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ORIGINAL ARTICLE

Expression of Stromal Caveolin- 1 May Be a Predictor for Aggressive Behaviour of Breast Cancer

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Abstract Caveolin-1 (Cav-1) is well known as a principal scaffolding protein of caveolae which are specialized plasma membrane structures. The role of Cav-1 in tumorigenesis of breast cancers is relatively less studied. The aim of the present study is to describe the biological roles of Cav-1 in breast cancers considering its contrasting dual functions as an oncogene and as a tumor suppressor. This study included 71 females with breast cancer who had been histopathologically diagnosed in Private Gunes Pathology Laboratory between the years 2007, and 2012. The mean age is 52.48 ± 12.8 years. Patients were followed up for a mean period of 47.97 ± 20.48 months. We didn't determine Cav-1 positive tumor cells. In 36 cases (50.7%), there were stromal expressions of Cav-1. In the statistical analysis, there was a statistically significant correlation between Cav-1 expression and ER (p = 0.033), metastasis (p = 0.005), lymphatic invasion (p = 0.000), nodal metastasis (p = 0,003), perinodal invasion (p = 0.003), metastasis (p = 0.005) and survival (p = 0.009). We found that Cav-1 expression is associated with tumor size, histological grade, lymph node involvement. Accordingly, we have suggested that Cav-1 may be a predictive biomarker for breast cancer.

Keywords Breast cancer · Caveolin 1 · Predictive biomarker

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Introduction

Breast cancer (BC) is a highly complex and heterogeneous malignancy as for its molecular features and clinical outcomes [1–4]. Indeed, different molecular subgroups with prognostic and therapeutic implications have been encountered in clinical practice. Despite the fact that novel therapeutic approaches for BC are increasing in recent years, management, and treatment of BC still remain a challenging task due to significantly higher recurrence and death rates [5]. To this end, well-established prognostic, and predictive molecular markers with therapeutic significance have been analyzed in patients with BC. In addition new diagnostic and therapeutic markers are being developed to predict clinical outcome and treatment response. Receptor C-X-C chemokine receptor type 4 (CXCR4), proliferating cell nuclear antigen (PCNA), chemokine (C-C motif) ligands 2 and 5 (CCL2 and CCL5), miRNA, and FOXP3 are among these new promising biomarkers which aim to guide the physicians to administer efficient and targeted therapy with low toxicity [6].

Caveolin-1 (Cav-1) is the principal protein of caveolae which are specialized flask-shaped invaginations of cell membranes

rich in proteins which involve in the pathogenesis of several cancer types including BC [7]. Cav-1 acts as a scaffolding protein so as to manage and organize signaling molecules associated with neoplastic transformation such as cell survival, proliferation, angiogenesis, and metastasis [8, 9]. Previously, Cav-1 expression in BC had been thought to involve only BC epithelial cells rather than tumor-associated stroma. It is recently well-known that tumor-associated stroma plays an important role in several cancer types including BC [10, 11]. Previously, loss of Cav-1 expression in peritumoral stroma of the BC had been associated with poor outcome [12, 13]. However, Cav-1 have opposing roles as either a tumor supressor gene or an oncogene in BC. It interacts with the signaling molecules and accordingly it may function as a moderately effective oncoprotein or a tumor supressor protein. Therefore, the role of Cav-1 in BC still remains a very controversial issue. Current and future researches related to Cav-1 peritumoral-stromal expression will most likely lead to a new diagnostic, and prognostic molecular marker which aids in the treatment of BC.

The aim of this study was to investigate the expression of Cav-1 in the peritumoral stroma of the BC by immunohistochemistry and to evaluate a possible relationship between Cav-1 expression levels, histopathological parameters, and survival rates.

Material and Methods

This retrospective study was approved by the Local Ethics Committe of Tepecik Education and Research Hospital, Izmir, Turkey.

Patient Characteristics and Evaluated Clinicopathologic Parameters

This study included 71 female patients who had been histopathologically diagnosed as invasive breast cancer in Private Gunes Pathology Laboratory between the years 2007, and 2012. The histopathology reports of the archived paraffin-embedded tissue samples were reviewed, and the diagnosis of each case was confirmed independently by two pathologists (NE and SA) using the World Health Organization (WHO) criteria [Reis-Filho JS, Ellis IO (2012) WHO classification of tumours of the breast. IARC, Lyon]. Archived preprepared H&E stained slides of the patients were attentively examined. Demographic data of the patients were obtained from electronic media records and from relevant clinicians. Histological type (according to WHO 2012 [Reis-Filho JS, Ellis IO (2012) WHO classification of tumours of the breast. IARC, Lyon] and grade (in accordance with Nottingham grading system) of the tumors were determined. Data were also collected on tumor size, presence of vascular and lymphatic invasion, ductal carcinoma in situ (DCIS), inflammatory breast tissue, and postoperatively assessed surgical margin positivity. All of excised, and also metastatic lymph nodes were evaluated. Metastatic lymph nodes were examined to reveal the existence of perinodal invasion. All tumor specimens were classified according to the classification system of AJCC-American Joint Committee on Cancer based on pathological tumor-nodal involvement-criteria of metastasis, and findings detected at the time of initial diagnosis [9]. Tumors were classified according to the largest diameters of the tumors as follows: T1, ≤ 2 cm; T2, >2 - ≤ 5 cm cm, and T3, >5 cm. Presence of chest wall invasion and/or direct invasion to skin (as ulcerations and skin nodules) was accepted as T4 without regarding the size of the tumor. Lymph node involvement was categorized as follows:

N0, Absence of metastases to regional lymph nodes
N1, BC has spread to 1–3 axillary lymph nodes
N2, BC has spread to 4–9 axillary lymph nodes
N3, BC has spread to ≥10 axillary lymph nodes

Metastatic lymph nodes were histopathologically examined to reveal the existence of perinodal invasion.

In addition, some molecular biomarkers of archived tumor tissue materials such as ER, PgR, p53, Ki67 and HER2 were immunohistochemically re-examined on H&E stained slides. ER and PgR receptor (≥10%), p53 (≥10%), and Ki67 (≥14%)-positivities were determined based on the percentage areas of immunohistochemical staining as indicated in parentheses. HER2 immunohistochemical staining was scored according to ASCO-CAP guidelines.

Immunohistochemical Evaluation of Caveolin-1

Cav-1 expression levels were detected by immunostaining 5-μm sections from formalin-fixed, paraffin-embedded archived materials breast tumor specimens, and the stainings were evaluated only on the parts which were found to include tumor sections by previous H&E staining. Immunohistochemistry was perfomed by streptavidine biotin peroxidase method (Invitrogen, Camarillo, 85–9043). Before immunostaining, tissue sections were baked over-night at 60 °C, dewaxed in xylene and exposed to graded alcohol for gradual hydration. The sections were treated with heat-induced epitope retrieval in microwave (in 10 mM/L citrate buffer, pH 6.0, for 20 min, followed by cooling at room temperature for 20 min). Blocking of endogenous peroxidase and biotin was perfomed. Samples were incubated with primary anti-Cav1 antibodies (Novus Biologicals, Littleton Co, NB100–615, USA) at a dilution of 1:200 for 60 min. Negative controls were analyzed on adjacent sections incubated using non-immune mouse serum devoid of primary antibody. Immunostaining for stromal Cav-1 expression was semiquantitatively scored on a grading scale as 0, 1, and 2 independent from the clinicopathological characteristics.

Statistical Analysis

Statistical analysis was carried out using SPPS 16.0 software. Descriptive characteristics and frequencies of all parameters were evaluated prior to statistical analysis. Correlations between categorical variables were tested with *chi*-square test. Mann-Whitney U test was applied for group comparisons. Kaplan-Meier method was used to estimate event-free survival (EFS) and overall survival (OS) rates. *P* value of <0.05 was considered to be statistically significant.

Results

Seventy-one patients aged between 28 and 81 years (mean age, 52.48 ± 12.864 yrs) were enrolled in this study. Patients were followed up for a mean period of 47.97 ± 20.48 months (range, 15.38–92.42 mos). According to the histopathological findings evaluated at the time of initial diagnosis, the mean tumor diameter was 0.5–7 (2.41 ± 1.18) cm. Patients were histologically diagnosed as invasive ductal carcinoma (IDC) (n = 61; 85.9%), invasive lobular carcinoma (n = 3; 4.2%), and other histological subtypes of BC (n = 7; 9.9%). 41 patients were DCIS (n = 41; 57.7%). Histological grades of 1, 2 and 3, were seen in 4.2% (n = 3), 69.0% (n = 49) and 26.8% (n = 19) of the cases respectively. Vascular invasion (n = 12; 16.9%), lymphatic invasion (n = 44; 62.0%), and inflammatory breast tissue (n = 4; 5.6%) were detected in respective number of tissue samples. Surgical margin negativity was detected for breast cancer in 67 (94.4%) cases. Nodal metastases were detected in 38 (53.5%) patients, while in 28 (39.4%) patients perinodal invasions were noted. Any local relapse/recurrence did not occur in 69 (97.2%) cases, while metastatic tumor was observed in 18 (25.4%) cases. At the end of the follow-up period 62 (87.3%) patients were alive, while 9 (12.7%) patients exited.

According to the frequencies of the moleculer parameters, among all cases 49 were ER positive (69,0%). 46 of all cases had PgR (64,8%), cerbB2 was positive in 32 cases, suspicious for 23 and negative for 16 cases among all (45,1%, 32,4% and 22,5% respectively). As assessed using Ki67 proliferation index, Ki-67 positivity, and negativity were detected in 25 (54.3%), and 21 (45.7%) cases, respectively. In 25 cases Ki67 SI data were missing, while in 21 (67.7%) cases p53 was detected as positive.

Cav-1 immunoreactivity was observed in the adipocytes and vascular endothelial cells adjacent to the breast cancer tissue (Fig. 1). This immunostaining was accepted as internal positive controls. Stromal fibroblasts and myoepithelial cells underlying the luminal epithelial cells were also positive (36 cases) for Cav-1 (50.7%) except for luminal epithelial cells (Fig. 2). In our study, we didn't determine Cav-1 positive tumor cells.

Statistical Evaluation of Caveolin-1 in Association with Other Parameters

Based on immunostaining results, Cav-1 expression findings were sub-classified as positive for grading scales detected as 1 and/or 2 and negative for grading scale 0. The histologic grade of the tumor was subclassified as low grade (incl. Grade 1 and 2) and high grade (incl. Grade 3) tumors. Also, histopathological stage of the tumor was also subclassified as early stage (incl. Stages 1 and 2) and late stage (incl. Stages 3 and 4) tumors. Statistical analysis was performed using *chi*-square tests in order to evaluate the correlation between Cav-1 expression and other clinical/molecular parameters such as DCIS, vascular and lymphatic invasion, inflammatory breast tissue, postoperative surgical margin positivity, lymph node metastasis, perinodal invasion, hormone-receptor and HER2 status, presence of p53, Ki67 proliferation index, local relapse/recurrence, and metastasis.

There was a statistically significant correlation between Cav-1 expression and ER (p = 0.033), metastasis (p = 0.005), lymphatic invasion (p = 0.000), nodal metastasis (p = 0,003), perinodal invasion (p = 0.003) and metastasis (p = 0.005). The p values of all *chi*-square test analysis results are listed in Table 1.

According to the Kaplan-Meier survival analysis by log- rank test, the mean overall survival for Cav-1 expressing cases was found be 54.04 ± 3.312 months, and for Cav-1 negative cases, it was 41.74 ± 3.287 months. The mean overall survival for Cav-1 expressing cases was found to be 62.62 ± 1.444 months, and it was 37.68 ± 1.444 months for Cav-1 negative cases. In addition, the mean event-free survival for Cav-1 expressing, and Cav-1 negative cases were 54.04 ± 3312 and 33.86 ± 3.461 months, respectively. The mean event-free survival for Cav-1 expressing, and Cav-1 negative cases were 61.63 ± 1.538 and 27.79 ± 2.817 months, respectively.

Both overall survival and event-free survival rates were found to be statistically significant (p = 0.009 and p = 0.000, respectively). The log- rank graphs are demonstrated in Figs. 3 and 4.

Discussion

The role of Cav-1 protein has not been well identified in various cancer types including breast cancer. Some studies have demonstrated that Cav-1 has both tumor suppressive and oncogenic functions. Although epithelial (tumoral) Cav-1 expression in breast cancer has been typically investigated, limited number of studies about stromal Cav-1expression have been reported so far. In this study, the expression of Cav-1 in stromal and epithelial tumor cells of the patients diagnosed as breast carcinoma was

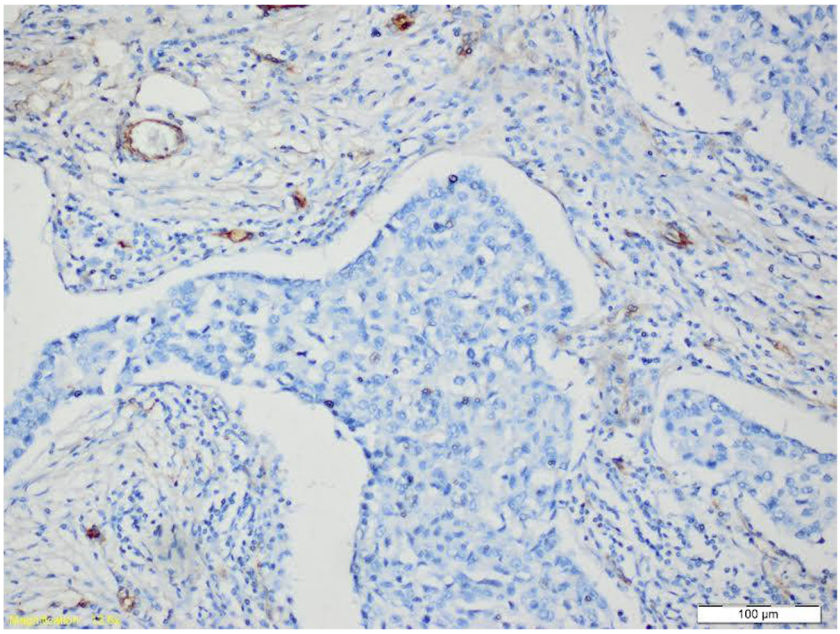

Fig. 1 Perivascular Cav-1 expression was accepted as internal control (DABX 400)

evaluated. Additionally, the relation between the disease progression and stromal Cav-1 expression was investigated.

Similar to other studies, Cav-1 immunoreactivity was found in non-tumoral breast tissue around carcinoma, in myoepithelial cells surrounding ductuli and lobules of normal breast tissue and in stromal fibroblasts [14, 15]. We encountered Cav-1 positive (immunoreactive) adipocytes and vascular endothelial cells, however Cav-1 expression was not detected in luminal epithelial cells. In some studies, researchers used polyclonal antibody-based enzyme immunoassays, and indicated the presence of minimal Cav-1 expression in luminal epithelial cells of breast tissue [16]. In a study where Cav-1 expression was determined using monoclonal antibody-based enzyme immunoassays, Cav-1 expression was not detected in non-tumoral luminal epithelial cells in accordance with our results [17]. This discrepancy may show that the type of primary antibody may affect the Cav-1 expression results. We observed positive Cav-1 expression in the stromal cells in 50.7% of our cases.

Many studies have shown that Cav-1 is a prognostic biomarker associated with tumor progression and clinical outcome. In a recent study, the importance of Cav-1 expression has been emphasized as a predictive biomarker for breast cancer [6]. In a study performed with primary cell cultures of excised breast cancer tissues Cav-1 was found to be down-

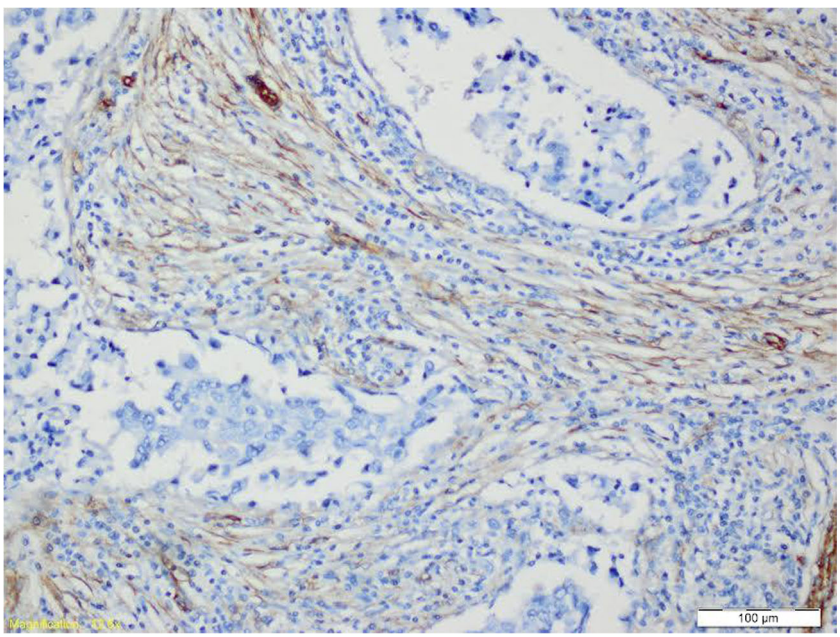

Fig. 2 Note the expression of Cav-1 in peritumoral stroma (DABX 400)

Table 1 *Chi*-square analysis results of Cav-1 expression and clinical/molecular parameters

		Parameters	*p*- values
CAVEOLIN-1	x	DCIS*	0.919
		Vascular invasion	0.051
		Lymphatic invasion	***0.000***
		Inflammatory breast tissue	0.054
		Postoperative margin assessment	0.357
		Nodal Metastasis	***0.003***
		Perinodal invasion	***0.003***
		ER	***0.033***
		p53 mutation	0.704
		HER2 status	0.268
		Ki67 proliferation index	0.806
		Dual Stage	***0.003***
		Local relapse/recurrence	0.239
		Metastasis	***0.005***

p values that are considered statistically significant are indicated bold-italic

* DCIS, ductal carcinoma in situ

regulated in human breast cancer fibroblasts [18]. On the contrary, any correlation between Cav-1 expression in epithelial cells and clinical outcome was not detected. A few in vivo studies demonstrated the presence, and significance of stromal Cav-1 expression. Our results showed that Cav-1 expression of cancer associated fibroblasts in the primary tumor microenvironment was associated with favorable clinical outcome.

Some parameters have been associated with high tumor grade and advanced stage. Similarly we grouped our patients in histological grades of 1 and 2, and disease stages of 1 and 2. According to statistical analysis among these groups Cav-1 expression was statistically significantly correlated with stage ($p = 0.030$) but not with histological grade ($p = 0.126$). Since only in 3 patients histological grade 1 was detected, we couldn't group grade 1 by itself, and consider combination of grades 2–3 as grade 2. If we grouped stage 1 as stage 1 alone and the rest (stages 2, 3 and 4 combined) as others then Cav-1 expression was quite statistically significant ($p = 0.005$) [12, 14, 19].

According to 2 studies performed by Witkiewicz et al. stromal loss of Cav-1 expression was associated with larger tumor size, higher nodal involvement and increased number of involved lymph nodes [12, 14]. Similarly, we grouped tumors based on the the size of the tumor, and extent to which it has grown into neighboring breast tissue as T1 (less than 2 cm) and others combined (T2, T3 and T4) then Cav-1 expression was statistically significant ($p = 0.003$). If we grouped T1 - T2 as a group and T3 – T4 as the other group then Cav-1 expression was not statistically significant ($p = 0.115$). Besides nodal involvement was found to be in increasing numbers in cases with loss of Cav-1 expression ($p = 0.003$). We evaluated the relation of Cav-1 expression (existent and non-existent) with tumor size and number of metastatic lymph node involvement according to independent samples t test, and *p* values of 0.006 for tumor size and 0.012 for the number of metastatic lymph node involvement were estimated.

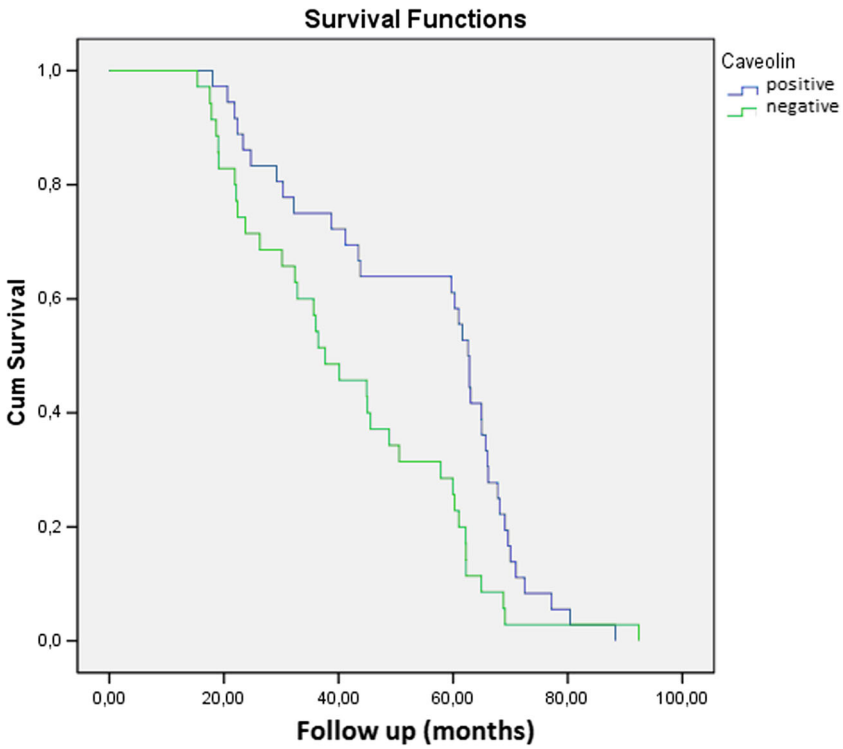

Fig. 3 Overall survival analysis of Cav-1 expression

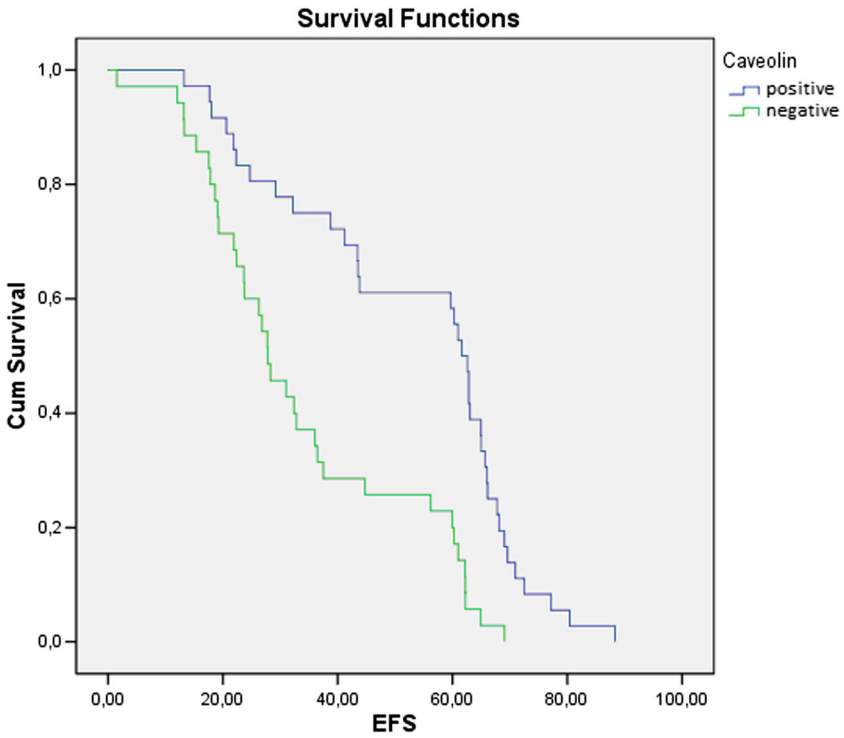

Fig. 4 Event- free survival (EFS) analysis of Cav-1 expression

In a meta-analysis of Cav-1 expression in breast cancer, it was indicated that loss of stromal Cav-1 expression was associated with a worse prognosis. According to the meta-analysis of breast cancer performed in 2013, contrary to epithelial cancer cells, stromal cells were found to be associated with survival [20].

It is well-known that hormone receptors (ER and PgR) and HER2 expression are quite important biomarkers for both diagnostic and therapeutic approach in breast cancer. Therefore we subgrouped patients according to these parameters and evaluated Cav-1 expression. In three studies performed, stromal loss of Cav-1 expression was found to be associated with positive HER2 expression, but not with hormone- receptor status [14, 19, 21]. Contrarily, we found a statistically significant correlation between Cav-1 expression and hormone- receptor positivity (p = 0.003), however Cav-1 expression did not correlate with HER2 expression p = 0.193).

There was no statistical significant correlation between Cav-1 expression and IDC/ non-IDC (p = 0.126), ER/PgR/ HER2 triple positivity (0.535).

Cav-1 has been demonstrated to have an oncogenic or tumor- suppressor role in breast cancer [22]. Also, it has been suggested that the high expression of caveolin-1 in stromal cells has a protective effect against tumor progression in breast cancer and could be a good prognostic indicator [19, 23]. In a study of Chung et al., a high level of Cav-1expression was found in 68.8% of breast cancer specimens. This incidence is similar to that of a study by Park et al. performed with 130 breast cancer patients [23]. However, in their study Cav-1 expression had been correlated inversely with HER-2 expression status [23]. This phenomenon was not observed in our series; possibly due to our small sample size. Meta-analysis from 19 eligible studies which included a total of 5926 patients with a median number of 312 patients per study failed to demonstrate Cav-1 expression in tumor cells as a predictive marker for breast cancer prognosis [19].

In a study by Savage et al., though not an independent prognostic parameter Cav-1 expression was found to be associated with worse overall survival [24]. In other studies, the status of stromal Cav-1 expression was suggested as a strong and reliable biomarker in breast cancer for the prediction of recurrence independent from standard clinicopathological risk factors and therapy applied [12, 19].

In our study, loss of stromal Cav-1 expression in triple negative (ER-, PgR-, HER2-) patients had not any predictive value (p = 203) which might be due to inadequate number of triple negative patients (n = 7).

Due to the growing recognition that the tumor microenvironment can influence tumor cell behavior, fibroblasts were indicated as key modulators of cancer progression in a study about breast cancer [7]. The researchers found that, breast tumors grown in a Cav-1 deficient microenvironment were more than five-fold larger than tumors grown in a wild-type Cav-1 containing microenvironment. Thus, a Cav-1-deficient tumor microenvironment was suggested as a fertile niche provider for breast cancer growth. The studies evaluating the role of Cav-1 in oncogenesis have been strictly focused on its epithelium-dependent functions, while completely overlooking its effect on the tumor-associated stroma.

Cav-1 had also been studied in other cancer types such as oral squamous cell carcinoma (SCC), pancreatic carcinoma, and ovarian tumors. In oral SCC, apart from stromal cells, only cancer cells have been evaluated by themselves, and the role of Cav-1 in oncogenic transformation have been demonstrated only in oral SCC cells. Cav-1 expression was not significantly correlated with tumor stage (T1-T3) and lymph node status (N0-N1) [25]. High Cav-1 expression in pancreatic carconoma cells was correlated with worse outcomes [26]. In a study which included the benign, borderline, malign ovarian serous tumors, it has been demonstrated a link between Cav-1 expression and agressiveness of ovarian cancer [27].

Conclusion

According to the recent studies, Cav-1 expression was found to be a significant biomarker in different cell types such as tumor cells and peristromal cells. Many studies concerning Cav-1 expression in epithelial cells of various cancers have been performed so far. However characteristic features of stromal cells should not be overlooked in consideration of the crucial role of tumor microenvironment in tumor growth, progression and clinical outcome.

We found that Cav-1 expression especially in stromal cells is associated with tumor size, histological grade, lymph node involvement. Accordingly, we have suggested that Cav-1 may be a predictive biomarker when evaluated in healthy breast tissues, and breast cancer cells.

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