Loss of Stromal Caveolin-1 Independently Predicts Poor Disease-Free Survival and Time to Recurrence in Patients with Prostate Cancer

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INTRODUCTION

In recent years it has become evident that stromal cell and extracellular matrix interact with tumor epithelium to influence cancer progression. Fibroblasts isolated from tumor stroma termed "cancer associated fibroblasts" show an ability to prevent cancer cell apoptosis, induce cancer cell proliferation, and stimulate tumor angiogenesis. Downregulation of the protein caveolin-1 (Cav-1) is one of the mechanisms implicated in the oncogenic transformation of fibroblasts. Cav-1 plays a major role in tumorigenesis through its various functions such as lipid transport, membrane trafficking, gene regulation, and signal transduction. Recently we demonstrated that loss of stromal Cav-1 expression has been associated with poor clinical outcome in breast cancer patients. In this study we sought to correlate tumor stromal Cav-1 expression with clinical outcome in prostate cancer patients.

METHODS

A tissue microarray (TMA) was constructed using tissue core samples from 167 human prostate cancers of varying stages and Gleason grades. Cav-1 expression was assessed in both epithelium and stroma using a standard immuno-peroxidase method (rabbit polyclonal pan-Cav Ab, BD Biosciences, 1:1000 dilution). The staining was scored semi-quantitatively as negative (0), equivocal (1), weak positive (2), or strong positive (3). Scores of 0-1 were considered indicative of loss of Cav-1 expression **(Figure 1)**. Statistical analysis of the association of Cav-1 expression and the usual markers of disease severity was performed using the Fisher exact test or the Kruskal-Wallis test. Kaplain-Meier curves were also generated.

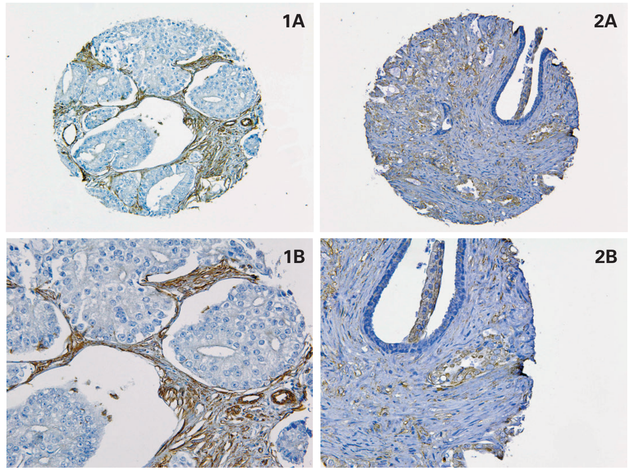

Figure 1: Medium and high power photomicrographs of two separate prostate cancers showing strong (3+) stromal immunohistochemical Cav-1 expression **(1A-B)** and equivocal (1+) stromal immunohistochemical Cav-1 expression **(2A-B)**.

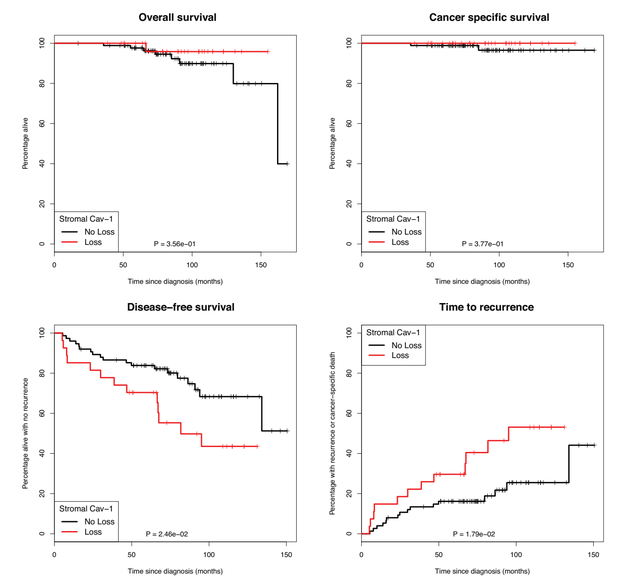

Figure 2: Kaplan-Meier curves for overall survival, cancer-specific survival, disease-free survival and time to recurrence.

	No Loss N=92	Loss N=32	P-value
Age	60.31507 63.62329 67.59315	62.03329 66.24658 68.94452	0.247[1]
Number of metastatic lymph nodes			0.454[2]
0	89% (81)	84% (26)	
1	3% (3)	13% (4)	
2	2% (2)	0% (0)	
3	2% (2)	3% (1)	
4	1% (1)	0% (0)	
5	1% (1)	0% (0)	
8	1% (1)	0% (0)	
Post-operation radiation			1[2]
No	93% (83)	93% (28)	
Yes	7% (6)	7% (2)	
Pathological T stage			0.569[2]
T2	50% (46)	41% (13)	
T3	45% (41)	56% (18)	
T4	5% (5)	3% (1)	
Pathological N stage			0.32[2]
N0	87% (80)	78% (25)	
N1	11% (10)	16% (5)	
Nx	2% (2)	6% (2)	
Tumor size mm	4.375 8.000 13.000	8.000 12.000 18.000	0.075[1]
Pre-op PSA	5.3450 8.8950 12.9950	7.8250 10.3400 15.4775	0.229[1]
Family history of prostate cancer			0.607[2]
No	76% (65)	83% (25)	
Yes	24% (20)	17% (5)	
Pathological grade			0.923[2]
3+3	9% (8)	6% (2)	
3+4	66% (61)	66% (21)	
4+3	24% (22)	28% (9)	
4+4	0% (0)	0% (0)	
4+5	1% (1)	0% (0)	
Gleason score (Low = 3+3 or 3+4)			0.815[2]
Low	75% (69)	72% (23)	
High	25% (23)	28% (9)	
Perineural invasion			0.567[2]
No	5% (3)	0% (0)	
Yes	95% (53)	100% (19)	
Small vessel invasion			0.358[2]
No	89% (81)	81% (26)	
Yes	11% (10)	19% (6)	
Capsular invasion			0.306[2]
No	52% (47)	41% (13)	
Yes	48% (43)	59% (19)	
Volume cc	2.0800 3.9400 8.6200	2.0075 3.7500 5.6675	0.425[1]
Last PSA	0.0050 0.0500 0.2000	0.0225 0.1000 0.4425	0.562[1]

Table 1: Association of stromal Cav-1 loss and the usual markers of disease severity.

RESULTS

Of the 167 patients originially included in the study, 43 were either lost to follow up or had insufficient clinical data for comparison. Of the remaining 124 cases, 32 showed loss of stromal Cav-1. Statistical analysis revealed no significant association between stromal Cav-1 loss and the usual markers of disease severity including Gleason grade, stage and presence of metastases **(Table 1)**. Kaplan-Meier curves showed a significant association between stromal Cav-1 loss and poorer disease-free survival and time to recurrence ($p<0.05$), but no significant association with cancer-specific survival **(Figure 2)**.

DISCUSSION

We found that loss of stromal Cav-1 in human prostate cancers predicts poor disease-free survival and shorter time to recurrence. In contrast to a recent paper by Di Vizio et al, (Cell Cycle, August 2009) we found no significant association between Cav-1 loss and the usual makers of disease severity and therefore conclude that loss of stromal Cav-1 is an independent factor in predicting poor clinical outcome. Since loss of Cav-1 is not prognostic of poor cancer-specific survival, the outcome may be affected through the recurrence rate. These observations are similar to those seen in breast cancer where loss of stromal Cav-1 has been associated with increased risk of recurrence independent of standard clinicopathological risk factors and treatment regimens. Thus, immunohistochemical evidence of stromal Cav-1 loss in biopsy and resection specimens may prove to be an important bio-marker for predicting poor clinical outcome in a variety of cancers.