Int J Clin Exp Pathol 2019;12(10):3901-3907
www.ijcep.com /ISSN:1936-2625/IJCEP0099832

Original Article

Fascin expression in urinary bladder urothelial carcinoma correlates with unfavourable prognosis

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Received July 18, 2019; Accepted August 29, 2019; Epub October 1, 2019; Published October 15, 2019

Abstract: Background: Urinary bladder crothelial carcinoma (UCB) is the most common urinary bladder neoplasm. The present study aims at investigating immunostaining of fascin in UCB in relation to clinicopathologiccriteria in Saudi Arabia. Methods: This study utilised 122 UCB and 25 apparently normal urothelium archival pathologic samples prior to local or systemic therapy. Tissue microarrays were constructed and the generated TMA blocks were used for Immunohistochemical staining. The mouse anti-fascin monoclonal antibody was used. A 25% was used to specify low and high fascin immunostaining. Results: Fascin immunostaining was detected in UCB and apparently normal urothelium. High immunostaining was statistically less frequent than low fascin immunostaining ($P \leq 0.001$). In UCB, high fascin immunostaining was associated with older patients (P=0.005) and local disease recurrence (P=0.002). High fascin immunostaining was an independent predictor of local disease recurrence (P=0.002) and associated with poor overall survival (P=0.027). Conclusion: High fascin immunostaining in UCB was associated with adverse prognostic factors and may be used as an independent prognostic marker. Fascin was detected in apparently normal urothelium and may contribute to UCB carcinogenesis. Further investigations (molecular and clinical) are required to understand the molecular interaction of fascin with UCB and its possible therapeutic applications.

Keywords: Urothelial carcinoma, fascin, immunohistochemistry, prognosis

Introduction

Urinary bladder urothelial carcinoma (UCB) is the most common urinary bladder tumour especially in western countries [1]. Worldwide, UCB is considered the ninth most common incidence of malignancy. In the genitourinary tract, it is the second most frequent malignancy [2]. UCB represents a 3.8% of cancers in Saudi males [3]. UCB with muscle invasion is a common presentation. Favourable prognosis following transurethral resection is seen low grade tumours. On the other hand, intravesical instillations of Bacillus Calmette Guerin and/or chemotherapy are required in case of high grade UCB. Recurrence following treatment is seen in 70% of patients with non-muscle invasive UCB. Invasion of muscle develops in 15% of non-invasive UCB. Also, the risk of tumour progression is greater in high grade UCB [4]. For UCB, comprehensive follow-up is still needed as the risk of recurrence and subsequent therapy is still high [5].

Fascin is a 55-kDa globular protein and is a member of the actin bundling family. Three forms of fascin are known. Fascin-1 (fascin) is commonly expressed in the nervous system and mesenchymal tissue, fascin-2 is expressed by cells of retinal photoreceptors, but fascin-3 is expressed mainly in the testis [6]. Fascin is known to induce membrane protrusions and cell motility [7]. Fascin overexpression was correlated with high grade tumours, risk of metastasis, and poor prognosis in many human neoplasms, including lung, stomach, pancreas, colon, gallbladder, thyroid, and kidney [8-15].

The aim of the current study is to find out the relation of fascin immunostaining to various

Table 1. Clinicopathologic findings of tumours (*n*=122)

Finding		Number (%)
Sex	Male	101 (82.8%)
	Female	21 (17.2%)
Age	<60 years	46 (37.3%)
	≥60 years	76 (62.3%)
Grade	Low grade	32 (26.2%)
	High grade	90 (73.8%)
Muscle invasion	Negative	59 (48.4%)
	Positive	63 (51.6%)
Pathologic stage (pT)	T1	50 (48.4%)
	T2	44 (36.1%)
	T3	8 (6.6%)
	T4	11 (9%)
Nodal metastasis	Negative	98 (80.3%)
	Positive	24 (19.7%)
Distant metastasis	Negative	109 (89.3%)
	Positive	13 (10.7%)
Lymphovascular invasion	Negative	101 (82.8%)
	Positive	21 (17.2%)
Anatomical stage	I	56 (45.9%)
	II	32 (26.2%)
	III	4 (3.3%)
	IV	30 (24.6%)
Local disease recurrence	Negative	82 (67.2%)
	Positive	40 (32.8%)
Survival	Alive	86 (70.5%)
	Dead	36 (29.5%)

Pathological stage (pT): T1: tumour invades subepithelial connective tissue. T2: tumour invades muscularis propria. T3: tumour invades perivesical tissue. T4: tumour invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, or abdominal wall. Anatomical stage/prognostic groups: Stage I: (T1, N0, M0). Stage II: (T2, N0, M0). Stage III: (T3 or T4a, N0, M0). Stage IV: (Any T, N1-3 or M1).

clinicopathological criteria and its possible role in prediction of disease outcome in UCB patients from Saudi Arabia.

Materials and methods

Patients

The study includes 122 UCB and 25 apparently normal urothelium are included in the current study. The used paraffin blocks were retrieved the Department of Pathology, King Abdulaziz University, Jeddah, Saudi Arabia. Patients were biopsied prior to any therapy whether local or systemic. UCB stages were confirmed using the cancer staging manual of American Joint Committee on Cancer regarding the T stage [16], and the World Health Organization classification of tumours was used while reviewing the grade [17]. The clinicopathological parameters of UCB are listed in **Table 1**. The study was approved by The Research Committee of the Biomedical Ethics Unit, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia, and an informed written consent was obtained.

Tissue microarray

Tissue microarrays were designed and constructed according previously studies [18, 19]. Tissue cores were punched from each UCB and apparently normal urothelial mucosa and inserted in recipient blocks. Construction of tissue microarrays was performed in an automated tissue arrayer {Master 3D Histech}. Orientation was marked by using placental tissues. For immunohistochemistry, the constructed blocks were cut at four micrometer thickness and sections kept on positive-charged slides.

Immunohistochemistry

Immunostaining was performed in an automatic immunostainer (Ventana Bench Mark XT, Ventana Inc., Tucson, AZ, USA). The mouse anti-human fascin monoclonal antibody {55 k-2} (obtained from Cell Marque™, Sigma Aldrich®, Sierra College Blvd. Rocklin, CA, USA) was used. Colorectal carcinoma was used as a positive control. Negative controls were treated by tris-buffered saline instead of primary antibody. Fascin immunostaining was considered positive when cytoplasmic immunoreactivity was seen. By using the percentage of positive fascin cells, a semi-quantitative scoring was used. The results were categorised as follows: (0) absolutely no immunostaining, (1) <25% of the cells are positive, (2) 25-50% of the cells are positive, (3) >50% of the cells are positive [14]. For statistical purposes, initial categories were dichotomized as follows; low immunostaining (category 0+1) and high immunostaining (category 2+3).

Statistical analysis

Mann-Whitney and Kruskal Wallis tests were used when testing the relation between two and three groups of patients alternatively. To test variance along one variable, non-parametric chi-square was used. Wilcoxon signed rank

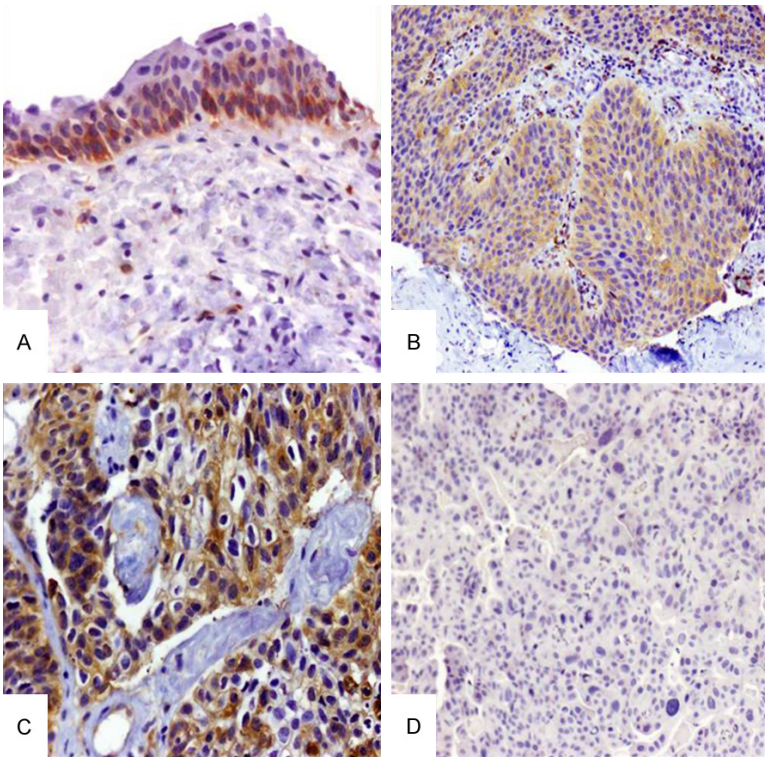

Figure 1. Fascin Immunostaining. (A) A section from an apparently normal urinary bladder mucosa shows low fascin immunostaining (cytoplasmic) in basal urothelial cells (200×). Sections from urothelial carcinomas show diffuse cytoplasmic fascin immunostaining in malignant urothelial cells (B {100×} and C {200×}). (D) A tumour is negative for fascin immunostaining (200×). Immunohistochemistry was done by using human anti-fascin antibody with diaminobenzidine as the chromogen and haematoxylin as a counterstain.

test was used to test differences between two related groups of paired variables. The overall survival and disease free survival were measured by Kaplan-Meier method and log-rank (Mantel-Cox) comparison test. To test the prognostic significance of fascin immunostaining as a predictor the binary logistic regression analysis was used to predict. Estimated odds ratio (exponential {B}), 95% confidence interval for exp (B) were expressed for each regression. Statistical analyses were performed using the SPSS® (IMB NY, USA) software packages version 16. Significance was set at $P<0.05$.

Results

Pattern of fascin immunostaining

The pattern of fascin immunostaining in UCB and apparently normal urothelial mucosa is shown in **Figure 1**. In apparently normal urothelial mucosa, fascin immunostaining was observed in 5 biopsies (20%) of which high fascin immunostaining was detected in 2 biopsies (8%). Fascin immunostaining was detected in basal layer while the umbrella cells were negative (**Figure 1A**). Cytoplasmic fascin immunostaining in UCB is shown in **Figure 1B-D**. Fascin immunostaining was detected in 77 tumours (63%). High fascin immunostaining was observed in 52 (42.6%) of UCB. The frequency of low fascin immunostaining was statistically more than high fascin immunostaining in apparently normal urothelial mucosa as well as UCB ($P<0.001$). Also, there was statistically significant higher fascin immunostaining in UCB than in apparently normal urothelium ($P<0.001$). Data are presented in **Table 2**.

The relation of fascin immunostaining with clinicopathological criteria and prognosis in UCB

The incidence of fascin immunostaining in UCB in relation to clinicopathological criteria is shown in **Table 3**. High fascin immunostaining was significantly statistically more frequent in tumours of older patients (above 60 years) (P=0.005) and tumours associated with local disease recurrence (P=0.002). No statistically significant difference was found with fascin immunostaining in relation to sex, tumour differentiation, muscle invasion, pathological stage (pT), nodal metastasis, distant metastasis, lymphovascular invasion, or anatomical stage. Logistic regression revealed that high fascin immunostaining was an independent predictor of local disease recurrence (P=0.002, Expβ=0.438, CI: 0.201-0.955). Lower overall survival was found in UCB with high fascin immunostaining than in those with low fascin immunostaining (Log Rank {Mantel-Cox}=4.896 and P=0.027) (**Figure 2**).

Discussion

The interaction of cell-cell adhesion and cell-matrix plays important roles in epithelial cell

Table 2. Categories of fascin immunostaining in urothelial carcinoma and normal urothelium

	Primary tumour (*n*=122)	Normal urothelium (*n*=25)	*p* value
Low expression	70 (57.4%)	23 (92%)	<0.001#
High expression	52 (42.6%)	2 (8%)	
p value	<0.001*	<0.001*	

*One sample non-parametric chi-square test; #Wilcoxon Signed Rank Test.

Table 3. Relation between fascin immunostaining and clinicopathologic features of urothelial carcinoma of urinary bladder

Feature		*p* value
Sex	Male	0.9*
	Female	
Age	<60 years	0.005*
	≥60 years	
Grade	Low grade	0.351*
	High grade	
Muscle invasion	Negative	0.491#
	Positive	
Pathologic stage (pT)	T1	0.55#
	T2	
	T3	
	T4	
Nodal metastasis	Negative	0.384*
	Positive	
Distant metastasis	Negative	0.466*
	Positive	
Lymphovascular invasion	Negative	0.535*
	Positive	
Anatomical stage	I	0.286#
	II	
	III	
	IV	
Local disease recurrence	Negative	0.002*
	Positive	

#Kruskal-Wallis Test; *Mann-Whitney test; Pathological stage (pT): T1: Tumour invades lamina propria (subepithelial connective tissue). T2: Tumour invades muscularis propria. T3: Tumour invades perivesical soft tissue. T4: Extravesical tumour directly invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall or abdominal wall. Anatomical stage/prognostic groups: Stage I: (T1, N0, M0). Stage II: (T2, N0, M0). Stage III: (T3 or T4a, N0, M0). Stage IV: (Any T, N1-3 or M1).

stabilisation and organisation. Malignant transformation is associated with abnormalities of the adhesion systems that lead to tumour invasion and metastasis [20]. Fascin (an actin binding protein) is important for diverse types of cellular protrusions with functions in cell adhesion, cell-cell interaction, and cell migration [21-23] suggesting that it may serve as an oncogene [24]. Fascin overexpression was associated with increased formation of actin and fascin containing surface protrusions [20].

Fascin was detected by immunostaining in endothelial cells, neurons, dendritic cells of lymphoid tissue, and epidermal basal layer cells, the oesophagus, and the uterine cervix [20, 25, 26]. The urothelium, ovary, and prostate showed no fascin positivity [27]. Fascin may have low level or absent in many normal epithelial cells [15, 27]. There are few studies investigating fascin expression in UCB [15, 24, 28-32]. In the present study, fascin immunostaining was detected in 20% of normal urothelium and high immunostaining was observed in 8%. These tissues were obtained from mucosa in the vicinity of malignant and benign lesions. This means that those mucosae are apparently normal, but may have some molecular changes as a part of field cancerization in malignant tumours. While in UCB, fascin immunostaining was detected in 63% of UCB, in about 42.6% of which high immunostaining was found. Fascin immunostaining was more frequent in UCB than in apparently normal urothelium which is similar to previous studies [28, 33]. Increased fascin expression in epithelial cells is associated with disruption of normal adherens junctions and decrease in cell-cell attachment [34, 35]. In another study, fascin positivity was detected in the non-neoplastic urothelium close to UCB [30]. However fascin was not detected in apparently normal urothelium by other studies [15, 28, 29, 33]. In addition, fascin was not detected in benign urinary lesions as inverted papilloma, nephrogenic adenoma, and exophytic transitional papilloma [15, 31]. The conflicting results may raise the need for further research on large scale cases including urothelial mucosa from normal persons and urothelial mucosa.

Advanced stages of UCB have higher potential for muscle invasion and poor survival rates. In

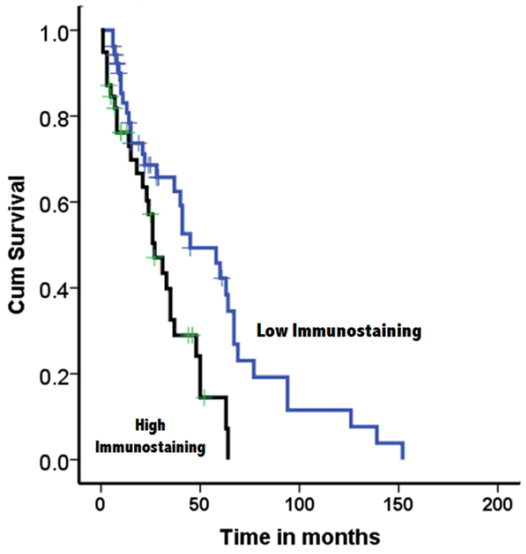

Figure 2. Overall survival curve (Kaplan Meier) according to fascin immunostaining. There is lower survival probability in patients with high fascin immunoexpression (log-rank =4.896, *P*=0.027).

UCB, muscle invasion was associated with lower survival and poorer prognosis [36]. Increased fascin expression may be associated with epithelial junction disruption, invasiveness, and metastasis [29]. In vitro, downregulation of fascin increased cell adhesion. Fascin knock-out decreased cell migration [33]. Fascin facilitates cell protrusion formation and may enhance invasion and metastasis. Fascin may be also associated with aggressive malignant phenotype and poor clinical outcomes [20]. In UCB, the role of fascin in progression and metastasis is still controversial. In the current study, we did not find association between fascin immunostaining and tumour invasion which is similar to a previous report [30]. However, several other studies showed that fascin immunostaining is associated with invasiveness of UCB [15, 24, 28, 29, 31-33]. Most of these studies used an arbitrary categorisation of immunostaining results as well as using the staining intensity. In our study we used a relatively objective method by dividing the immunostaining by the median value into two categories. The staining intensity is not reliable due to personal subjectivity and technical issues.

In the present study, no association was found between tumour grade and fascin immunostaining. Several studies found the same [15, 28-30]. Only one study reported that fascin expression was positively correlated with histological grade [33]. Fascin may be not related to the degree of differentiation.

In UCB, recurrence occurs in around 70% which is associated with 10%-15% muscle invasion and metastasis [37]. Investigations to find new molecular pathways involved in UCB invasion and metastasis are important. Fascin upregulation may correlate with unfavourable prognosis in some human carcinomas [8, 9, 24, 38]. In the current study, high fascin immunostaining was found to be an independent predictor of local disease recurrence. Similar results were reported [15, 28, 33] contrary to one study [30]. Fascin may be used as a prognostic marker. Also in the current study, high fascin immunostaining in UCB is associated with lower overall survival. There are very limited studies regarding the relation of fascin immunostaining with survival, only one previous study showed that there was an association with recurrence-free survival [28].

The limitation of this study is the use of apparently normal mucosa adjacent to non-healthy urothelium which is the same limitation in most previous reports. To be able to judge fascin immunostain, normal urothelium from healthy persons should be included.

Conclusion

In summary, we demonstrated an increased fascin immunostaining in UCB and apparently normal urothelium. Increased fascin immunostaining in UCB is associated with the incidence of recurrence and lower survival. Fascin immunostaining may be used as an independent predictor factor local disease recurrence in UCB. Further studies are recommended to clarify the difference in fascin in immunostaining across normal and diseased urothelium. In addition, the theory of using the fascin pathway for targeted therapy in UCB may be tested.

Acknowledgements

The study is supported by a fund from the National Plan for Science, Technology and Innovation (MAARIF-AH)-King Abdulaziz City for Science and Technology-the Kingdom of Saudi Arabia-award number (11-BIO1524-03).

Disclosure of conflict of interest

None.

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