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Significance of Fascin Expression in Renal Cell Carcinoma

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Abstract

Background: Renal cell carcinoma (RCC) is the most common form of renal malignancy. The existing prognostic factors (tumor staging and grading) are considered inadequate as many patients with similar tumor characteristics seem to show different clinical outcomes. This has increased the need for evaluating the role of many molecular biomarkers. This study was undertaken to determine the expression profile of Fascin, an actin bundling protein in RCC.

Methods: This cross sectional study was carried out among 64 RCC cases received in the Department of Pathology for a period of four years. Fascin immuno histochemistry was done on the representative paraffin blocks and the slides were examined for membrane and cytoplasmic positivity. The data was statistically analysed with "SPSS Version 23" software.

Results: There was a significant statistical correlation between the nuclear grade and fascin expression. However there was no correlation between tumor stage and fascin expression. We also observed a statistically significant correlation between fascin immuno staining and RCC with sarcomatoid changes ($p<0.05$).

Conclusion: Targeted therapy for Fascin may be used as a treatment modality for high grade RCC and RCCs showing sarcomatoid changes.

Keywords: Renal cell carcinoma; Fascin; Sarcomatoid changes.

Introduction

Renal cell carcinoma (RCC) is emerging as one of the most common malignancies with a high mortality rate. Globally, about 2,70,000 cases of renal cancer are diagnosed every year and nearly 50% of those diagnosed die of the disease.[1] Although the incidence rates are lower in countries like India, RCC causes significant mortality. In addition, the escalating health care costs increases the burden of the disease, especially in emerging economies like India. Therefore, the most effective and prudent choice in the management of RCC is early diagnosis. In addition, there is a growing need to predict the prognosis of the tumors in order to determine the treatment strategies.

Currently, pathological stage is the most commonly used factor to determine the prognosis of RCC.[2] This is due to the fact that it utilizes various tumor characteristics to stratify patients into clinically useful and relevant groups. Various studies indicate that tumor morphotype, presence of tumor necrosis, Fuhrman grading and microvascular invasion, sarcomatoid and rhabdoid differentiation are important prognostic parameters.[3] These factors are however, found to be insufficient as many patients with similar tumor characteriistics seem to show different clinical outcomes. Therefore, prognostic outcomes for renal cell carcinoma remain unpredictable, justifying the need to explore newer prognostic factors.

Several molecular biomarkers are being

evaluated for their usefulness as prognostic markers out of which Polybromo 1 and VHL have gained importance.[4] The expression profile of Fascin in renal cell carcinoma is currently unclear. Very few studies have been conducted with productive results.[5] Fascin is a 55-kD actin bundling protein localized predominantly in the dendritic cells, mesenchymal cells and in the cells of nervous system in non-neoplastic tissues. The morphological characteristic common to these specialized normal cells is that they have parallel actin bundles forming cell protrusions of plasma membrane thus playing a major role in cell migration. In cell culture, over-expression or depletion of fascin modulates cell migration and alters cytoskeletal organization. Recent studies have documented that, expression of fascin in Classic Hodgkins Lymphoma, Langerhan cell Histiocytosis, Lung carcinomas and other neoplasms, is of clinical significance. It has been shown that fascin expression correlates with the clinical aggressiveness of tumors. Hence, expression of fascin indicates poor prognosis.[6–7] Therefore, a study on expression pattern of fascin may facilitate the development of a specific targeted therapy, which could probably serve as a mile stone in the treatment of renal cell carcinoma.

Objectives

This study was carried out

1. To analyse the immunohistochemical expression of Fascin in Renal cell carcinoma.
2. To correlate the expression of Fascin with the pathological stage, nuclear grade and other clinicopathological parameters.

Methodology

Study setting and participants

This cross sectional study was carried out in the Department of Pathology of our tertiary teaching institution for a period of four years. All the nephrectomy specimens received during the study period with a diagnosis of RCC were taken up for the study. A total of 64 specimens were analyzed.

Ethical approval

Approval was obtained from the Institutional Ethics Committee prior to the commencement of the study.

Data collection

An immunohistochemical evaluation of the paraffin blocks was done to examine for Fascin expression. Previous studies showed that the endothelial cells of vessels are strong positivity with fascin and this was interpreted as positive control.[8–10] As negative controls, the slide treated by replacement of primary antibody with non-immune serum was used.

All slides were examined and scored according to the H score.[11,12] The intensity of membrane and cytoplasmic immuno staining of fascin in individual tumor cells was scored on a scale of 0- with no staining to 4- with strongest intensity. The percentage of cells with fascin staining at each level of intensity was estimated from 0 to 100. The proportion of cells at each level of intensity was multiplied with the corresponding intensity value, and the products were added to obtain an immune-staining score ranging from 0 to 400.

Data analysis

Statistical analysis was done on the data using the "SPSS Version 23" statistical program. All results were expressed as mean with standard error. Independent sample t test was performed to evaluate the association between Fascin expression and clinicopathological variables. The differences were considered statistically significant when p value was < 0.05.

Results

Majority of the participants in the study were over 50 years of age (71.9%) and were males (76.6%). Most of the participants had a BMI >25kg/m2 (57.8%) and were smokers (65.6%). Hypertension was present in 51.6% of the cases. (Table 1) In this study, in 53.1% of the cases, the tumor size ranged between 5.1 and 10 cm and in majority of the cases, the histological type corresponded to clear cell carcinoma (54.6%). (Table 2)

Fascin immuno scoring showed as significant correlation with hypertension. The association between fascin immunostaining and presence of hypertension was statistically significant ($p<0.05$). (Table 3).

The cases comprised of Clear cell RCC (54.6%), chromophobe RCC (18.7%), papillary RCC (15.6%), Collecting duct RCC (4.6%), Multilocular cystic renal neoplasm of low malignant potential (3.1%), Tubulocystic (1.5%) and unclassified sarcomatoid RCC (1.5%).(Table 4).

Table1: Background characteristics of the study participants:

S. No	Characteristics	Frequency N(64)	Percentage (%)
1	**Age**		
	<50 yrs	18	28.1
	>50 yrs	46	71.9
2	**Sex**		
	Males	49	76.6
	Females	15	23.4
3	**Diet**		
	Mixed	49	76.6
	Vegetarian	6	9.4
	Unknown	9	14.0
4	**Body mass index**		
	<25	26	40.6
	>25	37	57.8
	Unknown	1	1.6
5	**Smoking**		
	Present	42	65.6
	Absent	20	31.3
	Data not available	2	3.1
6	**Hypertension**		
	Present	33	51.6
	Absent	26	40.6
	Data not available	5	7.8

Table 2: Clinicopathological grading of RCC.

S. No	Characteristics	Frequency (N =64)	Percentage (%)
1	**Tumor size**		
	<5 cm	20	31.3
	5.1–10 cm	34	53.1
	10.1–15 cm	5	7.8
	15.1–20 cm	4	6.3
	>20 cm	1	1.5
2	**Histological type**		
	Clear cell RCC	35	54.6
	Chromophobe RCC	12	18.7
	Papillary RCC	10	15.6
	Collecting duct RCC	3	4.6
	Multilocular cystlic RCC	2	3.1
	Tubulocystic	1	1.7
	Unclassified RCC	1	1.7
3	**Nuclear grade**		
	1	11	17.2
	2	38	59.4
	3	5	7.8
	4	10	15.6

Table 3: Correlation between Fascin immunosttaining score and clinicopathological data.

S. No	Parameters		Number of study participants	Fascin Immuno scoring		P value
				Mean	Standard deviation	
1	Age (in years)	<50	18	119.4	129.545	0.336
		>50	46	96.6	123.159	
2	Sex	Males	49	60	125.28	0.278
		Females	15	75	124.89	
3	Body mass Index (in kg/m^2)	<25	26	106.2	120.003	0.382
		>25	37	103.6	129.498	
4	Hypertension	Present	33	114.24	136.589	0.036*
		Absent	26	80.15	95.048	
5	Tumor size (in cm)	<5	20	91.50	115.680	
		5.1–10	34	107.18	134.045	
		10.1–15	5	70.00	64.420	0.351
		15.1– 20	4	192.50	140.801	
		>20	1	0	0	

*statistically significant

Table 4: Mean immunostaining scores for various histological types of RCC:

S. No	Histological type of RCC	Number of cases	Percentage of cases (%)	Mean immuno scoring	Standard error
1	Clear cell	35	54.7	84.5	20.5
2	Chromophobe	12	18.8	110.8	36.2
3	Papillary	10	15.6	119	38.5
4	Collecting duct	3	4.7	200	70
5	Multilocular cystic	2	3.1	40	
6	Tubulocystic	1	1.6	80	
7	Unclassified	1	1.6	380	

Table 5: Association between immunostaining scores and RCC with sarcomatoid changes.

S. No	Sarcomatoid change	Total No of cases	No of cases with Fascin positivity	Mean immuno scoring	P value
1	Present	9	8	262	0.0001*
2	Absent	55	24	77	

*statistically significant.

Table 6: Association between nuclear grading (WHO/ISUP) with immunostaining score of Fascin.

S. No	Nuclear grade	Frequency	Percent	Mean	Standard error	P value
1	1	11	17.2	53.64	18.64	0.028*
2	2	38	59.4	73.9	15.6	
3	3	5	7.8	114	68	
4	4	10	15.6	265	43.9	

*statistically significant.

Out of the nine RCC cases with sarcomatoid changes eight (89%) showed positivity and one (11%) showed negativity for fascin. The mean immuno staining score of fascin was significantly higher in the RCCs exhibiting sarcomatoid changes (score 262) than the RCCs without sarcomatoid changes (mean score 77) with a significant association (p value - 0.0001). (Table 5).

Expression of fascin was found to increase with increasing grades of the cases with mean immuno staining scores of 54±19 for grade 1, 74±16 for grade 2, 114±68 for grade 3 and 265±44 for grade 4 tumors. The p Value was 0.028 showing significance. (Table 6).

Discussion

In the current study, the average immuno staining score of fascin did not show significant correlation with age, sex, diet, body mass index, smoking and hypertension. In the current study, the average immuno staining score for clear cell RCC was 84.57±20.5. According to the study by J.S. Jin et al[10] and Wen-Chiuan Tsai et al,[9] fascin immuno staining score for clear cell RCC was 95±18 and 53.6, similar to our findings. The immuno staining score of papillary RCC was 119±38.5 similar to the results of Wen-Chiuan.Tsai et al while the immuno staining scores of chromophobe RCC and collecting duct was higher. The expression score of fascin in RCC with sarcomatoid changes was significantly high in the studies done by J.S. Jin et al (263.21) and Wen-Chiuan Tsai et al (275.4).[5,13] The same trend (fascin immunoscore- 263) was seen in the current study also. There was a significant correlation of fascin immuno scoring of RCC cases with sarcomatiod changes as with studies done by J.S. Jin et al and Wen-Chiuan Tsai et al and Zigeuner R et al.[13,14]

In this study, immuno staining scores of fascin increased as the grade of tumor (p value 0.0001) increased, similar to both the studies done by J.S. Jin et al and Wen-Chiuan Tsai et al.[13] The correlation of immunoscoring score of fascin with clinical metastasis showed a positive correlation in the study by Wen-Chiuan Tsai et al.[13] However, a multicenter study involving large number of cases is to be done to evaluate the clinical significance and role of fascin in RCC.

Extensive research on Fascin has demonstrated an upregulation of Fascin in aggressive and metastatic cancers, indirectly implicating that presence of Fascin indicates poor prognosis. In certain tumors, fascin has been expressed to a great extent in tumor stroma, and this has been attributed to the presence of motile fibroblast and dendritic cells.[15] The phenomenon underlying this presentation has been hypothesized that the presence of actin modulating proteins act with fascin and thereby increases the motility thereby allowing morphological transition of the cell from epithelial to mesenchymal cells. This mechanism reasonably explains the linkages between fascin expression and aggressive proliferation and metastasis of the tumors. However, the causative implication of fascin in tumor aggressiveness needs to be established in the future through longitudinal research.

Conclusion

Renal cell carcinoma is the most common renal malignancy in elderly age group. Our study has demonstrated the presence of significant correlation of fascin with RCC cases showing sarcomatoid changes which is known to be aggressive and with ISUP/ WHO grade of tumors. This finding may play a major role in designing targeted therapy for Fascin that can be used as one of the modes of treatment for high grade RCC and RCCs showing sarcomatoid changes.

Declaration

Conflict of interest: none

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