Serum white blood cell count			
High (⩾ 10,000)	24.0 (13.0)	NR	0.30
Normal (< 10,000)	42.0 (3.4)	40.8 (7.9)	
Serum platelet count			
High (> 350,000)	25.0 (1.3)	NR	0.51
Normal (⩽ 350,000)	42.0 (4.9)	43.4 (7.7)	
Erythrocyte sedimentation rate			
High (⩾ 50/h)	25.0 (6.4)	NR	0.02
Normal (< 50/h)	NR	67.5 (15.5)	
Serum LDH level			
High (⩾ 450 U/l)	21.0 (10.9)	NR	0.11
Normal (< 450 U/l)	44.0 (4.4)	43.2 (8.8)	
Serum CEA level			
High (⩾ 10 ng/ml)	23.0 (12.4)	NR	0.01
Normal (< 10 ng/ml)	44.0 (17.0)	49.4 (8.6)	
Serum CA 19.9 level			
High (⩾ 40 IU/ml)	39.0 (10.2)	29.4 (10.5)	0.04
Normal (< 40 IU/ml)	NR	56.3 (10.0)	
Response to chemotherapy			
Yes	71.0 (23.5)	60.2 (15.9)	0.05
No	42.0 (9.6)	NR	
Seum caveolin-1 level			
< median	44.0 (NR)	48.7 (10.5)	0.16
> median	39.0 (7.2)	36.6 (9.5)	

Note: NR means not reached.

To our knowledge, no clinical trials have examined serum caveolin-1 levels in gastric cancer patients so far, instead all of the available results were deducted from studies conducted on gastric cancer tissue samples. Therefore, the significance of circulating concentrations of caveolin-1 values in gastric cancer patients' serum has not been known yet. Even though our study was conducted on serum samples (instead of tissue samples), which is first in the literature, we had to discuss our results with the findings provided by tissue immunohistochemistry.

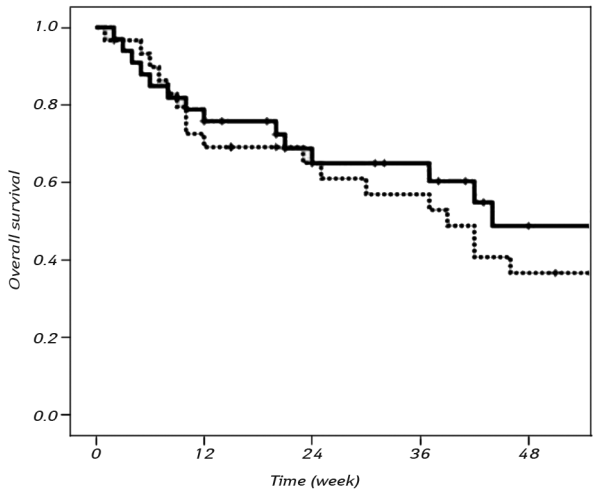

Figure. Survival curves of patients with gastric cancer according to serum caveolin-1 levels ($p = 0.16$) (< median = unbroken line and > median = dashed line)

Although its localization and expression have been examined in various human carcinomas, because of conflicting reports from a number of studies the functions of caveolin-1 in human gastric carcinoma have not been fully understood yet [4–16]. The caveolin-1 expression in gastric cancer was significantly lower than in premalignant gastric lesions [6, 8]. Similarly, other trials showed that gastric cancer cells in only 15.5% [14], 12.4% [15], 7.0% [5] and 5.4% [7] patients expressed caveolin-1. A reduced caveolin-1 expression was also encountered in 73% of gastric cancer cases [4]. In a novel study, the staining of caveolin-1 was downregulated in gastric cancer tissues [13].

Besides, contrary to what might be expected, we observed no significant correlations between the serum caveolin-1 levels and powerful prognostic factors of survival. However, histopathology [4–6, 10], invasion depth [8], tumor size [8], pathological grade [13, 14], lymph node involvement [6–8, 14], lymph node ratio [15], distant metastasis [5, 13] and clinical stage [7, 8, 13, 14] were found to be correlated with the expression of caveolin-1 in the various studies. Expressed caveolin-1 cases were all of the intestinal type histology [4, 5]. Likewise, positive rate of caveolin-1 was also found lower in diffuse type gastric cancer [6]. Positive rate of caveolin-1 was also found lower in advanced-stage gastric cancers than in early-stage cancers, but the difference was not statistically significant [6]. Positive rate of caveolin-1 was significantly lower in patients with lymph node metastases. Although caveolin-1 expression was low in primary tumor, it was increased in cell lines originating from distant metastases [5]. Moreover, low expressions of caveolin-1 were correlated with large tumor size, deep invasion depth, node involvement, and advanced stage of disease [8]. In other trial, expression level of caveolin-1 was correlated with the tumor's clinical stage, pathological grade, and metastasis status [13]. Likewise, it was significantly elevated in the advanced-stage and lymph node involved gastric cancer group [7, 14]. However, contrary to these correlations, several trials could not find any association with clinicopathological variables [4, 7, 9, 10]. No significant relationship was found between caveolin-1 expression and other parameters including patient age, gender, histological types according to Lauren's classification and distant metastasis [7, 14]. Similarly, no significant associations were showed between caveolin-1 expression and the other factors such as, age and sex of the patients, tumor localization, histological grade, pathological stage of tumor and node involvement, and the stage of the disease [4]. In a meta-analysis, caveolin-1 expression was not correlated with clinicopathological parameters except for the Lauren classification [10].

In literature, controversy exists about the prognostic role of caveolin-1 expression on outcome in patients with gastric carcinoma [4, 7, 9, 10, 14, 15]. Some studies have suggested that it mainly signifies a worse prognosis in association with an unfavorable outcome [7, 9, 14], whereas other has suggested that it signifies a favorable prognostic factor [10], whereas others have failed to show such correlations [4, 15]. Furthermore, high expression of tumoral caveolin-1 protein in metastatic lymph node instead of primary tumoral caveolin-1 expression was associated with unfavorable prognosis of curative resected gastric cancer, indicating the potential of novel prognostic markers [15]. In a meta-analysis consisting of six trials the caveolin-1 expression in gastric cancer predicted a better overall survival in gastric cancer and its expression in tumors has been accepted as a candidate positive prognostic biomarker for gastric cancer patients [10].

The differences in the results with caveolin-1 probably project the differences in source, kinetics of expression or destruction, and possibly signals including their expression and release. Moreover, these contrary findings of the trials might be ascribable to several other factors. Until now, no consensus has been agreed on which tumors and methods should be carried out for testing caveolin-1 expression. Over the last decades, IHC has become a beneficial integrated method in histopathology of diagnosis. However, there are several obstacles with IHC, the most important of which are as follows: the lack of assay standardization and alterations in the assessment of the IHC staining. Moreover, each of the trials was carried out on a relatively small sample size, which may have been unsatisfactory to show significant differences. A standardized method still needs to be introduced in wider prospective series.

In conclusion, with the intention of revealing its role we analyzed the soluble serum caveolin-1 levels in gastric cancer patients, and specified its associations with the prognosis, clinical factors, and responsiveness of chemotherapy. Serum caveolin-1 level was significantly elevated in gastric cancer patients. We believe that caveolin-1 might have a diagnostic

value in gastric cancer. The common clinical parameters were not found to be associated with serum caveolin-1 levels. Moreover, since we also found that serum of caveolin-1 level was not correlated with either survival outcome or chemosensitivity we suggest that serum caveolin-1 level might not be used as either a prognostic or a predictive biomarker in gastric cancer. The small sample size and short follow-up period of the study might have undermined the analysis and be considered as major limitations. Nevertheless, current study contributes to the literature in that to the best of our knowledge our study is the first in examining serum caveolin-1 levels in gastric cancer patients so far. Further trials in larger patient populations are necessary to detect the clinical importance of serum caveolin-1 in gastric cancer patients.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. Cohen AW, Hnasko R, Schubert W, *et al.* Role of caveolae and caveolins in health and disease. Physiol Rev 2004; **84**: 1341-79.

2. Parton RG, Simons K. The multiple faces of caveola. Nat Rev Mol Cell Biol 2007; **8**: 185–94.

3. Rothberg KG, Heuser JE, Donzell WC, *et al.* Caveolin, a protein component of caveolae membrane coats. Cell 1992; **68**: 673–82.

4. Barresi V, Giuffre G, Vitarelli E, *et al.* Caveolin-1 immuno-expression in human gastric cancer: histopathogenetic hypotheses. Virchows Arch 2008; **453**: 571–8.

5. Burgermeister E, Xing X, Röcken C, *et al.* Differential expression and function of caveolin-1 in human gastric cancer progression. Cancer Res 2007; **67**: 8519–26.

6. Gao X, Sun Y, Huang L, *et al.* Down-regulation of caveolin-1 in gastric carcinoma and its clinical biological significance. Ai Zheng 2005; **24**: 311–6.

7. Nam KH, Lee BL, Park JH, *et al.* Caveolin 1 expression correlates with poor prognosis and focal adhesion kinase expression in gastric cancer. Pathobiol 2013; **80**: 87–94.

8. Sun GY, Wu JX, Wu JS, *et al.* Caveolin-1, e-cadherin and β-catenin in gastric carcinoma, precancerous tissues and chronic non-atrophic gastritis. Chin J Cancer Res 2012; **24**: 23–8.

9. Zhao X, He Y, Gao J, *et al.* Caveolin-1 expression level in cancer associated fibroblasts predicts outcome in gastric cancer. PLoS ONE 2013; **8**: e59102.

10. Ye Y, Miao SH, Lu RZ, *et al.* Prognostic value of Caveolin-1 expression in gastric cancer: a meta-analysis. Asian Pac J Cancer Prev 2014; **15**: 8367–70.

11. Shen XJ, Zhang H, Tang GS, *et al.* Caveolin-1 is a modulator of fibroblast activation and a potential biomarker for gastric cancer. Int J Biol Sci 2015; **11**: 370–9.

12. Guo YL, Zhu TN, Guo W, *et al.* Aberrant CpG island shore region methylation of CAV1 is associated with tumor progression and poor prognosis in gastric cardia adenocarcinoma. Arch Med Res 2016; **47**: 460–70.

13. Zhang K, Yang G, Wu W, *et al.* Decreased expression of caveolin-1 and E-cadherin correlates with the clinicopathologic features of gastric cancer and the EMT process. Recent Pat Anticancer Drug Discov 2016; **11**: 236–44.

14. Seker M, Aydin D, Bilici A, *et al.* Correlation of caveolin-1 expression with prognosis in patients with gastric cancer after gastrectomy. Oncol Res Treat 2017; **40**: 185–90.

15. Sun DS, Hong SA, Won HS *et al.* Prognostic value of metastatic tumoral caveolin-1 expression in patients with resected gastric cancer. Gastroenterol Res Pract 2017; **2017**: 5905173.

16. Ryu BK, Lee MG, Kim NH, *et al.* Bidirectional alteration of cav-1 expression is associated with mitogenic conversion of its function in gastric tumor progression. BMC Cancer 2017; **17**: 766.